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PDA Letter

Volume LV • Issue 2 www.pda.org/pdaletter February 2019

PUPSIT & the Proposed Annex 1 Revision 20

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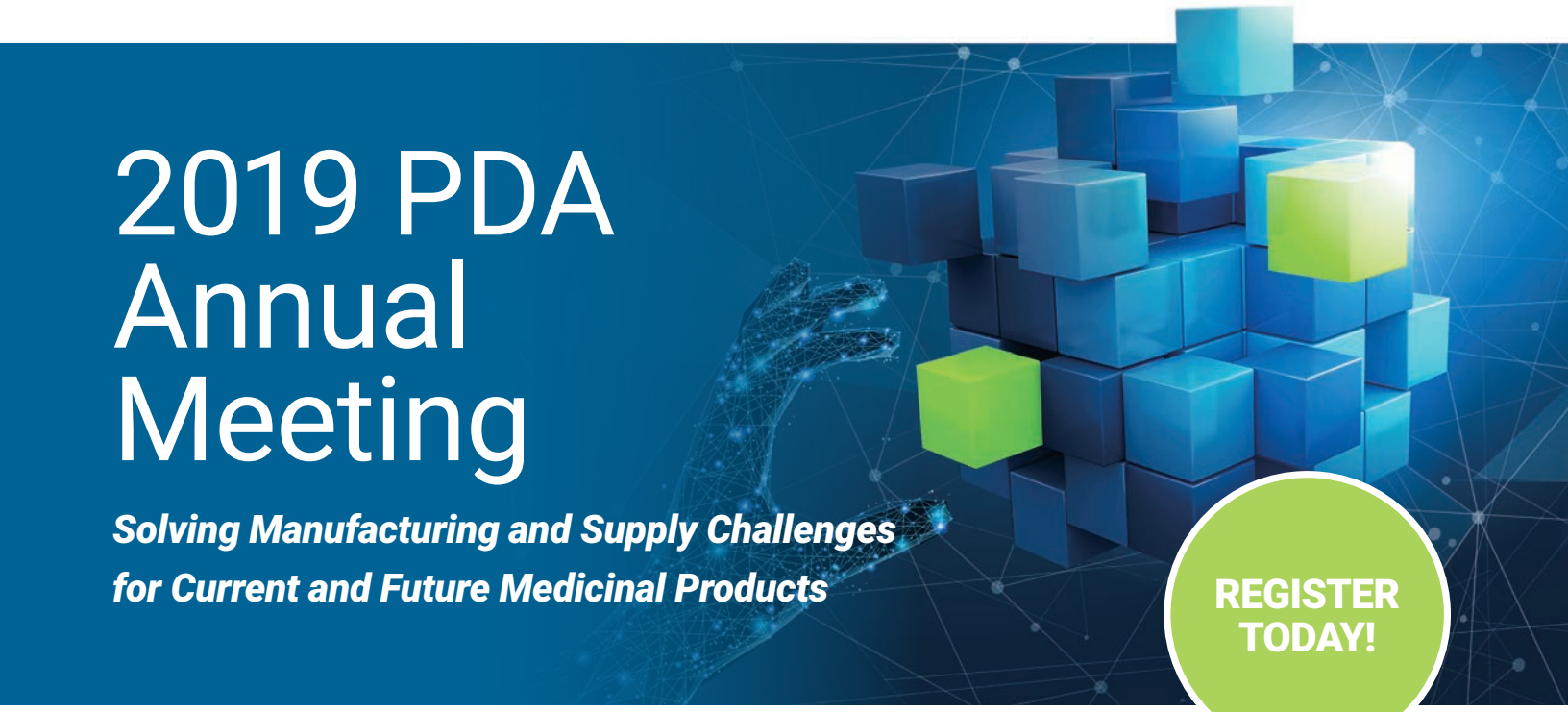

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- Embracing the contributions of Young Professionals in the industry

Here are just a few of the speakers who are already confirmed:

- **Brian J. Hawkins, PhD**, Scientific Applications Director, *BioLife Solutions, Inc.*
- **Chester Kitchen**, Director, Corporate Development, *Merck & Co., Inc.*
- **Divakar Ramakrishnan**, Vice President and Chief Digital Officer, *Eli Lilly and Company*
- **Nitin Rathore, PhD**, Director, *Amgen Inc.*
- **Per Vase, PhD**, Managing Partner, Applied Manufacturing Science, *NNE*

The full lineup of confirmed speakers and a detailed agenda can be found at **pda.org/2019Annual**.

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20

PUPSIT & the Proposed Annex 1 Revision

Hal Baseman, ValSource

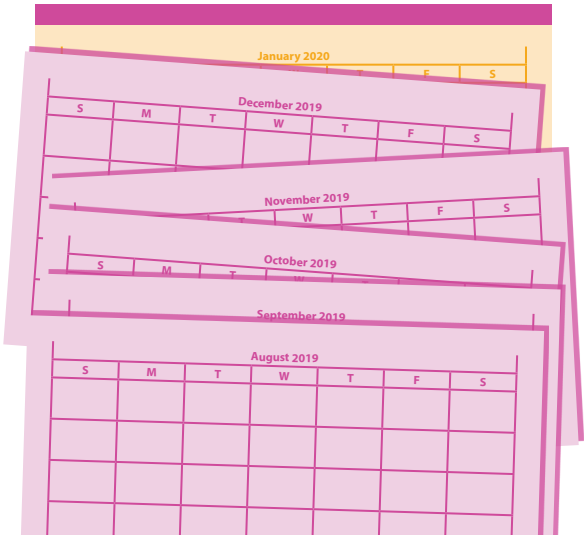
Since its publication in December 2017, the proposed Annex 1 revision has been much discussed. As coleader of the team that prepared PDA's comments on the revision, I am intimately familiar with the intricacies of the document. As such, I want to share some thoughts on the revision, culminating in four pieces of advice concerning one of the most debated points of contention within Annex 1.

Cover Art Illustrated by Katja Yount

InfoGraphic

28

Annex 1
Ready of Not?



The *PDA Letter* conducted an informal survey last year to ascertain how prepared PDA members are for the proposed Annex 1 revision.

PDA Letter

Volume LV • Issue 2 www.pda.org/pdaletter

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Departments

Digital Exclusives

> Alternative to LAL Gains Ground
As alternatives to the traditional LAL assay enter the market, what does this mean for the industry?

> Growth Promotion Testing for EM
Why are reference materials critical for environmental monitoring?

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New Tech Meets Current Regs

Rebecca Stauffer @RebeccaStauPDA

Back when I was planning my wedding in 2008, I needed to get a marriage license from the local government where the wedding was planned. So, one weekday during lunch, a friend and I traveled to the county courthouse to get the license.

It was a good thing I brought a friend along, as a sign near the courthouse door stated cellphones with camera functions were not allowed in the courthouse at all, something a security guard brusquely reminded people entering.

While the courthouse probably had good reason to forbid cameras, such as for the safety of witnesses, etc., the vast majority of cellphones (and I am not even talking smartphones) had cameras by 2008. In fact, I remember one of my colleagues had trouble even finding one *without* a camera back then. Curious, I checked the website for that courthouse a few weeks ago. Now, over ten years later, cellphones with cameras are allowed, but anyone caught using one to record anything can be cited criminally and the device confiscated. Quite a difference from a total ban!

This is just one of many examples of how existing regulations, many decades old, are colliding with new technology. Think about our industry. The move to digital healthcare and smart delivery devices requires adhering to privacy laws. And new technologies like robotics and even isolators mean potentially revising current GMPs.

In December 2017, the European Commission released the long-awaited proposed revision to Annex 1 that incorporates quality risk management (QRM) principles and addresses new technologies and procedures. Naturally, PDA commented on the document and the revision remains a hot topic for our readers. In particular, the document's requirement for a pre-use, post-sterilization integrity test (PUPSIT) for sterile products unable to be sterilized in their final container.

In the November/December issue, our infographic included a link to a short, anonymous survey about how prepared readers feel they are for the Annex 1 revisions. These results can be found in this issue's infographic on page 28.

As always, the Letter welcomes your feedback, so we welcome your thoughts on PUPSIT and other proposed Annex 1 changes. Not only can you email me but send me a tweet too. Also, even outside of Annex 1, other regions are facing the challenge of updating regulations to account for new technologies. We want to hear from you too!

Oh, and by the way, the wedding went off without a hitch, thanks in part, to my friend who babysat my phone while I ran into the courthouse.

Visit the Redesigned PDA Website

PDA recently launched its newly designed website! The completely redesigned and reorganized website makes finding information easier and features an overall improved user experience. Visitors to www.pda.org will instantly see the following changes:

- More refined, cleaner design
- Condensed navigation options
- Improved search capability
- Enhanced mobile functionality
- New & Noteworthy section for pertinent member-oriented information
- Up-to-date industry news with feeds from the *news uPDAte*

The new site also features "Topic Area" pages that consolidate all the relevant PDA activities, offerings and industry news onto pages dedicated to the following five areas of strategic interest to PDA members and customers:

- Aseptic Processing & Sterilization
- Biopharmaceuticals & Biotechnology
- Manufacturing Science
- Quality & Regulatory
- Supply Chain & Outsourcing

As always, PDA appreciates any feedback on the website. Send comments to info@pda.org.

Finding the industry news, tools and resources and related PDA events you need will be easier than ever. Visit www.pda.org to get started!

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PDA Volunteer Spotlight

Christine Bui

- Associate Director, QA
- *Audentes Therapeutics*
- Member Since | **2014**
- Current City | **Redwood City, California**
- Originally From | **Santa Clara, California**

Stay ahead of the curve through continuous learning

How did you learn about PDA?
I first learned about PDA through a PDA Education course I attended. At the time, I was just beginning my career and sought to learn more about the biopharma industry because you only get basic information in college. PDA helped to tie it all together.

What PDA volunteer activities have you been involved with?
In 2015, I started volunteering for PDA through my local PDA chapter, the West Coast Chapter. Later, I joined the *PDA Letter* Editorial Committee.

What advice do you have for new volunteers?
Get engaged by simply responding to PDA's emails and calls for volunteers. There is always something to lend a hand in, and we would love your help!

How has PDA contributed to your professional career?
I have learned to stay connected to my network over time as I may need advice from others facing the same challenges as me. I have also made a few connections through PDA; my most rewarding have come by attending dinner meetings held by the West Coast Chapter and by participating on the *PDA Letter* Editorial Committee. The more involved you get, the more you get back in return.

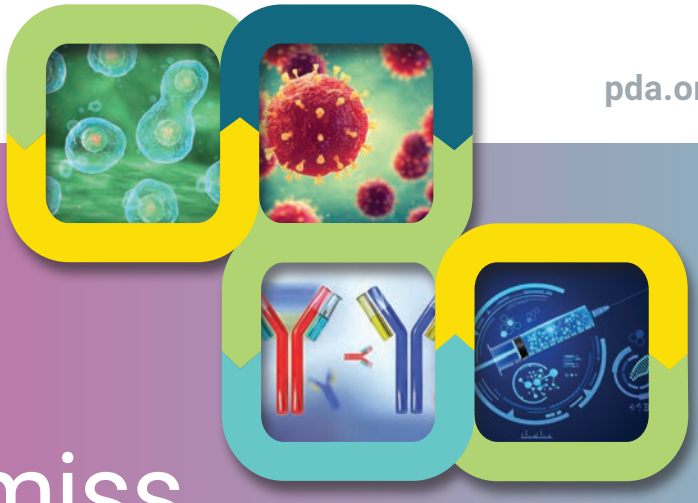
What significant changes do you see driving the future of the industry?
I have seen growing reliance on digitization and computerized processes at every company I have worked at. We are only now beginning to scratch the surface on how computer engineering/software/machine learning/AI algorithms can guide current processes within biotech.

Another significant change is the growth of cell and gene therapies. On the learning curve, most cell and gene therapy companies fall within the "conscious incompetence" phase of learning. And that makes things interesting!

What is your current binge-watch?

Right now, I am hooked on *The Wire*. It is an old show, but it is so good—every episode is *packed* with a story and the characters have great depth. There are also no filler episodes!

pda.org/2019BiopharmWeek



Register by March 22 and save!

Don't miss out on the first ever PDA Biopharmaceuticals Week!

PDA® Parenteral Drug Association

New for 2019, this week-long format features three hot topic events highlighting the latest key breakthroughs, industry research, and areas of inquiry in the biopharmaceutical manufacturing industry.

2019 PDA Cell and Gene Therapy Conference | **May 6-7** | *pda.org/2019CGT*
Explore the latest advances and key issues in this rapidly evolving area, including facility design, tech transfer and comparability, quality risk management, raw materials, and product characterization testing.

2019 PDA Virus Safety Forum | **May 8** | *pda.org/2019Virus*
Learn all you need to know about viral testing, mitigation, and clearance during this one-day forum, which includes a special session with the Advanced Virus Detection Interest Group.

2019 PDA Biosimilars and Vaccines Conference: Lifecycle Similarities and Challenges | **May 9-10** | *pda.org/2019BVConf*
Enjoy two full days of sessions covering the manufacture, supply, and quality development of biosimilars and vaccines and explore the parallels between the two.

Plan to attend one, two, or all three of these events – Register today

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Learn more and register at pda.org/2019BiopharmWeek

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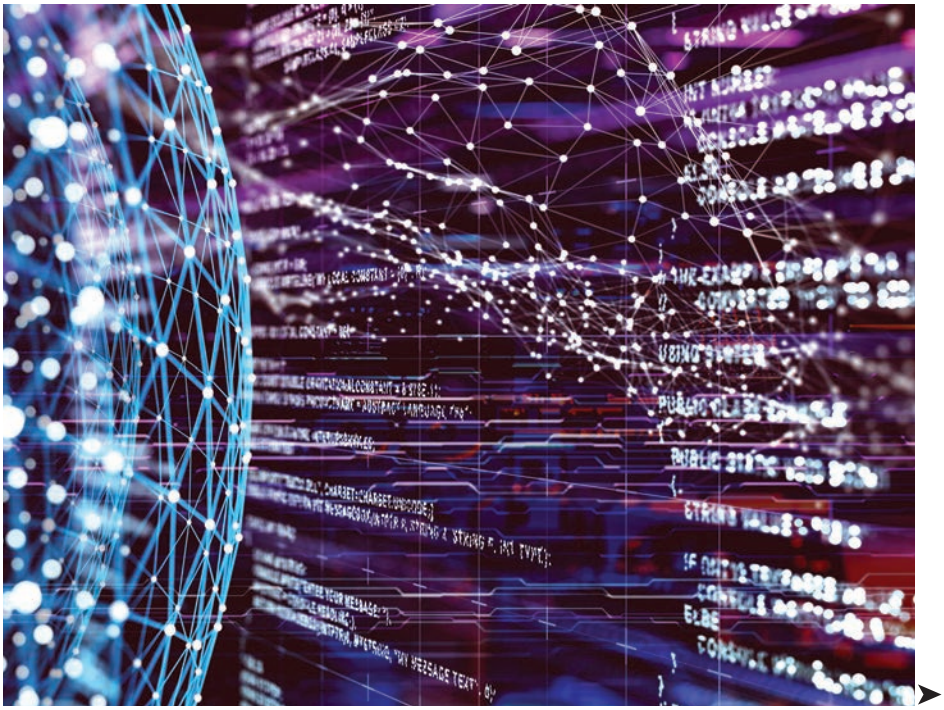
Chapter Meeting Validates Data Integrity as Key Issue

Bruce Loxley, GSK Vaccines, PDA Singapore Chapter Member-at-Large

Aug. 28 marked the most successful and well-attended event in the PDA Singapore Chapter's five-year history. The topic? Data integrity and computer systems validation.

Almost 60 pharmaceutical industry representatives attended the event which served as a follow-up to a data integrity roundtable hosted by the chapter in 2017.

After lunch, Chapter President **Dinesh Khokal** kicked off the event by highlighting how regulators' focus on data integrity has ramped up exponentially in the last ten years even though the topic is often regarded as "nothing new." Following his remarks, **Isara Isarowong** presented how assuring good computer systems validation ultimately ensures data integrity requirements are met. He made the point that the quality of computer systems



validation protocol writing and execution is often variable, and that some data integrity risks could be easily missed during initial qualification.

Mehul Patel then focused on the human element in microbiological QC testing, and how to reduce this risk by shifting as far as possible to more quantitative methods rather than relying on well-established but antiquated qualitative methods. Related to this, **Harry Benson** covered workplace quality culture and how a firm's leadership can encourage correct behaviors in a safe environment.

Data integrity is a very serious topic, so after the coffee break, **Bruce Loxley** livened things up by quizzing participants' knowledge of data integrity risks. Even some of the speakers had trouble! This shows that these types of meetings are essential to ensuring data integrity across the industry.

Thomas Halfmann then gave a very informative talk on what auditors are looking for in the context of data integrity and how to conduct data integrity maturity risk assessments.

For a positive note, **Kok Chia Phei** gave examples of some real-life data integrity issues, how they were discovered, how root cause was established, and how they were resolved. For the many participants working in data integrity remediation, this proved to be the highlight of the event. To close this successful event, **Sudhir Goudar,** helmed an interactive panel discussion.

The Singapore Chapter thanks all the speakers and those involved in making this a successful event.

PDA Who's Who

Harry Benson, Global Director, Human Performance Services, Commissioning Agents

Sudhir Goudar, Head, Compliance, Asia, Novartis

Thomas Halfmann, Founder and Managing Partner, HGP

Isara Isarowong, Novartis

Dinesh Khokal, PhD, Director, External Affairs, JAPAC and LatAm, Amgen

Bruce Loxley, Senior Manager, Audit I&TPO, GSK Vaccines

Mehul Patel, Global Marketing Director, Charles River Laboratories

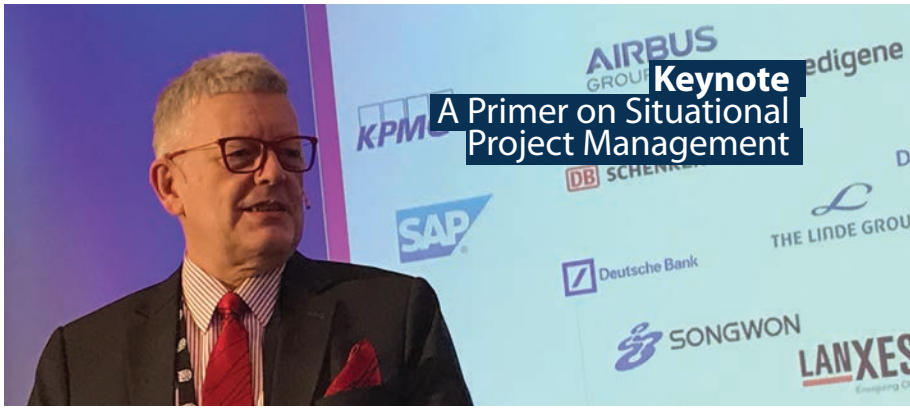
Kok Chia Phei, Senior Computer Systems Validation Consultant, Visentic Solutions

PDA Photostream www.flickr.com/parenteral-drug

Project Management in the Pharmaceutical Industry
November 22 | Berlin

Opening Remarks

Kerstin Wilken, PhD, PDA Europe



Keynote
A Primer on Situational Project Management

Oliver Lehmann, PMI Southern Germany Chapter

Session 1
When Worlds Collide – Project Management Across Industries

(l-r) Whitney Kutney, ValSource; Michael Walliser, Conscious Performance and Richard Harrop, Topa

(l-r) Whitney Kutney, ValSource; Laura McCloskey, Oxford Biomedica; Michelle Hutton, Oxford Biomedica; Resu Alloza, ReAl CMC Consultancy; Onne Siegersma, Progress PM&E BV; Anja Scheffel, Roche; Stefan Schuh, Bosch; Kerstin Wilken, PhD, PDA Europe; John Moehnke, Valsource; Michael Walliser, Conscious Performance; Falk Klar, PhD, PDA Europe; Peter Reichert, Zelect Quality – ZQI; Garrett van Vactor, Novartis; Thomas Bo Sølver, Eltronic; Dieter Nachtigall, Nachtigall International and Leander Grode, Vakzine Projekt Management

The planning committee plans an exciting agenda

PDA Visitors
2019 PDA/FDA Joint Regulatory Conference Planning Committee
December 3 | PDA U.S. Office Bethesda, Md.

Members of the 2019 PDA/FDA Joint Regulatory Conference Program Planning Committee post for a group photo

PDA Visitors
Chapter President Travels to PDA
January 15–16 | PDA U.S. Office Bethesda, Md.

Leonidas Orjuela (left), president of the PDA Brazil Chapter, visits the PDA U.S. headquarters to meet with Shanna Morgan (center), PDA's Manager of Membership and Chapters, and Trevor Swan (right), PDA's Director of Membership and Chapters

SNAPShot

Interest Group *Corner*

Lifecyle Management a Key Topic for Vaccines Interest Group at 2018 PDA/FDA JRC

Jane Halpern, Consultant, and North America Regulatory Lead, Vaccines Interest Group

The Vaccines Interest Group met for a face-to-face meeting Sept. 25 at the *2018 PDA/FDA Joint Regulatory Conference* to set an agenda for 2019 and discuss topics of interest to those in the vaccines community. Interest group leader **Sabrina Restrepo,** Director, Sterile and Validation Center of Excellence, Merck, opened the session with an overview of proposed activities for 2019. Following her talk, three speakers gave short presentations on topics pertinent to vaccine manufacturing.

Antu Dey, PhD, Senior Scientist, International AIDS Vaccine Initiative (IAVI) discussed the use of different platforms for vaccine production, focusing on examples for viral vector-based vaccines and recombinant protein vaccines. In their vaccine work, IAVI selects a specific cell substrate for suitability based upon the properties of the target vaccine antigen. Each cell substrate has technical and regulatory issues that must be addressed during product development and licensure. Next, **Lindsay Morse,** Associate Director, Engineering, Merck, discussed setting specifications and parameters for vaccines, focusing on approaches for changing process parameters and attributes over the lifecycle of the product. Morse noted that the long lifecycle of vaccines necessitates periodic changes to parameters and attributes, and that the development of standardized principles for legacy vaccines could be useful for the industry.

Restrepo then provided a short talk on vaccine lifecycle management with an emphasis on ensuring continuous supply. Changes to an approved product are driven by multiple reasons, including continuous improvement, capacity expansion, innovation and routine requirements. For a product used globally, these changes need to be reviewed by multiple regulators working under different regulatory systems. This can lead to an increase in the time from submission to approval.

The leaders of the Vaccines Interest Group encourage those interested in vaccine manufacturing to consider attending PDA's inaugural *Biopharmaceuticals Week* in May. The interest group will also convene at the *2019 PDA Annual Meeting.*

Response to "Standing Guard"

Kevin L. Williams, bioMérieux

The article "Standing Guard" was published on the *PDA Letter* website Sept. 26 (www.pda.org/pda-letter-portal/archives/full-article/standing-guard). This response addresses what we consider misleading conclusions within the article. As manufacturers of recombinant Factor C (rFC) endotoxin detection assays—known as the bioMérieux ENDONEXT™ family of products, we are committed to providing an accurate portrayal of the emerging *limulus* amebocyte lysate (LAL) replacement reagent rFC.

1. Recombinant Factor C is the cloned equivalent zymogen produced from the same natural gene sequence that produces Factor C in the horseshoe crab ***(1).*** Just as recombinant human insulin was cloned from the human insulin gene and produced as a medically equivalent therapeutic molecule, rFC is identical to the horseshoe crab zymogen in sequence and function ***(2).*** In fact, various Factor C molecules have been cloned and shown to be functionally equivalent ***(3,4);*** LAL and *tachypleus* amebocyte lysate (TAL) have been used interchangeably for some time now. Furthermore, Factor C is the only component present in the horseshoe crab cascade demonstrated to detect endotoxin. Factor G is another biosensor present in the natural LAL cascade which however reacts to beta glucans instead. Hence, in bacterial endotoxin testing, LAL is subject to false-positive results arising from beta glucans, whereas rFC is not.

2. The sensitivity of commercially available LAL and rFC tests is comparable. The kinetic LAL tests of two U.S. manufacturers share a sensitivity of 0.005 EU/mL with bioMérieux's ENDOZYME® II standard protocol. Extending ENDOZYME® II's reaction time beyond 60 minutes can enhance the sensitivity to 0.001 EU/mL which is more sensitive than most commercial LAL reagents.

3. "Standing Guard" further confused the ENDOLISA® (bioMérieux) assay with standard rFC assays such as ENDOZYME® II and PyroGene™ (Lonza), which follow bacterial endotoxin testing methodology equivalent to microplate-based kinetic LAL. Accordingly, they falsely claimed that rFC cannot detect several lipopolysaccharide types associated with some bacteria including *Enterobacter cloacae, Ralstonia pickettii* and *Serratia marcescens.* ENDOLISA® includes sample preparation by having an immobilized bacteriophage protein capture endotoxin prior to detection with rFC. Hence, results from using ENDOLISA® are not representative of rFC assays, per se. Data in **Table 1** refutes claims of insensitivity of rFC to specific endotoxin types ***(5).***

4. Alternative method validation for rFC tests can be performed in two days per USP <1225> Validation of Compendial Procedures. The remaining product-specific bacterial endotoxin testing interference testing is perfectly analogous to LAL verification (USP <85> Bacterial Endotoxin Test) and can be completed in a half day for each product to be validated. The U.S. FDA has indicated a willingness to accept rFC assays in lieu of LAL as evidenced by their comments in the 2012 Q&A guideline and recent approval of Eli Lilly's biologic drug, Galcanezumab-gnlm, that includes release bacterial endotoxin testing via rFC ***(6).***

5. Results from rFC and LAL have not been demonstrated to differ significantly. Testing two different LAL reagents on the same endotoxin samples revealed slightly poorer correlation than comparing either LAL to rFC or rFC to another rFC **(Figure 1).** Despite the correlation between the two LAL reagents deviating from 1 (perfect correlation), both of them are acceptable for bacterial endotoxin testing.

6. "Standing Guard" also confused the meaning of "correlation" by stating: "The authors report that all methods demonstrated a 94.4% correlation. But what about the 5.6% that did not agree?" Since the respective data was indiscrete and quantitative, the term "correlation" simply refers to the closeness of the two data sets to a linear relationship. All methods in the referred study detected all samples, i.e., 100% inclusivity of rFC and LAL. Hence, the subsequent conclusion that rFC would not detect all strains was false.

Table 1 Naturally Occurring Endotoxin (NOE) ***(5)***

Naturally Occurring Endotoxin						
	LAL			Synthetic LAL*	rFC	
Species	Endospecy	ES-II	Kinetic-QCL	Pyrosmart	PyroGene	EndoZyme
1. *Escherichia coli*	543	621	554	404	818	743
2. *Enterobacter cloacae*	897	1329	1176	298	1287	1098
3. *Pseudo aeruginosa*	2400	4141	2768	2840	3376	2456
4. *Ralstonia pickettii*	214	360	254	92	454	244
5. *Serratia marcescens*	400	504	447	108	459	312

* It should be noted that "Pyrosmart" shown above is a cocktail of three cloned horseshoe crab proteins rather than a "Factor C" recombinant product. PyroGene® (Lonza) and EndoZyme® (bioMérieux) are both typical recombinant single protein products. The three products on the left are LAL products.

The ability of rFC to detect endotoxin from various bacterial strains and preparations has been comprehensively demonstrated. In one study, all defined lipopolysaccharides, crude endotoxin extracts, here termed "naturally occurring endotoxins" (NOE) and environmental water samples (containing environmental endotoxins, i.e., real NOE were detected by three LAL and three rFC ***(5).*** Likewise, a comparison of rFC and LAL on several hundred clinical and environmental endotoxin samples did not reveal false-negative results. The

study has been supplied to pharmacopeial working groups and will be published in 2019.

7. "Standing Guard" also did not address the recent decline of the horseshoe crab in the United States and Asia. *Tachypleus* has been placed on the endangered species list in several Asian countries and is listed as "critically endangered" in Japan. In the Asian countries, there are no specific regulations or management plans for harvesting wild horseshoe crabs for either biomedical or for human consumption. The horseshoe crab was moved from "Endangered" to "Critically Endangered" in the Regional Red List of Japan, but despite being special status as a natural monument, no particular protection is provided for this species in Japan ***(7).***

   Of necessity, without the use of rFC, any supply shortage would need to be made up by U.S. producers who may already be straining under domestic supply increases…and if they are not, the horseshoe crabs may be. *Limulus polyphemus* is listed as "vulnerable" on the Red List with "decreasing" population trend ***(8).*** According to the Wetlands Institute, "…Delaware Bay's horseshoe crab population has declined by 90% over the last 15 years mostly due to overharvesting and habitat degeneration" ***(9).*** Simple mortality does not appear to encompass the entire impact associated with harvesting as recently reported:

   "While mortality rates after bleeding (18%) were similar to previous studies, we found significant decreases in the linear and angular velocity of freely moving animals, as well as changes in their activity levels and expression of circatidal behavioral rhythms. Further, we found reductions in hemocyanin levels, which may alter immune function and cuticle integrity. These previously unrecognized behavioral and physiological deficits suggest that the harvest of Limulus Amebocyte Lysate may decrease female fitness, and thus may contribute to the current population decline" ***(10).***

   Another report analyzes the practice of over-harvesting without penalty and as per regional confidentiality agreements while some, have argued for greater transparency:

   … in 2014, over 500,000 crabs were used for LAL production—a 285% increase from 1989 (Eyler et al. 2015). Although coast-wide biomedical harvest is reported to ASMFC [*Atlantic States Marine Fisheries Commission]* (Eyler et al. 2015), region specific biomedical harvest is not publically available due to confidentiality agreements (Novitsky 2015). This practice prevents accounting for mortality due to biomedical activity in regional assessments and harvest management (Millard et al. 2015). Biomedical harvest has exceeded the de minimis threshold to avoid regulatory attention since 2007 (Eyler et al. 2015), but ASMFC has not yet acted on that exceedance. Novitsky (2015) calls for "open" reporting of biomedical harvest and updating of enforceable LAL-industry best management practices (BMP) to support conservation of regional and embayment specific populations ***(11).***

8. Lastly, the validity of using recombinant proteins in lieu of natural ones is an established medical paradigm that is rarely debated today. The biologics revolution started in 1982 with the production of recombinant human insulin. Recombinant production quickly replaced the previous practice, that of harvesting from pig and cow pancreases. Since then, virtually every therapeutic protein has been replaced with a recombinant version that is safer and can be produced in unlimited amounts. This technology has led to the current biopharma revolution that is providing many life-saving therapies. Now, many classes of recombinant proteins exist on the market:
   - Recombinant insulins
   - Recombinant growth hormones
   - Recombinant blood clotting factors
   - Recombinant enzyme replacement drugs
   - Recombinant peptide hormones
   - Recombinant fusion proteins
   - Recombinant cytokines including interferon
   - More than seventy monoclonal antibodies (recombinant human IgG) FDA/EMA approved to treat disorders

Our research shoes that recombinant proteins are a valid alternative

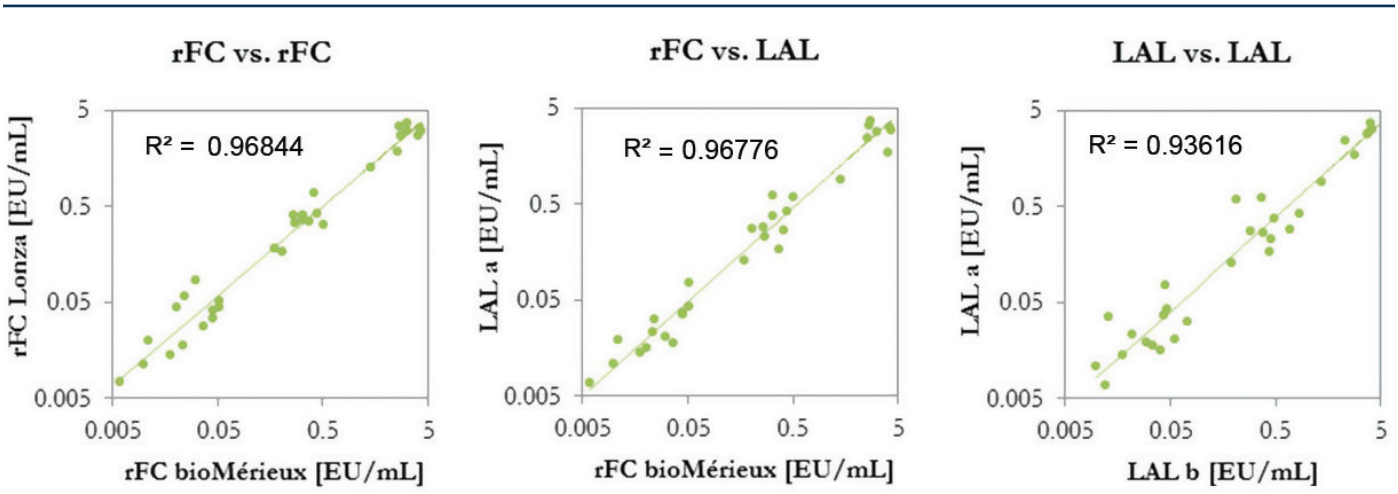


Figure 1 Comparison of Two Different LAL Reagents

Continued at bottom of page 19

Take C&GT Supply Challenges by the Horn

Michael Blackton, Adaptimmune

As T cell therapies have advanced into the marketplace, a new set of supply chain challenges has emerged, exacerbated by the fact that cell therapies can progress through clinical trials at lightning speed.

For these products, the scope of supply expands beyond the manufacturing center directly to the patient. This requires us to move away from traditional approaches toward a more holistic patient-centric path with reliable supply. Further, production capacity requirements must take into consideration patient scheduling, significantly impacting a firm's ability to schedule manufacturing. The bottom line? Traditional biotechnology focuses on material inventory while cell therapy products must account for the entirety of a patient's journey in order to develop a robust supply strategy.

In T cell therapy, the patient journey is critically important not simply because that patient is the one being dosed, but also because the patient supplies the raw material (their own T cells) for their therapy. The first step entails collecting the patient's T cells using apheresis. These cells are then shipped to the manufacturing site where they are transformed, packaged, tested and released back to the patient at the clinical site. The clinical site may further manipulate the cells (e.g., through thawing) prior to administration. From a supply perspective, the manufacturer must address patient cell collection and product administration across a host of different clinical sites.

Upon commercialization, strategies must be robust enough to address wider market needs. This may include standardization of equipment, development of robust procedures for collection and administration sites and enhanced monitoring of these centers so that product requirements can be met. Implementing processes supporting the entire patient journey requires organizations to think and act differently.

One patient, one batch means just in time inventory all the time. For autologous T cell products, each batch is made specifically for each patient, and patient's cells are often not collected until the patient is ready for treatment. Because of this, there is no opportunity to build an inventory of starting material to mitigate supply risk. In terms of scheduling, conflicts can ripple across the supply chain. For this reason, when planning for supply, companies need to rethink usage strategies. In the traditional world of biotech manufacturing, usage targets (uptime) north of 85% are common. Not so in cell therapy. In the brave new world of cell therapy, capacity use above 50% results in exponentially increasing schedule risks. In other words, in order to manufacture 100 patients, a company may require more than 200 manufacturing slots!

These concepts will be discussed in much more detail at the *2019 PDA Cell and Gene Therapy Conference*. The conference will provide insight on process development, supply chain, validation, new advances in gene therapy, the patient experience and more!

This conference will continue the gathering of knowledge from the previous *PDA Cell and Gene Therapy Conferences,* providing an opportunity to delve deeper into the exciting world of cell and gene therapy manufacturing.

2019 PDA Cell and Gene Therapy Conference

Long Beach, Calif.

May 6–7

www.pda.org/2019BiopharmWeek

Response to "Standing Guard" continued from page 18

to proteins harvested from animals in terms of purity, consistency and sustainability.

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About the Author

Kevin Williams worked for Eli Lilly for 30 years, developing QC tests for endotoxin detection, among other roles. He currently works for bioMérieux.

2019 PDA Annual Meeting

A Supplement to the PDA *Letter*

Are You Up to Speed with Pharma's Evolving Landscape?

Magaly E. Aham, Takeda Pharmaceuticals

The complexity of emerging technologies in our industry creates a range of challenges. New therapies require specialized manufacturing technologies. Varying levels of risk present potential issues spanning the globe, such as the fact that regulatory approvals vary country by country in addition to distribution challenges in the ever-intricate supply chain.

2019 PDA Annual Meeting

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

Companies need to constantly evaluate how to do things better. Planning ahead is critical to enabling a continuous and secure supply chain that adapts to changes in regulations, technologies and market demand.

PDA is a leader in the industry, always seeking to provide members with ways to address both current and emerging challenges. Every year, the *PDA Annual Meeting* provides a venue for attendees to gain insight into the latest "hot topics" impacting the industry.

The *2019 PDA Annual Meeting's* theme is "Solving Manufacturing and Supply Challenges for Current and Future Medicinal Products." The meeting features a packed agenda that provides the latest updates on disruptive technologies, innovative manufacturing technologies, rapid drug development and supply chain challenges.

The agenda also incorporates interest group presentations aligned with the theme, covering cell and gene therapies, technology transfer, biopharmaceutical manufacturing, filtration and microbiology. Finally, the conference concludes with case studies on disaster recovery strategies, including responses to recent natural disasters.

Anyone interested in gaining the latest information on upcoming manufacturing technologies should attend this meeting.

Expand Your Network…and Have Fun!

Monday, March 11

PDA Charity Walk/Run for Global Genes®

Put on your walking or running shoes the morning before the *2019 PDA Annual Meeting* commences to support Global Genes®, a nonprofit advocating for patients with rare diseases. Meet behind the Marriott Marquis for a scenic 5K run/3K walk along San Diego's Embarcadero seaside walkway. Meet at 6 a.m., $45 per participant.

PDA Orientation Lunch

Are you a new PDA member? Or are you a young professional? Is this your first time attending the Annual Meeting? If you answered "yes" to any of these questions, join your peers for a networking lunch. 11:30 a.m.–12:30 p.m. (*invitation only*)

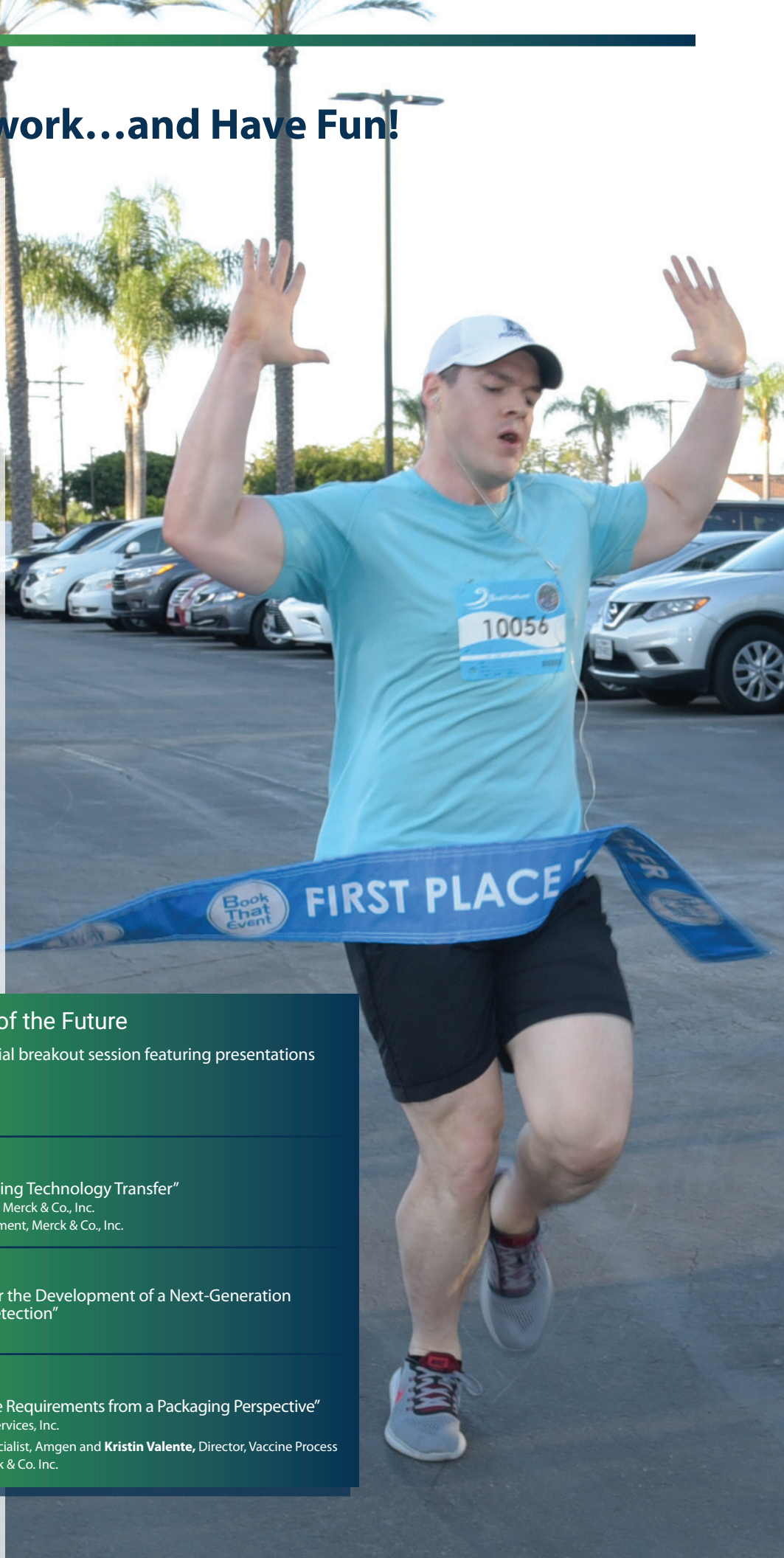
Exhibit Hall Grand Opening Reception

Join fellow attendees for the opening of the Exhibit Hall. Refreshments will be provided. 5–6:30 p.m.

Tuesday, March 12

Nautical Nights Reception

Anchors aweigh! Celebrate a successful two days with food, drinks and entertainment at the Marina Terrace. 6:30–9:30 p.m. Included with main conference registration. Guest tickets can be purchased for $70.



Workforce of the Future

This year, the Annual Meeting includes a special breakout session featuring presentations from young professionals.

Wednesday, March 13

10:45 a.m. – 11:15 a.m.

"Capture and Reuse of Critical Knowledge during Technology Transfer"
Paige E. Kane, PhD, Director, Knowledge Management, Merck & Co., Inc.
Martin J. Lipa, Executive Director, Knowledge Management, Merck & Co., Inc.

11:15 a.m. – 11:30 a.m.

"Considerations and Proof of Concept Data for the Development of a Next-Generation Sequencing Method for Adventitious Virus Detection"
Maria M. Bednar, Scientist I, AT Virology, Biogen

11:30 a.m. – 11:45 a.m.

"Antisense Oligonucleotide Therapies: Molecule Requirements from a Packaging Perspective"
Amy A. Kim, Analyst-Specialist, West Pharmaceutical Services, Inc.

Session Moderators: **Jason Kerr,** Quality Assurance Specialist, Amgen and **Kristin Valente,** Director, Vaccine Process Development & Commercialization, Downstream, Merck & Co. Inc.

Explore Specialized Topics!

PDA Interest Group Sessions

Are you looking for more information around a specific topic? PDA Interest Groups will convene during the *2019 PDA Annual Meeting*.

Note: These meetings are included with conference registration and open to non-PDA members.

Tuesday, March 12

10:45 a.m. – 12:15 p.m.

Cell and Gene Therapy Interest Group and Quality Risk Management Interest Group (*combined interest group meeting*)

Technology Transfer Interest Group

1:45 p.m. – 3:15 p.m.

Facilities and Engineering Interest Group

Vaccines Interest Group

4 p.m. – 5:30 p.m.

Biopharmaceutical Manufacturing Interest Group

Filtration Interest Group

Wednesday, March 13

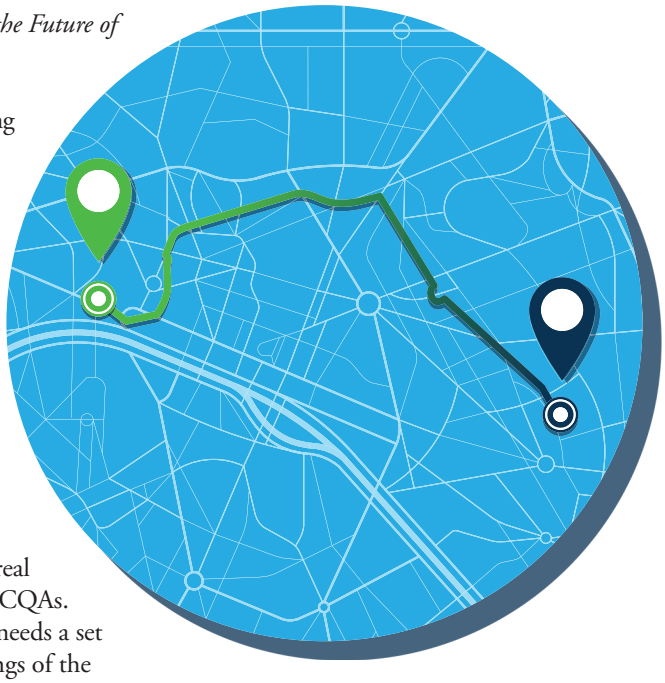
10:45 a.m. – 12:15 p.m.

Environmental Monitoring/Microbiology Interest Group

Featured Presentation: A Roadmap to a Continuous Control Strategy

Per Vase, PhD, NNE

See Per speak on this topic during "Plenary 4: Bridging Current Technology with the Future of Medicine," March 13, 9 a.m.



Throughout the manufacturing process, there can be risks. In particular, there is a risk of potentially overlooking errors due to uncertainty in estimations if verification is based on sampling. What if there was a way to account for this risk?

Many pharmaceutical manufacturers are working toward continued process verification per global regulators' expectations. "Continued" means an ongoing effort after validation, but it can be based on sampling. "Verification" is a passive act; a process is estimated to meet specifications without any adjustment of process parameters. In many cases, however, the current state is continued product verification where product critical quality attributes (CQAs) are tested after processing, similar to traditional batch release testing. The ideal state is to have **continuous** (always) **process** verification and **control**, meaning process parameters are adjusted to ensure processes remain on target. **Figure 1** depicts the ideal state. Here, each unit operation is continuously monitored, and actions are taken if quality standards are not expected to be met.

This requires three improvements to continued product verification: 1) ***process*** verification for early feedback with easier identification of causes, 2) ***continuous*** verification to corroborate the process, and 3) process ***control*** by using measured process signals as a criterion for changing process settings.

When moving to a continuous process control approach, three questions must be answered.

1. What to monitor?
2. When to act?
3. How to act?

1. What to Monitor?

Real-time monitoring requires a series of process indicators (PIs) that can be measured in real time and correspond with the CQAs. Typically, determining CQAs needs a set of PIs. Often, the critical settings of the process, i.e., critical process parameters (CPPs), are also included in predictive models for transfer function F:

$$\text{Predicted CQA} = F(CPP_1, \ldots CPP_n, PI_1 \ldots PI_m)$$

Next, the relationship between PIs, CPPs and CQAs must be established. The recommended procedure involves performing a design of experiment (DoE) that systematically varies CPPs. CQAs and PIs are then measured as responses. By conducting a DoE with uncorrelated CPPs, a relationship between CPPs and CQAs and/or PIs is due to a casual effect. In addition, this prevents inflated standard errors of model effects. The other advantage of a DoE is obtaining a large variation of CPPs, PIs and CQAs as two variables need to vary considerably to full explore their relationship.

If a DoE is not possible, relationships can be built on historical data. Yet this can result in mixed up correlations and causations, significantly incorrect estimates of model effects and overlooked correlations due to insufficient variation.

When the prediction model has been cross-validated, it can help establish the process design space. It can also be used as a performance-based approach for control as described in ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.* The predicted CQAs can be used as in-line release testing, replacing product testing.

2. When to Act?

CQA specifications can be broken down into PI specifications based on the transfer function between CQAs and PIs. Since the transfer function includes several PIs, this can be done multiple ways. If one PI has a larger tolerance, the others must ➤

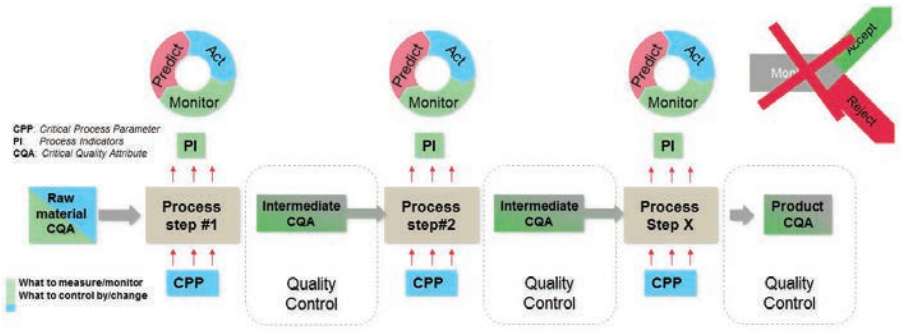


Figure 1 The Ideal State for a Continuous Control Strategy

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have narrower tolerances. It might be simpler to analyze trends in predicted CQAs and use specification limits narrowed by prediction uncertainty, e.g., two times root mean squared error (RMSE).

Specification limits on predicted CQAs should not be used as action limits. Acting when an out-of-specification (OOS) result occurs, e.g., faulty products, is too late. Instead, it is recommended to receive a warning when the predicted CQA is outside the normal operating window. This way, an alert is triggered before it is too late. The normal operating window is traditionally found by using a control chart. A control chart is a trend curve with warning limits centered around the mean, or the target, where the only risk of a false alert is a low number, typically, 0.00135. For normal distributed processes, the limits then become the classical +/- 3 standard error limits.

Yet there are several issues with traditional control charting. For one, it assumes that the true mean and standard deviation of the process is known. But there is only a limited dataset from which the estimation of mean and standard deviation is made.

It also assumes that predicted CQAs can be described by using a simple model with a single normal distribution. Most processes, however, are too complex to be described with a single normal distribution. Due to batch variation and drift within a batch, a variance component model is needed. In addition, there can also be systematic factors, such as production units if parallel processing is performed.

These issues can be solved by creating a statistical model of the process that includes random factors such as batch and timepoint within a batch, and, if needed, systematic factors. From this model, future measurements can be predicted. Predictions using statistical models is a standard functionality in statistical software packages. Predictions are based on the t-quantile instead of the normal quantile, taking into consideration the uncertainty inherent in estimates.

It is recommended then to use trend curves on predicted CQAs and act on observations outside prediction limits. Prediction limits must be inside specification limits, so alerts are obtained before an OOS appears. This is an obvious validation criteria for a process.

3. How to Act?

If observations are outside prediction limits, the process has changed compared to the validated state. In the case of a sufficient distance to specification limits, prediction limits could just be updated. Alternatively, CPP settings should be changed to bring the predicted CQAs back on track. The transfer function that relates predicted CQAs to CPPs should contain the information on how to act.

Case Study 1: Real-Time Release

A manufacturer of medical devices used injection molding to make components for the device. The concerns?

- 50–100 units per production site
- Extremely large volumes *and* low manpower
- 100% inspection of parts not considered realistic

Despite an intensive product QC sample inspection, there is a risk that random defects are not found.

The injection molding process was divided into phases and for each phase, PIs (green) and CPPs (blue) were found as shown in **Figure 2**. The DoE established relationships between CPPs, PIs and CQAs (dimensions and defects). Based on these relationships, product testing has been replaced by in-line release testing of PIs.

The major outcomes of implementing in-line release testing have been:

- Significantly reduced risk of approving random errors
- Validation time reduced from 20 weeks to three weeks
- Scrap rate reduced 70%
- Overall equipment effectiveness increased 7%

Case Study 2: Process Optimization

A manufacturer experienced yield issues after upscaling. The first 11 pilot runs after upscaling were analyzed for correlations between yield, PIs and CPPs. The challenge here was that CPPs (e.g., feed) and PIs (e.g., glucose consumption and lactate production) were functions of time as shown in **Figure 3**.

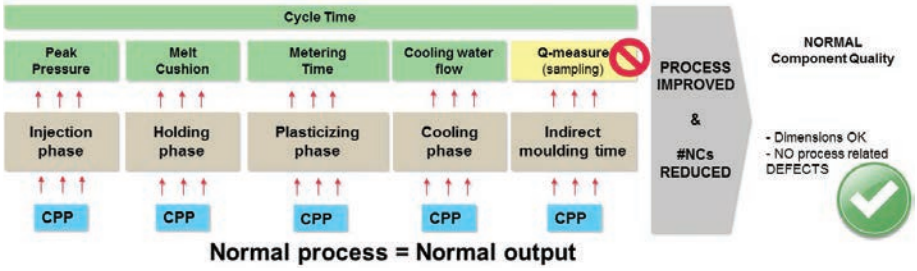


Figure 2 CPPs and PIs for Injection Molding Process

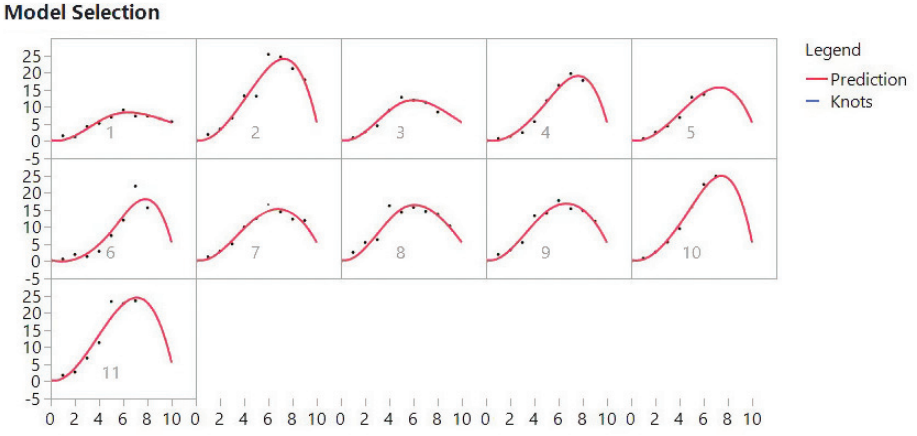


Figure 3 PI Development Over Time for 11 Pilot Runs

This issue was solved using the functional data explorer in JMP software from SAS. Functional principal components (FPC) of curve fits were used to describe the curves. Relationships between yield and PI FPCs were found using partial least squares modelling (due to heavily correlated PIs) and standard least squares modeling to establish relationships between PIs and CPPs. The combined relationships are shown in the **Figure 4,** namely, how the optimal PI curves were obtained by changing the CPPs.

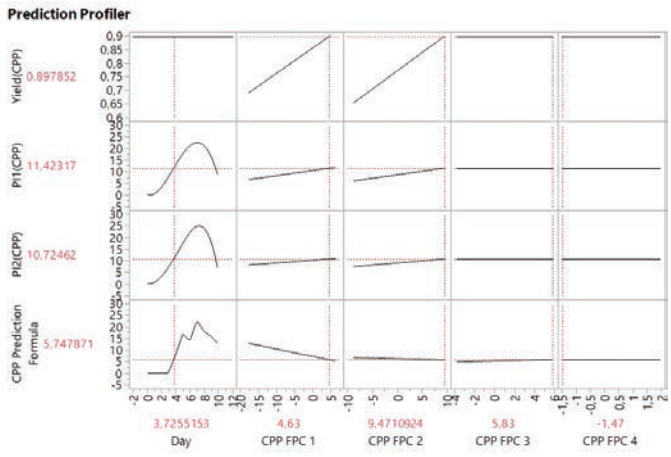


Figure 4 Relationships Between Yield, PIs and CPPs

By following this process, the manufacturer increased the average yield by 30% and reduced yield variation from batch to batch by 70%.

Conclusion

Continuous process control has many advantages compared to continued product verification. By conducting continuous verification there is a low risk of overlooking errors compared to traditional sampling. Knowing the relationships between CQAs and PIs forms the basis for real-time release testing. Process control is an active operation; process parameters are adjusted to keep process quality on target as opposed to process verification where it is only verified to be within specification.

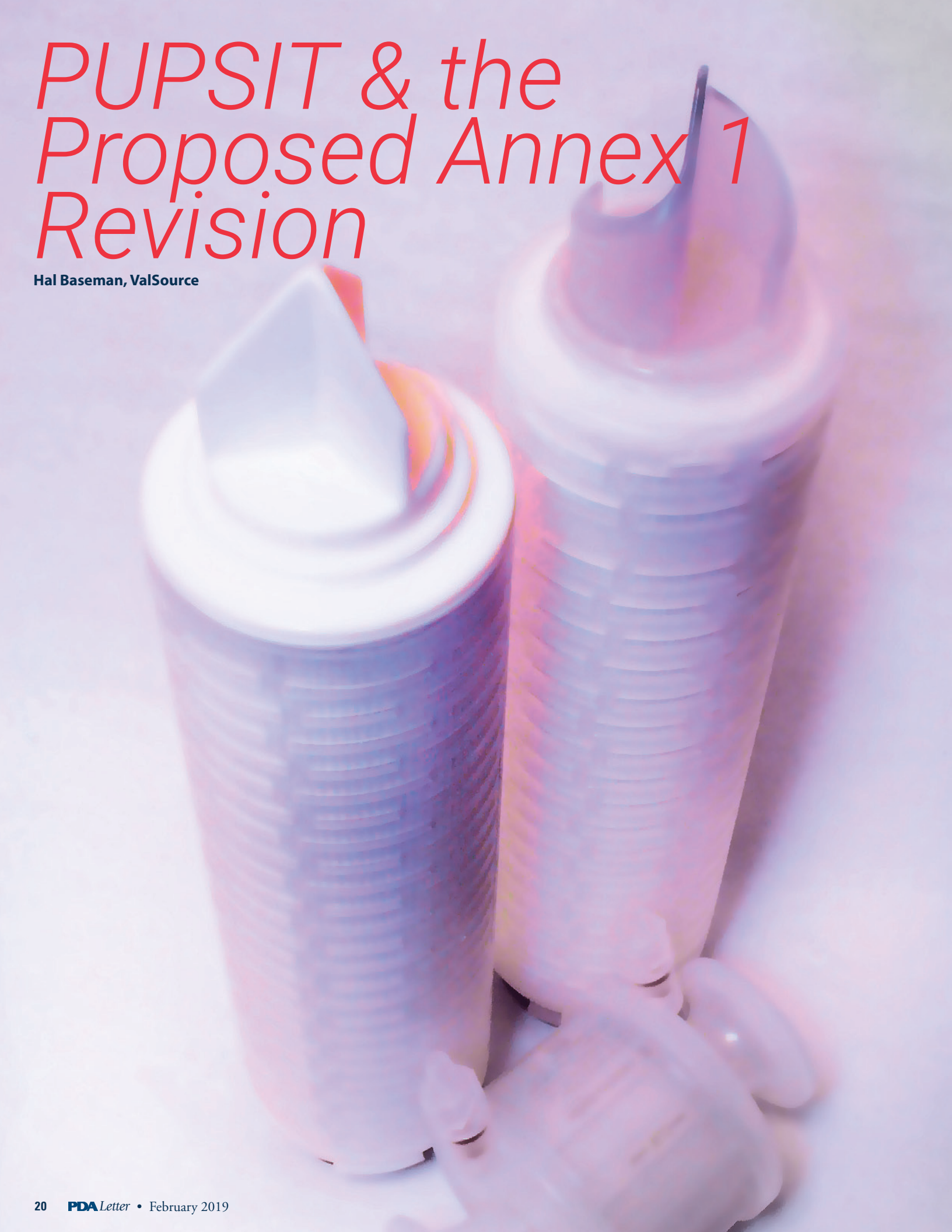
Robust manufacturing processes result from processes kept on target instead of merely just inside specifications. Continuous process control is also a prerequisite for continuous processing, which is becoming popular due to the smaller footprint, shorter processing times and increased flexibility.

About the Author

Per Vase, PhD, is a data analysis expert with more than 30 years of experience. He focuses on applying Six Sigma in GMP environments.

PUPSIT & the Proposed Annex 1 Revision

Hal Baseman, ValSource



PUPSIT has become the one most talked about issue regarding the draft Annex 1 revision

Since its publication in December 2017, the proposed Annex 1 revision has been much discussed. As coleader of the team that prepared PDA's comments on the revision, I am intimately familiar with the intricacies of the document. As such, I want to share some thoughts on the revision, culminating in four pieces of advice concerning one of the most debated points of contention within Annex 1.

The draft revision to the EMA Annex 1 (Manufacturing of Sterile Medicinal Products) strongly encourages the use of quality risk management (QRM) principles in the design and implementation of process control measures. The draft, however, continues to include prescriptive methods for process control that may dissuade companies from using alternative risk-based approaches.

Some European regulators have asserted that these prescriptive methods are guidance and should not be considered requirements. Yet there remains concern that these methods will be viewed by both industry and inspectors as requirements. Among these prescriptive methods, one in particular is drawing considerable scrutiny: the requirement that the sterilized filter and assembly be integrity tested prior to use, more commonly known by the acronym "PUPSIT" for "*pre-use, post-sterilization integrity testing.*"

Article at a Glance

- PUPSIT adds to complexity and may introduce risk to the process
- Language supporting PUPSIT appears in earlier versions of Annex 1
- True QRM precludes PUPSIT as a requirement

For industry, the use of PUPSIT presents a dilemma. There has been a significant increase in regulatory enforcement of PUPSIT by some regulatory bodies, thus posing a compliance risk to companies not using PUPSIT. But as companies use or contemplate the use of PUPSIT, they recognize that the complexity of the PUPSIT assembly and procedure may add significant risk to the aseptic process, exceeding the relatively low risk of undetected filter flaws. As a result, PUPSIT has become the one most talked about issue regarding the draft Annex 1 revision.

First, Some Regulatory Background

Although not specifically designated, the PUPSIT requirement has appeared in Annex 1 for decades. It is important to note that while the PUPSIT language has appeared in previous versions of Annex 1, enforcement as a requirement, has increased since the last publication in 2008, most notably within the last 2–3 years.

The current Annex 1 version states in Section 113 that … *"The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test."*

The draft 2018 revision language restates this requirement in Section 8.84, *"The integrity of the sterilized filter assembly should be verified by testing before use, in case of damage and loss of integrity caused by processing and should be verified by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test."*

The revised Annex then adds the following limited exclusion: … "*It is recognised that for small batch sizes, this may not be possible; in these cases, an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved.*"

At this point, PUPSIT is primarily a European concern but keep in mind that the current draft revision was prepared by an international PIC/S working group that included non-European representatives, such as the U.S. FDA. Currently there is no requirement, written guidance, or apparent expectation from FDA on the need for or use of PUPSIT. Risk assessments of PUPSIT assemblies may indicate an additional level of risk to aseptic process and product sterility posed by the inclusion of the PUPSIT procedure itself. To date, there does not appear to be much FDA official opinion one way or the other.

What is the PUPSIT Procedure?

PUPSIT is a test to mitigate situations where a sterilizing grade filter passes the supplier's initial integrity testing but may become defective during sterilization, and that defect is no longer detectable during end of use or post-use integrity testing. In this scenario, it is surmised that material in the solution being filtered can clog the hole or flaw in the filter, thus blinding or masking the defect during the end of use filter integrity test.

PUPSIT requires complex designs of the filtration system and filters downstream side. Since the filter must be wetted and the filtrate side set at atmospheric pressure conditions, additional vent filters, aseptic connections, valving and tubing is added to the typical filtration design. This means that test system leakage, sterilization process difficulties, condensation collection, improper value sequencing, back pressure, increase of user installation faults due to the higher complexity and other complications can pose additional risk to the performance of

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FEBRUARY

11-14 Fundamentals of Aseptic Processing – Option 1
Bethesda, MD | *pda.org/2019FebFundAP*

26-28 Understanding Sterilization Training Course
Albuzzano, Italy | *pda.org/EU/Sterile2019*

MARCH

4-7 Fundamentals of Aseptic Processing – Option 2
Bethesda, MD | *pda.org/2019MarFundAP*

18-22 2019 PDA Aseptic Processing – Option 2
Week 2: April 15-19
Bethesda, MD | *pda.org/2019Aseptic2*

18 Pre-Filled Syringes Interest Group Meeting
Venice, Italy | *pda.org/EU-IG-PFS19*

19-20 Parenteral Packaging
Venice, Italy | *pda.org/EU/parpack2019*

21 Container Closure Development
Venice, Italy | *pda.org/EU/CCD2019*

21 Packaging Science Interest Group Meeting
Venice, Italy | *pda.org/EU-IG-PS19*

21-22 Container Closure Integrity Testing
Venice, Italy | *pda.org/EU/CCI2019*

21-22 Extractables & Leachables
Venice, Italy | *pda.org/EU/EL19-spring*

21-22 Test Methods for Pre-filled Syringe Systems
Venice, Italy | *pda.org/EU/TestPFS19*

25-29 Freeze Drying in Practice
Osterode am Harz, Germany | *pda.org/EU/FDP2019*

26-27 Temperature Controlled Distribution
Voorhout, The Netherlands | *pda.org/EU/TCD2019*

26-28 Validation of Moist Heat Sterilization Processes – Option 1
Bethesda, MD | *pda.org/2019MarVMH*

27-28 Strategies for Formulations Development – How to Get the Right Data in the Right Amount at the Right Time
Bethesda, MD | *pda.org/2019SFD*

APRIL

8-12 QA/QC Training Course Series – Option 1
Bethesda, MD | *pda.org/2019QAQC1*

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

25-26 An Introduction to Visual Inspection – Option 1
Bethesda, MD | *pda.org/2018VisualIntro*

29-2 Fundamentals of Aseptic Processing – Option 3
Bethesda, MD | *pda.org/2019AprFundAP*

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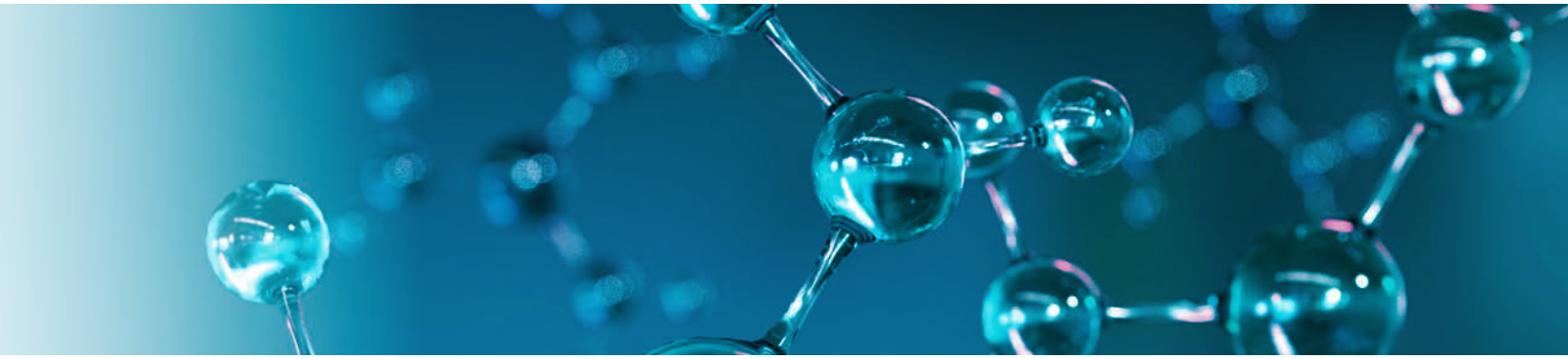

MAY

6-10 **2019 PDA Biopharmaceuticals Week**
Long Beach, CA | *pda.org/2019BiopharmWeek*

13-17 **2019 PDA Aseptic Processing – Option 3** ■
Week 2: June 10-14
Bethesda, MD | *pda.org/2019Aseptic2*

15 **Understanding Pharmacopoeia**
Geneva, Switzerland | *pda.org/EU/UnPharma*

16-17 **Pharmacopoeia Conference**
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Berlin, Germany | *pda.org/EU/AutoVI2019-spring*

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22-23 **Why Quality Culture? More Success by Reducing Human Errors**
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24 **Visual Inspection Interest Group Meeting**
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March 11-13 **2019 PDA Annual Meeting**
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March 13-14 **2019 PDA Practical Applications of Sterile Manufacturing Workshop**
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- Preparing for Regulatory Inspections for the FDA and EMA
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- Clean Room Investigations
- A Critical Thinking Approach to Improving Aseptic Process Manufacturing
- Change Management – A Practical Workshop
- Drug Device and Combination Product Risk Management and Safety Assurance Cases

Denotes laboratory courses taught in Europe.
■ This course is taught in PDA's U.S. Manufacturing Training Facility.

Failure to properly perform PUPSIT can place product quality at risk

the product filtration system, including microbiological contamination. These additional risks would very likely not be detected downstream by the sterility test.

Is the benefit of uncovering a yet-to-be established masking effect worth these risks? Some European regulators say "yes," many companies say "no." The draft revision allows the use of risk assessments to determine the answer to that question. Although not specifically mentioned in the PUPSIT sections of the draft revision, it has been suggested that those companies that do not think PUPSIT is appropriate, can perform a comprehensive risk assessment to support that position.

The draft revision of Annex 1 states in the Principles section that "*Risk assessments should be used to justify alternative approaches to those specified in this Annex only, if these alternative approaches meet or surpass the intent of this Annex."* Some European regulators have expressed concern that these PUPSIT related risk assessments appear biased with a predetermined outcome of avoiding PUPSIT. Therefore, the assessment is being found to be non-persuasive.

4 Pieces of Advice to Industry

1. Employ Unbiased QRM principles

In evaluating PUPSIT, consider the objective of the assessment less an indictment of the PUPSIT process and more of a QRM assessment for preventing filtration failures. PUPSIT is not a stand-alone objective, instead, the objective is a robust process to manufacture sterile product. The outcome of the QRM effort should be more than a rejection or defense of PUPSIT. It should recognize the steps to prevent and mitigate filtration-related risks in a holistic view of the overall contamination control strategy.

Employing QRM and risk-based thinking approaches to assessing the value and need for PUPSIT combines several efforts. Information from studies and data analysis would be useful in determining the conditions, product types and probability of masking. Risk assessments of the filter manufacturing, transport, sterilization and use processes help determine where potential process weaknesses that might result in filer defects, and that can be masked, might occur. Best practice guidance for filter integrity testing, including PUPSIT if warranted, helps determine effective process control strategies that minimize risk to product sterility.

2. Assess the Relative Risk of a Masking Effect

PUPSIT detractors claim there is no evidence of masking phenomenon occurring. PUPSIT supporters, including some European regulators, claim there is anecdotal evidence and a supposition of risk. Published data, however, is scarce at best, with little, if any, conclusive evidence of masking phenomenon cited in literature. The hypothesis that defects can form in integral filters during sterilization, and then be masked during filtration, to the extent that the flaws are not uncovered during end of use integrity tests, should be further investigated.

Analysis of existing filtration performance and historic study data can be useful in providing the missing data needed to show if, and under what conditions, filter defect masking can occur. This may be done at the end user level, showing that the post-use integrity test data are consistent without any unusual outliers, a sign that the membrane matrix and blocking rate has been as consistent. Furthermore, laboratory masking studies may also need to be performed to uncover under what, if any conditions, and with which products and product types masking may occur. It is believed that if this effect can occur, it would depend on a select *combination* of product, process conditions and filter defect characteristics.

3. Assess the Relative Risk of Filter Manufacturing and Use Related Defects and Failures

European regulators have expressed concern over the robustness of control measures designed to mitigate filter defects, the level of control by filter manufacturers, the robustness of the filter manufacturing process, user handling of filters and assemblies, and the effects of sterilization as possible failure modes for filter defects. The concerns were addressed in a joint statement by four major filter suppliers published in the April 2018 *PDA Letter* ***(1).*** To further address these concerns, QRM principles and assessments can be performed on the overall filter manufacturing, transfer, sterilization and use processes, conditions, and procedures. These QRM activities should include the assessment of potential risks to sterile filtration, the development of control strategies to prevent filter failure, and appropriate use of detection controls (e.g., PUPSIT). The focus of these assessments should be prevention of those conditions that might result in flaws and masking, rather than reliance on testing. Risk assessment guides for filter manufacturing, handling, shipping, sterilization, usage, and integrity testing can also be helpful as a guide for audit of the effectiveness of filter manufacturer control systems.

4. Determine Best Practices

If the data analysis and process assessments suggest that the filtration conditions, product composition and mitigation strategies should include PUPSIT, then it is important that PUPSIT be performed correctly. PUPSIT is a complex procedure, employing complicated valving, connections, interventions and sequencing procedures. Failure to properly perform PUPSIT can place product quality at risk. Therefore, best practice guidance, procedures, and training are needed for the selection, design, installation, qualification,and operation of PUPSIT.

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Some Final Thoughts...For Now

The question is not whether to perform PUPSIT, rather, are there conditions that pose a risk of filter flawing and masking, and if so, what steps can be taken to reduce or eliminate those risks? PUPSIT is not a process objective. The objective should be using QRM throughout the sterile filtration process to ensure reliable product sterilization and maintenance of sterility throughout the process.

More information is needed to determine the true risk of filter failure and the masking effect, as well as the relative risk of mitigating actions, including PUPSIT. Industry associations such as PDA are providing a valuable platform for conducting studies, analyzing data, drawing conclusions from results, providing QRM and risk assessment guidance, and helping develop best practices.

Regulators should avoid prescribing or requiring one control or test method. Instead, encourage companies to develop comprehensive well-designed control strategies. Sound, well-performed risk assessments of the overall filtration preparation and process should be designed to uncover the conditions that present risk of filter defects, and the integrity test failure to uncover those defects. PUPSIT may or may not be part of that depending on process specific conditions.

Once risks are understood, then control strategies and actions can be developed. Any actions or steps considered for inclusion in the aseptic process, including PUPSIT, should be first assessed for relative risk to product quality, and any resulting procedures should be carefully planned and performed with those assessed risks considered and adequately addressed.

Want to learn more about Annex 1 and PUPSIT?

At the *2019 PDA Annual Meeting,* PUPSIT will serve as the main topic of discussion in the Filtration Interest Group meeting (Tuesday, March 12, 4 p.m.)

Reference

1. "Sterilizing Grade Filters and PUPSIT." *PDA Letter* 54 (April 2018) 19 www.pda.org/pda-letter-portal/archives/full-article/sterilizing-grade-filters-and-pupsit (accessed Jan. 23, 2019).

About the Author

Hal Baseman is chief operating officer and a principal at ValSource LLC and ConcordiaValsource LLC. He has over 39 years of experience in pharmaceutical operations, validation, and regulatory compliance. He has held positions in executive management and technical operations at several drug manufacturing and consulting firms.

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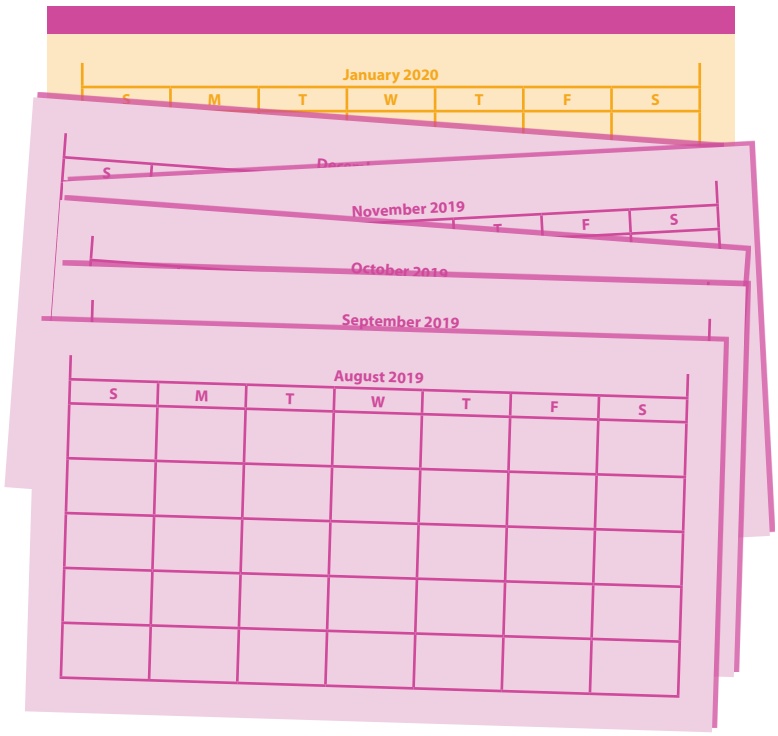
Annex 1

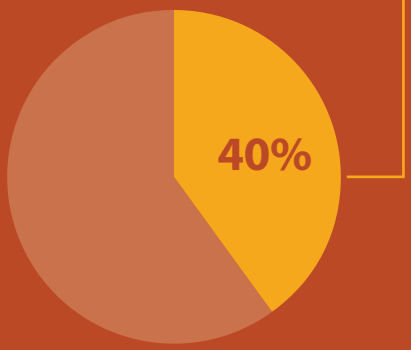
Ready or Not?

The *PDA Letter* conducted an informal survey last year to ascertain how prepared PDA members feel they are for the proposed Annex 1 revision.

30% of respondents expect it will take at least a **year** to implement the changes



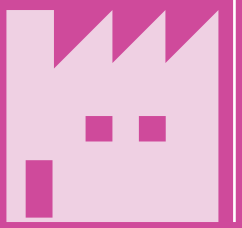
Less than half of respondents feel **prepared** for the proposed changes



And 36% anticipate a **20% increase** in resources to address the changes

The Top 2 Most Challenging Changes?

- Requalification of Facilities
- PUPSIT



The *PDA Letter* thanks its readers who completed the survey along with PDA's Scientific and Regulatory Affairs Coordinator **Valeria Shirvani** for developing the survey and collecting the data.

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Global Regulators Partner for Greater Patient Access

A Summary of the WHO Pre-ICDRA Meeting Workshop

Ursula Busse, PhD, Novartis

I had the pleasure of attending the pre-ICDRA meeting last September and was grateful much of the meeting was concerned with patient access to medicines. The event included short presentations, panel discussions and a workshop covering a lifecycle approach to medical product regulation, underscoring regulators' responsibility to maintain constant vigilance from development to end use.

The following is a brief summary of the proceedings.

Using Tech to Improve Global Safety

We currently live at the crossroads of two major trends in technology innovation: on the one hand, increasing numbers of highly innovative treatments now reach patients but with less safety data than established medicines. On the other hand, digitalization gives us capabilities to gather large amounts of data.

In highly developed countries such as the United States, regulators are investing in the use of electronic medical records, large safety databases and safety reporting via cellphones or the Internet. In low- and middle-income countries, regulators often lack the capacity to perform similar safety surveillance. In addition, some countries lack a culture of reporting.

The Bill and Melissa Gates Foundation, supported by WHO and the UK MHRA, recently launched a pilot program to test a set of guiding principles for smart safety surveillance, covering two drugs and one vaccine. Lessons learned to date show that reporting via mobile phones needs to be linked to a database that gives users access

Every two years since 1980, WHO holds the *International Conference of Drug Regulatory Authorities* (ICDRA). This meeting provides an opportunity for regulators to discuss challenges related to global health topics, share lessons learned and strengthen collaboration. Recommendations from ICDRA play an important role in setting WHO's policy agenda. Since 2002, a pre-ICDRA meeting gives industry representatives an opportunity to participate in discussions before the main ICDRA event.

Last year's pre-ICDRA and ICDRA meetings were hosted by the Irish Health Products Regulatory Authority (HPRA) in Dublin, Sept. 3–7. The meeting was titled, "Smart Safety Surveillance."

to additional information. Smart safety surveillance must be developed with users and adapted to each situation.

Strong Reg Systems=Greater Access

In resource limited settings, patients can wait up to seven years before innovative treatments become available. Hurdles include registration in the country of manufacture, WHO prequalification, registration with other global regulatory bodies, procurement and delivery. Divergence in regulatory requirements and registration procedures can delay a drug's availability, as illustrated by the example of a vaccine registered in 134 countries.

Almost half of WHO member states (99 out of 194 countries) have limited to no regulatory systems in place. A quarter have evolving national regulatory systems that partially conduct essential regulatory functions. Only 50 countries worldwide operate stable regulatory systems which can reliably guarantee that patients have access to safe and effective medicines.

These are the first results from a WHO global benchmarking tool that should be finalized by 2019. Intended to be continually improved and for voluntary use, the tool should provide a robust framework to promote transparency, trust and reliance among global regulators, encouraging effective use of resources.

Experience from the Pan-American Health Organization whose 20-member countries have applied a similar assessment over the last decade has shown a positive impact on strengthening of regulatory systems. Increased transparency increases trust, promoting work sharing and mutual reliance.

Access to ATMPs, Biosimilars Varies

Advanced therapy medicinal products (ATMPs), or cell and gene therapies, are being developed at a fast pace and give hope to millions of patients. Yet across the globe, regulatory approaches differ vastly.

On one end of the spectrum in the United States and European Union, regulatory pathways have been implemented to make these therapies available for patients. Standards and guidelines provide support to industry and regulators alike.

Brazil's ANVISA is currently developing a framework for ATMP registration with the support of EMA and the U.S. FDA. GMPs for ATMPs were recently published and the Agency intends to create an expert committee similar to EMA's Committee for Advanced Therapies (CAT).

Ghana, on the other hand, lacks a pathway to specifically register ATMPs. For patients in need, doctors need to fill out a patient-specific importation form and bear full responsibility for any risk related to the nonapproved product. The country also lacks the expertise to assess the quality, efficacy and safety of these ATMPs. Currently, Ghanaian regulators plan to use a regional regulatory network to provide support in building these capabilities.

For biosimilars, the situation is slightly different since regulators can rely on existing guidance for biotherapeutics. Some biosimilars are now on the WHO essential medicines list, and prequalification by the WHO should accelerate access. WHO has also developed a number of guidelines for biotherapeutics and is currently working on a Q&A to its 2009 guideline for biosimilars.

Implementing these guidelines, however, is far from simple. Challenges include:

- Lack of clarity about comparability requirements, especially for the quality comparability exercise
- Lack of information about the reference product, and how a global comparator can represent a "national" reference product
- Lack of a harmonized definition of what "interchangeability" means—most countries/regions, including the European Union and the United States, have different approaches; Brazil, South Africa and Tunisia also have their own unique approaches
- Lack of capabilities for assessment and analytical testing

South Africa's journey with biosimilars is telling about the many hurdles faced by regulators when dealing with novel therapies. South Africa started approving biosimilars in 2006 without guidelines. As a consequence, many patients experienced adverse events. The country's regulatory agency then developed a guideline, based on EMA guidance, which was adopted in 2012. Yet companies misunderstood the regulatory requirements, resulting in most applications being rejected. The first biosimilar in South Africa was finally registered in 2017.

The regulators in attendance at the meeting recommended WHO strengthen regulatory capacity, support member states in implementing guiding principles and further foster collaboration and work sharing. They encouraged joint assessments of biosimilars and recommended a special workshop about the analytical comparability exercise. They also voiced the need to strengthen lifecycle management activities for such as post-approval change registration and pharmacovigilance.

Regulators Build Partnerships

The overall goal for regulators and industry alike is to facilitate patient access to quality medicines worldwide. One way to reach this goal is through greater regional partnerships.

Regional regulatory networks exist in several parts of the world and increasingly leveraged by global regulators. These networks enable regulators to build expertise and share resources. For example, mutual reliance takes into account an assessment done by another regulator, yet the responsibility for the final decision is retained by the national regulatory authority.

The European Union has explored these approaches for several decades among member states. Regulatory systems are based on reliance and work sharing. They are anchored in a single set of standards, legislations, guidelines, inspections and application formats.

EMA itself is also part of global regulatory initiatives. For example, the EMA article 58 procedure can be used to give market access in other countries. Swissmedic is also involved with the East African Community intergovernmental organization in marketing procedures for global health products by offering support. Swissmedic noted, however, that the procedures do not always result in faster access, and that

Continued at bottom of page 37

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Thanks for the Warning Letter: Part II

5 Focus Areas for the C-Suite

Steven Lynn, Lynn Consulting

[Editor's Note: Part I appeared in the November/December issue**.]**

In my old U.S. FDA role, I would see companies terminate multiple quality and manufacturing heads shortly after receiving a warning letter and profess this action a big part of their overall remediation solution. But the CEO always remained unchanged. Why? While some of the terminations may have truly been warranted, I find it hard to believe that this was the case in every organization, especially since the CEO and his C-suite reports were never touched.

Based on my previous experience, I believe that an organization's quality culture is a huge piece of the solution. The CEO needs to be involved, invested and knowledgeable on the importance of quality. The best CEOs I worked with when I was at the Agency learned to understand the importance of quality.

Unfortunately, many CEOs neglect manufacturing quality until a warning letter is issued. The quality and manufacturing people I have spoken with found it frustrating that things did not improve until this point.

So, what can be done?

In my experience, I have repeatedly come across five things that need to be addressed in order for organizations to avoid a warning letter. I argue that these five items are part of the overall solution that will help companies improve, maintain and sustain robust pharmaceutical quality systems. Are they the only things? Absolutely not! Still, I think they comprise parts of a sustainable solution.

1. Budgets and Staffing

In my time, I saw budgets and staffing shoot up when companies experienced large compliance troubles. Sometimes, I even wondered if money trees grew outside of aseptic manufacturing facilities, because when a warning letter was sent, resources came pouring into the site to resolve the cited issues. Now, why did it have to take a warning letter for the site to get the necessary resources?

One of my old Agency colleagues recounted how this exact situation occurred at a company a few years back. Here, the Agency invited the company's CEO and quality and operational leaders in for a regulatory meeting. These meetings are usually (but not always) a step in the process FDA uses as an attempt to gain voluntary compliance before moving on to more rigorous actions.

It was a tough meeting. The Agency laid out the issues they had been observing at the company, bluntly explaining that the issues needed prompt correction, otherwise FDA would be forced to move into the next phase of compliance action.

A few months after the meeting, my colleague ran into the company's quality head at a conference and the quality head enthusiastically thanked him for a great regulatory meeting. Not knowing if the quality head was being sarcastic, my colleague asked someone else from the same firm. This second person affirmed the sincerity of the sentiment, explaining that for years the quality head had been requesting additional budgetary resources to improve their quality system but were always shot down. Following the regulatory meeting, the company entered their annual budget cycle and the quality head sought a modest increase.

Instead, the CEO tripled his budget.

Why do C-suite leaders need to experience this nightmarish scenario to finally act on the quality problems facing their organization? Some argue that the quality head did not know how to speak the same language as the other C-suite leaders. Others might say the quality head failed to adequately explain the situation. Still, others may argue he sugarcoated the facts. All of this could be true, but the bottom line is that the most senior leaders in the organization did not have their hands on the pulse of the organization, and it resulted in a bad situation for the company.

2. Conflicting Performance Objectives and Bonuses

Major compliance issues can arise when a performance objective tied to an annual bonus conflicts with elements of a robust pharmaceutical quality system. For example, deviations are not necessarily a bad thing. In fact, they are a sign of a healthy quality system. But in terms of performance bonuses, I have seen manufacturing sites with performance objectives tied to the number of deviations experienced over the year. A certain number of deviations equaled a negative review. What do you think happened? Deviations were not reported. Site management either tried to deal with the deviation outside the quality system or just brushed it under the rug.

3. Silos

Breaking down silos is another key to sustainable quality. Efficient intraorganizational communications are critical for a business to thrive. The same goes for robust organizational quality systems. Remember, quality is not the responsibility of the quality department. It is the responsibility of every unit, every person and every leader in the organization. Communicating between departments, units and people is critical. If there are silos within the quality system, problems can be missed, buried or not fully addressed, creating inefficiencies that cost additional money. Breaking down silos is not a one-time event. Silos form and reform repeatedly. Think about how often companies reorganize, sometimes even under the guise of breaking down silos. Then, after the reorg is finished and the new units start to normalize, the silos reform.

4. Trust and Transparency

Trust and transparency are two crucial attributes that must be addressed. If different organizational units do not trust ➤

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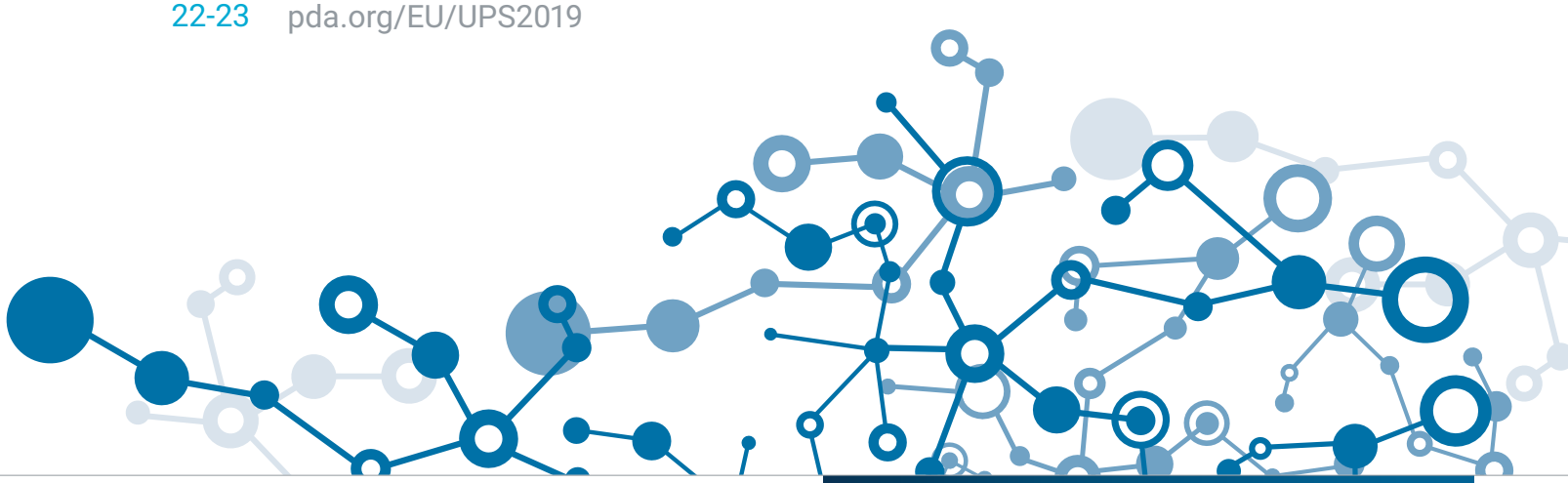

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each other, or people do not trust their leadership or what their leaders profess, it can stifle quality progress. Think about it at a basic human level. If you do not trust someone, what do you do? You probably shutdown and avoid sharing much with the other person. This is similar in an organizational setting. People go into self-preservation mode and communication ceases. In a lot of the whistleblower cases I reviewed at FDA, trust and transparency were some of the underlying issues.

5. Avoiding Compliance Rollercoasters

One last cautionary note: Quality sustainability means staying off the compliance rollercoaster. I have witnessed companies make huge strides in improving quality across the board and eventually getting their warning letter lifted. These remediations took considerable time and money. Consultants were involved, numerous steering committees organized, and massive amounts of progress reports generated for multiple levels of leadership—all serving as a resource drain that could have been avoided. One company even told me that by sending them a warning letter, I cost them a billion dollars. My response? They cost themselves a billion dollars, all a result of poor quality.

The companies I have watched ride the compliance rollercoaster usually sustain their quality progress for a few years, but eventually things settle down. The CEO and C-suite execs no longer see massive deviations, recalls, etc. Instead, they see the budgetary expenditures necessary for maintaining a robust quality system. Backtracking begins. I have even heard stories of companies chipping away at the quality and operation's budgets bit-by-bit because they believe the extra internal resources were only a temporary fix. Cost reductions lead to staff attrition and positions are not backfilled. Then, there are further cuts quality units. Naturally, after a few years, quality problems rear their ugly heads again. Why? People are what make the system work. Without qualified people working in the quality system, things start to breakdown. Compliance issues pop up again and another warning letter is issued. The cycle begins anew.

We need to continue working to avoid the compliance rollercoaster

Quality problems get fixed (up the roller coaster hill) and then the company has a period of sustainable quality (they level off and maybe go up/improve some more) and then they cascade back down after reducing their resources and quality becomes a sustainability risk. We need to continue working to avoid the compliance rollercoaster. It costs our industry too much and we fail to serve our patients.

In closing, I do not claim to have any of the solutions to these problems. My goal here is to raise these issues for future consideration, discussion and debate. Additionally, we need to keep beating the drum of robust quality systems and overall quality. Without them, patients will not benefit from the life-saving and life-sustaining products we produce

I want to close with one last quote from another famous quality guru, **Philip Crosby.** His famous saying was "quality is free." This does not mean to avoid investing in quality. Rather, after investing and continually funding quality, it pays for itself. In fact, the entire quote reads: "quality is free. It's not a gift, but it's free." What costs money are the nonquality things—all the actions that involve not doing jobs right the first time."

About the Author

Steve Lynn is currently a consultant. Previously, he worked for Novartis, Mylan and the U.S. FDA, where he led multiple major domestic and international drug programs designed to assure compliance with CGMPs.

Global Regulators Partner for Greater Patient Access continued from page 32

smaller countries do not always benefit to the same extent as larger countries. In some cases, national legislation prohibits collaborative procedures.

WHO is very active in promoting partnership initiatives. Several collaborative registration procedures are being piloted in regional regulatory networks. The biggest impact seen is on registration timelines, which have shortened.

As I left the meeting, I came away with the takeaway that trust seems to be the key ingredient for global collaboration towards sustainable healthcare systems. At the same time, this requires political will and greater support worldwide.

About the Author

Ursula Busse, PhD, is the Global Head of Quality Intelligence and External Affairs at Novartis. She drives the Novartis external engagement strategy in quality, technical and regulatory topics and leads global GxP regulatory intelligence.

Chapters: Another Way to Connect

Barbara Allen, PhD, Eli Lilly

Are you looking for industry contacts specific to your region? Do you want to volunteer for PDA but do not know where to start? Are you interested in attending a PDA event but not able to attend a major PDA conference?

PDA is a large community of members, over 10,000, in fact. Members help support many technical reports, conferences and publications. It is great to be part of a big group but sometimes you want a smaller community located closer to you with similar interests and challenges. This is where PDA chapters can be a great resource. Fortunately, PDA has 26 global chapters. Each of these chapters hosts special events in their respective locales and have their own forums on PDA Connect℠ (community.pda.org) where you can discuss topics of interest. Chapter events include workshops, presentations, networking events, vendor exhibitions and webinars. In addition, some chapters encompass student chapters consisting of college students enrolled in industry-related programs. These student chapters host their own events as well.

The first PDA event that I ever attended was one organized by the Ireland Chapter. As part of attending, I became a member of PDA and never left! Being involved with the Ireland Chapter has helped me grow my network within the Irish pharmaceutical community and kept me abreast of the key issues affecting this region. In addition to very useful one-day workshops, the chapter encourages professionals starting out in the industry. One of these efforts is the chapter's student bursary program. This program recognizes a student's project each year by covering their expenses to attend the *PDA Europe Annual Meeting*. This program has been a success and I always look forward to meeting these students and learning about their plans for a future in the industry.

I am also very familiar with the Midwest Chapter in the United States as I lived in that area for five years—my company has a large presence there and many of my colleagues there are actively involved in the chapter. I also want to extend a welcome to PDA's newest chapter, the Pacific Northwest Chapter. If you are in that part of North America, I recommend attending their events this year.

Chapters are very important to my heart because they are a great way to get involved, gain professional experience, grow as a leader and contribute to connecting People, Science and Regulation® (aka PDA's mission). As a chapter volunteer, you can organize events, join special project teams, contribute "Chapter Update" articles to the *PDA Letter* and lead discussions on PDA Connect℠.

I have only mentioned a few chapters—there are more I would also like to talk about, but the editors tell me I can only have one page! You can log on for yourself and catch up with all of the chapters by visiting the PDA website!

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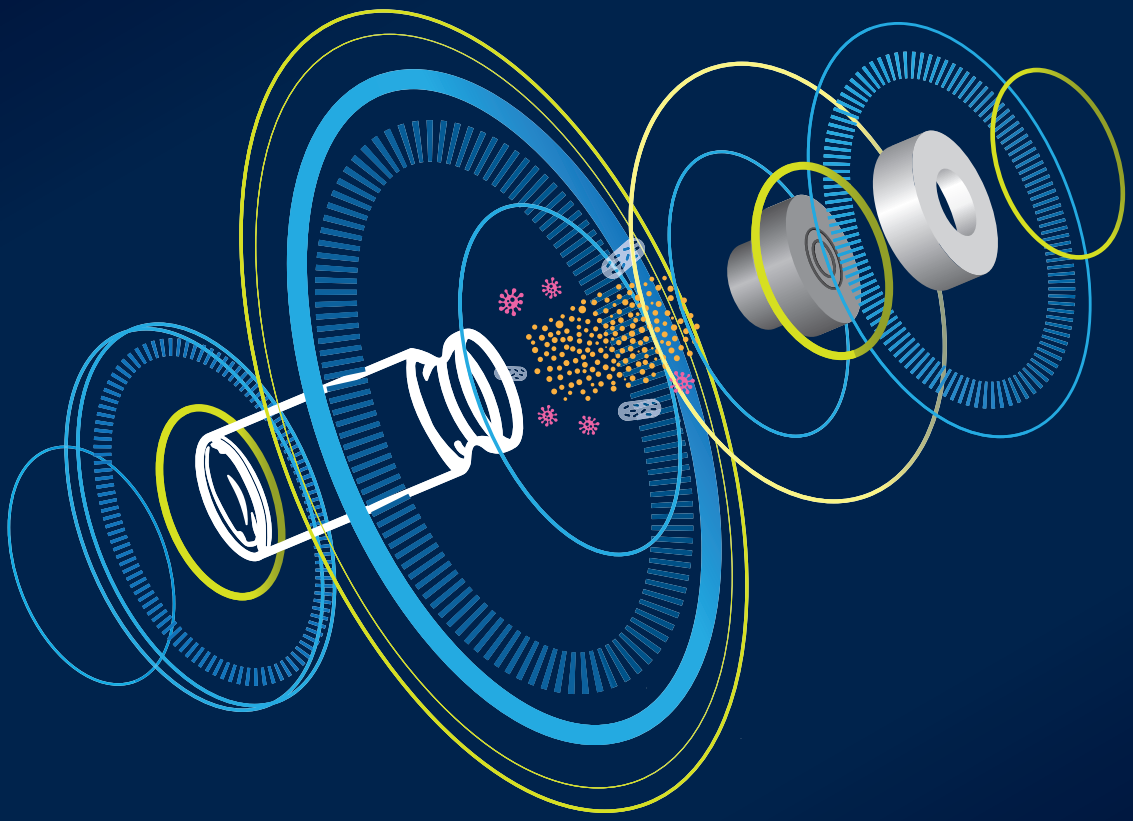

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