People • Science • Regulation

PDA Letter

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CMC Strategy
A Critical Foundation for Biosimilars

January 2017 PDA Letter

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Departments

News & Notes

People

Science

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> **On the Issue** | PAC iAM Packs PAC Punch
Find out what PDA's Post Approval Change: Innovation for Availability of Medicines (PAC iAM) Task Force is doing to tackle the challenges companies face when trying to implement post-approval changes.

> **On the Issue** | Change is Coming to USP Micro Chapters
Expert Committee Member David Hussong discusses recent changes to USP's general chapters relating to pharmaceutical microbiology.

> How Should Annex 1's Requirements be Interpreted?
As industry nears the Annex 1 revision, take a look at which areas of the regulation may have been interpreted in ways the original authors never considered.

pda.org/letter

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The Parenteral Drug Association presents the...

2017 PDA Annual Meeting

Innovation in Manufacturing Science and Technology

April 3-5, 2017 | Anaheim, California

Anaheim Marriott

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

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Register before January 20, 2017 and save up to $600!

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

At the *2017 PDA Annual Meeting*, you'll receive the latest information and understand future trends related to pharmaceutical manufacturing and associated science and technology.

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Hear the latest on:

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- Developments in Patient-Centered Precision Medicine
- Next Generation Manufacturing

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

Following the Meeting, on **April 5-6**, PDA will be offering the *2017 PDA Cell and Gene Therapy Workshop* to provide a more in-depth look at how these new therapies will impact the industry. ***Learn more and register at pda.org/2017CGT.***

On **April 6-7**, PDA Education will be hosting five courses as part of the *2017 PDA Annual Meeting Course Series* to help you further advance your knowledge. ***Learn more and register at pda.org/2017AnnualCourses.***

Staying Abreast of Change in 2017

Advanced therapies. Novel water systems. Industry 4.0. These are just three of the exciting topics the *PDA Letter* will cover in 2017. When we developed our Editorial Calendar for 2017, we distinctly focused on areas of technological/scientific change within parenteral manufacturing. And so, the 2017 volume of the Letter begins with a look at one such industry game changer—biosimilars.

While biosimilars have been part of the European pharma landscape for over a decade, they are still relatively new to the U.S. market. Not surprisingly, there are a number of regulatory and technical questions around biosimilar development. Our cover story looks at the importance of CMC to a biosimilar development strategy (p. 26). Teva's **Michael VanDerWerf** looks at how to prove comparability for biosimilar products impacted by a manufacturing change (p. 30). And another feature summarizes the *2016 PDA Biosimilars Conference*—our first ever conference on this topic (p. 33).

But before I forget, you probably noticed this issue looks a little different from previous ones. We thought that since it had been many years since our last redesign, it made sense to update the look and feel of the Letter with some cosmetic changes. I hope you like these changes as much as I do. And don't be afraid to tell us what you think.

In 2017 you can also expect to see at least six more "On the Issue" videos. We recently posted an interview with USP Expert Committee Member **David Hussong** discussing recent changes to USP's microbial chapters. And we're looking to focus our multimedia content next year ever more closely on the latest scientific developments within the aseptic/sterile processing space.

As I prepared this issue of the Letter, U.S. President **Barack Obama** signed the 21st Century Cures Act into law. This Act is intended to speed patient access to new drugs and medical devices. In addition, the law provides for an accelerated approval pathway for regenerative medicines. But more pertinent to PDA's members, the law includes a provision for the U.S. FDA to issue grants to encourage companies to implement continuous manufacturing. You can be sure that we plan to cover this in more detail as the story unfolds.

I hope everyone had a wonderful holiday season and wish all of our readers a prosperous 2017!

— **Rebecca Stauffer**

Rebecca Stauffer

2017 Board of Directors

PDA is pleased to announce the results of the 2017 Board of Directors election.

Directors

Congratulations to the following Directors elected by PDA's membership to the board:

Barbara M. Allen, PhD, Senior Director, Global Quality Systems, Eli Lilly & Company, looks forward to shaping "the future to meet the needs of each of the members."

Joyce Bloomfield sees this as her opportunity to continue doing "all that I can do to lead the advancement of medicine and manufacturing technology in order to facilitate availability of medicine to patients everywhere."

Véronique Davoust, PharmD, Senior Manager, Global Quality Intelligence, Pfizer, wants to contribute "even more actively to the success of PDA by enhancing PDA's activities in influencing regulations in the Quality/GMP arena."

Ghada Haddad, Director, Global Quality Risk Management Center of Excellence, Merck, plans to "devote greater service to the PDA and its members by working to ensure quality, accuracy and relevance to the technical reports, the programs and training events."

Outgoing Directors

PDA would also like to thank the following outgoing Directors for their service on the board:

Glenn Wright, Senior Director, Project Management TS/MS, Eli Lilly and Company

John Shabushnig, PhD, Principal Consultant, Insight Pharma Consulting

PDA to Comment on Revised FDA Metrics Guidance

Metrics conference offers first chance to hear from FDA

PDA is preparing comments on the U.S. FDA's recently revised draft guidance for industry: *Submission of Quality Metrics Data.* The revised draft was issued after strong public interest and comment on the first draft, which was published in 2015.

The *2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference,* Feb. 21–22, in Bethesda, Md., will provide industry representatives an opportunity to interact with FDA officials involved with developing the metrics guidance/program, including the U.S. FDA's **Tara Gooen Bizjak,** Senior Science Policy Advisor for Pharmaceutical Quality, CDER, the contact person for the current draft.

"PDA is committed to providing science-based commentary on the quality metrics draft guidance, as we did with the release of the first draft in 2015," said **Richard Johnson,** PDA President. "The quality metrics/culture conference will be the fourth held by PDA on this important topic since the FDA called for industry participation in 2013."

For more information about the conference, visit www.pda.org/2017metrics.

PDA V er Sp t

Myriam M. Sosa

- Executive Director, QA & Compliance
- *Merck*
- Member Since | **2012**
- Current City | **West Point, Pennsylvania**
- Originally From | **San Juan, Puerto Rico**

The longer and harder I work in my field, the more passionate I feel

Your term as Puerto Rico Chapter president has ended. How do you plan to participate with the chapter moving forward?
I plan to continue as part of the chapter's leadership team and remain totally committed to supporting our presence on the PDA global map.

You worked on *Technical Report No. 67: Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics.* How can this document help the industry?
There was insufficient information out there about excluding objectionable microorganisms in nonsterile drugs. TR-67 provides strategies on excluding objectionable microorganisms for dosage forms other than sterile drug product. Manufacturers of nonsterile products can use TR-67 for guidance on managing the microbial risks associated with manufacturing and storage, as well as determining what isolates should be deemed objectionable microorganisms in nonsterile products. This aligns with regulatory requirements for microbial limits in products released to the market.

Where do you see the industry in 2017?
Many companies today are searching for ways to increase productivity, decrease costs, and develop new treatment modalities that enhance profitability. The industry will be increasingly challenged to find a balance between the short-term profit demands of investors and the benefits of long-term strategies for researching and developing new drugs and treatments, including lifesaving and life-enhancing vaccines.

You previously worked for the U.S. FDA; how has your work there helped your career?
Thanks to my extensive previous experience working at FDA, there is hardly any aspect of the pharmaceutical industry that I am unfamiliar with. My FDA work experience has been a significant asset in my professional performance within industry.

What is a typical weekend like in Puerto Rico?
In Puerto Rico, people love to go to the beach, visit festive places, and also entertain family and friends.

The Parenteral Drug Association presents:

PDA Europe Conference, Exhibition

Parenteral Packaging

13 March
Secondary Packaging

13 March
Elastomers

16 March
Container Closure Development

16-17 March
Container Closure Integrity

16-17 March
Extractables and Leachables

16-17 March
Track and Trace – How to implement Pharma Serialization, Tamper Evidence and the EU-Falsified Medicines Directive

Register by 14 Feb 2017 and SAVE!

14-15 March 2017

Barcelona | Spain

pda.org/eu-parpack-2017

UK Chapter Explores Technology Transfer Requirements

Siegfried Schmitt, PAREXEL

PDA's UK Chapter recently hosted "From R&D to the Clinic and Commercial," a one-day event at Pfizer's research facility in Sandwich, Kent. Nearly 40 attendees gathered to hear a mix of presentations and panel discussions on the transfer of technology from clinical to commercial production.

Simon Morgan presented first on Qualified Person requirements for releasing Investigational Medicinal Products, followed by **Mark Gibson,** who explored the past and future of technology transfer. Next, **Neil Geach** discussed the early development of radiolabeled batches in preclinical and Phase 1 studies. And the final speaker, **Karen Van Hoey,** provided a commercial perspective on transferring technology from the clinical side to commercial production.

[Editor's Note: Read more about this event and the panel discussion at the *PDA Letter* website: www.pda.org/pdaletter.**]**

(l-r) Simon Morgan; Karen Van Hoey; Neil Geach; Mark Gibson

PDA Who's Who

Neil Geach, Head, Technical Sales, Selcia

Mark Gibson, Consultant

Ian Howard, Director, Pfizer

Simon Morgan, Manager, Contract Operations Quality Assurance, Pfizer Global Supply

Siegfried Schmitt, Principal Consultant, PAREXEL

Karen Van Hoey, Lead, Development Team, Pfizer

SE Chapter Awards Scholarships to Sci/Tech Students

Renee Morley, STERIS Corporation, and President, Southeast Chapter

On Dec. 8, the PDA Southeast Chapter presented three $1000 scholarships at its Winter Social in Raleigh, N.C. to students currently enrolled in a master's or undergraduate program in the sciences or engineering. Out of 20 applicants, the Chapter awarded scholarships to the following individuals:

- **Alexander Drennan,** North Carolina State University, Master of Science in Biomanufacturing
- **Caleb Nunn,** North Carolina State University, Bachelor of Science in Chemical Engineering
- **McKayla Webb,** North Carolina State University, Bachelor of Science in Chemical Engineering

In order to be considered for the scholarship, applicants had to meet the following requirements: current status as a student member of the Southeast Chapter; good academic standing; enrollment in a science, engineering or related degree program in the Southeast region; an overall GPA of 3.0 or greater; and a sealed letter of recommendation from a university representative or professional in the industry. Additionally, applicants had to submit a 500-word essay discussing a current topic of interest in the pharmaceutical industry and why it interests them.

The three scholarship winners' essays explored different facets of the industry. Nunn's essay discussed how the cost of healthcare impacts pharmaceutical manufacturing. Drennan, who also works as a Program Manager in Technical Sterility Services at Hospira, wrote about preuse, post-sterilization filter integrity testing for aseptic filling operations. And Webb covered how to interpret regulatory requirements using good science.

The Chapter is very proud of these students and looks forward to seeing what their future holds in the industry.

(l-r) Chapter Vice President Austin Caudle, Metabolon; Chapter Treasurer Ryan Phillips; McKayla Webb; Caleb Nunn; and Chapter President Renee Morley, Steris

PDA staff helped support the event. (l-r) Melanie Decker; Creixell Espilla-Gilart; and Faramarz Kolivand

2016 PDA Europe: Parenterals

Sept. 6–7 |Tehran, Iran

In September, PDA Europe organized its first conference in Iran with the support of the Iranian Food and Drug Administration.

(l-r) Zohre Bazaz, Senior GMP & Inspector, Ministry of Health, Iran; Akbar Abdollahiasl, Managing Director of Pharmaceutical Affairs, Iran FDA; Rassoul Dinarvand, Head of Iran FDA; Georg Roessling, PDA Europe

Zohre Bazaz, Senior GMP & Inspector, Ministry of Health, Iran, served as Chair of the conference

Bettine Boltres, PhD, SCHOTT

Rassoul Dinarvand, Head of the Iran FDA, provides an overview of the Iranian regulatory framework for medicines in the first session of the conference

11th Annual PDA Global Conference on Pharmaceutical Microbiology

October 24–26 | Arlington, Va.

(l-r) Kalavati Suvarna, PhD, CDER, U.S. FDA; Dmitri Iarikov, MD, PhD, CDER

(l-r) Raphael Bar, PhD, BR Consulting; Vinayak Pawar, PhD, CDER, FDA; Berit Reinmueller, PhD, Chalmers University of Technology; Bengt Ljungqvist, PhD, Chalmers University of Technology

(l-r) Marsha Hardiman, ValSource; Randall Thompson, Shire; Dona Reber, Pfizer

(l-r) Edward Tidswell, PhD, Merck; Maik Jornitz, G-Con Manufacturing

(l-r) Ed Balkovic, PhD, MicroBio Technical Support; Brandye Michaels, PhD, Pfizer; Kevin Hazen, PhD, Duke University School of Medicine

Charles River provided a booth where attendees could have photos taken against a horseshoe crab backdrop. For every photo taken, a donation was made to a fund for horseshoe crab advocacy (left). An attendee speaks with a Hardy Diagnostics representative at the company's booth in the Exhibit Hall (right).

PDA Photostream www.flickr.com/parenteral-drug

2016 PDA Outsourcing/CMO Conference

November 3–4 | Washington, D.C.

(l-r) Steven Falcone, Genzyme; Nick Beaumont, Samsung Biologics; Tara Gooen Bizjak, CDER, U.S. FDA

(l-r) Jessica Walker, Afton Scientific; Rich Levy, PhD, PDA; Dwayne Greathouse, Gilead Sciences

(l-r) Stanley Russell, Shire; Lada Laenen, PhD, Genzyme; Robert Beall, ProPharma Group

(l-r) Jessica Walker, Afton Scientific; Paula Katz, CDER, FDA; Scott Gunther, Catalent Pharma Solutions

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- Email advertising (*PDA Connector* weekly e-newsletter)
- Exhibits
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Resume Rule # 11
Everyone Likes a Good Story

Perry Newman

There is a reason authors like **James Patterson, John Grisham, Michael Connelly,** and **David Baldacci,** among others, are constant fixtures on *The New York Times Best Seller* list. They create compelling stories that grab readers' attentions, stirring their imaginations to read on and see how the characters develop and the story unfolds to its conclusion.

I've been writing resumes and advising people on how to interview for quite some time now. I've been told that the reason my clients' resumes and their resulting interviews are so successful is because I advised them to tell a story above all else.

I don't dispute that keywords, achievements, and accomplishments are important for success, but how you use them to tell your story trumps all else. So when you begin to prepare a resume or arrange to have a professional resume writer draft one, consider the following:

Define the story you want to tell. Is it one the reader wants to be told?

Is the main character (you) memorable in the reader's mind? If not, how do you make it so?

Does your story contain action and intrigue, or is it cliché, hollow, and boring?

Does the main character (you, again) come across as likeable and sincere or arrogant and braggadocious?

Is the content relevant to the story you want to tell, or is it mostly fluff/filler and self-aggrandizement?

Does your resume read more like a thriller, a classic novel, a textbook, or a horror story?

If you assimilate all this into your prep work and keep it in mind as you write, you can end up with a great resume, depending on how good of a writer you are in the first place. To really wow your readers, you also need to be a good researcher to find the right information that hits the right spot.

All of these points also apply to your how you prepare your responses in the interview, since a successful interview is also about storytelling. The difference is, for an interview, you need to strategize how you present your story verbally rather than in writing. For some, this is easy; for others, this is the hard part. In either case, you need to perfect your story and storytelling ability in both writing and speech.

About the Author

Perry Newman, CPC/CSMS, is a nationally recognized career services professional, an executive resume writer and career transition coach, a certified social media strategist and an AIPC-certified recruiter. He can be reached at perry@perrynewman.com.

2017 PDA Europe

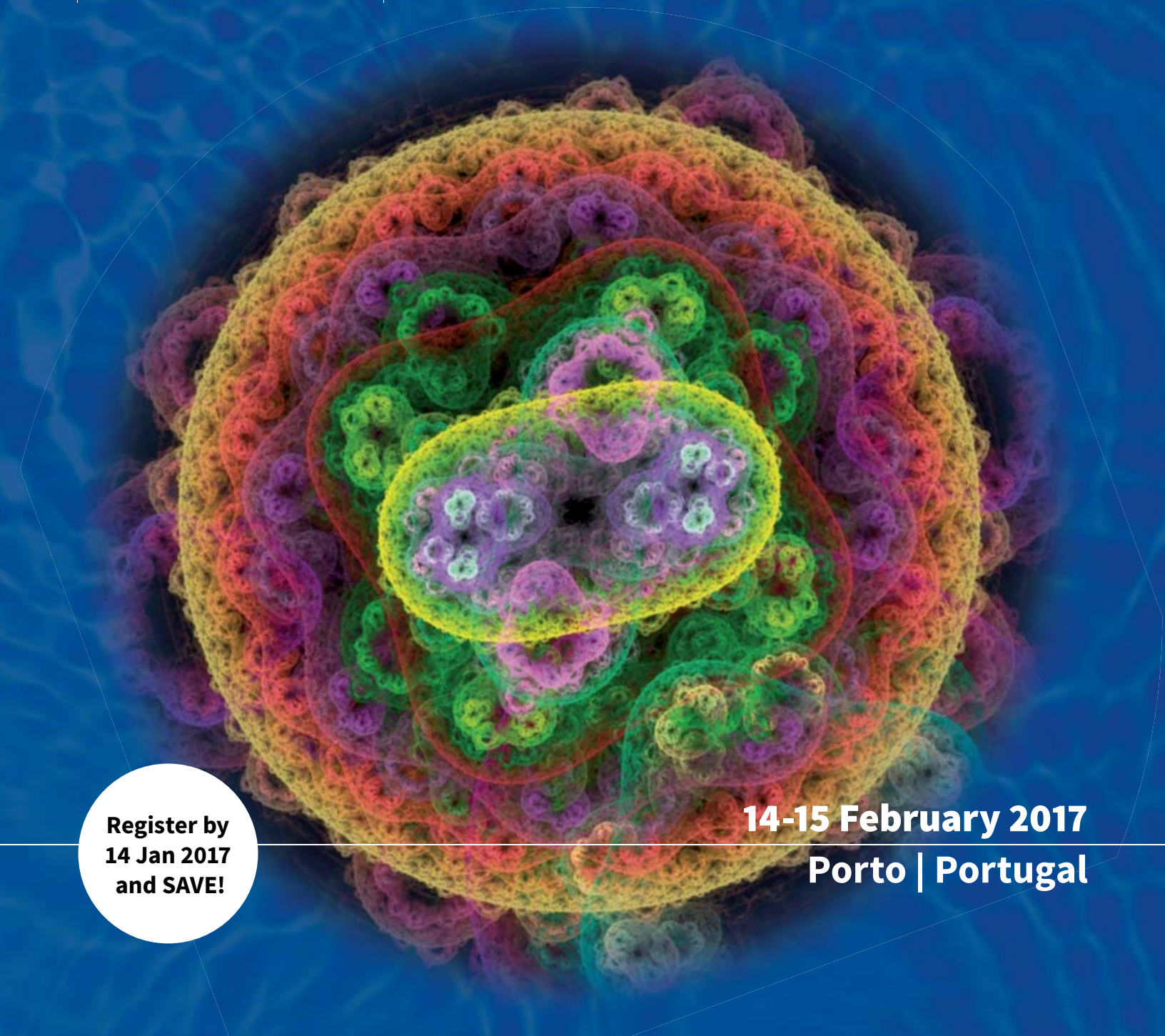
Pharmaceutical Microbiology

Microbiology in Pharmaceutical Manufacturing

PDA®
Parenteral Drug Association

16-17 February
Rapid Microbiological Methods

16-17 February
Practical Guide for Root Cause Investigations – Methodology & Tool Kit



Register by 14 Jan 2017 and SAVE!

14-15 February 2017

Porto | Portugal

SNAPShot

PDA Maintains a Productive Publishing Year

Walter Morris, PDA

PDA's Board of Directors, advisory boards, technical report teams and Science and Regulatory staff produced four technical reports, a Points to Consider document, and three PDA surveys in 2016—continuing a streak of highly productive publishing years. This batch of varied and interesting publications included:

- *Technical Report No. 56 (Revised 2016): Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (API or Biological Active Substance)*
- *Technical Report No. 74: Reprocessing of Biopharmaceuticals*
- *Technical Report No. 75: Consensus Method for Rating 0.1µ Mycoplasma Reduction Filters*
- *Technical Report No. 76: Identification and Classification of Visible Nonconformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging*
- *Points to Consider for Aseptic Processing, Part 2*
- *PDA Survey: 2015 Aging Facilities*
- *PDA Survey: 2015 Particulate Matter in Difficult to Inspect Parenterals*
- *PDA Survey: 2015 Particulate Matter in Oral Dosage Forms*

PDA technical reports go through the PDA peer review process, which includes a global review by subject matter experts, advisory board ballot, and Board of Directors (BOD) ballot. Both the advisory board ballot and BOD ballot can result in rejection of the document or changes to it. Surveys are produced as part of the development of a future document (usually a technical report)] but do not go through the peer review process. All PDA technical document projects are sanctioned, or approved, first by an advisory board (i.e., the Science, Biotechnology, or Regulatory Affairs and Quality Advisory Board). PDA also published two "PDA Papers" in the *PDA Journal of Pharmaceutical Science and Technology.* These are official position papers approved through the PDA peer review process.

Members can expect more of the same in 2017. The first technical report out this year will cover blow/fill/seal technology and will publish in January. Members can also look forward to other several other TRs covering important topics like glass handling, autologous cell therapy control strategies, and validation of protein manufacturing, along with more "PDA Papers" and surveys.

IG *Corner*

Facilities and Engineering Interest Group Gets Hot and Heavy with "Speed Dating" Exercise

Shelley Preslar, Azzur Group

On Sept. 13, PDA's Facilities and Engineering Interest Group convened on the second day of the *2016 PDA/FDA Joint Regulatory Conference.* Following a review of interest group business, group members came together in a large circle to participate in the interest group's first speed dating session. Originally developed for the Inspection Trends Interest Group, this exercise involves participants spending five to ten minutes on "dates" with topics of interest in the industry. During these "dates," participants discuss the topic and make recommendations until it is time to rotate to a new topic.

Stephen Roenninger, Director, International Quality External Affairs, Amgen, led the group discussion on health-based limits for dedicated facilities. Speed daters discussed the EMA's recent guideline on this topic. Overall, speed daters felt that the values behind the cleaning limits for these facilities should be risk-based and draw from normal production experiences.

Speed daters also met with **Christopher Smalley,** PhD, to discuss the Quality Risk Management (QRM) process for aging facilities. What is the key to QRM success? The group consensus is that it is critical to understand the process through an assessment, and then evaluate if the cost of the replacement overrides the cost benefit. Ultimately, the overall ROI needs to be evaluated.

Ravi Samavedam, General Manager, Azzur Group, led the group conversation on implementation of phase-appropriate GMPs. Here, discussions explored different requirements for Phase I products, ICH Q7: *Good Manufacturing Practice for Active Pharmaceutical Ingredients,* Quality Control, and audits of raw material vendors, to name a few.

In the final group, **Laurie Norwood** from the U.S. FDA covered Agency-related topics. Here, daters came to the consensus that while change can be hard, with many initial drawbacks (temporary slowdowns, "if it ain't broke, don't fix it" attitude, etc.), it is necessary. Daters left this round understanding that open communication with FDA about facility upgrades and improvements can only help as

Continued at bottom of page 28

2017 PDA Upcoming Events

SAVE THE DATE for PDA's 2017 Events

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

JANUARY

18
PDA New England Chapter Data Integrity Dinner Event
Boston, MA
pda.org/2017NE-DI

23-27
PDA #100 Aseptic Processing Option 1
Week 2: Feb. 20-24
Bethesda, MD
pda.org/2017Aseptic1

23-3
End-to-End Pharmaceutical Manufacturing Training
REGULATORY ONLY
Bethesda, MD
pda.org/2017PDAUMD

26
PDA Midwest Chapter Medical Packaging Case Study Dinner Event
Northbrook, IL
pda.org/2017MW-MP

26-27
Die Grundlagen erfolgreichen Auditierens
Berlin, Germany
pda.org/EU/GEA2017

FEBRUARY

6-9
Fundamentals of Aseptic Processing
REGULATORY ONLY
Bethesda, MD
pda.org/2017FundAPGOV

14-15
PDA Europe Pharmaceutical Microbiology
Porto, Portugal
pda.org/EU/Micro2017

16-17
Practical Guide for Root Cause Investigations – Methodology & Tool Kit
Porto, Portugal
pda.org/EU/RootCI2017

16-17
Rapid Microbiological Methods
Porto, Portugal
pda.org/EU/MicroMethods2017

21-22
2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference
Bethesda, MD
pda.org/2017Metrics

28-3
Train the Trainer Course Series
Bethesda, MD
pda.org/2017Trainer

MARCH

6-10
Visual Inspection Course Series
Bethesda, MD
pda.org/2017VI

13-17
Validation Course Series
Bethesda, MD
pda.org/2017VCS

13
Elastomers
Barcelona, Spain
pda.org/EU/Elastomers2017

13
Interest Group Meeting: Pre-filled Syringes
Barcelona, Spain
pda.org/EU/IGPrefilled2017

13
Secondary Packaging for Parenterals
Barcelona, Spain
pda.org/EU/SecondaryPack2017

14-15
Parenteral Packaging
Barcelona, Spain
pda.org/EU/ParPack2017

16
Container Closure Development
Barcelona, Spain
pda.org/EU/CCD2017

16-17
Container Closure Integrity: Regulations, Test Methods, Application
Barcelona, Spain
pda.org/EU/CCI2017

16-17
Track and Trace: How to Implement Pharma Serialization, Tamper Evidence and the EU-Falsified Medicines Directive
Barcelona, Spain
pda.org/EU/Track-and-Trace2017

16-17
Extractables & Leachables
Barcelona, Spain
pda.org/EU/EL2017

20
Particle Identification in Parenterals
Berlin, Germany
pda.org/EU/TCParticleID2017

21-23
Design, Operation and Qualification of Pharmaceutical Water Systems NEW COURSE
Bethesda, MD
pda.org/2017PWS

22-23
An Introduction to Visual Inspection: A Hands-on Course
Berlin, Germany
pda.org/EU/TCVisual2017

27-31
PDA #100 Aseptic Processing Option 2
Week 2: Apr. 24-28
Bethesda, MD
pda.org/2017Aseptic2

Denotes Laboratory Courses | Denotes Lecture Courses

A New Method for Streamlining Media Fills

Derek Duncan, PhD, Lighthouse Instruments; Tony Cundell, PhD, Microbiological Consulting; James Veale, PhD, Lighthouse Instruments

[Editor's Note: This is an abbreviated version of the article, "The Application of Noninvasive Headspace Analysis to Media Fill Inspection," published in the May/June 2016 *PDA Journal of Pharmaceutical Science and Technology*.**]**

Opportunities to improve and streamline the media fill process offer a number of benefits for aseptic processing. In particular, the manual visual inspection process used to inspect media vials for signs of contamination after incubation is tedious and time-consuming. Potential for human error exists as operators perform visual inspection. The inspection performance of individual human operators varies. Plus, fatigue is well known to affect performance. In addition, difficult-to-inspect containers, such as molded or colored glass, or certain plastic containers, pose inspection challenges for operators. An analytical, automated inspection method would improve media fill inspections, aligning with the industry trend toward removing human subjectivity from the process.

Automated Media Fill Inspection

Laser-based headspace analysis, a rapid, nondestructive, analytical technique, ***(1),*** has been demonstrated to detect microbial growth in media-filled pharmaceutical containers. For detecting microbial growth, tunable diode laser absorption spectroscopy is used to measure the levels of headspace oxygen and carbon dioxide. The study described here shows that once aerobic microorganisms begin to grow after the lag phase and enter the exponential growth phase, there will be a significant consumption of oxygen in the sealed container as well as a corresponding production of carbon dioxide ***(2)***. Headspace analysis can accurately measure these changes in the headspace gas composition, and could therefore, be used to detect pharmaceutical containers filled with an oxygen headspace and contaminated by aerobes. (The technique is also described as a deterministic container closure integrity test method in USP <1207>) ***(3).*** The measurement itself is rapid and nondestructive, meaning that results are obtained immediately, and the measured sample remains intact, allowing for repeated measurements over time.

A study was performed with five representative microorganisms. Sample sets of 20 media vials were inoculated with <100 CFU each of five representative microorganisms and incubated for 14 days. During the incubation period, the headspace oxygen and carbon dioxide levels in the sample vials were measured. **Figure 1** plots the measured headspace oxygen and carbon dioxide levels over the 14-day incubation period in media vials inoculated with <100 CFU of the mold *A. brasiliensis*. The results of three samples are plotted to indicate the spread between extremely high, medium, and low measurement results in the set of 20 vials. The dotted line indicates the start of exponential growth, and it can be seen that the headspace oxygen in the innoculated vials decreases rapidly from near atmospheric levels (i.e., 18% atm) to zero in the first 75 hours of incubation. At the same time, the plot shows headspace carbon dioxide levels rising from zero to over 16% atm. These changes in headspace gas composition are easily detectable with laser-based headspace measurements—the standard deviations of the measurements are smaller than the value range of the data points plotted in the graph. It is also clear from the graph in **Figure 1** that detectable changes in the headspace gas composition happened very early in the 14-day incubation period.

Figures 2 and **3** show the results from all twenty samples inoculated with the bacterium *S. aureus.* Again, the results show a drop of headspace oxygen levels (**Figure 2**) to zero during the 14-day incubation with a corresponding increase of headspace carbon dioxide (**Figure 3**). All 20 samples behaved identically, clearly demonstrating the consistency of the measured oxygen consumption and carbon dioxide production curves across the set of 20 contaminated samples.

The dynamics of the headspace oxygen consumption and carbon dioxide production curves are dependent on the microorganism. Work done subsequent to the study described here demonstrated the headspace method for the detection of more than 25 microorganisms in media vials, including the standard compendial microorganisms as well as typical house isolates detected in sterile drug manufacturing facilities ***(4).***

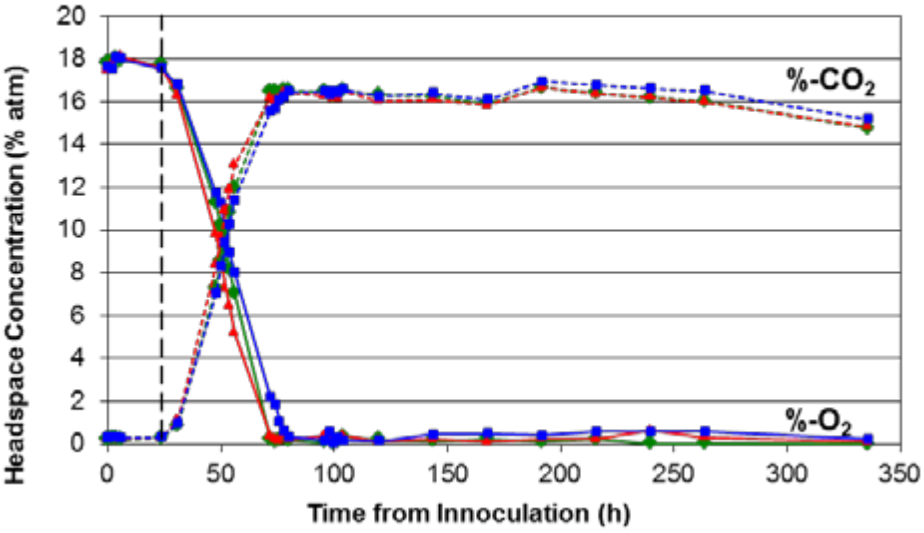


Figure 1 Headspace oxygen and carbon dioxide levels in TSB media vials contaminated with *A. brasiliensis*

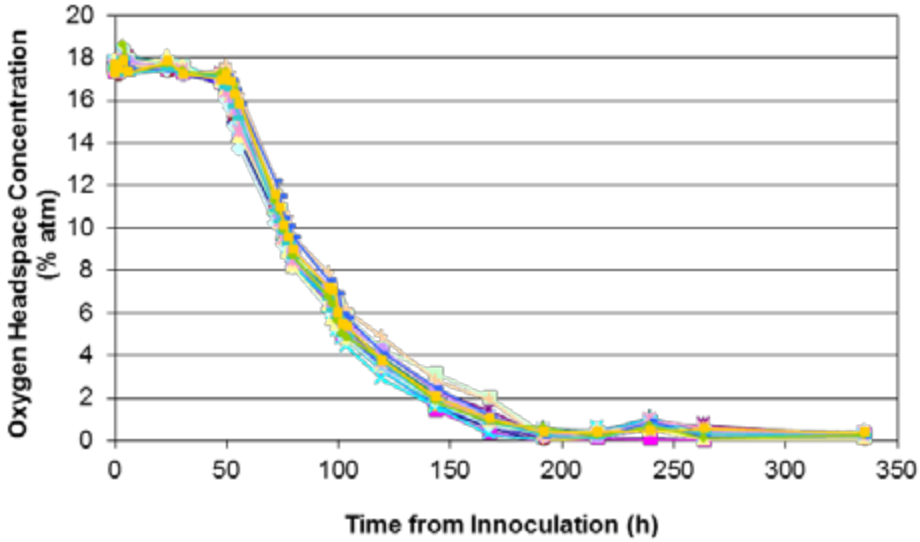


Figure 2 Headspace oxygen consumption in 20 TSB media vials contaminated with *S. aureus*

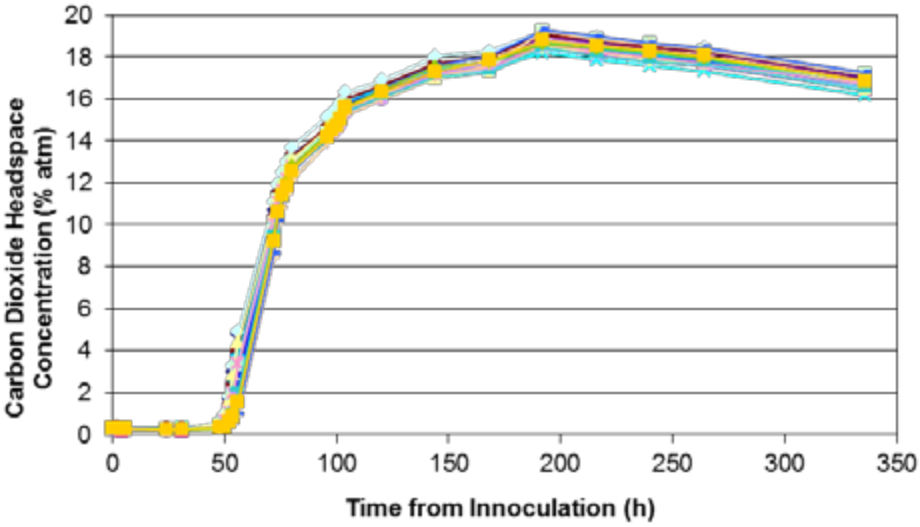


Figure 3 Headspace carbon dioxide production in 20 TSB media vials contaminated with *S. aureus*

Because headspace analysis can be automated at inspection speeds of several hundred vials per minute online on a conveyor belt with an inspection station, a feasible application is automated media fill inspections as part of aseptic filling process validation. This represents an opportunity for replacing the labor-intensive human visual inspection process (a subjective method) with an automated analytical inspection for media fills. This change would improve the reliability of media fill inspection, reduce the total inspection time and required human labor, and could improve vial reconciliation and data integrity (**Table 1**).

Table 1 Comparison Media Fill Inspection Methods

Media Fill Inspection Method	
Human Operators	Laser-based Headspace Analysis
Subject to human error	Quantitative analytical measurement
Slow, resource-intensive inspection	Fast automated machine inspection
Vial count done manually	Automative vial reconciliation
Some containers challenging to inspect	Challenging containers can be inspected
Difficult to qualify	Straightforward quantitative qualification

References

1. Veale, J. R. 2009. "New Inspection Techniques for Aseptic Processing," in *Practical Aseptic Processing Fill and Finish,* ed. Jack Lysfjord. Bethesda, MD: PDA/DHI, 305–372.

2. Duncan, D., et al. 2016. "The Application of Nonvinvasive Headspace Analysis to Media Fill Inspection." *PDA Journal of Pharmaceutical Science and Technology* 70 (2016): 230-247.

3. U.S. Pharmacopeia. 2016. USP 39 <1207> Sterile Product Packaging–Integrity Evaluation. Rockville, MD: U. S. Pharmacopoeial Convention.

4. Brueckner, D. et al. 2016. "Comparison of Tunable Diode Laser Absorption Spectroscopy and Isothermal Micro-calorimetry for Non-invasive Detection of Microbial Growth in Media Fills." *Scientific Reports, Vol.* 6. Nature Publishing Group.

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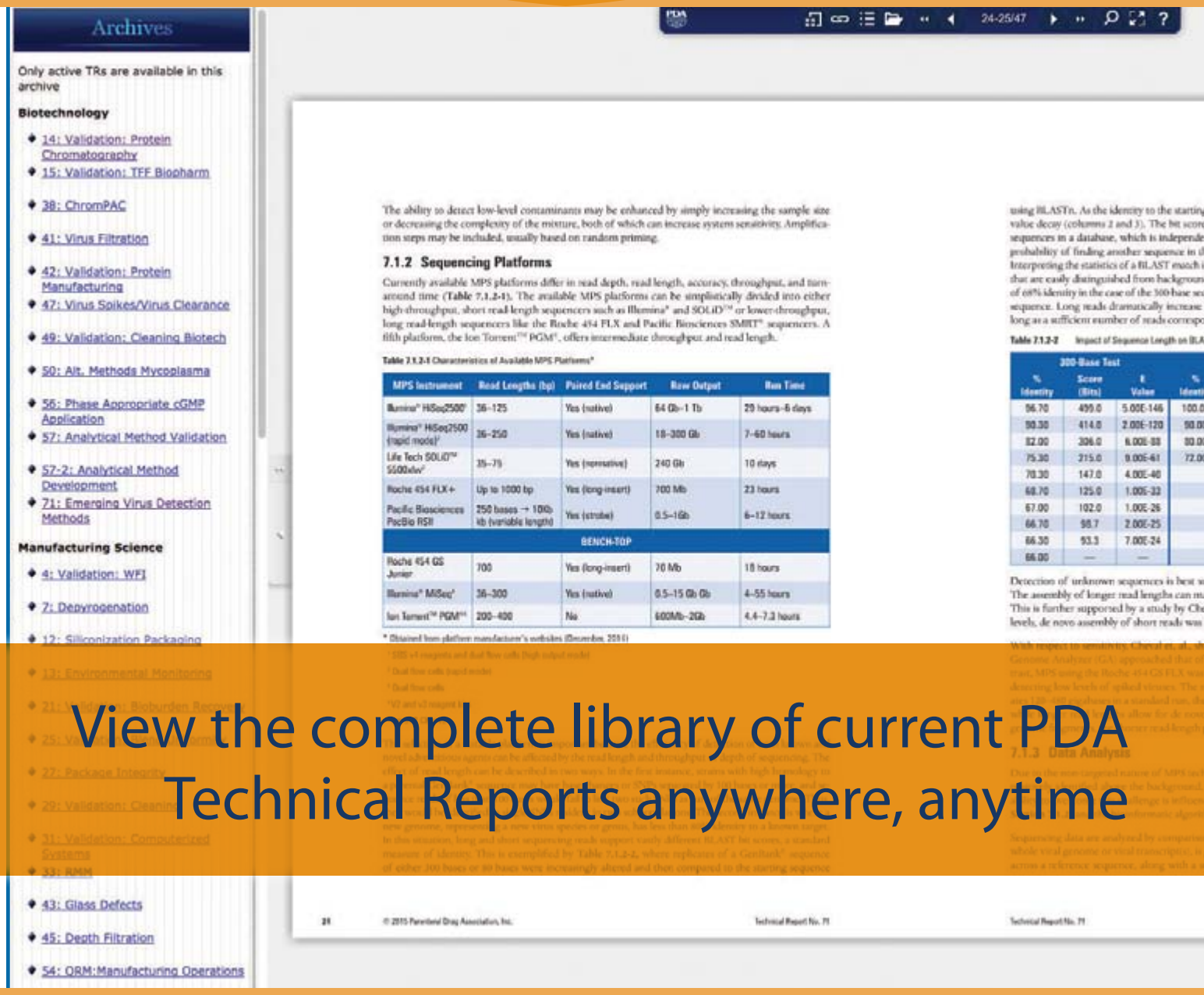

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CMC Strategy
A Critical Foundation for Biosimilars

John Geigert, PhD, BioPharmaceutical Quality Solutions

Biosimilars have finally arrived in the U.S. market with the recent U.S. FDA approvals of four biosimilars—a recombinant protein, a recombinant fusion protein and two monoclonal antibodies. This comes on top of more than a decade of European experience with biosimilars. While both EMA and FDA have been transparent about their review of biosimilars, the FDA deserves much credit for publishing extensive comparative product data covering CMC physicochemical properties and functional activity in the briefing packets that were initially provided to the members of its Advisory Committees, and then made publicly available on the Advisory Committees' websites ***(1).***

> **One can only hope that such sophisticated characterization methods can be developed for the next wave of new biologic products**

CMC is the first, and most crucial, step in ultimately establishing biosimilarity to an innovator's marketed product. Close collaboration among the CMC team members—spanning the development, manufacturing, and Quality Control groups—is a necessity. By using Quality by Design (QbD) principles, a biosimilar manufacturer can establish a CMC strategy that minimizes differences between the biosimilar and the innovator's product. This requires the biosimilar developer to collect numerous batches of the innovator's drug product over many years (e.g., Amgen collected 18 lots of EU-approved Humira and 24 lots of US-licensed Humira over a period of five years to compare against their biosimilar version, Amjevita). Physicochemical and functional activity analysis of these innovator batches defines the Quality Target Product Profile (QTPP) for manufacturing the biosimilar. The development group then matches the innovator's manufacturing process as much as possible, such as the choice of cell line, use of the same formulation excipients, etc. This group also applies target-directed reverse engineering to critical process parameters (CPPs) in an attempt to match the critical quality attributes (CQAs) of the innovator's expressed product, especially the molecular variant profile and glycosylation pattern.

Article at a Glance

- A strong CMC strategy for a biosimilar requires close collaboration
- Characterization methods are used to confirm the "CMC fingerprint"
- Interchangeability remains a holy grail for biosimilar developers

Table 1 Extensive CMC Comparative Testing for a Biosimilar

Some Comparative Physicochemical and Functional Activity Testing		
Quality Attribute	**Recombinant Fusion Protein (etanercept)** **Innovator:** Amgen (Enbrel) **Biosimilar:** Sandoz (Erelzi)	**Monoclonal Antibody (TNF blocker)** **Innovator:** Abbvie (Humira) **Biosimilar:** Amgen (Amjevita)
Primary Structure	• Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection (reduced) • Amino acid analysis • Intact molecular mass (MALDI-TOF-MS) • Mass analysis of peptides (EIS-MS) • Peptide mapping coupled with tandem mass spectrometry (MS/MS) • Disulfide bridging (nonreducing peptide mapping) and free cysteines	• Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection (reduced and nonreduced) • Amino acid analysis • Intact molecular mass (LC-MS) • Reduced and deglycosylated molecular mass (LC-MS)
Higher Order Structure	• Far and near UV circular dichroism • FT-Infrared • Differential scanning calorimetry • Hydrogen/deuterium exchange • 1D-NMR • X-ray crystallography	• Near UV circular dichroism • FT-Infrared • LC-MS (disulfide bond characterization) • Differential scanning calorimetry
Molecular Variants	• Size Exclusion Chromatography (SEC) with UV and light scattering detection (MALLS) • Field flow fractionation with MALLS • Analytical ultracentrifugation (AUC) sedimentation velocity • Capillary electrophoresis SDS • Capillary zone electrophoresis (CZE) • 2-D Differential gel electrophoresis • Reversed phase (RP) HPLC • N-linked glycan mapping by peptide mapping linked to ESI-MS • N-linked glycan analysis by normal phase (NP) HPLC multidimensional detection • O-linked glycan analysis by MALDI-TOF • Sialic acid analysis by HPLC • Glycation by boronate affinity chromatography	• Size Exclusion Chromatography (SEC) with UV and light scattering detection (LSD) • Field flow fractionation • Analytical ultracentrifugation (AUC) sedimentation velocity • Capillary electrophoresis SDS (reduced and nonreduced) • Capillary IEF (cIEF) • Cation Exchange (CEX) HPLC • Glycan mapping • Micro flow imaging
Functional (Therapeutic) Biological Activity	• Apoptosis inhibition bioassay • TNF-α and TNF-β neutralization reporter gene assays • Surface plasmon resonance • Binding and binding affinity assays for Fc • Binding assay for C1q • ADCC bioassay • CDC bioassay	• Apoptosis inhibition bioassay • ELISA binding assay • Cell-based and Fc binding assays • ADCC bioassay • CDC bioassay • Inhibition of induced IL-8 bioassay • Specificity against LTα bioassay • Inhibition of induced cell death, induced chemokines, T-cell proliferation bioassays • Induction of regulatory macrophages

Source: FDA briefing documents to Advisory Committees

Table 2 Minor CMC Differences in FDA Market-Approved Biosimilars

Biopharmaceutical	Minor Differences That Were Not Clinically Meaningful
Recombinant Fusion Protein (etanercept) **Innovator:** Amgen (Enbrel) **Biosimilar:** Sandoz (Erelzi)	"Some tests indicate that subtle shifts in glycosylation (afucosylation and high mannose) exist and are likely an intrinsic property of the GP2015 product due to the manufacturing process."
Monoclonal Antibody (TNF blocker) **Innovator:** Janssen (Remicade) **Biosimilar:** Celltrion (Inflectra)	"Some tests indicate that subtle shifts in glycosylation (a-fucosylation) and FcγRIII binding exist and are likely an intrinsic property of the CT-P13 product due to the biological production system."
Monoclonal Antibody (TNF blocker) **Innovator:** Abbvie (Humira) **Biosimilar:** Amgen (Amjevita)	"Some tests indicate that slight changes in quality attributes are observed, including glycosylation pattern and charge variant profile."

Source: FDA briefing documents to Advisory Committees

Next, the biosimilar manufacturer must extensively compare the innovator and biosimilar product batches in side-by-side assessments as much as possible. The sheer number of sophisticated physicochemical and functional activity characterization methods to confirm the high similarity "CMC fingerprint" for a biosimilar can seem overwhelming (**Table 1**), but it is the availability of these extensive analytical and biological test methods that have opened up the possibility for biosimilars of recombinant proteins and monoclonal antibodies. One can only hope that such sophisticated characterization methods can be developed for the next wave of new biologic products—gene therapies, genetically engineered virus products, and genetically engineered cell-based medicines.

From a CMC perspective, the comparative data for the expressed and purified biosimilar product do not have to be equivalent to the innovator's product. Instead, the goal is to be highly similar. Interestingly, no regulatory guidance defines the term "highly similar," but regulators clearly state that the term does allow for product differences as long as they are not clinically meaningful. **Table 2** shows that biosimilars have minor CMC differences.

No biosimilar has achieved the interchangeability label yet. Interchangeability means the biosimilar not only must meet the standard of being highly similar to the innovator's biologic, but also must demonstrate that it can be expected to produce the same clinical result as the innovator's biologic in any given patient. Furthermore, if the biosimilar is administered more than once to an individual, the risk in terms of safety, or diminished efficacy, due to alternating between the use of the biosimilar and the innovator's biologic, is no greater than the risk of using the innovator's biologic without the switch. Clearly this puts enormous pressure on the clinical comparability study design, but it might also put more pressure on the interpretation of the CMC comparative study, especially if minor differences are observed. FDA has promised to publish a guidance to clarify their expectations on this matter.

The number of companies pursuing biosimilars and the number of different biosimilars under clinical study continues to increase. Over 180 clinical trials are currently listed on the U.S. National Institutes of Health clinical trials website ***(2).*** According to FDA statements, there are over 60 biosimilar products for 20 reference products currently in development in the United States alone. Only with a comprehensive, effective, solid CMC foundation will these biosimilars have an opportunity to make it into the marketplace.

References

1. "Advisory Committees." *U.S. FDA*. www.fda.gov/AdvisoryCommittees/default.htm (accessed Nov. 17, 2016).

2. ClinicalTrials.gov. *U.S. National Institutes of Health*. https://clinicaltrials.gov/ (accessed Nov. 17, 2016).

About the Author

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IG Corner continued from page 21

the Agency really does want the industry to improve.

While speed-daters may not have found a "perfect match" in their dates, all in all, the discussions during the exercise showed that interest group members remain committed to finding solutions to the issues affecting manufacturing facilities.

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Challenges for Biosimilar Sponsors

Proving Comparability of Products Affected by Manufacturing Change

Michael VanDerWerf, Teva

Once a biosimilar sponsor has successfully presented their product to regulators and it has been approved as similar enough to the innovator product to enjoy the same labeling, how should that sponsor approach supporting post-approval manufacturing changes? Is the sponsor obligated to demonstrate biosimilarity to the innovator's reference product again? Or does the approved biosimilar undertake its own lifecycle, only needing to prove comparability to itself?

Before exploring this question, it is important to recall the extent of complexity and variability that exists in biologics manufacturing. Biologics are produced by living cells; thus, they are sensitive to culture and process conditions which leads to variability in the posttranslational structure of the proteins. Even with a well-controlled process, it is virtually impossible—even for an innovator—to show that the product is identical from one lot to the next. Due to their complexity, biologics cannot be fully defined and characterized by any one analytical method; their structure is deduced using a combination of multiple assays. Manufacturers propose and justify a set of process parameters and specifications that regulators agree characterizes critical quality attributes (CQAs). Lot-to-lot variability is allowed as long as the process stays under control and the product meets its specifications. Appreciating the variability of biologics manufacturing is fundamental to understanding the concepts of establishing biosimilarity and demonstrating comparability following a manufacturing change. Unlike small molecule products, where the generic must be "identical" to the innovator drug, biosimilar regulations allow the new entry to be similar enough. Any differences observed must be shown not to impact efficacy and safety.

It is useful to conceptualize establishing biosimilarity as an extreme version of the comparability exercise used by sponsors when they propose to make a change in the manufacturing process. Allowing manufacturers of complex biologics the capability to make changes to improve a process was first discussed in the 1996 U.S. FDA document, *Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Product.* As analytical capabilities evolved to better characterize biological molecules and more regulatory agencies gained experience in post-marketing changes for biologics, guidance documents by other regulatory agencies were provided and, eventually, a 2005 ICH consensus guidance was released, namely Q5E: *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.* In the same year, Q9: *Quality Risk Management* was released. Both these guidelines provide the framework for demonstrating comparability.

Comparable not Identical

Demonstrating comparability is not the same as demonstrating equivalence or identity. Biologics can be up to 1000 times larger in molecular weight and far more structurally complex than small molecule drugs and can tolerate slight modifications in their primary, secondary, tertiary, and even quaternary structures without impacting the molecule's potency, purity, or safety. There is a hierarchy to the data included in comparability assessments, namely: **1)** Quality (structural and characterization considerations on the structure-function); **2)** Nonclinical, i.e., effects on animal-model pharmacokinetics (PK), pharmacodynamics (PD), and toxicology; and **3)** Clinical (human PK and PD, safety and efficacy). All three aspects of comparability must be guided by a comprehensive risk assessment that considers the scope of the change and its potential impact, the history and experience with the existing product, knowledge of the analytical methods' limitations to detecting significant differences, and the safety database of the existing product. Often manufacturer, employ additional testing (e.g., further characterization, in-process testing) or nonclinical and/or clinical studies to demonstrate the quality of the product is comparable before and after the change.

If analytical testing demonstrates minimal to no impact on the structure-function of the biologic, and differences can be justified, nonclinical and clinical work is not required. Regulatory guidance (e.g., FDA's 2016 guidance, *Comparability Protocols for Human Drugs and Biologics*) suggests the sponsor define the comparability exercise in a protocol with the acceptance criteria specified in the protocol. It is wise to share this protocol with regulators to get their buy-in on the proposed studies and acceptance criteria. The risk assessment and communication with regulatory authorities will be the guide as to what is required to make a scientifically justifiable case to assure continued safety, efficacy, and stability.

Biosimilarity Requires Knowledge

Establishing biosimilarity involves the same fundamental aspects as showing comparability—comparative analytical, nonclinical, and clinical results—but the biosimilarity exercise is performed without the development history, without process knowledge, and often without a full understanding of the structure-function relationship of the innovator product. The typical first step involves analyzing the physiochemical and biological characteristics of the innovator product and learning as much as possible from publicly available documents (e.g., package inserts, Summary Basis of Approval documents, journal articles). This gathered knowledge defines the Quality Target Product Profile (QTPP), a summary of the quality characteristics of the innovator drug that ideally will be achieved to ensure the desired quality, safety, and efficacy. The QTPP is the target, and the sponsor must continue to refine it by assessing the variability from lot to lot and, over time, gauging the variability of the product using lots sourced in different markets.

Without knowing the development history of the reference product, the knowledge gap makes defining CQAs in the biosimilar process challenging. The biosimilar sponsor is obligated to perform a careful evaluation and risk ranking of all foreseeable consequences for the product, including the cell expression system, material attributes, and process parameters. This risk ranking, plus experiment design, allows developers to focus on what is important and defend the process ranges and their final product specifications. To weigh the criteria, FDA guidance recommends a three-tiered approach for risk ranking: **1)** equivalence testing for some high-risk attributes; **2)** quality ranges (mean ± x SD)

for other high-to-low risk attributes; and **3)** raw or graphical comparisons for other attributes. The ranges determined should be aligned with the risks and not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise justified. Only after this extensive analytical effort to understand the innovator's product, and an extensive program to define the proper materials and develop a process control strategy that delivers a product that mimics the innovator's, can the biosimilar sponsor begin to build their own manufacturing history and process knowledge. Once the product is on the market, the sponsor can then build a database of safety and an understanding of potential adverse events tied with their production history. With that history, they can build a baseline for establishing their own comparability before and after any given change.

Conclusion

Demonstrating comparability is possible when a firm has extensive process and product knowledge and can leverage that knowledge when assessing the impact of a change and any differences seen. Regulatory guidance allows the informed manufacturer to use this knowledge to assess any risks to safety and efficacy.

> **"Demonstrating comparability is not the same as demonstrating equivalence or identity"**

Establishing biosimilarity is a much more extensive endeavor where the sponsor must build fundamental molecular and functional knowledge and cannot always predict the nonclinical and clinical impacts of attributes of the biosimilar versus the innovator's drug product. Until sufficient product and process knowledge is developed, a biosimilar manufacturer cannot adequately assess the potential impact of a specific change. After approval, however, when the biosimilar sponsor is routinely manufacturing the biosimilar, learning about the variability of its own process, and accumulating its own pharmacovigilance history, they are in a position to reasonably perform a risk-based comparison of product quality before and after a proposed change in their own process without needing to repeat the biosimilarity exercise.

About the Author

Michael VanDerWerf is Director of CMC Regulatory Affairs at Teva. He has over 25 years of experience in regulatory affairs, quality assurance, operations, and research.

Notes from the First PDA Biosimilar Conference

Stephan Krause, PhD, AstraZeneca Biologics, and Emanuela Lacana, PhD, CDER, FDA

The development of biosimilar products is complex, and regulatory approval remains challenging. In response to the industry's need for current and reliable information on this rapidly growing area of pharmaceutical manufacturing, PDA offered the *2016 PDA Biosimilars Conference* last June. Cosponsored with the Product Quality Research Institute (PQRI), the conference drew a sizable crowd of attendees interested in advancing their knowledge of biosimilar development.

The opening plenary offered a peek into the U.S. FDA's expectations for biosimilar sponsors. **Steven Kozlowski,** MD, Supervisory Medical Officer, CDER, explained that a sponsor's goal should be to show biosimilarity without rehashing the innovator product's safety/efficacy studies. A biosimilar product should be highly similar to the innovator product with no clinically meaningful difference. Kozlowski expressed that sponsors must extensively compare pharmacokinetics (PK) and pharmacodynamics (PD), if appropriate, as this comparison offers a better analysis than the clinical endpoint study. The type and nature of the comparative clinical studies is typically discussed with the Agency during development.

In addition to review teams, Therapeutic Biologics and Biosimilars staff within the Office of Biotechnology Products oversees policy and ensures consistency. High level policy decisions are made by the Biosimilars Review Committee, a multidisciplinary group comprised of senior quality personnel, medical officers, pharmacologists, toxicologists, and statisticians.

The final FDA guidance regarding the demonstration of biosimilarity was published in April 2015, following three years of evaluating submissions. Upcoming guidances will address topics such as interchangeability, statistical approaches and labeling. As of June 2016, over 60 biosimilar submissions (based on 19 innovator products) were under FDA review.

While Kozlowski offered an FDA perspective on biosimilars, **Christopher Holloway,** PhD, Group Director, ERA Consulting, provided a European view. The first European biosimilar—Sandoz's Omnitrope—was approved in 2006. He recommended that sponsors considering a biosimilar application in Europe view the European Public Assessment Report (EPAR) for existing biosimilar products and review the data and assessment information used by EMA. In recent years, there has been a tendency within the European Union to see how far a sponsor can deviate from the paradigm and still receive approval. Holloway noted that this approach has only been applied to "simple" biosimilars, and is unlikely to continue with more complex biosimilar products. He also stressed that a sponsor

cannot extrapolate beyond the approved therapeutic range of the reference product.

EMA's Committee for Medicinal Products for Human Use (CHMP) makes recommendations regarding biosimilar applications; the Committee's recommendation can be reached by consensus or majority voting. The latter raises the question of how prescribers would react in the event that some of the top regulatory reviewers/experts do not recommend approval of a biosimilar approved by majority vote.

CDER's **Thomas Gwise,** PhD, Deputy Director, Division of Biometrics, and **Yi Tsong,** PhD, Deputy Director, Division of Biometrics, joined Kozlowski and Holloway for a panel discussion. The panelists addressed the lessons learned for both FDA and EU regulators and the advice industry can draw from these lessons. Kozlowski recommends biosimilar developers characterize the reference product as much as possible during development and provide plenty of data to FDA. In Holloway's opinion, the EU regulatory system—in terms of organizational structure—is not as centralized as the U.S. regulatory system. This has resulted in inconsistent advice and regulatory actions for sponsors of biosimilar products. Gwise reiterated that when working with FDA, the focus should be on analytical similarity instead of clinical studies. The goal of the biosimilar program is not to reestablish safety/efficacy but to demonstrate biosimilarity. Tsong emphasized that FDA has a more stringent three-tiered statistical approach for evaluating analytical similarity data. Statistical evaluation might be more challenging for some attributes, and Tsong encouraged the audience to wait for further guidance.

QTPP and Analytical Similarity The following session explored how to establish a Quality Target Product Profile (QTPP) for a biosimilar. **Margaret Karow,** PhD, Executive Director Process Development, Amgen, covered the application of risk ranking for similarity in the QTPP. According to Karow, QTPP ranges are influenced by risk ranking. She said that stability-indicating quality attributes may require a different approach to analytical similarity testing—one that requires collecting several years of data to estimate the rate of change between the biosimilar and reference product. An age correction may lead to enhanced evaluation of similarity. Global filing has proved challenging, Karow admitted, emphasizing that this type of work is new for Amgen.

> **"Upcoming guidances will address topics such as interchangeability, statistical approaches and labeling"**

Corinna Sonderegger, PhD, Head Pharmaceutical Development, Sandoz Biopharmaceuticals, looked at the QTPP for Zarxio, the first FDA-approved biosimilar in the United States. In her view, QTPP is a development target and serves as the basis for Sandoz's final analytical similarity studies. During this process, the criticality score does not change unless knowledge changes. Sonderegger uses an approach similar to failure mode and effects analysis (FMEA) to obtain the final risk scores. These risk scores may then impact analytical similarity testing of the biosimilar product.

Analytical similarity served as the focus of the next two sessions. **Marjorie Shapiro,** PhD, Biologist, Laboratory Chief, CDER, provided the FDA perspective on demonstrating analytical similarity. When high analytical similarity exists and there are similar PK/PD data, the risk of observing clinical difference is significantly lower, she explained. Methods validation, she recommended, should be started earlier in the process. Some posttranslational modifications are not important to safety or efficacy. For example, differences in N-terminal pyroglutamic acid and c-terminal lysine may not impact function or in vivo behavior. Noncovalent aggregates and/or overall charge differences, however, could impact PK. Shapiro also said that criticality risk ranking should be the same for the reference product and the biosimilar. She noted that sponsors sometimes hope the Agency does not notice certain differences, such as poor clone selection.

For an industry perspective on analytical similarity, **Alan Herman,** PhD, Chief Scientific Officer, Coherus Biosciences, discussed his experiences. His talk emphasized the different development processes required for a biosimilar compared to a reference product. It is imperative that a biosimilar sponsor understand the intellectual property/patents involved. Herman clarified that a biosimilar sponsor could generate its own intellectual property. Hydrogen deuterium exchange (HDX) can be a good method for analyzing 2-D and 3-D dimensional similarity as it evaluates the surface of the protein and the interaction of exposed residues with the aqueous environment, thereby providing information on structural similarity.

Jose Gomes, Senior Principal Scientist, Culture Process Development, Pfizer, illustrated the importance of using a proper expression system, host cell lines, cell line engineering and process engineering tools. Further, media additives should be studied for their impact on post-translational modifications. Appropriate addition of media additive would help generate a biosimilar product with structural characteristics highly similar to the reference product. **Harry Yang,** PhD, Senior Director, Biostatistics Group, MedImmune, then discussed statistical approaches to determining analytical similarity. By conducting additional testing, sponsors can reduce residual uncertainty.

Day 2 Talks Cover PAC, Controls
The first plenary of Day 2 covered post-approval change (PAC) management for biosimilars. **Mark McCamish,** MD, PhD, Global Head, Biopharmaceutical and Oncology Injectables Development,

Sandoz, discussed the clinical relevance of product attributes through PAC. In fact, he questioned whether clinical data is necessary. As far as PAC, he pointed to ICH Q5E: *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process,* which is used for manufacturing changes like any other approved product. He emphasized the power of ICH Q5E, noting that a PAC to Genzyme's Myozyme failed ICH Q5E comparability as it was determined the post-change product was too different from the prechange product, necessitating a separate BLA. Sponsors should also consider using the language of "essentially the same" instead of "highly similar" when communicating to clinicians. This same language can be used for biosimilarity and comparability. McCamish emphasized that while statistics are important, clinical relevance also needs to be considered.

Christopher Holloway provided additional PAC insights. He offered a hypothetical case study of a biosimilar held back in the European Union due to a major change, pointing out that the European Union does not like to deal with major changes just prior to market approval. Rather, sponsors should gain approval and submit variations if they intend to make manufacturing changes to a biosimilar product manufacturing process. In general, both industry and European regulators do not want additional analytical similarity studies following approval of a biosimilar. For biosimilars (as well as all biologics), any type of change is a type II variation. Holloway then used Sandoz's Zarxio as an example of PAC, pointing out that only PAC to the label were published, not the underlying details.

After this session, three panelists, including an FDA representative, explored control strategies for biosimilars. **Laurie Graham,** PhD, Acting Director, Division of Internal Policies and Programs, Office of Policy for Pharmaceutical Quality, OPQ, CDER, emphasized that a clinically relevant control strategy should be the goal and should link quality to patient outcomes. **Lisa Carlson,** Director, Regulatory Affairs, Amgen, then discussed how the control strategy for a biosimilar is more front-loaded and compressed compared to the reference product. Clone selection, small-scale modeling, and earlier analytical development are some factors that are absolutely critical for successful biosimilar development. A relatively large number of batches of the biosimilar product may be needed for the analytical similarity studies, and it might be larger than what is needed to meet clinical demand. **Shashi Prajapati,** PhD, Principal Scientist, High-Throughput Analytical Group, Biogen, then described Biogen's control strategy for biosimilars. At this time, the company has ten innovator products and two marketed biosimilars in Europe. Her group has achieved a 90% – 120% potency range in their biosimilars through purification/column adjustments.

In the next session, **Maria-Teresa Gutierrez Lugo,** PhD, Chemist, CDER, provided an agency perspective on setting product specifications. She said that the control strategy for a biosimilar should follow the recommendations outlined in the ICH Q8–11 guidelines. The Agency also does not recommend using the Tier 1–3 statistical classifications, which is restricted to analytical similarity, to set specification. Instead, the selection of critical quality attributes should be based on ICH Q6B: *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.* For high-risk CQA, the acceptance criteria should also consider the results from analysis of the reference product. The second speaker, **Emily Shacter,** PhD, Consultant, ThinkFDA, added that a difference in results for a biosimilar product's quality attribute evaluated with a Tier 2 statistical method should be justified through understanding of the clinical relevance of the attribute. Even so, some similarity criteria have to be met, and additional data and explanation would be insufficient. In some cases, reengineering is the only option. Shacter also stressed the importance of front-loading method development to obtaining robust analytical similarity data.

In the final session, **Stephan Krause,** PhD, Director, QA Technologies, AstraZeneca Biologicals, and co-chair of the conference, covered two topics: reducing analytical lifecycle steps and method qualification/transfer/validation considerations for biosimilars. More stringent performance expectations ideally exist for analytical method validation (for Tier 1 and 2 methods). When the analytical variation is very high relative to product variability, the Tier 1 pass rate remains relatively high for both small and large product mean differences and true product differences can be obscured.

Corinna Sonderegger then covered Sandoz's algorithm for clone selection. This algorithm factors in criticality, productivity, safety, etc. She explained that a strict Quality by Design target approach is needed to ensure successful development of a biosimilar.

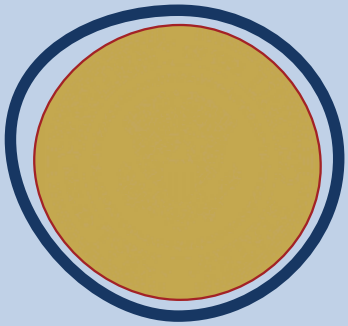
The conference served as a deliverable of PDA's biosimilars initiative which rose out of PDA's 2020 Strategic Plan. A group of PDA volunteers with expertise in biosimilars was established in 2015. A follow-up conference will be held June 26–27, 2017 in Bethesda, Md.

About the Authors

Stephan Krause, PhD, is AstraZeneca's Director of QA Technology. He manages the global biologics control strategy steering committee. He is also the co-leader of PDA's Biosimilar Initiative and a member of the BioAB and Education Advisory Board (EAB).

Emanuela Lacana, PhD, is currently the Associate Director for Biosimilars and Biologics Policy in the Office of Biotechnology Products in CDER. Prior to her appointment at the FDA, she worked at Georgetown University and at NIH.

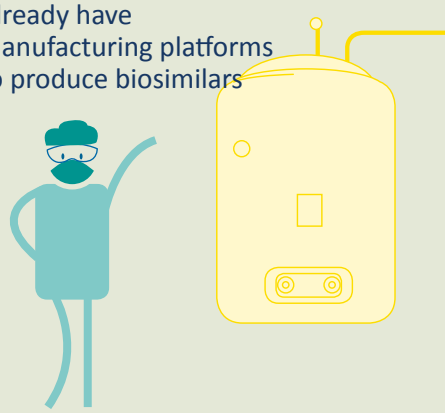
Biosimilars: A New Market for Biologics Firms



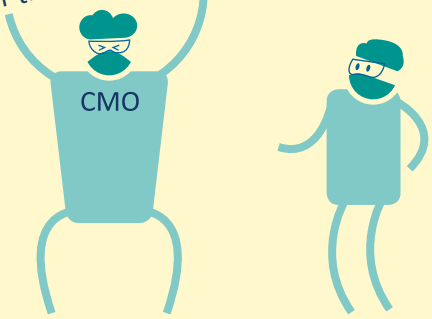
In 2010, the Patient Protection and Affordable Care Act went into effect. This law created a pathway for biosimilars in the United States. Now, innovator biologics manufacturers are testing the biosimilar waters. Some are even developing biosimilars of their own products.

Why are biologics companies looking at biosimilars?

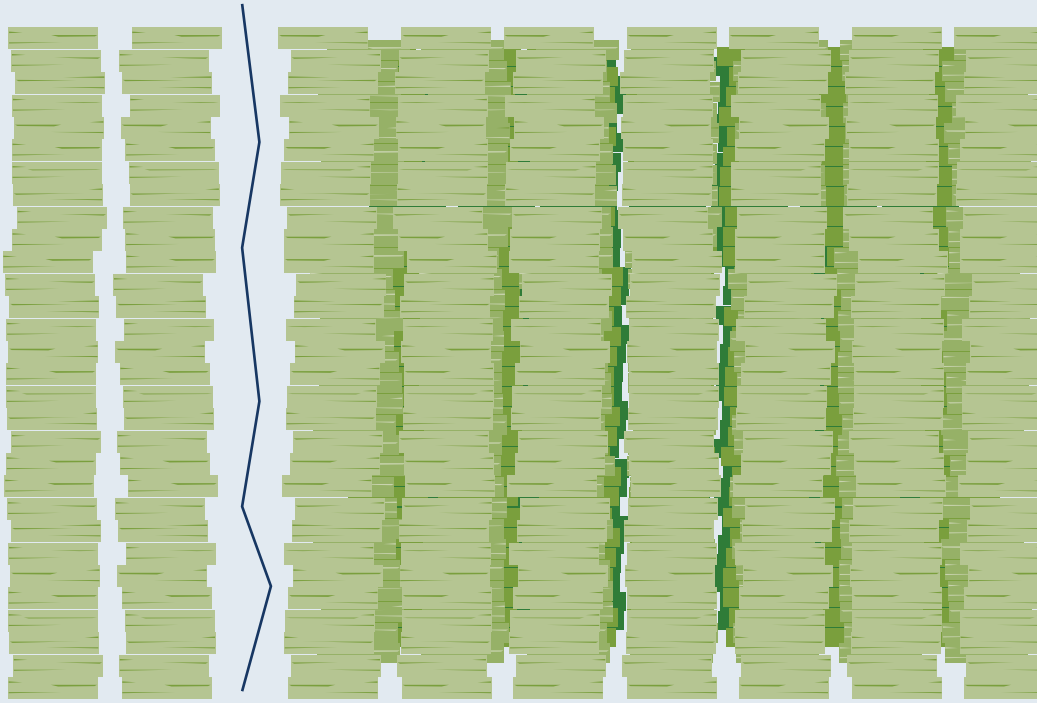
Already have manufacturing platforms to produce biosimilars



Can partner with a CMO for the "heavy lifting"



Cheaper to Develop

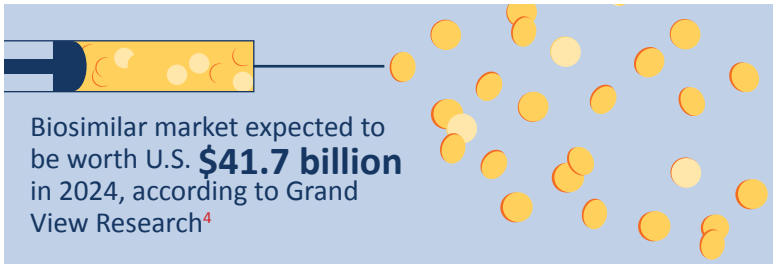


$200 million for a biosimilar[1]

$1.2 billion for an innovative product[2]

Who does this benefit?

RAND study suggests biosimilars could save the U.S. healthcare system **$44 billion** for the next decade[3]



Biosimilar market expected to be worth U.S. **$41.7 billion** in 2024, according to Grand View Research[4]

Sources

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/
2. DiMasi, J.A. and Grabowski, H.G. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" Managerial and Decision Economics 28 (2007): 469–479.
3. http://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf
4. https://www.grandviewresearch.com/press-release/global-biosimilars-market

PDA Chapters

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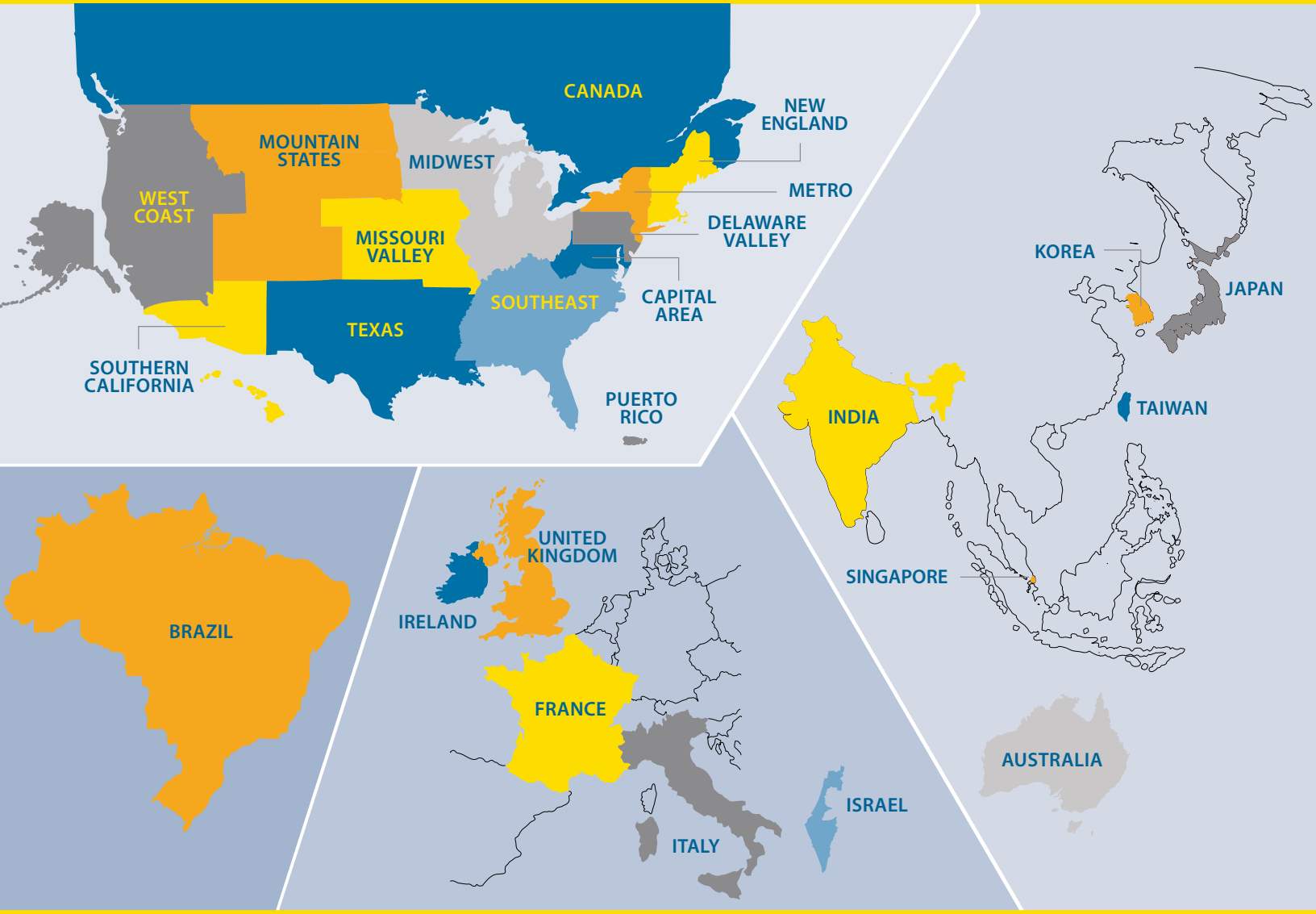

Are you curious about the issues unique to your region?

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

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

Aseptic Processing

2017 SCHEDULE

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

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

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

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

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

FOR MORE INFORMATION CONTACT:

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SNAPShot

Volunteer Manpower Leads to Growth in Reg Commenting

Denyse Baker, PDA

More than 100 PDA volunteers spent nearly 675 hours developing responses summarizing PDA's positions on a variety of draft regulations in 2016. In some cases, small teams of three to five experts came together to respond quickly to a pertinent guidance document with only a 30- or 45-day comment window. In other cases, a task force of 16 or 17 members worked for several months to reach consensus on the finer points of a regulation that warranted a thorough response from PDA. In every response, the comments focused on the important scientific/technical concerns posed by the proposed regulation, notably impact on patient protection and product quality.

As shown in **Figure 1**, PDA responded to comments from multiple regulatory agencies around the world, primarily to documents published by the U.S. FDA, EMA, the UK MHRA, and WHO. PDA is open to responding to documents from other regulatory agencies provided they fall under the Association's specialized areas of aseptic processing, validation, manufacturing, biotechnology, GMP/compliance, supply chain, and quality systems, among others.

Each regulatory agency has a different process and timeline for collecting comments. Sufficient lead time for comments is one of PDA's criteria for determining whether or not to comment as the Association relies on volunteers with appropriate expertise. These volunteers must then be available during the commenting period. PDA's internal balloting procedures for regulatory comments make it difficult to respond to regulatory proposals with commenting windows less than 60 days.

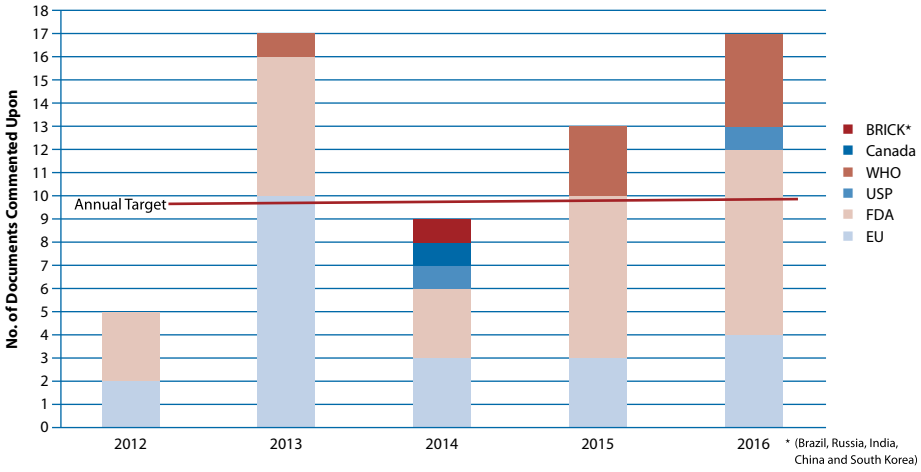

Figure 1 PDA Regulatory Commenting Activity

One of the important principles of PDA comments is to facilitate a common understanding and approach. Commenting task forces usually cite existing standards and technical guidance, encouraging the regulatory body in question to use these within the document. When applicable, the comments reference scientific principles right out of PDA's technical reports. At a recent PDA workshop in Dublin, both FDA and EMA investigators stated their support for referencing PDA technical reports in responses to regulatory documents. PDA comments are also valued by regulators. At times, PDA has been invited directly by authors from individual regulatory agencies to comment on draft guidelines. One agency even asked PDA to submit additional detailed responses on specific issues following the submission period.

The Regulatory and Quality Advisory Board (RAQAB) also tries to determine the impact PDA's official comments have on the final regulatory guidance documents. Although it could be several months, or even years, between the open comment period and publication of a final guideline, PDA retains a record of the Association's comments on each specific document. Task force members then compare the draft and final versions of the regulatory document to evaluate how many of PDA's comments were incorporated into the final version. From these observations, RAQAB has ascertained that about 50% of PDA's comments are accepted on average. Still, results for individual regulatory agency documents vary.

Once a task force has completed its draft, the responses are balloted by one of the three PDA Advisory Boards—Regulatory and Quality Advisory Board (RAQAB), Science Advisory Board (SAB) Biotechnology Advisory Board (BioAB)—with RAQAB balloting the majority. In 2016, RAQAB balloted 13 of the 16 commenting ballots. Following resolution of any Advisory Board questions, the responses proceed to the Board of Directors for ballot. Only after this final step can the document be considered the official position of the Association. Through this process, PDA ensures the highest level of technical content in each response and also consistency with PDA's values and mission.

PDA commenting task forces are open to any member with an interest and expertise in the topic of the draft publication. Requests for volunteers are sent out to the Advisory Boards and frequently posted to PDA Connect℠ in the most relevant interest group forum.

Overall, the commenting process is one way for all members to participate in the PDA mission of advancing manufacturing and regulatory science and support the PDA values of science, integrity and inclusion.

Formalizing a Risk Assessment for Excipients

Frithjof Holtz, Merck KGaA, Darmstadt, Germany

Excipients serve a critical role in the production of final dosage forms for drug products and biologics. They facilitate the manufacturing process (e.g., anticaking agents) and protect, support, and enhance stability. They may also improve bioavailability. In addition, excipients help maintain the safety, or function, of the product during storage and use.

No longer characterized as inert accompaniments to an active pharmaceutical ingredient (API), excipients are the target of an intensified push for more stringent quality management, placing new requirements on both suppliers and users. Regulating excipient quality, however, is no small task. The global market is expected to exceed $5 billion by 2020—with a growth rate of 6.0% from 2014 to 2020 ***(1).*** Thousands of different excipients are available, and only a small percentage of them are manufactured solely for pharmaceutical use.

For many years, there have been clearly defined GMP requirements for APIs, including EU GMP Part II, 21 CFR Part 11 and ICH Q7: *Good Manufacturing Practice for Active Pharmaceutical Ingredients.* But, until recently, well-defined and stringent GMP requirements for excipients did not exist.

A Focus on Quality

The pharmaceutical industry is increasingly using risk management principles to better protect patients; this renewed focus on safety now includes excipients. At the same time, regulatory authorities have called for more secure supply lines and clearly defined quality measures for excipients.

In 2011, the EU's Falsified Medicines Directive established that manufacturing authorization holders must use a formalized risk assessment to ascertain the appropriate GMPs for ensuring excipient suitability ***(2).*** As part of this risk assessment, manufacturers need to consider both the source and intended use of the excipients in question. The Directive went on to state that the European Commission planned to adopt guidelines for adopting appropriate GMPs for excipients. After robust discussion, guidelines for the risk management process and direction on the appropriate level of GMP for excipients were published in March 2015.

These guidelines apply not only for medicinal products produced in Europe but also for products produced outside Europe intended for the European market. Regulators now expect importers to provide risk assessments and related documents.

As of March 21, 2016, excipient users/drug product manufacturers in the EU were legally mandated to implement GMP requirements, including completed risk assessments for each excipient used. ➤

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Keep in mind, that while regulations regarding GMP for APIs clearly define what is needed for compliance, risk assessment guidelines for excipients are just that—guidelines that offer tools and a framework for determining appropriate GMPs. This leaves the full responsibility of defining what GMPs apply as "necessary" for the excipients of a specific drug product in the hands of the marketing authorization holder.

Other countries are also developing formal requirements for excipient GMPs. The U.S. FDA assesses and permits use of excipients as part of a New Drug Application. Under U.S. law, a new pharmaceutical excipient, unlike an active drug, has no regulatory status unless it can be qualified through one or more of the approval mechanisms available for components used in finished drug dosage forms.

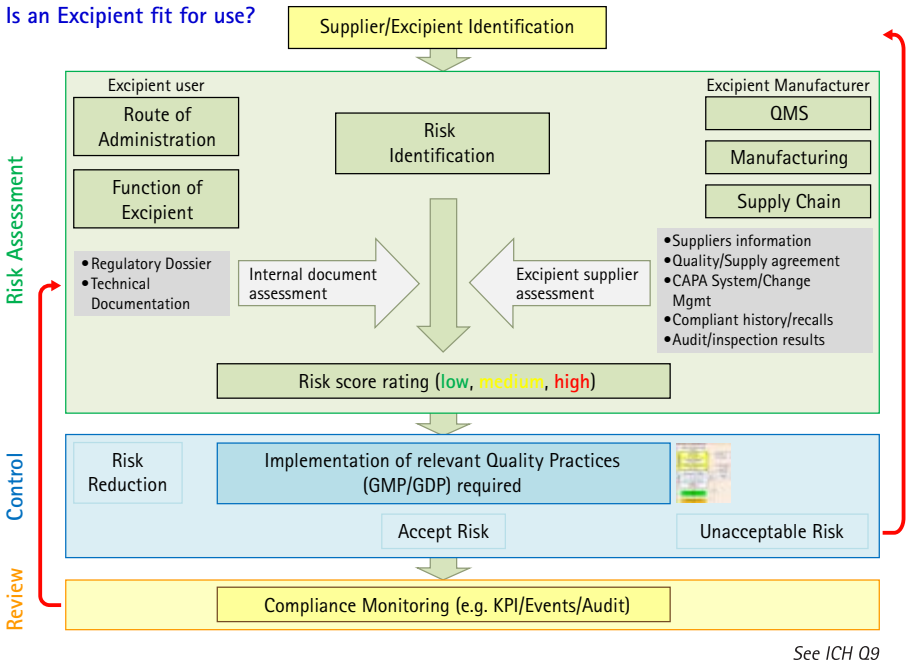


Figure 1 Excipient risk assessment process

* P. Rafidison, F. Holtz, S. Rönninger, A Practical Approach of Implementing GMP for Excipients, Pharm. Tech., September, 2014, 26-36 *(4)*

In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law, expanding the Agency's authority and strengthening its ability to safeguard and advance public health through a number of activities, including enhancing the safety of the drug supply chain. FDASIA includes a set of provisions, contained in Title VII of the statute, which give FDA new authorities to address the challenges posed by drug supply chains that are becoming increasingly global ***(3).*** One of these new authorities requires manufacturers to include, as part of a drug listing, the name, address, and unique facility identifiers of associated excipient manufacturers.

In 2013, the FDA initiated the Secure Supply Chain Pilot Program to strengthen controls on imports of drug products. The goal was to focus the Agency's import surveillance resources on preventing the entry of high-risk drugs that are most likely to compromise the quality and safety of the U.S. drug supply. The pilot program, which concluded in February 2016, enabled FDA to evaluate its effectiveness at enhancing imported drug compliance with FDA regulations and the security of the drug supply chain.

Implementing the Risk Assessment

ICH Q9: *Quality Risk Management* offers guidance for risk assessments through two principles:

- Outlining of risks should be based on scientific knowledge and should be linked to protection of the patient
- The level of effort, formality, and documentation of the quality risk management process (QRM) should be commensurate with the level of risk presented by the excipient

Excipient risk is assessed based on the harm posed by microbiological, chemical (toxicological, pathological effect) or physical (choking, irritation) hazards. Risk varies based on the route of administration of the drug product (oral, inhaled, injected) and the function of the excipient. An excipient used as a filler, e.g., a binder or colorant, might pose a lower risk than one used as a stabilizer or as a vehicle for controlled release, as the latter might affect bioavailability. The GMP requirements and control strategies for an excipient used as a filler in an oral application, however, would be completely different from one used for controlled release of a drug substance in a biologic.

A number of approaches for quality risk assessment and guidance are available. **Figure 1** presents a risk assessment model developed by the International Pharmaceutical Excipients Council (IPEC Europe) and the Pharmaceutical Quality Group (PQG), supported by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The model combines the approach of ICH Q9 with the specific requirements of the EU Risk Assessment Guideline and highlights the need for the excipient user and manufacturer to work closely together in the assessment process. An excipient manufacturer conducting a similar risk assessment would need to work in close partnership with the user to understand the function the excipient is expected to serve, as well as the route of administration.

Defining Appropriate GMPs

The good news is that manufacturers and users of excipients do not need to develop their own GMPs. A number of well-established, accepted and voluntary industry standards exist that can be followed. These include:

- IPEC-PQG GMP Guide, 2006
- USP General Chapter <1078>
- EXCiPACT™
- NSF/IPEC/ANSI-363-2014

In many cases, applying these standards is likely to be sufficient for most excipients.

But a small number of excipients could potentially pose hazards to patients. These may require application of more thorough controls than those recommended in the voluntary standards. For example, an excipient used in a parenteral might come under guidelines on the manufacture of sterile medicinal products as provided in Volume 4 of EudraLex, the rules governing medicinal products in the European Union ***(5).***

A Positive Outlook

A greater appreciation of the role excipients play in the safety and clinical performance of drugs has focused attention on the risk they can also pose to patients, which defines the need for robust excipient GMPs. Increased attention to supply chains and more robust communication between excipient suppliers and drug manufacturers are essential to ensuring patient safety. Drug manufacturers should expect their suppliers to provide dossiers accompanying each excipient with information supporting the drug manufacturer's risk assessment. This might be data on the manufacture, testing, supply chain and applied quality system or information showing alignment with regulatory guidelines.

The risk assessment and quality risk management principles widely used in the pharmaceutical and biotechnology industries are now being adopted for excipients. The European risk assessment guideline is one that both suppliers and users can apply in order to determine the appropriate level of GMPs, increase the assurance of supply chain integrity and provide better protections for patients.

References

1. "Excipients Market Analysis By Polymers (MCC, HPMC, CMC, Ethyl Cellulose, Povidone), Alcohols (Glycerine, Sorbitol, Mannitol, Propylene Glycol), Minerals (Clay, Silicon Dioxide, Titanium Dioxide), Sugars And Segment Forecasts To 2020." Grand View Research. September 2015. http://www.grandviewresearch.com/industry-analysis/excipients-market-analysis (accessed Dec. 6, 2016).

2. "Directive 2011/62/EU." *Official Journal of the European Union* 54 (2011): 74-87.

3. "FDASIA Title VII Overview." U.S. Food and Drug Administration. Sept. 15, 2015. http://www.fda.gov/regulatoryinformation/legislation/significantamendmentstothefdcact/fdasia/ucm366058.htm#703 (accessed Nov. 16, 2016).

4. Rafidison, P., Holtz, F., and Rönninger, S. "A Practical Approach of Implementing GMP for Excipients," *Pharmaceutical Technology* 38 (2014): 26–36.

5. "Annex 1: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use." European Commission. Nov. 25, 2008. http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf (accessed Nov. 16, 2016).

*Special thanks to: **Patricia Rafidison,** Dow Corning, and **Stephan Rönninger,** Amgen (Europe) GmbH

About the Author

Frithjof Holtz is a biologist who has worked for the life science business of Merck KGaA, Darmstadt, Germany, for 25 years, more than ten years of which have been spent in quality assurance and regulatory affairs.

PDA Plans for an Exciting 2017

Martin VanTrieste

I am proud and honored to serve as Chair of the PDA Board of Directors. I am excited both for what has been accomplished in 2016 and our plans for 2017.

The future of PDA depends on a diverse Board of Directors, which includes all disciplines and stakeholders from our industry. The Board wants, and recommends, that our members nominate and elect leaders with backgrounds in manufacturing, the supply chain, and key supplies to the Board.

What each of us accomplishes every day is extremely important, hard, and noble. Our work enhances the lives of millions of patients globally. Serving patients is a privilege—and this privilege comes with significant responsibilities. PDA is a weapon to assist you in fulfilling these responsibilities.

Last year, we published PDA's Strategic Plan, four technical reports, three surveys, and several other publications. We also led the industry by taking your feedback on recent regulatory developments to draft formal responses to several global regulatory documents. We also hosted interesting conferences that provided valuable information to enhance your ability to excel in your professional careers.

2017 plans to be a busy year with more technical publications and great events, including the *2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference* in February, training on Track and Trace in Barcelona in March, the *2017 PDA Annual Meeting* in April, the *2017 PDA/FDA Joint Regulatory Conference* in September, etc. I strongly recommend that you attend one of these events to gain and share knowledge, solve your work-related challenges, network with colleagues from around the world, and even have some fun.

I want to focus now on three important initiatives that will be ongoing in 2017, **1)** Quality Metrics; **2)** Post-Approval Change: Innovation for Availability of Medicines (PAC iAM); and **3)** Eliminating Visible Particles from Parenteral Medicines.

Quality Metrics

PDA supports U.S. FDA CDER Director **Dr. Janet Woodcock's** vision of "a maximally efficient, agile, flexible, pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight." In that light, PDA has worked with regulators and its members to reduce drug shortages, culminating with the publication of *Technical Report No. 68: Risk-Based Approach for Prevention and Management of Drug Shortages.* PDA has also supported FDA's efforts to develop quality metrics by hosting three conferences on the topic, conducting surveys, publishing articles, presenting at an FDA open meeting in 2015, and commenting on the various draft FDA guidance documents.

I am very excited to announce that PDA will host its 4th *Pharmaceutical Quality Metrics and Quality Culture Conference* with input from the FDA February 21–22, in Bethesda, Md. The timing of this conference is perfect in light of the recent release of the Agency's revised draft guidance, *Submission of Quality Metrics Data*.

Post-Approval Change: Innovation for Availability of Medicines

The objective of this program is to address the complexity of post-approval change (PAC) management in order to reduce the time to implement PACs from years to months. This is critical for ensuring uninterrupted operations, driving innovation, and promoting continual improvement in order to ensure reliable availability of products to patients across the globe.

In August 2016, PDA issued a Call to Action* to accelerate awareness of the current challenges of PACs. PDA is activating dialog on a broader scale through various conferences, workshops, and industry/regulatory forums (including ICH, International Federation of Pharmaceutical Manufacturers, WHO, etc.). PDA is also driving application of science and risk-based approaches to streamline PAC management processes and enable international regulatory convergence and mutual reliance to reduce global regulatory filing burdens and expedite PACs. Two valuable PDA Points to Consider papers are scheduled for early 2017 (technical product lifecycle management and leveraging an effective pharmaceutical quality system for faster PAC implementation).

You also have an opportunity to participate in a survey to collect data on industry experiences with PACs. This survey will also cover the consequences regional regulatory differences have on cycle times for PACs and supply chain complexity.

All this activity will culminate into a PDA technical report on Post-Approval Change Management Protocols (PACMPs) and a library of examples. These protocols will provide practical implementation guidance on ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* concepts that companies can leverage.

Watch **Anders Vinther** and **Emma Ramnarine,** the PAC iAM co-chairs, share their thoughts on this topic at www.pda.org/pda-letter-portal/multimedia/videos.

Eliminating Visible Particles from Parenteral Medicines

We have all read the number of FDA 483 citations, Warning Letters, and far too many recalls related to visible particles in parenterals, some of which have led to drug shortages. I am proud to announce that PDA has embarked on a unique effort with the aspiration to eliminate visible particulate in parenteral products!

What makes this effort unique is that PDA brought together a group of senior operations leaders from most of the top 20 global pharmaceutical and biopharmaceutical companies, such as EVPs of Operations, along with CEOs from many of the major suppliers of parenteral containers and closures, for a one-day summit to understand: **1)** the nature and scope of the issues; **2)** regulators' viewpoints; and **3)** what, if anything, could be done scientifically to address the issues.

The meeting was extremely productive, leading to a shared reality among participants and desire to accelerate continuous improvement of container/closure systems using sound scientific principles so that we can better serve patients.

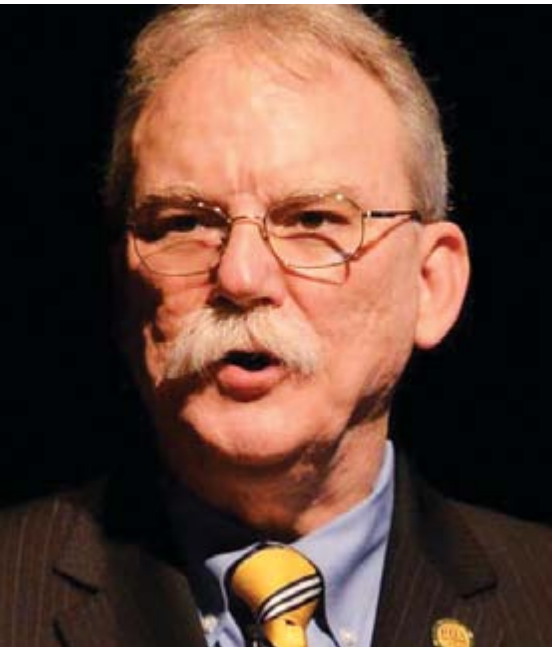
With executive support from suppliers, pharmaceutical and biopharmaceutical companies, PDA has created a task force lead by both **Jennifer Johns** at Pfizer and **Paolo Golfetto** from the Stevanato Group. The task force will aggressively work to discover best practices, collect and analyze existing data, develop common approaches, and eventually publicize its findings in various publications, including a series of technical reports.

Summary

PDA is uniquely positioned to connect people, science, and regulation® to influence industry and regulatory solutions for quality metrics, PACs, and elimination of visible particles. So, I encourage you to join your colleagues from around the world to help PDA enhance the quality and reliability of medicines so we all can live up to our responsibilities to serve patients!

*Access the "Call to Action" online at: www.pda.org/pdaletter.

Volunteers: A Message of Thanks



Richard Johnson, PDA President

As 2017 begins, the PDA staff and I have been reflecting on all we have accomplished in 2016. What is clear to each of us is that we could not have achieved the success we did without the important contributions of our volunteers.

I want to take this opportunity to thank our volunteers for giving their time, energy, and expertise to PDA, and for balancing their volunteer activities with so many other personal and career commitments. We sincerely appreciate their dedication and the impact they have made as volunteers.

Through the efforts of our corps of 2,500 active volunteers, we have delivered a wide range of exceptional technical and educational resources to the industry, including conferences, training courses, technical reports, and other publications. With their help, we have built a global network of more than 10,000 strong, and mentored the next generation of pharmaceutical industry professionals, ensuring a lasting commitment to quality manufacturing. And, together, we have helped companies keep up to date and comply with regulatory expectations, all in support of our goal to ensure patients have access to the quality medicines they need.

We recognize the countless hours our volunteers have spent on committees and task forces, collaborating with colleagues around the world to advance PDA's important mission. To all of our volunteers, thank you! Our achievements would not have been possible without you.

I encourage all of our volunteers to take the opportunity to tell us about their experiences volunteering for PDA. Email us with your feedback at volunteer@pda.org.

In this new year, I am confident that our volunteers will continue to play an integral role in maintaining PDA's position as an industry leader. And, we will continue to value and appreciate all of their contributions!

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Next Steps: Using Quality Metrics to Advance Quality Culture

The U.S. FDA recently released its revised Quality Metrics draft guidance. The *2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference* provides the *first opportunity* to hear directly from the FDA about the changes to and implications of the revised guidance as the collection and use of metrics to enhance pharmaceutical product quality moves from theory to practice.

Industry and regulatory experts will take an in-depth look at the new guidance, the benefits to industry and patients and potential challenges to implementation across various segments of the pharmaceutical industry. Key topics to be addressed include:

- FDA Update on the Reissued Quality Metrics Draft Guideline
- Analytical Approaches
- Implementation Approaches
- Quality Culture and What We Are Learning as an Industry
- What Moves the Needle for Maturing Quality Culture?
- Assessing Quality Systems and Quality Culture

Don't miss out on this unique opportunity to join the conversation on the latest developments in quality metrics and quality culture!

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