People • Science • Regulation

PDA Letter

Volume LI • Issue 1 www.pda.org/pdaletter January 2015

Strategies for Controlling Raw Materials in Biologics Manufacturing

22

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PIC/S

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PDA Letter

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Cover

Cover Art Illustrated by Katja Yount

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Voices of PDA

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Features

2015 Board of Directors

PDA is pleased to announce the results of the 2015 Board of Directors election.

Directors

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

Deborah M. Autor, Senior Vice President, Strategic Global Quality and Regulatory Policy at Mylan, is excited to "help PDA continue to be a leading organization for manufacturing science, quality, and innovation, as well as an important bridge between industry and regulators worldwide."

Masahiro Akimoto, General Manager, Compliance Division, Toray Industries, looks forward to continuing "to encourage the use and sharing of PDA knowledge among membership by coordinating or facilitating interactive communication."

Emma Ramnarine, Global Head, Biologics QC Network, Genentech/Roche, plans to help "drive PDA's strategy from the board level and further strengthen PDA's collaboration with FDA, EMA, PIC/S and other health authorities."

Ursula Busse, PhD, Head GxP Regulations Coordination, Group Quality External Relations, Novartis, will "work to strengthen PDA's presence in Europe and other regions of the world."

Outgoing Directors

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

John Finkbohner, PhD, Senior Regulatory Policy Director, AstraZeneca

Junko Sasaki, Quality Principal, Investigational Drug Quality, Dainippon Sumitomo Pharma

Christopher Smalley, PhD, Director, BioSterile Validation, Merck

Save up to $100 when you register for this workshop and the *2015 PDA Annual Meeting!*

When we talk about an aging facility, we are, in most cases, talking about not only the facility but also the manufacturing processes and analytics used in producing the drug substance or drug product. How does one approach the task of modernizing an aging facility, taking into account the complex financial, technical, regulatory, and supply chain impacts?

The *2015 PDA Aging Facilities Workshop* will use an interactive format to explore the need for continuous improvement, what happens when continuous improvement is not performed, risk management of new technology implementation and modernization planning.

Learning will be fostered through expert presentations and breakout sessions where attendees will work together to learn from each other, understand and develop concepts and approaches for modernization and identify current challenges that slow improvement efforts.

Learn from past experiences and hear recommendations from industry experts such as:

- **Phil DeSantis,** Principal Consultant, *DeSantis Consulting Associates*
- **Craig W. Johnson,** Vice President, Global Engineering, *Hospira, Inc.*
- **Susan Schniepp,** Vice President, Quality and Regulatory Affairs, *Allergy Laboratories, Inc.*
- **George Skillin,** Senior Director, Global Technology Services, *Pfizer, Inc.*
- **Glenn Wright,** Senior Director, Project Management, Manufacturing Science and Technology, *Eli Lilly & Company*
- Many more!

Update your outlook (and processes) by attending this workshop!

Visit **www.pda.org/aging-facilities2015** for more information and to register.

The Parenteral Drug Association presents the...

2015 PDA Aging Facilities Workshop

March 18-19, 2015
Red Rock Casino Resort and Spa, Las Vegas, NV

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PDA Volunteer Spotlight

Tony Cundell, PhD

- Consultant
- *Microbiological Consulting*
- Member Since | **1985**
- Current City | **Scarsdale, New York**
- Originally From | **Christchurch, New Zealand**

Reach out to collaborate with colleagues working on as many technical challenges as possible

Mathematics was the only subject Tony failed at university

Where do you see yourself in five years? How about the industry?

After a 30-year career in the pharmaceutical industry, I am actively working as a consulting microbiologist while maintaining my involvement as a PDA volunteer and member of the USP Microbiology Committee of Experts. It surprises me when colleagues, friends and relatives ask how I am enjoying retirement. My wife asks "what retirement!?"

As for our industry, I am impressed by the transition in the R&D pipeline from small molecules to biological products, and felt privileged to contribute in a minor way to the success of the antitumor drug Anti-PD-1 for which Merck recieved accelerated FDA approval, especially since I personally have experienced melanoma. As for the future, I predict more personalized medicine based on cell-derived products.

What piece of advice has been most helpful throughout your career?

When I was in high school, my dad and I brewed beer in the garage which may have spurred my interest in microbiology. He presented me a beer mug with the engraving, "The world owes you a living but you must work hard to earn it"—obviously, good advice.

Why did you decide to volunteer for PDA?

At a Microbiology Interest Group meeting I was asked if I would lead a PDA task force to write a technical report on the validation of alternative microbiological test methods. This resulted in PDA Technical Report No. 33 in 2000.

Of your PDA volunteer experiences, which have you enjoyed the most?

Working on the early organizing committees that established the annual PDA pharmaceutical microbiology conference; this is now the go-to conference for microbiologists in our industry. More recently, working with my co-chair, **Anil Sawant**, and other volunteers on the objectionable microorganism technical report was rewarding.

Tell us something surprising about you

My passion is history, especially the history of science. I am writing a biography of **William Hallock Park**. He made the first diphtheria antitoxin in America in 1894.

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chapter update

Chapter Tours FDA Lab, Addresses QRM and Rapid Methods

Jeff Hargroves, ProPharma Group

The PDA Missouri Valley Chapter held its Fall Meeting in St. Louis, Mo. on Sept. 22. The meeting began with a tour of the U.S. FDA's Division of Pharmaceutical Analysis laboratory in St. Louis. This laboratory moved into new facilities within the past year, and this group was the first to receive a full tour. **Cindy Buhse** hosted the tour which consisted of laboratories equipped for chromatography, mass spectroscopy, particle size determination and assessment, UV spectroscopy, and dissolution, along with a variety of both research and compliance-related analytical applications.

Following the tour, **Eldon Henson** provided an overview on the practical application of risk management to pharmaceutical manufacturing. He outlined the contents of PDA Technical Report No. 54 , and provided a number of uses of quality risk management (QRM) approaches for both retrospective (e.g., quality and compliance events that have already occurred,) and prospective (e.g., potential concerns) issues.

John Albright then provided a presentation on Technical Report No. 33. Albright stated that FDA has been very open to the approval of rapid microbiological methods, though key elements of cGMPs, such as assessment for the specific application, validation, training, etc., must be included in the conversion process.

After Albright's presentation, a panel discussion on rapid methods convened that included Albright, along with **Erin Patton, Dave Mason** and **Julie Sperry**. This panel addressed a significant number of questions from the 75 or so members in attendance.

PDA Who's Who

Cindy Buhse, Director, Division of Pharmaceutical Analysis, FDA

Eldon Henson, Director, Operations Technical Services, Mallinckrodt Pharmaceuticals

John Albright, BioMerieux

Erin Patton, Account Specialist, Endotoxin and Microbial Detection, Charles River Laboratories

Dave Mason, Lonza

Julie Sperry, Chief Commercial Officer, Rapid Micro Biosystems

New England Chapter Learns About Supply Chain Risks, Solutions

Myron Dittmer, Jr., MFD & Associates

The New England Chapter held its first meeting of the fall in Burlington, Mass. with 80 members in attendance to hear speakers discussing topics related to supply chain risks. Chapter President **Roland Bizanek** welcomed members and guests and also thanked the 11 vendor meeting sponsors since their participation helps make meetings possible.

Peter Norton, whose talk was titled, "Cold Chain Risk Aversion Planning" began the meeting. In his presentation, Norton introduced two new regulations: an EU regulation and a Chinese guidance. **[Editor's Note:** See Peter Norton's article on these two regulations on p. 28 of the June 2014 issue.**]** Both of these regulations make recommendations for improving the control and management of the supply chain. He also broke down supply chain risks into five basic areas: internal, network, industrial, environmental and compliance.

The second speaker was **Adam Green,** whose talk covered temperature-sensitive supply chain solutions. He provided the audience with information on the many packaging options one may choose to ship temperature-sensitive products. If cooling is required, it can be a passive system (using coolers or ice) or an active system (refrigeration system). Green also described the many different types of insulation materials which can be used depending on their costs. He noted the following factors one needs to consider before selecting these materials: payload size, temperature sensitivity based on stability data, duration of shipping, available budget, and other variables such as seasonable vs. universal, ambient temperature profile, and product load variability.

For information about upcoming New England Chapter events, please visit www.pda.org/chapters/north-america/new-england.

PDA Who's Who

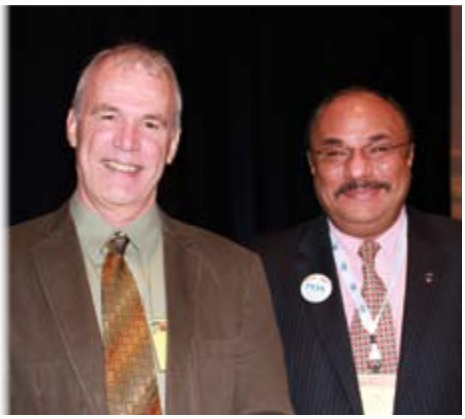
Roland Bizanek, PhD, President, Compass Pharma Consulting

Peter Norton, Business Development Director, DeltaTrak

Adam Green, Strategic Account Engineer, Cold Chain Technologies

PDA 9th Annual Global Conference on Pharmaceutical Microbiology

Sessions



Opening Keynote

(l-r) Jan Vinjé, PhD, CDC; Osama (Sam) Elrashidy

B1: Parametric Release

(l-r) Kim Sobien, BD Rx; Michael Sadowski, Baxter; Marla Stevens-Riley, PhD, U.S. FDA; Jeffrey Weber, Pfizer

A1: Biofilms and Bioburden Control

(l-r) Shane Manning, GSK; Chris Knutsen, PhD, Bristol-Myers Squibb; Kalavati Suvarna, PhD, U.S. FDA; Igor Gorsky, ConcordiaValSource; Matthew Kennedy, GSK

B2: Objectionable Microorganisms in Non-Sterile Pharmaceutical Drugs

(l-r) Julie Barlasov, Perritt; Barry Friedman, PhD, Friedman Consultant; Thuy Bui, Pfizer; Anil Sawant, PhD, J&J

P2: Urban Myths

(l-r) Richard Levy, PhD, PDA; John Metcalfe, PhD, U.S. FDA; Dona Reber, Pfizer

A2: Developing Sterilization Technologies

(l-r) Fatima Hasanain, Nordion; Edward Tidswell, PhD, Baxter; Jason Mantei, PhD, Baxter; John Logar, J&J

P3: LAL Recognition

(l-r) Jack Levin, MD, University of California School of Medicine, San Francisco; Kalavati Suvarna, PhD, U.S. FDA; Osama "Sam" Elrashidy

A3: Endotoxin Testing

(l-r) John Dubczak, Charles River; Cheryl Platco, Merck; Patricia Hughes, U.S. FDA; Masakazu Tsuchiya, PhD, Charles River

A4: Innovative Technologies: Microbiology Testing Technologies

(l-r) Peter Noverini, Azbil Biovigilant; Ed Balkovic, PhD, Genzyme; Yongqiang Zhang, PhD, Becton Dickinson Diagnostic; Tony Cundell, PhD, Consulting Microbiologist

B4: Risk Assessments

(l-r) Amy McDaniel, PhD, Pfizer; Sean Toler, Baxter; Marsha Hardiman, ConcordiaValSource; Ruth Daniels, PhD, Genzyme

Program Planning Committee Committee

(front row l-r) Renee Blosser, U.S. FDA; Kim Sobien, BD Rx; Kalavati Suvarna, PhD, U.S. FDA; Anna McLernon, PhD, J&J; Amy McDaniel, Pfizer

(back row l-r)Leon Lewis, PDA; Osama "Sam" Elrashidy; Cheryl Platco, Merck; Edward Tidswell, PhD, Baxter; Marsha Hardiman, ConcordiaValSource; Marla Stevens-Riley, PhD, U.S. FDA; Julie Barlasov, Perritt; John Metcalfe, PhD, U.S. FDA; Ed Balkovic, PhD, Genzyme

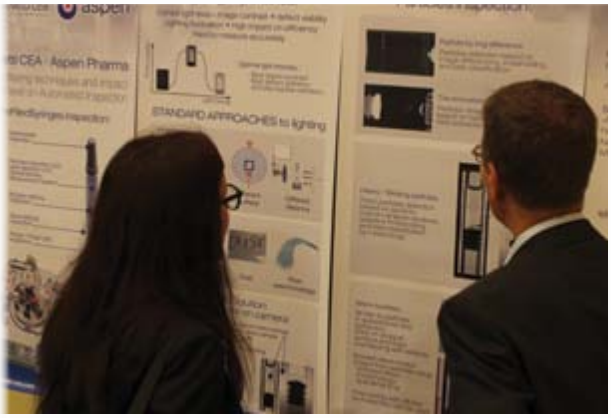
2014 Universe of Prefilled Syringes and Injection Devices

Sessions

B1: Trends and Challenges in Formulation & Development
(l-r) Christina Braden-Moore, BD Medical; Carolin Rether, PhD, Vetter; Prashant Varma, GlaxoSmithKline

A3: Quality Aspects in Injectable Delivery Systems
Diane Paskiet, West

Poster Presentations



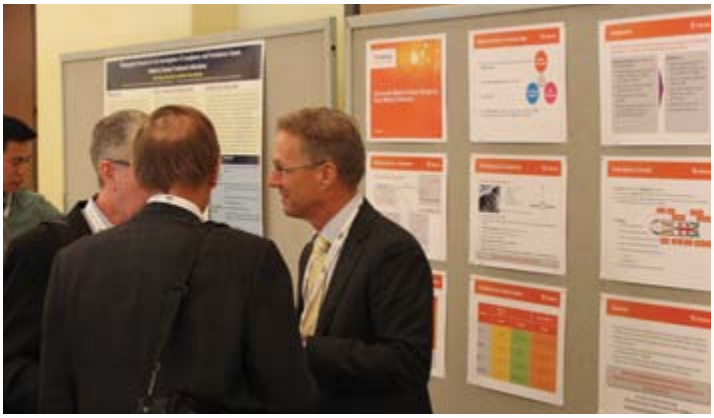


Exhibit Hall

PDA California Fun Run/Walk

PDA's fun run/ walk raised $4,500 to support the CSP Huntington Beach Youth Shelter.

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Networking for the Nervous

Michael Birchmore, MSB Networking

In my work as a professional networker I am privileged to meet a wide range of people. Most are quite happy with their networking performance but some are not. They view it as a fate worse than death. To some, this is a very real social anxiety issue to which several "phobias" are accredited. For one, there is *agoraphobia* which is fear of crowded public places. Another has three terms: *enochlophobia, demophobia* or *ochlophobia* which is fear of crowds or mobs. One other is *xenophobia* which is a fear of strangers. Of course, these relate to very extreme conditions whereas the majority is just nervous at the thought of going into a room full of strangers.

Nowadays, networking is widely regarded as a regular business activity. Although there is some evidence of business networking groups going back as far as the 1950s, we tend to think of the first real groups being started around 1985 with the birth of BNI—Business Networking International. Now networking has become an industry in itself. Most members are from smaller firms, but at events run by such organizations as Chambers of Commerce people from the larger companies do get involved.

Size, however, is really not important. I have met just as many nervous networkers from large corporations as I have from sole traders.

I hope this will help prepare you and equip you so that your networking event, whether it is for a first time or not, will be as profitable for you as it can be.

As the heading suggests, the first action you can take is all about meeting preparation.

Forewarned is forearmed. Since there are now a great abundance of different groups, you can afford to be quite choosy about which one you go to. There are groups that meet for breakfast, lunch or dinner. Groups involved with activities such as golf or walking. A general view that is widely held is that it isn't what you know but who you know that matters. Although it has also been suggested that it isn't who you know that matters but who knows you. When you go to a meeting for the first time, this becomes moderately irrelevant since you are not likely to be giving free access to your contact list to people you've only just met.

When preparing for an event take a look at their Web page, if they have one, and see if there is a members list you can look at. If there is, see if there is anyone who you already know. If so, you could perhaps ask them about the group. How do they operate? What sort of meeting agenda do they have? Costs? And so on. This way, when you go you will have a rough idea of what is expected of you.

If there is someone you know who is a member, perhaps you could arrange to meet them before and arrive together. Friends and allies like this can be a great asset at such events as they can guide you and introduce you to others saving you the task of having to break the ice which can be one of the most daunting aspects. If you have previously looked at the group's website and they have a Members page, you can do some preparation research on them so that when you do get there you will know something about them which you can talk about.

Some of the basic facts I would always suggest people research before going include:

- **Location—** be sure you know how to get where you need to get to
- **Time and date—** arriving late can be embarrassing for some
- **Cost—** some meetings are free but most aren't
- **Agenda—** this can be included on the website
- **Membership requirements—** some organizations are quite relaxed but some, such as BNI for example, are known for having stringent rules and regulations about what is required from the members. Being your first meeting, these are not likely to be important but still worth knowing.
- **What sort of people already go**
- **Things you need to take**

So having done your research, off you go.

About the Author

Michael Birchmore is a professional networker with over 20 years' experience. His company is MSB Networking Ltd. (www.msbnetworking.co.uk).

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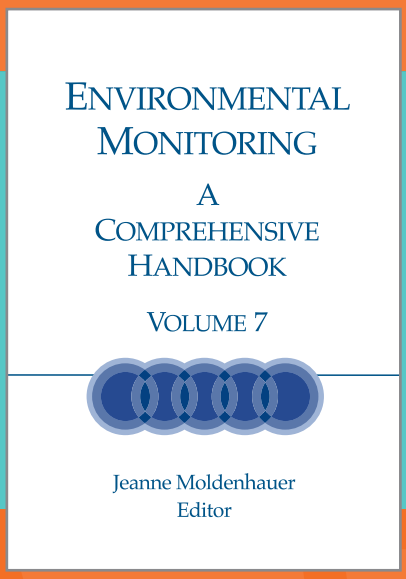

Environmental Monitoring: A Comprehensive Handbook, Volume 7

EDITED BY: JEANNE MOLDENHAUER

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ABOUT THE AUTHOR

JEANNE MOLDENHAUER, VP at Excellent Pharma Consulting, has close to 30 years of experience overseeing the development and management of sterilization and validation processes in the pharmaceutical industry. She is a Scientific Advisory Board member and chairs the Environmental Monitoring/Microbiology Interest Group at Parenteral Drug Association (PDA). Jeanne has published a number of publications, the most recent of them include: Recent Warning Letters Review for Preparation of a Non-Sterile Processing Inspection, Volume 2; Recent Warning Letters Review for Preparation of an Aseptic Processing Inspection; The Editor of Steam Sterilization: A Practitioner`s Guide; Laboratory Validation: A Practitioner`s Guide; Systems Based Inspections for Pharmaceutical Manufacturers and Thermal Validation in Moist Heat Sterilization. As a two time winner, 2010 and 2005, of the PDA/DHI Distinguished Editor/Author Award Jeanne's words of advice to the industry should be taken to heart.

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snapshot Report From 2014 Parenterals Conference

PUPSIT Task Force Continues to Push for Revised Q&A

Rebecca Stauffer, PDA

PDA's PUPSIT (post-sterilization/pre-use integrity testing) task force recommends that the 2007 EMA Q&A on the topic be replaced to allow for an option to use a risk-based approach, according to task force leader **Hemisha Ly,** Associate Director, Merck, who provided an update at the *Parenterals* conference in November in Germany.

In addition, she maintains that "the decision on whether or not to perform the PUPS [post-sterilization/pre-use] integrity testing should be made by the filter user upon a thorough documented risk-based analysis in accordance with the current ICH guidelines."

Thus, the official position of PDA and the task force is that since the risk of performing a PUPS test depends upon the application and design of the process, it should not be mandatory and instead be left to the discretion of the filter user.

The task force was formed in 2011 following a meeting between PDA and the EMA after drug manufacturers reached out to PDA for clarification. The task force then drafted a position paper eventually published in the September/October 2012 issue of the PDA Journal. The group has also led discussions at a PIC/S workshop in Geneva and at the PDA/IMB joint conference in Dublin.

Also at the *Parenterals* meeting, support for clarifying the current post-sterlization/pre-use integrity testing requirements to allow for risk-based approach was further strengthened when, during a session on the Annex 1 revision delivered by a British regulator, post-sterilization/pre-use integrity testing was identified as a topic for the revision to Annex 1 discussion.

Ly said the task force continues to work with EMA on replacing the 2007 Q&A and has also offered to train inspectors as well.

About the Expert

Hemisha Ly joined Merck & Co in 2001 and has since held various positions in Operations, Technology and Quality. She has more than ten years of sterile pharmaceutical experience.

Journal *Preview*

January–February Issue Includes Proceedings from *2013 Viral Clearance Symposium*

This issue of the *PDA Journal of Pharmaceutical Science and Technology* also includes conference proceedings from the *2013 Viral Clearance Symposium* in addition to regular content. Due to the size, we are including only the titles of the articles.

Review

"Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: A Literature Review"

Research

"Extractables Analysis of Single-Use Flexible Plastic Biocontainers"

"Manufacturing of High-Concentration Monoclonal Antibody Formulations via Spray Drying—the Road to Manufacturing Scale"

Case Studies

"Non-Destructive Vacuum Decay Method for Pre-Filled Syringe Closure Integrity Testing Compared with Dye Ingress Testing and High-Voltage Leak Detection"

Conference Proceeding

"Viral Clearance of Traditional Unit Operations: Virus-Retentive Filtration"

"Viral Clearance Using Traditional, Well-Understood Unit Operations: Session 1.2. Anion Exchange Chromatography; and Session 1.3. Protein A Chromatography"

"Viral Inactivation: Low pH and Detergent"

"Session 1.5: Other Viral Clearance and Inactivation Approaches (MMC, Membrane Chromatography, Chemical Precipitation)"

Technology/Application

"Implementation of a High-Throughput Ion Chromatographic Assay To Assess Glass Degradation in Drug Product Formulations"

"Scale-up of Sterilizing-grade Membrane Filters from Discs to Pleated Cartridges: Effects of Operating Parameters and Solution Properties"

"A Strategy for the Prevention of Protein Oxidation by Drug Product in Polymer-Based Syringes"

PDA Paper

"Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products"

"Session 2/3: Integrated Viral Clearance Strategy and Case Studies"

"Session 4: Overall Integrated Viral Clearance and Adventitious Agents Strategy"

"Session 5: Conference Summary: Key Discussion and Outcomes, Pending Questions and Proposed Experiments"

"Appendix: Organizers, Participants and Contributors: 2013 Viral Clearance Symposia"

Alternative Growth Media for the Sterility Test

Kate Shara, PhD, Sommer Vogel, and Julie Schwedock, PhD, Rapid Micro Biosystems

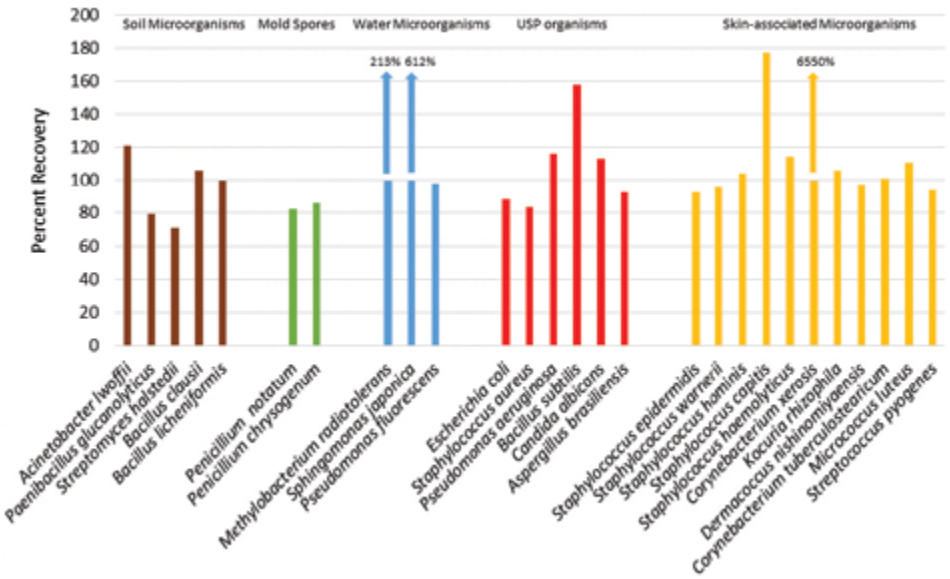
The compendial sterility test (USP <71>) relies on visual confirmation of turbidity; thus, the growth media used must start as optically clear. In the traditional test, soybean-casein digest medium (SCD) and fluid thioglycollate media (FTM) are used. Unfortunately, the time necessary for some microorganisms to grow to numbers large enough that they create visual turbidity can be lengthy. In some cases, such as with *Methylobacterium radiotolerans,* a common cause of sterility failure, growth may not be visible to the human eye until after 14 days—failing to be detected in a test performed according to the specifications in USP <71>. Likewise, turbidity is a qualitative assessment, and can be subjective based on the observer, making it nonideal for such an important assay.

What if there existed sterility methods that didn't rely on turbidity? This would allow for the use of a more nutrient-dense medium, such as one enriched with blood, that promotes the growth of a wider variety of microorganism contaminants than does SCD and FTM. As illustrated in a poster presentation at the *PDA 9th Annual Global Conference on Pharmaceutical Microbiology* in October 2014, by employing a novel, one-of-a-kind rapid sterility test, modified Schaedler Chocolate Broth (mSCB) was evaluated with a suite of microorganisms, comprising groups such as soil microbes, water microbes, molds, human flora, and the USP complement. Also tested was a subset of organisms treated by several different types of stressors, including heat, bleach, SporKlenz™ and nutrient deprivation. These organisms encompassed the majority of pharmaceutical sterility test failures, and provided a thorough overview as to the efficacy of this new growth medium.

The Growth Direct™ sterility system used three conditions that mirror the three environments in the compendial test: aerobic at 32.5°C, anaerobic at 32.5°C (these replicate the FTM portion), and aerobic at 22.5°C (mimicking SCD). The agar form of media from USP <71> was used as a proxy to achieve an enumerated result. Microorganism suspensions were filtered through either the system's cassettes or through on-market MCE 0.45µm pore size membrane with transfer to the agar plates. As shown in **Figure 1,** the mSCB media exceeded the 70% cutoff, and in many cases surpassed 100% recovery compared to SCD agar. Stressed organism performance on mSCB showed high results as well. In order to yield a quantitative result from the broth-based compendial test, Most Probable Number assays are being used to further evaluate SCD and FTM against mSCB.

Advances in sterility testing methods now allow for the use of superior growth media such as modified Schaedler Chocolate Broth, which may have been previously discounted due to incompatibility with the traditional sterility format. The mSCB medium recovered a wide variety of microorganisms from groups encompassing the most common pharmaceutical contaminants.

Figure 1 Recovery of Various Microorganisms on Modified Schaedler Chocolate Broth as Compared to Soybean-Casein Digest Agar



About the Authors

Kate Shara, PhD, is a Scientist II at Rapid Micro Biosystems on the Sterility Test project team.

Sommer Vogel, MS, is a microbiologist at Rapid Micro Biosystems on the Sterility Test project team.

Julie Schwedock, PhD is currently the Director of Microbiology R&D, where she has worked on rapid methods for over 15 years.

Think Like a Baker When Classifying Raw Materials

The following blinded, unedited remarks are taken from PDA Connect℠, a new online forum that allows members of PDA interest groups and chapters to discuss and share some of the most challenging issues confronting the pharmaceutical industry. The discussions on PDA Connect do not represent the official views of PDA, PDA's Board of Directors or PDA members.

Join at community.pda.org.

Questioner

Hi All,

I was posed a question that I would like some feedback on.

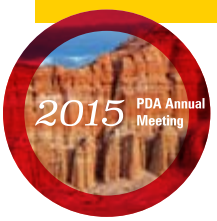
What are the best practices for classifying raw materials (critical, etc.)? Or what do you do to classify raw materials?

Respondent 1

You probably guessed what the answer would be…risk assessment *based on us*e.

The example I always use is baking a chocolate cake. The specifications for the chocolate are *critical*—if you use baking chocolate (Critical Process Parameter, or CPP) which is something like 60% margarine, it will taste *awful* (Critical Quality Attribute, or CQA). If you use Belgian dark chocolate (CPP) it will taste *fantastic*—get it over to me ASAP! It's about inputs and their impact on outputs—some raw materials are less important—like the flour in the cake which, even if lumpy, can be sifted. So, you look at the *intended use* of the material.

One more thing that is critical—what is known about that material? Unfortunately, we live in an age of counterfeits and deliberate tampering with supply chain. Therefore, some starting materials are high risk just because they are what they are—Glycerol, Propylene Glycol, commodity chemicals are just a few examples. In those cases, you must verify the pedigree so while they may or may not be critical to the success of your process, they would certainly cause major harm if you used them and you wouldn't want that. Therefore, *risk assessment* is the answer so that you ask "what could go wrong" and put appropriate controls in place and communicate them to purchasing, warehouse and other stakeholders.



Future Technologies Hold Promise for Industry

Maik Jornitz, G-Con, and Susan Schniepp

We are all very much aware of the rapidly evolving technology trends within our industry. Not only are we experiencing the introduction of new technologies—raising the quality and safety levels of our manufacturing processes—but we are also trying to comprehend the efficiencies and flexibilities these emerging technologies offer for our facilities. These advances are necessary in order to gain capacity utilizations and continuous improvement opportunities as well as to help our industry become more agile and flexible—abilities required for developing new products and shifting manufacturing demands. In addition, these technologies may help to alleviate the current drug shortage situation and to avoid potential new shortages.

Manufacturing innovation and improvements determine the efficiency of our processes and facilities, usually resulting in advancements in quality and finances. The latter are often viewed as contradictory, although unjustly, as appropriate quality approaches can result in economic gains.

Besides technology and science improvements, quality and safety remain a major focus for us. New technologies help to either sustain or improve the quality of our manufacturing processes and/or safety of our products. Economic considerations, however, often clash with quality consciousness, which may result in delayed improvement investments.

PDA, as always, is the leading facilitator of innovation and knowledge exchange. With this in mind, the theme for the *2015 PDA Annual Meeting* is "Efficiency: Achieving Quality Performance in Sterile and Biopharmaceutical Operations." This meeting will once again show PDA's commitment to bring manufacturing technology advances to the forefront and be a platform of constructive discussion among industry, suppliers and regulators. At the same time, the Annual Meeting does not shy away from the need to evaluate economic requirements, but also reflects on what happens when improvements are not implemented with quality in mind, which can result in greater economic impact due to an ineffective focus on quality within an organization.

Furthermore, PDA is known for proactively seeking solutions to current issues like drug shortages, aging facilities, advances in personalized medicine and production paradigms, modern aseptic processing technologies and analytics, newly evolving adventitious agents and finding detection and inactivation methods, to name a few initiatives.

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Strategies for Controlling Raw Materials in Biologics Manufacturing

Annemarie Möritz, PhD, Novartis Pharma AG

Controlling the quality of raw materials used in cell culture-based biotech manufacturing processes is a particularly challenging and critical task, because unlike traditional, small molecule manufacturing, an adventitious agent contamination event or other serious quality deviation has the potential to cause significant disruption to the manufacturing process and availability of the product ***(1).***

The key to effective raw material control lies in developing a strategy that relies on thorough understanding of the role of raw materials in the manufacturing process as well as testing and supplier assessments.

Raw materials used in cell culture processes can be very diverse, ranging from inorganic salts to complex components like soy hydrolysates, animal-derived peptones or serum. Other raw materials commonly used in cell culture processes include carbohydrates, vitamins, trace elements, recombinant proteins such as insulin, defoaming agents, amino acids or nucleotides, among others. Examples of molecules manufactured by such processes are monoclonal antibodies or bifunctional fusion proteins.

Raw materials require clear control strategies in order to assure their quality. Therefore, the strategies presented herein can also be applied to other processes such as bacterial fermentation or chemical synthesis. As an example, Vitamin B_{12} (also called Cyanocobalamin) is used to illustrate the development of a raw material control strategy. Its role in mammalian cell culture processes is to serve as a cofactor for DNA synthesis in the cell, thus making it an essential material for any such process.

Vitamin B_{12} is mostly manufactured by bacterial fermentation, a well-known process applied for many years. Vitamin B_{12} is readily available on the global market, so continuous supplies are not an issue. It is possible to purchase directly from manufacturers which guarantees a good traceability of the material.

Definition of Raw Materials

The first step in setting a control strategy involves defining the raw materials in question. Due to the diversity of raw materials and also due to many other materials being used in the manufacture of biologics, it is important to be clear which material definition is applied for developing quality control strategies. In most cases, biologics are manufactured for distribution on the global market, therefore, the raw material definition of ICH Q7 ***(2)*** applies.

Elements of a Control Strategy For Raw Materials

Once the definition is set, a brainstorming exercise can be used to chart out the specific elements needed for a control strategy. The most important element is knowing *why* the material is being utilized, thereby understanding its role in the cell culture process. By this, the critical material attributes of a given raw material which may influence cell growth, and also product quality, are defined. The sidebar "Elements of a Raw Material Control Strategy" on p. 26 describes additional elements of the brainstorming exercise.

During this exercise, supplier qualification questionnaires—used to evaluate the quality system of the manufacturer and the quality of the raw material—are distributed, material for in-use/analytical testing is ordered, and if deemed necessary, audits may be performed at selected manufacturers based on the evaluation of the questionnaires and testing results.

Using the example raw material, the evaluation of materials from different Vitamin B_{12} providers consists of:

- Performing comparative small-scale cell culture with monitoring of the cell growth characteristics ("in-use testing"),
- Conducting a comparative assessment of whether there are differences in the results of analytical testing between manufacturers, and

Article at a Glance

- Raw materials used to produce cell culture products require clear control strategies
- Risk evaluation is a key part of the supplier qualification process
- Raw materials of human/animal origin necessitate extra attention

- Testing additional to pharmacopoeial and/or manufacturer test methods may be needed due to special requirements of the cell culture process under assessment

When a criticality assessment is performed for all raw materials of a mammalian cell culture process, the outcome will most likely be that the criticality of Vitamin B_{12} will be considered "lower" compared to, say, serum components or recombinant proteins, but "higher" compared to buffers/salts used in the cell culture process.

Defining the Supplier Qualification Process

To optimize the supplier qualification process, this risk evaluation result can be used to identify items critical to raw material quality. Proposed elements crucial to the criticality assessment can include the following:

- **Origin/complexity risk:** Raw materials of human/animal/recombinant origin or premixed media are more complex, equaling higher risk than less complex components.
- **Product contact:** Raw materials with direct contact to product present higher risks (e.g., media component vs. fermenter cleaning).
- **Impact on drug substance process:** Raw materials used during cell culture with other functionality than cell growth promotion (e.g., antifoam agent for cell protection) present higher risk than those needed for cell growth.

These elements may then serve to refine the supplier qualification process, depending on the identified material risk. **Table 1** shows an example of a material risk assessment for the general components of a mammalian cell culture process. A material cannot be rated with a category of "low" risk as a "yes" in a Product Contact category leads to a medium criticality material. This is due to the unique nature of a cell culture process. All components contribute and are in some way critical to ensure the proper manufacture of a biologic. As a next step, the elements of a manufacturer/supplier qualification for a raw material can be set up per criticality of material. **Table 2** presents how medium and high criticality raw materials for cell culture processes could be assessed during the supplier qualification exercise.

Table 1 General Example of a Material Risk Assessment

Definition: 1y=medium, 2-3y=high criticality (product contact risk = y prevails)

Criteria/Material	Origin/ complexity	Product Contact	Impact on DS process	Risk
Inorganic salts/buffer components	n	y	y/n	Medium/ High
Defoaming agent	n	y	y	High
Carbohydrate/energy source	n	y	n	Medium
Trace elements	n	y	n	Medium
Amino acids	n	y	n	Medium
Vitamins, Antioxidants	n	y	n	Medium
Nucleotides	n	y	n	Medium
Recombinant proteins	y	y	n	High
Serum or serum components	y	y	n	High
Hydrolysates/Peptones	y	y	y	High

Table 2 Supplier Qualification Elements Identified per Raw Material Criticality Definition

Manufacturer/Supplier Qualification for a Raw Material

Define supplier qualification requirements for risk categories

Medium Risk	Provide CoA, specifications, test methods, MSDS
	Logistics, packaging, labeling
	Supplier risk assessment based on questionnaires/supplier documentation
	Change notification agreement
	Testing of separate sample lots
High Risk	+ Process flow diagram, origin of materials used during manufacture, assess risk of cross-contamination
	+ On-site audit
	+ Confidentiality agreement, if needed
	+ Contract, if needed

Raw Material Testing

Raw material testing is an essential part of a raw material control strategy. For testing, specifications need to be set up per raw material in order to evaluate the quality provided by the selected supplier. If this regime is applied to the Vitamin B_{12} example, the test list would entail testing as per pharmacopoeias, in-use testing, complete retesting of supplier CoA tests, and additional tests if required for a particular purpose.

The raw material testing regime mentioned above is outlined for materials to be used for market manufacture of a biological molecule. During development, a risk-based matrix for control is highly recommended in order to accommodate the phase of development. Minimal requirements for raw material control during development are defined in PDA Technical Report No. 56 ***(3).*** A tabular presentation can be found in **Table 3.** One element which requires a lot of time and effort during raw material supplier qualification is raw material supplier/manufacturer audits. Raw material suppliers are faced with multiple requests for audits by industry, and therefore, the Rx-360 initiative ***(4)*** was put in place as an option for audit information sharing. ➤

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19–20
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3–4
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5–6
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9–13
GSA Schedule Contract GS-02F-113BA
Fundamentals of Aseptic Processing
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23–27
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2015 Aseptic Processing Training Program – Session 1, Week 1
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Elements of a Raw Material Control Strategy

Know Why Material is Used and its Role in Process

- Understand critical material attributes which may influence cell growth/product quality

Analytics

- Characterize material using appropriate methods
- Stability studies may be needed for raw materials which are exclusively made for purpose

Testing Methods

- Tests for identity, content, potency, purity
- In-use testing in a small-scale setup
- Assess necessity of specific testing if critical for process performance. Example: control of an impurity having an impact on cell growth
- Use multiple lots during development of your manufacturing process (small, large-scale) to gain experience with the material (> 3 lots)

Lot-to-lot consistency

Ensure minimum variation to avoid variation of process and consequently, product quality

Supply Chain and Supplier Qualification

- Evaluate market availability
- Evaluate shipping storage conditions of supplier
- Option to buy directly from manufacturer?
- If not, ensure supply chain integrity by change control provisions
- Continuous supplies possible?
- Audit supplier/manufacturer
- Establish back-up supplier(s)
- Ensure material compliant with pharmacopoeias is assessed

Safety

- Keep track of material lots tested and used in process development to be able to quickly troubleshoot if needed
- Retain samples for investigations
- Ensure adventitious agent safety provisions are in place, if needed
- Perform routine identity testing on incoming materials

Table 3 Risk-based Matrix for Raw Material Control During Development

Note: Minimal requirements as per TR-56

Development Phase	Analytics	Supplier Qualification	Supply
"pre-GMP" phase (cell line/process development)	CoA/CoO In-use testing Document lots used	Documentation of sources	Use well known and accepted suppliers, if available Get multiple lots, if feasible
Phase I/II	+ Identity testing + Investigations + Method Development & Qualification	+ Supplier risk assessment (questionnaires) + On-site audit for high risk materials	+ Evaluate availability options + Logistics, packaging, labeling
Phase III/ Validation	+ Full testing (CoA & in-house tests) + In-house stability + Method validation	+ On-site audits + Monitoring of approved Raw Materials	+ Prepare supply/ QA agreement (incl. change notification)
Market (Annual Product Review) (Phase IV)	+ Check suitability of specifications for purpose	+ Frequency of on-site audits based on experience	+ Supplier monitoring

Special Cases Need Special Attention

Raw materials used in the "pre-GMP" phase during establishment of the cell substrate are a concern to authorities, as they present a risk of contamination with adventitious agents. Whereas ICH Q7 defines the start of GMP activities with "Establishment of the Working Cell Bank (WCB)," the updated EU Annex 2 requires the start of GMP activities at Master Cell Bank establishment level ***(5).*** This means that qualified raw materials should be used for these activities. As described in **Table 3**, at minimum, CoA/CoO/Transmissible spongiform encephalopathy (TSE) information are mandatory to be available for each raw material. In TR-56, Appendix 6.0 deals with "Quality Systems Applicable To Cell Culture Development." The EU even goes one step back into cell line development and requires that for stages prior to the cell bank generation, "...documentation should be available to support traceability including issues related to components used during development with potential impact on product safety..." (from EU Annex 2 No. 41). These requirements are not new, as the ICH Guideline Q5D ***(6)*** section 2.1.2 also has separate paragraphs applying to cell substrate and the cell line used for transfection. It is highly recommended to obtain parental cell lines from trusted sources with appropriate documentation and source any raw materials used during cell line development from GMP-qualified raw materials as much as possible. In addition, keeping good track of raw material documentation ensures data integrity. Only then, it can be assured at the time of filing a biologics application that the safety risk brought by raw materials of all development stages—even those prior to GMP—can be appropriately assessed, rather than starting with worst case considerations.

The use of raw materials of animal/human origin in a cell culture process bears a significant risk for contamination with adventitious agents. These typical raw materials are: fetal calf serum/fetal bovine serum, bovine serum albumin (BSA) and human serum albumin (HSA). Guidance is available from either ICH or WHO, as well as the ICH regions: the United States, European Union and Japan, which

Continued at bottom of page 30

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Proposed EP Chapter Addresses ATMP Raw Material Quality

Rebecca Stauffer, PDA

Advanced therapy medicinal products (ATMPs), such as cell- and gene-based therapies, represent the cutting edge of pharmaceutical science, but developing such products poses unique challenges. Extremely short shelf lives present difficulties, requiring extra considerations as well as a holistic understanding of all the variables in the process ***(1).*** At the same time, both industry and regulators fear being too proscriptive lest companies cease developing these products.

This challenge also encompasses the quality requirements for raw materials used in the manufacture of ATMPs. For the past few years, there has been movement toward a harmonized approach to quality requirements for raw materials used in the production of ATMPs, notably in Europe. In 2012, the European Directorate for the Quality of Medicines and Healthcare (EDQM), the entity responsible for the European Pharmacopoeia, formed the Raw Materials for the Production of Cell-Based and Gene Therapy Products Working Party with the goal of harmonizing requirements for these types of raw materials ***(2)*** in a chapter in the European Pharmacopoeia.

This EP chapter was published in draft form Sept. 22, 2014, closing for comments Dec. 31 ***(3).*** Publication of the chapter followed two years of meetings among manufacturers, regulators and related organizations that resulted in general recognition of the need for clear guidelines in this area. But there was also clear consensus on the need to avoid the burden of too many regulations for developers.

The *PDA Letter* spoke with **Jean Stanton,** Director, Regulatory Compliance, Johnson & Johnson, who served as an industry delegate at the April 2013 EDQM/EMA symposium on raw materials and gene and cell-based therapies.

"There was a general consensus from all in attendance that a need existed for more guidance around the quality requirements for raw materials," she said of the meeting. "However, there was also a concern that a guidance or standard created not slow the pace of development."

In her opinion, the new proposed chapter "does advance the goal to harmonize with other standards."

It's a win-win for both end users and suppliers when the expectations are clear

According to Stanton, the proposal outlines two important tenets: "It is the responsibility of the drug developer to have an appropriate understanding of the raw materials they use in production. They must have a robust process to qualify raw materials and the manufacturers of those raw materials."

She believes the proposal along with other standards in process "provide the means and/or tools that can aid in the execution of these types of assessments."

At this time, few guidance documents are available specific to raw material control for ATMPs. These include a section in the U.S. FDA guidance *Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)* on supplies and reagents; USP Chapter <1043>, Ancillary Materials for Cell, Gene and Tissue-Engineered Products; the EU EudraLex Volume 4 Good Manufacturing Practice (GMP) Guidelines: Annex II Manufacture of Biological active substances and Medicinal Products for Human Use; and specific ISO and ICH raw material standards.

Stanton views the EP chapter as more "analogous" to USP <1043>.

"The purpose of this [USP] chapter is to provide guidance in developing appropriate qualification programs for ancillary materials employed in cell, gene, and tissue-engineered product manufacturing. Where they differ, is USP <1043> provides a tool to estimate quality, safety and efficacy to assist with risk-based decision making," she explained.

On the other hand, she noted, "this EP chapter groups specific raw materials into 'families' based on certain criteria. It provides more information regarding the specific families with respect to general qualify identity/testing, production, storage and labeling. They offer no tool but the information can be used by both the manufacturer of the raw material and the developer to assess the quality aspects of the material for use in cell therapy production."

Ultimately, the proposed EP chapter, like other standards can potentially assist companies in determining the criticality of each raw material, in addition to offering an opportunity for a Quality by Design approach to raw material management.

To determine the criticality of raw materials in the production of ATMPs, Stanton said "it is necessary for developers to prioritize risk in order to better focus their development efforts and time. Part of determining criticality of raw materials is to understand the information gaps for the product and production. Drafts like this can assist developers [to] structure their evaluations of raw materials in a way to understand what they need, and create this essential knowledge space for their products."

Little Regulatory Guidance, Even Fewer Suppliers

Stanton believes the draft chapter meets the working party's goal to avoid over-regulation. "It does not add to the ➤

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current regulations. What is detailed in this draft offers means to comply with current regulations," she said.

In fact, Stanton feels that industry could benefit from additional guidance clarifying regulatory expectations for raw material quality. She noted, referring to a talk from the April 2013 EDQM/EMA symposium, that a recurrent objection raised by EMA during evaluation of ATMP Marketing Authorization Applications concerned the lack of risk/benefit analysis associated with those materials used during manufacturing and the impact of raw materials on the final quality profile.

Another big challenge for ATMP manufacturers involves a limited supplier market. In a talk at the *2012 PDA/FDA Joint Regulatory Conference* ***(4),*** Stanton described how the ATMP market remains a niche area within pharma which means the number of suppliers is minimal. In some cases, ATMP developers can end up working with less-than-adequate suppliers simply due to lack of competition. But with clearer compendial standards, she hopes this will give companies more leverage to push for higher quality from suppliers.

"As ATMP developers learn what's necessary to advance such a product, they can communicate their requests or needs with a common language, to potential suppliers. Suppliers can also use drafts such as this one in their business planning," she said. "It's a win-win for both end users and suppliers when the expectations are clear."

Now that the deadline for comments on the proposed EP chapter has passed, it remains to be seen how industry has responded to the proposal. The next steps will entail careful review by EDQM of any concerns raised. Regardless, it is clear that a compendial document outlining quality requirements for raw materials used to develop ATMPs is needed that also recognizes the need for regulatory flexibility necessary for the production of these specialized, high-tech products.

[Editor's Note: For more information about compendial updates impacting ATMPs, consider attending the *Advanced Therapy Medicinal Products* conference hosted by PDA Europe in Amsterdam June 2–3. For more information, visit https://europe.pda.org/atmps2015**.]**

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About the Expert

Jean Stanton has been with Johnson and Johnson since 2008 and is in the Regulatory Compliance group. She is responsible for leading the integration of novel products regulations into the processes that support product development.

Strategies for Controlling Raw Materials in Biologics Manufacturing continued from 26

describe what testing is required to assure safe use of such raw materials. As an example, use of HSA requires fulfilling a lot of provisions in all regions, so it is highly advisable to source globally registered and authority-released products only. Look-back procedures in case of HSA recalls need to be in place; the timeline for this is very long (30 years), so HSA manufacturers have to ensure in their SOPs that these requirements are met. The use of any other human-origin material which is not covered by licenses bears an even higher risk as there is no authority oversight, and the "end user" will be required to comply with provisions very similar to those for HSA which can cause significant additional documentary needs, testing and risk assessments. The use of raw materials of animal/human origin in cell culture processes is difficult and may necessitate additional measures to assure the safety of the product manufactured. It is also highly recommended to apply the relevant authority guidance, as well as any supplier qualification provisions, to animal/human–origin materials used in the "pre-GMP" phase. A sourcing and QA agreement should be in place from the start in order to mitigate any adventitious agents risk.

Conclusion

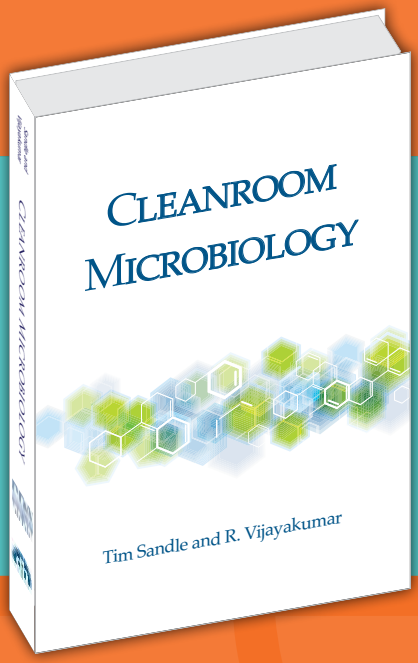
Raw material quality control strategies are a very important element to ensure the safety, quality and efficacy of the biological molecule to be manufactured. Several aspects have to be considered to achieve this:

- Understanding the role of the raw materials in the process
- Developing testing strategies to ensure raw material quality
- Evaluating whether specific tests are needed for the particular raw material in order to ensure consistent material quality
- Setting up material/supplier risk assessments in the context of a supplier qualification exercise
- Having a supplier qualification system in place which assesses all risks of a raw material: origin risk (safety), supply risk (availability, back-up options, audits, contractual agreements) and quality risk (testing, evaluation of lot-to-lot consistency).

If implemented diligently, raw material quality control strategies help to assure the quality of the product, and contribute to mitigate the risk of adventitious agent contamination.

Continued at bottom of page 42

PDA Bookstore New Release



Cleanroom Microbiology

WRITTEN BY: TIM SANDLE AND R. VIJAYAKUMAR

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While there are books on cleanrooms available, these focus almost entirely on the physical and rarely address microbiological risks. Similarly, there are various books on microbiology (even a few about pharmaceutical microbiology), yet these books rarely mention cleanrooms, or, where they do, give controlled environments limited coverage.

To the authors of Cleanroom Microbiology, these two domains, normally separated by different functions, are inseparable. This book is about cleanrooms and controlled environments in relation to the pharmaceutical and healthcare sectors and is applicable to both the sterile and non-sterile pharmaceutical sectors with its focus on cleanroom microbiology.

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ABOUT THE AUTHORS

Tim Sandle has over twenty-five years of experience in pharmaceutical microbiology. Tim is the site microbiologist at the Bio Products Laboratory and he is a visiting tutor at the University of Manchester, where he teaches pharmaceutical microbiology. In addition, Tim is a longstanding committee member of the Pharmaceutical Microbiology Interest Group (Pharmig).

Dr. Vijayakumar is an Assistant Professor of Microbiology in the College of Science, Zulfi, Majmaah University in the Kingdom of Saudi Arabia. He has over twelve years' experience in the field of Pharmaceutical and Clinical Microbiology. He has a doctorate in Microbiology from Bharathidasan University, India. His past experience in the sterile pharmaceutical industry includes (Aurolab, India) as Microbiology Manager where he was involved in QC and QA activities.

Raw Material Control Strategy Key to Overall Control

Parag Kolhe, Pfizer

From quality risk management principles to the U.S. FDA's recent proposals for quality metrics, industry faces pressure—both internally and externally from regulators—to ensure the quality of drug products. But quality is not just an end-game approach; it also begins at the bottom with the selection of raw materials.

ICH Q8 (R2), Q9 and Q10 provide complementary guidance on pharmaceutical development, quality risk management and quality systems, respectively, to improve product quality ***(1-3).*** A scientific and risk-based approach to quality product development has been outlined in these guidelines. Robust control strategy is the key for ensuring consistent process performance and product quality. ICH Q10 defines control strategy as:

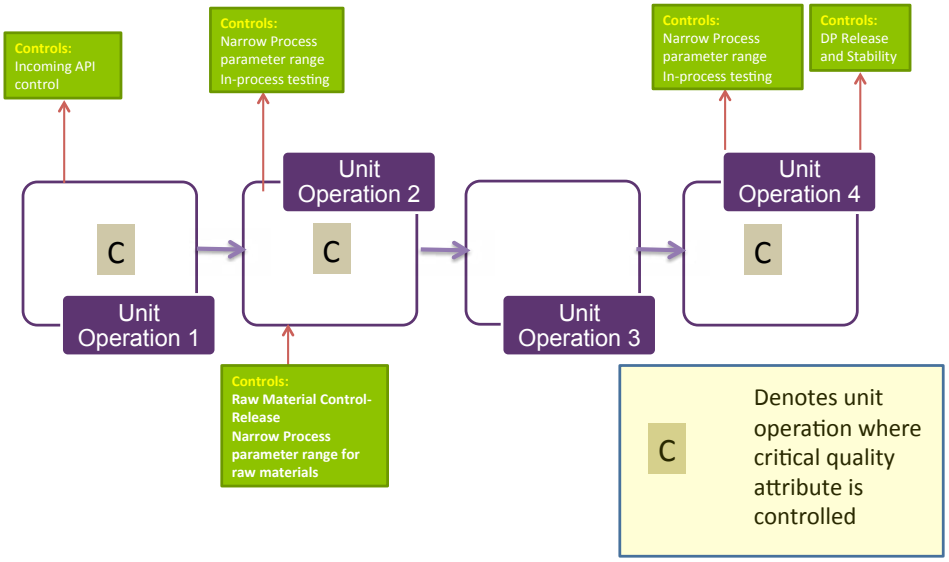
"*A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control*" ***(3).***

As described in ICH Q10, control strategy encompasses various sets of controls to ensure product quality. Process and product understanding is the foundation of control strategy. The scientific and risk-based approach outlined in the ICH documents is the basic principle for constructing robust control strategy and process parameter ranges ***(1-3).***

Figure 1 provides a schematic of control strategy for a given critical quality attribute (CQA) of drug product. Process flow comprising of associated unit operations and various sets of control as defined in ICH Q10 are depicted. Raw material control is one of the controls shown in the figure. Raw material control strategy cannot stand alone—rather it should be part of the overall control strategy for the product.

The obvious question is "what should be the starting point for raw material control strategy?" The approach to material control strategy is no different than for any other control strategy. Understanding raw material attributes and their effect on product quality constitutes the first step. In order to develop a robust control strategy for raw materials, understanding of "how and what" (*how* material attributes affect the CQAs of product and *what* controls are needed to be in place) is critical to achieve consistent end product.

Figure 1 Schematic of overall control strategy and how the raw material control strategy feeds into overall control strategy



Understanding the Effect of Raw Material Attributes on Product Quality

Establishing the relationship between raw material attributes and product CQA is the key first step in designing control strategy. It is important to start thinking about control strategy for raw materials during early development and as product knowledge evolves. It is imperative that the rationale for having specific control strategy for excipients should be driven through risk assessment. Raw material risk assessment should be included as a part of process risk assessment. A clear, documented, team discussion on raw material risk assessment can result in robust control strategy.

Typically, material attributes of raw material are evaluated against the effect on CQA based on process and product understanding. **Table 1** shows an example of a cause and effect matrix where the links between the raw material attributes and product CQA are assessed. This risk-based approach provides good insight into important material attributes. As shown in the example presented in **Table 1,** the impact on CQA is weighed on a low **(1),** medium **(5)** and high scale **(9).**

Cause and effect matrix assessment suggests that material attributes 1 and 3 do not impact any product CQAs. It is clear that material attribute 2 (MA2) has medium impact on CQA1 and CQA 3 in addition to strong impact on CQA 3. Hence, MA1 and MA3 can be classified noncritical material attributes and MA2 can be classified as critical material attribute. The impact of MA2 should be carefully evaluated on CQA and it should be assessed whether further control of MA2 is required.

Examples of a raw material attribute that

Table 1 Example of cause and effect matrix relationship for material attributes effect on CQA of final product

	CQA 1	CQA 2	CQA 3
Material Attribute 1	1	1	1
Material Attribute 2	5	9	5
Material Attribute 3	1	1	1

may impact CQA would be particle size, bioburden, and pH. Process and product characterization can point toward essential control strategy. For example, if the CQA is not affected by MA2 within the incoming specification range, release of raw material as control strategy could be sufficient. If it is determined that significant changes in CQA are noted, narrow control of MA2 may be warranted.

Narrow Raw Material Control

If the narrow control of material attributes is warranted, this can be achieved by narrow specification on release of raw material through raw material manufacturing process/additional controls. Process understanding of the raw material manufacturing process and process parameters that impact MA2 are important inputs in determining the required control for raw material manufacturing process.

Bringing Control Strategy together for Raw Materials

Risk assessment and product/process knowledge (QbD or QbD-based approach) provide input in control strategy. An overall process and decision tree with an example of MA2 is demonstrated below. It is clear that the controls for raw material for MA2 could range from release and stability of raw material for MA2, control of process parameters that impact MA2 and possibly in process check for MA2.

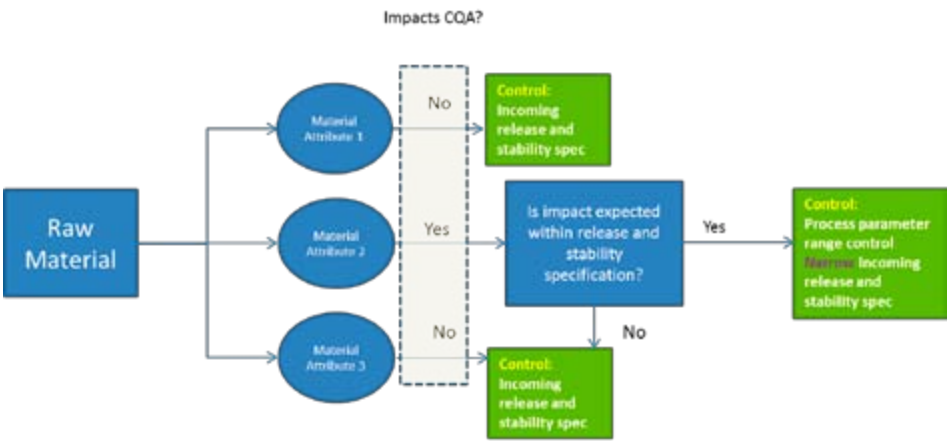
Connecting Control Strategy to Process Validation Guidelines

Guidance from FDA and EMA on process validation stresses the importance of a lifecycle approach toward process validation rather than a onetime approach to demonstrate process consistency and control to manufacture a robust product ***(4).*** Control strategy forms the basis of this approach and feeds into a continuous process verification program ***(4).*** It is important that raw material control strategy is integrated in overall product control strategy.

Summary

Product and process knowledge along scientific and risk-based approaches drives the development of control strategy. Various controls constitute overall control strategy for product development. Input raw material quality should be one of the considerations for overall control strategy and can be achieved through the basic premise of product/process knowledge space and scientific/risk based approach. It is imperative that the raw material control strategy be a part of overall control strategy.

Figure 2 Example of decision on control strategy for raw material



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About the Author

Parag Kolhe is Group Leader-Senior Principal Scientist at Pfizer, Biotherapeutics Pharmaceutical Sciences. He has been working in the pharmaceutical industry for more than ten years. He has vast experience in development of monoclonal antibodies and vaccines.

Mapping the Raw Material Supply Chain

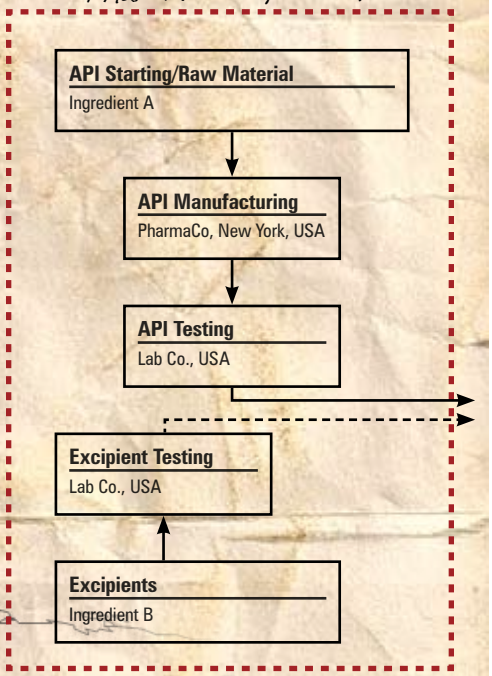
The Number one Risk Cited by Life Sciences Companies? **Supply Chain & Supplier/Vendor Concerns** [1]

How can companies deal with increasing supply chain complexity?

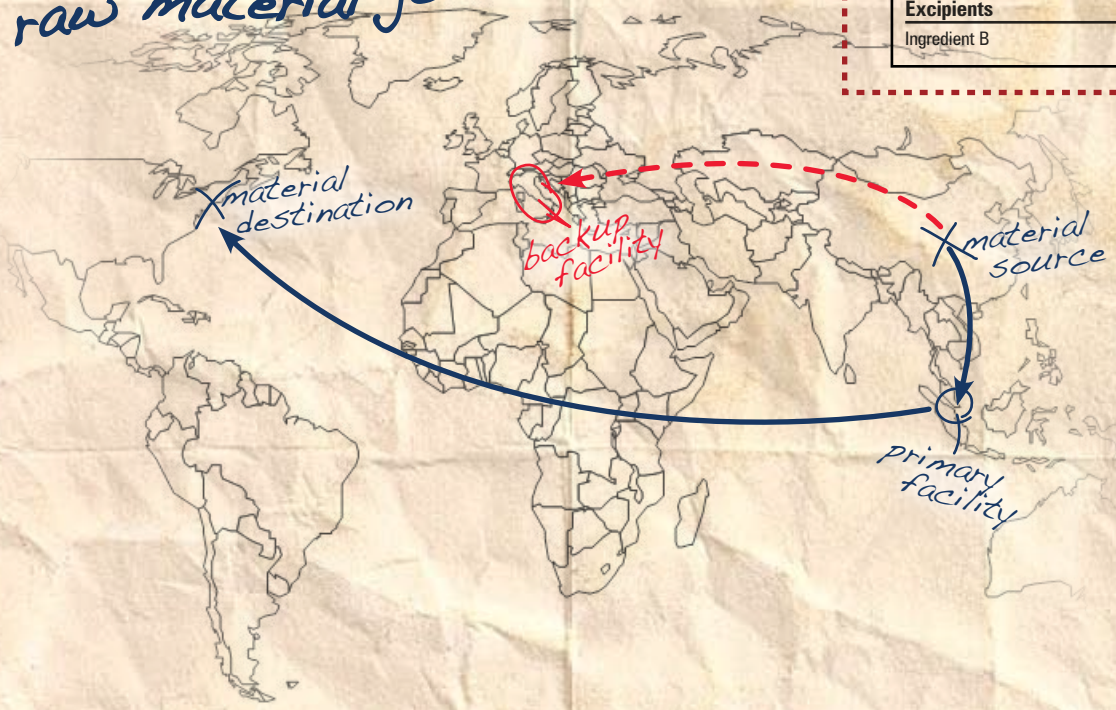
Many use a supply chain map, a tool that accounts for all the facilities within the supply chain.

But only 55% of companies surveyed use any sort of supply chain mapping documentation [2]...

PharmaCo map example



The raw material journey



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Special thanks to Rx-360 Upstream Work Group Co-Chairs: **Rob Welsh,** VWR, and **Bretta Lichtenhan,** EMD Millipore, for their assistance with this infographic.

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snapshot Report From 2014 Parenterals Conference

Task Force *Corner*

Task Force Hopes Revision of Aseptic Processing Points to Consider Paper is of Interest to Regulators

Rebecca Stauffer, PDA

In 2003, PDA published the paper, "Points to Consider for Aseptic Processing" as a commentary on the then draft U.S. FDA guidance on GMPs for aseptic processing ***(1).*** Since then, there have been considerable changes within the industry resulting in additional knowledge, including new regulatory guidance in this area. Due to this increase in expertise, PDA has set up a task force comprised of experts in several areas to revise this document.

This revision also comes at a time when regulatory authorities are updating or developing regulations and guidelines in the area of sterile manufacturing, such as Annex 1 of the European GMPs. PIC/S also established a working group in this space as well in 2014. According to **Gabriele Gori,** Global Head GMP Compliance and Auditing, Novartis Vaccines and Diagnostics, the task force believes that the revised Points to Consider document may be of interest to those regulators working on these GMP initiatives.

"We felt after 11 years it was time to revise this PDA document to consider the new technologies, the new approaches," Gori said at the *Parenterals* conference in November in Munich. "We also noticed that by working on this Points to Consider document this may also be useful, possibly, for regulators for their revision of Annex 1 or any other guidance or standard."

The basis for the revision lies in five related regulatory goals: 1) Use of science and risk-based approaches; 2) Application of modern technology; 3) Reevaluation of traditional control strategies; 4) Consideration of new product/container presentations; and 5) Harmonization of global regulatory expectations.

Gori stressed how important harmonization is, "specifically, for people like me who on a regular basis deal with different regulatory authorities from different parts of the world. So, all the science is the same everywhere, so we really hope to come to some common agreement as to what are the requirements."

The task force hopes the revised PDA Points To Consider addresses specific areas in need of clarification, reflects current state-of-the-art practices, and supports the effort to revise the current Annex 1. "We truly believe that only with open communication with experienced professionals and, in particular, between regulators and industry can we really achieve the target, which is a common target for us and regulators because we are all trying to get the best out of this for the interest of our patients."

Some of the topics included in the revision are airflow velocity and patterns, unidirectional flow versus laminar flow, grade A environment over cappers, differential pressure, testing of HEPA filters and HEPA filters patching, tube length and bend radii for total particulate sampling, monitoring of ≥ 0.5µm and ≥ 5.0 µm particles and room classification, environmental monitoring alert and action levels setting, location and frequency of monitoring of total particulates and viable particles, sterilizing filter integrity testing, and more.

Currently, the Points to Consider revision is still in process and has not yet been approved by the Science Advisory Board or the Board of Directors.

Reference

1. "Points to Consider for Aseptic Processing." *PDA Journal of Pharmaceutical Science and Technology* 57, no. 2 (2003).

About the Expert

In his role, **Gabriele Gori** provides oversight into the GMP Compliance status of all the Novartis Vaccines and Diagnostics facilities worldwide, and coordinates the divisional auditing team which is in charge for the assessment of Novartis Vaccines facilities and for the evaluation and monitoring of third parties and critical suppliers. He is also the chair of the Novartis Sterility Assurance Expert Network (SAEN), which provides guidance to all Novartis divisions on Sterility Assurance matters

Points to Consider in the Manufacturing of Sterile Products Revision Task Force

Hal Baseman, Valsource, Co-chair
Gabriele Gori, Novartis, Co-chair
Masahiro Akimoto, Toray
Marc Besson, Sanofi
Jette Christensen, Novo Nordisk
Veronique Davoust, Pfizer
Vincent O'Shaughnessy, Amgen
Phil DeSantis, Consultant
Richard Johnson, PDA
William Miele, Pfizer
Janie Miller, PDA
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Michael Sadowski, Baxter
Edward Tidswell, PhD, Baxter

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Potential for Confusion with Proposed Compounding cGMPs

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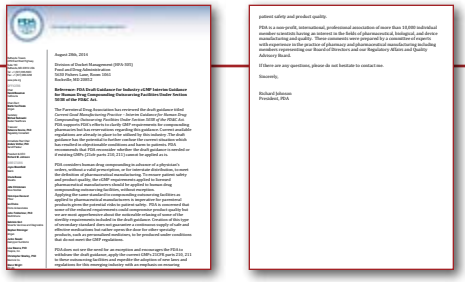

August 28th, 2014

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: FDA Draft Guidance for Industry cGMP Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act.

The Parenteral Drug Association has reviewed the draft guidance titled Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act. PDA supports FDA's efforts to clarify GMP requirements for compounding pharmacies but has reservations regarding this guidance. Current available regulations are already in place to be utilized by this industry .The draft guidance has the potential to further confuse the current situation which has resulted in objectionable conditions and harm to patients. PDA recommends that FDA reconsider whether the draft guidance is needed or if existing GMPs (21 CFR parts 210, 211) cannot be applied as is.

PDA considers human drug compounding in advance of a physician's orders, without a valid prescription, or for interstate distribution, to meet the definition of pharmaceutical manufacturing. To ensure patient safety and product quality, the cGMP requirements applied to licensed pharmaceutical manufacturers should be applied to human drug compounding outsourcing facilities, without exception.

Applying the same standard to compounding outsourcing facilities as applied to pharmaceutical manufacturers is imperative for parenteral products given the potential risks to patient safety. PDA is concerned that some of the reduced requirements could compromise product quality but we are most apprehensive about the noticeable relaxing of some of the sterility requirements included in the draft guidance. Creation of this type of secondary standard does not guarantee a continuous supply of safe and effective medications but rather opens the door for other specialty products, such as personalized medicines, to be produced under conditions that do not meet the GMP regulations.

PDA does not see the need for an exception and encourages the FDA to withdraw the draft guidance, apply the current GMPs 21CFR parts 210, 211 to these outsourcing facilities and expedite the adoption of new laws and regulations for this emerging industry with an emphasis on ensuring patient safety and product quality.

PDA is a non-profit, international, professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. These comments were prepared by a committee of experts with experience in the practice of pharmacy and pharmaceutical manufacturing including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,
Richard Johnson
President, PDA

PDA Commenting Task Force

Susan Schniepp, Allergy Laboratories (Chair)
Alan Burns, Romark Laboratories
Denyse Baker, PDA
Christopher Smalley, PhD, Merck

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Report from PDA/FDA

"Speed Dating," Role Play Liven Up Compliance Sessions

Susan Schniepp, PDA Regulatory Affairs and Quality Advisory Board

When most of us think about attending a conference session on compliance, the first image that comes to mind is of attendees seated in a conference room while a presenter clicks through slides and takes questions. But two popular sessions at the *2014 PDA/FDA Joint Regulatory Conference* offered attendees two new ways to take in and put into practice pertinent compliance information through lively, interactive exercises that also allowed attendees to enjoy some fun and share a laugh or two in the face of often serious subject matter.

The first new session of note occurred at the Inspection Trends Interest Group Meeting led by **Zena Kaufman**, Senior Vice President, Global Quality, Hospira. She required the participants to discuss three of five compliance topics by "speed dating" the topic leader. Participants spent 15 minutes debating and sharing their experience on compliance issues ranging from statistics to data integrity and everything in between. Approximately 100 people attended the session. The attendees were allowed to choose their choice of the three topics to attend. Some participants chose to spend their speed dating time focusing on one topic while others freely rotated among all five topics. The session became so animated, the groups had to relocate farther from each other so participants could hear and be heard in their chosen dating session.

The second new session of note was a breakfast session held at 7:15 a.m. titled "Fishbowl Role Play: Responding to a 483 Right the First Time." **Susan Schniepp,** Chair, PDA Regulatory Affairs and Quality Advisory Board, **Joyce Bloomfield,** Executive Director, Global Quality Systems Center of Excellence, Merck, and **Denyse Baker,** Senior Advisor, Scientific and Regulatory Affairs, PDA, led this session, expecting only about 30 people. Imagine their surprise when 100 people showed up for the session! They designed this session to maximize audience participation by having attendees role play responses to inspection questions during an audit within small groups. The session leaders prepared three scenarios for discussion based on real-life examples and allowed the groups to choose whether they would be a contract manufacturing organization, a contract test organization or a pharmaceutical company. The groups were then presented with the scenario and provided three to four possible answers. They were also allowed to come up with alternate answers to the ones provided. After 15 minutes of discussion the groups presented their scenario and solution to the group. After all the groups presented their answers to the compliance questions, the session leaders revealed exactly how the company actually responded during the audit. Needless to say, there were some surprises when the real answers were revealed.

These two interactive sessions provided an entertaining way for attendees to act on the knowledge gained at the meeting as well as consider how to apply these lessons learned to a real-life scenario. And don't think these were one-off events either! PDA Chair and Training and Research Institute Instructor **Hal Baseman** recently introduced a modified version of the fishbowl exercise in his "Management of Aseptic Processing" course. He also plans to include it in future aseptic courses as well. Visit www.pda.org/courses to learn more.

Due to the demand for these sessions, along with the high attendance, look for more interactive exercises at future conferences. It's not easy responding to an audit or thinking about the implications of poor compliance but participation in these exercises offered those attending a chance to think about and learn from one another without the pressure of being onsite or on the manufacturing floor.

Strategies for Controlling Raw Materials in Biologics Manufacturing continued from 30

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About the Author

Annemarie Möritz, PhD, has over 20 years of experience both in the pharmaceutical and IVD industry, and is a member of the PDA BioAB.

Regulatory Briefs

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

North America

FDA Releases SUPAC Equipment Guidance

The U.S. FDA is concerned that scale-up post-approval changes (SUPAC) equipment addenda published in 1998 and 1999 may not reflect current practices and possibly limit manufacturers from continually evaluating and updating their practices. For this reason, on Dec. 2 the Agency released the guidance *SUPAC: Manufacturing Equipment Addendum.* Comments on the guidance may be submitted at any time.

NDA Reviewers to Follow QbR Template

The U.S. FDA has updated its Manual of Policies and Procedures to require reviewers to use Question-based Review (QbR) for NDAs submitted using a QbR format. In addition, reviewers may choose to follow a QbR review template for NDAs not submitted in a QbR format.

Previously, QbR had been used solely for ANDAs. This format grew out of the FDA's Pharmaceutical cGMP's for the 21st Century Initiative.

Europe

EMA Guideline Seeks to Avoid Repetition in Biosimilar Development

EMA has adopted a new guideline on biosimilars. This guideline allows for companies to use a comparator authorized outside the European Economic area during clinical investigation. This is expected to facilitate global development of biosimilars as well as avoid repetition in clinical trials.

The guideline becomes effective April 30.

EMA Releases Guideline on New Flu Vaccine Framework

EMA has released the third module of a new overarching guideline on influenza vaccines. This guideline proposes establishment of a revised regulatory framework to facilitate more efficient assessment of new flu vaccines. It applies only to vaccines which have received ample regulatory experience as well as some new forms.

Comments are due January 30.

Asia-Pacific

Australia and New Zealand Agree to Shut Down Joint Regulatory Body

The Australian and New Zealand governments confirmed in late November that both governments will cease efforts to establish the Australia New Zealand Therapeutic Products Agency (ANZTPA), a joint therapeutic products regulatory body, following an assessment of the costs and benefits for both countries.

Australia's Therapeutic Goods Administration (TGA) and New Zealand's Medicines and Medical Devices Safety Authority (Medsafe), however, plan to continue exploring other harmonization activities between both regulatory authorities, including the development of a new agreement on information sharing as well as a formalized mutual recognition of GMP audits.

International Inspections

PIC/S Establishes Inspectors Academy

At the PIC/S Committee meeting in Paris Oct. 20–21, the Committee established the PIC/S Inspectors Academy (PIA). This Academy—a PIC/S initiative—will feature a Web-based educational center with a focus on harmonizing and standardizing GMP training at the international level using an accredited qualification system.

PIA should be in operation by the third quarter of 2015.

Key Regulatory Dates

Comments Due

January 30 — EMA Releases Guideline on New Flu Vaccine Framework

EMA and FDA Confer in London on Mutual GMP Inspections

Representatives from the U.S. FDA met with a cross-agency team comprised of members from EMA and the European Commission as well as GMP experts from various EU member states in London Nov. 14 and 17 to discuss progress on mutual reliance between FDA and the European Union on GMP inspections.

Although there has been an ongoing initiative on GMP inspections and mutual recognition for many years, due to increased momentum, this meeting is supposed to be the first face-to-face meeting of both teams.

International CMC

Final Concept Paper on ICH Q12 Endorsed

The ICH Steering Committee recently endorsed the final concept paper *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.* This new document offers guidance on building a framework to facilitate efficient management of postapproval CMC changes.

ICH Q12 is a continuation of the Q8–Q11 guidelines and seeks to promote innovation and continual improvement while also strengthening QA and reliable supplies of the product.

ICH plans adoption of a Step 2 document in 2016.

PDA Chair Harold Baseman, ValSource

Looking Ahead at 2015 and Beyond

Five years ago, PDA's board and staff leadership developed a strategic plan. That plan helped us set objectives and implement actions based on a common mission and vision. Through the efforts and direction of insightful, talented and hardworking staff and volunteers, that plan has been realized. Today, PDA is the foremost global provider and educator of science, technology and regulatory information for the pharmaceutical and biopharmaceutical community. For the past 68 years, this institution has developed sound, practical information to advance science and regulation for the industry it serves, through the expertise of its global membership.

As we enter 2015, it is time to reflect on our vision, to look beyond today to what our industry will be in five years, ten years—even longer out. The objective of our industry will likely remain to manufacture and distribute high quality healthcare products and therapies that benefit the public. These products must be safe, effective and compliant with global regulatory requirements. They must also be available, affordable and a reasonable business proposition for the companies that manufacture them. This means that in order to supply drug products to a global market and meet the expectations of those this industry serves, we will need to better prevent drug shortages, protect the supply chain, provide trust in the integrity of data, define a culture of quality, prioritize resources, reduce costs, utilize technology, and strive to achieve true manufacturing excellence.

It is not enough that scientific and trade associations make their members aware of industry practices and health authority expectations. Challenges need answers. Answers involve improvement. Improvement means change. Change is action. We learned these past years that there is a connection between the issues in our industry and science and technology. Science and technology should be the answer to meeting many of our new challenges and solving many of our old problems.

No one reading these words should disagree with the value of improvement, the need to meet challenges, and of the importance of our role in accomplishing that objective. But no one group or group of individuals can do this alone. It will take a partnership of all stakeholders. If science and technology are an answer, then we will need a partnership of suppliers, drug manufacturers and regulators to develop, recognize and enable. PDA's role is to facilitate the partnership that will drive change. PDA allows us, its members, to improve our industry—an industry which affects the lives of so many people worldwide, to a significant extent.

This past year, PDA's U.S. and European-based organizations brought together hundreds of our colleagues through conferences and workshops, interest group meetings, training courses, and chapter events. Through its many task forces, technical advisory boards, surveys and member feedback, PDA continued to be an important industry venue to accumulate scientific information, define best practices, and provide scientific guidance on regulatory positions and requirements. PDA provided valuable information to countless people in industry, academia, and health authorities through technical reports, position papers, points-to-consider papers, articles, books and other scientific publications. Toward that effort, this past year, PDA launched PDA Connect℠, an interactive online community that enables members to engage and exchange information with others in their respective chapters and interest groups.

All of PDA's important global efforts deserve more mention than can be provided in this brief commentary. Suffice it to say that PDA, through the collective knowledge and efforts of its members, continues to advance pharmaceutical and biopharmaceutical manufacturing science and regulation to better serve our industry and the patients we serve. PDA and its members promote innovative and globalized, science-based regulation, educating the community on innovation and science-based technologies for the global pharmaceutical, biopharmaceutical, and medical device community; and through these efforts, helps maximize healthcare product quality, availability and cost-effectiveness.

Where does this leave PDA as we enter 2015? It leaves us actively filling a much needed role to help facilitate the industry partnership which will advance us through this year, the next decade, and beyond. PDA will neither alter its fundamental mission nor change its direction. What we will do is continue what has made us valuable to our members. We will strive to recognize, refine and focus on topics and services which better align with that mission. PDA will continue *connecting People, Science and Regulation®*, actively serving our members, our industry, and those who depend on the products and services our industry provides.

Thank you and best wishes for a happy, healthy and prosperous new year.

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Examine the components of a quality culture, how to measure it and strategies for changing it in order evaluate and improve your company culture.

NEW COURSE **Six Sigma in Process Validation** | March 19

Review the fundamental steps in the Six Sigma process, discuss the use of risk assessments in assigning appropriate sample sizes and provide cases studies demonstrating the appropriate data analysis methods in commissioning, qualification and validation.

Technical and Regulatory Challenges of Drug Delivery Combination Products – Pre-filled Syringes, Autoinjectors and Injection Pens | March 19

Identify the requirements and elements of a successful drug delivery combination product development program that needs to be implemented or enhanced in order to minimize project risk.

Sterile Pharmaceutical Dosage Forms: Basic Principles | March 19-20

Focus on clean room design, environmental monitoring and control, sterilization principles, manufacturing unit operations, aseptic filling, dosage form development, packaging and stability requirements, validation of aseptic processing (media fills), product specific validation, QA/QC for parenterals, and regulatory trends.

Developing a Robust Supplier Management Process | March 20

Explore current regulatory expectations regarding supplier management and learn to implement these concepts in your own company to reduce the risks associated with supplier management.

To register and to learn more, visit **pda.org/annualcourses**

The Parenteral Drug Association presents the...

2015 Annual Meeting Course Series

March 19-20, 2015
Red Rock Casino Resort and Spa, Las Vegas, NV

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2015 PDA Letter: Calendar Full of Pressing Topics

The way pharmaceutical companies control the manufacturing of their traditional and biological drug products is under increasing scrutiny from regulators all over the world. Patient safety and access are two of the primary forces driving this renewed regulatory focus. In the United States, FDA's Center for Drug Evaluation and Research (CDER) is looking at using quality metrics and, in January, opened its new Office of Pharmaceutical Quality. European regulators are watching these developments with great interest, as they too wish to see companies improve their risk-based controls.

PDA is at the forefront of helping its members keep abreast of these changes. With our Pharmaceutical Quality Metrics and Drug Shortages initiatives already producing Points to Consider documents, surveys and a technical report, volunteer member task forces are already contributing. The *PDA Letter* is the definitive source of all PDA activities for these and other important initiatives. The Science and Regulation "Snapshots" bring you updates from task forces, interest groups and PDA staff on our ongoing initiatives. The "Voices of the Board" and the "President's Message" provide insight on PDA's current accomplishments and member value, as well as the Association's short and long-term strategic goals. The "Regulation Department" is also were PDA publicizes its comments on draft regulations, guidelines and guidances.

Our feature stories are also selected for their importance to the industry, and in 2015, thanks to the input of our diverse and experienced Editorial Committee, I think we have the timeliest topics since we began setting an editorial calendar a decade ago. To kick off the year, raw material control is the focus of three features and the Infographic in this issue. In February, we will bring you articles on the future of manufacturing, which will include an update on PDA's new initiative, the Manufacturing Science Program℠. For March, we are working on articles from the December *PDA Pharmaceutical Quality Metrics Conference* and updates from the Quality Metrics Task Force. We are still soliciting articles on Data Integrity, a new focus of regulators, for April, Technology Transfer (May), Sterile Processing (June), FDASIA (July/August), Pharmaceutical Microbiology (September), and Biosimilars (October)—all hot topics. The last issue of the year is a people-focused edition as we will take a look once again at career advancement.

The Letter would bring you neither expert information nor interesting articles without the contributions of our members. So I hope you look at the list of topics presented here and decide to send in an article. We work with experts, both experienced and inexperienced authors, to help them get their thoughts published.

I also want to thank the following Editorial Committee members whose terms have ended for their service on the Committee: **Suzanne Auckerman, Peter Noverini, Barbara Sneade** and **Elisa Yee.** And I welcome new Committee members **Anne Connors, Michele Creech, Sy Gebrekidan** and **Cecilia Turoff.**

2015 promises to be one of the most productive in PDA's history. I'm looking forward to it!

PDA Letter

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

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

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The manufacturing environment within our industry is changing rapidly in response to new products with increasing complexity, evolving regulatory expectations, changing technologies, and a need to improve our manufacturing performance.

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- **Sumant Ramachandra, MD, PhD, MBA,** Senior Vice President R&D, Medical and Regulatory Affairs, Chief Scientific Officer, *Hospira*
- And many more!

The *2015 PDA Annual Meeting* is the only event that gives you a view into the future, enabling you and your company to prepare today for the industry of tomorrow.

Want to learn more? From March 19-20, five in-depth education courses will be held. These courses will teach you about:

- **Technical and Regulatory Challenges of Combination Drug Delivery Products – Pre-filled Syringes, Autoinjectors and Injection Pens** (March 19)
- NEW COURSE **The Quality Culture and Its Measurement** (March 19)
- NEW COURSE **Applying Six Sigma Techniques to the Process Validation Lifecycle** (March 19)
- **Sterile Pharmaceutical Dosage Forms: Basic Principles** (March 19-20)
- **Developing a Robust Supplier Management Process** (March 20)

For more information and to register, please visit **pdaannualmeeting.org**
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