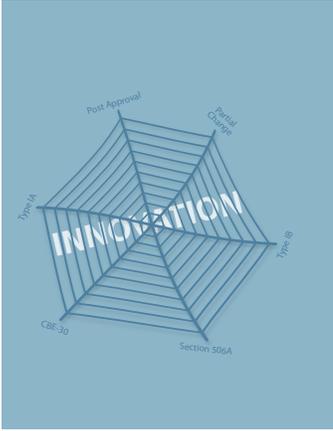


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20 **Managing Post-Approval Changes in a Global Environment: The Case for Product-Based Impact Assessments** **Jenifer Avenatti, Baxter Healthcare**

As regulatory agencies push industry toward risk management and product design space knowledge, how can organizations with global products manage change control in a robust and efficient way? The answer to this question is multifaceted but certainly achievable.

Cover Art Illustrated by Katja Yount

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26 **EU Procedures for Transferring a Marketing Authorization** **Barbara Jentges, PhACT GmbH**

When it comes to the global post-approval management process, procedural and administrative differences are unavoidable per se in view of the various legal and political systems in the different regions of the world. Yet, simplification and harmonization could potentially reduce administrative burden. To illustrate the regulatory administrative hurdles faced within the European Union alone, the procedure/process for transferring a marketing authorization (MA)—also referred to as a change in ownership of an MA—is one example where harmonization of administrative procedures could significantly reduce the burden for both industry and regulatory agencies.



30 **Reports from the 2015 PDA/FDA Joint Regulatory Conference** **Leticia Quinones, Bristol-Myers Squibb, and Cecilia Turoff, Baxter Healthcare**

PDA volunteers Leticia Quinones and Cecilia Turoff provide their perspectives on the first and second days of the 2015 PDA/FDA Joint Regulatory Conference.



32 **The Hoops of Post-Approval Change Complexity**

When it comes to post-approval changes, it can seem like jumping through a series of challenging hoops, especially due to the globalization of the industry. Ultimately, all this can impact the reliable supply of product for the patient.

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20 Four Steps to Modernizing Aging Control Systems Timothy Miller and Andy Miller, Xellia Pharmaceuticals USA

Obsolete manufacturing control systems are one of the challenges typically encountered in aging pharmaceutical facilities. Often, the control systems become outdated well in advance of the process or equipment it controls. When this is the case, upgrading the control system can be as complicated and expensive as replacing the manufacturing system itself. That is why an effective strategy for upgrading or replacing control systems is important.

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28 Older Pharmaceutical Factories – What Does FDA Say? Thomas Peither, Maas & Peither AG

Older factories can indeed exemplify the state of the art. This was the opinion expressed by **Sharon Thoma** of the U.S. FDA at the *PDA Annual Meeting* in March 2015.



30 Signs Your Facility Might Need an Upgrade

What are some signs that your facility is aging and requires upgrades? Find out in this issue's infographic.

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22 Pharma Seeks Long Tail of Flexible Manufacturing Rebecca Stauffer, PDA

The pharmaceutical industry is at the cutting edge in terms of types of products and technologies offered and under development. The last 30 years has seen the biopharm boom, and most recently, the marriage of cutting-edge therapies with high-tech delivery systems, particularly prefilled syringes and other injection devices. The industry is moving into new areas of advanced therapies with personalized medicine, stem cells, nanotech and 3-D printing (in fact, the U.S. FDA approved the first 3-D printed pill last year).

Photo courtesy of Jens Liebchen. Representatives from Bausch + Ströbel showcase the company's VarioSys machine at the 2015 Universe of Pre-filled Syringes and Injection Devices.

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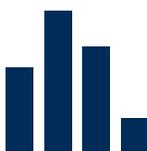
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28 Survey of Industry Leachables Best Practices Completed BPOG Disposables Team Shares Results

Over the past five years, the use of disposable systems/equipment (aka single-use systems) in biopharmaceutical manufacturing processes has reached a pivotal point. Disposables are being implemented beyond research and development and are now being used in clinical and commercial manufacturing. The benefits of disposables are well known and publicized. A 2014 article in the *PDA Journal of Pharmaceutical Science and Technology* outlined a number of advantages, including lower initial capital investment, elimination of cleaning validation, reduced turnaround time, reduced cross-contamination, reduced steam sterilization burden and operations, the possibility of reducing room classification, and the ability to scale up and down.



32 The Future of Manufacturing

As new solutions and technologies enter the market, manufacturing will certainly see significant changes over the next ten years. To get a sense for what these flavors might be like, we asked some long-time PDA volunteers the question: **“What technology do you believe will revolutionize pharmaceutical manufacturing in the next 10 years?”**

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20 Virus Retentive Filtration in Biopharmaceutical Manufacturing

Dayue Chen, PhD, Eli Lilly and Company, and Qi Chen, PhD, Genentech

Virus removal using retentive filters designed to provide effective and consistent clearance of parvovirus (~20 nm) has now become an established standard in downstream purification processes for biologics produced using mammalian cells. Compared to other commonly used virus clearance methods, such as chromatography and low pH inactivation, retentive filtration is superior in its ability to clear almost all potential viral contaminants while also avoiding adverse effects on product quality. While commercially available retentive filters vary in chemical composition and structural configuration, all of these filters primarily clear viruses through the mechanism of size exclusion.

Photo courtesy of Pall Corporation. Copyright Pall Corporation 2016

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26 Missed Opportunities for Adventitious Agents Testing Sven M. Deutschmann, PhD, Roche Diagnostics GmbH

Current adventitious agent test methods feature numerous limitations. Assays based on polymerase chain reaction (PCR) offer the potential to lift these limitations and offer better overall detection of adventitious agents. This is an area that biologics manufacturers are actively exploring, and current research indicates that PCR-based testing is not only scientifically valid but also acceptable to regulators.



30 The "Usual Suspects" of Viral Contamination

Biopharmaceutical manufacturing utilizes cell lines from living organisms. These cell lines can be contaminated with viruses. This issue's InfoGraphic offers some examples of viruses that have contaminated cell lines in biologics manufacturing.

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26 **Big Data Meets Vaccine Manufacturing** Rebecca Stauffer, PDA

Since the late 2000s, “Big Data” has become a buzzword used throughout various industries. The term itself refers to datasets “so large and complex that they become awkward to work with using standard statistical software” (1). Big Data is about more than just the collection of data. It’s about using it to make decisions based on efficient analysis. Making sense of it is the challenge facing most companies. But companies are solving this challenge and taking specific actions based upon the information gained.

Cover Art Illustrated by Katja Yount

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30 **The Dangers of Underestimating Method Variability** **Nanda Subbarao, Biologics Consulting**

As a consultant, I have personally observed how method variability is often underestimated in pharmaceutical laboratories. This can lead to misinterpretations of data presented in the CMC. Such underestimations of variability should not occur in laboratories with robust overarching quality systems that cover all facets of a pharmaceutical laboratory's operations. Yet, in practice, I have seen quality systems breakdown for various reasons during routine laboratory operations, mostly due to limitations of time and resources.



34 **The Economics of Vaccines**

This issue's Infographic showcases some economic facts about vaccines.

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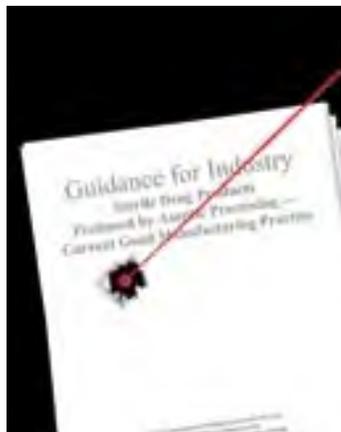
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22 A Line of Sight Approach for Assessing Aseptic Processing Risk Hal Baseman, Marsha Hardiman, Walter Henkels and Mike Long, ValSource

Aseptic processing of sterile drug products can and should be improved. The same challenges, problems and issues seem to appear, reappear, or never really disappear from year to year. These problems persist despite more awareness of the issues due to increased training, conference sessions on the topic, guidance documents, quality system management approaches and metrics. Each year, regulatory audit observations, 483s, and warning letters continue to cite the same problems and issues over and over. Admittedly, aseptic processing is challenging and there are obstacles to improvement, but it is the job of those working in this area to resolve these challenges.

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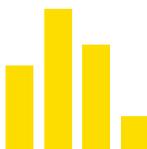
Features



30 7 Steps for a Reproducible Cycle Development Plan

Stefan Kleinmann PhD, Matthias Scheu, Christian Fecht, METALL+PLASTIC

Decontamination cycle development takes place between the completed operational qualification and the subsequent process validation. It also determines the parameters for a successful, effective and repeatable decontamination process that complies with the requirements of both regulatory agencies and end users. The PIC/S guide for isolators states that an isolator decontamination cycle using a minimum 6-log spore reduction is often applied. During routine operation, pharmaceutical isolators and material transfer chambers use decontamination cycles to yield a theoretical 10- to 12-log spore reduction for additional safety.



34 Is the Sterility Test Holding Your Batches Hostage?

Find out how you can liberate your terminally sterilized batches with parametric release.

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28 PDA Celebrates 25 Years of Industry, FDA Collaboration

Take a step back and revisit some *PDA/FDA Joint Regulatory Conferences* of yesteryear!

Cover Art Illustrated by Caroline Cruz Design

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32 How to Avoid a Data Integrity Citation

Brad Mercer, Mylan, Deborah Autor, Mylan, Zena Kaufman, ZGK Quality Consulting

One specific topic continues to draw extensive regulatory attention, including numerous citations in U.S. FDA Warning Letters: data integrity.



39 ²⁵ What Recent FDA Warning Letters Can Teach Us

Zena Kaufman, ZGK Consulting

Data integrity emerged as a common theme following a review of six recent U.S. FDA Warning Letters.



42 A Line of Sight Approach for Assessing Aseptic Processing Risk

Hal Baseman, Marsha Hardiman, Walter Henkels and Mike Long, ValSource

In this article, the authors present examples of how REM can be used to evaluate aseptic process interventions.



46 4 Ways to Ensure Data Integrity

Find out how your company can better ensure its data integrity in this issue's infographic.

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22 **Heads or Tails: Statistical Methods for Interpreting Multiple Biological Indicator Results**

Donald Eddington, PhD, Eddington and Bond Associates, Inc.

One of the main advantages of using an isolator for an aseptic processing application is that it creates a physical separation between the operator and the aseptic workspace. Another main advantage is that an isolator can be completely sealed before aseptic work begins, allowing for the exposed interior surfaces within to be biodecontaminated, typically, via hydrogen peroxide vapor or mist.

Cover Illustration by Katja Yount

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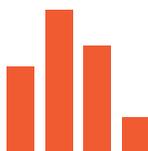


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A QbD Approach to Mitigating Risk in Prefilled Syringes Fran DeGrazio, West Pharmaceutical Services

Over the past several years, we have seen a steady shift in the pharmaceutical industry toward an even more patient-centric approach related to the development of prefilled components. Nearly every aspect of the industry—from drug discovery to regulatory guidance, trial design and drug delivery system—is focused on developing new approaches to put patients first. The impact of this shift can be seen in the types of many new drugs proliferating the pipeline—namely cutting-edge biologics.



32 Visible Particulate Matter in Injectable Drug Products

Learn about the nature of visible particulate matter in parenteral products and its effects in this issue's infographic.

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22 The Role of a Person in Plant for Early Development Projects One Company's Experience

Xiaona Jing, Jesper Valbjørn, Pernille Hemmingsen, Christian Cimander

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

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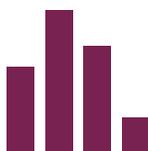
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28 **Microbiologists: Get to Know Manufacturing's Raw Material Suppliers** **Christine Massaro, Johnson & Johnson**

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



32 **Common CMO Audit Allergens**



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

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34 **Four Global Pharma Concerns in an Expanding World** Kelly Waldron, Dublin Institute of Technology (DIT) and Sanofi

Globalization of the pharmaceutical, biopharmaceutical, and medical device industries offers numerous benefits, but brings with it increased complexity. Seasoned industry practitioners can attest to this evolution, as evidenced by new challenges in navigating the international regulatory climate, the intricate nature of the supply chain, and an increases in the number/diversity of patients reached.

Cover Art Illustrated by Karol Keane

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38 Latin America: Moving from Importer to Exporter Luis Caveda, PharmaBioServ

The Latin American pharma industry has traditionally been an importer of medicinal products, unable to generate revenue through exporting drugs or medical devices.



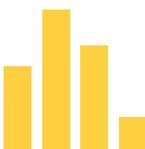
40 How Global Orgs Can Achieve Process Validation Success Ajay Pazhayattil, Apotex Inc.

The pharmaceutical market has transformed into a global industry within just a few decades. Many companies have sites across the globe, presenting challenges when it comes to harmonizing process validation approaches.



44 PDA Member Reports from the 2016 PDA/FDA Joint Regulatory Conference

Missed this year's *PDA/FDA Joint Regulatory Conference*? Find out what happened from three attendees who reported on the sessions.



46 PDA Then and Now

Nov. 18 marks PDA's 70th anniversary. In light of this momentous occasion, the *PDA Letter* wanted to highlight significant milestones in PDA's history, and compare where we were then to where we are today.

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