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### 22 Strategies for Controlling Raw Materials in Biologics Manufacturing

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.

Cover Art Illustrated by Katja Yount

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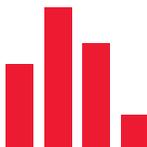


### 28 Proposed EP Chapter Addresses ATMP Raw Material Quality

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. At the same time, both industry and regulators fear being too prescriptive lest companies cease developing these products.

### 32 Raw Material Control Strategy Key to Overall Control

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 endgame approach; it also begins at the bottom with the selection of raw materials.



### 34 PDA InfoGraphic: Mapping the Raw Material Supply Chain

How can companies deal with increasing supply chain complexity?

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### 22 Does Pharma Really Need Continuous Processing?

Continuous processing (also known as continuous manufacture or flow processing) and semicontinuous processing have been around for quite a while, and are the norm in the majority of other manufacturing industries. For example, continuous processing is prevalent in paper production, automobile manufacture, petroleum and gas production, food processing, and electronic components industries. In the pharmaceutical industry, it is primarily used to produce over-the-counter products considered nonpharmaceutical by regulators, such as toothpaste

Cover Photo courtesy of Dominick Reuter

Pictured is a prototype continuous manufacturing system developed by the Massachusetts Institute of Technology and Novartis as part of a collaborative research project.

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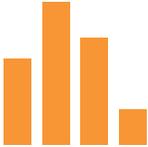
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Is the state of manufacturing in the global pharmaceutical industry on par with the troubled state of the U.S. and European auto industry in the 1980s and 1990s?



### 32 PDA InfoGraphic: Upstream BioManufacturing: Batch vs. Continuous

This issue's infographic offers a comparison of continuous and traditional batch processing for upstream biomanufacturing.

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### 22 Want to Make the FDA Quality Dean's List? Take a Look at Your Metrics

Walter Morris, PDA

No one can say for sure what the ultimate impact of the U.S. FDA's pharmaceutical quality metrics initiative will be on both pharmaceutical manufacturers and the Agency's enforcement practices. A vision of what the future holds, however, materialized during the *2014 PDA Pharmaceutical Quality Metrics Conference* in Washington, D.C., Dec. 2–3.

Cover Art Illustrated by Katja Yount

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Transcript from the final panel discussion at the 2014 PDA Pharmaceutical Quality Metrics Conference

During the last session of the 2014 PDA Pharmaceutical Quality Metrics Conference, the following regulatory representatives from the U.S. FDA, EMA and MHRA each offered a final statement: **Janet Woodcock**, MD, Director, CDER; **Howard Sklamberg**, Deputy Commissioner for Global Regulatory Operations and Policy, FDA; **Ellen Morrison**, Assistant Commissioner for Operations, ORA; **Cynthia Schnedar**, Director, Office of Compliance, CDER; **Karen Midthun**, MD, Director, CBER; **Emer Cooke**, Head of International Affairs, EMA; and **Gerald Heddell**, Director, Inspection, Enforcement, and Standards Division, MHRA.



### 34 Making a Masterpiece of Manufacturing

A classic painting is the sum of its parts. Quality metrics are just one piece that comprises industry and PDA members' vision for manufacturing.

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## 22 Data Integrity Issues: Causes and Solutions Elayne Best, Biogen Idec

The integrity of the data collected and recorded by pharmaceutical manufacturers is critical to ensuring that high quality and safe medicines are produced. What exactly is data integrity and why is it so important?

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### 28 **Incorporating Data Integrity into Your Quality Management System** **Anthony C. Warchut, PAREXEL**

ICH Q10, Pharmaceutical Quality Systems was recommended for adoption to the regulatory bodies of the European Union, Japan and the United States in 2008. EMA then formally approved it that same year. In 2009, the U.S. FDA adopted it as a guidance document. This begs the following question, if companies have adopted the principles of ICH Q10, why have the FDA and EMA been experiencing an increase in the number of data integrity issues found during recent inspections?



### 32 **PDA InfoGraphic: Data Integrity Citations in 2014**

This issue's infographic features a compilation of data integrity issues cited in U.S. FDA warning letters and EU statements of noncompliance.

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### 28 **Key Considerations for Successful Technology Transfers** Jose Caraballo, Bayer HealthCare

The pharmaceutical industry is constantly engaged in transferring processes between organizations or locations; these transfers are critical to get product to market. The number of transfers is expected to increase as countries act on the need to manufacture drug products locally. This activity is part of the normal lifecycle of a drug product, and it can range from very successful transfers to problematic ones, based on a myriad of factors. Among them are process and product robustness, the readiness of organizations to engage in transfer activities, availability of experts, and the timely execution of all the work needed to complete a transfer.

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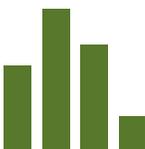
### 32 Portable Pods Part of New Strategy for Pfizer Rebecca Stauffer, PDA

On March 17, the *PDA Letter's* **Walter Morris** and **Rebecca Stauffer** interviewed **Michael O'Brien**, Vice President, Technology and Innovation, Worldwide R&D – PTx Pharmaceutical Sciences, Pfizer, following his presentation, “Portable, Continuous, Miniature, & Modular (PCM&M) Development and Manufacturing: The Foundation for a Transformational Development, Manufacturing & Distribution Model” at the *2015 PDA Annual Meeting*.



### 35 Quality's Role as Financial Officer – Can you speak \$, €, £, ¥, CHF? Jennifer Magnani, Sanofi Pasteur, and Anders Vinther, PhD, Sanofi Pasteur

Why is it that Finance and Quality are seen as immiscible as oil and water? Rarely do you experience a financial discussion in a Quality meeting setting. Likewise, rarely do you see a cGMP compliance or quality discussion when the organization gets together to discuss budget. Having financial discussions with Quality professionals is generally linked to production volumes and the cost of the Quality organization as overhead.



### 36 6 Obstacles to Avoid for Successful Tech Transfer

Just like achieving a good golf game, achieving a successful tech transfer requires hitting a precise target while moving from one end (the Sending Unit, or SU) to the other (Receiving Unit, or RU). And like the best golf players, the most successful tech transfer players invest in training and preparation, require considerable teamworking skills and have many responsibilities in order to reach success.

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### 20 Inconsistent Expectations Clash with Industry Best Practices for Sterile Products

Paul Larocque, Acerna Inc

When it comes to manufacturing sterile drug product, discrepancies exist in the available regulatory guidances/compendial documents and industry best practices that cause tension in the industry. These divergences often affect my recommendations to clients regarding updating or adding new facilities. As examples, I discuss several of these divergent interpretations as they relate to environmental programs.

Cover Art Illustrated by Katja Yount

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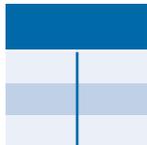
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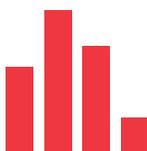
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### 26 USP <1116> and its Implications for Measuring Microbial Recovery Rates Claudio Denoya and Gilberto Dalmaso, Particle Measuring Systems

The recently revised United States Pharmacopoeia (USP) chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments* includes a thorough description, definitions and guidance on microbiological control and monitoring in aseptic processing environments. Chapter <1116> is arguably one of the most comprehensive informational chapters from the USP, and it is particularly challenging due to its proposal regarding measurement of microbial contamination based on Contamination Recovery Rates (CRR) rather than the conventional enumeration of colony forming units (cfu). Instead of using the microbial limits currently endorsed by aseptic guidances—which are based on cfu—<1116> proposes CRR values expressed in maximum allowed percentage of contaminated samples. The proposal is generating a broad range of discussions among pharmaceutical professionals regarding potential implications of these changes.



### 30 PDA InfoGraphic: The Future of Aseptic Processing is Now!

This issue's infographic showcases a fully automated system used to develop a personalized regenerative medicine.

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### 34 FDASIA: Three Years of Success Rensi Sutaria, Banner Life Sciences

It has been three years since the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted. This Act expands the U.S. FDA's authorities and strengthens its ability to safeguard and advance public health by giving it the power to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products; promote innovation to speed patient access to safe and effective products; increase stakeholder involvement in FDA processes; and more. FDA has established a three-year implementation plan to help the public track the progress of these, and other provisions, established under FDASIA. As the three-year anniversary approaches, it presents a critical milestone to evaluating the success of this multifaceted law.

Cover Art Illustrated by Katja Yount

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**Dipti Gulati, PhD, PJI Biotech**

How is FDASIA affecting the global drug supply chain?

### 41 **Analyzing FDASIA's Progress Since 2012**

**Jeffrey Broadfoot, Emergent BioSolutions**

July 2015 marks the three year anniversary of FDASIA. This law—specifically Title VII of it—gives the U.S. FDA new tools and authorities to address the challenges of an increasingly complex and globalized drug supply chain. So, what has FDA been able to accomplish in these past three years, and what is yet to come?



### 42 **Continuous Manufacturing Success Lies in New Technologies, Integration and Education**

**Rebecca Stauffer, PDA**

On Sept. 30, Salvatore Mascia, CEO, CONTINUUS Pharmaceuticals, will present his talk on integrated continuous manufacturing at the *2015 PDA Manufacturing Science Workshop* following the *2015 PDA/FDA Joint Regulatory Conference*. Mascia spoke with the *PDA Letter* about his upcoming talk.



### 44 **The ABCs of the PDA/FDA Joint Regulatory Conference**

This issue's infographic looks at the various acronyms that have dominated the alphabet soup that is the *PDA/FDA Joint Regulatory Conference*.

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### 20 Science Driving New State-of-the-Art Practices for Microbial Control Rebecca Stauffer, PDA

While microbial contamination control in pharmaceutical manufacturing is at a level needed to ensure safe products, most would not characterize it as “state-of-the-art.” An outsider taking a stroll through most pharmaceutical operations might question why 21st century products produced primarily with 21st century technologies are monitored using 19th and 20th century microbial tests. It is fair to say that this is one area where the science and its practical applications have left the industry far behind.

Cover Art Illustrated by Katja Yount

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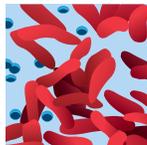
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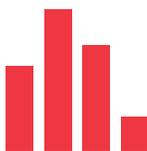
### 26 **The Story Behind the 0.45 $\mu\text{m}$ Membrane Pore Size Rating** Claire Fritz Briglia, EMD Millipore

Production personnel generally conduct filtration using membranes with pore size ratings of 0.22  $\mu\text{m}$  or lower, focusing on retention of microbes and particulates, while those in the microbiology laboratory choose membranes with 0.45  $\mu\text{m}$  pore size ratings. This begs the question, do your QC analysts understand why they use a different membrane pore size rating than that used in production?



### 30 **Profiling Leachables in Single-Use Biocontainers** Jian Liu, PhD, Hans Lee, PhD, Kiyoshi Fujimori, Michael Ronk, Matthew R. Hammond, PhD, and Yasser Nashed-Samuel, PhD, Amgen

In the face of unprecedented competition within the industry, biopharma companies must now undergo significant transformation in order to meet the challenge of reducing costs while also providing safe and effective therapies. The adoption of single-use systems (SUS) is one key strategy for those companies actively involved in this transition. Compared to traditional manufacturing technology, SUS deliver many advantages, such as reduced requirements for process validation, higher manufacturing flexibility, etc., which ultimately translate into higher operating efficiency and reduced manufacturing costs.



### 34 **The Value of Import Testing versus Surveillance Testing**

This issue's infographic compares import and surveillance testing of drug products.

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### 28 **Biosimilar Developers Must Scale Mountains of Data** Rebecca Stauffer and Walter Morris, PDA

On March 6, the U.S. FDA approved Sandoz's filgrastim product, Zarxio, a biosimilar of Amgen's Neupogen. This was a big step for the Agency, and one some feel was long in coming. The same product was approved for marketing in Europe six years earlier (under the name Zarzio). Incidentally, the following year, the Biologics Price Competition and Innovation Act (BPCIA) was signed into law in the United States, which was seen as opening the gateway for biosimilars in the United States.

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### 32 Tools Available to Reduce Risk During Drug Development Mark Tunkel, Insight Product Development

The market for combination products continues to grow ever increasingly competitive, especially as innovative therapies and high-volume generic alternatives crowd the marketplace. To achieve success within this new paradigm, combination product manufacturers must get their products to the market quickly and efficiently. At the same time, manufacturers also face substantial lead time required to meet U.S. FDA approval, resulting in intense pressure.



### 36 PDA Letter InfoGraphic: Approval Process for Biosimilars vs. Biologics

The processes for evaluating the effectiveness of a biosimilar and a reference biologic can, in some ways, be considered inverses of each other. Still, the review process for both relies on carefully controlled studies and quality data.

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### 34 Career Breaks: Paths to Reentry Enith Morillo, Complya Consulting Group

Those of us in the industry who choose or are forced to take a break from a thriving career face the challenge of taking the road “less traveled,” to quote poet **Robert L. Frost**, when reentering the workforce. Whether to raise a family, care for elderly parents, serve in the military or travel the world, professionals who take a break compete for employment with those who have uninterrupted career paths. A similar challenge faces “late entrants”—college graduates who, for many reasons, do not immediately enter the workforce right after finishing school.

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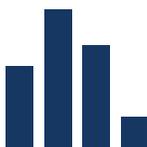
### 38 Which Laboratory Software is the Right One For Your Lab? Joe Liscouski, Institute for Laboratory Automation

“Why do you need this laboratory information management system (LIMS)?” “We have an enterprise resource planning (ERP) system, why do we need to purchase yet another software product?” “How will the system you’re recommending improve lab operations?”



### 42 Change is Coming to FDA Inspections: Are You Prepared? Rebecca Stauffer, PDA

Organizational changes within the Office of Regulatory Affairs and CDER’s new Office of Pharmaceutical Quality will impact the nature of U.S. FDA inspections in the coming years. Naturally, companies are anxious to see how these new approaches to inspections will look like as they get off the ground.



### 46 The State of U.S. Pharma Manufacturing Jobs in 2014

Each year, the U.S. Bureau of Labor Statistics collects occupational data covering a wide range of industries—including our own. This data is then published the next year. Below are statistics for pharma manufacturing in 2014.

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