People • Science • Regulation

PDA Letter

Volume LI • Issue 2 www.pda.org/pdaletter February 2015

Does Pharma Really Need Continuous Processing?

22

Photo courtesy of Dominick Reuter

Show Issue

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- **Jeff Boyd,** Head of Technical Operations & Gene Therapies Unit, *Novartis*
- **H. Gregg Claycamp, PhD,** Research Biologist, CVM, *FDA* – ***Newly confirmed***
- **Kathryn King,** Biologist, CDER, *FDA* – ***Newly confirmed***
- **Jeff Levy, PhD,** Vice President, Technical Services, Manufacturing Science, *Eli Lilly & Company*
- **Mark McCamish, MD, PhD,** Global Head, Biopharmaceutical Development, *Sandoz International GmbH*
- **Michael O'Brien,** Vice President Technology & Innovation, Worldwide R&D – PTx Pharmaceutical Sciences, *Pfizer, Inc.*
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Red Rock Casino Resort and Spa, Las Vegas, NV

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Exhibition: March 16-18 Post-Conference Workshop: March 18-19 Courses: March 19-20

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Cover

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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Learn It, Experience It: The PDA/INTERPHEX Partnership

PDA and INTERPHEX have partnered to bring to those involved in bio/pharmaceutical manufacturing unrivaled exposure to education, networking and technology.

Together, PDA and INTERPHEX present, "Learn It, Experience It," a power-packed, two-event series that delivers the latest in bio/pharmaceutical manufacturing science, innovation and technology.

The "Learn It" part begins at the *2015 PDA Annual Meeting,* March 16–18 at Red Rock Casino Resort and Spa in Las Vegas, where a robust lineup of industry and regulatory experts will provide the latest updates on the evolution of manufacturing in the bio/pharmaceutical industry and strategies for remaining competitive. View the agenda to see the complete list of daily plenary sessions and parallel tracks addressing the evolving manufacturing environment and the importance of a science- and technology-based approach to quality culture (www.pdaannualmeeting.org).

Then, from April 21–23 at the Jacob K. Javitz Convention Center in New York, NY, participants can "Experience It" at INTERPHEX 2015, which features exhibits of the same technologies discussed at the PDA Annual Meeting. This year, INTERPHEX's footprint will be 30% larger to accommodate even more cutting-edge technology, product, and value-added services.

In addition, in the PDA Learning Center on the INTERPHEX 2015 show floor, PDA will offer technical education that builds on the content provided at the *2015 PDA Annual Meeting.*

The combination of informative discussions and technology demonstrations in areas most important to the biopharmaceutical and pharmaceutical manufacturing industry, including the future of manufacturing, aging facilities, biosimilars, and drug quality and safety, makes this two-event series a "must attend" for anyone involved in the bio/pharmaceutical industry.

The *2015 PDA Annual Meeting* and INTERPHEX 2015—the best and only way to Learn It, Experience It!

Hear What FDA Has to Say at the Annual Meeting

In addition to industry experts, this year's Annual Meeting will feature U.S. FDA speakers **Kathryn King** and **H. Gregg Claycamp**. King, a biologist with CDER, will discuss "Emerging Methods for Virus Detection and Removal" during Session "C3: Virus Contamination," Tuesday, March 17, 10:45 a.m. –11:15 a.m. Claycamp, a research biologist with the Center for Veterinary Medicine, will speak on "Enhanced Decision Making Using ICH Q9" at Breakfast Session IV on Wednesday, March 18, 7:15 a.m.–8:15 a.m.

In addition, **Sharon Thoma,** PharmD, National Expert, Pharmaceutical Inspections, ORA, has been invited to speak on inspection trends during the final plenary session on March 18 at 11 a.m.

Continue to visit www.pdaannualmeeting.org as speakers are confirmed and added to the agenda.

Continue the Conversation at PDA Connect℠

PDA invites members to join our new online collaboration tool that allows members to communicate and share knowledge about our industry. This site features forums and listservs, file libraries, event calendars and more! Members can select different forums based on chapter or interest group; at this time 14 interest groups and seven chapters have forums on the site.

Visit community.pda.org to sign up and to continue the conversation!

PDA Volunteer Spotlight

John Ayres, MD

- Senior Director, Product Safety Assessments
- *Eli Lilly*
- Member Since | 2003
- Current City | Indianapolis, Indiana
- Originally From | Frankfort, Indiana

PDA provides a forum that is sufficiently broad to cover the spectrum of pharmaceutical science and regulation

John was a weatherman while serving in the U.S. Navy aboard the USS Kitty Hawk

Why did you decide to volunteer for PDA?

I wanted an opportunity to bring a physician's perspective into the discussions around parenteral therapeutics as well as interact with scientists outside of my company.

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

They've all been really enjoyable. But I think that the *Visual Inspection Forum* is probably at the top of my list. Here, good science from manufacturing control and inspection strategies, visual inspection technologies, and the impact those factors have on patient safety all seem to come together in a very tangible fashion.

What led you to join PDA's *Visual Inspection Forum* Program Planning Committee?

John Shabushnig was leading a discussion at a Visual Inspection Interest Group meeting I attended at one of my first PDA meetings. The questions they explored were interesting and intersected with my personal interest in the clinical implications of parenteral therapies. A few years ago, John asked me to participate as a speaker at one of the meetings and subsequently to serve on the planning committee. It has been a great learning experience for me.

What is your dream job?

This is it. I have the privilege to work with some very bright people, learn something new every day, and feel that my work makes a difference in the lives of patients.

What would you tell someone who is just starting out in the industry?

We are making medications, diagnostics and medical devices intended to promote a healthy life and longevity. It is a special profession and an opportunity that few have to make lives better. Never forget that patients, their families and their healthcare providers depend on your diligent attention to detail, quality and scientific curiosity.

What was your least favorite subject in school?

Probably "Introduction to Psychology"

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The interactive, members-only online community exclusively *for you!*

With PDA Connect℠, you can:

- Connect and engage with your local chapter
- Participate in discussions about niche topics in your private interest group
- Network and build collaboration with fellow PDA members around the world
- Gain access to members-only digital resources

Attending the Annual Meeting? Stop by the PDA Booth to set up your online profile and take and upload your profile photo!

CONTINUE THE CONVERSATION @ PDA CONNECT℠!

PDA®
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tales from the trail

Exciting PDA Events from Opposite Sides of the Globe

Rebecca Stauffer and Katja Yount, PDA

During the final quarter of 2014, PDA publishing team members **Rebecca Stauffer** and **Katja Yount** went to opposite parts of the globe as part of a greater effort to cover PDA events worldwide. Rebecca hopped across the pond (only her second trip to Europe) to attend the PDA Europe *Parenterals* conference in Munich, Germany—finally putting to use her four years of high school German! Katja, on the other hand, stayed stateside and flew to the great state of Texas to attend the Nov. 14 PDA Texas Chapter meeting in Austin on critical manufacturing systems.

On Nov. 3, Rebecca arrived in Munich following a harrowing transatlantic flight. Upon her arrival, she met **Georg Rössling,** the head of PDA Europe. Later that day, he introduced her to some of the PDA Europe staff diligently working onsite in preparation for the conference. That evening, she attended a dinner for conference speakers and presenters, and thoroughly enjoyed time spent talking with these fascinating individuals.

The following two days proved to be a blur of engrossing talks on trends and innovations impacting parenteral manufacturing. **[Editor's Note:** For an overview of these talks, see p. 29**].** She also interviewed some of these speakers as well as conference chair **Mauro Giusti.** During refreshment breaks when she was not interviewing, she met a number of individuals, including Saudi Arabian regulator **Turki Ibrahim Almuhanna, Derek Duncan, Jason Orloff, Christian Wölbeling** and others.

Meeting co-chair Wenzel Novak (l) and Georg Rössling (r) share some German camaraderie at the Hofbraeuhaus

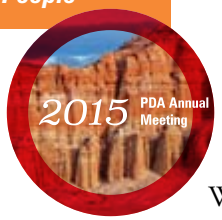
The first day of the conference concluded with a trip to the famous Hofbraeuhaus to enjoy German delicacies and beer and to toast a successful first day. Many even dressed up in traditional Bavarian attire, though Rebecca stuck to her traditional D.C. attire of khaki pants and a nice shirt. It was also unseasonably warm for southern Germany and she regretted her choice to bring mostly heavy winter clothes!

The next day offered regulatory-focused presentations from **Gabriele Gori, Hemisha Ly, Andrew Hopkins** and others, concluding with a panel discussion also featuring regulator **Beate Reutter.** All in all, Rebecca was impressed by the energized atmosphere of the conference and attendees' dedication to advancing the state of the industry. The Q&A discussions were filled with fascinating dialogue and it was easy to see that the presentations made a lasting impact on attendees. She could hardly wait to return to D.C. and begin writing articles about the meeting!

Just a few days later on Nov. 13, Katja flew in to the Lone Star State, looking forward to representing PDA and the publishing team. She eagerly anticipated a milder climate compared to D.C., but after landing, she found to her dismay that Austin was in the throes of a recordbreaking cold snap for that entire weekend. Much like Rebecca, she too regretted her decision not to pack for the unseasonable weather.

Katja represented PDA's publishing team for this newly formed chapter. As such, she offered an overview of the benefits of writing for

Continued at bottom of page 12



Take a Gamble and Network at this Year's Annual Meeting

What happens in Vegas doesn't necessarily have to stay in Vegas! This year's *PDA Annual Meeting* offers many exciting networking opportunities for you to make lasting connections, which are critical to advancing your career in the industry.

Here is a list of some of this year's exciting events at the Annual Meeting, broken down by day:

Sunday, March 15

PDA 9th Annual Fun Walk/Run

Starts at 8 a.m. Participants can choose to sign up for either the 5K run or 3K walk. $40 per attendee or guest. Proceeds support the Cure 4 the Kids Foundation.

Meet and Greet Reception

3 p.m. to 6 p.m. near the registration area.

Bowling for the Stars

7 to 9 p.m. at Red Rock Lanes Bowling Center. $60 per person. Participants will be divided into teams of four. There will be food, prizes and music.

Monday, March 16

Orientation Breakfast

Begins at 7 a.m. before the first plenary session. New members will learn about the Association from board members, volunteers and Membership staff. *(By invitation only)*

Networking Reception

5:30 p.m. to 7 p.m. in the Exhibit Hall. Refreshments and drinks will be served while attendees mingle.

There will be additional opportunities for networking during refreshment breaks throughout the conference. For more information please visit www.pdaannualmeeting.org.

Tales from the Trail continued from page 11

PDA publications to Texas members—an opportunity to get their research and observations out to the wider community.

While at the event, she ran into regular PDA volunteer and contributor **Marsha Hardiman,** who, along with collaborator **Cheryl Zaman-Zadeh,** presented data on aging facilities. This gave those attendees who could not make it to the *PDA/FDA Regulatory Conference* session on the topic a chance to hear the findings in person and to ask their own questions.

Another PDA member, **Stephen Wiggins,** stressed the importance of design commissioning in critical systems. For the first presentation of the day, Katja found this talk to be especially energetic in breaking down the importance of system design. As someone who professes to love spacial design, she was especially interested in his descriptions of a particular facility. The day was wonderfully bookended by **Jim Polarine's** light yet informative discussion on facility contaminants.

For a small chapter event this was a pretty excited group. The Texas Chapter may still be new but it presents a lot of potential due to the energy and commitment of its members.

Both Katja and Rebecca enjoyed these opportunities to attend PDA events outside the D.C. area. Look for us at future upcoming chapter and international events but hopefully in more seasonably appropriate attire!

PDA Who's Who

Rebecca Stauffer, Writer/Editor, PDA

Katja Yount, Publication Design Specialist, PDA

Georg Rössling, Sr. Vice President, PDA Europe

Derek Duncan, Director, Operations, Lighthouse Instruments

Mauro Giusti, PhD, Director, Technical Services and Manufacturing Sciences, Eli Lilly

Gabriele Gori, Global Head, GMP Compliance and Auditing, Novartis Vaccines

Marsha Hardiman, Senior Consultant, Concordia ValSource

Andrew Hopkins, Senior GMP Inspector, MHRA

Turki Ibrahim Almuhanna, Pharmacist, Saudi Food and Drug Authority

Jason Orloff, Statistical and Chemical Engineering Consultant, PharmStat

Jim Polarine, Technical Services Specialist, Steris

Hemisha Ly, Process Engineer, Merck

Wenzel Novak, Director Pharmaceutical R&D, Groninger

Beate Reutter, Head, GMP Inspection, National Office for Social Services, Schleswig-Holstein

Stephen Wiggins, Newcomb & BOYD

Christian Wölbeling, Senior Director, Werum IT Solutions

Cheryl Zaman-Zadeh, NovaTek

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2014 PDA Pharmaceutical Quality Metrics Conference

Sessions

Opening Plenary: FDA Update on Quality Metrics

(l-r) Neil Stiber, PhD, CDER, U.S. FDA; Theresa Mullin, PhD, CDER; Emer Cooke, EMA; Steven Mendivil, Amgen; Guy Villax, Hovione

Closing Plenary

(l-r) Karen Midthun, MD, CBER, FDA, and Gerald Heddell, MHRA

P6: Quality Leadership Panel Discussion

(l-r) Anders Vinther, PhD, Sanofi Pasteur; Guy Villax, Hovione; Martin VanTrieste, Amgen; Erwin Vanhaecke, PhD, Novartis; Zena Kaufman, Hospira; Jacqueline Elbonne, PhD, Merck; Eric Drape, Teva; Deborah Autor, Mylan

Closing Plenary

(l-r) Janet Woodcock, MD, CDER, U.S. FDA, and Russell Wesdyk, CDER

Ellen Morrison, ORA, FDA (third from the left), answers a question during the U.S. FDA and EMA Senior Leadership Panel

Invigorated by discussions during the plenary sessions (above) and the interactive breakout sessions, attendees discussed the metrics-related topics of the day during refreshment breaks.

snapshot

Manufacturing Science Progam℠ Launches

Walter Morris, PDA

PDA is launching a Manufacturing Science Program℠: Enabling Pharmaceutical Manufacturing's Future. The Manufacturing Science Program℠ will fulfill the following goals:

- Highlight the ongoing focus PDA has on pharmaceutical and biopharmaceutical manufacturing.
- Strengthen and build practical solutions by filling known gaps in current manufacturing science as well as gaps that will become apparent based on ongoing developments and analyses.
- Identify and encourage use of new manufacturing technology and methods.
- Provide Portfolio Analysis and Management of these activities across PDA.

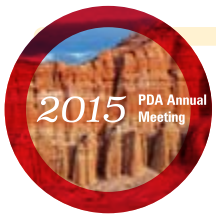
"PDA is based in science with a long tradition of providing the science needed to advance our industry and benefit the public health," said PDA President **Richard Johnson.** "While we have always been active in manufacturing science, we want to focus more attention on our contributions. The upcoming *2015 PDA Annual Meeting* has an entire track dedicated to improving manufacturing performance, in line with this Manufacturing Science Program℠."

A steering committee will oversee the Manufacturing Science Program℠. It will consist of a representative of PDA's volunteer Board of Directors, up to five other selected volunteers, and members of PDA's professional staff.

The deliverables for the Manufacturing Science Program℠ are:

- Catalogue of all manufacturing-related PDA activities
- Heightened internal and external awareness of these activities
- Identification/prioritization gaps where additional activities are needed
- Recommendations to the PDA Board of Directors, Advisory Boards, and staff for new projects based on gap/needs assessment
- Steering committee oversight of projects to identify slow moving projects, projects requiring additional attention, and projects that may no longer be needed or have a low priority
- Periodic reports on the progress to the Board of Directors and PDA President

The Manufacturing Science Program℠ is the successor to PDA's Paradigm Change in Manufacturing Operations (PCMO)®, which formed in 2008, a highly successful program aimed at helping companies establish an innovative environment for continual improvement of products and systems, integrate science into manufacturing practice, enhance manufacturing process robustness, risk-based decisionmaking and knowledge management, and foster communication among industry and regulatory authorities, All the deliverables of PCMO® have been accomplished.



Meeting *Preview*

Interest Group Schedule

As always, relevant interest groups will meet for the first two days of the *2015 PDA Annual Meeting.* Below is a schedule of interest group meetings that fall under the Science and Biotechnology Advisory Board umbrellas. **Note:** All interest group meetings are open to meeting registrants (For RAQAB interest group meetings, see p. 34).

Monday, March 16	Tuesday, March 17
4 p.m. – 5:30 p.m.	4 p.m. – 5:30 p.m.
Filtration Interest Group	Sterile Processing/Parenteral Drug Manufacturing Interest Group
Biotechnology Interest Group	Microbiology/Environmental Monitoring Interest Group
Combination Products Interest Group	Visual Inspection of Parenterals Interest Group
Vaccines Interest Group	Packaging Science Interest Group
Pre-filled Syringe Interest Group	
Process Validation Interest Group	
Facilities and Engineering Interest Group	

Combination Products Continue to Face Challenges

Lee Leichter, P/L Biomedical

The number and types of drug delivery combination products currently under development are growing rapidly, fueled by the increasing trend toward self-administration and the shift of clinic-oriented treatment to the home environment. Almost half of the biologics now marketed are self-administered, with many more in development. Other trends, such as the conversion of intravenous to subcutaneous formulations have fueled the demand for new, more complex delivery products.

By their nature, combination products raise issues and challenges that do not fit the standard approaches appropriate and/or successful for standalone drug, biologic or medical device products. For global companies, these challenges are amplified as each region has its own approach; many regions have not even begun to address the complexities of these products.

In the United States, the expectations extend to products that have been safely and successfully marketed for years. Recent clarifications of the cGMP regulations for combination products in the United States have reinforced the importance of additional relevant drug, device and biologic cGMP obligations for products, including prefilled syringes and many "kits," that may not have been contemplated as combination products by the manufacturer during their development.

Below are some of the issues and challenges surrounding drug delivery combination products.

Medical Device GMPs (Quality System Regulation): Integration of the Medical Device Quality System requirements for drug delivery combination products has been, and remains, a challenge since the publication of the draft U.S. FDA guidance in 2004. The proposed rule on cGMPs for combination products reinforced FDA's position on what would be required, and how the rule would be enforced. When the final rule became effective in 2013, many of FDA's policy positions were explained, however, additional clarifications were promised.

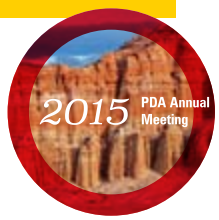
Design Controls: Design controls are part of the Quality System requirements for devices and combination products. Design control requirements extend to the combination product as a whole. Integration of pharmaceutical elements, such as Quality by Design, Process Analytical Technology and current thinking on criticality analysis presents unique challenges.

Technical Documentation: Application of existing pharmaceutical requirements, such as stability and container closure integrity testing, takes on new elements when applied to an integrated drug delivery combination product.

Postmarketing Requirements: In addition to the challenges faced for bringing legacy products into compliance, other postmarketing challenges include change and risk management and adverse event reporting.

Cross-labeling: The United States is the only region that has identified cross-labeled products in their combination product regulatory paradigm, embracing certain separately marketed products that work together to achieve the intended therapeutic effect. The regulatory definition is confusing and has challenged both industry and the FDA. In many cases, such products are developed by two separate companies, and difficulties arise when the two companies do not collaborate.

The *2015 PDA Drug Delivery Combination Products Workshop* will address these challenges with advice from experts, case studies from pharmaceutical and biotech companies and regulatory updates. For more information about this workshop, please visit www.pda.org/2015-pda-drug-delivery-combination-products-workshop. For information about the PDA Education course following the event, visit www.pda.org/technical-development-of-prefilled-syringes-autoinjectors-and-injection-pens.



Industry Ready to Tackle Numerous Challenges

Ursula Busse, PhD, Novartis, and Morten Munk, NNE Pharmaplan

The pharmaceutical industry is facing a new reality where new challenges have been added to the already long list of complex tasks needed to supply the market with safe and effective products. The issue of drug shortages is one example, rising from a relatively rare local issue to a significant global concern. The increased complexity of the supply chain, greater competition and new types of products and treatments have increased the pressure on cost-effective manufacturing and distribution as well as forced international regulatory bodies to catch up to this new reality.

Moreover, new therapeutic approaches such as cell and gene therapy entail a complete change in the pharmaceutical industry's traditional manufacturing paradigm. In order to stay competitive, companies are looking for ways to improve the efficiency of operations while also keeping fully compliant with global regulatory requirements.

Updating current facilities as well as applying innovative approaches and cutting edge technologies to new facilities and manufacturing strategies will enable the industry to meet these existing and future challenges.

A key requirement to be successful in this challenging environment is to keep updated about those new approaches, technologies and therapies in the pharmaceutical industry. But how can those involved in the industry expand their knowledge in these new areas? The most effective way to gain this knowledge is to attend the *2015 PDA Annual Meeting,* March 16–18 in Las Vegas. This meeting will provide industry with first-hand opportunities to stay current about advances in modern sterile manufacturing.

Plenary sessions will address key areas of a sustainable, effective and compliant manufacturing environment and highlight the importance of a science and technology-based approach to quality culture. They will cover manufacturing of the future, current inspection trends and aging facilities, and also feature new classes of therapeutics such as cell/gene therapies and biosimilars.

On behalf of PDA, we look forward to seeing you at the Annual Meeting. Visit www.pdaannualmeeting.org to learn more. For information on PDA Education courses following the meeting, visit www.pda.org/2015-pda-annual-meeting-course-series.

Aging Facilities: A Global Issue with Many Solutions

Maik Jornitz, G-Con

Aging facilities have become a rising concern in the pharmaceutical and biopharmaceutical manufacturing industry, as quite often, aging manufacturing can be connected to drug shortages. This is not a region-specific concern; instead, it represents a global issue. Too often, cases of aging or obsolescence of equipment, unit operations, processes or entire facilities have been encountered. Not only are the facilities getting older, less maintained or just plain out-of-date, but so are the analytical methods that control the processes and drug quality. In some cases, a facility was designed to manufacture a product no longer produced, and a new product was forced into that process, potentially not fitting in with the environmental conditions or flows used for the previous product. In other instances, the facility received additions to fulfill capacity increases. These additions may have different technology levels and could experience difficulties during integration.

Aging manufacturing can be distinguished into three categories. A facility could be impacted by all three or just one. These categories are: facilities, processes and analytics—each playing a crucial part for manufacturing efficiencies, but moreover, quality.

The *2015 PDA Aging Facilities Workshop* following the Annual Meeting will address the topic of the definitions of "aging" and what constitutes an aging facility. Case study presentations will show examples of failures and successes of modernization and improvement actions. The case studies will highlight crucial lessons learned. Not only is the workshop filled with exceptional speakers and up-to-date content, but two breakout sessions allow participants to get actively involved by discussing their experiences, sharing their know-how and learning from each other. PDA has shown to be an outstanding facilitator for such active participation and discussions. The *2014 PDA Drug Shortage Workshop* showed how lessons learned and proactive suggestions can be concentrated to further action items and improvement options.

Join us at the *2015 PDA Aging Facility Workshop*. Interact and learn with us! Be prepared, proactive and on top of your continuous improvement undertakings to eliminate the risks of aging manufacturing. Visit www.pda.org/2015-pda-aging-facilities-workshop to learn more.

Hundreds Converge for the Latest in Microbiology

Tricia Vail, Pall, and Youwen Pan, PhD, Genentech/Roche

PDA's *9th Annual Global Conference on Pharmaceutical Microbiology,* held in Bethesda, Md. in October, offered attendees an opportunity to explore a breadth of pharmaceutical microbiology concerns and topics. Beginning with a look at norovirus and ending in an open discussion with U.S. FDA regulators, attendees could learn about the latest in water system sanitation, gamma sterilization, objectionable organisms, media fills, the past and present of LAL, and real-time risk assessments—among many other micro-centric talks. Over 300 attended this conference, representing all four corners of the globe.

The conference started off with a look at the very contagious norovirus, and its significance in the travel and food industries from **Jan Vinjé,** PhD, Head, National Calicivirus Laboratory, Division of Viral Diseases, CDC. He discussed the pathological history of norovirus and control measures, including the potential for a vaccine. One of his surprising revelations was that while the virus is most well known for affecting cruise ship passengers, it is also the leading cause of most foodborne illnesses.

Topics explored during breakout sessions included: biofilms and bioburden control, utilization of emerging sterilization technologies, methodologies used in detection and control of objectionable organisms in nonsterile products, implementation of parametric release on terminally sterilized products, and more.

Bacterial endotoxin testing (BET), notably the issue of LER, was also highlighted. Several sessions and poster presentations were dedicated to endotoxin testing, including a keynote address delivered by **Jack Levin,** MD, Professor of Laboratory Medicine, University of California School of Medicine, one of the key scientists responsible for developing BET using *Limulus* amebocyte lysate (LAL). Levin introduced the method development history of using LAL assay for bacterial endotoxins in a test sample and some of the challenges in applying this multichain enzymatic reaction based bioassay. Other talks primarily focused on the development and progress of methodologies in overcoming LER effects generated from certain types of buffers used in biologics formulations. FDA Lead Safety Officer **Patricia Hughes** talked about the history of LER issues and concerns, new challenges from the review of BLAs, and outlined new regulatory perspectives on how to manage products exhibiting LER for new product BLA and IND filings.

The conference concluded on the third day with pharmacopoeial and regulatory updates. The first talk centered on the upcoming USP <1223>, <1228>, and <1229> chapters and their subsequent subchapters. The USP is in the process of revising chapter <1211> on the topic of sterility assurance only while creating two new chapters: <1228> and <1229>. The overarching new chapter <1229> is devoted to general principles of sterilization, and its subchapters will cover individual sterilization techniques. Likewise, the new chapter <1128> is dedicated to the principles of depyrogenation; its subchapters cover individual depyrogenation processes. The discussion on USP <1223> highlighted the upcoming revision that is expected to facilitate the validation of alternative microbiological methods by easing implementation concerns and regulatory hurdles.

The last two talks focused on regulatory updates with a presentation by FDA inspection expert **Sharon Thoma,** PharmD, followed by the "Ask the Regulators Panel Discussion." Thoma discussed the types of inspections conducted and how she categorized both 483 observations and Warning Letters based upon cGMP requirements. The largest number of microbiology-related issues are due to failure to validate microbiological methods.

The "Ask the Regulators" session offered all attendees a chance to ask FDA regulators from CDER, CBER and ORA questions on any topic including common challenges in the micro environment such as the issues regarding disinfectant efficacy testing of sanitizers used in the facilities, endotoxin specification setting of biologics, and microbial control strategies of biological drug substance processing. Attendees from industry expressed their concerns on the benefit of DET results in the laboratory as the conditions used in the DET may not represent the conditions in the actual environment. The FDA panelists recognized the challenges in setting up endotoxin specification of biologics requiring involvement of endotoxins from dilu ent and they emphasized the importance of microbial control in each step.

Once again, the microbiology conference was a big success, fostering inquisitive discussions, providing thoughtful insight, exploring regulatory expectations and overall providing an enjoyable atmosphere for learning. We eagerly look forward to next year's conference in October! It will be the 10th anniversary meeting, so expect some surprises.

About the Authors

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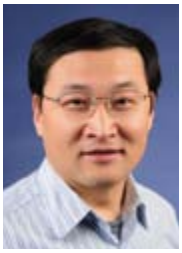

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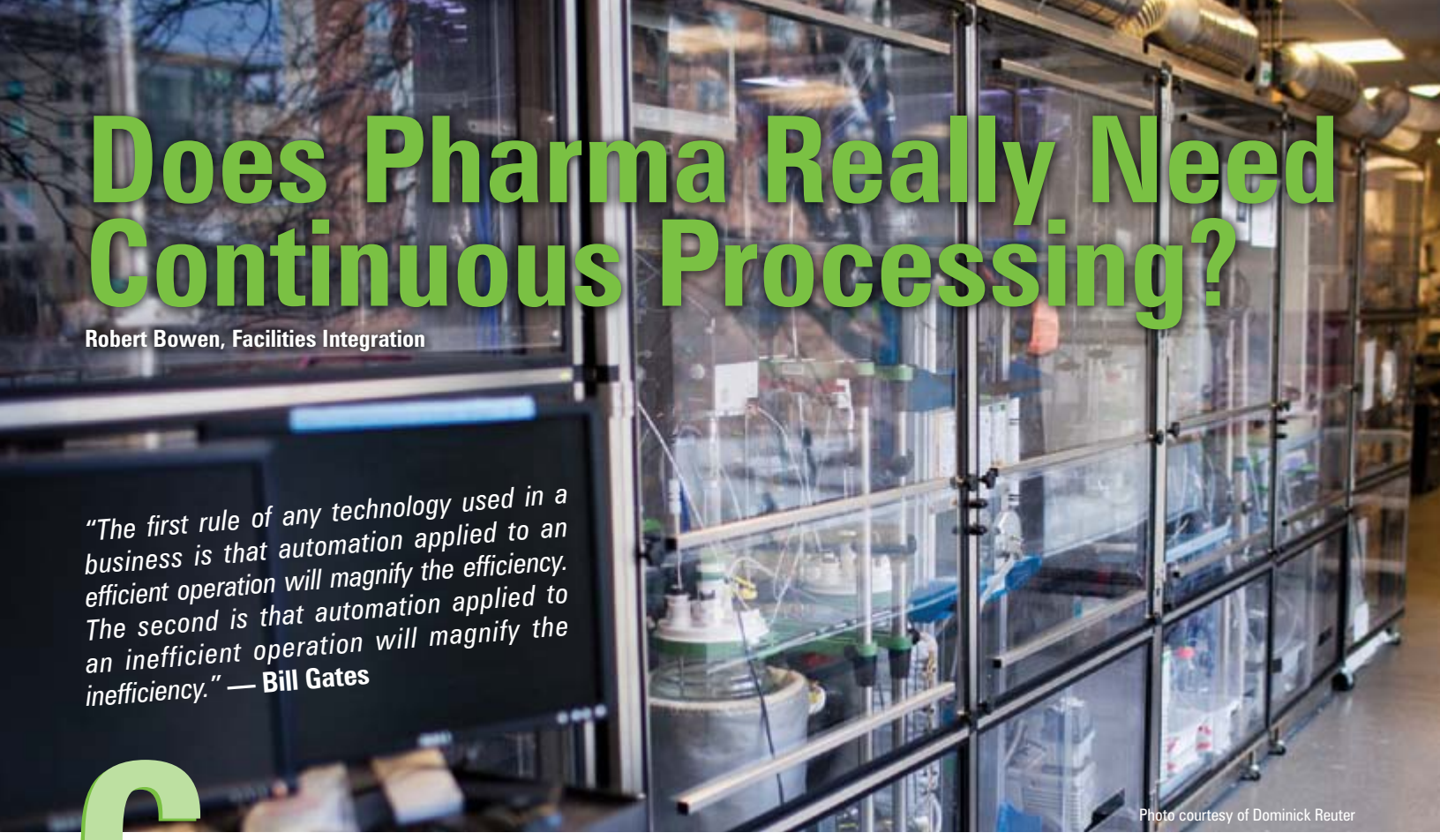
Does Pharma Really Need Continuous Processing?

Robert Bowen, Facilities Integration



"The first rule of any technology used in a business is that automation applied to an efficient operation will magnify the efficiency. The second is that automation applied to an inefficient operation will magnify the inefficiency." — **Bill Gates**

Photo courtesy of Dominick Reuter

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

The opportunity to change the manufacturing paradigm from predominantly batch manufacturing to a fully integrated continuous manufacture-based supply chain model is—with some governmental pump priming and some manufacturing vision—becoming possible. Batch processing methods allow for the capacity to manufacture without stop for 24 hours a day, seven days a week, 365 days a year as well as the flexibility to respond to market needs. But continuous processing offers the opportunity to achieve improved, leaner results in less time, at reduced cost, with minimum waste and a flexible delivery system. Still, it is neither common nor currently available other than for partial systems or prototype plants.

What is Continuous Processing?

The term "continuous" is applied to all production or manufacturing processes that run with a continuous flow, or, alternatively, for all stages or interlinked stages that run based on a continuous feed and interfeed of material—generally powder or fluid—for that or any stage of manufacture. So, it is important when discussing continuous processing to understand what element of the process, or even of the overall supply chain, is continuous or, otherwise, has those qualities within a specific industry context that may reasonably be considered continuous.

In regulatory terms, the U.S. FDA definitions of both lot and batch in 21 CFR 210.3 are both applicable to continuous processes. The EMA has adopted the ICH Q7 definition: "In the case of continuous or semicontinuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval." Thus, from a regulatory standpoint, there is no barrier to development of continuous processing, at least in principle, in the case of manufacturers producing for markets that accept U.S. and/or European regulatory findings.

Batch Processing: The Industry Norm

Batch processing has been the pharmaceutical industry norm since the modern industry began in the 19th century, when manufacturers started using new materials and processes to concoct pills and other medicines. Previously, these were developed using mortar and pestle or mixing spoon stirred liquids from mug to mug or glass to glass ***(1).*** Large scale

Article at a Glance

- Drug shortages show the need for flexible manufacturing systems
- Many factors lead manufacturers to avoid switching processes
- Moving to continuous requires a shift in culture

manufacturers generally still follow a simple volume controllable recipe process that is staged and can be readily stage tested and quality checked with reasonable surety. Even now, the tools used are scaled-up items similar in most instances to those of a domestic kitchen—bottle and bag, sieve, mixing bowl and whisk, oven, kettle, etc. This is also the way we teach the processes we have designed, developing the next steps of our curative journey of kitchen experimentation from school laboratory through university laboratory to commercial laboratory research and development and onward, once proven, to developmental research and manufacture.

These readily controllable methods have served our industry well and are sufficient to keep increasing volume through increasing batch sizes, through increase of equipment size, speed or efficiency, or both, of the process. If there is a need for a settlement or resting time between process stages, it is easy to plan to hold over (work in process or WIP). If product forms differ or involve a mix and match of ingredients, it is easy to split at a batch stage to do so. If a batch is found to be out of specification, it is readily discovered by holding in quarantine and testing at each stage prior to retention or rejection. It is a process to which it is easy to apply protocols—for materials, for loading, for cleaning, for holding, for quality checking, etc. The individual automation of stages allows the overall process be maintained without rocking any throughput or quality parameters. If this is all so simple and easy, why consider something as radical as changing the well tried and tested method? After all, consider the common saying, "If it ain't broke, don't fix it."

Shortages Illustrate Need for Change

According to the wisdom of **Henry Ford:**

> *Time waste differs from material waste in that there can be no salvage. The easiest of all wastes and the hardest to correct is the waste of time, because wasted time does not litter the floor like wasted material.*

Continuous processing offers the opportunity to achieve improved, leaner results in less time

Drug shortages are highlighting inefficiencies in the pharmaceutical industry's traditional process. This is borne out by both aging facilities and inflexibility in the production methodologies used. A recognized key issue with the prevalent production method of batch processing is that—certainly at larger throughputs—it is a lengthy process that retains large volumes of partially developed product within the process and can be significantly wasteful if an ingredient or process step is found to be wanting. The training of staff in lean techniques, while locally useful within product stages, does not significantly address the fundamental issue of maintaining product quality with assured and timely output volume, nor overcome any of the other failings of large scale batch manufacture—large cumbersome equipment requiring primarily manual cleaning, thus making changeovers slow and costly and large inflexible, costly facilities reflecting the process method, etc. With small-scale batch processing or, depending on the process, intermediate-scale manufacture, this is not such an issue, but with the larger scale processing of oral solid dose products, for example, this can be both wasteful and highly inefficient.

Due to the prevalence of significant drug shortages, the use of fundamentally inefficient and inflexible systems illustrates the need to move to less wasteful and more flexible manufacturing methods.

Inevitably, making this change requires considerable confidence for an industry founded on product quality and assurance, where mistakes are both costly and, more significantly, affect patient health. Inevitably, this also means that the industry is reluctant to change from long-proven processes and entrenched cultures and strategies. Inevitably, during a period of recession, companies only invest in new processes if risks and issues can be resolved satisfactorily. Inevitably, research and development is, therefore, focused on development of new products, fixing the existing system or transferring old products to new markets using tried and tested methods without the need to change the vocabulary.

The lack of earlier investment and take up of continuous processing has meant that at larger scales, and for multiple products, the plant layouts for batch manufactured product have become highly cellular, reflecting and at least adopting the techniques of Six Sigma and lean-focused, automotive industry-based lower volume production cells. Newer plants have at least started to recognize the use of smaller scale multiples of quasi-modular equipment supplied by automated retrieval and supply systems (ASRSs) linked with sealed dispensing systems, enclosed automated feeds and semirobotic operation and transfer provides for flexibility in use. This still results in plants and operations physically large and inflexible, costly to build and significantly reliant on many operators following multiple and complex SOPs —both, arguably, at risk to themselves and the product. This issue is being exacerbated by high volume multiproduct facilities currently planned and under construction that are not using continuous processes—missing the potential benefits of continuous processing realized in other industries.

Moving to Continuous Requires Understanding, Planning

Continuous processing is not necessarily a panacea that will cure all the ills of the industry in one fell swoop through pouring raw materials in at one end and retrieving desired product in its appropriate packaging form at the other with real-time release documentation in hand. Neither can it be implemented for all manufacturing stages for every ➤

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FEBRUARY EVENTS

16
Pre-Conference Workshop Water Systems
Berlin, Germany
europe.pda.org/PWSWater2015

17–18
Pharmaceutical Microbiology
Berlin, Germany
europe.pda.org/Microbiology2015

19
Endotoxins and Pyrogens in Parenterals
Berlin, Germany
europe.pda.org/Endotox2015

19–20
Rapid Microbiological Methods & an Overview of the Technical Report
Berlin, Germany
europe.pda.org/RMM2015

19–20
The A to Z's of Biofilm Control, Monitoring, Validation, and Excursion Investigations of Pharmaceutical Water Systems
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20
Cleaning and Disinfection
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MARCH EVENTS

2
IG Meeting Pre-filled Syringes
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3–4
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5
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Container Closure Development
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5–6
Container Closure Integrity
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5–6
Extractables & Leachables
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5–6
Glass Handling
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9–13

GSA Schedule Contract GS-02F-113BA

Fundamentals of Aseptic Processing
Bethesda, Maryland
pda.org/FAP1

16–18
2015 PDA Annual Meeting
Las Vegas, NV
pdaannualmeeting.org

18–19
2015 PDA Aging Facilities Workshop
Las Vegas, NV
pda.org/Aging-Facilities2015

19–20
2015 PDA Annual Meeting Course Series
Las Vegas, NV
pdaannualmeeting.org/courses

23–27

GSA Schedule Contract GS-02F-113BA

2015 Aseptic Processing Training Program – Session 1, Week 1
(Week 2: April 13–17)
Bethesda, Maryland
pda.org/2015aseptic2

APRIL EVENTS

7-8

NEW COURSE

Airflow Visualization Techniques and Practices
Bethesda, MD
pda.org/air

14-15
Aseptic Manufacturing
Berlin, Germany
europe.pda.org/AsepticManu2015

16-17
Introduction to Aseptic Processing Principles
Berlin, Germany
europe.pda.org/TCAseptic2015

20-23
Train the Trainer Week
Bethesda, MD
pda.org/trainer

27-29

GSA Schedule Contract GS-02F-113BA

Validation of Biotechnology-related Cleaning Processes
Bethesda, MD
pda.org/biotechclean

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Consider attending **John Bonham Carter's** talk, **"Continuous Bioprocessing – Trends and Challenges,"** during Session C1: **"Advances in Manufacturing,"** March 16, 2:15 p.m.–2:45 p.m. at the *2015 PDA Annual Meeting.* This talk will address the challenges and benefits of implementing continuous manufacturing in the biopharma space.

product without investment in research. Issues around actual required volume, quality of raw product, homogeneity of mix, residence time distribution (RTD), surety and characterization of intermediate, continuity of throughput relative to chemical or biological interaction and resting times are all very specific to individual product. That product must also be assured through proof of quality and validation in a way that is acceptable to the regulators and, more importantly, without risk to the consumer, i.e., the patient—this last respect more so than in any other industry. This, in many ways, underlines reluctance for change.

For this industry, unlike others, product verification has to be controlled and risks managed to an extremely high degree. Each product has variances in material and mass balance that affects throughput parameters along with differing expectations of residence times to allow chemical interactions between stages, and so there is a criticality of equipment response that is needed in continuous processing not present in batch production. The need to understand the process stages and interactions relative to volume throughput is significantly more acute as each element of the process needs to be matched to the volume demand of the output—not a prerequisite for batch operation where stages and WIP act as protectors to what otherwise may be seen as a wasteful process.

Quality by design (QbD) addressing a drug's critical quality attributes (CQAs) from the outset, improving understanding of flow chemistry with recognition of the need for developments in conversion chemistry, modelling and simulation and the acceptance of risk assessment methodologies, provides routes to the development of fitness for manufacture from the earliest stage of product development. This suits a path to the adoption of continuous processing. Linked with current developments of in-process characterization available through process analytical technology (PAT) and opportunities for feedback/feedforward, as opposed to steady state-based process control systems, the level of surety required for appeasing regulatory expectations does not exist for continuous manufacture's introduction. The adoption of these checks and system/process balances, however, is still in an early stage of development.

Commercially, continuous processing assuredly places demands on a manufacturer's procurement options as well as on equipment manufacturers. No pharmaceutical company likes to be seen tied to one manufacturer, and the purchase of a fully integrated line from one source—unless the IP is held by the purchaser—tends to mean that there is little appetite for purchasing something on which warranties and service agreements tie to one option. Likewise, recession-hit equipment manufacturers will tend to avoid putting money into researching something for which there is a dubious market.

Left to its own devices, continuous processing will unavoidably be a slow build to anything like a totally integrated line set. That is, unless companies follow the example of Novartis—which partnered with MIT on a continuous processing research initiative—and invest in technologies open marketed sufficiently for manufacturers to take the risk, allowing them to see the value in investment.

Operational Challenges, Threats and Concerns

Culture: Changing processes often means changing systems; this is often considered a threat rather than an opportunity. The challenge with changing to continuous processing—and in many ways the biggest obstacle—is that for existing products it means reregistration, both a costly and time consuming business not considered acceptable without the availability of proven systems when the time to market is restrictive. This means that refiling is avoided and a facsimile of the previous process is adopted, further restricting opportunities for new options for a significant time period thanks to ROI/amortization considerations.

Supply Chain: Changes based on an end-to-end paradigm will challenge current material procurement methodologies often founded on acceptance of the cheapest rather than the best value. A focus on raw material suppliers to the pharmaceutical industry is long overdue.

The introduction of fully integrated through flow continuous processing systems will challenge current facility feed systems founded, in most cases, on pallet-based nonautomated warehousing that dispenses with the retention of large stocks of, again, pallet-based, WIP and quarantined product. Opportunities for improved supplier control upstream, facility size and flexibility will lead to the potential for more diverse, decentralized operational models that include location at point of need and, downstream, greater response to the local regulatory and patient environment with more personalized patient-focused delivery models.

The Path Forward

Size reduction in manufacturing equipment based on continuous processing, with a move to matrix- and cassette-based rather than pure modular design solutions, will provide new opportunities for plant packaging. The disintegration of the static factory model with resources centered on one or two locations feeding a global market has, to an extent, already begun but is still based on a few API facilities feeding secondary factories with local packaging operations. It is increasingly recognized that, with global energy costs increasing, the unsustainable transport of lightly packaged drugs is often the equivalent of transporting high quantities of air.

The availability of small-scale continuous manufacturing facilities capable of being colocated with the area of drug concern or shortage will change the dynamic of material deliveries based on prepackaged, preapproved, and precontained raw materials to location.

Drug designs focused on personalization on one hand and controllable flow for large-scale operation on the other will inevitably change the pharmaceutical landscape.

The benefits of continuous processing are without dispute. The path to introduction, however, is less stable and dependent on conviction. Does the industry need continuous processing? Continuous manufacture is a natural progression in the technology of production and, as techniques develop and systems improve, take up is inevitable.

[Author's Note: This is the first of two papers on continuous processing. This paper sets the scene and considers philosophical, social and supply chain issues; the second reports on the perceived current status of the developing art of continuous processing related to drug product with some thoughts on the way forward.**]**

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1. Daemmrich, A. and Bowden, M.E. Emergence of Pharmaceutical Science and Industry: 1830-1930. *Chemical Engineering News* 83: tinyurl.com/oet66cb.

About the Author

Robert Bowen is director of Facilities Integration, a consultancy specializing in master planning, concept design and design development. He is a practicing architect with considerable experience in the design of complex specialist facilities from research and development, CT and API through biopharmaceutical manufacture to oral solid dose, fill/finish and warehousing.

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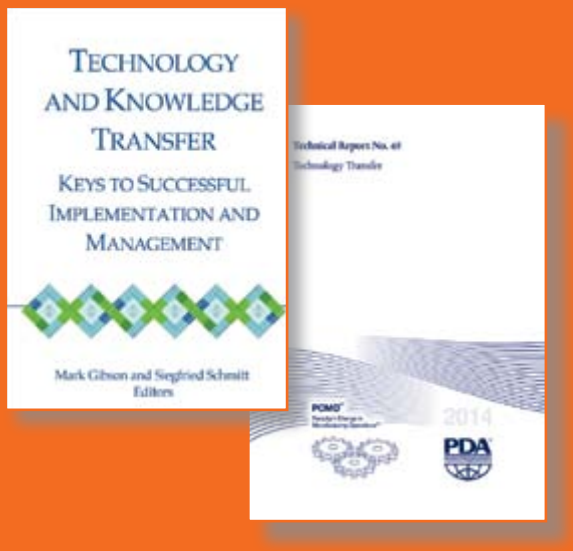

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Pharma Manufacturing at a Crossroads

Rebecca Stauffer, PDA

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?

Some experts argue that large pharma companies indeed face similar challenges that plagued the top automakers in the late 20th Century. They cite similarities such as increased outsourcing to suppliers, contraction of major players and global competition from new markets, among others ***(1, 2).***

The pharmaceutical industry and those who regulate it are not blind to the problems. At PDA Europe's *Parenterals* conference in Munich last December, several speakers addressed these concerns and proposed flexible, innovative solutions.

The dialogue took off like a supercharged roadster with Porsche Consulting's **Dirk Pfitzer's** presentation on the similarities between current pharmaceutical manufacturing and the auto industry a few decades ago. Porsche Consulting, an arm of the well-known sports car company, conducted a survey of the pharma industry manufacturing in 2013.

While there are many differences between the two industries, "one of the similarities is that we are all striving for operational excellence," he said. According to Pfitzer, "operational excellence" is "the desire and ability of an organization and its employees to consistently deliver top performance time and again."

He described how Porsche was close to bankruptcy in 1992, and a stalled manufacturing culture was largely to blame. To drive home his point, he showed a photo of a chaotic manufacturing floor complete with disorganized stacks of inventory. That year the company turned to Japanese consultants, beginning a dramatic cultural change that has since resulted in a 6% increase in productivity year after year.

Pfitzer believes Porsche's experience offers lessons learned for the pharmaceutical indsustry.

"Operational excellence is not industry-specific. Operational excellence does not happen by itself. It's a result of hard work. And it takes time. It takes years," he said. "And no company has core competencies in all areas, and recognizing this fact really does extend your horizons and gives you time—gives you money and resources to really focus on your real competencies."

Achieving operational excellence requires flexibility on the part of automakers. Manufacturing flexibility will also be key to the future of the pharma industry, according to **Friedrich Haefele,** PhD, Vice President, Head of BP Fill/Finish Germany, Boehringer Ingelheim.

His company decided that its Fremont, Calif. plant needed a more flexible parenteral filling operation to accommodate both vials and syringes. In a technology partnership with SKAN and Bausch + Stroebel, Boehringer moved to modular isolators. These are interchangeable isolators that can be configured to meet the needs of different product lines, such as syringes and vials (see photo on p. 30). In addition, at the rear of the isolator, ready-to-use (meaning already manufactured for patient use) components such as plungers and vials can be entered into the system for syringe filling.

Wenzel Novak, PhD, Director, Pharmaceutical R&D, Groninger, discussed new technologies he's observed as a supplier. ➤

Take a Glimpse into the Future of Manufacturing at the Annual Meeting

PDA will unveil its new Manufacturing Science Program℠ at the *2015 PDA Annual Meeting*. This initiative seeks to advance the industry through modernization and embracing new technologies and processes. Additionally, the meeting will feature a number of enlightening sessions looking at the future of manufacturing.

The first plenary session, on March 16 at 8:15 will explore "Changing Manufacturing – Fulfilling Future Treatment Options and Financial Necessities." Speakers in this session include **Chad Juros,** Novartis' **Jeff Boyd** and **Adwait Bhagwat**, the latter offering a financial view of the changing manufacturing landscape.

Plenary 3, "Flexible Manufacturing – Current Solutions and Future Visions," will feature talks from **Michael O'Brien,** Pfizer, and **Duncan Low,** PhD, Amgen, at 8:30 a.m., March 17. That same day, the breakout session C2 ("Cell Therapies – New Processes / New Challenges," 10:45 a.m.–12:15 p.m.) will look at the manufacturing of certain types of cell therapy products with presentations by **Knut Niss,** PhD, Novartis, and **Ali Siahpush,** Pharmefex Consulting.

The final plenary session (March 18) will feature a talk on aging facilities ("Aging Facilities – Upgrading your Manufacturing Facilities") by **George Wiker,** M+W Group, at 10:30 a.m.

And following the conference is a one-and-a-half day workshop on aging facilities that will include case studies, regulatory overviews and interactive working group discussions.

To learn more about these talks and the workshop, please visit www.pdaannualmeeting.org.

His company supplies equipment and systems for manufacturers. He's seeing more product processed in nested containers including syringes, vials, cartridges and polymers. "Nested" refers to product that lies side-by-side in rows contained within a fitted tray or tub. New configurations such as this require flexible equipment for production lines. Prefilled syringes are often processed this way.

In the area of decontamination, he sees potential in decontamination of outer polystyrene tubs containing sterile syringes with plasma, which he thinks could prove to be a cost-efficient solution. This technology also offers less risky options for handling compared to current methods such as electron beam sterilization.

Companies are also looking to suppliers to design solutions for manufacturing smaller batch sizes. Newer biotech drugs are produced in small batches, requiring equipment that can handle different production needs based on size and speed.

Novak explained that isolator manufacturers also recognize that companies want to adapt the equipment by format part, even buying different modules or isolators from filling fill-finish companies and putting them together based on specific needs.

"So, at the end, the idea on this kind of process is, you have your known processes…don't invent the wheel once again," he emphasized. "You gain that by flexibility and reproducibility of your processes and your equipment."

Novak also offered his observations as far as his customers' needs in ten years based on conversations with colleagues. With respect to manufacturing and control, he sees the increasing uptake of parametric release, electronic batch documentation systems, robotic technologies, systems with flexibility for all types of containers within isolators, and movable factories. Regarding the latter, companies might construct a mobile production facility that can be moved to another location based on need.

Flexibility is also key when working with suppliers, Novak said. He recommending that companies work closely with their suppliers to address current and future needs effectively. This will be a lengthy process, he emphasized, as developing a state-of-the-art manufacturing system requires investment in both money *and* time.

Frank Lehman, Head, Sales Engineering, SKAN, addressed a different proposition on flexibility. His company developed a standard, modular aseptic barrier isolator for a variety of filling machines and packaging equipment. In addition, this singular, or linked module isolator, can be used for small-scale production, startup batch sizes, clinical trial materials, stability batches, formulation, compounding, freeze dryer interfacing, stopper processor discharge, aseptic toxic products, etc. Like a chameleon, this solution can adapt to changes as new uses are defined.

Pictured above is SKAN's modular single chamber isolator PSI-L with a Bausch+Stroebel Variosys vial filler. Photo courtesy of SKAN

"It provides great flexibility," said Lehman. "One can start with a single chamber or depending on the application a multiple chamber and add another chamber later if the demands increase. And there's another big advantage. When you have a large cleanroom and you initially set up one isolator, if you need

Continued on page 34

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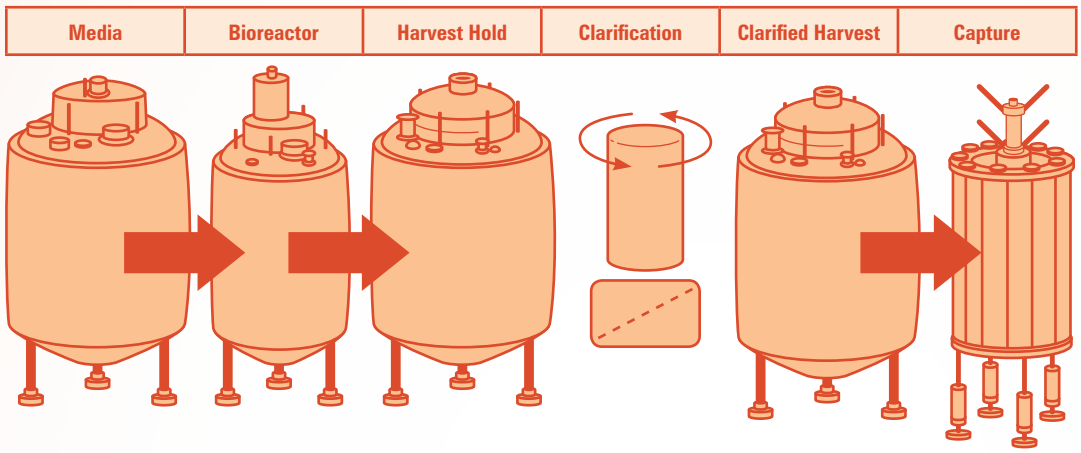
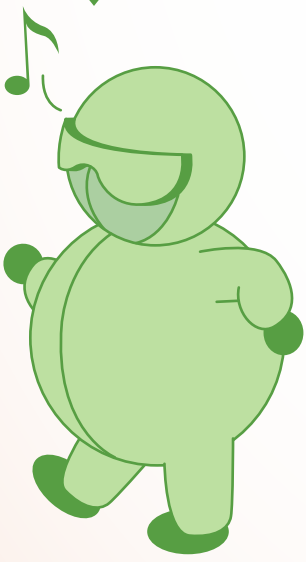
Upstream BioManufacturing: Batch vs. Continuous

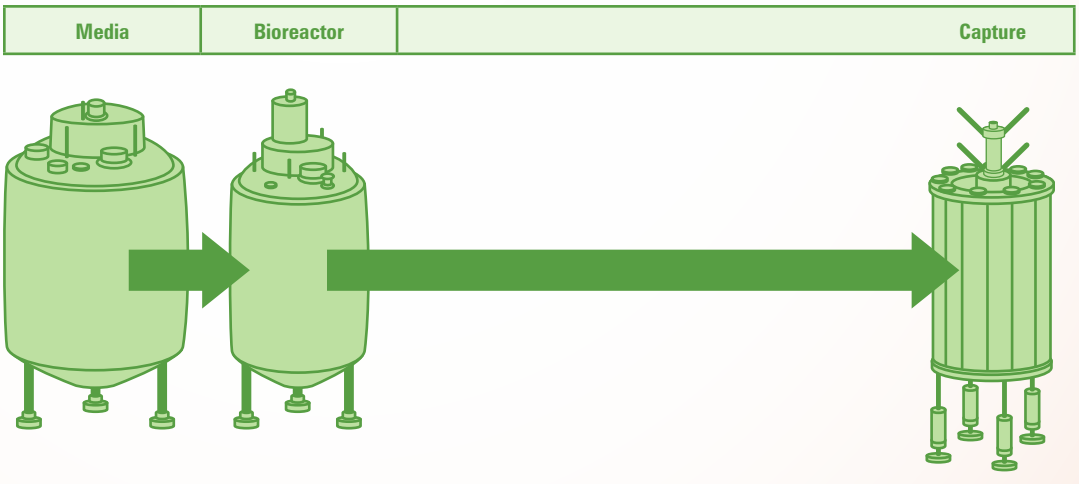
Traditional Batch Processing



In traditional batch processing **operators play a key role.**
In continuous manufacturing, the human element is less hands-on,
operators serving more like observers in the event something goes wrong.



Continuous Processing



Special thanks to **Robert Dream,** HDR COMPANY, for his assistance with this infographic. The continuous processing system depicted above is based on systems developed by leading biotech companies.

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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!

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PDA® Parenteral Drug Association

snapshot

EMA to Explore Advocating PDA Drug Shortage Templates

Anders Vinther, PhD, Sanofi Pasteur

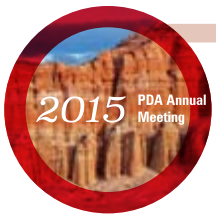
On Dec. 2, **Emma Ramnarine, Georg Rössling, Stephan Rönninger,** and I presented PDA's work on the prevention of drug shortages caused by manufacturing quality issues from a product perspective—work that has culminated in the form of PDA *Technical Report No. 68: Risk-Based Approach for Prevention and Management of Drug Shortages*—in London to EMA senior staff and the EU Inspectors Working Party (IWP)

We started working on TR-68 in 2012. It describes a **risk-based triage of products** (i.e., how to establish preventive controls for drug shortage risks in the end-to-end product value chain based on product criticality and patient impact) and the **establishment of a Drug Shortage Risk Register and a Drug Shortage Prevention and Response Plan**—a holistic framework as well as product level templates. TR-68 has been discussed at several PDA meetings and been reviewed by EMA, the U.S. FDA, other regulatory agencies and by hundreds of PDA members.

We presented this work as part of an interassociation group to address the issue of shortages. This group consisted of members from the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Generic Medicines Association (EGA), and the International Society for Pharmaceutical Engineering (ISPE), the Association of the European Self-Medication Industry (AESGP), Plasma Protein Therapeutics Association and PDA. Approximately 60 inspectors and EMA staff attended this meeting as well as 20 people from "interested parties," including PDA.

The meeting went very well. **David Cockburn,** Principal Scientific Advisor, EMA, and **Brendan Cuddy,** Head of Manufacturing and Quality Compliance, EMA, said that the work was very informative and that they will promote the results including the template and tool. Our work will also be considered as a recommendation for national implementation as input to the second version of EMA's drug shortage implementation plan. There was a suggestion that it might even be proposed as a best practice into the Site Master File expectations. Additionally, some inspectors suggested that the marketing authorization holders could be recommended to use the PDA template to assess and mitigate potential drug shortage risks.. The deliverables will be made available from the EMA website with recommendations that national competent authorities post them online as well.

Now that the technical report has been published, we will work to establish training using this material. Visit www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/drug-shortage to access these tools.



Meeting *Preview*

Interest Group Schedule

On the right is a schedule of RAQAB interest group meetings at the *2015 PDA Annual Meeting.*

Tuesday, March 17

4 p.m. – 5:30 p.m.

Management of Outsourced Operations Interest Group
Supply Chain Management Interest Group

Pharma Manufacturing at a Crossroads continued from page 30

more capacity, for example, you place another inside the same cleanroom. Or, if you need additional production flexibility and you have an isolator concept in your room, you can work with different substances. That was not possible with conventional cleanroom technology."

The technology's flexibility, in addition to the modularity, lies in an exchangeable L-shaped flange where different process equipment can be installed. This L-flange is secured using a pressure tight inflatable seal, assuring an aseptic condition, after the decontamination cycle.

Just as automakers had to move to different, more flexible models of production, pharma will have to do the same. For pharma to embrace operational excellence, it will require implementing flexible, more efficient technologies.

[Author's Note: This month's podcast features interviews with speakers from this meeting. Visit www.pda.org/pdaletter to hear these.**]**

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2. Hirschler, B. and Burger, L. Analysis: Big Pharma gets a driving lesson from carmakers. *Reuters* (December 14, 2011) tinyurl.com/6usIns8.

Task Force *Corner*

PDA Task Force Submits Comments on Chinese FDA Draft Guidance on Qualification and Validation

Denyse Baker, PDA

As part of the Regulatory and Quality Advisory Board (RAQAB) initiative to expand PDA involvement in the BRICK (Brazil, Russia, India, China and Korea) regions, a process for preparing and submitting regulatory comments in these countries was developed in 2013. An opportunity to test this new process arose in mid-2014 with the publication of the Chinese FDA's draft guidance *GMPs Draft Annex 1: Qualification and Validation.* Since PDA has deep expertise in process qualification and validation and had recently commented on both U.S. FDA and EMA draft guidances on this topic, the task force had a good starting point.

One of the challenges of commenting on documents from China is that frequently no certified translation is provided, or if one is ever developed it is published long after the commenting window has closed. The task force initially attempted to use Google Translate, which provided a general idea of the content of the draft in English but otherwise was not of meaningful use to the task force. Instead, the commenting task force chose to rely on an industry translation as well the expert interpretation of Task Force Leader **Hongyang Li**, PDA's regional liaison from China and RAQAB member. Also contributing to the development of the response were **Anil Sawant, Veronique Davoust** and **Jeffrey Hartman. Hal Basemen, Scott Bozzone** and **Wendy Zwolenski-Lambert** reviewed the comments for consistency with other PDA responses. Because most of the document's development was done in English, volunteers retranslated the final versions back to Chinese for submission. The task force is grateful for the efforts of PDA Member **Jerry Zhang** for his work to complete the final product.

The CFDA draft was very similar in general to the EMA's Annex 15 but the ongoing discussions and interpretations of "continued" and "continuous" process validation happening with the FDA and EMA documents were made even more complicated by the translation issues in this draft. In the end, PDA recommend caution to the CFDA on their use of the word "持续" or "chixu." PDA recommends that, if translated, this word should be interpreted as "ongoing," used commonly by EMA, or "continued," used by the FDA. PDA advises not to use translate "chixu" as "continuous" since that term is less well understood across multiple languages. The final comments were submitted in both Chinese and English.

Although the overall timeline to develop and submit these comments was longer than normal, it was a good learning experience and will allow us to refine the commenting procedure for the future.

Anyone working with the BRICK regions is encouraged to recommend a draft document for PDA commenting through a RAQAB member or by contacting **Denyse Baker** at baker@pda.org.

PDA Who's Who

Hongyang Li, Vice President, Quality, Novartis
Anil Sawant, PhD, Vice President, Enterprise Regulatory Compliance, Johnson & Johnson
Veronique Davoust, PhD, Manager, Global Quality Strategy, Pfizer
Jeffrey Hartman, Director, Quality Systems Validation, Merck
Hal Baseman, ValSource, Chief Operations Officer
Scott Bozzone, PhD, Senior Manager, Quality Systems and Technical Servicecs Validation, Pfizer
Wendy Zwolenski-Lambert, Global Validation Leader, Novartis
Jerry Zhang, QA Supervisor, CSPC
Denyse Baker, Senior Advisor, Scientific and Regulatory Affairs, PDA

Knowledge Management: A Topic with Many Tomes

By Chris Smalley, Merck

Those who possess knowledge have traditionally been respected in society. We know who these fonts of knowledge were because they were well-respected people—great authors, outstanding teachers and valued mentors.

But we need to understand the nature of the knowledge held by these leaders. Is it just an accumulation of data? No! Allow me to use two books about Hawaii as an example. Fodor's series of travel guides includes a book on Hawaii that is an accumulation of data that many tourists find useful—listings of restaurants, hotels, maps and sights of interest. **James A. Michener** wrote a novel on Hawaii that is a true book of knowledge, beginning with how the Hawaiian Islands were formed, describing how the culture evolved and the impact of significant events in the life of its people. This novel was regarded as enhancing business and travel to Hawaii.

The PDA Task Force on Knowledge Management is developing a technical report to define data, information and knowledge, and discuss the role of knowledge in our industry. Knowledge management, after all, is one of the key enablers of ICH Q10 (the other being Quality Risk Management, or QRM). Knowledge management is an enhancement of the culmination of all data that we, as an industry, are very good at collecting. When we add context to the data it becomes knowledge.

The *2014 PDA Knowledge Management Workshop* held last May was a key part of the effort. The workshop served as a means to learn what others in the industry are doing about this enabler. In addition, we reached beyond the pharma/biopharma industry to gain insight from NASA and the American Productivity & Quality Center, or APQC.

Naturally, knowledge management goes hand-in-hand with QRM, as **Stephan Rönninger,** PhD, Head External Relations Europe, Amgen, explained at the workshop. Without knowledge of your process, a risk assessment cannot provide a basis for decision making. Decision makers in a site look to various departments within their organization for information. They look to the accountants for financial data. They look to the quality group to see how they are performing. Finally, they look to their operations people to tell them whether or not they're meeting customers' needs. These are very basic knowledge needs; however, management might benefit from better visibility of what constitutes the processes and systems, and how they are directly controlled. They do not deserve to be caught unaware when a drug shortage occurs, for example, because a batch is rejected. Knowledge management used as a tool gives management the ability to understand and disseminate information needed to carry out responsibilities properly.

Other presenters at the workshop provided additional keen insights on not only what knowledge is, but also its value when gathered properly.

Keynote Presenter, **Justin Neway,** PhD, Vice President and Chief Science Officer, ADQM Solutions, Dassault, described the Knowledge Pyramid, where there is an abundance of data at the base of the pyramid, which has the least value. As it becomes information, it gains value and you can act on it, and then finally it becomes knowledge.

For knowledge to be effective, it is important to accumulate it, make it accessible, and disseminate it at every teachable moment. It is the level of knowledge gained, not the volume of data, that is important. Process Knowledge consists of two major parts—Process Reliability and Process Robustness. Individual users need to have self-service, no obstacle access to the data they need. Reconcile self-service with the teachable moment to involve tacit knowledge. Multiple systems store data differently. Consequently, an additional tool is needed to integrate and contextualize the data.

David Reifsnyder, PhD, Head of Biologics Process Validation, Global Biologics, Genentech, discussed the platform approach process based on knowledge management in place at Genentech. The basis for the platform is a Product History File, which contains the registration information, QRM, Development Report, Annual Product Quality Review among others. This approach uses viral validation as an example since it follows the same manufacturing process including types of resin and washing steps.

Eda Ross-Montgomery, PhD, Senior Director, Technical Steward, Shire Pharmaceutical, described how knowledge management is regarded as a journey, not a destination. This is important to consider when working with a CMO. Her company treats CMOs as if part of the company.

DSM Greenville, now part of Patheon, is one of those CMOs for Shire. The Monthly Product Technical Dashboard is uniform across the Shire network, including reports on CMOs. A Monitoring Plan, uniform for each platform, is used to collect information.

Paige Kane, Director, PGS Knowledge Management at Pfizer, said that there is more knowledge within our organization than we could buy. Pfizer utilizes its KM Portal, which preserves, manages and exploits all available Product and Process Knowledge. Within the portals are structures, called Pillars, that:

- Connect people to people

Continued on page 43

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Giovanni Migliaccio, *Istituto Superiore di Sanità (ISS)*
Michele Myers, *GSK*
Valerie Pimpaneau, *Voisin Consulting*
Sol Ruiz, *AEMPS*
Georg Roessling, *PDA Europe*

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2-3 June 2015

Amsterdam | The Netherlands

Register by 4 May 2015 and SAVE!

PDA's PCCIG Presses on with Conferences, Tech Reports

Erik van Asselt, PhD, Merck, and Rafik Bishara, PhD, Pharmaceutical Cold Chain Interest Group

Each October, best practices in cold and supply chain logistics are shared, discussed and debated during PDA's *Pharmaceutical Cold and Supply Chain Logistics Conference*. Members of PDA's Pharmaceutical Cold Chain Interest Group (PCCIG) help plan this conference, as well as spearhead the development of a series of PDA Technical Reports on the topic.

The 2014 conference in Berlin was no different; attendees and speakers from various organizations came together to learn about the goal of "Ensuring Product Integrity and Visibility across the Supply Chain"—the theme of the meeting. It was clear from the discussions during the two-day event that the supply chain faces many challenges that might impact product integrity and/or the business. These include but are not limited to: outsourcing of manufacturing and logistics, serialization, regulatory pressure for temperature control of warehouses and shipments, supply chain globalization, cost reduction pressures, theft, counterfeiting, length of shipments, thermal protection of room temperature products, ground handling at airports and GDP certification of cross-docks including airport warehouses.

The first day of the conference featured talks on supply chain visibility, stability budgets and contract management. Product integrity, temperature control, new GDP regulations, inspections, and transport integrity were subjects of the second day. Engaging exchanges on the use of stability budgets and the impact of the new EU GDP regulation happened during roundtable discussions with global regulators.

Serialization of finished goods has a major impact on the supply chain. For example, packaging sites need to invest in new equipment and procedures. Therefore, **Ulrike Kreysa,** Vice President, Healthcare, GS1, underlined the importance of a global single standard for 2D matrix coding. Rolling out such standards-based systems globally could prevent tens of millions of dollars' worth of counterfeit drugs from entering the legitimate supply chain. GS1 estimates that healthcare costs could be reduced by $40 to $100 billion globally from the implementation of global standards. **Hans Vanderwegen,** Managing Director, 4XScience, then indicated that aggregation to shipping case is not a requirement according to the EU Directive on Falsified Medicines, thus packaging sites should not overengineer serialization as this will drive additional cost.

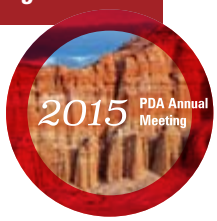
Andrea Gruber, Manager, Cargo Standards, International Air Transport Association, talked about the certification program, "Center of Excellence in Pharmaceutical Logistics," or "CEIV Pharma," for supply chain partners at airports. This program has been developed by IATA to prevent sanitary issues caused by temperature excursions during transportation of pharmaceuticals, to improve handling of pharmaceuticals in compliance with existing regulations and standards, to elevate level staff competency through efficient and robust training program, to create a globally consistent and recognized certification that industry can rely on, and to ensure product integrity is maintained during transportation until it reaches the ultimate patient. Companies at the Singapore and Brussels airports follow this program and more airports are moving to certification.

On the last day, regulators **Belén Escribano Romero,** Deputy Director/Head of Pharmaceutical Inspections and Enforcement Department, Spanish Agency for Medicinal Products and Medical Devices, **Darren Scully,** Inspector, Health Products Regulatory Authority, and **Riekert Bruinink,** GMP Inspector, Dutch Healthcare Inspectorate, shared the first results of GDP inspections using the new EU GDP guidance as reference in Europe. The result was reasonable and many companies are still working on the implementation of the new EU GDP. From all presentations it was evident that standardization of guidances, procedures and processes, and proactive partnerships in supply chain are important elements to ensure product integrity and visibility across the supply chain.

the draft *PDA* Technical Report: Passive Thermal Protection Systems for Global Distribution – Qualification and Operational Guidance *has been submitted to PDA's Science Advisory Board as of Nov. 21*

As a follow up to some of the discussions at the conference, as well as the training courses following the meeting, the co-chairs of the conference planning committee and PDA's PCCIG are pleased to announce that the draft PDA *Technical Report: Passive Thermal Protection Systems for Global Distribution – Qualification and Operational Guidance* has been submitted to PDA's Science Advisory Board as of Nov. 21 for review and approval for publication.

Please mark your calendar for next year's event on October 6–9. We will be meeting in Amsterdam to celebrate the 10th anniversary of PDA's cold chain conferences and training courses in Europe. We are looking forward to meeting and greeting you in person in the new location and promise an agenda that will present you some new activities, current challenging topics and details of best practices in the business.



Quality Culture and its Measurement

Robert G. Kieffer, PhD, RGK Consulting

The Pharmaceutical Quality System (PQS) is composed of interlinked processes, such as the production process, the supplier process, supporting processes (validation, training, change control, investigation of nonconformances, audits, etc.) and management processes (review and ownership of the PQS, etc.). Underlying the PQS, and critical for its success, is the culture of the company, i.e., the quality culture.

The culture or values of an enterprise serve as a guide to decisionmaking. They indicate what is important to the enterprise and are largely attributable to the organization's leadership. Culture can be defined as the behaviors and beliefs characteristic of a social group.

More often than not, when a thorough root cause analysis of failures is done, the root cause is a problem with the culture. Another consequence of deficiencies in the culture is lack of continuous improvement of operations, and thus, of the PQS.

Today, the U.S. FDA is concerned about drug shortages caused by process and product failures in the industry. In response, FDA is pushing for quality metrics, and industry groups, such as PDA, are responding to this interest. Unfortunately, the metrics being considered—batch rejection rate, OOS, complaints, etc.—are all lagging indicators and do not address the root causes of these process and product failures.

Components of the Quality Culture

What are the desired components of the quality culture? Below are some things to consider.

1. Customer focus

The patient, the recipient of our products is the primary customer, not the regulatory authorities. The product must be safe, effective, available and affordable. All employees must understand what they are doing from the customer's point of view. For most employees, the immediate beneficiary of their work is a group or person inside the company, i.e., an internal customer. They need to understand the needs of their internal customers and assure that these needs are being met right first time and every time. This would apply to several QA-owned processes such as auditing, change control and documentation. Remember that only the production process provides an output used by the patient, the external customer.

2. Quality is the responsibility of every employee

Every employee is responsible for the quality of their work. It should be done right first time with no errors. Senior management is responsible for the PQS, compliance with it and its continuous improvement, as per ICH Q10. They are the owners of the PQS. Production is responsible for the production process and the quality of its output, the drug product.

The quality department works with process owners and subject matter experts in production, R&D, engineering, etc., to assure that processes are well designed for their purpose. It periodically provides data to senior management on process performance through analysis of the quality metrics and through audits. It provides expertise and facilitation, when needed, for preventive and corrective action to improve processes. It promotes and sells good quality practices by example, shares best practices and rewards good performance.

3. Quality before cost

Although the cost of the drug product is important to both the patient and the company, quality must never be compromised for the sake of money. On the other hand, all processes should be designed to be efficient as well as effective. Waste, in all its forms, should be ruthlessly eliminated.

4. Employee empowerment

All employees should be given power and responsibility as well as held accountable for the quality and efficiency of their work in proportion to their capabilities.

The goal of the company is to increase each employee's capability through training and experience.

5. Continuous improvement

For continuous improvement to be more than a wish or a slogan it must be driven by senior management; and the employees need the skills and the time for improvement activities. Improvement activity should include preventive actions not just corrective ones. Periodically, processes need to be completely redesigned; i.e., they require breakthrough or radical improvement. All processes should be measured as right first time. Aim for at least 95% right first time; critical processes should approach 100%. Six Sigma should be the long term goal.

6. System approach to management (ISO 9000)

A system is a group of parts, components or departments/people working together to achieve a common goal. The PQS is a system composed of various processes. Interrelated processes are managed as a system. Processes are well designed, capable, fail-safe and controlled. We manage processes not departments.

7. Scientific approach

Use good scientific principles. Decisions, specifications and limits are based on data. If data does not exist, experiments are performed to obtain the data.

Use statistical and quality tools as needed. Statistical tools are used for validation and process control.

8. Emphasis on prevention, not appraisal

Shift from quality by inspection to Quality by Design. Focus on process under-

standing so that processes can be designed that are robust and fail-safe. Balance the "CA" in CAPA with more "PA."

9. Balance between the short term and the long term

Excellence requires years of consistent effort. The winners of the Malcolm Baldrige National Quality Award speak of a ten-year journey. Achieving Class A certification for Operational Excellence usually takes at least three years.

This requires a strategic improvement plan for the PQS which should be a part of the company's strategic plan.

10. Teamwork

As was said above about a system, all departments need to work together, openly and honestly, to achieve common objectives. Cross-department communication, respect and trust are essential. Understand that all important processes are cross-functional which requires interdepartmental cooperation in their design, control and continuous improvement.

11. Integrity

This should be an obvious requirement. At the end of the day we must be proud, not ashamed, of what we have done. Management must hold themselves and their employees accountable for their actions.

12. Drive out fear (Deming's 14 points)

Perhaps this should be at the top of the list. Fear can be the most pernicious and deadliest cultural disease; in particular, fear of saying the truth.

An aspect of this is the need for a communication path for all employees directly to senior management for all high risk quality problems.

13. Risk Management

Risk analysis and risk thinking permeates all processes and decision making. The concern is to minimize risk to the patient, to the employee and to the company. Priorities and resource allocations should be made based on a risk analysis. Risk management is a skill the quality department should provide if it does not exist elsewhere in the organization.

Figure 1 Here on this continuum line, employees can rate their perception of the relative importance in the company of cross-functional teamwork

Departmental Teamwork				Departmental Conflict
1.	2.	3.	4.	5.

14. Give priority to learning — individual and organizational

Benchmark and learn from other more advanced industries. Make training more effective. Training should result in change and improved performance, otherwise it is a waste. Allocate sufficient time for training in the weekly schedule. WHO recommends 3–5% of available time for skilled and experienced individuals. Training needs to exist at all levels from senior management down. Continuous improvement requires continuous learning.

Measurement of Culture

A positive culture change requires active involvement of management. It must be measured and planned. Culture or values are usually measured by employee surveys. There are many companies that provide this service. These companies can design a valid survey based on your specific desired culture.

See **Figure 1** for an example of a simple survey with scaled responses.

For example, an employee would rate the following statement: "Employees are empowered to take direct action whenever they encounter a problem that is likely to impact customer satisfaction, product or service quality, cost and/or schedule," with a rating of Excellent, Very Good, Fair, Poor or Not Doing ***(1).***

The self-assessment maturity scale in Table A of ISO 9004-2009 provides a long list of key elements many of which relate to culture. For each element it provides a description for each level, 1-5.

Change of Culture

It is inevitable that a company will want to change or improve some aspects of its culture. As with any improvement, there needs to be an assessment of the current reality, a vision of the desired state, a concrete plan to achieve the desired state and a way to measure progress. This is obviously a responsibility of senior management. They must model the desired behavior by their actions and also reward behavior consistent with the company's values, refusing to tolerate behavior inconsistent with the values. In the latter case, sometimes it may be necessary to terminate the employee. Some companies as part of their hiring process give "value" tests. These companies recognize that it is easier to train an employee technically than to change the employee's values. Personal values become more important the more senior the position.

The company culture or values—which should not be distinguished from quality culture—is critical to product and service quality, for consistent compliance and the long term success of the company. And it can, and should be, measured and managed.

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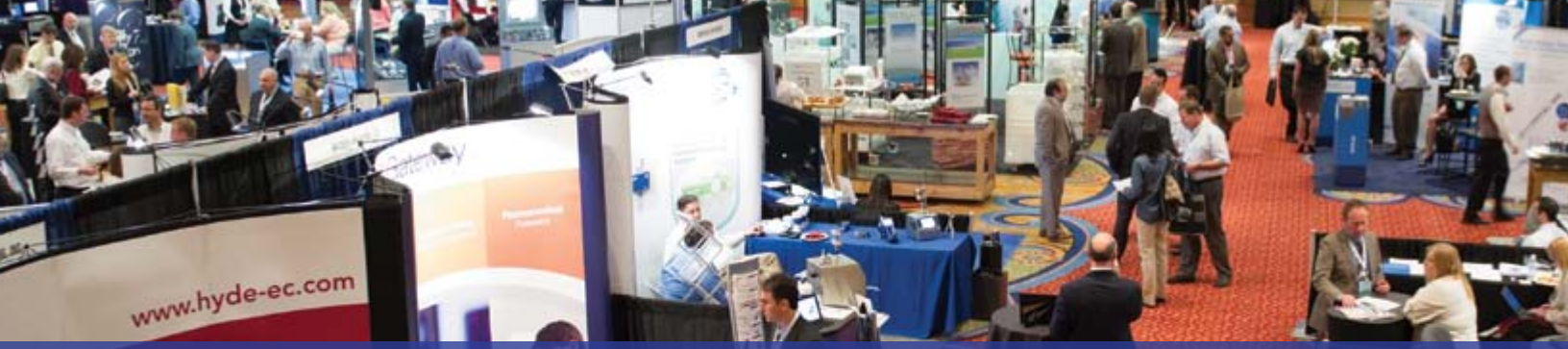
1. Oliver Wight International, Inc. *The Oliver Wight ABCD Checklist for Operational Excellence.* John Wiley & Sons, Inc: Hoboken, NJ, 2000.

About the Author

Robert Kieffer is an authority on quality management and on quality system design.

Hear more about this topic from Robert at the new PDA Education course, "The Quality Culture and its Measurement," following the *2015 PDA Annual Meeting,* March 19. To learn more, visit www.pda.org/2015-pda-annual-meeting-course-series.



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Knowledge Management: A Topic with Many Tomes continued from page 36

- Connect people to content
- Retain knowledge
- Transform data

The tool used is commercially available. To be used throughout the organization, a tool must be seen as to have a value—"What's in it for me?," as well as being user friendly.

For a nonpharma perspective, **Edward Hoffman,** PhD, Chief Knowledge Officer and APPEL Director at NASA asked, "What is the catalyst for major change?" His answer: "A crisis." The number one issue for knowledge management is the difficulty in finding the documents needed. The value belongs to those who can "find" answers. He asked if success is considered networking on finding solutions, that begs the question, is learning occurring? Hoffman explained that NASA's solution entailed establishing a community, operated on a federated model as a people-centric organization. The website for this community is km.nasa.gov.

Knowledge management entails finding the right information and applying it at the right time to form a solution, shared **Cindy Hubert,** Executive Director, APQC, who also recommended managing explicit knowledge differently from tacit knowledge.

"We really don't manage knowledge," she said. "We manage the flow."

Providing a European perspective, **Tor Graberg,** Chief Pharmaceutical Inspector, Swedish Product Agency, and former PIC/S President, outlined three key points: trust, collaboration and communication. He recommended always using the ICH Q10 definition of knowledge management (see EU-GMP Part III). An effective knowledge management process maintains the state of control and facilitates continuous improvement. As an inspector, he is often asked how will knowledge management be inspected? His usual response is that inspectors are not looking to examine the formal system, however, they do expect that knowledge from different processes and systems will be appropriately used.

The task force will continue its work, anticipating that our next deliverable will be a detailed proceeding from this workshop to make the learnings sustainable. Look for those proceeding to come mid-year in 2015 and be published in the *PDA Journal of Pharmaceutical Science and Technology!*

The author would like to thank **Stephan Rönninger** of Amgen for his assistance in preparing this article.

About the Author

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Glenn Wright, Eli Lilly

The Future of Pharmaceutical Manufacturing

The word that comes to mind when I think about the future of pharmaceutical manufacturing is "divergent." While the traditional methods of manufacturing pharmaceutical products will certainly be part of the future, many of the new products will require an entirely different approach. Thinking back 20 years, the concept of manufacturing large glycosylated complex protein products was at the cutting edge of the industry. This expansion—from manufacturing focused mainly on small molecule and naturally expressed protein products—to include these complex recombinant protein products was a significant change. Today, we are again standing on the edge of what will most likely be a significant expansion as novel products, such as cellular therapies that reprogram patients' own cells to fight or cure disease, move out of development and into commercial manufacturing. The reason I use "divergent" to describe the future is that just as the technologies used to produce complex recombinant proteins were much different from the manufacturing practices of the day, so too will be the technologies used to produce these novel products. In many cases, the manufacturing operation will become more patient-focused and will blend conventional manufacturing with the medical protocol used to treat the patient. This divergence will increase complexity within the supply chain as companies will need to retool their operations and processes for these new products while also maintaining a continued focus on their existing manufacturing operations. At this year's *PDA Annual Meeting* in Las Vegas, we will be taking a closer look at some of the challenges facing the industry as we make this shift.

The other reason I like the term divergent is that the technologies used in the production of existing products are continuing to rapidly evolve from what was the industry standard. The use of ultrahigh pressure liquid chromatography, rapid micro methods, single-use systems, nested and closed vial filling machines, and expanded use of prefilled devices are just a few examples. How we approach and decide on the implementation of new technologies in the modernization of our facilities (infrastructure, processes and analytics) is a question that the industry seeks to answer. One thing is certain: modernizing facilities that are producing pharmaceutical products is a complicated challenge based on the complexity of the processes and systems used. It is also something that we cannot do alone; engaging with regulatory agencies around the world will be a critical part as most of the technology changes will require some type of postapproval supplements. In 2014, PDA initiated a special task force on aging facilities to look into these challenges. The task force is charged with developing examples and approaches that can be used. PDA will hold a special workshop on aging facilities March 18 and 19 in Las Vegas following the Annual Meeting, bringing together industry leaders and regulators to discuss approaches and challenges to modernization.

So what can we count on in the coming years in regard to the future of pharmaceutical manufacturing? As I said, divergence! Breakthrough products will, in many cases, require breakthroughs in manufacturing processes. While we as an industry work to deliver on these new products, we must at the same time continue to modernize and maintain our existing facilities. Ultimately, this is both a challenging and exciting time to be involved with pharmaceutical manufacturing!

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editor's message

Let's Talk Publishing @ the Annual Meeting

The PDA Annual Meeting is only weeks away! This issue provides several glimpses into the important and topical content attendees can expect to hear there. For the past three years, I, as PDA's Director of Publishing, have led a luncheon on publishing with PDA. This invitation-only session offers the PDA Journal Editor **Govind Rao,** PDA's book publishing partner **Amy Davis,** and myself a chance to hear from members of the *PDA Letter* Editorial Committee, Chapter and Interest Group Leaders and other PDA members. Over the years, we have covered the challenges of publishing, including, for example, getting works out in a culture that requires restrictive legal review, helping novice authors, and mentoring. The sessions usually include lengthy brainstorming, as well.

This year, I want to extend an invitation to the *PDA Letter* readership. While space is limited, I am inviting the first ten readers who email me (with the subject line "Annual Meeting Publishing") to join the discussion. This year, we will be focusing on the Reader Experience. What content do you like? What content do you want to see? How can PDA's publications help you do your job? Of course, you will have to be attending the Annual Meeting to participate. Following the meeting, we will launch readership surveys for both the *PDA Letter* and the Journal.

Hopefully not lost in this issue, which celebrates the upcoming Annual Meeting, is a small article in the Science Snapshot on a very big initiative: the PDA Manufacturing Science Program℠. This new PDA initiative is an important and exciting one that will help PDA promote and tailor its many activities to help the industry modernize manufacturing operations.

The *PDA Letter* podcast is available at www.pda.org/pdaletter

For this latest podcast we intereviewed:

Mauro Giusti
Wenzel Novak
Frank Lehman
Sergio Mauri
Andrew Hopkins

We start the year off with new *PDA Letter* Podcasts. Go online to hear the latest interviews and all the past interviews posted over the last two years. Speaking of the website, we are initiating an overhaul of the *PDA Letter* website. Soon, all the content in new issues will be available in HTML and optimized for mobile devices, and more importantly, all the *PDA Letter* content will be searchable. This is another exciting development that will enhance the reader experience.

I'm looking forward to seeing many of our readers at the *2015 PDA Annual Meeting.*

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See you next year in San Antonio!

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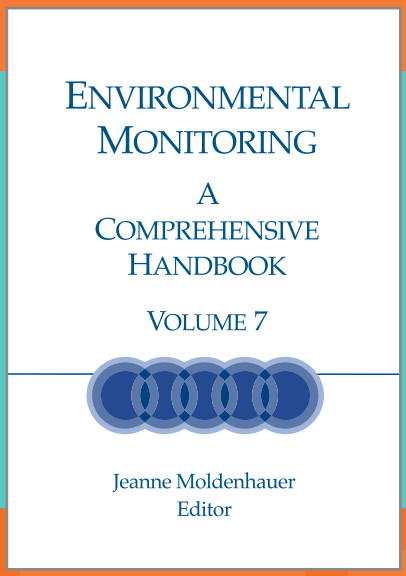

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