People • Science • Regulation

PDA Letter

Volume LII • Issue 2 www.pda.org/pdaletter February 2016

Follow the icon for content about the 2016 PDA Annual Meeting

The Parenteral Drug Association presents...

2016 PDA Annual Meeting

New Technology, New Facilities to Support Current and New Therapies and Drug Products

March 14-16, 2016 | San Antonio, TX

JW Marriott San Antonio Hill Country Resort and Spa

Exhibition: March 14-15 | Post-Workshop: March 16-17 | Courses: March 17-18

Conference Theme: Achieving Manufacturing Excellence: Current Trends and Future Technologies in Bioprocessing

Join us at the *2016 PDA Annual Meeting* as industry and regulatory experts share their experience, address challenges and provide a platform for engagement and knowledge exchange with conference participants.

Celebrating its 65th Anniversary in 2016, the *PDA Annual Meeting* has distinguished itself with a long history of providing the latest on development and manufacturing sciences, coupled with identifying the important connections to compliance and regulatory considerations. This Conference will have an increased focus on biopharmaceutical approaches and bioprocessing technologies.

The growing list of noted regulatory and industry experts include:

- **Chris Chen, PhD,** Senior Vice President & Chief Technology Officer, *WuXi AppTec*
- **Harry Lam, PhD,** Senior Vice President, Manufacturing, *PCT-Caladrius*
- **Mahesh Ramanadham, PharmD,** Branch Chief (Acting), OMPQ, CDER, *FDA*
- **Ranjit Thakur,** Senior Principal Engineer, *Janssen Pharmaceuticals*
- **Tongtong Wang, PhD,** Senior Director, Bioprocess R&D and Operations, *Eli Lilly & Company*

This is a unique opportunity to learn about defining and designing future efficient manufacturing platforms, and how to handle novel drug products and post approval changes. Take advantage of the ideal forum in which to learn and gain valuable information that will not only help you in your daily activities, but also benefit your entire organization!

For more information and to register visit pda.org/2016Annual.

Want to learn more? Expand your knowledge March 17-18 with six in-depth education courses:

- Recommended Practices for Manual Aseptic Processes (Mar. 17)
- Establishment of a Risk-Based Environmental Monitoring (EM) Program (Mar. 17)
- Quality Metrics: Performance Indicators (Mar. 17-18)
- Process Validation and Verification: A Lifecycle Approach (Mar. 17-18)
- Clean Room Design, Contamination Control and Environmental Monitoring for Controlled Environments (Mar. 18)
- Process Simulation Testing for Aseptically Filled Products (Mar. 18)

To find out more about these courses and how to register visit pda.org/2016AnnualCourses

PDA ***Education*** *– Where Excellence Begins*

The Parenteral Drug Association Education Department presents the...

2016 Annual Meeting Course Series

March 17-18, 2016 | San Antonio, TX

JW Marriott San Antonio Hill Country Resort and Spa

EXTEND YOUR KNOWLEDGE!

At the *2016 Annual Meeting Course Series*, you'll have the opportunity to learn more about manual aseptic processes, risk based environmental monitoring, quality metrics, process validation and verification and more!

Recommended Practices for Manual Aseptic Processes | March 17
Receive practical insights into the technological challenges associated with designing, operating and evaluating manual aseptic processing.

Establishment of a Risk Based Environmental Monitoring Program | March 17
Learn about the establishment of new environmental monitoring programs as well as reassessment of current programs to bring them into compliance with industry standards.

Quality Metrics: Performance Indicators | March 17-18
A recognized industry expert will present his perspective on selecting the appropriate quality metrics, determining how best to collect the data and how to use the data to improve the quality system.

Sterile Pharmaceutical Dosage Forms | March 17-18
This introductory course will address clean room design; environmental monitoring and control; sterilization principles; dosage form development, packaging and stability requirements; QA/QC for parenterals, and much more.

Clean Room Design, Contamination Control and Environmental Monitoring for Controlled Environments | March 18
Case studies and practice failure investigations will be used to demonstrate common errors to avoid as well as best practices to implement.

Process Simulation Testing for Aseptically Filled Products | March 18
This course will address all the various elements required in the design and execution of a media fill and the use of risk-based decision making will be considered.

To register and to learn more, visit pda.org/2016AnnualCourses

PDA is accredited by ACPE and offers continuing education for professional engineers.

PDA Letter

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FDAers Offer Agency Perspectives at Annual Meeting

The Annual Meeting is not just about great science and technology. It also provides a touchpoint to hear about the perspective of the U.S. FDA on important regulatory topics.

Mahesh Ramanadham, PharmD, Acting Branch Chief of CDER's New Drug Manufacturing Assessment Branch, will offer a regulatory perspective on post-approval changes at the breakfast session, "Post-Approval Life-Cycle Management Plans/Change Management," on Wednesday, March 16 at 7:15 a.m.

Dorota Matecka, a chemist with CDER, will provide a case study on expedited approval designations for breakthrough products in the meeting's fourth plenary session, "Rapid Product Development" (March 16 at 9:00 a.m.).

At the postconference workshop, *Preparing for the Next Generation of Regulatory Inspections*, **Rick Friedman,** Deputy Director, Science and Policy, OMPQ, CDER, will serve as a facilitator in a fishbowl discussion exercise on post-approval changes (1:30 p.m., March 17).

FDA representatives have also been invited to speak on other topics like data integrity during the workshop.

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

The Parenteral Drug Association presents...

2016 PDA Biosimilars Conference

June 20-21, 2016 | Baltimore, MD

Hilton Baltimore

The *2016 PDA Biosimilars Conference* will bring together industry experts and regulators to discuss new development strategies and updates on recent regulatory expectations for the approval of biosimilars. Successful case studies will be presented to illustrate how analytical similarity can be demonstrated and practical control strategies (process validation and specifications) can be developed. You will receive current updates from the regulatory agencies about which CMC aspects have been most challenging for the CMC reviewer, and will have several opportunities to raise questions and concerns to experts throughout the Conference.

Gain best practices from industry and regulators on topics such as:

- **Clinical development**
- **Product specifications for Tier 1 and 2 CQAs**
- **Process validation**
- **And much more**

For more information and to register today, please visit pda.org/2016Bio
#2016Bio

New Annual Report Explains How Members "Lead the Way"

PDA recently published its Annual Report with a new design and focus. The report laces PDA activities with the important initiatives driven by our volunteers. A more visual document than in the past, the 2014 Annual Report focuses heavily on PDA's membership.

In particular, the document highlights PDA's drug shortage, quality metrics and manufacturing science programs that unfolded in 2014.

If you are not sure of the impact PDA and its volunteers have on the industry, then check out "PDA: Leading the Way Through a World of Changes," available now at https://www.pda.org/footer/about-pda/annual-reports.

PDA Volunteer Spotlight

Lucy Cabral

- Head of Global Supplier Quality
- *Genentech*
- Member Since | 2003
- Current City | San Francisco, California
- Originally From | Portugal

I enjoy working with dynamic and innovative people

Lucy enjoys reading The Scientist, The Economist *and* PDA Letter *magazines*

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

Leading the Supply Chain Interest Group. Here, I can help the industry at large and bring forth best practices useful to the PDA membership.

Why did you start volunteering?

I started by attending PDA's many meetings, including ones held by the West Coast chapter. I really liked the content as well as meeting other PDA members. Then, I began volunteering with PDA so I could personally participate in improving the pharmaceutical industry. Additionally, I found PDA's leadership very engaging and captivating as a new member.

What is your favorite thing about being a PDA member?

Participating in a great organization for a great cause. In addition, the PDA leadership is a pleasure to work with. They motivate me to give more time to PDA.

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

In five years, I want to be an industry leader on the use of best practices to supply high quality products to patients worldwide. While the industry has steadily improved in the last few years, I would like to see a sea change in the culture of quality as well as greater leadership accountability in supplying quality products to patients.

How has your field changed since you started your career?

My field has evolved in a direction of improvement by focusing on Quality by Design (QbD) principles. Partnerships in operations and quality units have also greatly improved in the last few years.

What is your ideal work environment?

I am passionate about learning. I seek new areas that need development and improvement. I enjoy a dynamic environment where change is needed and welcome.

Tell us something surprising about you.

I come from a family of eight children.

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

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

You can too!
Authors wanted

For more information on PDA publishing please visit:

www.pda.org/pdaletter **http://journal.pda.org**

Chapter Seminar Explores Aseptic Manufacturing Concerns

Mark Gibson, AM PharmaServices Ltd, Treasurer, UK Chapter

On Nov. 18, PDA's UK Chapter hosted a networking seminar on aseptic manufacturing. Attendees learned about the Centre for Process Innovation (CPI) and its new National Biologics Manufacturing Centre (NBMC) in Darlington, England. CPI's **Juliana Haggerty** discussed the development and purpose of NBMC, which was planned in 2012 as part of a greater initiative in the United Kingdom to promote the country as a global leader in the life science sector.

NBMC provides companies open access facilities and expertise to help with development of new processes and technologies for manufacturing biologics. This facility will enable companies to test out new ideas cheaply and quickly with minimal risk, allowing innovative medicines to reach the market faster. Ultimately, CPI intends to use the Centre to bridge the gap between business and academia by growing existing networks so that great ideas can become commercial realities.

Next, participants were treated to a tour of this impressive £38m investment, comprising a state-of-the-art facility with 14 laboratories, including an analytical suite, cytotoxic and viral vector labs as well as two GMP standard labs.

Judi Sutherland then spoke about a skills gap in the bioprocess industry. Now, more than ever, companies seek scientists and technicians with relevant practical experience. But, according to her, employers are finding that recent graduates lack a good grasp of technical skills as university courses contain little practical work. In addition, apprenticeship opportunities are lacking. Thus, it falls upon employers to do most of the training. For this reason, CPI entered into a joint venture with Teesside University to devise a new building, the National Horizons Center (NHC), which will provide high quality training, particularly in aseptic practices. As well as containing technical facilities and equipment, the NHC will be designed specifically for training, with classrooms and teaching laboratories. In the interim, the NBMC has labs, conference rooms and an open plan lecture theatre that could be used for training purposes. The first training courses will begin this month.

After Sutherland's talk, **Ian Symonds,** a microbiologist with a wealth of experience in the pharma industry, offered the thought-provoking presentation, "Aseptic Manufacturing – A Rare Skill-Set." He challenged some of the traditional views on the merits of microbiological testing to demonstrate product sterility following aseptic manufacture and explained why these tests were flawed.

During the discussions, it became clear that there is a general consensus among chapter members of a need to train more scientists in technical skills, including aseptic manufacturing techniques. The UK Chapter plans to host additional events to address this and other aseptic manufacturing issues.

PDA Who's Who

Juliana Haggerty, Business Development, CPI Biologics
Ian Symonds, Aseptic Intelligence and Strategy, GlaxoSmithKline
Judi Sutherland, PhD, Project Manager (Biologics), CPI National Horizons Centre

Make Memories at the 2016 PDA Annual Meeting

Just like the city of San Antonio with its slogan, "Something to Remember," this year's Annual Meeting will offer lots for attendees to remember. Join fellow attendees at some of our exciting networking events and make lasting memories.

Here is a list of some of this year's exciting events, broken down by day.

Sunday, March 13

PDA 10th Annual Walk/Run Event

Starts at 7 a.m. Participants can choose to sign up for either the 5K run or 3K walk. $45 per attendee or guest. Proceeds support the Fisher House.

PDA Golf Tournament

Starts at 7 a.m. at TPC San Antonio. $250 per person which includes tee time, bag valet, range of balls, tournament management and lunch. Club and show rentals not included.

Meet and Greet Reception

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

Monday, March 14

Networking Reception

End the first day of the conference by joining fellow attendees for refreshments in the Exhibit Hall. Starts at 5:15 p.m.

Tuesday, March 15

70th Anniversary Gala Event

2016 marks PDA's 70th anniversary. Come celebrate this momentous occasion with other PDA members at this exciting event! (6–8 p.m., location: TBD)

Additionally, there will be further opportunities for networking during morning and afternoon refreshment breaks as well as at the networking luncheon on Monday held in the Exhibit Hall.

TOOLS FOR SUCCESS

Brought to you by the PDA Career Center.
Go to www.pda.org/careers for the latest opportunities.

The 20-Point Job Search Game Plan

Perry Newman

IN AMERICAN FOOTBALL, more than in any other sport, regardless of the level of talent, a game can be won or lost based on a coaching staff's game plan designed around the team's strengths and the perceived weaknesses of the opposition, with the deciding factor lying in the execution as well as the coach's ability to adapt midstream as needed.

This is also true about conducting a job search. Below are 20 basic steps I recommend incorporating into a job search game plan.

1 Define the job/s you're seeking and the *Hire Profile* of the ideal candidate employers seek to interview and hire

2 Define, qualify and quantify your qualifications, strengths and weakness based upon the *Hire Profile*

3 Identify your relevant achievements and accomplishments based upon the *Hire Profile*

4 Investigate how employers for these positions recruit and prefer to receive and process resumes and referrals

5 Craft a resume(s) with a unique personal brand in the favored style and format based on points 1–4

6 Critique your resume and LinkedIn profile before (not after) you begin to use it

7 Prepare all addendum documents you will need for your document portfolio

8 Craft a generic cover letter that is also adaptable for specific positions

9 Create a LinkedIn profile with a unique personal brand based on factors 1–4 listed above

10 Identify existing LinkedIn connections and other people you know who you can reach out to for networking

11 Set a reconnect and follow-up plan for all the existing people you want to network with

12 Set a goal of acquiring 5–25 new connections each week and define how you will approach them

13 Identify people who will recommend and endorse you on LinkedIn and how to approach them

14 Vet your references or have them vetted for you by a trustworthy third party

15 Identify interview questions you are likely to be asked and prepare brief, on-point responses

16 Have people conduct mock interviews with you as part of the prep process

17 Research potential employers and how you can get on their radar screens

18 Make a list of company websites you will check constantly for new postings

19 Create an Action Plan tracking booklet

20 Keep focused on working the Action Plan a minimum of 25 to 40 hours each and every week

About the Author

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

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

2016 1st PDA Europe Annual Meeting

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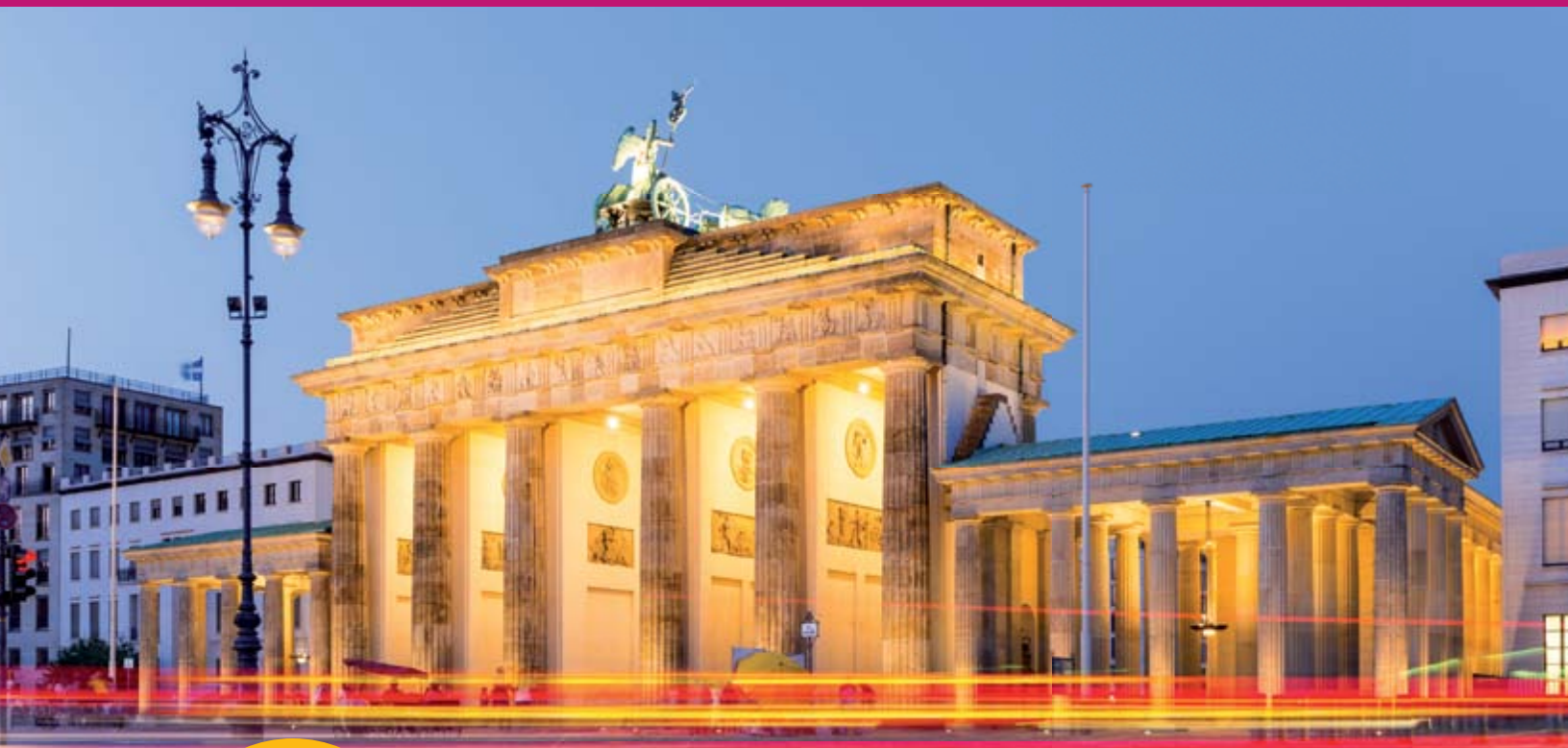

Register by 25 March 2016 and SAVE!

28-29 June 2016

Estrel Hotel Berlin
Berlin | Germany

europe.pda.org/Event2016

snapshot

Meeting *Preview*

Interest Group Schedule

As always, relevant interest groups will meet in the afternoon for the first two days of the *2016 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. 33).

Monday, March 14	Tuesday, March 15
4 p.m. – 5:15 p.m.	**4 p.m. – 5:15 p.m.**
Vaccines Interest Group	Process Validation Interest Group
Biotechnology Interest Group	Sterile Processing Interest Group
Combination Products Interest Group	Visual Inspection of Parenterals Interest Group
Facilities and Engineering Interest Group	Prefilled Syringes Interest Group
Microbiology/Environmental Monitoring Interest Group	
Lyophilization Interest Group	

PDA Journal *Top 10*

Data Integrity Case Study Tops Most-Read PDA Journal Articles for December

1. Case Study

Nader Shafiei, Regis De Montardy, and Edwin Rivera-Martinez, "Data Integrity—A Study of Current Regulatory Thinking and Action" November/December 2015

2. PQRI Special Section – Research

Dennis Jenke, et al., "Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products" September/October 2013

3. Conference Proceeding – Introduction

Lixin Xu, et al., "Role of Risk Assessments in Viral Safety: An FDA Perspective" January/February 2014

4. Technology/Application

Raphael Bar, "Charting and Evaluation of Environmental Microbial Monitoring Data" November/December 2015

5. PDA Paper

Pritesh Patel, et al., "Quality Culture Survey Report" September/October 2015

6. Research

Dennis Jenke, "Development and Justification of a Risk Evaluation Matrix To Guide Chemical Testing Necessary To Select and Qualify Plastic Components Used in Production Systems for Pharmaceutical Products" November/December 2015

7. PDA Paper

Steve Mendivil, et al., "PDA Points to Consider: Pharmaceutical Quality Metrics Updated September 2014" September/October 2014

8. PQRI Special Section – Review

Diane Paskiet, et al., "The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)" September/October 2013

9. Research

Elinor H. Zarour-Shalev, et al., "Filtration of Glass Delamination Particles with West Pharmaceutical Vial Adapters" November/December 2015

10. Research

Harry Yang and Jianchun Zhang, "A Generalized Pivotal Quantity Approach to Analytical Method Validation Based on Total Error" November/December 2015

Don't Be a Daredevil When Retrofitting Your Facility

Bob Ferer, The Ferer Group

When I was a kid, I used to collect leftover pieces of wood from my father's projects. My friends and I would build bicycle ramps used for jumping over obstacles (famed U.S. stuntman **Evil Knievel** was big back then). Luckily, we didn't have iPhones and YouTube to record the outcome for all the world to view. From what I see, rigging together disparate materials to build something that fails remains a popular pastime.

In our industry, there exists an expectation for a facility to be purpose-built to our specifications. At the same time, regulators are keen to ensure companies demonstrate that the facilities are suitable. With mergers/acquisitions, as well as costcutting initiatives, however, facilities are being shut down and product lines consolidated into existing facilities—risking suboptimal layout and design. Certainly, I am not suggesting that our industry is building the equivalent of a backyard bicycle ramp, but as engineers and facility operations professionals, we sometimes may act as daredevils skating on that edge.

The placement of products into facilities not initially built for purpose does not necessarily present an objectionable practice if we understand the product and process requirements, and more importantly, the impact of the proposed new product/process within the facility. Contamination control for both microbial and chemical crosscontamination is an often overlooked assessment that should occur each time we plan to bring a product into a facility. It must also be a standard part of our change control process for new product introduction. The European Union has already issued instructions requiring the use of Quality Risk Management (QRM) principles to assess and control the risk of crosscontamination. These requirements are contained in the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Part 1, Chapter 3: Premises and Equipment and Chapter 5: Production.

The risk assessment should start with understanding new product's vectors of contamination, and how these can impact existing products and processes in the facility. The risk assessment should consider the current design of the facility, and how this may be sufficient (or deficient) to exclude the introduction and transmission of organisms and chemicals. This stage presents the perfect opportunity to correct deficiencies as corrections made during this phase occur before there is an adverse impact on existing operations.

The following examples represent a few of the missteps I have seen in repurposing rooms. I hope these can help you avoid similar difficulties. Remember, the greatest risk in repurposing an area is lacking a full understanding of the original design.

Lack of Holistic Thinking=Disaster

A company decided to take an active tableting room out of service and utilize it as a clean parts storage area. It conducted a risk assessment, which found that the storage room presented less of a risk to product than as an active tableting room. The firm felt that the room air supply filtration and active air changes were well in excess of that needed for a storage room, choosing to leave that functionality in place to save time.

The company failed to recognize, however, that the filling room was designed for negative pressure to the hallway due to potential dust generation of the tableting operation. As a storage room, the proper design is to have the room be positive pressure to the hallway to prevent migration of particulate into the storage space.

In another example, a room originally designed as a small parts washroom was repurposed to wash larger equipment, including portable tanks. Engineers focused on the plumbing availability in the space, concluding that the drains could handle the larger quantity of water used as the primary utility in a wash bay. ➤

But they failed to consider the impact to other utilities within the space. The Air Handling Units (AHU), for example, did not have the capacity to remove the excess heat and moisture generated by the new washing processes, and failed to keep the room in a state of control during use, impacting nearby rooms as well. Secondly, the AHUs did not have the ability to keep the moisture in the vapor phase as the uninsulated duct work passed through nontemperature-controlled mechanical spaces prior to venting outside. While it is not uncommon for exhaust ductwork to remain uninsulated as there is no energy efficiency to be reclaimed, in this case, the moisture collected on the ductwork, dripped back down the duct, and leaked into interstitial and mechanical spaces. Needless to say, a mold problem ensued.

In another case, a firm decided to expand their production area because of an expected increase in manufacturing orders. It correctly isolated construction zones from the current manufacturing areas and proceeded to build and validate the new processing rooms. When the new processing rooms were put into service, it put an increased load on the existing preparations areas. As a result, more supplies were needed in the preparations room, and work in process was also being accumulated. Operators were unaware that the additional materials were disrupting the airflow in the room due to partial obstruction of low wall returns. The airflow disruption negatively affected the environmental monitoring results of the room, leading to high viable and nonviable particle counts. The engineers failed to account for the impact on the other production spaces during planning for their new production rooms. While the equipment was physically capable of handling the increased capacity, the staging before and after processing was not considered. This led to employees "making do"—violating the operating principles of the space.

Conclusion

Retrofitting of existing spaces is possible, and sometimes necessary to maximize effective use of existing infrastructure. These changes must be proactively assessed, however, and planned in advance of product line consolidation. Only then can we ensure that the facility is purpose-built, and will not become a patchwork activity that regulators will refuse to approve.

About the Author

Since entering consulting, **Bob Ferer** has focused his efforts on mentoring to share knowledge and experiences. He will teach the PDA Education course, "Clean Room Design, Contamination Control and Environmental Monitoring for Controlled Environments," following the *2016 PDA Annual Meeting* on March 18. For more information and to register, visit www.pda.org/2016AnnualCourses.

Keep Your Facility Up-to-Date in a Complex Market

Vijay Chiruvolu, PhD, Kite Pharma, and Ghada Haddad, Merck

As manufacturing facilities operate for years and years, running the same processes and using the same process equipment, the odds are these facilities are not up to current standards. While the infrastructures, systems and equipment may have been "state-of-the-art" when the facility was commissioned, these may now be less-than-adequate by today's standards, necessitating improvements in technology.

Not to mention that upgrades are now driven by a changing healthcare market that, in turn, is affected by issues such as complex molecules, smaller batch sizes, and increasing regulatory requirements.

So what types of upgrades to equipment, support systems or containment options are required to ensure facilities remain current with changing technologies and also meet compliance requirements?

Answers may be found by attending the *2016 PDA Annual Meeting* session, "Adapting Manufacturing Facilities." **Tsutomu Ota** from Takeda will share his experiences using single-use systems as enablers for converting a dedicated cytotoxic parenteral facility into a multipurpose manufacturing site. **George Wiker** from AES Clean Technology will share a case study on how to implement changes to a facility while it continues to operate and ensure the ability to maintain quality production, meet regulatory requirements and secure drug supply to patients.

Another session, "Ensuring Supply by Using Multiproduct Facilities and Reducing Supply Chain Risk," addresses how manufacturers, under pressure to control costs, are moving to smaller, more flexible multiproduct facilities. These facilities bring different types of challenges—ranging from traceability—especially in cell therapy manufacturing, to contamination control. The interdependency of manufacturing systems in a multiproduct facility increases the risk of product supply disruption due to a potential breakdown of any one of the systems. Sanofi's **Harry Lam** and Kite Pharma's **George O' Sullivan** will present these challenges and highlight options for mitigating this risk.

2016 PDA Annual Meeting and PDA Education courses

San Antonio, Texas
March 14–18
www.pdaannualmeeting.org

The Future of the Glass Ampoule

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

The PDA Letter will periodically publish selected dialogue from PDA Connect℠. Join at community.pda.org and continue the conversation!

The following is taken from the Packaging Science Interest Group Forum.

Questioner

What is future of glass ampoule? Is it going to be replaced with glass vials, PFS or plastic packaging in near future?

Respondent 1

That view has been with us for decades, and ampoules are still here. I don't know of any new drugs being developed in ampoules, but many generic drug products, especially outside the United States, continue to be supplied in ampoules.

Respondent 2

Certainly glass ampoules provide one of the simplest containment systems and offer the best opportunity for minimizing product-package interaction, which promotes long-term solution stability. However, one must be concerned with the generation of glass fragments upon opening. It would be most reasonable to promote the use of syringe filters for injection of ampoule-based products, but of course that is a significant cost and possibly potency consideration for many producers.

[**Editor's Note:** Interested in the latest developments in glass and other packaging? Consider attending the *Parenteral Packaging* conference in April. For more information, visit https://europe.pda.org/ParPack2016.]

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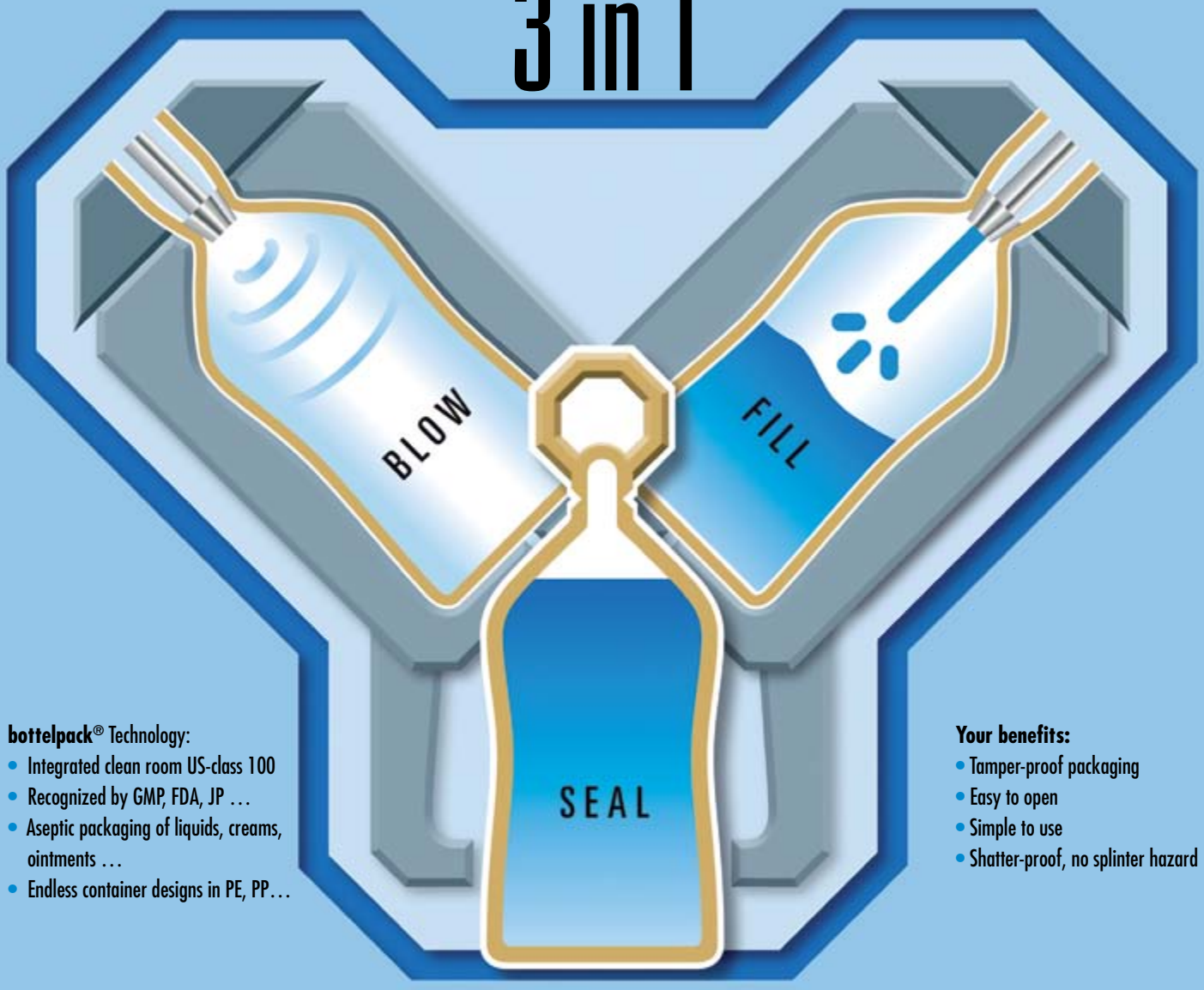

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Four Steps to Modernizing Aging Control Systems

Timothy Miller and Andy Miller, Xellia Pharmaceuticals USA

Obsolete manufacturing control

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

How do you know your control systems are getting dated? Here are a number of signals:

- The original equipment manufacturers (OEMs) have gone out of business, leaving behind proprietary control systems and code
- The original control systems are based on an out-of-date operating system or require obsolete hardware (e.g., the controls are not compatible with drivers for more recent hardware), meaning that if a human machine interface (HMI) or other piece of hardware fails, there is no way to repair the system without sourcing a vendor of superseded hardware
- The original control system does not meet current processing requirements, networking and monitoring needs, or regulatory expectations (e.g., continuous risk improvement per ICH Q9, 21 CFR §11, etc.), and no upgrade packages meet these constraints

While many equipment manufacturers continue to support and offer upgrades to their control systems, situations often still arise requiring system owners to develop and implement upgrades to their control systems.

Upgrades or replacements of control systems can be difficult yet worthy projects. A piece of pipe does not become obsolete, and components such as motors, pumps, valves, and analytical instruments perform their functions regardless of what controller sends the signal or collects the data. Control system modernization can harness the established, qualified function of the system and its components, saving the cost and effort of replacing the entire system.

4-Step Strategy Offers Possible Solution

When vendor upgrades and packaged improvements are not available, redevelopment of control systems or novel redeployments can extend system life while also meeting cGMP requirements. The following four-step strategy can reduce the cost and effort of implementation, and minimize the impact on the production schedule and system availability for manufacturing.

1. Develop the new control system while the original system remains in place and in use. Many options exist to modernize a control system. Consider one of the following options:
   a) Create an entirely new control system from the ground up (see the first case study below)

   b) Develop a set of improvements and upgrades to the current controls system (e.g., vendor upgrade packages)

c) Virtualize the controls system to a custom virtual environment that supports the original operating system, but also capable of supporting modern hardware and drivers, networking and security standards (see the second case study below)

Developing a new control system to the original system performance is the most difficult of these options, but occasionally may be needed. Regardless of the option taken, the new control system needs to conform to the original equipment user, functional, and design requirements; deviations from these need to be identified for specific assessment and challenge during qualification.

2 Install the new control system and hardware adjacent to the existing control system, but without connecting it to the system

The goal in this step is to have two functional control systems, both capable of operating the hardware of the system. This generally requires that the new control system be installed on its own set of hardware. Ideally, none of the functions of the original control system will be disabled by installation of the new control system; nor will the system be "aware of" or impacted by the installation

3 Switch between the original control system (for production) and the new control system (for qualification) using the out-of-service system

4 Permanently activate the new control system once qualification is complete

Article at a Glance

- 4-step strategy can alleviate control system upgrade headaches
- Risk management needs to be factored in early on in the process
- Case study shows qualification can occur during shutdown

Upgrades or replacements of control systems can be difficult yet worthy projects

The advantages of this strategy include:

- Reduced equipment downtime and production impact, since the unit can be returned to operation by reconnecting the original control system
- Reduced operational risk, as a qualification failure may be remediated while the original control is used to control the equipment
- Reduced cost, as the control system upgrade is generally less expensive than replacing the entire piece of equipment
- Increased scheduling flexibility for installation and qualification of the upgrade as compared to removing the original control system prior to installing the new one
- More complete retention and access to the previous operating condition to support trending, investigations, and continuous improvement efforts
- Reduced qualification requirements, as many system component functions (outside the control system) will not change or be reinstalled, meaning that qualification of the control system is focused on interaction with the hardware, reducing the qualification effort and time on the component devices themselves

Risk management and documentation is a central tenet of cGMPs and integrated in effective change control systems, as detailed in most guidance documents, including the FDA guidance, *Quality Systems Approach to Pharmaceutical CGMP Regulations,* Eudralex Chapter 4, Annex 15, ICH Q7, Q9, and Q10, ISPE Baseline Guides and GAMP 5. Implementing the risk evaluation early in the design phase allows early evaluation of the impact, ensures consistent function of field devices between the original and new control systems, and offers an organized qualification effort driven by the actual risks associated with the upgrade.

The following are examples of how firms can use the four-step strategy.

Case Study 1: Parts Washer Control System Redesign

Situation: The OEM of a parts washer was acquired by another company that eventually stopped supporting the original software of the unit. Hardware components of the system were no longer available and the software was not compatible with more recent drivers. The only modernization support offered was a very expensive transfer to the new company's control hardware, software and support; however, other functions beyond hardware operation were not included with the upgrade.

Modernization Strategy: The cost of the vendor upgrade (not including establishing the historian function) was approximately twice the cost of developing a new control system to the original functional specification. Therefore, the system owner contacted an automation developer to develop a new control system compatible with current hardware and upgradable for the foreseeable future. The following two constraints were placed on the development:

All component controls must be identical with the original controls. This meant that valve tables were copied from the original control system specification; alarms and alarm responses were exactly the same, and control points in the unit operation were unchanged.

The wash recipes use the same steps and flowpaths, with the same (or greater) durations for each step, so that no wash cycle on the new control system could be considered worst case relative to the qualified cycle on the original control system.

Building Agile, Flexible Facilities

***Morten Munk** will discuss the agile and flexible facility of the future at the* 2016 PDA Annual Meeting. *The* PDA Letter *asked him about his presentation:*

What are some signs that indicate a company should consider modernizing existing processes?

There are many signs, but in short they can be summarized as a low degree of manufacturing robustness. Some specifics are:

- Produced product does not meet current quality standards
- High number of deviations
- Breakdown of equipment
- Frequent manufacturing stops
- Difficult to find replacements for equipment or spare parts
- Difficult to maintain the automation system – both software and hardware
- High fear for customer and regulatory inspections/audits

What is the bigger challenge: Upgrading equipment? Or upgrading processes?

Generally, it is easier to upgrade equipment than processes. However, most of the issues from problematic aging facilities are probably from the equipment rather than the processes. Some older facilities use very old equipment for old types of processes that would benefit from an upgrade toward new and efficient solutions where the change affects both process and equipment. One example is upgrading to barrier technology in old cleanrooms.

You mention "de-risking," inferring that there is risk involved in aging systems/facilities.

There are many examples that confirm that significant changes to aging facilities can be a risky challenge. In fact, many of the upgrades to existing facilities experience unforeseen problems from areas that were not foreseen to be in scope for the change project. Some facility upgrade projects have run into problems that have affected product availability, sometimes leading to drug shortage situations. This risk can be significant and calls for extra caution in planning. ➤

This was simplified in that each washer system component was controlled in an on/off manner (reducing the complexity of PID logic and tuning) and the cycle disposition logic was simple. In addition, the temperature and durations of each step matched the programmed limits, and the final rinse conductivity stayed below a defined limit.

Results of Implementation: A new control system was created and the new control system (on an Advantech industrial PC) was installed.

Figure 1 shows the system with both control systems in place, but the original (proprietary) system controlling the washer. When the unit was available for qualification, the washer was taken out of service and the HMI, the I/O ControlNet card, and the printer were disconnected from the original controller and connected to the Advantech hardware (See **Figure 2**). When the washer was required for production, the three cables were returned to the original controller and the unit returned to service **(Figure 1).**

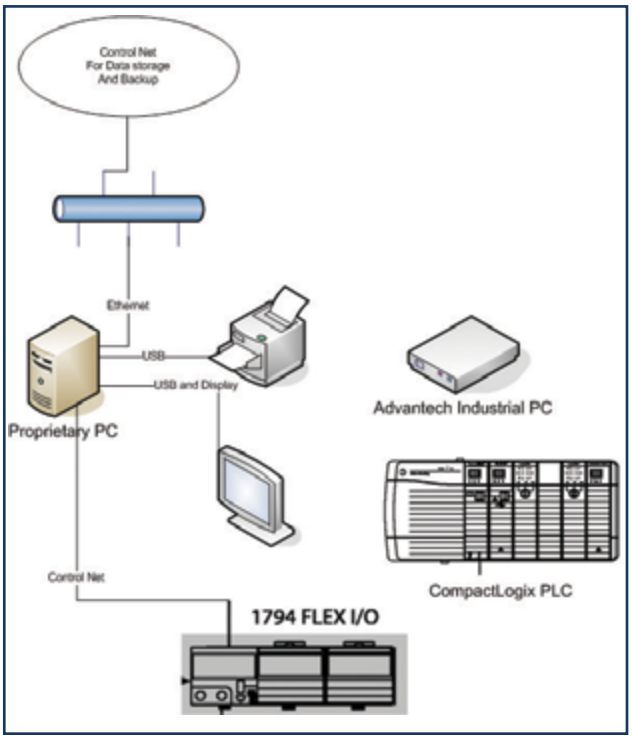
The total qualification required was reduced relative to a new washer and comparable to the vendor upgrade. Full installation qualification was executed, including configuration, alarms, communication, and security/Part 11 compliance. No installation qualification was required on the original system components, however, as they had not been touched.

Cleaning validation was not impacted, as each parameter of the cleaning cycles were transferred. Because the same pumps were pushing the same solution through the same pipes at the same pressures and flowrates to the same spray-arms, the cleaning coverage and efficacy of the original system were maintained. With the constraint that each wash cycle on the new controller have the same steps, and at least the same durations as the original, the existing cleaning qualifications covered the washer performance with the new controller. Due to some differences in the development software used in the new system when compared to the function of the original, each step was slightly extended (by a few seconds) ensuring the integrity and applicability of existing cleaning validations.

The system downtime only impacted nonproduction periods, so the overall cost of modernizing the system was reduced in terms of price and implementation cost, while the resulting functionality included the historian.

Upon completion of the upgrade and qualification, the original system remained in place and is accessible for cycle reports and other historian functions.

Figure 1 System configuration with the original (proprietary system) functional and the new control system (Advantech) in place but not connected



Are technological advancements driving your production into the unknown?

Success in the new pharma reality relies heavily on successful implementation of new manufacturing technology

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2016 PDA Upcoming Events

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FEBRUARY

16-18

Environment Monitoring Course Series
Bethesda, MD
pda.org/2016EMCourses

23

PDA Delaware Valley Breakfast Symposium on Aseptic Processing
Malvern, PA
pda.org/DVAP

23-24

Pharmaceutical Microbiology
Berlin, Germany
pda.org/EU/Microbiology2016

25-26

Rapid Microbiology Methods
Berlin, Germany
pda.org/EU/MicroMethods2016

25-26

Control, Validation and Monitoring of Biofilms in Water Systems
Berlin, Germany
pda.org/EU/Biofilms2016

25-26

Charting and Trending of Environmental Data
Berlin, Germany
pda.org/EU/EnvironmentalData2016

29 – MAR. 3

GMP Week
Bethesda, MD
pda.org/2016GMPWeek

MARCH

1

Visual Inspection IG Meeting
Berlin, Germany
pda.org/EU/IGVisual2016

2-3

An Introduction to Visual Inspection: A Hands-on Course
Berlin, Germany
pda.org/EU/WSVisual2016

4

Particle Identification in Parenterals
Berlin, Germany
pda.org/EU/ParticleIdentification2016

14-16

2016 PDA Annual Meeting
San Antonio, TX
pda.org/2016Annual

16-17

Preparing for the Next Generation of Regulatory Inspections: A 2016 PDA Manufacturing Science Workshop
San Antonio, TX
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17-18

2016 PDA Annual Meeting Course Series
San Antonio, TX
pda.org/2016AnnualCourses

29-31

Risk-Based Qualification of Sterile Drug Product Manufacturing Systems
Bethesda, MD
pda.org/2016Sterile

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pda.org/calendar

APRIL

4-8

GSA Schedule Contract GS-02F-113BA

Aseptic Processing Training Program – Session 2 SOLD OUT

Week 2: May 2-6
Bethesda, MD
pda.org/2016aseptic2

11

Interest Group Meeting Pre-filled Syringes
Venice Italy
pda.org/EU/IGPrefilled2016

12-13

Parenteral Packaging
Venice, Italy
europe.pda.org/ParPack2016

12-14

Validation of Moist Heat Sterilization Processes
Bethesda, MD
pda.org/2016MHSP

14

Container Closure Development
Venice, Italy
pda.org/EU/CCD2016

14-15

Extractables & Leachables
Venice, Italy
pda.org/EU/E&L2016

14-15

Container Closure Integrity: Regulations, Test Methods, Application
Venice, Italy
pda.org/EU/CCI2016

19-20

LONDON – 2016 PDA Data Integrity Workshop
London, United Kingdom
pda.org/2016datalondon

19-20

SAN DIEGO – 2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision
San Diego, CA
pda.org/2016annexwest

19-21

GSA Schedule Contract GS-02F-113BA

Validation of Biotechnology-Related Cleaning Processes
Bethesa, MD
pda.org/2016biotech

21

GMPs for Manufacturers of Sterile and/or Biotechnology Products
San Diego, CA
pda.org/2016ManufGMP

25-29

Praxis der Pharmazeutischen Gefriertrocknung
Osterode, Germany
pda.org/EU/Gefriertrocknung2016

26-28

INTERPHEX NY – PDA Educational Program
New York, NY

Finally, can companies running old facilities and processes meet the demands for quality metrics from the U.S. FDA?

Yes, the draft FDA guidance for quality metrics is not giving new requirements for old facilities or processes, but is expected to increase ongoing quality awareness, which also may point to existing processes, facilities and equipment if they are causing deviations or other problems that affect quality metrics. We have not seen the final guidance on quality metrics, but manufacturing facilities should be aware that ongoing manufacturing problems or deviations may become more visible in some of the suggested quality metric definitions.

About the Expert

Morten Munk is the Senior Technology Partner at NNE Pharmaplan. He has over 25 years of industry experience in biopharmaceutical development and manufacturing in both the United States and Europe.

Implementing the risk evaluation early in the design phase allows early evaluation of the impact

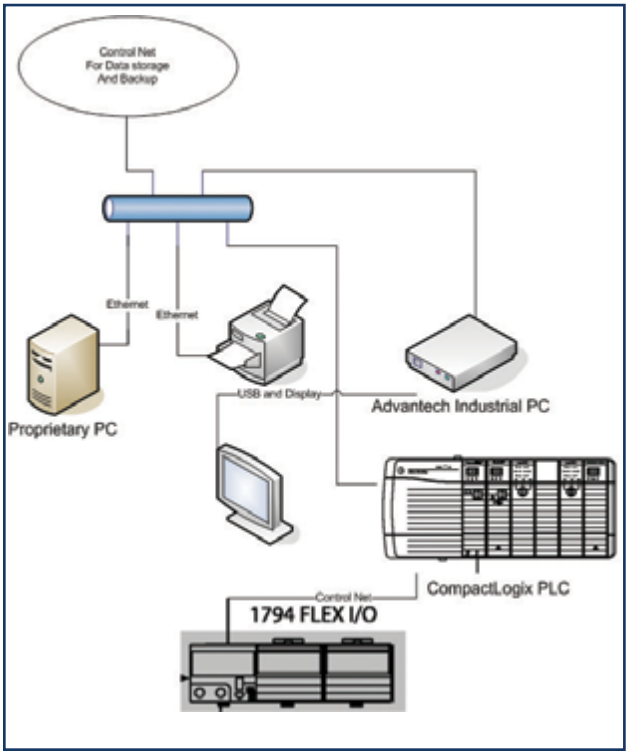
Case Study 2: Virtualization of Control Server

Situation: The server components on a large system installed and run from a Windows 2000 server were reaching the end of their service life. Replacement components were unavailable and new ones incompatible with the Windows 2000 server. The OEM was no longer in business, and the companies offering support for the system did not have a straightforward upgrade strategy.

Modernization Strategy: The controls of this very large system were quite complex, including several hundred field devices as well as sensitive control strategy tuning and responses. In addition, the system was critical to the production process. Therefore, redevelopment was not a suitable option.

The system owner chose a virtualization strategy since the primary concern was that the hardware for the control would fail and could not be replaced. In this case, a Windows 2000 Server environment was created on a virtual machine host using the tools from the virtual machine provider. The virtual machine center in this setup contained upgradable hardware and drivers, while maintaining the virtual server in a secure, RAID-1 backup setting.

Figure 2 System out-of-service with the new control system (Advantech) active



Results of Implementation: The virtual server was created and the most recent backup of the physical server restored to the virtual server at the beginning of a facility shutdown. During the shutdown, the system was connected to the virtual server; when qualification of the new environment was complete, the system was reconnected to the physical server. Before the shutdown was over, the qualification package had been completed and approved with the system permanently reconnected to the virtual server.

Qualification was primarily limited to creation and identity of the virtual server (GAMP challenges such as backup/restore, security, etc.) and communication with the system and alarm-out systems. Since backup/restore tools were used to recreate the physical server on the virtual machine, communication between the server components (the I/O server, the SCADA, the historian, the recipe database, etc.) was not changed as compared to the current qualified condition.

Qualification was further expedited by challenging the virtual server with complex tasks (loading and executing recipes, generating reports for the recipes, and retrieving the historical data) that while not time consuming, inherently challenged all functions performed by the server. In short, by demonstrating that the server could download a recipe to the field PLC from a server terminal at the physical system, communication between the recipe database, the field devices, and the field PLC was confirmed. Likewise, challenging control of field devices such as valves demonstrated functional communication between the I/O server, the historian's ability to correctly trend information, and server terminals at the system.

Had qualification not been completed during the shutdown, the system owner planned to use the out-of-service strategy for the washer as in the first case study, so that qualification work could be completed while also minimizing downtime. An additional step would

Continued at bottom of page 44

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Older Pharmaceutical Factories – What Does FDA Say?

Thomas Peither, Maas & Peither AG

[Editor's Note: This is an expanded version of an article published in the August 19 issue of Maas & Peither's cGMP newsletter.**]**

Older factories can indeed exemplify the state of the art. This was the opinion expressed by **Sharon Thoma** of the U.S. FDA at the *PDA Annual Meeting* in March 2015 ***(1).***

However, all too often FDA inspectors also see older sites that are having problems with cGMP. The "c" in cGMP stands for "current," up-to-date GMP. This means that a company should be using technologies and systems that correspond with the state of the art.

"Are your systems and equipment adequate enough to prevent contamination, to eliminate potential mix-ups?" Thoma asked the audience.

If systems and processes are convincingly applied, then an old plant does not have to be an obsolete one. The more fitting question that arises is whether a company has established appropriate processes. These processes must ensure that the plant always runs at its best.

Specific risks of older factories

Older factories nowadays are confronted with a wide variety of challenges, such as:

- Inefficient processes
- Inappropriate flows of material and personnel
- Antiquated or obsolete ventilation systems
- Old equipment that no longer meets current requirements

These groups of problems entail great risk or a high risk potential for GMP deficits. These challenges must be familiar to all.

How Can Existing Factories Keep Pace?

Ask yourself the following questions to discover whether or not your factory is still up to date:

- **Is your facility in need of a major overhaul or upgrade in order to meet todays' standards of technology and compliance expectations?** This means looking at how the HVAC system fulfils hygienic aspects as well as air change rates, energy consumption, etc. Is your material and personnel flow adequate? Surfaces (floor, wall and ceiling) should adequately fulfil hygienic design. The infrastructure must meet current GMP requirements (piping, wastewater, IT network, computer systems, monitoring systems, etc.). SOPs and quality procedures should support manufacturing. Do these need to be rewritten or improved?

- **Have you looked at your facility? Are there ways you could better maintain or upgrade your 10-, 20-, 30-, 40-year-old facility?** Look into how much time is wasted in quality, documentation and administration procedures. Your facility requires regular investments. Do you have adequate trained personnel in your maintenance department? Are adequate SOPs and maintenance protocols in place? Analyze your numbers of defect rates, deviations, etc.

- **Have you conducted a quality risk assessment? Do you have appropriate controls in place to ensure there are no potential risks to product quality and, ultimately, to patient safety?** Every critical system (e.g., purified water, air pressure, IT network, building access, etc.) should have a risk analysis. Risk assessments must be taken into consideration when drawing up the budget for investments and maintenance. And your meetings should be structured to ensure you identify the right risks, i.e., appropriate participants invited, an outline of responsibilities, regular schedule, meeting minutes, etc.

- **Is it time to rebuild or install new technology/new equipment to protect products, meet current regulations, and to keep up with today's demands, e.g., RABS, isolators, improved lockers, HVAC design, continuous manufacturing, Six Sigma and continuous improvement, process analytical technologies (PAT), etc.?**

FDA Focuses on Older Operations

Thoma quoted CDER Director **Janet Woodcock** to illustrate the FDA's position on older factories: "Some inspections have found operations with antiquated or obsolete facility or process elements, and operations with high defect rates in violation of cGMP. These operations are receiving higher focus, while manufacturing operations that have been upgraded and are more dependable have been deemphasized."

Production methods must be modernized. This action should be taken utilizing the progress made in operational and process concepts, such as:

- Automating manual processes
- Using closed systems
- Integrating process analytical technologies (PAT)

Process monitoring can be improved in this way. The gateway to new manufacturing concepts should be found. These technologies help achieve the following goals:

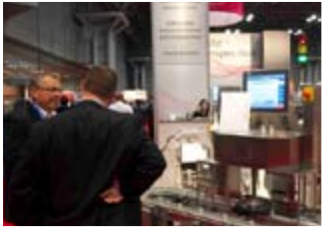
- Improving production reliability
- Enhancing robustness
- Lowering costs

Summary

The FDA is well aware of the problems involved with older factories. Therefore, in the next few years the FDA will be watching these facilities. There are very many pharmaceutical manufacturing sites that not only meet current requirements but are actually exemplary facilities. In her talk, Thoma described what

Continued at bottom of page 33





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- Lisa Birmingham

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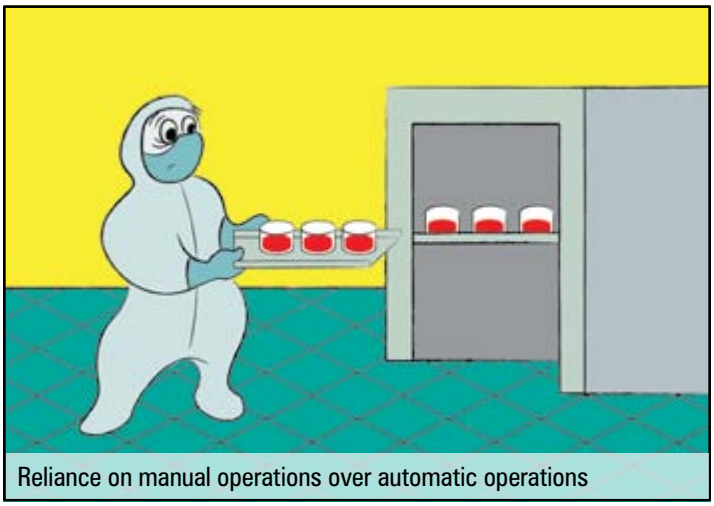
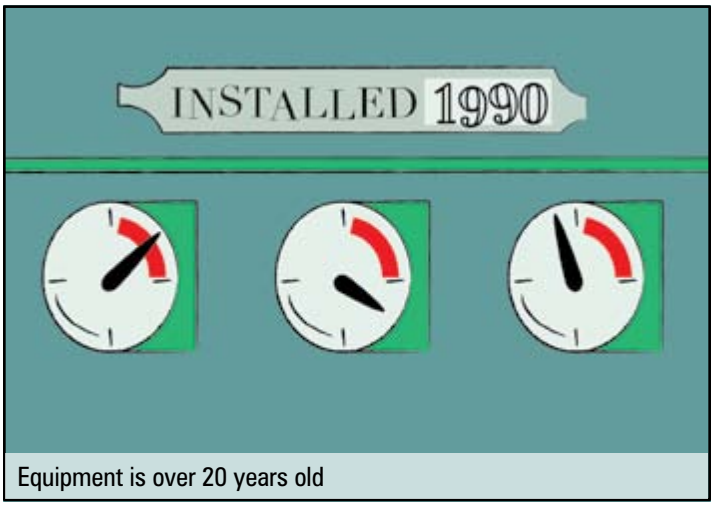
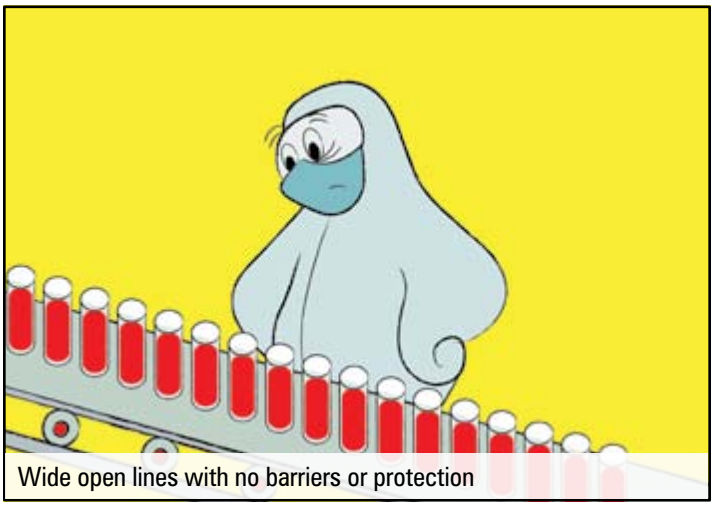
Signs Your Facility Might Need an Upgrade

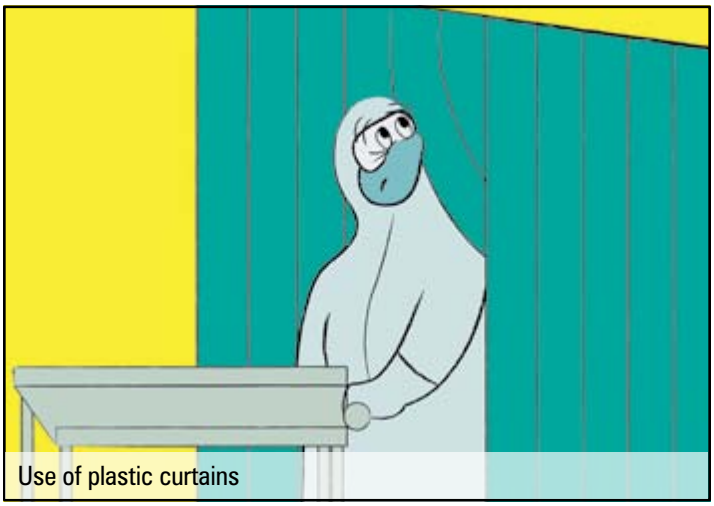
It can be hard during day-to-day operations to recognize your facility is aging. Below are some indications your site may need an upgrade.

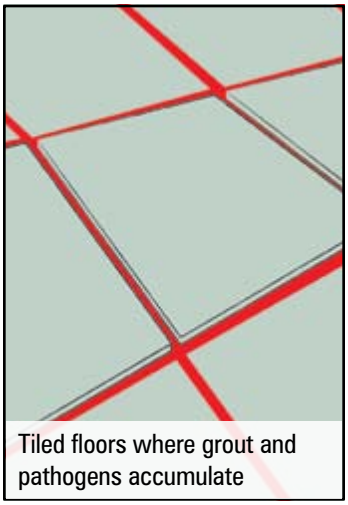

Reliance on manual operations over automatic operations

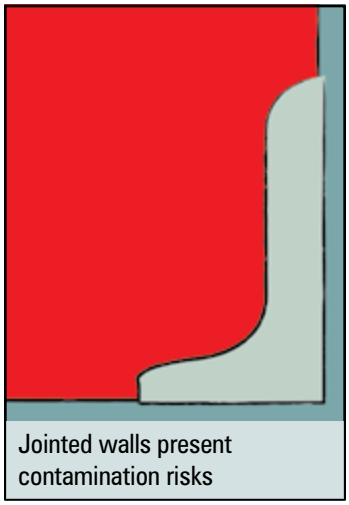


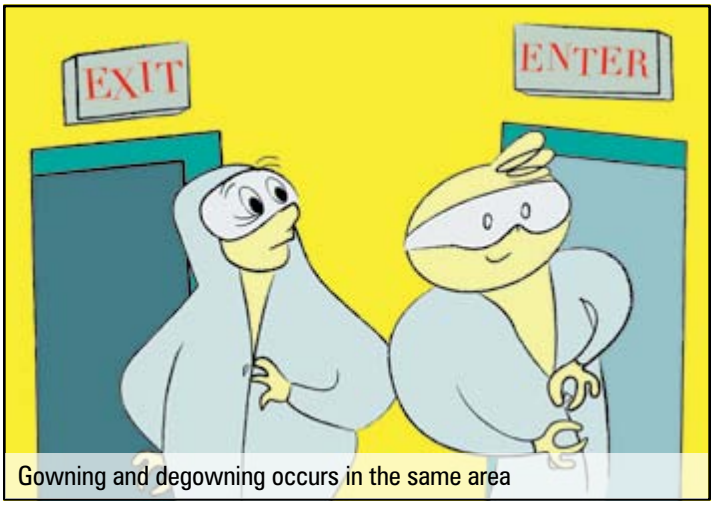
Equipment is over 20 years old


Wide open lines with no barriers or protection


Use of plastic curtains


Tiled floors where grout and pathogens accumulate


Jointed walls present contamination risks



Gowning and degowning occurs in the same area

Special thanks to **Susan Schniepp,** Regulatory Compliance Associates, and **Robert Dream,** HDR Company, for their assistance with this infographic.

PDA Europe
Activities and Events

2016

23-24 February	**Pharmaceutical Microbiology**	CONFERENCE	**Berlin Germany**
25-26 February	Rapid Microbiology Methods	TRAINING COURSE	
25-26 February	Trending Environmental Data	TRAINING COURSE	
1 March	**IG Meeting Visual Inspection**	INTEREST GROUP MEETING	**Berlin Germany**
2-3 March	Introduction Visual Inspection	TRAINING COURSE	
4 March	Particle Identification	TRAINING COURSE	
11 April	IG Meeting Pre-filled Syringes	INTEREST GROUP MEETING	
12-13 April	**Parenteral Packaging**	CONFERENCE	**Venice Italy**
14-15 April	Extractables and Leachables	TRAINING COURSE	
14 April	Container Closure Development	TRAINING COURSE	
7-9 June	**Advanced Therapy Medicinal Products**	CONFERENCE	**Berlin Germany**
9 June	ATMPs	TRAINING COURSE	
28-29 June	**1st PDA Europe Annual Meeting**	CONFERENCE	**Berlin Germany**
30 June - 1 July	Root Cause Investigation	TRAINING COURSE	
30 June - 1 July	Development Pre-Filled Syringe	TRAINING COURSE	
30 June	Test Methods Pre-Filled Syringes	TRAINING COURSE	
30 June	Cleaning and Disinfection	TRAINING COURSE	
20-21 September	**9th Workshop on Monoclonal Antibodies**	WORKSHOP	**Rome Italy**
22-23 September	Compliance Biopharmaceuticals	TRAINING COURSE	
22-23 September	Extractables and Leachables	TRAINING COURSE	
22 September	Elastomers	TRAINING COURSE	
22-23 September	Introduction Aseptic Processes	TRAINING COURSE	
27-28 September	**Pharmaceutical Freeze Drying Technology**	CONFERENCE	**Strasbourg France**
29-30 September	Development Freeze Drying	TRAINING COURSE	
29 September	Risk Based Freeze-Drying	TRAINING COURSE	
10 October	IG Meeting Pharmaceutical Cold Chain	INTEREST GROUP MEETING	**Amsterdam The Netherlands**
11-12 October	**Pharmaceutical Cold & Supply Chain Logistics**	CONFERENCE	
13-14 October	Education Programm		
24 October	Particle Identification	TRAINING COURSE	**Berlin Germany**
25-26 October	**Visual Inspection Forum**	CONFERENCE	
27-28 October	Introduction Visual Inspection	TRAINING COURSE	
15-16 November	**Outsourcing & Contract Manufacturing**	CONFERENCE	**To Be Confirmed**
17-18 November	Root Cause Investigation	TRAINING COURSE	
17 November	Quality by Design	TRAINING COURSE	

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Shortlist 3 Dec 2015

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Meeting *Preview*

Interest Group Schedule

As always, interest groups falling under the Regulatory Affairs and Quality Advisory Board (RAQAB) will convene at the *2016 PDA Annual Meeting*. Below is the schedule for the RAQAB interest group meetings. For interest group meetings falling under the Science and Biotechnology Advisory Boards, see page 14.

Tuesday, March 15

Pharmacopeial/Management of Outsourced Operations Interest Groups (joint meeting)

Quality Risk Management Interest Group

Supply Chain Management Interest Group

Older Pharmaceutical Factories – What Does FDA Say? continued from page 28

to do to achieve these goals:

- **Always look for ways for improvement.** This can involve implementing improvement procedures, performing risk assessments and risk analysis and setup actions, and documenting improvement efforts.

- **Regarding technology, always stay on the ball.** Inform yourself about new technologies and processes through conferences, publications, interest groups, associations, suppliers, etc. Work with your supplier to try to improve the machinery on your shop floor.

- **Continuously adapt the organization to the changes.** Try to implement a culture of quality and improvement. Follow the Deming circle—plan, do, check, and act. And remember the words of **Heraclitus:** "The only thing that is constant is change!"

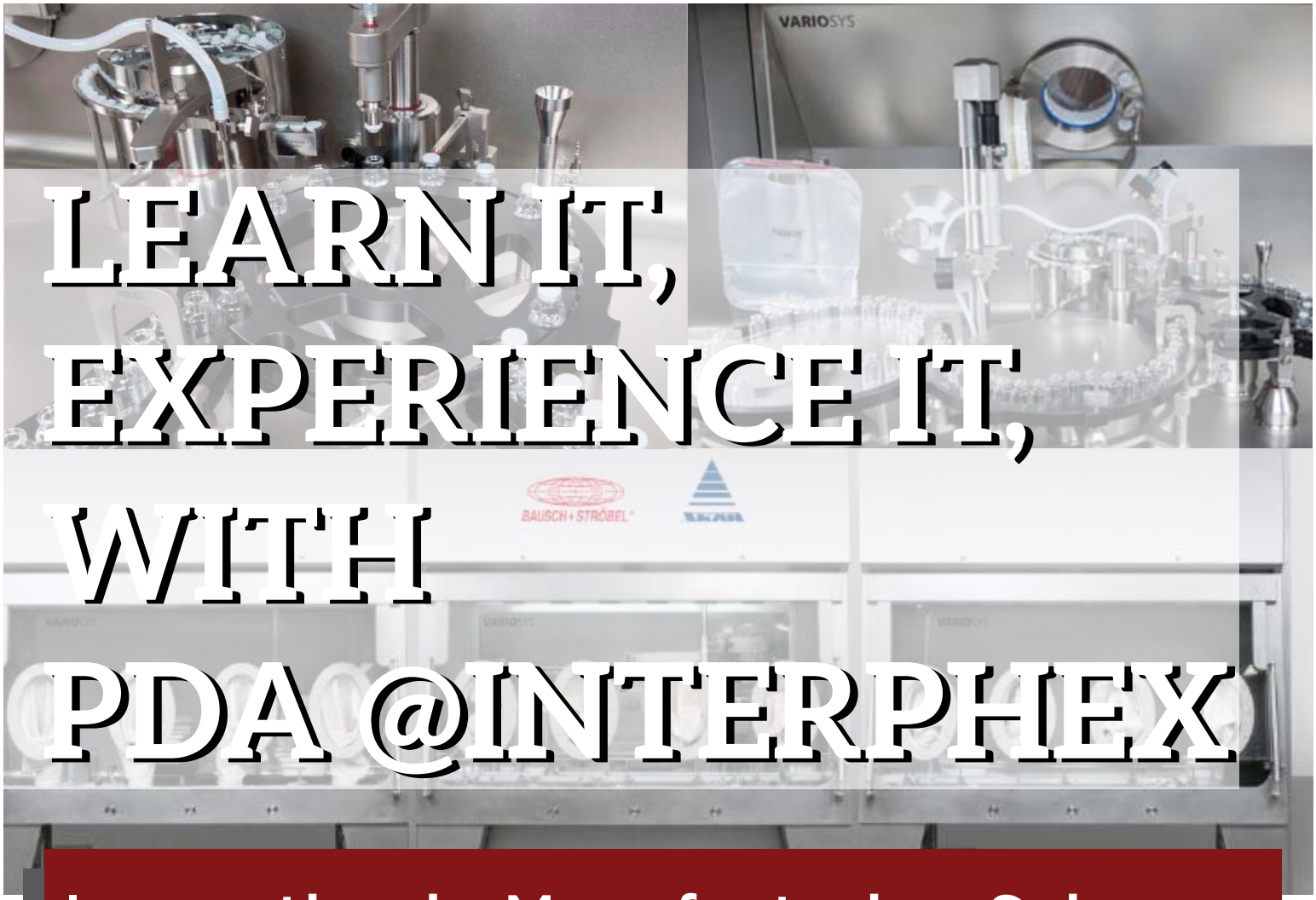
- In other words…keep up to date!

Reference

1. Thoma, S. "Inspection Trends." Presented at the 2015 PDA Annual Meeting, Las Vegas, Nevada, March 2015.

About the Author

With more than 20 years as a GMP consultant and more than 15 years as owner of Maas & Peither GMP Publishing, **Thomas Peither** supports the pharmaceutical industry in implementing GMP requirements. As Executive Editor, he focuses especially on the practical interpretation of guidelines.



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Quality Risk Management Meets Aging Facilities

Jim Butler and Karim Bibawi, Cimetrics Inc.

Aging production facilities are a particular challenge for the pharmaceutical industry due to the regulatory requirements for managing changes and the consequences that can result if production problems reduce availability of product for patients. After all, reduced supply also impacts company profitability. For these reasons, decisions about how to manage aging pharmaceutical manufacturing facilities are complex.

The pharmaceutical industry is increasingly applying risk-based methods to quality management. These methods can also help guide the tactical and strategic decisions concerning aging facilities and equipment. But companies must have effective processes for creating and updating risk assessments for their manufacturing systems, so that risk control measures can be applied where they will be most beneficial.

Risk Throughout the Lifecycle

ICH Q9, *Quality Risk Management* (QRM) is a widely accepted guideline for QRM in the pharmaceutical industry, and its principles are applicable to aging facilities. Best practices in implementing ICH Q9 involve application of risk management throughout the lifecycle of a manufacturing system from initial design through operations to final decommissioning.

During the design process of a system, an initial design review/risk assessment (DR/RA) is produced, utilizing well-understood engineering methods such as Failure Mode Effects Analysis (FMEA). The DR/RA then becomes the baseline for periodic risk reviews during the operational phase of the system, in which the risk assessment is updated based on system operating experience, changes to the system and other factors. A best practice for characterizing risk is to calculate a Risk Priority Number (RPN) for each identified failure mode based on an evaluation of the failure mode's severity, estimated frequency of occurrence, and detectability.

DR/RAs tend to focus on the foreseeable hazards inherent to an individual piece of equipment or system, and may disregard potential risks not rooted in engineering. For example, an equipment risk assessment may not consider the availability of spare parts, which may pose a risk to the continued operation of the equipment over time.

As a facility ages, it is useful to do a periodic risk review of the facility as a whole, or of individual production lines, as appropriate. The review should make use of all available risk assessments of equipment, and it should also take into account nonengineering hazards that could affect the ability of a facility to perform its mission, such as supply chain risks and the availability of experienced operations personnel. A risk review should provide information that will enable better decisions about managing the facility, notably how to prioritize investments and noncritical maintenance.

For a meaningful risk review of a particular piece of equipment, it should take into account the actual operating history of that particular equipment as well as similar equipment, and not rely excessively on anecdotal evidence. The relevant data are often contained in several information systems, such as the process control system historian, the maintenance management system and the CAPA database. Gathering and analyzing all of the relevant data for a risk assessment can be time consuming; software systems designed specifically to facilitate the risk review process improve the productivity of subject matter experts and allow them to spend more time applying their expertise other areas.

Risk Control Increasingly Important

As manufacturing systems and equipment age, additional risk control measures may be needed in order to ensure that the overall risk of a production line continues to be acceptable. As time passes, the level of acceptable risk may change due to drug shortages or other external forces. Typical measures designed to improve the detectability, reduce the severity or reduce the frequency of occurrence of failures of an individual system may not be sufficient over time.

As aging production equipment becomes obsolete and spare parts scarce, the importance of preventing equipment failure and maintaining acceptable equipment performance increases. The ongoing analysis of operational data can reduce the incidence of quality deviations and unplanned shutdowns by providing early detection and diagnosis of equipment or system-level problems.

In some cases, modernization of processes and production equipment may be the best option to achieve the manufacturer's quality requirements and profitability goals. But as described recently ***(1),*** there are substantial regulatory hurdles to implementing post-approval changes to an existing production process and the associated equipment; the required investment may also be a significant deterrent.

Aging facilities represent a sizeable challenge for the industry. If not managed appropriately, aging facilities can cause elevated risk to patient safety, noncompliance with regulations, drug shortages and erosion of profitability. Risk-based approaches enabled by software technology provide a means to prioritize human and financial resources, resulting in effective management and mitigation of the business risks caused by aging facilities.

Continued at bottom of page 39

GMP Oversight of Medicines Manufacturers in the EU

A System of Equivalent Member States, a Coordinating Agency and a Centralized Institution

Riccardo Luigetti, EMA, Emer Cooke, EMA, Brendan Cuddy, EMA, Sebastien Goux, European Commission, and Ian Rees, MHRA

[Editor's Note: This is Part III of an overview of the EU regulatory system for pharmaceuticals. The article can be accessed in its entirety at www.pda.org/pdaletter.**]**

Overview of Inspection Activities

The figure below shows a summary of the inspections carried out by EEA competent authorities in 2014. Domestic inspections are inspections carried out by EEA competent authorities within the EEA territory. Foreign inspections are inspections carried out by EEA competent authorities outside the EEA. The data are extracted from EudraGMDP.

Data in **Figure 1** show that foreign inspections accounts for a substantial part of the EEA GMP inspectional activities (about 15%). In the figure below (**Figure 2**), the geographical location of the foreign inspections carried out by EEA competent authorities is shown.

Equivalence Among Inspectorates

In order to ensure the functioning of the EU system for GMP supervision of manufacturers and inspections described above, it is necessary to ensure that all the National inspectorates in the Member States are equivalent as regards the level of supervision they are able to provide. A number of measures are put in place to ensure that this is the case, summarized below.

Legislation

The pharmaceutical legislation is developed at EU level, mainly in the form of Regulations and Directives. Both are applicable to all the Member States, the difference being that Regulations are directly applicable to the entire EU territory while Directives have to be transposed into national legislation, in a timeframe established in the Directive itself, usually 18 months.

The EU legal framework for medicinal products is intended to ensure a high level of public health protection and to promote the functioning of the EU internal market. The system is also designed to encourage innovation. It is a large body of legislation that ensures extensive harmonization within the European Union, including GMP and inspections. The pharmaceutical legislation is published in the *Official Journal of the European Union*.

The EU GMP guide

A single GMP guide is in use in the European Union. The guide is referenced in the EU legislation (Directives 2001/83/EC for human products, 2001/82/EC for veterinary products and in clinical trial legislation) and has long since replaced any previously existing national GMP guide. The EU GMP guide provides the standards and requirements used by EU inspectors for any GMP inspections, both in or outside of the European Union.

The guide is subdivided into tree parts and 19 annexes dealing with specific types of manufacture. Part 1 is the GMP for finished products, Part 2 GMP for active substances and Part 3 includes GMP-related documents. The EU GMP guide is harmonized with the PIC/S GMP guidelines on an ongoing basis. EU GMP Part 2 reflects the EU's agreement to the ICH Q7 guidelines and forms the basis of the detailed guidelines.

EU Procedures on Inspections and Exchange of Information

The Compilation of European Union Procedures on Inspections and Exchange of Information (CoUPs) is a collection of procedures for GMP and Good Distribution Practice (GDP) inspectorates, applicable to all the inspectorates in the European Union. It provides a tool to facilitate cooperation between EU Member States and a means to achieve harmonization. The CoUP covers, among

Figure 1 Foreign Inspections

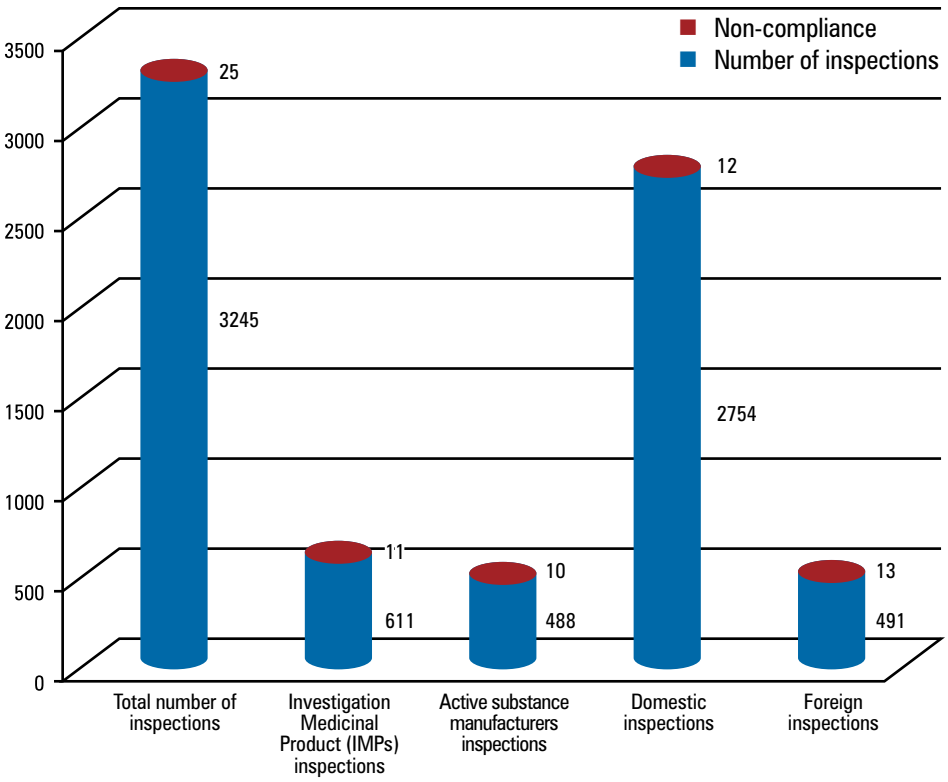
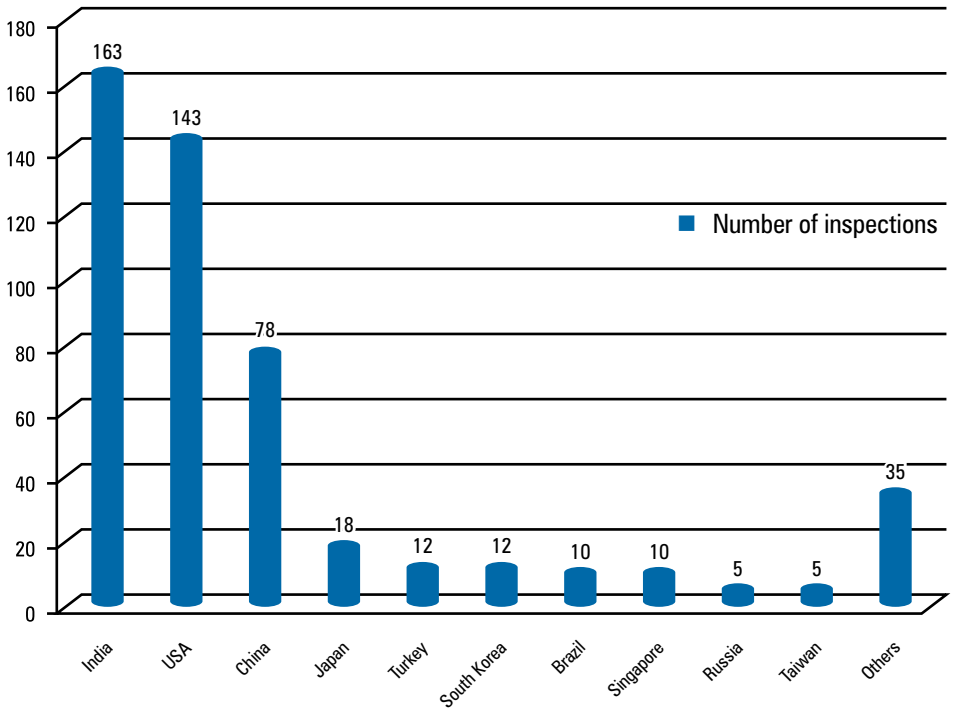


Figure 2 Geographical Location of the Foreign Inspections Carried out by EEA Competent Authorities



other things, the basis for national procedures that form part of the national inspectorates' quality systems, how quality defects and noncompliance are handled and how GMP and GDP inspections are carried out and reported.

The contents of the CoUP are constantly updated, developed and agreed, under the coordination of the EMA, by representatives of the Inspectorates of each Member State, including those supervising the manufacture and import of veterinary medicinal products only. Once agreed, they are adopted by the European Commission and then published on its behalf by the EMA.

Common Union formats for manufacturing and import authorizations, GMP certificates and for statements of noncompliance with GMP have been agreed and published in the compilation and implemented by EU competent authorities in order to enhance communication, collaboration and cooperation between authorities. This common format enables Member States to enter manufacturing, importing and distribution authorizations in the Union database, EudraGMDP.

GMP/GDP Inspectors Working Group

The GMP/GDP Inspectors Working Group (GMDP IWG) is a group of senior inspectors appointed by all the EEA competent authorities which meets at EMA premises four times a year. It is chaired by EMA and a European Commission representative attends the meetings, as well as observers from the European EDQM, accession countries (countries which have applied to be part of the EU but have not joined yet) and MRA partners. Representatives from other international authorities can be invited on a case-by-case basis.

The group is a forum for harmonization and discussion of common issues which are taken by the inspectors back to their NCA for implementation. Any new or amended text of the EU GMP guide is developed by this group, with the European Commission responsible for the final adoption. The GMDP IWG also maintains the CoUP and oversees, on behalf of the Heads of Medicines Agencies (HMAs) the Joint Audit Programme.

Training

The GMDP IWG organises training for EEA inspectors and inspectors from accession countries, aimed at raising the technical capability of the inspectors, ensuring common understanding of issues related to GMP and harmonization. In addition, EMA has signed a partnership agreement with PIC/S on cooperation on training for GMP inspectors, which recognizes the role that PIC/S plays in this area and avoids duplication of effort. ➤

Equivalence and Joining the EU

Becoming a member of the European Union is a complex procedure and there are strict conditions for EU membership to ensure that new members are admitted only when they are fully able to take on the obligations of membership, including compliance with all the EU's standards and rules. For the purpose of accession negotiations, these are divided into 35 different policy fields (chapters).

For acceding to the EU, a candidate country must implement the EU rules and regulations in all areas. The length of the membership negotiations can vary and depends on the time needed to complete the necessary reforms and the alignment with EU law. The candidates are supported financially, administratively and technically during this preaccession period.

In order to ensure that new Member States joining the European Union have reached the same level as the other members before the date of accession, a number of measures are put in place. These include:

- The European Commission checks compliance with the EU legislation (including pharmaceutical legislation)
- Through the TAIEX program, financed by the European Commission, technical support may be provided
- Accession countries are invited as observers to EU meetings (including the GMDP IWG)
- Specific training on EU procedures is organized

Auditing Member States

Auditing is an important part of the measures put in place in order to oversee the equivalence of Member States. There are a number of contexts in which Member States NCAs and/or inspectorates can be audited.

The Joint Audit Program (JAP) of the EU NCAs' GMP inspectorates is an internal audit program under the Heads of Medicines Agencies (HMA) and is run on behalf of HMA by the GMDP IWG. JAP aims at achieving and maintaining equivalence between Member States' national inspectorates responsible for GMP. It was established in October 2000 and is an important part of the quality system adopted by all GMP inspectorates in the EU.

JAP auditors are senior GMP inspectors, further qualified for auditing inspectorates through specific training. A list of qualified JAP auditors is maintained by the Compliance Group, which is a subgroup of the GMDP IWG. JAP auditors also provide technical advice and support to accession countries before they become EU Member States.

EU inspectorates are audited through the JAP onsite, at intervals established through a risk-based approach (typically every five to six years). Mutual Recognition Agreement and other international partners are invited on a case-by-case basis to join JAP audits of EU Member States inspectorates as observers.

Audits are also organized in the framework of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) and Mutual Recognition Agreement (MRA) (see International Cooperation Activities below). Since most of the EU authorities and all MRA partners are member of PIC/S, synergies between the various audit schemes are used in order to avoid duplication.

BEMA Audits

The Benchmarking of European Medicines Agencies (BEMA) is an internal EU program managed by the Heads of Medicines Agencies, based on assessment of the systems and processes in individual agencies against a set of indicators in four main areas:

- Management systems
- Assessment of marketing authorization applications
- Pharmacovigilance (drug safety) activities
- Inspection services

The assessment identifies strengths and best practices in agencies and any opportunity for improvement. The program has concluded its third cycle in 2015.

International Cooperation Activities

The European Union and its Member States are involved in several bilateral and multilateral cooperation activities with international partners in the GMP area. The main advantage is that international cooperation allows, by relying on information received from trusted international authorities, to reallocate foreign inspections towards areas more at risk. It thus optimizes available inspection resources.

PIC/S

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) aims at harmonizing inspection procedures worldwide by developing common standards in the field of GMP and by providing training opportunities to inspectors. It also aims at facilitating cooperation and networking between competent authorities, regional and international organisations, thus increasing mutual confidence. Most EU Member States are members of PIC/S while EMA is participating in PIC/S activities as a partner organization.

Mutual Recognition Agreements

Mutual Recognition Agreements (MRAs) are official agreements on the mutual recognition of assessment of conformity of regulated products which are negotiated and signed at EU level. MRAs concluded by the European Union include pharmaceuticals and cover GMP. Consequently, inspection results carried out by MRA partners in their territory are recognized by EU Member States and vice versa and retesting upon importation into the European Union is not needed in the QP batch certification process. The MRA scope can cover both human and veterinary products, finished products, active substances and Investigational Medicinal Products, but there are differences in scope between the various MRAs.

Currently, the European Union has operational MRAs in place with Australia, Canada, Japan, New Zealand and Switzerland. The EU also has in place an Agreement on Conformity Assessment and Acceptance of industrial products (ACAA), which includes GMP, with Israel. An ACAA is a specific type of MRA; the main practical difference is that in the ACAA case results of inspections carried out outside the territory of the agreement partners are mutually recognized as well, in addition to inspections carried out in the partners' territory. An MRA between the European Union and the United States was signed in 1999; at the time of this writing it is operational only toward rapid alerts.

International Coalition of Medicines Regulatory Authorities

The European Commission, EMA and some EU Member States (France, Germany, Ireland, Italy, Spain and UK) participate to the activities of the International Coalition of Medicines Regulatory Authorities (ICMRA). ICMRA is a recent initiative started by Heads of Medicines Agencies worldwide, which aims at providing global strategic coordination and direction on areas that are common to many regulatory authorities' missions worldwide, and which builds on existing arrangements such as those of PIC/S. The ICMRA has the objective to establish synergies and to foster global cooperation among regulators and GMP is one of the ICMRA main areas of interest.

Other International Cooperation Activities

In addition to MRAs, the European Union is involved in several less formalized cooperation schemes on GMP with international partners and/or in areas not covered by an MRA.

The API international cooperation project has as main objectives the sharing of information on inspection planning, policy and inspection reports and joint inspections on manufacturers located outside the participating countries. It includes the following participants: the EMA and all EU member States, the European EDQM, the U.S. FDA, the Australian Therapeutic Goods Administration (TGA) and WHO.

Several bilateral pilots and programs between EMA and FDA were also developed during the last ten years with the view to increase collaboration on domestic and third country GMP inspections.

This less formal form of cooperation in the last years has allowed the building of confidence among cooperating countries and regions, mainly through joint inspections and exchange of information, and is opening new possibilities of mutual reliance on inspection results. In this perspective, it is worth noting that the European Union has identified the recognition of GMP inspections carried out in the European Union and the United States and in third countries as a main objective for the pharmaceutical sector in the context of the negotiations of the Transatlantic Trade and Investment Partnership (TTIP).

Disclaimer: The views expressed in this article are those of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the Agencies or Institutions with which the authors are affiliated.

Quality Risk Management Meets Aging Facilities continued from page 35

Reference

Jornitz, M. "A Review of the Aging Process and Facilities Topic." *PDA Journal of Pharmaceutical Science and Technology* (2015) 69: 553-556.

About the Authors

Jim Butler, CTO of Cimetrics Inc., directs the company's R&D activities, principally the development of software for analytical applications and networked control systems.

Karim Bibawi, Executive Vice President of Cimetrics Inc., is responsible for developing key relationships and solutions based on the company's data analytics platform, Analytika.

Annex 1 Update: What Does it Mean for Industry?

Gabriele Gori, GSK Vaccines, and Hal Baseman, ValSource

The manufacture of sterile healthcare products using aseptic processes requires specialized efforts. At the same time, companies face challenges recognizing evolving global regulatory expectations, incorporating new technologies, and modifying traditional methods for process control in order to better meet today's aseptic processing needs. EMA, through its joint EMA–PIC/S committee, has signaled their intent to refine their expectations and requirements based on science and risk by revising Annex 1 of the European GMPs. For the industry, it is not just a matter of anticipating what the regulators want to see, it is a matter of going beyond compliance by using critical thinking to better understand the aseptic process and the associated risk of contamination, then using this knowledge to develop optimal process control strategies.

For too long, industry has wrestled with this challenge. Real improvement of aseptic processing is necessary. Achieving meaningful improvement in today's environment is not easy, but the tools and methods to achieve such improvement are available.

In April, PDA will hold the first of a series of four global workshops addressing new developments in aseptic processing by providing a forum for industry and regulators to discuss scientific and risk-based approaches supporting modern aseptic processing and control strategies. This workshop will utilize the recently revised *PDA Points to Consider for Aseptic Manufacturing*.

It is up to both industry and regulators to use critical thinking to identify what is needed, what works best, articulate its value and put it into practice. This workshop will facilitate that process by presenting current expectations, exploring how to meet those expectations, and identifying what still needs to be changed.

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North America

CDER Plans Ambitious 2016

In late December, the U.S. FDA's CDER office released its 2016 priorities. These include renegotiating parts of PDUFA and GDUFA, a continuing focus on drug compounding and furthering implementation of Track and Trace.

CDER Director **Janet Woodcock** also outlined the Center's 2015 accomplishments. During the past year, CDER stabilized the new Office of Generic Drugs, completed the standup of the Office of Pharmaceutical Quality, established multiple guidances pertaining to pharmacy compounding and responded to congressional queries related to the 21st Century Cures Act.

precisionFDA Launched

The U.S. FDA launched its precisionFDA platform in mid-December. This Web- and cloud-based portal allows scientists across industry, academia and government to collaborate on the science behind next-generation sequencing (NGS) of DNA. The Agency launched this portal as part of the Precision Medicine Initiative, which began in early 2015 and focuses on fostering the development and expansion of personalized medicines.

Europe

EMA Adopts 4-Year Network Strategy

On Dec. 18, EMA announced that its Management Board and Heads of Medicines Agencies have adopted a network strategy for the next four years. This strategy outlines common challenges and opportunities across the EMA network that pertain to regulating public health, setting out a roadmap for addressing these priorities by 2020. It also builds on EMA's roadmap to 2015 and the HMA strategy for 2011–2015, and will result in multiannual implementation plans for EMA and related bodies.

Asia-Pacific

China, U.S. to Combat Drug Counterfeiting

At the China-U.S. Joint Commission on Commerce and Trade in Guangzhou, China in late November, both countries agreed to enhance cooperation on efforts to prevent the selling of counterfeit drugs online.

Susan Schniepp, Regulatory Compliance Associates

Think "Facility," "Process" and "Analytics" When Updating Your Aging Manufacturing Site

Are your deviations on the rise? Are your manufacturing processes generating more scrap material than usual? Is your equipment breaking down more frequently? Is your batch rejection rate going up?

If you answered "yes" to one or more of these questions, this may be a sign that your manufacturing facility is aging. What can you do about it? Well, first of all, don't panic because the situation can be remediated.

Last year, PDA sanctioned a task force on aging facilities. This task force is actively working on offering possible solutions for solving the dilemma of maintaining an older facility while also remaining compliant and up-to-date with current expectations. The task force has identified three areas of assessment for aging sites: facilities, processes and analytics. Each one of these areas plays a critical role in the efficiency of manufacturing and, of course, the overall quality of the product. The term "facility" refers to the structure as well as the building-wide systems that support manufacturing operations, including personnel, material and waste flows, and overall facility layouts, such as cleanroom classifications and pressure cascades. "Process" refers to the manufacturing procedures (e.g., formulation, sterilization, filling, etc.) and related equipment specific to those procedures. Process flows, product transfers and flow of raw materials or components into process unit operations are also considered part of the process. And "analytics" refers to the in-process or inline tests performed during the manufacturing process, process analytical technology (PAT) tools, sensor technology, signal and test results captured via automation, and the resulting statistics and potential corrections.

When considering whether to update aging equipment, processes or methods, there are four common steps that must be assessed in order to achieve a desired outcome. First, identify what needs to be updated and why. Second, develop a quality risk assessment—for facilities and processes the risk assessment should be based on product impact while the risk assessment for analytics should be based on the criticality of the method in determining product quality. Third, construct and develop the plan and timeline required to make the recommended upgrades. And finally, implement the plan.

Following these simple steps might help you update your facility before it results in citations for poor compliance.

For more information about updating your aging facility, I recommend attending this year's *PDA Annual Meeting* as there will be sessions covering this topic. I hope to see all of you there!

Four Steps to Modernizing Aging Control Systems continued from page 26

have been required upon permanent activation of the virtual server to restore the most recent backup of the physical server to the virtual server, so that the historian database would be complete on the active server.

Conclusion

Careful planning and management of control system upgrades can reduce the qualification required to perform an upgrade, as well as the cost of implementation, extending the life of systems and postponing obsolescence.

About the Authors

Timothy Miller is Manager of Validation and Technology Transfer for Xellia Pharmaceuticals. He has worked in biotechnology and pharmaceuticals for fifteen years.

Andy Miller is a Senior Controls, Automation, and Plant Engineer at Xellia Pharmaceuticals, where he has been part of the lean Engineering and Maintenance group for four years.

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editor's message

Old Facilities Don't Enjoy Many Happy Returns

PDA is celebrating 70 years in 2016. That's old. I will turn 45 before many of you read this issue. That's also old. But an organization and a human don't just deteriorate as they age. Well, some people might, but most of us actively work hard to retain our youth and health, and many of us are living well into our 80s and 90s nowadays. As to organizations, those that provide value and service thrive on the influx of new generations of employees and/or volunteers.

Your facility, on the other hand, ages, and ages quickly. Not many pharmaceutical factories make it to 45 years like me, and fewer make it to 70 like PDA. In fact, I've seen reports suggesting that most pharma plants are built to last between 20–25 years.

Our industry is not the only one dealing with aging plants. It is a serious concern for industries ranging from energy to professional sports.

The United States' stock of nuclear facilities is hitting its limit—the majority are now over 30 years old. In recent years, four nuclear plants were shuttered, due mostly to their age. I'm happy to report that I have outlived the active life of the last reactor to shut down—Vermont Yankee, which powered down at the end of 2014 after 42 years of operation. Plants like Vermont Yankee could continue to operate given proper upgrades, but their owners felt that, with dropping energy costs, there was no reasonable return on investment. As such, closure made more business sense than continued operation. Sound familiar?

The economics of professional sports is infinitely different, yet aging facilities drives decisions all the time. Take a look at the recent decision of the National Football League to relocate the St. Louis Rams to Los Angeles, the city in which the team played back in the 1980s and 90s. The move back to LA from the Rams' perspective has to do almost entirely with the 20-year-old stadium in St. Louis. The Rams moved from LA to St. Louis in 1995 because of the then brand new Trans World Dome, now called the Edward Jones Dome, but all these years later, the stadium has been deemed too old and outmoded to house a professional football team. Despite over $30 million in upgrades to the facility since 2010, even Rams' fans despise the facility. And you think your plant is outdated?

PDA members are at the forefront of helping the industry upgrade facilities and solve the problems inherent to them. Through the Manufacturing Science Program℠, the Aging Facilities Task Force and other initiatives, the Association will be a leader in finding solutions to this growing issue.

Before you think that your old facility is hopeles, keep in mind that there exist numerous factories that have been in operation for really, really long times. In New Hampshire, for instance, one can find the oldest continuously operating paper mill. The Monadnock Paper Mill in Bennington, N.H. has been in operation since 1819. But that is "New World" old. What is really impressive is the lifespan of the Guangzhou Chenliji Pharmaceutical Factory, recognized by the Guinness World Records in 2010 as the oldest operating pharmaceutical factory. How old is it, you might ask? 416 years. But they have nothing on the world's oldest continuously operating brewery, located, of course, in Germany. The Weihenstephan brewery is the oldest in the world and has been brewing the suds since 1040. One can only imagine the amount of routine maintenance and equipment upgrades to keep a facility going for nearly a thousand years!

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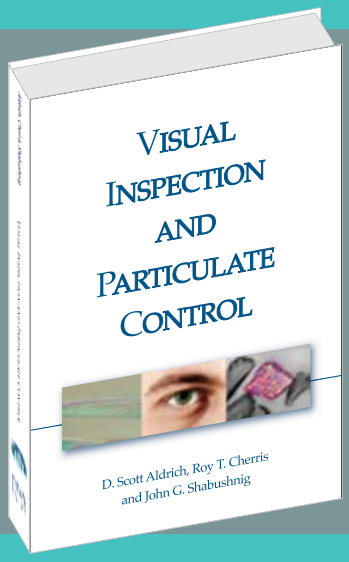

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