People • Science • Regulation

PDA Letter

Volume LII • Issue 3 www.pda.org/pdaletter March 2016

Pharma Seeks Long Tail of Flexible Manufacturing

EXPERIENCE SCIENCE THROUGH COMMERCIALIZATION

Courtesy of Fette Compacting

> INTERPHEX gave us an opportunity to meet with many of our pharmaceutical clients in one location, saving us four weeks of travel time. INTERPHEX continues to be the best and most important conference in North America for pharmaceutical manufacturing.
>
> *- Sterling Kline, Vice President, IPX Integrated Project Services*

INTERPHEX

April 26-28, 2016
Javits Center | New York City

MORE Innovation & Technologies State-Of-The Art Technologies Launches
MORE Free Full Product Life Cycle Technical Education led by PDA

- Learn It, Experience It with PDA Education @INTERPHEX
- INTERPHEX Live: Valuable Insight from Industry Experts
- Keynote Series @INTERPHEX
- 3D Printing Demo Experience
- SKAN Engineering Olympics
- CRB Tech Tank
- DME Facility Focus
- IPS Technologies Tours

FREE CONCERT:
RIGHT TURN AT 40

ALL OF THE SOLUTIONS YOU NEED TO COST EFFECTIVELY DEVELOP & MANUFACTURE PRODUCT

Register for your FREE Technical Conference and Exhibit Hall Pass at: www.INTERPHEX.COM/PDA

PDA Letter

Volume LII • Issue 3 www.pda.org/pdaletter

Cover

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

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

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

Departments

News & Notes

People

Science

Regulation

Voices of PDA

Contents

Features

PDA's Mission

To develop scientifically sound, practical technical information and resources to advance science and regulation for the pharmaceutical and biopharmaceutical industry through the expertise of our global membership

PDA's Vision

To be the foremost global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community

PDA® Parenteral Drug Association

Connecting People, Science and Regulation®

PDA Publishes First-of-its-Kind GMP Comparison

If you're looking for an easy guide to compare the relevant sterile processing GMP guidances issued by global regulatory bodies then look no further than PDA's recently published *Global Sterile Manufacturing Regulatory Guidance Comparison – With link to Comparison Spreadsheet.* This document offers a comparison of regulatory guidance documents issued by the U.S. FDA, the European Union, PIC/S and WHO on sterile processing GMPs.

PDA's Global Sterile Task Force, comprised of experts from leading pharmaceutical companies, drafted the document by carefully and thoroughly poring over each sentence of these guidances. This process resulted in an extensive comparison of each element. The team then conducted an extensive analysis of the similarities and differences in the four documents.

"The task force has done a great service for industry by producing this first-of-its kind document, which was reviewed and approved by PDA's Regulatory Affairs and Quality Advisory Board and Board of Directors," said PDA President **Richard Johnson.** "The analysis and comparison table are easy-to-use references for companies that need to adhere to the four regulatory documents. The spreadsheet is a tool which allows companies to do their own assessment of their status for each element."

Global Sterile Manufacturing Regulatory Guidance Comparison – With link to Comparison Spreadsheet is available to PDA members and nonmembers at the PDA Bookstore (www.pda.org/bookstore). The publication includes a link to the Microsoft Excel® spreadsheet, which can be downloaded at no additional cost.

Share Your Expertise

Submit an Abstract for Presentation

PDA is seeking poster presenters for both the *2016 PDA Universe of Pre-filled Syringes and Injection Devices* Conference and the *11th Annual PDA Global Conference on Pharmaceutical Microbiology.*

For the *2016 PDA Universe of Pre-filled Syringes and Injection Devices* conference, poster topics of interest include, but are not limited to:

- Advances in primary containers, technology, application systems/devices
- Development and manufacturing
- Global market and regulatory trends

To view the complete list of suggested topics, please visit www.pda.org/pfspdf. Abstracts for proposed poster presentations are due by April 1 and can be submitted at www.pda.org/prefilled-2016CFP.

For those interested in submitting poster presentations at the *11th Annual PDA Global Conference on Pharmaceutical Microbiology*, the program planning committee is most interested in topics that cover:

- Filters and filtration
- Microbial control
- Risk assessment

The complete list of topics can be found at www.pda.org/micropdf. Abstracts must be submitted by April 8 via www.pda.org/micro2016CFP for consideration.

If you have questions, please contact **Jason Brown** at brown@pda.org.

PDA Journal Now Publishing in "Real-Time"

The *PDA Journal of Pharmaceutical Science and Technology now* is publishing all articles accepted for publication in advance to final issue designation. "Accepted Articles" are the unedited, unformatted manuscripts submitted by authors for review. These drafts will be removed from the "Accepted Articles" when the final and typeset version of record are published in an issue of the Journal. "Accepted Articles" will post once or twice each month.

PDA Volunteer Spotlight

Marc Glogovsky

- Veltek Associates, Inc.
- *Global Business Manager – Environmental Monitoring Division*
- Member Since | **2000**
- Current City | **Absecon, New Jersey**
- Originally From | **Rockaway, New Jersey**

Recognition for my subject matter expertise has greatly assisted me professionally

Marc enjoys shipwreck diving

Tell us about your volunteer activities

Currently, I am coauthoring a new technical report, serving as a member of the PDA Exhibit Advisory Committee, and providing training as a faculty member at the Training and Research Institute (TRI). In addition, I'm also involved in the Microbiology/Environmental Monitoring and Vaccines Interest Groups.

What contributions have you made since joining PDA?

Since becoming a PDA member back in 2000, I have written two book chapters, presented numerous posters and delivered presentations on subjects such as mycoplasma, rapid microbiology, identification of microorganisms and environmental monitoring.

What advice would you give a PDA member interested in joining a task force?

Getting involved in a task force is a fantastic opportunity to work with other experts and individuals passionate about a particular topic. It gives you the opportunity to contribute your perspectives and experiences to create guidelines which others can use to improve their operations. Participating in a task force takes time and dedication, but, ultimately, is a rewarding and valuable experience.

What skills do you recommend developing in order to succeed in this industry?

Become highly effective at working with PowerPoint and Excel. Nothing is more substantive than a well-prepared and easy-to-understand presentation or spreadsheet.

Also, I recommend taking the initiative to learn another language and be conscious of how business is conducted in other parts of the world.

What book has influenced you the most?

As an undergraduate, I dreaded reading my microbiology textbook, *Microbiology, 2nd Edition.* Around Chapter 26, however, I realized I wanted to become a microbiologist and subsequently changed my major to microbiology.

India Chapter Elects New Officers

On behalf of its India Chapter, PDA would like to congratulate the winners of the elections for chapter officers. Each individual brings considerable industry experience to this growing chapter. This committed team looks forward to providing another year of informative programs to its members.

The new officers are:

- **Ivy Louis,** President-Elect
- **Vikram Shukla,** Secretary
- **Vishal Sharma,** Treasurer
- **Shirish Belapure,** Member-at-Large
- **K. Anand,** Committee Chair
- **Kumar Nanavati,** Committee Chair

PDA Who's Who

K. Anand, EVP, Global Head of Quality & Regulatory Affairs, Dr.Reddy's

Shirish Belapure, President, Cadila Healthcare Ltd.

Ivy Louis, Founder, Vienni Training and Consulting LLP

Kumar Nanavati, Senior Vice President, Quality Assurance, Sun Pharmaceuticals Industries Limited

Vishal Sharma, Co-Founder Director, Vienni Training and Consulting LLP

Vikram Shukla, Board of Director and Sr. Vice President, Zydus Pfizer

The new officers of the India Chapter look forward to offering an exciting schedule of programs for 2016

Membership Survey Winner Nets Donation for Local Charity

PDA congratulates **Lisa McNeill,** whose name was entered into a raffle following her completion of the 2015 PDA Membership Survey.

A donation of $500 was made in her name to the Western Washington Female Hockey Association (WWFHA) for the Girls' Beginner Program. WWFHA supports girls' hockey by providing not only on-ice experiences but also programs in conditioning, training, nutrition and college admissions.

PDA is excited to support the WWFHA's Girls' Beginner Program which subsidizes players' dues for each team and offers financial aid to players who may not be able to participate.

WWFHA's Washington Wild roster of players for 2015–2016

Congratulations to Lisa and thanks to all our members who completed the survey. Look for the 2016 PDA Membership Survey later this year!

PDA Who's Who

Lisa McNeill, Director, Quality Control, Infectious Disease Research Institute

Your Local PDA Connection

Are you curious about the issues unique to your region?

Another layer of PDA leadership resides at the grassroots level in the Chapter organizations. Regional PDA Chapters provide local services to the membership, including translations of PDA publications, networking social events, student scholarship and annual regulatory and technical conferences. Each Chapter is managed by volunteer leaders.

Learn more about your local Chapter at www.pda.org/Chapters

2016 Marks Year of Changes for PDA Education

Craig Elliott, PDA

As we dig out from the blizzard of 2016, I would like to take a moment to introduce myself and the exciting things we have planned for PDA Education this year. After over ten years with PDA, **Bob Dana**, Senior Vice President, Education, officially retired at the end of 2015. During his tenure, Bob made tremendous advancements to PDA's education programs, culminating in a successful final year as head of PDA Education.

Under Bob's leadership, 2015 marked the most successful year ever for PDA Education on multiple fronts. All five of our two-week aseptic training courses, held in the state-of-the-art Training and Research Institute (TRI) at PDA headquarters in Bethesda, Md., were sold out, leaving many on the waiting list for open slots. By the end of 2015, we sold out our entire aseptic training course offerings through June 2016. We also trained a record number of students in 2015, including over 150 employees from the U.S. FDA in seven courses specifically tailored for FDA personnel.

I want to talk about our exciting plans for 2016, but first a little bit about me. After six years with PDA as the head of finance, IT and administration, I look forward to returning to my pharmaceutical and scientific roots. Prior to joining PDA, I began my career at Merck & Co., in their manufacturing plant in Elkton, Va. As a chemist and microbiologist, I spent five years in their aseptic manufacturing facilities, performing various QA and QC jobs. By the end of my stay, I was reviewing lot releases of aseptic filled product. I also spent three years at Covance Laboratories in Vienna, Va. and five years at Genentech, Inc. in South San Francisco before coming to PDA.

2016 is an exciting year for PDA Education. As we build on the strong foundation already established, we plan to continue PDA's path to be a world class education provider. In 2016, we plan to expand our current facilities, add exceptional new talent and staff, continue to improve our products and services, explore our online learning opportunities and expand into new topics and offerings for the industry.

In December, PDA signed a new lease with our current building in Bethesda, Md. As part of this new lease, we've added an additional 2,500 square feet of training space to TRI's existing 10,000 square feet. This additional space will allow for new and updated classrooms, laboratories, and cleanroom teaching facilities. We plan to open the new classrooms and cafeteria by June with additions to the laboratory and teaching spaces soon after.

We're also looking at expanding our education staff. In 2015, **Falk Klar** joined PDA as the full time Senior Director of our European Training courses. Falk is located in PDA's Europe office in Berlin. We also have many exciting candidates for the Director of Education position in the U.S. office. We hope to make an announcement soon regarding this position. Once this position is filled, PDA's global education department will be fully staffed with seven full-time employees.

Craig Elliott

To continue PDA Education's journey to be a world class education provider, we are exploring online learning platforms that allow us to offer our content on-demand, anywhere in the world. We also continue to expand our offerings this year as we begin partnering with our chapters to offer courses in conjunction with local chapter meetings. We are planning many new courses in 2016, covering topics such as data integrity, how to conduct effective investigations, and an introduction to FDA's New Inspection Protocol Project (NIPP).

For decades, PDA has been a leader in providing science-based education for our industry. I look forward to building on this tradition and continuing our journey provide a world class education.

PDA Visitors | PDA Headquarters

Points to Consider for Aseptic Processing Task Force

(l-r) Masahiro Akimoto, Otsuka; Michael Sadowski, Baxter Healthcare; Gabriele Gori, GSK Vaccines; Richard Johnson, PDA; Jahanvi (Janie) Miller, PDA; Hal Baseman, ValSource

Consensus Method for Rating Mycoplasma Reduction Filters Technical Report Team

Back (l-r) Allen Burgenson, Lonza; Vinayak Pawar, PhD, U.S. FDA; Hans Noordergraaf, Abbott Biologicals; John Duguid, Vericel; Martha Folmsbee,PhD, Pall; Kurt Brorson, PhD, FDA; Laura Okhio-Seaman, Sartorius; Robert Kiss, PhD, Genentech; Rich Levy, PhD, PDA

Front (l-r) Josh Eaton, PDA; Kerry Roche Lentine, MilliporeSigma; Leesa McBurnie, Meissner Filtration Products; John Geigert, PhD, BioPharmaceutical Quality Solutions

Post-Approval Change Processes Technical Report Team

(l-r) Anders Vinther, PhD, Sanofi Pasteur; Emma Ramnarine, Genentech/Roche; Rich Levy, PhD, PDA; Ursula Busse, PhD, Novartis; Franck Chassant, PharmD, Sanofi Pasteur; Denyse Baker, PDA

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

The Parenteral Drug Association Education Department presents the...

GMPs for Manufacturers of Sterile and/or Biotechnology Products

GSA Schedule Contract GS-02F-113BA

Apr 21, 2016 | San Diego, CA

Hyatt Regency Mission Bay Spa and Marina

Interested in the practical implementation of GMPs in facility and equipment design, process design and operations?

When you take this course, you will leave with an understanding of the regulatory expectations for equipment and utility qualification and sterile process validation in order to assure that the products manufactured are proof-positive sterile.

This course is designed as an intermediate level course for supervisors and managers needing to understand the theoretical and practical background for the successful manufacture of sterile pharmaceutical and biotechnology products.

Upon completion of this course, you will be able to:

- Describe the unique concerns for biotechnology facility design
- Summarize requirements, installation issues, qualification of HVAC, water and compressed air, and nitrogen systems
- Discuss terminal sterilization technologies, theoretical and practical considerations in sterilization processes, depyrogenation issues, and the essential differences between designing and operating a facility for terminal sterilization and for aseptic processes
- Identify the challenges of aseptic processing in the manufacture of sterile and/or biotechnology products

Learn more and register at pda.org/2016ManufGMP

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

GSA Schedule **Denotes GSA Schedule Contract**

Task Force *Corner*

Task Force Collaboration Looks to the Future of Aging Facilities

Jahanvi (Janie) Miller, PDA

In March 2014, PDA's Aging Facilities Task Force began developing recommendations for effectively updating aging facilities, processes and analytics—a pressing need for the industry. Subgroups of the task force were formed to recommend solutions and develop modernization plans for each of those three areas. The collaborative efforts within the task force led to the launch of two major work products: a benchmarking survey and a PDA white paper.

The raw survey results will be published in the second quarter of 2016. The white paper will feature an analysis of the survey data and will address concerns within industry and preventative measurements taken, how effective these activities are, what obstacles are experienced in the industry, and when continuous improvements are applied.

In 2016, PDA will continue to leverage existing resources and expertise to fuel valuable discussions related to aging facilities. PDA's Facilities and Engineering Interest Group has offered great support for this initiative and aging facilities will continue to be a topic of discussion within the interest group.

[Editor's Note: For more on aging facilities, check out our February 2016 issue featuring numerous articles on the topic.**]**

In *Print*

Pharma Has its Eyes on the Sky as it Looks to the Future of Healthcare

[Note: The following is an excerpt from "Taking Flight" by guest editorialist **Norman Augustine,** retired Chairman & CEO of Lockheed Martin Corporation, which pubished in the Jan/Feb issue of the *PDA Journal of Pharmaceutical Science and Technology.* The full article can be read at http://journal.pda.org/content/69/6/667.short**]**

What does healthcare, including pharma, have in common with my profession, aerospace? The answer is quite a lot, not least of which is that both are pursuing unsustainable business trajectories.

Exactly fifty years ago I plotted a graph of the cost of new military tactical aircraft vs. time beginning with the Wright Brothers Model A through what were then the most modern fighters. To my surprise I discovered that the cost of new aircraft was following a highly predictable path. Further, with a little bit of extrapolation, I demonstrated that if we were to continue "business as usual", in the year 2054 the entire defense budget (also readily extrapolated) would purchase just one tactical aircraft! (I have often been criticized for such extrapolation, but many Washington economists extrapolate based on one data point. Furthermore, I am a rocket scientist!)

This conclusion was, in 1965, greeted with considerable humor by the cognoscenti. But it doesn't seem so funny today. In fact, *The Economist* recently updated my chart and concluded that we are right on my prediction—with only 39 years now remaining until the cost of that singular aircraft will equal the entire defense budget. Indeed, there are people now alive who will be around to watch it fly…if it does. Worse yet, its cost will equate to the entire gross domestic product (GDP) if we continue until exactly one century from today.

So what can all this have to do with healthcare, particularly pharma? This one is easy. The equation describing the cost of healthcare as a fraction of GDP over the past two-thirds of a century is also simple and goes as follows: cost, as a fraction of GDP (in percent) = 0.25 Y—487, where Y is the calendar year of interest. This very unfortunate "law" (my various rules of aerospace behavior—or misbehavior?—somehow became known as "Augustine's Laws", to my later chagrin as CEO of an aerospace company) asserts that, again following business as usual, the cost of healthcare will equal fully half of the nation's GDP in 2148 and all of it in 2348. The good news is that healthcare has a bit more time to find a better business model than does aerospace…but pressure is building.

Journal *Preview*

The Latest Research in Container Closure Integrity

Check out two research articles on container closure systems and integrity in the March/April issue of the *PDA Journal of Pharmaceutical Science and Technology.*

Research

Direct detection of Burkholderia cepacia in susceptible pharmaceutical products using semi-nested PCR

Influence of Different Container Closure Systems and Capping Process Parameters on Product Quality and Container Closure Integrity (CCI) in GMP Drug Product Manufacturing

Evaluation of Container Closure System Integrity for Frozen Storage Drug Products

Semi-Quantitative Analysis of Inherent Visible Particles for Biopharmaceutical Products

Filling of High-Concentration Monoclonal Antibody Formulations: Investigating Underlying Mechanisms Impacting Precision of Low-Volume Fill by Peristaltic Pump

A Bayesian Approach to Residual Host Cell DNA Safety Assessment

Commentary

Summary of the EMA Joint Regulators/Industry QbD workshop (London, UK; 28-29 January 2014)

Report from 2015 Universe of Pre-filled Syringes & Injection Devices

Pens, Injection Devices Get "Smarter"

Rebecca Stauffer, PDA

Smart technologies, or smart medications, were a topic of a few sessions at last year's Universe of Pre-filled Syringes and Injection Devices *conference in Vienna. The* PDA Letter *spoke with **Markus Bauss,** Managing Director, SHL Connect and CEO, ConnectMeSmart GmbH, who presented at the conference and facilitated a preconference workshop on the topic.*

PDA Letter: Tell us more about the preconference workshop you facilitated on smart medications.

Bauss: We had a workshop on smart medication where electronics meet drug delivery. It was very interesting because we started the workshop with an introduction to technology, where we had different people showing what kinds of technologies are out there, and how you can connect drug delivery devices to smartphone applications, then we moved forward and looked into real applications. So, we moved on and had examples where people applied these kinds of technology or are planning to do so in the coming year.

We also looked at the ecosystem you need behind it, because we realized it's a lot about data. [We looked at] the question of how do you handle the data and how do you deal with privacy and everything? We realized the intelligence or the value comes from looking at the data.

It was also very interesting to have a discussion of the patient experience by a nurse specializing in diabetes. She mentioned there are really some open areas and there is some room for improvement also with the new technology.

We covered real systems where things like this have been applied in daily use, for instance, in Germany. And we covered the regulatory environment...what needs to be considered if you want to make it happen.

PDA Letter: It sounds like it was beneficial to have feedback from the healthcare provider (the nurse). Should companies developing these products proactively reach out for feedback from healthcare providers during the development process?

technology: innovation

Bauss: Absolutely. This was also one of my takeaways…The other thing was what I've been doing over the course of this year: I've been meeting with patients, different patient groups, starting with diabetes patients, working with hemophilia patients, and also meeting MS patients. It was so interesting, I mean, talking with them about the disease…how they encounter drug delivery technology.

The more important thing is still the drug—that the patients say the drug works. That's what it's all about. Ideally, if we can take a pill that you can swallow, perfect, if it's that easy. If you have to take an injection, that's the next level. And the worst case is if you get an infusion, which is where you have to go to a hospital. But I mean, if the drug works, people are going to take this hurdle. The interesting thing is, certainly, I had these encounters too where you talk to some patients, that said—and these were MS patients—and they said, "You know what, as a patient, we feel somewhere in between. On the one hand, sometimes we feel like a 'junkie' when we get all these components of a freeze dried product and we have to mix things in public and so on," and the other extreme, and this was really something, some patients said they felt self-conscious when the device makes a loud noise, such as a "pop!" So, this was the patient's perspective. On the other hand, they appreciated the new tools that help remind them of things and learn about their medications. I think there is room for improvement to also listen to the people. But I mean, still, the most important thing is definitely that the drug works.

PDA Letter: It sounds as if they're seeking products that are a little more low key.

Bauss: Yes, I mean, that's the other thing about the user interface. What we saw yesterday and also what we will see in the exhibition here, there's some kind of hype right now with how we present technology and the question is, is it not a little bit too much? The question also came up, it does not always have to be a smartphone because not everyone is using a smartphone.

Also, many questions come up from a regulatory perspective, and sometimes there might be tools that are very intuitive and easy to use. And this also goes back to the recommendations from the diabetes specialist nurse, who really said: "Make it very simple." "Make it very intuitive." "Think about how the end user has to handle it." and "It shouldn't be confusing."

It shouldn't have things where you have to mess around to create a Bluetooth pairing or something. Things have to be simple.

PDA Letter: What about data security?

Bauss: On the one hand, it was interesting to have a presenter from the ➤

West
By your side
for a healthier world™

Empower your patients

The SmartDose® electronic wearable injector combined with the HealthPrize adherence program makes for a powerful combination. The SmartDose injector helps your patients leave the treatment center behind, making self-administration at home simple and easy. And while at home, HealthPrize helps your patients stay on track with their therapeutic routine, through rewards-based patient education and adherence tracking.

HealthPrize

West seeks partners for its SmartDose electronic wearable injector technology platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company. The SmartDose system, HealthPrize platform integration is for conceptual purposes only.

SMARTDOSE®
Electronic Wearable Injector

Advancing Care, Improving Lives

www.smartdose.com | (800) 345-9800

#9572 0216

electronics industry mention the latest issues we've seen in the car industry. Everybody has heard about these hacked cars in the U.S., right, which is also dangerous. But the other thing is, when you deal with healthcare and data, you get some very sensitive data and get into privacy issues. [In the U.S., you have HIPAA but] we have different data privacy laws here in Europe and one interesting thing... there was this presenter from the company Smart Medications that issued a platform for hemophilia patients to have a logbook, and the software they created is considered a medical device. So, what this guy did...he showed the terms of use that Apple shows and that you accept when you have an iPhone, and it was very interesting. He translated it and he basically said that it states that Apple may use your information. So, this was one reason they do not deliver their product through the Apple store, because they work with hemophilia patients where you have to know the patients who are 40 years old... they are very likely to suffer from AIDS and from Hepatitis C because there was this situation with blood products 20 years ago. By downloading such a product, you would immediately reveal some information that you might suffer from this disease. And then you get pretty fast into some serious privacy issues.

How can you on the one hand get better privacy...and also the security and be sure that [patients] use the medication device and so on? There are definitely still some areas that you have to accomplish.

[There] also was a presentation in the afternoon where someone had a device that reactivated and the smartphone recognized it right away. So, you have to ask the question, "What happens if another patient is sitting there with the same smartphone...could it happen they both detect this signal?"

PDA Letter: What about demographics? In the United States, there is a rapidly aging population of Baby Boomers.

Bauss: Well, you have specific age groups, you have specific patient groups, and so on. It is something we also mentioned yesterday: If somebody in the U.S. goes to Europe and he has to drive for the first time in his life a stick-shift car, so how does he learn this now? Today, the night before he checks out a video on YouTube and then he gets it. There are just different learning styles. How different generations handle these things also needs to be considered.

Other than that, what I believe, in drug delivery it's still the case that you've got product in vials, prefilled syringes, safety devices, autoinjectors, pen injectors, automatic pumps—so if you do something, one important thing is that you really cover a broad range of product. That you listen to real patients' needs carefully. We

Continued at bottom of page 43

Biosimilar Development Needs More Practical Guidance

Vince Anicetti, Coherus Biosciences, and Stephan Krause, PhD, AstraZeneca Biologicals

The development of biosimilar products is complex and challenging; regulatory approval remains difficult to obtain in the United States. Despite the existing need to bring more low-cost biologics to patients, only one biosimilar product has been approved in the United States. It is currently not well established what constitutes a suitable control strategy for biosimilars. It is also unclear what totality of evidence means practically for analytical similarity. Can a Tier 1 or Tier 2 quality attribute fail the analytical similarity acceptance criteria without causing a regulatory rejection?

The use of platform processes for typical biologics has simplified product development steps and lowered the regulatory approval time once clinical safety and efficacy has been established. Biosimilar product approval is currently less certain as regulatory acceptance is heavily focused on demonstrating analytical similarity to the reference product.

What remains challenging for biosimilar product developers is the current lack of practical guidance on how many reference lots are to be tested. The developer has no access to the reference product specifications and/or knowledge of the true process and product manufacturing capabilities of the reference product. The combination of testing only recently manufactured reference drug product lots, together with the lack of knowledge about the reference product historical batch variation and the product release/stability specifications, raises the regulatory acceptance bar for biosimilars. The apparent narrow product quality window of the reference product thus leads to relatively narrow acceptance criteria for the analytical similarity testing.

The *2016 PDA Biosimilars Conference* will bring together industry experts and regulators to discuss new development strategies for biosimilars. Attendees can expect to receive regulatory updates and hear from CMC reviewers on which CMC issues have been the most challenging to approve.

2016 PDA Biosimilars Conference and PDA Education courses

Baltimore, Md.
June 20–22
www.pda.org/2016bio

Pharma Seeks Long Tail of Flexible Manufacturing

Rebecca Stauffer, PDA

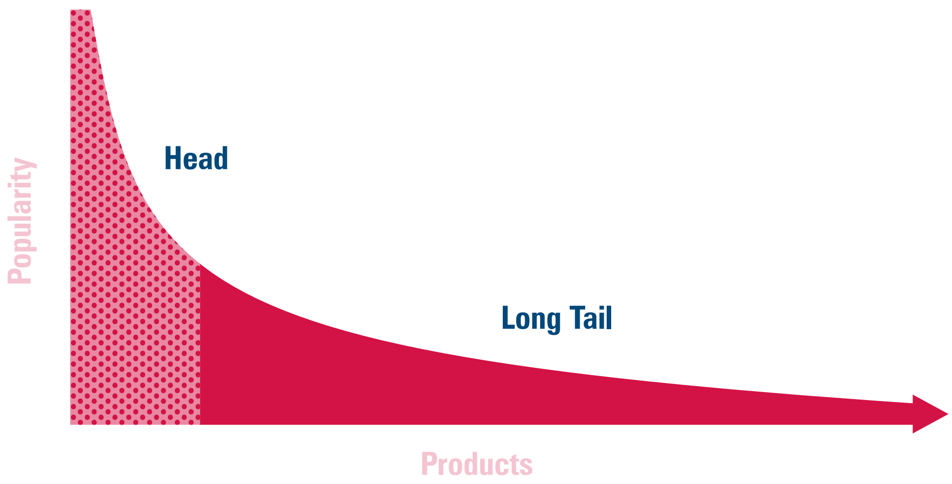
The pharmaceutical industry is at the cutting edge in terms of types of products and technologies offered and under development. The last 30 years has seen the biopharm boom, and most recently, the marriage of therapies with high-tech delivery systems, particularly prefilled syringes and other injection devices. The industry is moving into new areas of advanced therapies with personalized medicine, stem cells, nanotech and 3-D printing (in fact, the U.S. FDA approved the first 3-D printed pill last year) ***(1).***

But do the manufacturing systems used to produce these products showcase the state-of-the art in manufacturing?

Article at a Glance

- Move away from "blockbuster" drugs to specialized products necessitates flexible equipment
- Facility moves to modular line to support multiple product types
- As CMO use increases, so does need for flexibility in design

Figure 1 The "Long Tail" Concept



"There are very, very few solutions at the moment, and we need this if the trend toward smaller and smaller batches is going to continue," he said.

But there are technological solutions available. These include continuous manufacturing, single-use systems, flexible aseptic filling (e.g., nested cartridges and vials), white line packaging (i.e., packaging that occurs during a single production process), flexible aseptic assembly and drug delivery manufacturing platforms such as disposable pen assembly machines.

While it is no secret that pharma lags behind other industries when it comes to innovation in manufacturing, industry speakers at last year's *Universe of Prefilled Syringes and Injection Devices* conference in Vienna, Austria demonstrated that industry does have its eye toward new models of manufacturing.

Pharma Meets the Long Tail

Shifting to more flexible and agile forms of manufacturing certainly makes sense when factoring the new economic realities of drug development. **Gert Moelgaard,** Vice President, Strategic Development, NNE Pharmaplan, explained that injectable biologics will comprise almost half of all new drug products by 2020 ***(2).*** At the same time, companies are projected to move away from developing "blockbuster" drug products to focusing more on on specialized products for smaller segments of the population, such as orphan drugs.

"It's basically a shift from traditional medicine to [specialized] medicine," he said, explaining that "as a matter of fact, I think we're probably approaching the new facilities of the future…we're facing the 'Long Tail' of [our] products."

The "Long Tail" Moelgaard refers to is the concept that industries are now moving away from focusing on a small number of mainstream "hit" products at the head of the demand curve to a number of niches in the tail (see **Figure 1** for a depiction of the "Long Tail" concept) ***(3).*** Think of the film industry. In the past, obscure films and documentaries would have made little money, with almost no recognition by the general public, and film companies would have reserved resources for summer blockbusters. Now, thanks to streaming online video services, consumers have easy access to a wide range of movies, enabling even little-known films to generate money as incremental sales of individual offerings add up to revenue.

But producing smaller, more specialized drug products means developing flexible manufacturing systems capable of producing smaller batches and even switching between different product batches.

"The challenge of the future is going to be how fast can we change it [the manufacturing line] over from one batch to another," Moelgaard emphasized.

Further, he explained there is a "missing link" in aseptic processing between high-speed, high-capacity production of mass batches and low-speed production of small clinical batches. What is needed are manufacturing systems that can handle medium production between high-capacity mass production and low-capacity production. This means flexibility to switch among vials, cartridges or syringes, fast changeover and continuous production.

"Personally, I think this is only the beginning," he said. "There are a lot of breakthroughs waiting for us out there."

At the same time, Moelgaard worries that the slow adoption of new technologies for manufacturing parenterals will not keep up with anticipated growing demand.

BI Team Makes Magic in Short Time

What about implementation? Are companies implementing flexible and innovative forms of manufacturing? In short, yes. Take a look at Boehringer Ingelheim. In 2013, the company decided to install a flexible filling line at its Fremont, Calif. location ***(4).*** Purchased in 2011 as an existing biotech manufacturing site, the facility had been designed to produce a single commercial product. The company, however, wanted to produce more than one type of product in the facility, necessitating development of a flexible manufacturing unit.

According to **Raimund Geidobler,** PhD, Associate Director of Clinical Trial Drug Product Manufacturing, "The background of this site was that it was a traditional cleanroom facility…and was built for a single commercial product," adding "it was decided to do some major investing…in the drug substance area" and convert the space into a single-use drug substance facility.

With a moderate investment, Boehringer opted to implement a highly flexible ➤

2016 PDA Upcoming Events

SAVE THE DATE for PDA's 2016 Events

MARCH

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
pda.org/2016MSW

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

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

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

12-13

Parenteral Packaging
Venice, Italy
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/EL2016

14-15

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

14-15

Good Glass Handling Practices in Parenteral Packaging
Venice, Italy
pda.org/EU/GoodGlass2016

19-20

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

1946 70TH ANNIVERSARY 2016

PDA® Parenteral Drug Association

For an updated PDA calendar of events, please visit:

pda.org/calendar

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

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

MAY

2-3
From Extractables and Leachables to Hospital Applications Addressing Critical Demands on Modern Pharmaceutical Packaging
Bern, Switzerland
pda.org/EU/WSEL2016

9-12
GSA Schedule Contract GS-02F-113BA
Lyophilization Week
Bethesda, MD
pda.org/2016Lyo

16-17 & 19-20
Visual Inspection Course Series
Bethesda, MD
pda.org/2016VisualCourses

18
2016 PDA Visual Inspection Interest Group Workshop
Bethesda, MD
pda.org/2016VisualWorkshop

24-26
GSA Schedule Contract GS-02F-113BA
Management of Aseptic Processing
Bethesda, MD
pda.org/2016ManageAP

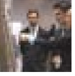
31-1
BERLIN –
2016 PDA Workshop:
Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision
Berlin, Germany
pda.org/2016AnnexBerlin

Stay engaged, informed and ahead of the complex challenges of the bio/pharmaceutical manufacturing world by following PDA on:

Follow us on Twitter at @ **PDAOnline**

Join us on LinkedIn at **LinkedIn.com/company/PDA**

Join the conversation on PDA Connect℠ **@PDA Connect** ℠
PDA's members-only online discussion forum



filling line in the existing space (approximately, 6,000 square feet) for aseptic processing of biologics using isolator technology. In addition, the new filling line had to be installed and qualified within a short timeline and meet both current and future regulatory expectations.

"It was decided not to install a vial washer and depyrogenation tunnel, but to focus on ready-to-use syringes and vials," Geidobler said, explaining the project team also elected to include disposable assemblies, meaning no clean-in-place or steam-in-place. The new filling line would need to be capable of both vial and syringe filling, clinical and commercial scale filling, internal and external product fills—all on top of handling a quick changeover between product lines.

"For our filling line, we needed a high degree of flexibility," he said. "The project was approved in Q1 of 2013 and the facility was ready for GMP production in 2015."

The company ended up choosing a modular isolator and portable filling skids through a partnership with suppliers SKAN and Bausch + Stroebel Machine Co.

The standard isolator, produced by SKAN, offers greater flexibility due to its unique feature: an L-flange on a rolling skid that enables part of the filling equipment to be switched, without necessitating a separate isolator. Here, the company can "move out one filling machine and then move in another filling machine," which means the company can utilize the same isolator to fill syringes as well as vials.

When it comes to filling syringes, "We use a tub…the machine automatically pushes the next into the isolator," Geidobler said of the process. "We have complete separation of the operator from the process."

Supporting systems in the layout include a weigh station and an autoclave cannister.

This only the beginning. There are a lot of breakthroughs waiting for us out there

Vial filling occurs in three chambers. Chamber 1 is a preparation area where the tubs are unpacked. Filling and stoppering then takes place in Chamber 2 while capping occurs in Chamber 3. For ready-to-use vials, the vial tubs (which are placed in bags) enter the isolator and then the lid and liner are manually removed using the isolator glove ports. Next, a vacuum tool removes the nest out of the tub and transfers it to the denester. The nest is then pushed toward guiding rails that move the vials through the machine. A rack transfers the vials to the in-feed tray and then waste is removed from the isolator via an airlock.

Although it is early on in the process, Boehringer already expects to see a a reduction in operating costs (i.e., reduced utilities) due to the small footprint of the modular isolator. In addition, this flexibility means Boehringer could even function as a CMO for other companies ***(5).***

What About CMOs?

It's no surprise that CMO work factored into Boehringer's decision to adopt flexible manufacturing. Considering that the contract manufacturing share of the market continues to grow; a 2015 survey of biopharmaceutical manufacturers found that 15% of respondents outsourced manufacturing to domestic service providers in the past year to reduce costs—an increase from 9% in 2014 and the highest number this decade ***(6).***

At the same time, some traditional manufacturers like Boehringer are moving to a CMO model. For example, Mithra Pharmaceuticals is a Belgian company specializing in drug products marketed for women's health. The company decided to move into the contract manufacturing space to partner with other companies in order to "cross-fertilize" within the industry ***(7).***

"Mithra is still a small company…to become a world leader we decided to change our business model [to one] which is based on a CDMO (contract development and manufacturing organization) model…and that's why we are setting up a CDMO site in Belgium," explained **Rudi Meurs,** Chief Production Officer, Mithra Pharmaceuticals.

At the same time, the company itself is growing its own product line, adding injectable drugs to its catalog in addition to oral tablets and polymeric forms, such as vaginal rings, biodegradable subcutaneous implants and long-term delivery nonbiodegradable implants.

"Injectables is for us a new market, and it's for this that we are setting up a new platform," said Meurs.

Construction of Mithra's CDMO site in Liège, Belgium began in December 2014 and the company expects to finish the cleanroom installation in May 2016. The site will be capable of handling multiproduct production, i.e., polymers, tablets and injectables. Activities will consist of formulation development, clinical trial batches, scaling-up activities and large-scale production batches according to U.S. and EU GMP standards.

"We have just one filling line," Meurs pointed out. Like Boehringer, Mithra Pharmaceuticals needed flexible technology in order to use their singular filling line to produce more than one type of injectable product as a CDMO. And like Boehringer, the company turned to nested solutions to allow for production of syringes, cartridges and vials.

"So that combination was why it might be [easier] to combine this all on the same line," he said. The company also required a solution that limits the potential for contamination.

"That's why we combined the filling line with…no touch technology. That was for

us very important," Meurs said, further explaining that this no-touch technology enables less risky debagging. "For Mithra, this no-touch configuration was the best fit."

"I think that the key word is 'flexibility,'" emphasized **Andrea Cecchetto,** Product Manager, OMPI, noting that flexibility was a topic of many sessions that day at the conference.

"We are working on a quite flexible approach" due to the requirements of the system, added **Dirk Schuster,** Regional Sales Director, Groninger & Co. GmbH.

In the end, Mithra chose a tub and nest model similar to Boehringer's configured for all sterile containers entering the filling process. The company elected to purchase OMPI's EZ-Fill nested tubs and Groninger's filling line.

The filling process begins with removal of the bag covering the nested tub followed by Tyvek removal. Next, is filling and closing, followed by unloading of the object out of the nest (this can be manual or automatic), concluding with the capping process. Optional process steps include unloading of objects out of the nest and labelling and plunger rod insertion.

With this flexible manufacturing process, Mithra has not only developed a method for producing smaller batches of product but also an opportunity to grow a new business opportunity.

The future will bring many advances in drug delivery. Even the day of the prefilled syringe will pass. Smart devices and injection systems will become a core area of focus, if the U.S. FDA's recent draft guidance on cybersecurity for medical devices is any indication ***(8)***. But new forms of drug delivery will necessitate novel and flexible approaches to manufacturing. The industry is on the cusp of not only a transformation in product but also in manufacturing. It is no longer a question of will industry innovate but when.

References

1. Kopcha, M. "Modernizing Pharmaceutical Manufacturing to Improve Drug Quality: Ensuring a Safe and Adequate Supply of Drugs." *FDA Voice Blog* Feb. 1, 2016 (accessed Feb. 9, 2016) tinyurl.com/hwrofu4
2. Moelgaard, G. "Requirements and Opportunities for the Parenteral Facility of the Future." Presented at the Universe of

Continued at bottom of page 44

Survey of Industry Leachables Best Practices Completed

BPOG Disposables Team Shares Results

Over the past five years, the use of disposable systems/equipment (aka single-use systems) in biopharmaceutical manufacturing processes has reached a pivotal point. Disposables are being implemented beyond research and development and are now being used in clinical and commercial manufacturing. The benefits of disposables are well known and publicized. A 2014 article in the *PDA Journal of Pharmaceutical Science and Technology* outlined a number of advantages, including lower initial capital investment, elimination of cleaning validation, reduced turnaround time, reduced cross-contamination, reduced steam sterilization burden and operations, the possibility of reducing room classification, and the ability to scale up and down ***(1).***

Although many disposable components, such as filters, tubing and connectors, have been widely used for about two decades, there is no specific regulatory guidance that speaks to what is required to support the use of these disposables. Nevertheless, manufacturers must comply with Title 21 of Code of Federal Regulation (CFR) Part 211.65, which states that: "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements." Equally, other regulatory bodies have similar requirements such as EMA/EU Eudralex Vol. 4, Chapter 3.

As such, regulators commonly request that companies assess the risk of disposable systems and support these assessments with extractables and leachables data, where necessary, at any point throughout the manufacturing process. The absence of such data has resulted in delayed submissions, requirements for manufacturers to commit to follow up measures, refusal by regulators to approve market applications, and the issuance of warning letters.

Members of the BioPhorum Operations Group (BPOG) frequently discuss these issues within the organization's Disposables Team.

Leachables: An "Unspoken" Challenge

Although there are several publications and presentations around extractables ***(2,3),*** leachables remain an unspoken challenge within individual companies.

To gain a better understanding of biopharma industry practices with regard to studies of leachables, a new BPOG Leachables subteam kicked off in January 2015 with the goal of developing a best practice approach to guide biopharmaceutical manufacturers on risk assessment and testing for leachables.

The first step entailed creating a survey to understand the current approaches to leachables studies performed across member organizations. The team intended for the survey to identify challenges and "pain points," as well as discern the types of practices for leachables studies that the team would want to promulgate as "Best Practices."

Seventeen BPOG member companies participated. The following is a high level summary of the survey to better understand the variations of the leachables study approach, analytical method validation, study design and the leachables stability study.

Summary of Survey Results

1 When asked what solvents and data points companies require to perform an extractables risk assessment, the general consensus is that they evaluate extractables data using some form of risk assessment. Some respondents rely on the vendor data as long as the data is generated using model solvents bracketing the composition of drug substance (DS) or process solutions. If the data is found insufficient, then this vendor data is supplemented with their own internal simulated studies using model solvents, such as 50% Ethanol, 0.1% PS 80, 0.1M HCl or 0.1M phosphoric acid, 0.1M NaOH or 0.5 M NaOH, etc., exposed to different numbers of days (e.g. 0, 7, 21, 70 and 90 days) as needed to bracket the intended use of the disposable(s).

2 Regarding how companies currently use extractables data to determine the type and number of leachables studies, the general practice is to perform a risk assessment on the extractables data to determine if the extractable compounds pose any risks to patient safety. But post-risk assessment, companies vary in how they leverage the data. Some companies send identified extractables compounds for further toxicological assessment. Others follow up with additional extractables testing with simulated solutions or model solutions to further assess the risk, leveraging the study results toward their leachables study design. If the reported/evaluated extractables results are well within the threshold toxicological assessment, some companies choose not perform any leachables studies. Some companies also do additional leachables studies on drug substance containers.

3 Practices vary for justifying the overall approach to regulatory agencies. Some use a risk-based approach for extractables evaluation supported by just the toxicological assessment and/or additional leachables studies acceptable by regulatory agencies. Companies often receive divergent expectations from various regulatory agencies, however, leading to confusion as to what exactly is required.

4 The survey also asked if leachable studies would be reduced based on the information specified by the BPOG standardized extractables for the components of disposables. Most companies indicated that this would not reduce leachable studies, instead it would reduce the number of extractable studies currently conducted while minimizing the timeline and clarifying the target leachables for further study.

5 The types of methods employed for leachables testing is considerably consistent among respondents: HS-GC-MC, GC-MS, LC-UV/MS and ICP-MS.

6 When asked if the leachables methods are verification tests, limit tests, quantitation tests, other, or a mixture of these, respondents overwhelmingly answered that the leachables methods are quantitation tests. A few said their leachable methods are a mixture of verification, limit, quantitation, and others, depending on the objective of the study.

7 An even split of companies indicated that their leachables methods are either validated or demonstrated to be fit for purpose. A few respondents validate the leachables methods to full ICH, or very close to ICH guidelines, whereas others verify or qualify the methods. The companies using methods demonstrated to be fit-for-purpose rely on various subsets of validation, including system suitability, standard mixes, linearity, specificity, precision, recovery and LOD. The regulatory agencies have not questioned these fit-for-purpose methods.

8 Respondents unanimously indicated that they test for elemental heavy metals in their leachables studies.

In determining which elemental heavy metals are required for monitoring, the approach varies from standard screening based on USP, ICH Q3D and known product specific concerns to more circumstantial screening such as knowledge of disposable systems within a given process, previously detected Class I and/or II elemental impurities and toxicologist recommendations.

9 The majority of the responding companies said they do include screening methods in addition to the qualified/validated leachable method(s) for specific leachable(s).

10 When asked if screening methods are used for a leachable study and how the controlled samples are prepared, responses were not sufficiently detailed enough to draw specific conclusions. A small number of companies store controlled samples in containers of different materials. They generate enough control for each time point for the entire leachable stability study.

11 12 13 Most survey respondents indicated that their leachables studies are designed to provide data for at least the full duration of the stability hold. In addition to that full stability hold, many respondents also perform leachables testing at intermediate time points.

In most cases, respondents indicated that the leachables study is a separate activity from the stability protocol, though some respondents generate samples by working collaboratively with stability.

Occasionally, in leachables studies, unknown compounds are identified. In these instances, survey respondents indicated that they refer to the extractables data and try to make a correlation between the unknown and the extractables. In addition, many respondents move forward with various analytical techniques to identify the unknown compounds. The analytical techniques mentioned include: MS-MS structure elucidation, LCMS/MS, High Resolution-MS, NMR and TOF Accurate Mass.

If the respondents are still unable to identify a leachable compound, most move forward with a toxicology assessment using the threshold of toxicological concern approach to determine whether further evaluation is required.

14 When asked how often in the last two to three years a leachables test uncovered an issue that impacted yield, patient safety, product release or sample analysis, member companies indicated the following:

- Yield has been impacted (for example, during cell expansion) two times.
- Patient safety has been impacted one time.
- Product release has been impacted six times.
- Sample analysis has been impacted two times.

15 Companies offered dissimilar responses when asked if regulatory agency inspections/queries led to changes incorporated into the leachables testing program in the past two to three years. Of those who responded, few made no changes over that time period. The remainder focused mostly on either study design or analytical methods (overall extractables and leachables approach, leachable study endpoints, extension even to upstream process storage container, introduce/maintain state of the art analytics).

When asked whether the changes they implemented were deemed acceptable by regulators, some of the companies stated that their changes were found acceptable. The others presumably did not receive feedback.

16 Most of the survey respondents indicated that, absent changes, only one leachable study is performed during each drug substance lifecycle. This is mentioned as part of a comprehensive study involving three batches as part of the stability program. When a change occurs, such as a polymeric primary contact material, most companies clarified that stability studies would be required and would entail a minimum of three batches. Therefore, the BPOG Dispos-

Continued at bottom of page 34

The Future of Manufacturing

As new solutions and technologies enter the market, manufacturing will certainly see significant changes over the next ten years. To get a sense for what these flavors might be like, we asked some long-time PDA volunteers the question:

"What technology do you believe will revolutionize pharmaceutical manufacturing in the next 10 years?"

Maik Jornitz
President
G-Con Manufacturing

Prefabricated cleanroom manufacturing, laboratory and processing spaces will convert the industry's thought process about cleanroom and facility infrastructures. Since manufacturing processes, volumes and location are changing, so too are manufacturing facilities and infrastructures evolving. We will see a dramatic change in facilities and cleanroom design and construction to fulfill requests by the industry for flexibility, scalability, repurposability and rapid deployment.

John Shabushnig
Principal Consultant
Insight Pharma Consulting

I think the use of modular and disposable technologies at increasingly smaller scales to support development of personal medicines along with the rapid deployment of critical, novel medicines such as vaccines will be truly transformative.

Gabriele Gori
Vice President, Audit and Risk Management – Global Quality
GSK Vaccines

"Augmented reality will allow operators to see working/maintenance instructions directly where applicable, for example, by wearing something like Google Glass. Also, continuous manufacturing will become a common practice thanks to advanced testing methods and self-controlled manufacturing equipment."

Claudio Denoya
Senior Applications Specialist
Particle Measuring Systems

Automation will be at the forefront of pharmaceutical manufacturing. This area of technology will increasingly be considered in any new innovative process development plan.

Needleless parenterals. This technology allows users to insert drug doses through intact skin using solvents or nanotechnology.

Ghada Haddad
Director, Engineering,
Sterile & Validation CoE
Merck & Company

Govind Rao
Editor
PDA Journal of Pharmaceutical Science and Technology

Point-of-care manufacturing

Horst Koller
CEO
HK Packaging Consulting GmbH

I personally think that 3-D printing will become ever more sophisticated over the next few years and will play an important role in the design and manufacturing of pharmaceuticals.

Jim Akers
President
Akers Kennedy & Associates

Developments in the area of regenerative medicine, including tissue engineering and stem cell therapies, will likely spawn a revolution that will affect manufacturing as part of the drive toward personalized healthcare treatments.

snapshot

PDA Offers Elements of a Code of Conduct for Data Integrity

Denyse Baker, PDA

Data integrity is a major global concern for both global regulators and the pharmaceutical industry. Recent enforcement actions in the United States include warning letter citations, import alerts, product detentions, and suspension or revocation of product licenses.

Failure to ensure data integrity can result from lack of awareness of regulatory requirements, employee errors, failure to check accuracy of data, software or system malfunctions, configuration problems with electronic data handling, or even malfeasance by employees.

To holistically address this issue, PDA's Data Integrity Task Force is developing a set of tools in the form of technical reports, training, workshops, and other documents that can be used by industry.

One of the group's most important outputs is its Code of Conduct for Data Integrity. Through industry outreach, the task force identified the need for a common understanding of the expectations for employees and management conduct when it comes to data integrity. For this reason, PDA is pleased to make available to the industry a collection of recommended best practices related to data integrity in a ready-to-use format.

This document outlines the key elements necessary to help ensure the reliability and integrity of information and data throughout all aspects of a product's lifecycle. These elements are intended to reinforce a culture of quality and trust within the pharmaceutical industry. It is not intended to be a regulatory standard or guidance, nor is it intended to supersede any country-specific or local laws and regulations governing labor, privacy and/or employee rights. The document has been developed through the collaboration of PDA members with experience in manufacturing operations, quality, auditing, compliance, and consulting and has been peer reviewed by attorneys with extensive food and drug law experience. It is intended, in whole or in part, to guide a company's internal practices or for use in developing agreements with outsourcing partners or other suppliers.

The Code of Conduct is available for free at www.pda.org/CodeofConduct. The Food and Drug Law Institute (FDLI) will highlight the value of the document in an upcoming issue of its journal.

If you have questions about the code or want more information about PDA's data integrity activities, please contact **Denyse Baker** (baker@pda.org).

For more, check out *PDA Letter* "On the Issue" videos 1 and 2 at: www.pda.org/pda-letter-portal/multimedia/video.

On the Issue letter.pda.org

Survey of Industry Leachables Best Practices Completed from page 30

ables Team will focus on alignment for qualification when developing the Best Practices document.

Collaboration Opportunities

This article will be followed up with another article outlining proposed best practices for leachables studies. After reviewing the available survey results and current regulatory trends during the BPOG leachable subteam workshop, the team identified three key areas of collaboration:

- A consistent and user-friendly risk assessment model and process
- Common grounds for designing leachable studies, and
- A consistent analytical method approach.

The BPOG Disposables Team is continuing its efforts to drive best practices within the industry and to allow users to efficiently qualify new materials for use while also maintaining the high level of quality assurance and safety expected for pharmaceutical/biopharmaceutical products.

(Acknowledgement: This effort would not be possible without the groundwork and effort of the BPOG Extractables and Leachables Team, which is a larger group of subject matter experts from participating pharmaceutical and biopharmaceutical companies working collaboratively to advance the science of extractables and leachables.)

References

1. Jenness, E., and Walker, S. "Advantages of Single-Use Technology for Vaccine Fill-Finish Operations." *PDA Journal of Pharmaceutical Science and Technology* 68 (2014) 381-383.
2. Wang, P., "Risk-based extractable data assessment and its application to the evaluation of materials used in biomanufacturing", *BioPharma Asia* 3 (2014): 4-19.
3. Ding, W. "Determination of extractables and leachables from single-use systems," *Chemie Ingenieur Technik* 85 (2013): 186-196.

Defining New Expectations for Aseptic Processing

Richard M. Johnson, PDA

Aseptic processing continues to be the principle methodology for the production of critical medicinal products, but the techniques and expectations are continually changing. Some of these changes are driven by a better understanding of the risks to the patient, and how to manage that risk. Other changes are an outcome of improvements in technology for the manufacture and control of aseptic production, and every manufacturer has to assess the cost/benefit of implementing these improvements. Together these also lead to changes in the expectations of regulators who protect public health while also supporting the availability of life-sustaining medications to the public.

With the rise in the number of biologic products, more and more manufacturing requires aseptic processing. All the stakeholders involved, R&D and manufacturing, quality and regulatory, industry and regulators, suppliers and consultants, need to work together to define the best practices to that sterile medical products are safe, effective and available.

On April 20, PDA will hold the first of a series of four global workshops addressing new developments in aseptic processing. The objective of the workshop is to provide a forum for industry and regulators to discuss science- and risk-based approaches supporting modern aseptic processing and control strategy.

PDA has long been active in defining the current best science for aseptic processing, as can be seen in PDA's recent *Points to Consider for Aseptic Processing*. PDA's intention is to use these workshops to gather input from a cross-section of the industry as to the current best practices, challenges and interpretations for some of the more difficult questions of the day, including those that may be addressed in the pending revision of PIC/S-EMA Annex 1. The results from each workshop will be used to provide a true benchmark for industry.

2016 PDA Workshop: Current Challenges in Aseptic Processing and PDA Education course

San Diego, Calif.
April 19–21
www.pda.org/2016annexwest

USP <790> Generates Industry Questions

Markus Lankers, PhD, rap.ID Particle Systems GmbH

Visual inspection, especially the detection of particles, remains a focus of concern regarding product manufacturing control, quality assurance and regulatory compliance. In recent years, glass delamination issues triggered a flurry of particulate matter-related recalls. There were 55 recalls in the United States in 2014 due to foreign particles, making it the leading reason for recalls that year. This is likely an indication of heightened sensitivity of both regulators and manufacturers, rather than a measure of decreasing product quality.

The introduction of USP <790> has been a major step toward defining inspection conditions and giving a clear definition of the term "essentially free." But as with all pharmacopeial guidelines, questions continue to be raised regarding best methods for implementing the chapter. Companies attempting to implement <790> must factor in requirements for supplemental testing, unique requirements for biopharmaceutical products and acceptance sampling for assessing batch quality.

To address companies concerns regarding implementation <790>, PDA will offer its first one-day workshop on visual inspection in May at its Training and Research Institute (TRI), following a low-cost format that has been used for similar PDA workshops in Europe for many years. In addition to coverage of <790>, the workshop will also address the transition from manual to automated inspections. The second topic is more process oriented and covers practical aspects of manual inspection and automated inspection in a daily routine.

The main idea behind this workshop is to focus on topics raised by attendees and to have a more in-depth discussion compared to usual presentation-driven meetings. Attendees can bring questions for discussion and work together to develop possible solutions to challenging issues. Industry experts will participate by facilitating the discussion.

2016 PDA Visual Inspection Interest Group Workshop and PDA Education courses

Bethesda, Md.
May 16–20
www.pda.org/2016visualworkshop

The Impact of Waste on the Cost of Quality

Robert G. Kieffer, PhD, RGK Consulting

Waste has a significant impact on the cost of quality (COQ)—or more exactly, the cost of poor quality—in the pharmaceutical industry. As a consultant with many years of experience in the industry, I've observed the negative effects of waste at many companies, and I want to identify activities that can be defined as "wasteful."

When I refer to waste, I refer to activities within a process that are not value-added nor performed correctly the first time, and/or process outputs that are not desired by the customer. Ultimately, it is the customers, our patients, who pay for this waste, which also negatively impacts our employees' morale and motivation.

This means there is a strong business case for reducing waste. Waste adds to the cost of pharmaceuticals. Today the cost of pharmaceuticals is a public issue and consumers are demanding government action to curb drug costs ***(1).***

Based on my 40+ years in the industry, I estimate that waste amounts to at least 25% of the COQ ***(2, 3)***. Here lies an opportunity to reduce the COQ and thus reduce the cost of the pharmaceutical product.

Traditionally, COQ is divided into:

- **Prevention —** money spent on reducing the probability of failures before they occur
- **Appraisal —** money spent on evaluating process and product quality (testing, inspecting, checking, etc.)
- **Internal Failures —** the cost of process and product failures discovered while the product is still in the company's possession
- **External Failures —** the cost of failures or problems that occur after the product has left the company (recalls, complaints, returns, regulatory actions, etc.)

I want to make it clear that waste impacts COQ, particularly in the areas of appraisal and internal failures. As I stated above, COQ can comprise 25% or more of sales but should ideally comprise only 2.5% of sales ***(4).*** FDA's "Case for Quality" initiative shows that the Agency believes it is possible to reduce COQ by 20–30%, increasing profits by 3–4%.

Waste can be divided into two types: process waste and conditions that waste managers' time, which I discuss below.

Process Waste

The basic process model takes input, materials and/or information, and through a number of value-added activities, transforms these into an output of use by the customer. Examples of obvious process waste are rejects, recalls, reworks, low yields and returns, and complaints due to quality problems. The COQ model identifies these as failure costs. We can also add to this list the costs of regulatory problems, such as a consent decree, as well as costs associated with loss of reputation due to poor quality.

Most companies are aware of the types of waste listed above and their costs. The waste I want to discuss now, however, is usually not identified as waste and its cost in dollars is generally unknown. Below are some examples of these oft-unrecognized forms of waste.

Failures and Deviations: Out-of-specification results or out-of-trend results require at minimum an investigation. Deviations from an SOP or the batch card require a correction and sometimes an investigation. These are instances of not Right First Time practice and thus, are waste. Failures and Deviations have a cost associated with them. The lack of finding and correcting the root cause continues the cost and waste.

Repeats: Another example of not Right First Time practice is when it is necessary to repeat a laboratory test or repeat a production step.

Validation studies that do not result in improvement of the production process, lead to recurring production problems, or fail to reduce finished product testing: In the past, running three batches and evaluating whether they met specifications without determining process capability produced minimal value to the company or the customer while also costing a huge amount of money. Following the revised FDA guidance ***(5)*** should result in a lower COQ.

Training without an improvement in performance of the trainees is waste: Much "GMP" training is waste since, after the training, trainees continue to perform their work exactly as they did before the training.

Failure to use risk analysis to prioritize activities: When resources are used on low risk tasks or problems, this wastes limited resources as well as takes resources away from higher risk corrective and preventive actions. Some examples are:

- **CAPA —** frequently the CAPA system is loaded with low risk corrective actions—and these are usually the ones that get done because they are the easiest. Also, where are the preventive actions in the system? Why include low risk corrective actions in a CAPA?
- **Audits —** Again, frequently the audit program does not use risk analysis for determining which processes to audit and which activities in the process to focus on. Also, why include low risk problems in the audit report?
- **Change Control —** Change control processes still exist that do not distinguish between low and high risk changes. In these processes, low risk changes require the same amount of review as high risk ones.

- **Documentation —** Are risk considerations (severity and probability of failure) considered in determining the number and length of procedures? Likewise, why do we need more than the two required signatures from the responsible person and someone from QA?

Checks: We love checks. Why? Do they improve quality? They certainly increase costs. The GMPs specify that a second check is required only *when necessary*. When is it necessary? When the risk is too high; i.e., the severity of a mistake is high and/or the probability (high complexity) of a failure is high. More than two checks is always wasteful and dilutes accountability.

Waiting: This is when we need to wait for a result, for material, for information, etc., before we can proceed with our task.

Reviews: Here we refer to the review of a protocol or document. As mentioned above under Documentation, the number of reviewers can be minimized, generally to a maximum of two, if the process owner is competent and held accountable.

Annual Product Review: I have audited many annual product reviews. Most of the time, I find them to be a waste because they do not generate any product or process improvement activities. No one denies that they take a lot of time and resources to complete. Perhaps the annual review is an obsolete concept. If there is a regular management review as required by ICH Q10, and the computer is monitoring process performance in real-time, batch-by-batch, why the big paper- exercise annually? The GMPs indicate the review should be done "at least annually." The best practice is to conduct the review continuously.

Time Wasters for Managers

Although the two time wasters specified below are not unique to the pharmaceutical industry, I included them because they impact cost (specifically, the Cost of Goods), employee morale and the cost of our products to patients.

Emails: Perhaps the number one "polluter" of management's time today is emails. In 2012, a McKinsey Global Institute study found that employees spent 28% of their day reading and responding to emails. ***(6)*** It takes only one click, one second, in the address book to send an email to 100 people in the company. It takes many times longer for the 100 employees to sort out their emails and determine that the one they received from you really is spam. I know one executive of quality who received on average 200 emails per day of which *only* five were worth reading.

Meetings: These are close to or greater than emails as time wasters. Any meetings that don't start on time, don't end on time, don't have an agenda or clear objective, don't result in a decision, don't have an effective leader, etc. are usually ineffective and a waste of time. On the internet you can find many useful ideas for making meetings more effective, but it takes discipline. Before you set up a meeting, ask yourself: "Do we really need a meeting on this?"

Waste Impacts Cost

But what does all this waste mean for the industry? Ideally, each pharmaceutical company knows and measures the cost of waste and works conscientiously to reduce it. The costs of poor quality are significant and numerous. Nonroutine quality events—such as major observations, recalls, warning letters, and consent decrees—cost the medical device industry between $2.5 billion and $5 billion per year ***(7)***. The price of a consent decree can easily exceed $1 billion for larger companies ***(8)***. And the cost of compliance enforcement exceeded $30 billion in cumulative penalties in the United States alone between 1999 and 2012 ***(9)***.

The pharmaceutical industry continues to lag behind other industries when it comes to doing things right-first-time. Here, pharma usually scores 85–95% compared to world class factories that score 99.6% on right first time ***(3)***. Pfizer's former head of global quality **Gerry Migliaccio** famously said of the industry, "We produce 6-sigma products from 3-sigma processes;" this occurs due to the application of very costly and less reliable Quality by Inspection practices ***(10).*** The COQ for 3-sigma processes is 20–25% ***(3).***

Survey data also show that the cost of poor quality is rarely measured in our industry. A Georgetown survey found that 62% of respondents do not calculate the cost of poor quality and 92% do not evaluate the cost of improving quality against the potential cost of failure ***(11).*** The investigation of a simple failure can cost $10,000 while the cost of a complex one can be $100,000 ***(12).*** In general, the cost of poor quality is not measured and this severely impacts pharma.

I hope I have convinced you that there is a lot of opportunity to improve efficiency and reduce costs. This will not only benefit our customers, but also reduce frustration and improve morale of our employees, and improve the profitability of our company. The obstacles perhaps are many. In a future article, I will discuss these as well as some possible strategies for overcoming them.

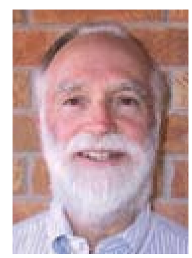
References

1. Wechsler, J. "Drug-Pricing Backlash Reaches Fever Pitch." *Pharmaceutical Executive* (Nov. 4, 2015) www.pharmexec.com/drug-pricing-backlash-reaches-fever-pitch
2. "American Society for Quality,"*ASQ*, Accessed Dec. 21, 2015, www.asq.org
3. Benson, R.S. and McCabe, D.J. "From Good Manufacturing Practice to Good Manufacturing Performance." *Pharmaceutical Engineering* 24 (2004) 26-34
4. Crosby, P.B. 1980. *Quality is Free*. New York: Mentor.
5. Guidance for Industry: Process Validation: General Principles and Practices, U.S. Food and Drug Administration, 2011 http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf
6. Yeager, M. "How to Stop Wasting Time on Email," *AOLJobs.com*
7. Fuhr, T., George, K., and Pai, J. *The Business Case for Medical Device Quality*. Oct. 2013, McKinsey Center for Government http://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/public%20sector/regulatory%20excellence/the_business_case_for_medical_device_quality.ashx
8. "Prescribed Behavior: Operating Under a Consent Decree." *Pharmaceutical Executive* (Dec. 1, 2013) http://www.pharmexec.com/prescribed-behavior-operating-under-consent-decree
9. Knoebel, J. "Quality Culture vs. Cost of Quality—Quality Culture Is Understanding the *Value*, not Just the Price, of Quality." *PDA Journal of Pharmaceutical Science and Technology* 69 (2015) 562-565.
10. Calnan, N., O'Donnell, K., and Greene, A. "Enabling ICH Q10 Implementation—Part 1. Striving for Excellence by Embracing ICH Q8 and ICH Q9." *PDA Journal of Pharmaceutical Science and Technology* 67 (2013) 581-600
11. Shanley, A. "The Cost of Poor Quality, Too High a Price."*Pharmaceutical Manufacturing* (Feb. 29, 2012) www.pharmamanufacturing.com/articles/2012/033/
12. Zipp, F. "The Cost to Manufacturing for Poor Quality." Presentation at the 2015 PDA Annual Meeting, Las Vegas NV, March 2015

Additional Reading

1. "The Art of Finding More Time." *PDA Letter* 46 (October 2010) 34-35.
2. Friedli, T., Basu, P., Bellm, D., and Werani, J., eds., *Leading Pharmaceutical Operational Excellence: Outstanding Practices and Cases.* New York: Springer, 2013.
3. *PDA Survey: Business Case for Pharmaceutical Quality.* Bethesda, MD: PDA, 2012. (Available free at PDA Bookstore.)

About the Author



Robert Kieffer is an authority on quality management and on quality system design. He will teach the course, "Quality Metrics: Performance Indicators," following the *2016 PDA Annual Meeting,* March 17–18.

Pharma Seeks Long Tail of Flexible Manufacturing from page 27

Pre-filled Syringes and Injection Devices, Nov. 4, Vienna, Austria.

3. Anderson, C. "The Long Tail." *Wired* (Oct. 4, 2004) www.wired.com/2004/10/tail/
4. Geidobler, R. "Flexible and Modular Isolator Fillng Line." Presented at the Universe of Pre-filled Syringes and Injection Devices, Nov. 4, Vienna, Austria.
5. Gladd, T. "Boehringer Ingelheim Revolutionizes Filling Line Flexibility." *Pharmaceutical Online* (Feb. 15, 2015) tinyurl.com/h3rx4mc
6. Langer. E. "Outsourcing Becoming More Cost Competitive." *BioPharm International* (Aug. 1, 2015) tinyurl.com/h4vxo9w
7. Meurs, R., Cecchetto, A., and Schuster, D. "Implementing a Flexible AsepticManufacturing Process Based on Nested Containers (PFS, Vials, Cartridges): Adopting a CMO Perspective." Presented at the Universe of Pre-filled Syringes and Injection Devices, Nov. 4, Vienna, Austria.
8. Draft Guidance for Industry and Food and Drug Administration Staff: Postmarket Management of Cybersecurity in Medical Devices, U.S. FDA, Jan. 22 tinyurl.com/gtkyq6j

Compliance: Its Meaning for Industry, Regulators

Shane Killian, Johnson and Johnson, and Renee Kyro, AbbVie

What is compliance? Can compliance be a competitive advantage? For those of us in quality, regulatory or manufacturing roles in the pharmaceutical industry, articulating the answer to this question, particularly to our business stakeholders, is paramount.

As the drug supply chain becomes increasingly global, the U.S. FDA and other international regulatory agencies have placed increased emphasis on the importance of compliance to cGMP as a mechanism to ensure product quality and safeguard patient safety. Operating in compliance gives us the right to do business. Although you would think defining compliance would be simple, there appear to be many ways to define it. Is it following a minimum set of regulations? Is it a successful FDA inspection with no 483s? Is it doing routine audits? Is it all of the above? Is it more than the above? Does it take into account the patient's needs?

Throughout the *2016 PDA/FDA Joint Regulatory Conference,* you will find answers to the question: "What is compliance?" Conference speakers will offer their views on how to get there, discuss the role quality culture plays in achieving compliance, and explain the relationship that science and compliance have with one another. Challenging subjects such as the financial cost of poor quality/compliance will be discussed, using case studies to help simplify the subject matter. Understanding the cost of poor quality/compliance allows your organization to accurately determine the extent to which its resources can remediate noncompliance issues.

In addition, the conference will offer a more personal look at the importance of compliance as **David Fajgenbaum,** MD, cofounder and Executive Director of the Castleman's Disease Collaborative Network, will talk about not only his personal experience battling Castleman's disease but also his work as a medical professional working in a research capacity to treat rare and deadly diseases.

In the end, we can agree that compliance in the pharmaceutical industry touches us all as both patients and employees in the workforce. The *2016 PDA/FDA Joint Regulatory Conference* will provide you a great opportunity to seek answers to your compliance questions. See you there!

2016 PDA/FDA Joint Regulatory Conference and PDA Education courses

Washington, D.C.
Sept. 12–16
www.pda.org/2016pdafda

Pens, Injection Devices Get "Smarter" from page 20

have patients, and many of them are not on a single medication, so you look for something convenient. Also, you have to ask the provocative question, "Do you really need all of that?"

If the user interface is something that people like, the question is really, "Do you need all these technical gadgets?" I think it's really the user interface and the value added to specific groups who can decide if a product under development will be successful or not.

letter.pda.org

[Editor's Note: You can listen to this interview as a podcast on the *PDA Letter* multimedia page.**]**

About the Expert

Markus Bauss has over ten years of experience in the area of pharmaceutical packaging in various leading roles, such as global key account management, research and innovation, and business development.

Glenn Wright, Eli Lilly, MSP Steering Committee Chair

PDA's Manufacturing Science Program[SM] Links Manufacuring Science and Operational Excellence

In early 2015, we kicked off PDA's Manufacturing Science Program[SM] (MSP[SM]) initiative, which seeks to ensure PDA's continued focus on pharmaceutical manufacturing. In September, the MSP Steering Committee held its first meeting at PDA's headquarters in Bethesda, Md. Made up of industry leaders in manufacturing operations and manufacturing science, the MSP Steering Committee is already helping PDA better understand the areas of manufacturing where we need to focus in order to ensure we effectively serve our membership—and the committee is just getting started!

So what does the program cover? I believe one of our MSP Steering Committee members said it best when commenting that it's really a program of manufacturing science (the science and technology part) and operational excellence (the execution part). We need both to move our industry into the future.

It's incredibly exciting when you think about the science and technology improvements needed to move our current manufacturing processes forward as well as to enable us to deliver the next generation of innovative products. But to fully realize these benefits, it is clear that we must also work to improve the way we think and approach our operational execution. As stated above, the two are inexplicitly linked and I am very excited that the MSP Steering Committee members are discussing both.

So how are we doing? PDA has already executed on its plan to run multiple manufacturing science-focused workshops. In 2015, PDA held workshops on aging facilities and continuous manufacturing—both received very positive reviews. This month, PDA's Annual Meeting, as in years past, will heavily focus on manufacturing and manufacturing science with this focus continuing in the postmeeting workshop, which will feature topics like using statistics and manufacturing control strategies to understand and improve manufacturing processes.

So where are? We may just be getting started but we are already making great progress on our journey, so stay tuned for more on PDA's Manufacturing Science Program[SM].

Living History in San Antonio

Many PDA members will pick up this edition of the *PDA Letter* at this year's *PDA Annual Meeting* in San Antonio, Texas. It is our 65th *PDA Annual Meeting.* It is a historical month for the city, too, as it is also the 180th anniversary of the fall of the Alamo to the Mexican army. This event became the rallying cry for the eventual independence of Texas from Mexico, which was achieved less than two months later.

In case you are reading this at the Annual Meeting and not sure you want to visit the Alamo, it is worth a trip downtown to see it. Less than 300 Texan soldiers defended the outpost against about 1,500 Mexican soldiers from February 23 until the climactic battle on March 6. Nearly all of the Texan forces were killed along with hundreds of Mexican soldiers. It was truly a bloody and tragic scene. But it did rally the Texans to continue their fight for independence. At the final battle of the Texas revolution, the Battle of San Jacinto, Texan soldiers won the day after a surprise attack and famously cried, "Remember the Alamo" as they ruthlessly pursued the fleeing Mexican army.

You too can leave San Antonio with a rallying cry. Not "Remember the Alamo" (I imagine your colleagues would look at you funny if you came back from the *PDA Annual Meeting* shouting that) but instead, "We can do it better." What can you do better? Manufacture products. Over the course of its 70-year history and 65 years of holding Annual Meetings, PDA's members have used their collective knowledge to solve a host of challenges. Today, the industry is challenged to upgrade aging facilities and create state-of-the-art manufacturing processes to ensure that a steady supply of drug products are available to patients all over the world. That's why the planners of this year's historic Annual Meeting chose "Achieving Manufacturing Excellence" as the overarching theme.

Following conference sessions on various aspects of manufacturing, PDA is holding its *2016 PDA Manufacturing Science Workshop.* This interactive event aims to uncover the barriers companies face in modernizing their facilities.

PDA's Manufacturing Science Program℠ also is underway. Led by a steering committee of executive-level experts at leading pharmaceutical companies, and chaired by PDA Director **Glenn Wright** (Eli Lilly), this group will be producing documents and other deliverables to help the industry move beyond the hurdles.

In closing, I want to highlight two other March historical events, both occurring 80 years ago. I find these events punctuate the need for not just continual improvement, but also anticipating future innovations.

On March 4, 1936, the largest flying machine ever operated, the Hindenburg, took its maiden flight in Friedrichshafen, Germany. Earlier in the month, the *Spitfire* made its first test flight in England. The *Hindenburg* went on to tragically and spectacularly crash in 1937 in New Jersey, bringing to an end the brief history of passenger flight on dirigibles. Meanwhile, the *Spitfire* went on to become one of many well-known airplanes central to military strategy in WWII. Airships also played a prominent role in the war, but not to the same level as the airplane. Post-WWII, the commercial airplane industry was born, quickly surpassing all other forms of mass transit. Meanwhile, travel by airship had gone the way of horse and buggy.

PDA *Letter*

The PDA Letter is published 10 times per year, exclusively for PDA members.

Articles published in the PDA Letter do not represent the official positions of PDA, Inc., but are the opinions of the authors submitting the articles.

Subscriptions are not available.