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DECEMBER 2015 VOLUME 35, NUMBER 6

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AstraZeneca China

Overall Winner

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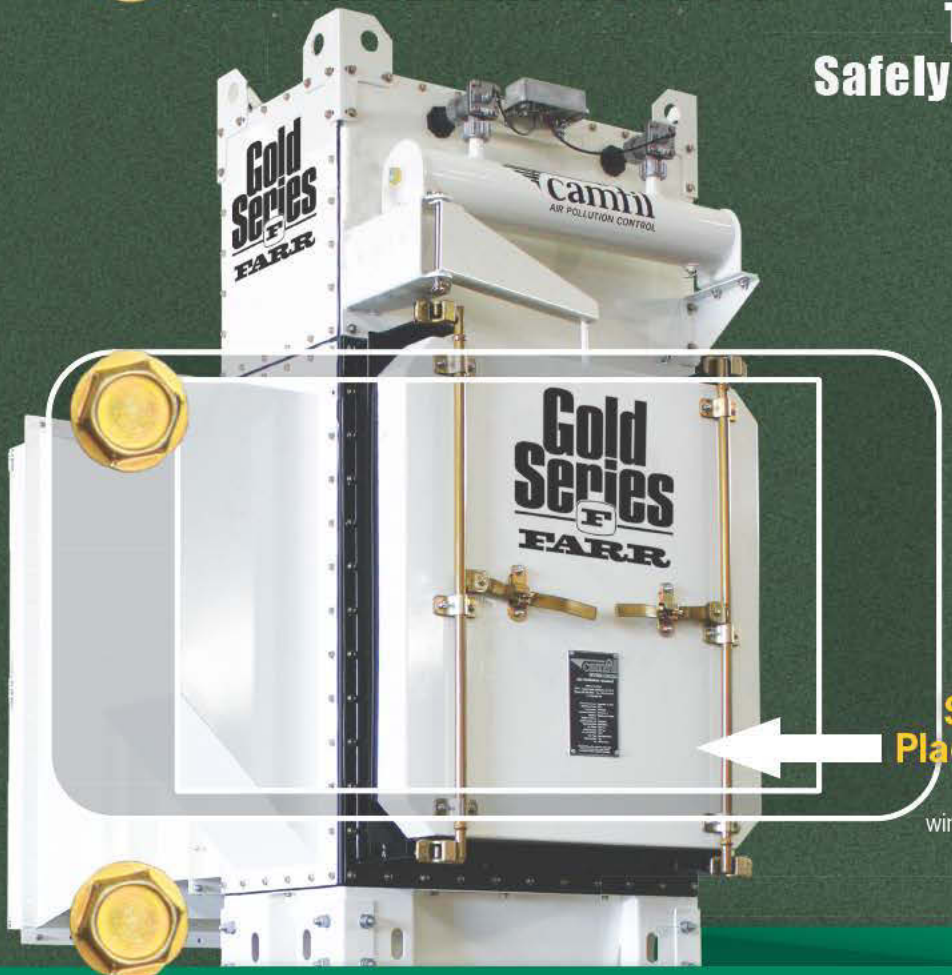


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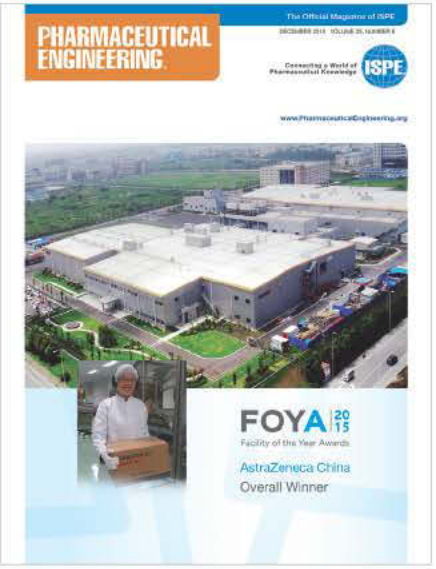

Cover Photo: AstraZeneca China

AstraZeneca's Tiazhou Supply Site Project is honored as ISPE Facility of the Year, page 15. Alfonso Izarra, President of the ISPE Brazil Affiliate, sits down for an interview, page 21. Roger Nosal talks about the value of process capability, page 26. Bob Dream reviews biopharmaceutical research and manufacturing through the decades, page 54. Learn some pharmaceutical industry history, page 102.

PHARMACEUTICAL ENGINEERING®

Volume 35, Number 6
Published since 1980

AstraZeneca China: ISPE Facility of the Year Overall Winner.

Best practice, innovative project management, and detailed planning turned a farmer's field into a fully functional pharmaceutical facility in two years — under budget and ahead of schedule. See page 15.

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DECEMBER 2015

1–2 **ISPE DACH Affiliate GAMP 5 Conference**
Mannheim, Germany

3 ISPE UK Affiliate Plant Tour and Presentation
Tredegar, Gwent, UK

CASA Education Event & Charity Event
Raleigh–Durham, North Carolina, US

San Francisco/Bay Area Chapter Evening Meeting
Location TBD

4 Delaware Valley Chapter Volunteer Day

Rocky Mountain Chapter Holiday Event
Boulder, Colorado, US

7–8 Australasia Affiliate Best Practices in Aseptic Processes
Melbourne, Victoria, Australia

Cleaning Validation Principles (T17) Training
Tampa, Florida, US

Oral Solid Dosage Forms: Understanding the Unit Operations, Process, Equipment and Technology for OSD Manufacture (T10) Training
Tampa, Florida, US

Q7A—Implementing Good Manufacturing Practices (T30) Training
Tampa, Florida, US

7–9 **HVAC (T14) Training**
Tampa, Florida, US

8 Delaware Valley Chapter Holiday Party

Great Lakes Chapter CSV Guide for Regulated Environments

9–10 **Sterile Product Manufacturing Facilities: Applying the ISPE Baseline® Guide and FDA Guidance Principles to Design and Operation (T12) Training**
Tampa, Florida, US

Facility Project Management in the Regulated Pharmaceutical Industry* (T26) Training
Tampa, Florida, US

Applying Quality Risk Management (QRM) (T42) Training
Tampa, Florida, US

10 ISPE Italy Affiliate Xmas Night & Single Use Technology
Milan, Italy

Midwest Chapter End of Year Dinner

Boston Area Chapter Industrial Wireless Network
Andover, Massachusetts, US

San Diego Chapter Networking Event
San Diego, California, US

Pacific Northwest Allen Institute for Brain Science Tour
Seattle, Washington, US

16 New Jersey Chapter Holiday Party
Princeton, New Jersey, US

17 Pacific Northwest Chapter Annual Holiday Social
Seattle, Washington, US

JANUARY 2016

12 Delaware Valley Chapter January Program
Philadelphia, Pennsylvania, US

21 ISPE DACH Affiliate Stakeholder Management
Frankfurt, Germany

21–22 ISPE DACH Affiliate Stakeholder Management: Wie Geht Das?
Neu-Isenberg, Germany

23 Delaware Valley Chapter Future Cities Competition
Philadelphia

25–27 **Basic Principles of Computerized Systems Compliance Using GAMP® 5, Including Revised Annex 11 and Part 11 Update (T45) Training**
Tampa, Florida, US

28–29 **A GAMP® Approach to Data Integrity, Electronic Records and Signatures, and Operation of GxP Computerized Systems (T50) Training**
Tampa, Florida, US

FEBRUARY 2016

1–3 **HVAC (T14) Training**
Tampa, Florida, US

4–5 **Applying the Biopharmaceutical Manufacturing Facilities Baseline® Guide Principles (T31) Training**
Tampa, Florida, US

8–10 **Practical Implementation of Process Validation Lifecycle Approach (T46) Training**
Tampa, Florida, US

9 Delaware Valley Chapter 26th Annual Symposium and Exhibition
Philadelphia, Pennsylvania, US

www.ispe.org/globalcalendar

11 **ISPE Nordic Affiliate Cleaning Validation Conference Copenhagen, Denmark**

11–12 **Process Validation in Biotechnology Manufacturing (T32) Training Tampa, Florida, US**

18 Rocky Mountain Chapter 21st Annual Vendor Exhibition Westminster, Colorado, US

18–19 **Practical Application of Technology Transfer (T19) Training Tampa, Florida, US**

19 Rocky Mountain Chapter Denver Networking Event Copper Mountain, Colorado, US

20 Delaware Valley Chapter Windows on Industry Philadelphia

22–23 **GMP Auditing for the Pharmaceutical Industry (G07) Training Tampa, Florida, US**

25–26 **Science and Risk-based Commissioning and Qualification: Applying the ISPE Good Practice Guide—Applied Risk Management for Commissioning and Qualification (T40) Training Tampa, Florida, US**

29 **February–March 1 A Risk-Based Approach to GxP Process Control Systems: Applying the GAMP® Good Practice Guide—A Risk-Based Approach to GxP Process Control Systems (2nd Edition) (T21) Training Tampa, Florida, US**

ISPE 25th Aseptic Conference Arlington, Virginia, US

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How Patent Law Can Block Even Lifesaving Drugs

New York Times, 28 September 2015, Austin Frakt

Hillary Rodham Clinton's prescription drug policy proposal, released last week, would hold drug manufacturers accountable to their level of investment in research. But there are some potentially valuable drugs we'll never get drug companies to invest in—those that cannot be patented.

By granting temporary monopolies to innovators, the patent system is widely credited with protecting and promoting innovation. But when it comes to pharmaceuticals, it may be preventing valuable therapies from coming to market.

www.nytimes.com/2015/09/29/upshot/how-patent-law-can-block-even-lifesaving-drugs.html

Will a New FDA Head Usher in More Enlightened Era?

Forbes, 22 September 2015, Henry I. Miller

President Barack Obama has nominated a deputy commissioner of the US Food and Drug Administration (FDA), Dr. Robert Califf, to head the agency. The post, a presidential appointment, is one of the most important in the government because the FDA regulates products worth more than $1 trillion, 25 cents of every consumer dollar. Those products affect every American in innumerable ways every day.

Moreover, the FDA is a "gatekeeper," which means that it must issue affirmative approvals of many classes of products before they can be marketed.

Califf, a distinguished cardiologist, has many of the qualifications necessary for the job. Although he has spent most of his career in academia, he is deeply versed in FDA issues, especially the clinical testing of drugs and medical devices (which is performed by companies, which then submit the data to the FDA for review). He is a longtime innovator in various aspects of clinical-trial design and interpretation.

www.forbes.com/sites/henrymiller/2015/09/22/will-a-new-fda-head-usher-in-a-new-era

Clinton Tanks Biotech Stocks as She Comes Out for Price Controls

Wall Street Journal, 22 September 2015

The political blaze over drug costs that kicked up a year ago over the hepatitis C cure Sovaldi has moved on to therapies for more diseases—and beyond white heat too. Now Hillary Clinton and others upset with the price of medical progress are proposing government remedies, including price controls.

www.wsj.com/articles/the-assault-on-drug-innovation-1442964103

Turning to Drugs and Treatments before They Are "Ready for Prime Time"

Harvard Health Publications, 21 September 2015, Amy Ship, MD

It's not a situation any of us would wish for. What if you had a terminal illness like cancer or ALS (Lou Gehrig's disease), or a rare, debilitating disease, and there was treatment that might help you but was not yet approved by the FDA? Fortunately, there is a way to gain access to experimental treatments or drugs. Your doctor can request their use through the FDA's "expanded access" or "compassionate use" programs.

But some patients and doctors seeking treatment through these programs have felt the process was just too long. And when time is short, delays of any kind are intolerable. Since 2014, 21 states have enacted legislation to help speed up this process. These laws, called "right-to-try" laws, enable patients to bypass the cumbersome FDA process and allow doctors to request certain medications (which have already been FDA-tested for safety but are not yet on the market) directly from the drug companies that manufacture them.

www.health.harvard.edu/blog/turning-to-drugs-and-treatments-before-they-are-ready-for-prime-time-201509218324?utm_source=twitter&utm_medium=socialmedia&utm_campaign=092115kr1&utm_content=blog

The Printed Pill

Journal of the American Medical Association, 15 September 2015, Rebecca Voelker, MSJ

In early August, the US Food and Drug Administration (FDA) approved the first drug made with three-dimensional printing technology. The medication, marketed as Spritam, is an oral formulation of levetiracetam that is indicated as an adjunctive therapy for partial-onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures in children and adults with epilepsy.

Aprecia Pharmaceuticals Company, which is headquartered in Langhorne, Pennsylvania, manufactures Spritam with its proprietary ZipDose Technology delivery platform. Based on research developments at the Massachusetts Institute of Technology in the late 1980s, the platform repeatedly spreads thin layers of powdered medication on top of one another while liquid droplets are printed onto specific regions of each layer to bond them together.

jama.jamanetwork.com/article.aspx?articleid=2441246&utm_source=TWITTER&utm_medium=social_jn&utm_term=234177855&utm_content=|article_engagement&utm_campaign=article_alert&linkId=17149738

Companies Struggle to Get New Medicines Adopted across Europe

Reuters, 7 September 2015, Ben Hirschler

Pharmaceutical companies, currently enjoying a bumper wave of new drug launches, are struggling to get recently introduced products adopted in key European markets as governments bear down on costs.

While a number of countries have pledged in recent years to encourage the use of innovative medicines, Europe remains a much tougher market than the United States, prompting many companies to offer significant price discounts.

www.reuters.com/article/2015/09/07/us-pharmaceuticals-europe-idUSKCN0R71JZ20150907?feedType=RSS&feedName=healthNews

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Life-Extending Cancer Drugs to Be Axed by NHS

Guardian, 3 September 2015, Sarah Boseley

New and costly cancer drugs developed to extend the lives of patients are expected to be axed on Friday from a National Health Service (NHS) list. Among the drugs NHS England is expected to delist from the Cancer Drugs Fund is Kadcyla, which holds the record as the most expensive cancer drug brought to market, costing £90,000 annually per patient.

Kadcyla, made by Roche, was rejected from general NHS use by the National Institute for Health and Care Excellence (NICE), the body that assesses new medicines for their cost-effectiveness.

NICE agreed the drug was effective for women whose advanced breast cancer no longer responded to Herceptin, but its chief executive, Sir Andrew Dillon, was outspoken about the "unacceptable" price tag. "We had hoped that Roche would have recognized the challenge the NHS faces in managing the adoption of expensive new treatments by reducing the cost of Kadcyla to the NHS," Dillon said in April 2014.

www.theguardian.com/society/2015/sep/03/life-extending-cancer-drugs-to-be-axed-by-nhs

Poll Finds Prescription Drug Costs Emerging as a Top Health-Care Issue for Consumers

Fox Business/Associated Press, 20 August 2015

A new poll finds that Americans strongly support government action to control prescription drug costs, regardless of their political affiliation.

The 2016 presidential candidates continue to spar over President Barack Obama's 5-year-old law that expanded coverage for the uninsured. But the latest survey by the nonpartisan Kaiser Family Foundation suggests that the public is moving on to other health-care issues.

Overall, 72 percent say the cost of prescription medications is unreasonable.

www.foxbusiness.com/markets/2015/08/20/poll-finds-prescription-drug-costs-emerging-as-top-health-care-issue-for

The FDA's "Off-Label" Drug Policy Leads to Free-Speech Fight

New York Times, 10 August 2015, Peter J. Henning

It certainly seems odd that speaking the truth can violate the law. Yet the US Food and Drug Administration (FDA) takes the position that when it approves a drug for a particular treatment, the manufacturer of that drug cannot promote it for other uses, even if those statements are true.

But that policy has been called into question in a decision by Judge Paul A. Engelmayer of the Federal District Court in Manhattan, who found that the First Amendment protects drug companies that want to make truthful statements about their drugs, even if it is for an unapproved use. His decision sets up a likely appeal to determine just how far the government can go to punish speech that is truthful.

www.nytimes.com/2015/08/11/business/dealbook/fdas-off-label-drug-policy-leads-to-free-speech-fight.html?emc=edit_tnt_20150810&nlid=33652061&tntemail0=y

Frances Oldham Kelsey, FDA Officer Who Blocked Thalidomide, Dies at 101

NPR, 8 August 2015, Scott Neuman

Dr. Frances Oldham Kelsey, whose tireless efforts uncovered a link between the drug thalidomide and severe birth defects, has died at age 101.

In 1960, Kelsey was the new medical officer at the US Food and Drug Administration (FDA) when an application arrived for FDA approval of the sedative Kevadon, the trade name of thalidomide, manufactured by drug company William S. Merrell Company of Cincinnati.

Thalidomide had already been sold to pregnant women in Europe and elsewhere as an antinausea drug to treat morning sickness, and Merrell wanted a license to do the same in the US.

www.npr.org/sections/thetwo-way/2015/08/08/430709628/frances-kelsey-fda-officer-who-blocked-thalidomide-dies-at-101?utm_medium=RSS&utm_campaign=health

New Analysis Underscores Improving Pharma R&D Productivity

Reuters, 4 August 2015, Ben Hirschler

Drug industry productivity is continuing to improve, with a bumper haul of new products being launched and companies proving more successful in the final stages of clinical testing, according to a new analysis.

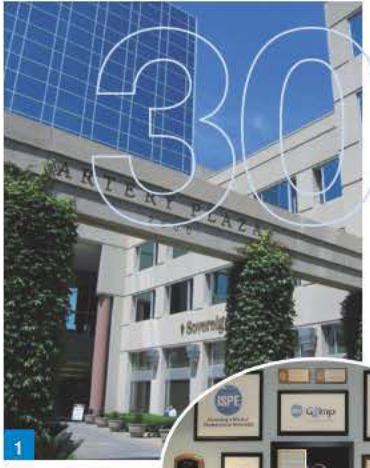
Data from Thomson Reuters published on Tuesday showed the number of innovative medicines, or new molecular entities, launched globally in 2014 hit a 17-year high of 46, up from 29 in 2013.

Last year's entrants included two cancer drugs that help the body's own immune cells fight tumors as oncology remained the top area for drug research, attracting nearly one-third of all R&D spending.

www.reuters.com/article/2015/08/04/us-pharmaceuticals-r-d-idUSKCN0Q909620150804 ◂

The gang's all here ...

Members, colleagues, and friends celebrate the opening of ISPE's Bethesda, Maryland, office on 8 October 2015. Attendees are identified from left to right.



1. ISPE's new offices in Bethesda, Maryland, US

2. IPSE's Vice Presidential "Hammer" Award, presented in 1997 by then–Vice President Al Gore for ISPE's Scale-Up and Post-Approval Change guidance

3. Jan Bult, President and CEO, Plasma Protein Therapeutic Association; and Mike Arnold, Business Process Owner for Investigational Products and Sr. Dir. Strategic Partnerships, Pfizer Global Clinical Supplies, and ISPE Board of Directors Vice Chair

4. Laura Hodgson, ISPE Executive Assistant to the CEO; and Victoria Smoke, ISPE VP Administration and CFO, share a hug

5. Domenico Schiavone, Associate Research Scientist, Fresnius Kabi; and Bill Paulson, Editor in Chief, International Pharmaceutical Quality

6. Melanie and Dan Mouyard with John Bournas, ISPE President and CEO

7. Chuck Hoiberg, Executive Dir., Pfizer; Paul Vogel, Chairman and CEO, Lachman Consultant Services; John Bournas, ISPE President and CEO

8. Maurice Parlane, Principal/Director, New Wayz Consulting, Inc.; and Dr. Theodora Kourti, ISPE Sr. VP Regulatory Affairs

9. Mike Arnold, Business Process Owner for Investigational Products and Sr. Dir. Strategic Partnerships, Pfizer Global Clinical Supplies, and ISPE Board of Directors Vice Chair; Dr. Paula Pohlmann, Asst. Prof. MedStar Georgetown University Hospital; George Millili, Genentech Senior Principal Technical Advisor and ISPE's 2015 member of the year; Carol Winfield, ISPE Dir. Regulatory Operations

10. An ISPE group portrait: Shane Osborne, VP Marketing, Communications, and Membership; Susan Krys, VP Program Development; Maria Robertson, Sr. Dir. Marketing Communications; and Laura Hodgson, Executive Assistant to the CEO

11. Nate Roman, VP Azzur Group LLC, and ISPE Chesapeake Bay Chapter VP; Bill Deckert, Sr. Consultant, Commissioning Agents, Inc.; Jennifer Lauria Clark, Dir. Technical Services, Commissioning Agents, Inc., and ISPE Board of Directors Member; and Tony Crincoli, Executive Dir. and Head of Global Engineering, Bristol-Myers Squibb, and ISPE Board of Directors Member

12. Melanie Mouyard; Jan Bult, President and CEO, Plasma Protein Therapeutic Association; and Rose Bult

13. Domenico Schiavone, Associate Research Scientist, Fresnius Kabi; Bill Paulson, Editor in Chief, International Pharmaceutical Quality; and Joanne Barrick, Advisor in Global Validation Support, Eli Lilly & Co., and ISPE Board of Directors Member

A NEW SANDBOX FOR ISPE AND ITS MEMBERS AROUND THE WORLD

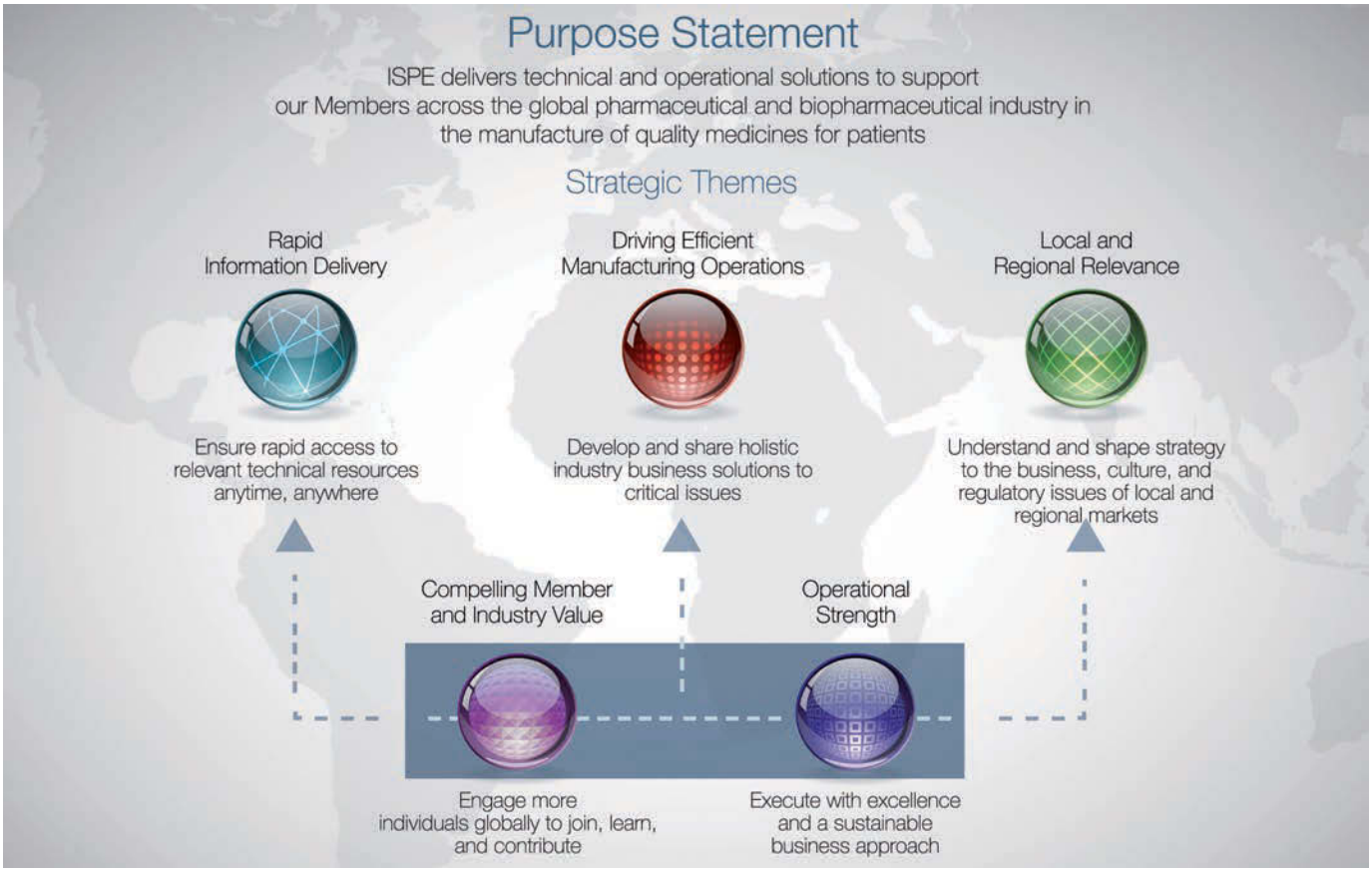
Community at the heart of ISPE's new strategic plan

John E. Bournas
ISPE CEO and President

The ISPE International Board of Directors has undertaken a strategic planning process for the years 2016–2019 and the final strategic plan, now complete, was launched at the 2015 Annual Meeting in Philadelphia.

When we began work planning the development and process for a new direction for ISPE, our intent was to address the changing landscape in which we operate. Specifically, the Board wanted to ensure ISPE continues to anticipate and respond to the challenges of the pharmaceutical and biopharmaceutical manufacturing industry.

Central to our planning was the notion that ISPE's strategic plan needed to be truly global, inclusive, relevant to members and staff alike, and, most importantly, easy to execute and measure. And so the Board's Strategic Plan Work Group spent six intense months working toward the realization of that aspiration. Various stakeholders were consulted in this process, including Affiliate and Chapter Leaders, CoP/knowledge network leaders, staff, advisors and key industry thought leaders both within and outside of ISPE. We received input from 97 individuals in all, through surveys, focus groups, and interviews. The entire process was facilitated by consultant Lyn McDonell CAE, C. Dir., CMC of The



▸ ISPE delivers technical and operational solutions to support our members across the global pharmaceutical and biopharmaceutical industry in the manufacture of quality medicines for patients. ◂

The 2016–2019 strategic plan provides an excellent sandbox that focuses on thematic issues, but then also addresses areas such as emerging markets, which are areas of growing importance to pharmaceutical manufacturing and engineering and how they intersect with regulatory affairs. It builds on our past successes and while its emphasis may be on the strategic imperatives of the next four years, it will help us lay the groundwork to meet the challenges and opportunities of the future. ◂

Accountability Group, Inc., who also worked to fine-tune the language and intent of the final draft.

What I believe makes the plan distinctive is that it is intended to be as inclusive as possible. We purposely adopted an approach that allowed room to share and hear disparate views. And I believe *that*, above all else, speaks well of the people involved in this process.

It also speaks of the respect we have for our members and ISPE staff. We want it to address your concerns. We attempted to be equitable in the different areas of expertise our members operate in—facilities, regulatory, quality, suppliers, large and small companies, etc. That type of mosaic construct might be something new. By recognizing these different areas, not only have we drawn our own parameters but also highlighted the playing areas we are comfortable working within.

All for One and One for All

- Input received from 97 total individuals through surveys, focus groups and interviews:
- 38 Affiliate and Chapter Leaders
- 10 knowledge network leaders
- 33 ISPE staff and advisors
- 16 industry thought leaders
- Six individuals representing various stakeholder groups (geographic regions, industry segments) were given draft strategic plan to “pressure test” overall direction.

25th Annual Aseptic Processing Technology Conference

29 February 2016 – 1 March 2016
Crystal Gateway Marriott, Crystal City

The two day conference is filled with track presentations, case studies and group discussions highlighting technological achievements in robotics, dispensing systems, disposables and recently developed best practices.

Each day will kick off with an opening plenary followed by Aseptic and Barrier breakout sessions and concluding with a closing FDA question and answer session.

What's New at **2016** Aseptic Conference?

- Qualification and Validation of Disposables in Production Processes
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- Robotics within Isolators
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FOYA 2015
Facility of the Year Awards

AstraZeneca China: FOYA CATEGORY WINNER FOR PROJECT EXECUTION TAKES TOP PRIZE

Best practice, innovative project management, and detailed planning turned a farmer's field into a fully functional pharmaceutical facility in two years — under budget and ahead of schedule.

When AstraZeneca set out to turn a farmer's field into a fully functional pharmaceutical facility capable of manufacturing five billion tablets of high-quality, affordable medicines within two years, it may have seemed next to impossible.

However, the AstraZeneca China team was up to the challenge. With backing from the company's Board of Director and Senior Management, and an initial budget allocation of US$217 million, the project team used both best-practice and innovative project management techniques to complete the facility 18% under budget, three months ahead of schedule, all while maintaining an exemplary safety record.

"The team worked very hard and very smart from the beginning," said Martin Teo, Project Director, Taizhou Project. "This was a large project, with 80 management, designer and engineering staff in addition to 1,000+ workers on the site. We managed the project and all its resources by developing a one team, one goal approach from Day 1. Throughout the execution, we used planning tools extensively along with innovative supplier procurement and cost saving strategies."

AstraZeneca

ISPE 2015 Facility of the Year Overall Winner

Project: Taizhou Supply Site Project, Phase 1

Location: Taizhou, Jiangsu Province, China

Project Mission:
Deliver a high-volume, cost-effective manufacturing facility to supply 5 billion tablets of modern medicine per year to the China market.

Site area: 90,000 m^2

Floor space: 49,600 m^2

China is recognized as an exciting and challenging market to execute any project. It presents an operating environment that is both new and unpredictable. In launching what, at the time, was the company's largest ever investment in a lesser known but ambitious "third tier" city like Taizhou, AstraZeneca knew the project might face challenges.

"The major contributor to this project's success has been good planning," said Alan Osborne, AstraZeneca's Regional Head of Global Engineering, Asia-Pacific. "Setting up expectations, defining requirements, working through what really could be done and then blending that with the right cultural strategy and a good understanding of the local environment and the people we had here."

Project Overview

The Chinese government's action plan was launched in 2009 to deliver quality and affordable medicines to China's burgeoning population, particularly in less affluent rural areas were the need was largely unmet. Already one of the leading pharmaceutical companies in China with a large portfolio of innovative medicines, AstraZeneca was in good position to meet these needs when, in late 2011, the AstraZeneca Board of Directors and Senior Executive Team approved a five-year investment program to establish a high-throughput, cost-effective site that would support China's health initiative.

Seeing the opportunity to develop a close working relationship with the regional China Food and Drug Administration (CFDA) as well as the commitment of local government, the decision was made to locate the site in China Medical City (CMC), Taizhou, Jiangsu Province. An initial budget of US$217 million was allocated for Phase I of the project to build a site to accommodate formulation, packing, laboratories, warehousing, an administrative wing and site utilities in a 49,600 m^2 facility. AstraZeneca's cardiovascular product Betaloc and its asthma medicine Bambec were to be supplied from Taizhou for this first phase of the project.

One Team. One Goal.

A highly-integrated and multinational team from China, Sweden, Denmark, the UK and the Americas was built. The team included an AstraZeneca engineering team, engineering and construction management consultants, local trade contractors, equipment suppliers and cross-functional AstraZeneca end-users. From the beginning, the AstraZeneca mantra "One Team, One Goal" was embraced.

"Everyone's roles and responsibilities were clearly defined. We made sure everyone knew what they needed to do and how they could contribute to the project. We had clear communications and meeting plans; whether we would meet by teleconference or videoconference or have everyone come to China every two or three months for a face-to-face discussion. It was all in the project plan," said Martin Teo.

Recruiting and retaining a high-performance work crew also played an important role in meeting the project's objectives. In China, employee turnover rates are routinely in the 15-20% range; for this project, the turnover rate was only 6%. "We made sure our people worked in a healthy and safe environment every day and we frequently used small but appropriate recognitions for teams that performed well or reached certain milestones. I think these things helped our people realize that AstraZeneca is a place they wanted to be," said Osborne.

To meet the project's fast-track schedule, Teo and his team used an innovative "Plan-Do-Review" interactive visual planning method throughout the construction stage. The process results in the production of a clear and concise visual tool for the sequencing of project works and their interfaces. For this project, it allowed teams to condense a 3,000 line schedule into one visible board. All contractors were trained on the use of the tool and it was used at each stage of the project.

The detailed planning and visual tools used by the project team helped shortened an already tight project schedule from 23 to 20 month and also resulted in impressive Health & Safety results. Thanks to careful selection of manufacturing partners along with an emphasis on employee training and engagement, the project delivered an outstanding safety performance of zero OSHA (Occupational Safety and Health Association) recordable accidents and only two first-aid incidents in 3.26 million man-hours.

To further reduce lead times and generate cost savings, the project team endeavored to source locally as much as possible. A total of 32 out of 37 manufacturing equipment packages were manufactured locally, including granulators, fluid bed dryers, tablet presses, coaters and blenders. Quality was maintained through an aggressive program of vendor support, including in-factory engineering monitoring and training. Benefits included the anticipated reduction in lead times, proximity to after-sales support and over $10 million in cost savings.

Design and sustainability

Lean design principles were applied throughout the design phase to eliminate operational inefficiencies and deliver optimum manufacturing performance from the start of operation. From design to the first three months of manufacture, overall lead time was reduced by 10%, or one working week though continuous improvement.

In addition, the project focused on having a minimal impact on the environment. Using a novel electro-oxidation process in addition to conventional biological treatment, the AstraZeneca Taizhou facility has achieved over 99% Active Pharmaceutical Ingredient (API) removal rate from API containing waste water. This not only far exceeded local regulations, but also surpassed AstraZeneca's own stringent standards.

With two additional phases expected, the Taizhou site has the potential to expand to nine billion tablets per year, placing AstraZeneca in a position to supply China with affordable, safe, efficacious medicine in support of the government's healthcare reform plans for over 1 billion people.

In addition to the FOYA category award, the Taizhou facility project has received both internal and external recognition, including an "Excellent Site" award from Taizhou City regulators and a "Safe and Orderly Construction Site" award from the Jiangsu provincial government.

FOYA Judges' Panel Conclusion

"This facility was one of the earliest large pharmaceutical facilities developed in partnership with the CFDA and local authorities, to establish the city of Taizhou as a new pharmaceutical hub. Programs including a fully integrated project execution team including all key internal and external stakeholders, and a Plan-to-Do Review process helped drive this project to success."

In Their Own Words

The following is an excerpt from AstraZeneca China's submission, stating the top reasons why their project should win the ISPE 2015 Facility of the Year Award:

Project Execution

We went from 'Farmers Fields to Pharma GMP Sample' in less than two years. The team implemented existing project execution tools into parallel work streams which allowed them to go from farmers' fields to pharma GMP sample in a mere 22 months and to supply medicines to Chinese patients three months early. This would be considered a remarkable feat in the US or Europe. However, given the added complications of construction in China, this was truly a remarkable achievement. The facility was held to the same design and construction standards as every other facility built by AstraZeneca. In addition, the project was delivered 18% under budget with zero OSHA recordable accidents after 3.26 million safe man hours.

We implemented a business first in working with Taizhou authorities for contractor permitting. Close cooperation with the local Taizhou authorities in the early planning phases and then throughout the project allowed us to contract individual construction packages, rather than a main contract as is the standard in China. This gave us greater control over quality and schedule and reduced the construction schedule by four months.

We set a new standard in China for sourcing strategy. Of the 37 manufacturing equipment packages purchased, 32 were manufactured in China, leading to over US$10 million in savings. All packages purchased have been tested and validated and are 100% operational. This was facilitated by an extremely thorough assessment of local suppliers, including ensuring that we procured responsibly and avoided intellectual property infringement. We also invested efforts in improving suppliers' fabrication and mentoring them through the AstraZeneca GMP validation documentation requirements.

Sustainability

We installed an industry first in innovative waste water treatment. Using an innovative electro-oxidation process as a pre-treatment step to treat waste water containing Betaloc, the site is able to convert toxic API into smaller non-toxic molecules. This has exceeded the already stringent AstraZeneca waste water treatment standard and achieved over 99% API removal.

We exploited our automated HVAC system to dramatically reduce energy consumption. In addition to extraordinarily low air change rates, we introduced an automated system that further reduced air changes by 45% during non-operational hours such as nights and weekends, resulting in considerable energy and carbon savings.

Key project participants	
Engineer	NNE Pharmaplan (Tianjin) Co., Ltd. Shanghai Branch Company / Xin Ning (Matthew) Zhang (XNZ)
Construction Manager	Cockram Projects (Shanghai) Construction & Enginering Co.,Ltd / David Mazou
Civil and Structural Contractor 1	Shanghai Yangzijiang Construction (Group) Company Ltd / Zeng Xianfu
Civil and Structural Contractor 2	Jiangsu Huaxin Engineering Project Management Co.,Ltd./ Zhou Ke
Piling Contractor	Jiangsu Province Rock-soil Engineering Ltd / Deng Zhi Song
Interior Decoration Contractor	Shenzhen Overseas Decoration Engineering Co.,Ltd / Dai Bo
HVAC / Cleanroom Contractor	China Electronica System Engineering No.2 Construction Co./ Chen Ming Rong
MEP(MEch&Elec&Plumb) Contractor	Yixing Industrial Equipment Installation Co.,Ltd. / Huang You Kang
Fire Fighting Contractor	China Fire Engineering Co., Ltd / Wang Zhixin
BMS Contractor	Siemens Building Technologies (Tianjin) Ltd / Ye Guo Quan
Security/IT/ISTS System Contractor	Wuxi Anji Electrical Engineering Co.,Ltd / Xin Nuo Ping
AHUs supplier	Shanghai Bennovest Energy Saving Technology Co., Ltd. / Xie Zhiming
Fluid Bed Dryer supplier	GEA PROCESS ENGINEERING CHINA LIMITED / Kathy Lam
Packing Line supplier	MARCHESINI GROUP S.p.A./ Leonardo Ercolani
Tablet Press	FETTE (Nanjing) COMPACTING MACHINERY CO., LTD / Jiang Jiyun
Coater	Zhejiang Xiao Lun Pharmaceutical Machinery Co., Ltd. / Su Changhua
Purified Water System	BWT WATER TECHNOLOGY (SHANGHAI) CO., LTD / Janson zhu
Business Process Management	Tibco Software Ltd.
Software Provider	Susanne Palmehag

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ISPE ANNOUNCES 2015 – 2016 BOARD OF DIRECTORS ELECTION RESULTS

ISPE is pleased to announce the results of its 2015–2016 International Board of Directors election. The Board is responsible for the governance and strategic direction of the Society, and will assume their elected positions at the 2015 ISPE Annual Meeting, 8–11 November in Philadelphia, Pennsylvania, US.

The following pharmaceutical industry leaders have been elected to positions on the 2015–2016 ISPE Board of Directors:

Officers

- Chair: Joseph Famulare, Vice President, Global Quality Compliance and External Collaboration at Genentech/Roche, Pharma Technical Operations
- Vice Chair: Michael A. Arnold, RPh, Business Process Owner for Investigational Products and Senior Director of Strategic Partnerships, Global Clinical Supply Chain, Pfizer
- Treasurer: Timothy P. Howard, CPIP, PE, Vice President of Global Operations, Commissioning Agents, Inc.
- Secretary: James Breen, Jr, PE, Vice President, Worldwide Engineering and Technical Operations, Johnson & Johnson

Directors

Reelected Directors

- Thomas Hartman, Vice President of GMP Operations, Biopharm CMC, GlaxoSmithKline
- Robert (Bob) Matje, PE, CPIP, Vice President of Technical Operations, Qualitest/Endo
- Christopher Reid, CEO, Integrity Solutions Limited
- Fran Zipp (Sakers), President, Lachman Consultant Services, Inc.

New Directors

- Tony (Antonio) Crincoli, PE, Executive Director and Head of Global Engineering Services, Bristol-Myers Squibb
- Antonio (Tony) R. Moreira, PhD, Vice Provost for Academic Affairs at the University of Maryland, Baltimore County (UMBC)

Continuing Board Members

In addition to those named above, the Board will include the following Directors, who were elected in 2014 to a two-year term.

- Joanne R. Barrick, RPh, Advisor in Global Validation Support, Eli Lilly and Company
- Jeffrey A. Biskup, President and CEO, CRB Consulting Engineers, Inc.
- Jennifer Lauria Clark, CPIP, Director, Technical Services, Commissioning Agents, Inc.
- Britt Petty, Director Global Engineering and Facilities, Biogen

The 2014–2015 Board Chair will also continue service on the 2015–2016 Board as Immediate Past Chair:

- Andrew D. Skibo, Head of Global Biologics Operations & Global Engineering, MedImmune/AstraZeneca

Outgoing Board Members

ISPE gratefully acknowledges these outgoing Board members for their years of service:

- Past Chair: Damian J. Greene (Past Chair), Global Network Strategy Lead, Zoetis
- Director: Mark W. Fitch, Consultant

Complete biographical information on all Directors can be found at ISPE's "Meet Your New Board" webpage (www.ispe.org/meet-your-new-board).

ISPE BRAZIL AFFILIATE: STRIVING FOR GROWTH BY MEETING LOCAL NEEDS

The ISPE Brazil Affiliate is a relatively small yet enthusiastic group serving one of the largest pharmaceutical markets in the world. Their mission, as they define it, is to create, develop, and share knowledge related to life sciences. And that mission statement is the common thread in their three-year growth plan.

Founded in 1999, the Brazil Affiliate is a volunteer organization led by an executive board and a board of directors. It currently features 12 technical committees, each focused on one of the Affiliate's core areas of interest and each with its own activities, objectives, and yearly outputs. As its mission statement suggests, the Affiliate's 250-member community represents all aspects of life sciences, from pharmaceuticals, biotechnology, veterinary medicines, and cosmetics to related areas like consulting, project management, equipment, raw materials, and supplies.

"Early on, we had a lot of people from the pharmaceutical industry, but today we have a lot more from the services industry," says Alfonso Izarra, President of the ISPE Brazil Affiliate. "The professional profile of our associates is that 55 to 60 percent are people who used to work in the pharmaceutical industry but are now working for the services industry."

A native of Venezuela, Izarra fits that profile. His 25+-year career features stints at Johnson & Johnson and Pfizer. Izarra, who has worked in Brazil for almost 15 years, is now a consultant for the industry. He joined ISPE in 2009 and served on the Brazil Affiliate's executive board prior to being elected president. He is now in the third year of his term.

According to Izarra, the Brazil Affiliate relies heavily on its 12-person advisory board for guidance. "We understand that the Brazilian pharmaceutical industry is demanding," he says. "That's why the advisory board is so important. It provides us with the insight of what we need to do for the industry."

Activities Concentrated in Two States

Brazil is the largest country in South America and the fifth largest in the world, by both geographical area and population. Its pharmaceutical market, evaluated in an IMS Health report to be the world's sixth largest, has activities concentrated mainly in two states: São Paulo and Rio de Janeiro, which are also the names of the country's two largest cities. The ISPE Brazil Affiliate is a reflection of that, with about 60 to 65 percent of associates from São Paulo, 30 percent from Rio de Janeiro and 5 to 15 percent from other states.

Consequently, most of the Affiliate's activities take place in São Paulo and Rio de Janeiro. When the Affiliate attempts to extend its activities outside of these two states, it is sometimes met with resistance. "We contact people from other states and say we'd like to set up a meeting in, say, Paraná –a smaller southern state—where we could have three or four activities during the year, but they tell us 'No we prefer to come to São Paulo,'" says Izarra with a laugh. "It's a cultural thing; they would rather come to the big city."

Track and Trace

In December 2013, the Brazilian government's health surveillance agency, ANVISA (Agência Nacional de Vigilância Sanitária) adopted a new law that established the rules for implementation of a national system of drug product identification and tracking throughout the pharmaceutical supply chain: track and trace.

According to Izarra, the new law is aimed at ensuring end-user safety by combatting two main issues that currently affect Brazil's pharmaceutical market: counterfeit and stolen medicines. Its main objective is to avoid the use of counterfeit drugs –those that are not legally produced or imported. The second is perhaps more complex. "Sometimes medicines that are in transport are stolen on their way to the final customer and then sold in smaller towns where they don't have inspections or any way of knowing if the drugs are stolen or not," says Izarra. "This law really comes down to final user security."

The law requires that by December 2015—or two years from the effective date—drug manufacturers must provide ANVISA with a set of complete tracking data for three lots of product, including all transactions down to the point of dispensation. Likewise, by December 2016—or three years from the effective date—all drug products must be serialized, tracked, and reported; in addition, all supply chain participants must have the required identification and tracking systems in place.

"ANVISA put a very tight agenda of three years, and the industry was not ready to meet the government's track & trace requirements, especially when you have to set up a centralized database to add all the information from different points of the supply chain," says Izarra. "I would say that that's the main discussion topic for our Brazil Affiliate."

Nonstandard Inspections

A second issue facing the Brazilian pharmaceutical industry is inspections. These are handled by state agencies instead of ANVISA. "But these state agencies don't have enough knowledge to do the inspections," says Izarra. "Some inspectors are quite knowledgeable about certain aspects but lack a more complete understanding of the industry. If they are knowledgeable about one aspect, they'll probably ask a lot of things about that. But if an inspector doesn't have any knowledge about, say, water purification or air-conditioning controls, they will never ask anything about it. So we don't have a standard way to run inspections."

Izarra believes that ISPE can provide an invaluable transfer of knowledge to the state agencies and to ANVISA. "It's part of our

plan for 2016," he says. "We are preparing the plan and the courses that we are going to be able to deliver to them."

Getting Closer to ANVISA

Perhaps the most important pillar in the Brazil Affiliate's three-year plan is its endeavor to build a relationship with ANVISA. The agency, located in the capital, Brasília, has a very bureaucratic contact process. The Affiliate has struggled to build ties with ANVISA because it lacks associates in the capital city who could act as liaisons to the agency. However, Izarra and his team hope to get past that limitation.

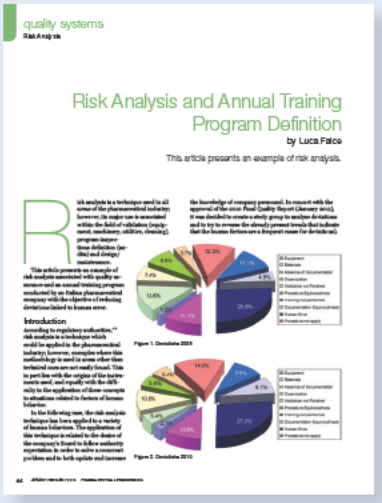
"In ISPE's case, we represent knowledge," says Izarra. "We need to demonstrate to ANVISA that we have the knowledge and experience they need. Part of our 2016 plan is to set up a program with ANVISA in order to pass our knowledge and experience according to ISPE guidelines for good manufacturing practices to them. We want to strengthen our relationship with them to make sure that they will be part of us. We can give them the training that they need, and we can set up the training the way they want, all at no cost for them. "I hope that it will give us a good chance to grow. If we are able to tell people we have ANVISA as a speaker, we will have plenty of people coming into the room."

A Plan for Growth

In discussing the Affiliate's plans for growing its membership, Izarra raises the possibility of learning from other industries. "When I arrived here from Venezuela in 2001, I was looking for people with good project-management knowledge," says Izarra. "It was very hard to get those people, because at that time project-management methodology was not well known here. But then in 2005, the Project Management Institute (PMI) opened in São Paulo and it demonstrated the value of having someone certified at the PMI. Then all the human resources [departments] were asking for candidates with project-management certification and PMP. So a lot of people went out to look for project-management methodology, and they were asking how to get the certification from the PMI; and then suddenly we had 10,000 certified.

"If we at ISPE were able to set up a very simple certification that could be attained after working five years in the pharmaceutical industry in a particular area, and then make the industry aware of that certification, then I think this is a way to grow ISPE, in not only Brazil but perhaps around the world." ◀

ARTICLE OF THE YEAR


quality systems
Risk Analysis

Risk Analysis and Annual Training Program Definition

by Luca Falce

This article presents an example of risk analysis.

Introduction

Congratulations to this year's winner Luca Falce for his article "Risk Analysis and Annual Training Program Definition," *Pharmaceutical Engineering* 35, no. 1 (January/February 2015): 44–52.

ISPE's Roger F. Sherwood Article of the Year Award recognizes an outstanding author contribution to *Pharmaceutical Engineering*. Finalists are chosen from the September/October issue of the previous year through the July/August issue of the current year. Each is evaluated by a panel of volunteer reviewers a variety of criteria, including the importance and timeliness of the subject matter and the quality of the presentation. ◀

ISPE MEMBERS CONTRIBUTE TO SECOND EMA WORKSHOP ON DRUG SHORTAGES

On 9 October 2015, seven ISPE members joined more than 50 health care professionals at the second European Medicines Agency (EMA) workshop on drug shortages. Organized as a follow-up to the inaugural EMA workshop held in November 2013, the gathering was intended to increase awareness and investigate possible causes of shortages in the supply chain. Attendees included industry association and patient group delegates, EMA members, national competent authority (NCA) inspectors, and US Food and Drug Administration regulators, who joined by phone.

Following a preliminary meeting for regulators, the workshop was opened by EMA's Executive Director Guido Rasi, who noted that while drug shortages could be affected by economic, political, and legislative forces, the workshop was intended to focus on the role of manufacturing and quality issues. Brendan Cuddy, EMA head of manufacturing and quality compliance, outlined his hope for continuing discussions of the virtual group[1] and the interassociation task force[2] on implementation progress, as well as a third workshop in two years' time.

Morning Session

PIC/S

Inspectors recommend updating Site Master File guidance through PIC/S to encourage manufacturers to focus on supply chain continuity. Inspectors also proposed that a section on supply continuity be added to PIC/S guidance on quality risk management.[7] A further proposal is to integrate continuity principles into the pharmaceutical quality system by updating Chapter 1 of EudraLex Volume 4: *Good Manufacturing Practice (GMP) Guidelines*—especially the section on product quality review, which makes the vital link between the manufacturer and the marketing authorization holder (MAH).[3]

ICH Q12

The relevance of the ICH Q12[4] guideline was reviewed by David Cockburn, EMA principal administrator. He hoped that Q12 could help reduce shortages by facilitating the benefits and operational flexibility intended by many earlier ICH guidelines, thereby encouraging manufacturers to improve their facilities and processes.

NCA Survey

The workshop also surveyed NCAs on their experiences with notification of shortages. Feedback showed that while 21 authorities require notification, only 10 have definitions of shortages. NCAs are seeking a harmonized, best practice approach to remediation, including common data sets and consistent responses to MAHs.

Drug Shortages Prevention Plan

ISPE Member John Berridge, the interassociation task force moderator, brought attendees up to date with the group's deliverables, including the DSPP.[5]

Drug Shortage Assessment and Prevention Tool

Frances Zipp, a member of the ISPE Board of Directors, introduced ISPE's *Drug Shortage Assessment and Prevention Tool*[6] at the ISPE Annual Meeting, 8–11 November, in Philadelphia, Pennsylvania, US. The tool provides a simple, cost-effective approach for risk assessment and preparedness for prevention or management of supply disruption.

Oher Organizations

The European Federation of Pharmaceutical Industries and Associations described its recommended template for supply disruption notification, and the Parenteral Drug Association reviewed their product-specific approach to shortages.

Afternoon Session

ISPE members contributed to each of the afternoon's four breakout groups.

Group 1 addressed implementation of task force deliverables and their value to inspectors.

A DIFFERENT KIND OF CONTINENTAL PIPELINE

John Bournas (left) met ISPE Canada Affiliate President **Vern Solomon** during the Affiliate's two-day conference in Ottawa, Ontario, Canada. Bournas, who delivered the keynote address to a group of 100 pharmaceutical engineers, facilities experts and vendors, on September 21, emphasized the need for the two organizations to build a stronger pipeline of knowledge and joint activities. ISPE Canada counts close to 400 members. Watch the next issue of *PE magazine* for a profile of ISPE Canada. ◂

Group 2 discussed the need for accepted terminology to aid in measurement of shortages. The group proposed that definitions be established for supply disruptions at the industry level (perhaps focusing on unplanned disruptions) and for shortages at the patient level, which might need to acknowledge time for mitigation.

Group 3 focused on the importance of communication, especially for notification about a disruption. The group encouraged industry to undertake an internal assessment, after which the responsibility for defining criticality and assessing impact would pass to the NCA, in accordance with regulatory procedures. The group expressed hope that a single EU platform for notification could be established, and noted that many different communications should be considered, with varying levels of confidentiality and detail.

Group 4 looked at additional reasons for shortages. Although the workshop scope excluded business and economic contributions, the group examined supply chain elements such as suppliers and wholesalers. A future discussion might focus on applying principles contained in the task force products to these areas, and how product criticality assessment could be propagated through the whole supply chain.

Regulator Survey

Following the public sessions, regulators conducted a closed review of the workshop's recommendations; these will be published at a later date. Workshop presentations will be made available on the EMA website.

Conclusion

The workshop was well received by attendees, who agreed that it made an important contribution to the prevention of drug shortages. A big vote of thanks goes to all the ISPE members who attended and contributed their expertise to the production of ISPE's plans and tools, and to their companies for supporting them.

References

1. A network group of NCA inspectors that meets periodically to discuss shortages.
2. Established following the first EMA workshop to deliver shortage prevention plans and a harmonised notification template. Comprised of ISPE, PDA, European trade association, and PPTA members.
3. European Commission, Directorate General Health and Food Safety. EudraLex Volume 4: Good Manufacturing Practice (GMP) Guidelines. ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm.
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Q12: "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management." www.ich.org/products/guidelines/quality/article/quality-guidelines.html.
5. International Society for Pharmaceutical Engineering. ISPE Drug Shortages Prevention Plan: A Holistic View from Root Cause to Prevention. October 2014. ispe.org/drug-shortages-initiative.
6. International Society for Pharmaceutical Engineering. *ISPE Drug Shortage Assessment and Prevention Tool*. November 2015. www.ispe.org/drug-shortages-initiative/faqs.
7. Pharmaceutical Inspection Co-Operation Scheme. "Quality Risk Management: Implementation of ICH Q9 in the Pharmaceutical Field—An Example of Methodology from PIC/S." www.picscheme.org/pdf/65_psinf012010exampleofqrmimplementation-copy1.pdf

DR. THEODORA KOURTI: SENIOR VICE PRESIDENT GLOBAL REGULATORY AFFAIRS

Dr. Theodora Kourti began her new role as ISPE's Senior Vice President, Global Regulatory Affairs on 5 October 2015. A subject matter expert for FDA and EMA, Dr. Kourti brings technical expertise as well as significant experience with international regulatory agencies.

"We are pleased to have such a high-caliber professional joining the ISPE team. Theodora brings a wealth of technical knowledge and an incredible international reputation from the continuous manufacturing arena," said John Bournas, President and CEO of ISPE. "She will be a critical part of our global regulatory efforts and help us continue the robust and ongoing dialogue ISPE has with the international agencies and national competent authorities," he added.

Before joining ISPE, Dr. Kourti served as senior technical director for GlaxoSmithKline's Global Manufacturing & Supply division at its New Product Introduction Centre of Excellence, where she had significant regulatory interactions with FDA, EMA, Japan, and other markets. She has earned a stellar reputation in the pharmaceutical community for her technical competence, innovation, and ability to explain regulatory requirements within a scientific framework. She has coauthored papers with FDA and EMA, organized and cochaired numerous scientific sessions with FDA and EMA at international pharmaceutical conferences, and has been an invited speaker at many key meetings dealing with leading-edge topics.

"The pharmaceutical industry and the regulatory agencies have a common goal: fast, efficacious and safe delivery of drugs to patients. We live in era where enormous strides are being made by both sides to improve the ways they deliver on this goal," said Dr. Kourti.

"Close collaboration, dialogue, and scientific exchange between industry and the regulatory authorities at the international level facilitate and speed up these efforts and spearhead new initiatives," she continued. "All facets of the pharmaceutical industry, from excipient providers, equipment and instrument suppliers to drug developers and manufacturers have a role to play in achieving this common goal. As Senior Vice President, Global Regulatory Affairs, I intend to work closely with all facets of the industry and the regulatory agencies in these exciting times, and I am looking forward to the challenges ahead."

Dr. Kourti earned her PhD in chemical engineering from McMaster University in Hamilton, Ontario, Canada and a diploma of engineering (chemical) from Aristotle University in Thessaloniki, Greece.

NEW RELEASES

ISPE is pleased to announce that two new guidance documents are scheduled for release: *Sustainability Handbook* (Q4 2015) and *Operations Management Good Practice Guide* (Q1 2016).

Sustainability Handbook

ISPE's first handbook is written to provide information at the front end of projects that will be useful to the project team in understanding sustainability criteria, with examples where considered useful. It is based on the premise that there is a viable path to achieving sustainability that corresponds to all of the precepts of the life sciences industry. This is an especially important ethical consideration for the health care industry, which has a focus centered on maintaining or improving the health of the patient.

Objectives

Key objectives of this handbook are to:

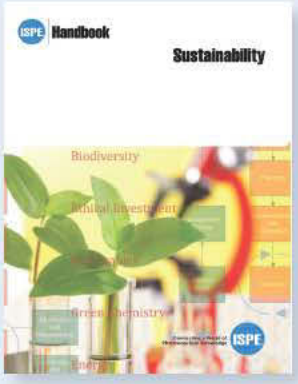
- Provide a reference point for sustainability in the life sciences industry for project teams
- Provide a global pharmaceutical sustainability baseline for the life sciences industry through promotion of the reduction of consumption of finite resources and consideration of the effects of environmental shifts.
- Respect the industry's advanced engineering traditions by providing an informative and easy-to-use document.
- Directions of research for project teams are given in each of the engineering areas from product development through to facility development.
- Provide a route map to understanding the legislative conditions worldwide that either exist at the time of writing or are understood to be in progress.

The *ISPE Sustainability Handbook*, taken with suitably amended Baseline and Good Practice Guides, will help in aiming to provide that opportunity for a sea change toward ensuring an ethically acceptable yet financially viable and secure pharmaceutical industry.

Operations Management

The *Operations Management Good Practice Guide* establishes a framework for all of the major topics in operations management. It's an impressive body of knowledge representing tremendous experience from around the world and throughout the industry; it's intended to promote excellence and integrate the complex body of

SUSTAINABILITY HANDBOOK



Part 1: Principles/Policy

Sustainability in the Context of the Life Sciences Industry
Legislation
Regulation
Sustainability Policy Development
Sustainability Assessment for Buildings and Products
Future Directions and Opportunities
Energy

Part 2: Design/Engineering Application

Process Development and Bulk Drug Products Manufacture
Formulation and Packaged Drug Product Manufacture and Logistics
Pharmaceutical and Biopharmaceutical Manufacturing Supply Chain
Site and Facility Design Considerations
HVAC
Electricity
Utilities
Waste Management

Appendices

Appendix 1: Sustainability Policies, Legislation, and Guidance Net Resources
Appendix 2: Components of a Corporate Sustainability Policy
Appendix 3: Environmental Assessment Methods
Appendix 4: References
Appendix 5: Glossary

knowledge within pharmaceutical operations enterprises and systems.

This Good Practice Guide is the first ISPE document that pulls together topics like facility design, validation, regulatory and quality assurance, goods import/export in a in a ready-to-use "toolbox." This multidisciplinary document provides a 360-degree review of everything involved in the manufacture and supply of life sciences products in pharmaceuticals, biotechnology, and medical devices. It also defines a common language with which to discuss operations management, and introduces lean concepts—a pharmaceutical industry first.

The authors call *Operations Management* a toolbox because it's designed as a reference to help identify appropriate solutions for specific problems, whether readers are addressing issues in manufacturing plants or need guidance in developing a manufacturing strategy or establishing an operational excellence program. Where it doesn't provide an answer, it will help users frame the questions necessary to move their projects forward.

This GPG is designed for pharmaceutical professionals who:

- Are involved in the manufacture and supply of products, irrespective of discipline
- Are in operations management, regardless of seniority,
- Work anywhere in the industry, from management to the shop floor
- Aspire to operational excellence

Objectives

The guide addresses all operations along the supply chain from the selection of raw materials through the distribution of drug products to customers, and ultimately patients. It provides many tools for measurement that will help readers become more effective and efficient. Finally, it provides up-to-date information that supports good practices across the board.

Key concepts include:

- Supply chain strategy and management
- Manufacturing operations strategy and management
- Key performance indicators
- Continuous improvement and innovation
- Lean simulation for continuous improvement, capacity analysis, planning, and scheduling
- Industry benchmarking
- Lean Six Sigma
- Facility/site master planning ◂

OPERATIONS MANAGEMENT

Introduction
Supply Chain Strategy and Management
Manufacturing Operations Strategy and Management
Key Performance Indicators
Continuous Improvement and Innovation
Appendix 1: Case Studies
References
Glossary

THE VALUE OF PROCESS CAPABILITY

Roger Nosal
Vice President of Global Chemistry, Manufacturing and Controls, Pfizer Inc., and Chair of the *Pharmaceutical Engineering* Committee

In July 2015, the US Food and Drug Administration issued its "Draft Guidance for Industry: Request for Quality Metrics. One of the optional metrics proposed in this guidance is a statistical assessment of process capability/performance. In August of the same year a select group of industry thought leaders met in Washington, DC, under ISPE's auspices to consider the intrinsic value of process capability, monitoring, and control as a quality metric.

Process monitoring, control, and capability are useful indicators of process performance. Process capability, in particular—a statistical index of the state of control (or degree of variability) of a given process—may encourage continuous process improvement that could, in many cases, reduce the source of drug shortages. Process capability, however, represents only one measure that may translate to product quality and is not applicable in differentiating process-oriented quality in all cases, especially without therapeutic context and due consideration for other important control criteria.

After sharing respective industry experiences to level-set the intrinsic value of using process capability, the focus group reviewed preliminary outcomes from the ISPE PQLI Process Capability Team and developed the following industry perspective, recommendations, comments, and observations:

- Benefit to patients should be the primary motivation to assess process capability.
- Process capability should be used internally to assess process robustness and enable continuous improvement.
- Computation of process capability may improve an understanding of variability.
- Computation of process capability may enable risk management.
- Process monitoring and control assessments may improve consistency across manufacturing sites.
- Process capability may enable appropriate alignment of control strategy elements.
- A minimum number of manufacturing batches (i.e., 25 lots) are generally necessary for an appropriate statistical measure of process capability.
- Process capability and dissolution can be utilized as predictive performance indicators of product stability, particularly for breakthrough therapies.
- Process capability can be leveraged during development to predict the probability of launch success (i.e., supply chain reliability).
- Process capability may be adopted as an optional part of the annual product quality review as a part of overall quality assessment.
- Statistical models or quantitative measures of performance, like process capability, may be useful for improving manufacturing processes. However, without appropriate expertise or context, these measures may be counterproductive and misleading.
  - Process capability is part of a product's overall quality assessment, and not the sole indicator of quality.
  - Process capability indices are not standardized universal measures of product quality and should not be a reportable quality metric.
    - Process capability, monitoring, and control may be variable across functions.
    - Process capability assessments enable resource capacity prioritization.
    - A low process capability index does not necessarily warrant the adoption of a corrective action and preventive action.
- Process capability in conjunction with comprehensive knowledge of the variance in process control may be used to effectively assess supply reliability.

As quality metrics evolve, the ISPE PQLI Process Capability Team plans to expand engagement and examination of the global process capability concept at conferences and in publications. If you are interested in contributing to this topic, please contact George P. Millili at millili.george@gene.com. ◂

Roger Nosal, on behalf of the ISPE Process Capability Focus Group:

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Philippe Cini, Tunnell Consulting
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Steven Tyler, AbbVie
Roel de Meest, Jansen
Eda Ross Montgomery, Shire

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COMPLIANCE ↑

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Clemens Berger Appointed New CEO of Körber Business Area Pharma Systems

Medipak Systems, 9 October 2015

Clemens Berger comes from Krones AG, one of the worldwide leading providers of machines and complete lines in the area of process, filling, and packaging technology, where he worked for 11 years in several managing positions. He recently headed the Business Line Primary Packaging.

"We are very happy to have found an experienced manager like Clemens Berger with so much know-how in a technology-driven environment for this ambitious role," says Richard Bauer, chairman of the executive board of Körber AG.

The Cell Therapy Catapult Has Appointed M+W Group to Construct its £55-Million Large-Scale GMP Manufacturing Centre in Stevenage, UK

M+W Group, 9 October 2015

M+W Group, whose UK headquarters are in Chippenham, Wiltshire (UK), has been appointed following a comprehensive *Official Journal of the European Union* (OJEU) compliant tendering process. Planning permission was granted by Stevenage Borough Council on 18 August 2015.

The manufacturing centre is scheduled to open in 2017 and will be managed by the Cell Therapy Catapult. It will be used to manufacture products for late-phase clinical trials and commercial supply of advanced therapeutic medicinal products, including cell and gene therapies.

The facility is expected to create up to 150 jobs, and its position on the Stevenage Bioscience Catalyst campus will support SME biotech and life-science companies based in the UK, complement the country's existing capability, and attract additional inward investment from global companies.

GEA Strengthens Pharmaceutical Solids Technology Business

GEA, 8 October 2015

As part of the company's Fit for 2020 project, GEA is introducing a new global group configuration to optimize its organizational structure, reduce current levels of complexity, and maintain a competitive position in an increasingly challenging market environment.

During this transitional phase, the company, one of the largest suppliers of technology for the food sector and a wide range of other process-based industries, remains committed to designing, manufacturing, delivering, and servicing market-leading plant, technology and components for sophisticated production processes, particularly the life-science and pharmaceutical industries.

Vetter Embarks on a €300-Million Investment Strategy for Further Development to Its Manufacturing Sites and to Make Available Additional Manufacturing Capacities

Vetter, 30 September 2015

Vetter has announced that in keeping with its commitment to providing customers with the manufacture of high-quality drug products, the company will invest approximately €300 million to expand and upgrade its manufacturing facilities over an estimated 5-year period. As a leading contract-development and manufacturing organization, Vetter is continuously developing its manufacturing sites and techniques to prepare them for future needs and requirements. The upgrades are being driven by a changing health-care market that is affected by issues such as ever-more-complex molecules, smaller batch sizes, and increasing regulatory requirements.

Karolinska Development Divests Its Holding in XSpray Microparticles to an Investment Consortium Led by Östersjöstiftelsen and Recipharm Venture Fund

Karolinska Development, 29 September 2015

Karolinska Development AB today announces that it divests its entire shareholding in the drug delivery company XSpray Microparticles AB to a consortium led by the Foundation for Baltic and East European Studies (Östersjöstiftelsen) and Recipharm Venture Fund.

Thermo Fisher Scientific Announces Winners of 2016 Winter Conference Awards in Plasma Spectrochemistry

Thermo Fisher Scientific, 21 September 2015

Thermo Fisher Scientific Inc., the world leader in serving science, today announced the winners of the 2016 Winter Conference Awards in Plasma Spectrochemistry. Selected by an independent awards committee, these industry-leading scientists have made noteworthy contributions over time or through a single, significant breakthrough in the field of plasma spectrochemistry. Award winners will be honored during the Winter Plasma Conference in Tucson, Arizona, 11–16 January 2016.

Established in 2009, the biannual Winter Conference Awards in Plasma Spectrochemistry are sponsored by Thermo Fisher and acknowledge achievements in conceptualization and development of innovative instrumentation as well as the elucidation of fundamental events or processes involved in plasma spectrochemistry. The Lifetime Achievement Award is presented to a scientist who has made noteworthy contributions in the field of plasma spectrochemistry. The Young Scientist Award recognizes achievement by a scientist under the age of 45 years. The independent awards committee, comprising scientists from across multiple industries, will award each recipient $5,000.

2016 award winners include:

- Lifetime Achievement Award: Professor Nicolò Omenetto of the University of Florida
- Young Scientist Award: Professor Steven J. Ray, assistant professor at the State University of New York at Buffalo

PureTech Appoints Michael MacLean as Chief Financial Officer

PureTech Health plc, 14 September 2015

PureTech Health plc, a science-driven health-care company seeking to develop disruptive solutions to address unmet medical needs and improve the lives of patients, today announced that Michael MacLean has been appointed to PureTech's management team as chief financial officer and executive vice president. MacLean joins PureTech from Iron Mountain Inc., the Fortune 1000 global storage and information-management company, where he was chief financial officer for its North American business and oversaw $2.2 billion of annual revenue and approximately $1 billion of earnings before interest, taxes, depreciation, and amortization (EBITDA). Previously, MacLean was senior vice president, finance, and chief accounting officer at Biogen, a global biopharmaceutical company with annual revenues of more than $9 billion, during which time he managed many of the finance and accounting functions and was responsible for structuring and managing collaborations and strategic acquisitions. He was also an audit partner at global public accounting firms including KPMG, one of the largest professional-services companies in the world, where he supported global clients in industries including pharmaceuticals, medical devices, and diagnostics.

For the Seventh Year Running, Roche Ranked Most Sustainable Health-Care Company in the Dow Jones Sustainability Indices

Roche, 11 September 2015

For the seventh consecutive year, Roche has been recognized as the group leader in sustainability within the pharmaceuticals, biotechnology, and life-sciences Industry.

"We are very proud of this recognition," said Severin Schwan, CEO. "As an innovator in health care, we consider sustainability as both a responsibility and a value driver. The three elements of sustainability—societal, environmental, and economic—are completely integrated into our business practices and the cornerstone of how Roche does its business."

NewAge Industries Promotes Two Team Members to Executive Director Positions

New Age Industries, 2 September 2015

Tubing manufacturer NewAge Industries announces the promotions of Robert Volk and Michael Allard to newly created positions. Volk is now the company's executive director of operations, and Allard's new position is executive director of sales and marketing. "These moves were made to keep up with the growth of our organization and planning for the future," stated Ken Baker, CEO. "The changes will enhance communication between teams, improve collaboration, and better utilize labor resources across teams."

USP Helps Partners in Lower- and Middle-Income Countries Safeguard the Quality of Medicines through National and Regional Supply Chain Systems

USP, 31 August 2015

The US Pharmacopeial Convention (USP), in its role as a global partner and trusted resource for quality assurance, will work with national governments to secure health supply chain systems and safeguard the quality of medicines and health commodities as part of the Global Health Supply Chain (GHSC) Technical Assistance program, a consortium funded by the United States Agency for International Development (USAID).

Shire Appoints Sara Mathew to Board of Directors

Shire plc, 1 September 2015

Shire plc announces the appointment of Sara Mathew to its board of directors as a non-executive director. Mathew will also be a member of the Audit, Compliance & Risk Committee of the Shire board. Both appointments will be effective as of 1 September 2015.

Mathew previously served as chairman, president and chief executive officer of Dun & Bradstreet, Inc. (D&B), retiring in December 2013. During her 12-year tenure at D&B, she helped drive the transformation of the company from being a data provider to an innovative digital enterprise that leverages big data, insights, and analytics. In 2013, she was named the top value creator in the S&P 500 by Chief Executive magazine.

Before joining D&B, Mathew spent 18 years at Procter & Gamble Company in a variety of global senior finance and management positions, including vice president, finance, in Australia, Asia, and India. She is currently a director of Avon Products, Inc., Campbell Soup Company, and Freddie Mac and a member of the International Advisory Council for Zurich Financial Services Group.

Honeywell to Acquire Elster, a Global Leader in Gas Heating, Controls, Metering, and Advanced Technologies

Honeywell, 28 August 2015

Honeywell today announced that it has signed a definitive agreement to acquire the Elster Division of Melrose Industries plc, a leading provider of thermal gas solutions for commercial, industrial, and residential heating systems and gas, water, and electricity meters, including smart meters and software and data analytics solutions, for approximately $5.1 billion. Elster also manufactures flow computers and regulators for the gas industry. Elster consensus sales for 2015 are estimated to be $1.8 billion. The price translates to approximately 12.6 times Elster's estimated 2015 consensus earnings before interest, taxes, depreciation, and amortization (EBITDA), and the acquisition is anticipated to occur in the first quarter of 2016. The agreement is subject to customary closing conditions, including regulatory review and Melrose shareowner vote. ◂

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ORGANIZATIONS

ASTM

ASTM Proposes to Revise Existing Standard E2968-14 [1]

"WK51471—Standard Guide for Application of Continuous Processing in the Pharmaceutical Industry" is a work item revision to the existing standard E2968-14. It proposes to revise sections 6 and 7 of the standard in order to give additional clarification and alignment with regulatory requirements with regard to the application of various control strategies in continuous manufacturing.

ICH

ICH M4E(R2) Guideline Reaches Step 2b of the ICH Process [2]

The International Conference on Harmonisation (ICH) M4E(R2) Guideline reached Step 2b of the ICH process in August 2015 and is now entering the consultation period (Step 3). Section 2.5.1 on Product Development Rationale and Section 2.5.6 on Benefits and Risks Conclusions of the M4E(R1) Guideline have been revised to include greater specificity with regard to the format and structure of benefit-risk information; the goal was to harmonize the presentation of this information in regulatory submissions to facilitate communication among regulators and industries.

PIC/S

Revision of PIC/S GMP Guide [3]

The PIC/S GMP Guide (PE 009-12) has been revised to incorporate the revised Annex 15 and will enter into force on 1 October 2015. The document can be found at http://www.picscheme.org/bo/commun/upload/document/gmp-guide-pe-009-12-copy1.zip.

USP

USP Helps Partners in Lower- and Middle-Income Countries Safeguard the Quality of Medicines through National and Regional Supply Chain Systems [4]

The United States Pharmacopeial Convention will work with national governments to secure health supply chain systems and safeguard the quality of medicines and health commodities as part of the Global Health Supply Chain (GHSC) Technical Assistance program, a consortium funded by the United States Agency for International Development. USP will support the GHSC Technical Assistance program and its partners by setting up and managing quality-assurance systems, training and building quality-assurance workforces, helping suppliers properly apply standards and other quality-assurance and quality-control tools, building capacity for maintaining product quality during distribution, and raising global awareness about supply chain threats and vulnerabilities.

WHO

European Commission and WHO Europe Scale Up Cooperation [5]

The European Commission (EC) and the World Health Organization's Regional Office for Europe (WHO EURO) are renewing their commitment to work together toward their shared objective of better health in Europe. Health and Food Safety Commissioner Vytenis Andriukaitis and WHO EURO Director, Zsuzsanna Jakab outlined the objectives, principles, and modalities of their continued cooperation to further develop synergies and complementary action. The Commission and WHO EURO have committed to scale up cooperation in the following areas: innovation, health security, health information, health inequalities, health systems, and chronic diseases.

AFRICA

IGAD successfully convenes the First IGAD Regional Medicine Regulatory Authorities Conference on Regulatory Collaboration and Harmonization [6]

The need for sustained collaboration in strengthening the ability of National Medicines Regulatory Authorities (NMRAs) in Africa to ensure timely access to safe, effective, and quality medical products is of paramount importance. In recognizing this need, NMRAs of the Intergovernmental Authority on Development (IGAD) – Djibouti, Ethiopia, Kenya, Somalia, South Sudan, Sudan, and Uganda – held the first IGAD Regional Medicine Regulatory Authorities Conference on Regulatory Collaboration and Harmonization on 3–5 August 2015 in the Ethiopian capital, Addis Ababa.

West African Health Organization makes progress in developing Regional and National GMP Road Map for the ECOWAS Region [7]

Ensuring the safety, quality, and efficacy of medicines is crucial for the public health of the population. This requires that medical products in circulation, including those imported and produced by local pharmaceutical manufacturers, meet high-quality international standards. To this end, the West African Health Organisation (WAHO) recently held two meetings in Ouagadougou, Burkina Faso, to develop a regional and national Good Manufacturing Practice (GMP) road map for the Economic Community of West African States (ECOWAS) region. The first meeting, held 24–25 July 2015, sought to support the progressive transformation of the West African Pharmaceutical Manufacturers Association (WAPMA). The second meeting, held on 26–27 July 2015, was supported by the African Medicines Regulatory Harmonization (AMRH) Programme with the aim of structuring the development of national and regional road maps for GMP in the ECOWAS region.

AUSTRALIA

TGA Participation in the IMDRF Table of Contents (ToC) Pilot [8]

The International Medical Device Regulators Forum (IMDRF) has developed a table of contents (ToC) that is intended to provide a comprehensive submission structure that can be used as a harmonized international electronic submission format for medical device premarket evaluation. The intent is to reduce regional divergence for device submission requirements to reduce burden on industry and also to provide more uniformity in submissions to increase efficiency of assessment bodies when reviewing submitted data.

The Therapeutic Goods Administration (TGA) will participate in the IMDRF pilot to trial the ToC submission format. Industry is invited to submit applications for conformity assessment using the ToC structure for the supporting data. Combination prod-

ucts (devices incorporating a medicine) are out of scope for the IMDRF pilot, however, the TGA will accept such submissions on a regional pilot basis.

ASIA

China

China Food and Drug Administration Publishes "Medical Device Software Technical Review Guidelines"[9]

China Food and Drug Administration has issued *Medical Device Software Registration Technical Review Guidelines*. The document provides guiding principles for medical device manufacturers to submit software registration dossiers while standardizing technical review requirements of medical device software. The guidance applies to medical device software, product registration, and applicable software development methods.

China Aims to Reduce Backlog of Drug Approvals[10]

China has decided to reform its appraisal and approval system for drugs and medical instruments with the aim of improving drug safety and quality and encouraging innovation. According to a guideline issued by the State Council on 18 August, China aims to set up a more scientific and efficient system to ensure the safety and quality of medicines and medical instruments entering the market. The relevant authorities will make efforts to strike a balance between the number of registration applications received and those that are approved by the end of 2016. They will also ensure that by 2018 every application will be approved or rejected within a certain time limit.

CFDA Issues Announcement on Starting Using the New Version of Drug Manufacturing Certificate and Pharmaceutical Preparation Certificate for Medical Institution 09 September 2015[11]

On 9 September 2015, the China Food and Drug Administration (CFDA) issued an announcement stating that it will start using the new version of the Drug Manufacturing Certificate and Pharmaceutical Preparation Certificate for Medical Institution from 1 January 2016.

India

India Issues Strengthening of State Drug Regulatory System Memorandum of Understanding (MoU)[12]

The pharmaceutical industry is one of the most vibrant sectors of the Indian economy and has been growing at the rate of 10 to 12 percent per annum. It is the third largest in the world by volume and 10th by value. The total size of the Indian pharma-

ceutical industry is about Rs.2 lakh crore ($30 billion) out of which exports account for nearly 55 percent. To ensure the quality, safety, and efficacy of medicines both for domestic use and export, the state regulatory system will be strengthened.

The major concerns relating to state drug regulatory systems are:

- Inadequate or weak drug control infrastructure at the state level
- Inadequate drug-testing facilities
- Non-uniformity in the enforcement of law and rules
- Lack of training of regulatory officials
- Lack of database
- Inadequate IT services

There is a need for the systematic collection and testing of a sufficient number of samples in laboratories. The laboratories in states are, therefore, required to be strengthened. The capacity and the strength of the technical manpower also need to be augmented. It is proposed to achieve an optimum system of regulation ensuring uniform enforcement of the laws across the country through a strengthened drug regulatory mechanism.

Japan

International Pharmaceutical Regulatory Harmonization Strategy – Regulatory Science Initiative [13]

Japan's Ministry of Health, Labour, and Welfare (MHLW) has formed the International Pharmaceutical Regulatory Harmonization Strategy – Regulatory Science Initiative. This strategy clarifies the country's medium- to long-term vision and policy priorities in the sectors of pharmaceuticals, medical devices, etc., in order to more effectively promote initiatives for international harmonization and cooperation under the direction of the MHLW.

The strategy aims to demonstrate Japan's proactive leadership in Asia and other regions across the global community. It includes policies such as establishing the Asian Pharmaceuticals and Medical Devices Regulatory Training Center within the Pharmaceuticals and Medical Devices Agency (PMDA) to promote understanding of pharmaceutical regulations in Japan by regulatory authority officials in Asia. In addition, Japan will construct the global action frameworks of the MHLW and PMDA and conduct periodic progress control and necessary reviews of this strategy to promote the initiatives in an ongoing and consistent manner.

PMDA Releases International Strategic Plan 2015 [14]

The Pharmaceuticals and Medical Devices Agency (PMDA) has succeeded in shortening the review period for medical products to the world's top standard through its first and second midterm plan periods (FY 2004 to 2013). Going forward, in order to respond to the domestic and global expectations, the PMDA has developed and announced its strategic plan titled "PMDA International Strategic 5."

Below are the key international actions set forth in the PMDA International Strategic Plan 2015:

- Establish the Regulatory Science Center for conducting first-in-the-world product reviews, implementing safety measures, and undertaking other activities, as well as publishing the outcomes.
- Launch the Asian Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs to share the PMDA's accumulated knowledge and experience in product reviews, implementation of safety measures, and provision of relief services with Asian and overseas regulatory authorities.
- Cooperate with overseas regulatory authorities for the expansion of harmonization activities (such as the ICH and the IMDRF) and work-sharing (such as GMP/QMS inspections).

EUROPE

European Union

Comments Sought on Addendum to Guideline for Good Clinical Practice E6(R2) [15]

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. This guideline has been amended to encourage the implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human-subject protection and data integrity. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated. This guideline addendum provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. Stakeholders are invited to send their comments using the template provided by 3 February 2016. The completed template should be sent to ich@ema.europa.eu.

EMA's Medical Literature Monitoring Enters into Full Operation [16]

The European Medicines Agency (EMA) started its full medical literature monitoring service on 1 September 2015. A total of 400 active-substance groups (300 chemical active-substance groups and 100 herbal active-substance groups) will now be monitored by the EMA. The service will benefit over 4,000 companies. The list of active-substance groups and a reference to the journals covered by the EMA's medical literature monitoring service are available on the "monitoring of medical literature" page. Companies are advised to consult the list to check whether their products are covered by the service.

Making IT Services for Medicine Regulation in Europe More Efficient [17]

The European Medicines Agency (EMA) Management Board endorsed the European Union (EU) Telematics Strategy and Implementation Roadmap 2015–2017 on 6 August 2015 that had already been adopted by the Heads of Medicines Agencies in July 2015. The road map provides a concrete outline of the EU Telematics strategy and its implementation from 2015 to 2017 describing how specific projects will address the information-technology (IT) needs arising from European pharmaceutical policy and legislation.

The work of the EU medicines regulatory system in promoting and protecting public health is underpinned by common IT services, which are put in place and maintained by EU Telematics. EU Telematics facilitates efficient and effective coordination and exchange of information on medicines between the EMA, the European Commission and the national competent authorities for medicines regulation in the EU.

Four New Public Consultations Concerning Good Manufacturing Practices and Clinical Trials for Human Medicinal Products are Opened 28 August 2015 with Closing Date 24 November 2015 [18]

They are:

1. Commission Delegated Act on principles and guidelines on Good Manufacturing Practices for investigational medicinal products for human use and inspection procedures
2. Detailed Commission guidelines on Good Manufacturing Practices for investigational medicinal products
3. Commission Implementing Act on principles and guidelines on Good Manufacturing Practices for medicinal products for human use
4. Detailed arrangement for clinical-trial inspection procedures, including the qualifications and training requirements for inspectors

Consultation on EU GMP Guidelines, Revised Annex 17 on the Real Time Release Testing [19]

DG SANTE launched a consultation on the revision of Annex 17: Real Time Release Testing. Stakeholders and other interested parties are invited to comment on this document, which can be found at http://ec.europa.eu/health/human-use/quality/pc_quality/consultation_document_annex_17.pdf. Comments should be sent at the latest by 11 December 2015 by email to: sante-pharmaceuticals-D6@ec.europa.eu and ADM-GMDP@ema.europa.eu.

EMA Releases New Guidance to Speed Up Development of Antibiotics [20]

The European Medicines Agency (EMA) has released a draft guideline for public consultation on the use of pharmacokinetics and pharmacodynamics analyses in the development of antibiotics. The document provides guidance for the conduct of robust analyses to facilitate and speed up the development of new antibiotics, in particular those targeting multidrug-resistant bacteria. Comments on this draft guideline should be sent to IDWPsecretariat@ema.europa.eu no later than 31 March 2016.

CHMP Chair Reelected [21]

The Committee for Medicinal Products for Human Use (CHMP) reelected Dr. Tomas Salmonson as its chair at its September 2015 meeting. Salmonson will serve a second three-year term beginning this month. He is Senior Scientific Advisor at the Swedish Medical Products Agency, where he has worked since 1986. He has been a member of the CHMP for more than 15 years and served as Chair of the committee since September 2012.

50 Years of EU Pharmaceutical Legislation [22]

2015 marks the fiftieth anniversary of the adoption of the first law on the authorization of pharmaceuticals at EU level, which set the basis for some of the key principles that are still valid today.

Much of the impetus behind the adoption of the first law on pharmaceuticals at EU level stemmed from the determination to prevent a recurrence of the thalidomide disaster of the late 1950s and early 1960s, when thousands of babies were born with limb deformities as a result of their mothers taking thalidomide as a sedative during pregnancy. This experience, which shook public health authorities and the general public, made it clear that to safeguard public health, no medicinal product must ever again be marketed without prior authorization. Over the past 50 years, a large body of legislation has been developed around this principle, with the progressive harmonization of requirements for the granting of marketing authorizations and post-marketing monitoring implemented across the entire EU.

Belgium

FAMHP Publishes Annual Report 2014 [23]

The Federal Agency for Medicines and Health Products (FAMHP) released its annual report *Transparent Communication*, which outlines the most important statistics and core activities of the agency for 2014. The charts and data tables offer a clear illustration of the tasks and the results achieved. In addition to the traditional annual report, the FAMHP has elected to publish the most notable facts, realizations, and stories in the newspaper *FAMHP Times*.

The annual report and newspaper can be found at http://www.fagg-afmps.be/en/Publications/Publications.jsp.

Croatia

Republic of Croatia Signed the MEDICRIME Convention [24]

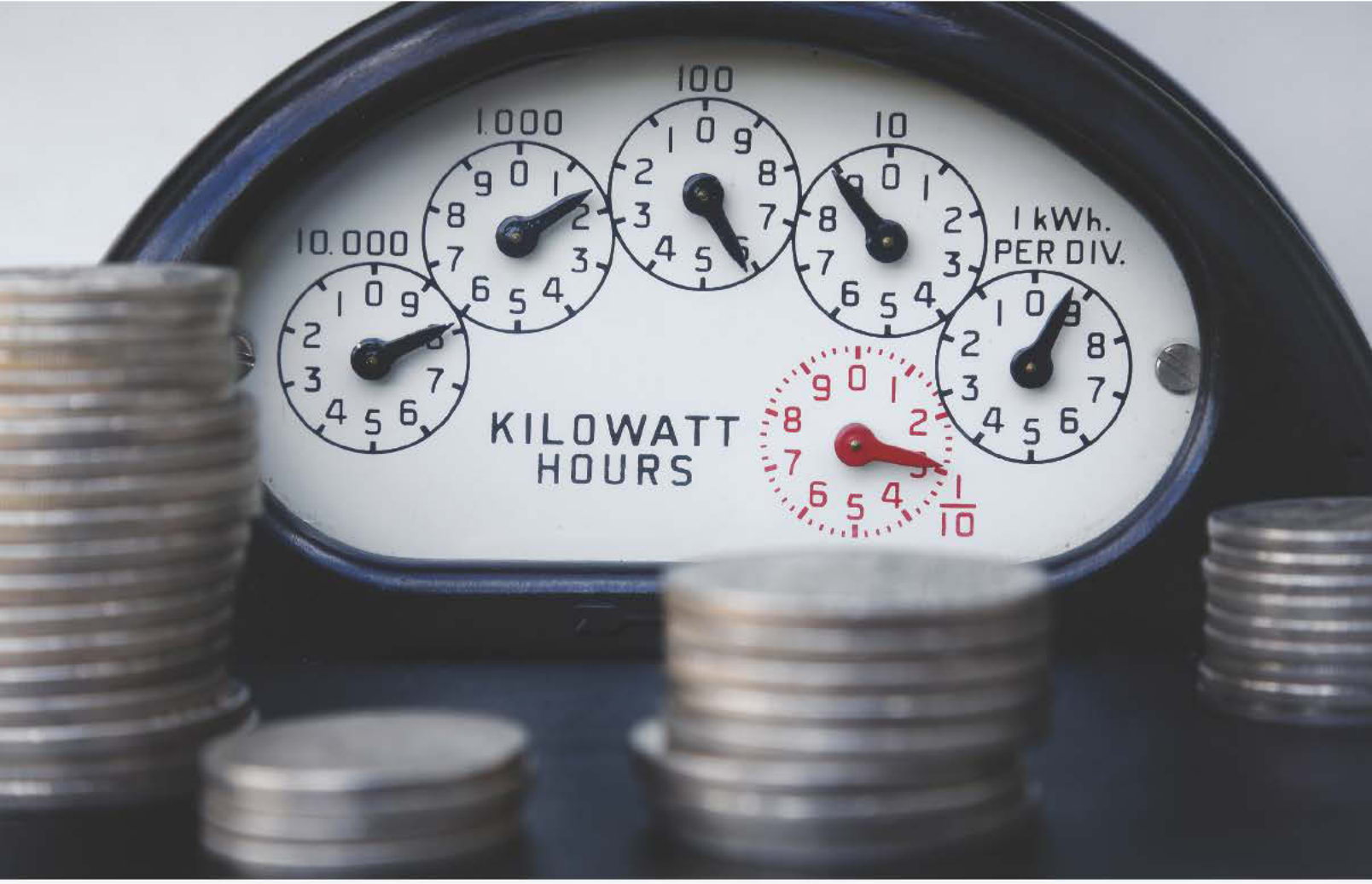
On 3 September 2015, the Republic of Croatia signed the MEDICRIME Convention that, for the first time at the international level, defines the counterfeiting of medicinal products and medical devices, as well as their manufacturing and placing on the market without marketing authorization or compliance with safety requirements, as a pharmaceutical crime.

Denmark

Danish Medicines Agency to be Reestablished as an Independent Agency [25]

At the turn of the year 2015/2016, the Danish Health and Medicines Authority will be split into four agencies:

- Health agency: will be dedicated to disease prevention, health planning, and radiation protection.
- Medicines agency: will focus on clinical-trial authorizations and the marketing of new medicines in Denmark.
- Patient-safety agency: will handle the supervision and registration of healthcare professionals and deal with complaints.
- Health-data agency: will make health data available to researchers and authorities and strengthen the overall digitization development in the healthcare system.



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Finland

Changes in the Reporting of Medicine Shortages [26]

Fimea, the Finnish Medicines Agency, has introduced a form that holders of medicine marketing authorizations or their representatives should use to report any problems with the availability of medicines. The form should be sent by email to Fimea's registry office at registry@fimea.fi.

Fimea requires marketing authorization holders or their representatives to inform it of any actions they will take with regard to supply problems involving medicinal products intended for human use and the grounds for such actions. If the actions are based on adverse effects, efficacy, a negative risk to benefit ratio, or problems with drug safety, the European Medicines Agency (EMA) must also be notified. A link to forms on the EMA website is provided on Fimea's reporting form.

Fimea Issues Guidelines Applicable in Finland Regarding the Advertising of Medicines under Additional Monitoring [27]

Fimea, the Finnish Medicines Agency, is issuing more detailed guidelines regarding the color, size, and location of the inverted black triangle and the standardized explanatory sentence for the advertising of medicinal products under additional monitoring. The guidelines apply to all marketing authorization holders and interest groups involved in the marketing of medicinal products.

Ireland

Health Products Regulatory Authority Publishes 2014 Annual Report [28]

Ireland's Health Products Regulatory Authority (HPRA) published its annual report of key activities and performance highlights for 2014. The report, which is the first to feature the organization's new name and brand identity, highlights a year of significant activity for the national regulator of health products. There was a continued focus on tackling the issue of falsified and illegal prescription medicines as well as on drawing attention to the associated dangers. The list of interchangeable medicines, which facilitates generic substitution by pharmacists and is linked to the HSE's reference pricing system, was significantly expanded during the year.

United Kingdom

MHRA Publishes Third Installment of Blog on Good Manufacturing Practice Data Integrity [29]

The Medicines & Healthcare products Regulatory Agency (MHRA) published the last in a series of three blogs exploring the impact of organizational behavior and procedures on reliable, consistent, and accurate data in medicines manufacture. The first blog looked at the impact of organizational behavior, and the second blog discussed ways in which systems can be designed to ensure data quality and integrity.

The final blog in this series looks at the recurring problem of "trial analysis" and ways in which organizations within the supply chain can take steps to build confidence and reliance on one another's data. It can be found at https://mhrainspectorate.blog.gov.uk/2015/08/27/good-manufacturing-practice-gmp-data-integrity-a-new-look-at-an-old-topic-part-3/.

MHRA Support for Innovation – Inspectorate Input to Case Studies [30]

The Medicines & Healthcare products Regulatory Agency (MHRA) has published seven case studies highlighting the work of its Innovation Office and showing how it helps organizations that are developing innovative medicines or medical devices or using novel manufacturing processes to effectively navigate regulatory processes so they can progress their products or technologies.

British Pharmacopoeia Launches New Website [31]

A new British Pharmacopoeia (BP) website has been launched, bringing together the online BP publication the British Pharmacopoeia Chemical Reference Substances (BPCRS), catalog, and sales, making it easier for users to find what they need quickly and easily. It is smartphone and tablet compatible, making it easier to use at any location.

Risk-Based GLP Quality Assurance Programme [32]

The UK Good Laboratory Practice (GLP) Monitoring Authority's (UK GLPMA) guidance on the implementation and maintenance of a risk-based GLP quality assurance (QA) program has been published. The GLPMA has, for some time, recognized that there was a need to provide guidance to GLP facilities that would allow them to utilize modern quality risk assessment techniques in support of the conduct of GLP studies. This has become particularly apparent for those facilities engaged in activities that require compliance with other quality systems in addition to GLP, such as Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). Having a risk-based GLP QA program should offer facilities the flexibility to focus their resources in areas that present the biggest risk to their compliance status.

NORTH AMERICA

Canada

Updates to Drug Establishment Licence Applications and Good Manufacturing Practice Evidence Requirements for Active Pharmaceutical Ingredients [33]

Canada's Food and Drug Regulations were amended to extend the requirements of Division 1A – Establishment Licensing and Division 2 – Good Manufacturing Practices (GMP) to active ingredients used in pharmaceutical drugs for human use only. As stated in the Regulatory Impact Analysis Statement accompanying the Regulations Amending the Food and Drug Regulations (1475 – Good Manufacturing Practices) and published in the *Canada Gazette, Part II*, on 25 April 2013, the Active Pharmaceutical Ingredients (API) program will be implemented over a three-year period. Therefore, aligned with the stated timeline, 8 November 2016 will mark the full implementation of the regulations.

Updates to the Guidance Document Labelling of Pharmaceutical Drugs for Human Use [34]

On 19 June 2013, Health Canada published in the Canada Gazette, Part II, amendments to the Food and Drug Regulations. "The Regulations Amending Cer-

tain Regulations Concerning Prescription Drugs (Repeal of Schedule F to the Food and Drug Regulations)" provided for the repeal of Schedule F and incorporation by reference of a list of prescription drugs. This regulatory amendment came into effect on 19 December 2013.

In addition, on 2 July 2014, Health Canada published in the Canada Gazette, Part II, other amendments to the Food and Drug Regulations. The "Regulations Amending the Food and Drug Regulations (Labelling, Packaging, and Brand Names of Drugs for Human Use)" introduced targeted amendments to emphasize the importance of plain-language labeling. These regulatory amendments came into force on 13 June 2015 for prescription products and products that are administered or obtained through a health professional.

Accordingly, the Guidance Document: Labelling of Pharmaceutical Drugs for Human Use has been updated. The document change log has been revised to reflect these changes and other minor revisions.

Labelling Changes for Certain Homeopathic Products [35]

Canada took additional steps to protect and ensure the safety of Canadian children by introducing changes for certain homeopathic products that fall under the Natural Health Product Regulations. Many Canadians choose to purchase natural health products, including homeopathic products, to maintain and improve their health. The government of Canada is committed to ensuring that they continue to have access to a wide variety of these products; however, current package labeling for some homeopathic products may not be adequate for Canadians to make informed choices. The changes apply to the labeling of some homeopathic products, specifically nosode products as well as homeopathic cough, cold, and flu products for children 12 and under.

United States

Upgraded Drug Shortages App for Android Devices Adds Alert Feature [36]

The US Food and Drug Administration (FDA) launched the Drug Shortages 2 mobile application for Android devices. The upgrade will enable users to receive notifications when the agency adds or updates shortage information about a drug product or about a drug within selected therapeutic categories. This update adds a feature requested by many health-care professionals. Notifications for the iOS version of the mobile app are under development and will be available soon. The app for Apple devices is available for free download via iTunes.

Drug Shortages 2 for Android devices is available for free download via Google Play. First launched 4 March 2015, the app identifies current drug shortages, resolved shortages and discontinuations of drug products. The agency developed the drug shortages app to improve access to information about drug shortages, as part of the FDA's efforts outlined in the Strategic Plan for Preventing and Mitigating Drug Shortages.

Rare Diseases: Common Issues in Drug Development Guidance for Industry [37]

This new guidance assists sponsors of drug and biological products intended to treat or prevent rare diseases in conducting more efficient and successful development programs through a discussion of selected issues commonly encountered in rare-disease drug development. Although similar issues are encountered in other drug development programs, they are frequently more difficult to address in the context of a rare disease with which there is often little medical experience. These issues are also more acute with increasing rarity of the disorder. A rare disease is defined by the Orphan Drug Act of 1983 as a disorder or condition that affects fewer than 200,000 persons in the United States. Most rare diseases, however, affect far fewer persons.

Nonproprietary Naming of Biological Product [38]

The US Food and Drug Administration (FDA) has released a draft guidance that details the FDA's proposal on the nonproprietary naming of biological products. This draft guidance describes the FDA's current thinking on the need for biological products licensed under the Public Health Service Act to bear a nonproprietary name that includes an FDA-designated suffix. The current thinking is that shared nonproprietary names are not appropriate for all biological products. There is a need to clearly identify biological products to improve pharmacovigilance and, for the purposes of safe use, clearly differentiate among biological products that have not been determined interchangeable.

Accordingly, the FDA intends to designate a nonproprietary name for biological products that includes a suffix composed of four lowercase letters. Each suffix will be incorporated into the product's nonproprietary name. This naming convention is applicable to biological products previously licensed and newly licensed under the PHS Act. The nonproprietary name designated for originator biological products, related biological products, and biosimilars will include a unique suffix. However, the FDA is considering whether the nonproprietary name for an interchangeable product should include a unique suffix or share the same suffix as its reference product. The FDA invites comments on the draft guidance and on ways to improve active pharmacovigilance systems for the purposes of monitoring the safety of biological products.

The FDA is also issuing a proposed rule to designate nonproprietary names that contain a suffix for six previously licensed biological products. Each of the six products is either a reference product for an approved or publicly disclosed biosimilar product application or a biological product that is either biosimilar to or related to one of these reference products.

Guidance for Industry Two-Phased Chemistry, Manufacturing, and Controls (CMC) Technical Section [39]

This guidance provides recommendations to sponsors submitting chemistry, manufacturing, and controls (CMC) data submissions. For review efficiency, the Center for Veterinary Medicine prefers that CMC information be submitted in a single technical section. However, there may be instances when a two-phased technical submission process is more beneficial to improve the overall time to drug approval. Sponsors may submit the phased CMC technical section as a single technical section or a two-phased technical section.

This guidance describes the use of the two-phased technical section submission process.

The FDA Announces First-Ever Patient Engagement Advisory Committee[40]

The US Food and Drug Administration (FDA) announced its first-ever Patient Engagement Advisory Committee (PEAC). This body will provide advice to the FDA commissioner on a range of complex issues relating to medical devices and their regulation and use by patients. It will give the FDA the opportunity to obtain expertise on various patient-related topics, with the goal of improving the communication of benefits and risks and increasing the integration of patient perspectives into the regulatory process. Some questions that the PEAC may discuss include where and how to best engage patients across the device development and assessment life cycle as well as how the FDA and sponsors should communicate patient preference information to patients. The PEAC represents a new and exciting opportunity to foster patient partnerships with the FDA, and it complements other efforts at the FDA to bring the patient into the medical device regulatory process. This includes studies to evaluate patient preferences in medical devices and a recently published draft guidance on patient preference information for PMAs, HDE applications, de *novo* requests, and inclusion in device labeling that describes how patient tolerance for risk and perspective on benefit, in addition to clinical data and other information, may be considered in the FDA's assessment of the benefit-risk profile of certain devices.

FDA Publishes Progress Report[41]

The US Food and Drug Administration (FDA) released a progress report entitled FDA Science Moving Forward that highlights advances the FDA has made since the Science Board's 2007 report *FDA Science and Mission at Risk*. As the report illustrates, FDA regulatory science programs have made dramatic advances over the past eight years. These advances are critical because regulatory science underpins virtually every decision made at the FDA.

FDA Names Director of OPQ[42]

Michael Kopcha, PhD, RPh, a globally recognized expert in product innovation and development, has been selected as the permanent director of the Office of Pharmaceutical Quality (OPQ). He will join the agency's Center for Drug Evaluation and Research in November, pending ethics clearance. OPQ—with close to 1,000 employees—was stood up in January 2015 to carry out new processes and policies to provide better alignment among review, inspection, and research functions. Mike recently served as vice president and global

research and development franchise head for cough, cold, and respiratory products at Novartis Consumer Health, Inc. in New Jersey.

SOUTH AMERICA

Argentina

ANMAT and CONICET Sign Agreement for Mutual Technology Consulting[43]

On 29 September 2015, the National Administration for Medicines, Foods and Medical Devices (ANMAT) signed an agreement with the Council on National Scientific and Technical Research (CONICET) in order to coordinate activities of mutual advice in science and technology. In recent months, the federal government has initiated the restructuring of areas dedicated to the evaluation, control, and product research of biological, biotechnological, and radiopharmaceutical products. Interested in establishing highly complex laboratories that address the challenges of the new control products and technologies, it requires professionals dedicated to the study and understanding of the developments in the area of biotechnology. In this regard, the agreement on scientific and technical cooperation with CONICET will allow ANMAT to intensify the training of professionals and receive advice on specific topics such as advanced therapies, bioinformatics, and the characterization of biomolecules. ◂

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GMP OR NON-GMP WASHERS AND STERILIZERS: HOW TO CHOOSE

Marcel Dion and Matt Hofacre

This article presents the standards and guidelines typically used by manufacturers to design and build GMP washers and sterilizers. It describes the characteristics that differentiate GMP from regular laboratory equipment.

Automated washing systems and steam sterilizers (autoclaves) are often used in research and drug-manufacturing facilities to clean and sterilize a variety of items. Washers use water, cleaning agents, and mechanical action to remove residues from soiled laboratory and manufacturing-component surfaces. Sterilizers use steam to deactivate biological waste, sterilize cleaned laboratory and drug-manufacturing components, or terminally sterilize drug products.

Since a wide range of washers and sterilizers designed for various applications is available on the market today, the following questions are often raised:

- What is a GMP washer?
- How do you describe a GMP sterilizer?
- Why are GMP washers and sterilizers so much more expensive than laboratory units?
- What are the most significant differences between the two types of equipment?
- Why does it take more time to procure a GMP unit?
- When do I need to consider a GMP system instead of a non-GMP system?
- Can I turn my existing regular equipment into a GMP system?

These are all good questions!

What Are GMPs?

GMP stands for "good manufacturing practice," a standard that is observed in regulated pharmaceutical-manufacturing facilities. GMP is also often used, rightly or wrongly, as a qualifier when describing pieces of equipment, such as the washers and steam sterilizers that are used in these facilities.

This article highlights the standards and guidelines typically used by manufacturers to design and build GMP washers and sterilizers. It describes the characteristics that differentiate GMP from regular laboratory equipment. Finally, a side-by-side comparison summarizes the main differences between the two types of equipment and describes typical applications for each.

cGMP

The US Food and Drug Administration (FDA) ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its current Good Manufacturing Practice (cGMP) regulations. These contain the minimum requirements for the methods, facilities, and controls used in the manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use and that it has the ingredients and strength it claims to have.[1]

One can see that the word "manufacturing" in GMP actually refers to the production of food, drug products, and active pharmaceutical products; it does not refer to equipment. So, the term "GMP washers and sterilizers" could be somewhat misleading. "Pharmaceutical-grade washers and sterilizers" is perhaps a more appropriate term, so it will be used throughout the rest of this article.

GMPs for pharmaceutical-grade washers and sterilizers

FDA cGMP regulations for finished pharmaceuticals are provided in the Code of Federal Regulations (CFR), Title 21, parts 210[2] and 211.[3] Unfortunately, the regulations provide limited information concerning the way equipment used for this application should be designed and manufactured. However, four sections in subpart D of Part 211 do refer specifically to equipment:

Section 211.63—Equipment design, size, and location: "Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance."

Section 211.65—Equipment construction: "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."

Section 211.67—Equipment cleaning and maintenance: This section covers mostly maintenance aspects, and does not provide much information concerning the design of the equipment itself.

Section 211.68—Automatic, mechanical, and electronic equipment: "Equipment used in the manufacture, processing, packing, or holding of a drug product shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained."

In short, the FDA regulations provide general guidelines and few specific details related to the design and manufacture of equipment for the pharmaceutical industry. Therefore, manufacturers of such equipment must rely on other standards and guidelines, such as the American Society of Mechanical Engineers Bioprocessing Equipment (ASME-BPE) standard and the International Society for Pharmaceutical Engineering (ISPE) good automated manufacturing practice (GAMP®) guidelines.

The BPE standard is intended for design, materials, construction, inspection, and testing of vessels, piping, and related accessories—such as pumps, valves, and fittings—for use in the biopharmaceutical industry.[5] *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, published by ISPE, provides guidance on achieving compliant computerized systems that are fit for intended use in an efficient and effective manner.[10]

Other health care sterilization references, such as British Standard EN285,[11] UK Department of Health HTM 2010[12] (now CFPP 01-01),[13] and ISO 17665,[14] are also commonly applied in pharmaceutical applications. These standards do contain some basic information on machine construction, performance, and testing requirements. Many pharmaceutical-grade units comply with elements of these standards.

Pharmaceutical Grade vs. Laboratory

The characteristics can be grouped into five categories:

- Manufacturer's quality assurance program
- Mechanical design
- Process monitoring
- Control and software system
- Design, manufacturing, and qualification documentation

Manufacturer's quality assurance program

The ASME-BPE standard indicates that "the manufacturer shall implement a quality assurance program describing the systems, methods, and procedures used to control materials, drawings, specifications, fabrication, assembly techniques, and examination/inspection used in the manufacturing of bioprocessing equipment."[6] A third-party certification such as ISO 9001[15] is generally well accepted and recognized; in some cases, however, users prefer to conduct an audit of the supplier. Such a certification is not necessarily required for regular non-GMP applications.

Mechanical design

The ASME-BPE 2014 Part System Design (SD) provides methods and guidelines to create a design framework, using proven practices for supporting efficient cleanability and bioburden control in bioprocessing systems.[7] The overall objective is to prevent contamination of drug products due to inadequate cleaning or sterilization of surfaces that come in contact with the products during their manufacturing process. While it would be challenging to attempt to summarize the entire content of ASME-BPE in this article, some sections that relate directly to the design of washing and sterilization systems used in GMP facilities can be highlighted: SD-2.4—Fabrication: "Fabrication shall be performed in facilities where the product contact surfaces are protected from contamination."

SD-2.4.1.1—Material of construction: "Generally, materials such as 316 and 316L, stainless steel, duplex stainless steels, and higher alloys have proven to be acceptable. … When nonmetallic materials are used (e.g., polymeric materials or adhesives), the owner/user shall specify which one of these materials shall carry a Certificate of Compliance. The conformance of material shall be explicitly stated (e.g., conforming to FDA 21 CFR 177 and USP Section <88> Class VI)."

Parts MM and PM provide additional guidelines for the selection of metallic and nonmetallic materials.

SD-2.4.2—Cleanability: This section describes how equipment should be designed so that all surfaces are cleanable: "Surface imperfections (e.g., crevices, gouges, obvious pits) shall be eliminated whenever feasible, horizontal product contact surfaces shall be minimized, the equipment shall be drainable and free of areas where liquids may be retained and where soil or contaminants could collect, and areas of low flow and low velocity or impact where soil or contaminants could collect. Fasteners or threads shall not be exposed to the process, steam, or cleaning fluids. Design of corners and radius shall have the maximum radius possible for ease of cleanability (minimum 3.2 mm)." (See Figure 1.)

SD-2.4.3—Drainability: "For sterility and cleaning, gravity is an effective way to facilitate drainage. To achieve gravity drainage, lines should be pitched to designated points at a specific slope." The recommended slope varies between 0.5% and 2%, depending on the application (Figure 2).

SD-3—Process components: This section describes how piping, connections, and fittings should be designed to be hygienic.

Figure 1 Pharmaceutical-grade washer chamber with large radius, round corners

The number of connections should be minimized; hygienic fittings should be used since threaded fittings are not recommended. Dead legs should ideally have a length/diameter ratio of less than 2 where possible. Stainless steel surfaces should be passivated, the use of blind welds should be avoided, and the design of pumps and associated connections should be hygienic (Figure 3).

Part SF—Surface finish: "Product contact surface requirements shall apply to all accessible and inaccessible areas of the systems that directly or indirectly come in contact with the designated product." These requirements may vary from one application to another, but typically, for pharmaceutical-grade washers and sterilizers, the acceptable range varies between 20 and 30 µin Ra (0.51 and 0.76 µm).

Part MJ—Material joining: This part provides specific requirements for the joining (welding) of metallic materials. In general, welds in pharmaceutical-grade washers and sterilizers are expected to be "hygienic."

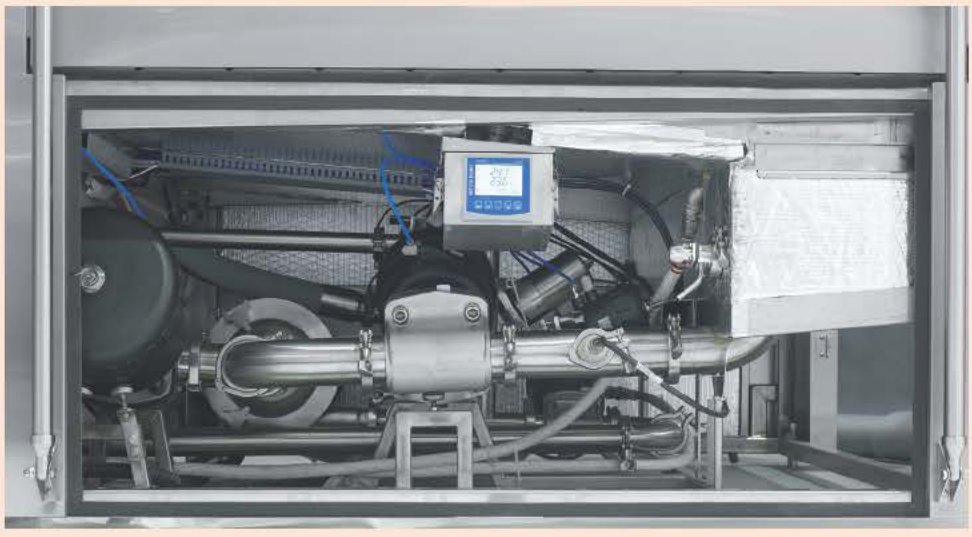
Part PI—Process instrumentation: This section is dedicated to the definition of minimum requirements for process instrumentation in hygienic applications. In practice, the design of all instrumentation that is in contact with the washing or sterilization process has to be hygienic.

Specifications for regular laboratory washing or sterilization systems typically do not include any of these mechanical requirements.

Process monitoring

Section SD-5.3 of the ASME-BPE 2014 standard includes information on process-monitoring functions that are specific to washing and sterilization systems. As an example, section SD-5.3.3.1.3 indicates that the "instrumentation and control architecture should be designed to communicate, monitor, and synchronize the clean-in-place (CIP) cycle and report CIP variables." These variables, which are very similar in clean-out-of-place (COP) washers (also referred to as parts or components washers), include parameters such as time of exposure, temperature of wash and rinse solutions, chemical concentration by conductivity or volume, final rinse water conductivity or residual cleaning chemical concentration, water flow and pressure, and rotation of spray devices. Similar requirements for sterilizers (or autoclaves) are outlined in section SD-5.3.2. It is also mentioned that provisions for recording process parameters should be included and that "recording may be achieved by paper or 21 CFR Part 11 compliant electronic means." EN285 and HTM2010 (CFPP) have specific process monitoring requirements for temperature and pressure in steam sterilizers.

Figure 2 Sloped piping in a pharmaceutical-grade washer



The majority of pharmaceutical-grade washers and sterilizers are equipped with advanced process monitoring systems. New technologies now make it possible to perform online mon-

Figure 3 Hygienic piping skid for a pharmaceutical-grade sterilizer

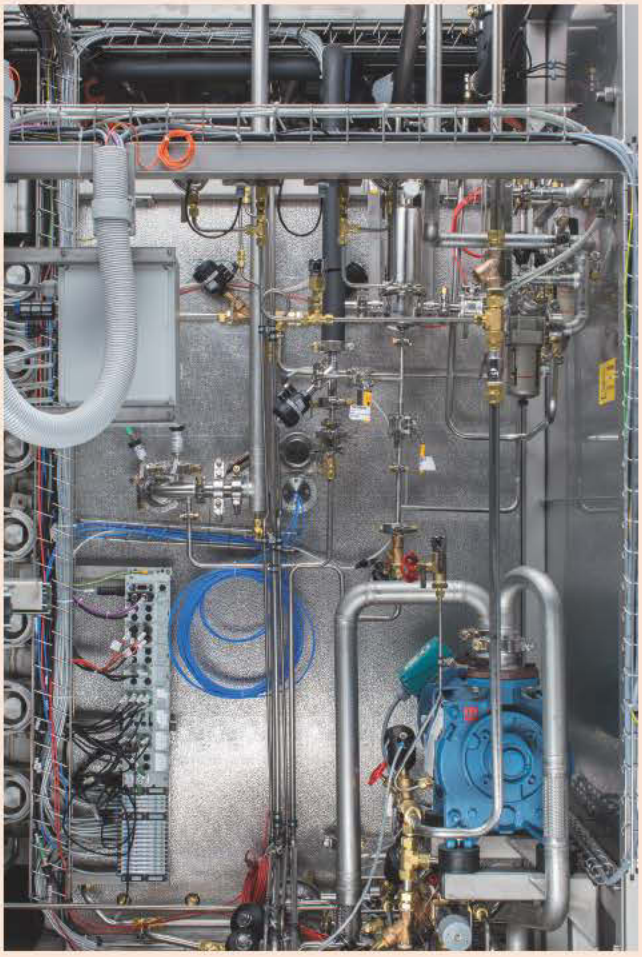


Figure 4 Online TOC monitoring system used in pharmaceutical-grade washers to measure the level of organic residues left in final rinse water

itoring of total organic carbon (TOC) content in the final rinse water of CIP or COP washing systems (Figure 4). Of course, laboratory washers and sterilizers monitor critical parameters such as time, temperature, and pressure; but as an example, basic washers typically do not monitor parameters such as conductivity of final rinse water, TOC content, or rotation of spray devices.

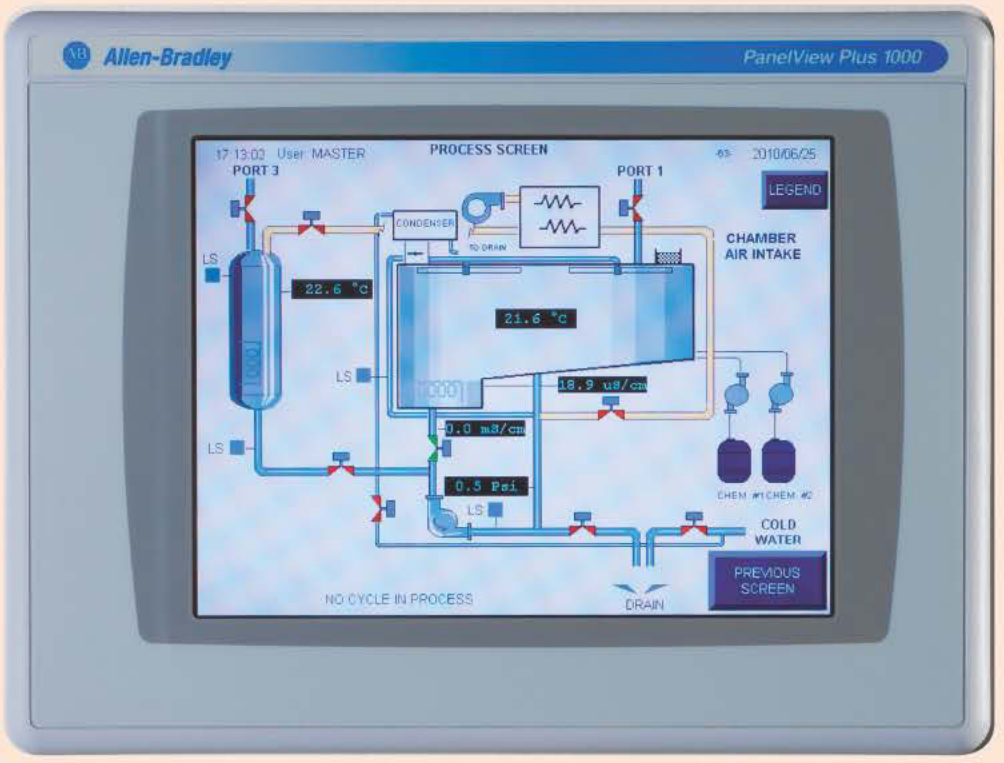
Control and software

For regular laboratory applications, the type of control with which the washer or sterilizer should be equipped is rarely specified. In many cases, proprietary microprocessor-based control systems are provided and accepted. Units are typically stand-alone and rarely connected to centralized supervisory control and data acquisition (SCADA) systems. However, in GMP environments, non-proprietary commercially available control platforms are generally preferred and, in many cases, interfaced with a higher-level centralized control or data management system (Figure 5). In most cases, users expect that equipment suppliers will follow GAMP guidelines.

GAMP guidance aims to achieve computerized systems that are fit for intended use and meet current regulatory requirements.[8] It is also meant to provide life sciences industry suppliers with guidance on the development and maintenance of systems by following good practices.

As mentioned previously, records of process parameters must be maintained for GMP applications. While printers are still commonly used, many users now opt for electronic records, in which case, CFR Title 21, Part 11[4] automatically applies. "This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations."[4] Again, this type of requirement does not typically apply to regular research facilities and equipment.

Figure 5 Programmable logic controller typically used in pharmaceutical-grade washers and sterilizers, showing process monitoring screen



Design, Manufacturing, and Qualification Documentation

Washers and sterilizers used in research facilities are typically supplied with sufficient documentation to assist with uncrating, installation, operation, and maintenance of the equipment. General layout drawings with dimensions and information on utilities may be sent for approval prior to manufacture. Occasionally, some users may want to attend a factory approval test (FAT), which will generate the need for a dedicated FAT protocol. Good laboratory practices followed in some research facilities may dictate the need for protocols to execute installation and operation qualifications.

On the other hand, regulated industries such as drug manufacturers require *a lot more* documentation to support the validation process. In this area, various guidelines are available and several companies have developed their own checklists. The Parenteral Drug Association (PDA) provides some guidance in Appendix B of its Technical Report 48.[9] But again, BPE offers a good summary of the typical requirements in section GR-5. Not all the requirements apply to washers or sterilizers. The following is a list of those that are commonly seen:

- Complete manufacturing and certification documentation for pressure vessels: ASME, pressure equipment directive (PED), etc.
- Material test reports and heat number/code traceable to test report
- Welding documentation for pressure vessels, tanks, and piping
  - Welding procedure specifications (WPSs) and procedure qualification records (PQRs)
  - Welder performance qualifications (WPQs) and welding operator performance qualifications (WOPQs)
  - Examiner qualifications
  - Weld maps and weld logs
  - Weld examination and inspection logs, coupon logs
  - Purge gas certifications
- Testing and examination documentation
  - Passivation reports
  - Electropolishing documentation
  - Surface finish report
  - Spray system testing (also referred to as "coverage test")
  - Pressure testing
  - Slope check documentation
  - Calibration verification documentation
  - Heat numbers of components must be identified, documented, and fully traceable to the installed system
  - Calibration reports
  - Factory acceptance test protocol and report
- Certificates of compliance for instrumentation
- Control system documentation
  - User requirement specifications (URS)
  - Functional requirement specifications (FRS)
  - Software history
  - Hardware design specifications (HDS)
  - Software specifications and test reports
  - Loop diagrams
- Equipment arrangement diagrams (layout drawings)
- Traceability matrix

And the list goes on …

So why are pharmaceutical-grade washers and sterilizers so much more expensive than laboratory units? The higher cost can be partly attributed to a more expensive mechanical design. Hygienic-designed components such as valves, pumps, instrumen-

tation, sensors, and so on can be several times more expensive than their standard counterparts. The additional time required for welding and polishing to obtain the acceptable surface finish, the additional process monitoring systems, and extensive documentation also contribute to the increased cost. Another factor is that laboratory washers and sterilizers are typically standard products that can be mass-produced. Pharmaceutical-grade equipment is generally customized and made to order. This also explains why the manufacturing process for pharmaceutical-grade units is longer than that of laboratory units.

Can an existing laboratory unit be upgraded to meet GMP requirements? It is definitely possible to upgrade some components (such as the control system, piping, and instrumentation) and add some process monitoring systems. However, that is not possible for all components. Replacing a washer chamber made of stainless steel 304 with one made of stainless steel 316, for example, may prove very difficult, if not impossible. Furthermore, obtaining necessary manufacturing documentation for critical components is likely to be a challenge.

Table 1 provides a condensed comparison between pharmaceutical-grade washers or sterilizers and standard laboratory units used in research facilities. It also includes a description of the typical applications for each type of equipment. Other good references include Section 3.4 and Appendix A of the PDA Technical Report (TR) 48.[9] This includes design considerations of steam sterilizers.

Which One Should I Choose?

This is a common question that arises when washing and steam sterilization equipment is being selected for a facility. The most important first step is to develop a URS to define the intended use and then develop detailed design requirements according to the facility, local codes, or other requirements. Many times, units are over- or underspecified based on their intended use, and this can lead to increased costs or performance issues. A steam sterilizer used for waste disposal may not need all the features of a unit used for pharmaceutical-manufacturing area components. A laboratory washer may be able to provide the cleaning quality required without the expense of a pharmaceutical-grade unit. A pharmaceutical-grade unit can be as much as three to four times more expensive than the standard laboratory version and is more costly to validate and maintain, so having a well-defined unit is critical to the project and ongoing support cost.

In general, pharmaceutical-grade equipment is required in drug-manufacturing facilities when used to clean or sterilize surfaces, parts, or components that are in contact with the drug product during its manufacturing process. For example, the following items are typically processed in pharmaceutical-grade equipment:

- Change parts from drug-manufacturing filling lines such as pumps, needles, and transfer hoses
- Components from manufacturing equipment such as blenders, mixers, blister machines, tablet presses/counters, and filter housings
- Various containers, drums, and trays that come in contact with the manufacturing ingredients or the final drug product itself
- Vials, ampoules
- Process media

Laboratory-grade washers and sterilizers are generally used for research applications and decontamination of waste. Here are a few examples:

- Glass- and plasticware used in research or hospital laboratories
- Animal surgery and cage processing
- Laboratory media preparation
- Deactivation of biologically contaminated waste from laboratory research or biologic and vaccine drug-manufacturing processes.

Table 1 Comparison between Pharmaceutical-Grade Washers or Sterilizers and Standard Laboratory Units Used in Research Facilities

Laboratory Washers or Sterilizers	Pharmaceutical Grade Washers or Sterilizers
Application	
Washing, drying and sterilization of glassware and plasticware used in laboratories, cages used for laboratory animal research	**Validatable** cleaning, drying and sterilization of various materials and components used in the biotechnology and pharmaceutical **manufacturing** process.
Design	
Ball valves, angle body valves in stainless steel 304 or 316 or brass material	Hygienic diaphragm valves, angle body valves, ball valves and butterfly valves in stainless steel 316 material
Surface finish: R_a is typically not specified.	Surfaces in contact with process are typically 20 - 30 µin R_a (0.51–0.80 µm), measured and documented
Some blind welds may be present	No blind welds, or welds must be inspected with boroscope or other visual means
Some overlaps in chamber may be present	No overlaps in chamber
Dead legs are minimized, but not specified	Maximum 3D dead legs
Chamber and piping are sloped but no specific data available	Approximately 2% slopes, measured and documented
Standard stainless steel 304L or 316L chamber	Stainless steel 316L construction
Regular plastic parts	FDA approved plastics
No radius specified	Minimum radius of ½ inch (13 mm)
Regular circulation pump, stainless steel 304 or 316 (washers)	Sanitary circulation pump, stainless steel 316 (washers)
Regular piping in stainless steel 304 or copper with threaded, clamped or brazed fittings.	Hygienic piping in stainless steel 316, hygienic clamp-type fittings, orbital welds, or polished welds, no threads
Regular instrumentation	Hygienic instrumentation
Single-pass rinsing system is typically not available for washers	Single-pass rinsing system generally available for washers
Standard filtration	HEPA or 0.2 µm filtration. Filtration may have steam-in-place and integrity test capabilities.
Process Monitoring	
Pump pressure	Pump pressure
Time	Time
Temperature	Temperature (redundant monitoring in sterilizers)
Detergent concentration for wash solution (conductivity or flow)	Detergent concentration for wash solution (conductivity or flow)
Rinse water residues (conductivity) may be available as an option for washers	Rinse water residues (conductivity) almost always provided for washers
N/A	TOC can be available on washers
N/A	Spray arm monitoring can be available on washers
Integral printer	Integral printer
Interface with SCADA system is possible	Interface with SCADA is readily available
Pressure in sterilizer chamber and jacket	Pressure in sterilizer chamber and jacket
Temperature distribution within the sterilizer chamber, including drain temperature, is guaranteed to be within ± 1.0°C (1.8°F) of the process sterilization temperature (exposure set point)	Temperature distribution within the sterilizer chamber, including drain temperature, is guaranteed to be within ±0.5°C (±0.9°F) of the process sterilization temperature (exposure set point)
Control System	
Proprietary microprocessor-based system or commercially available programmable logic controller	Commercially available programmable logic controller or industrial PC
Programmable cycles	Programmable cycles
Color touch screen	Larger color touch screen
No CFR 21, Part 11 capability	System provides capabilities to allow for compliance with CFR 21, Part 11
GAMP guidelines may not be used	GAMP guidelines are followed

Table 1 Comparison between Pharmaceutical-Grade Washers or Sterilizers and Standard Laboratory Units Used in Research Facilities

Laboratory Washers or Sterilizers	Pharmaceutical Grade Washers or Sterilizers
Accessories for Washers	
Design may not be fully hygienic, screws, welds not polished, stainless steel 304, plastic parts may not conform to FDA 21 CFR 177 and/or USP Section <88> Class VI	Hygienic design, no screws, polished welds, stainless steel 316, plastics conform to FDA 21 CFR 177 and/or USP Section <88> Class VI
No manufacturing documentation provided	Manufacturing documentation provided (welding, material certificates, surface finish, etc.)
Documentation and Qualification	
Basic submittal package typically limited to technical data sheets and equipment drawings.	Complete submittal package, typically includes equipment drawings, process & instrumentation diagram with parts list, general arrangement drawings, wiring diagrams, functional specifications, project schedule, FAT protocol
Uncrating, installation, operating and maintenance instructions are provided	Uncrating, installation, operating and maintenance instructions are provided
Manufacturing and certification documentation for pressure vessels (ASME, PED, etc.) is supplied	Manufacturing and certification documentation for pressure vessels (ASME, PED, etc.) is supplied

Manufacturing documentation is typically not provided	Complete manufacturing documentation can be provided:
	▸ Material test reports and heat number/code traceable to test reports
	▸ Passivation reports
	▸ Electropolishing documentation
	▸ Surface finish report
	▸ Spray system testing (also referred to as coverage test)
	▸ Pressure testing
	▸ Slope check documentation
	▸ Calibration verification documentation and reports
	  ▸ Certificates of compliance for instrumentation
	  ▸ Welding documentation
	  – WPSs and PQRs
	  – WPQs and WOPQs
	  – Examiner qualifications
	  – Weld maps and weld logs
	  – Weld examination and inspection logs, coupon logs
	  – Purge gas certifications

Control system documentation typically not provided	Control system documentation can be provided ▸ URS ▸ FRS ▸ Software history ▸ HDS ▸ Software specifications and test reports ▸ Loop diagrams
FAT protocol and execution is possible but not typically performed	FAT protocol and execution is very common
Installation and operation qualification protocols and execution, site acceptance tests can be provided but this is not typical	Installation and operation qualification protocols and execution, site acceptance tests are available

Note: These are typical descriptions and may vary by manufacturer.

Finally, a previously owned unit or unit procured from another area may not have the required features or cycles to meet pharmaceutical-manufacturing process needs. In this case, the upgrades, documentation, and qualification may cost more than the unit itself. PDA TR 48 provides comprehensive system design guidance in section 4.0 for steam sterilizers,[9] and this methodology can be used for other types of equipment.

Conclusion

Pharmaceutical-grade washers and sterilizers used in regulated pharmaceutical-manufacturing facilities are significantly different from those used in the research industry. The requirements for these applications directly affect the mechanical design of the equipment, the process monitoring systems that need to be provided, the control system and associated software, and, most

importantly, the documentation required to ensure a smooth validation process. As a result, pharmaceutical-grade systems are more expensive and take more time to procure. In general, this grade of equipment is required only if the items to be processed are in contact with the drug product that is being manufactured. It is recommended to conduct a risk assessment to help determine if a pharmaceutical-grade washer or sterilizer is really required. ◂

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About the Authors

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Matt Hofacre has been with STERIS Corporation since 1999 and has 15 years' experience in the pharmaceutical-production and laboratory-research-equipment industries. He is responsible for the global applications team with STERIS Life Sciences Capital Equipment Solutions. In this role, he and his team are responsible for design applications, project maintenance, and technical guidance for GMP steam sterilizers; multiple-effect water stills; pure-steam generators; continuous effluent decontamination systems, laboratory and high-containment steam sterilizers; GMP laboratory- and cage-washing systems; and mobile and integrated vaporized-hydrogen-peroxide systems.

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BIOPHARMACEUTICAL RESEARCH AND MANUFACTURING THROUGH THE DECADES

Manufacturing, Processing, Handling, Packaging, and Storage

Robert Dream

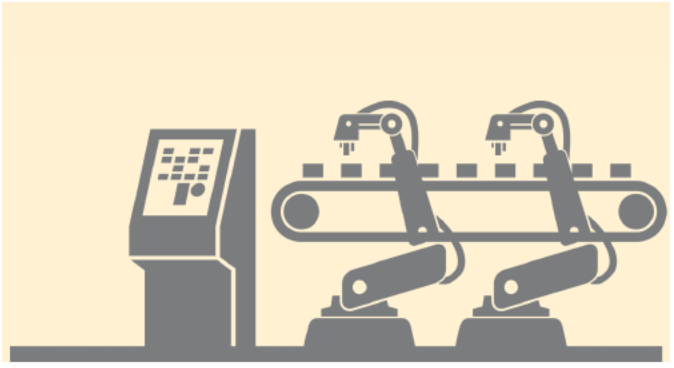
This article presents how biotechnology, bioprocessing, and biomanufacturing matured and advanced over the last 35 years into a complex and patient-centered industry with record solutions that compete one-to-one and surpass older small-molecule drug substance technology, opening the door to game-changing production efficiencies in biopharmaceutical production and drug delivery.

The manufacturing process for a biological product is different from the process of small-molecule drug products. The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes develop to meet such. A manufacturer responsible for production and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology, and veterinary medicine.

The degree of environmental control of particulates, microbial, and viral contamination of the production premises should be adapted to the product and the production steps. Mammalian cells, microbes, fungi, plant cells, insect cells, and other organisms and species are employed in the process and manufacture of a number of biological products. In many instances these could also be used in the quality control of most sera, antibodies, and vaccines. All biological products should be clearly identified by labels that should be approved by the regulatory authority with jurisdiction in the applicable country and/or territory.

The evaluation of stability may necessitate complex analytical methodologies. Assays for biological activity, where applicable, should be part of the pivotal stability studies. Throughout the twentieth century the world witnessed great discoveries in the biological sciences, many of which led to the prevention or eradication of diseases that devastated populations in the past.

What is now known as US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) has played a significant role in ensuring the safety and efficacy of the fruits of these scientific discoveries. CBER is responsible for the regulation of biologics, which are medical products such as vaccines, blood and blood derivatives, allergenic patch tests and extracts,



HIV and hepatitis tests, gene therapy products, cells and tissues for transplantation, and new treatments for cancers, arthritis, and other serious diseases.

Biological Products, Industry History

Biological products were created with biotechnology engineering procedures that manipulate organisms or their biological components at the cellular, subcellular, or molecular level. These manipulations were carried out to make and/or modify plant, mammalian, and/or other biological substances with desired traits. Examples of primitive biotech processes date back to ancient times (such as the use of fermentation and brewing).

The use of biotechnology in medical and pharmaceutical applications was an innovation of the latter decades of the twentieth century. Biotech researchers produced products in essentially three ways: by developing ways to achieve commercial production of naturally occurring substances, by genetically altering naturally occurring substances, and by creating entirely new substances. Some of the tools used by biotech researchers include recombinant deoxyribonucleic acid (DNA) and monoclonal antibodies. Recombinant DNA involved the ability to take the DNA from one organism and combine it with the DNA from another organism, thereby creating new products and processes.

By using recombinant DNA techniques, researchers were able to select specific genes and introduce them into other cells or living organisms to create products with specific attributes. Monoclonal antibodies were developed from cultures of single cells using cloning techniques. They were designed for use in attacking toxins, viruses, and cancer cells. Because the biological products presented for approval often involved new technologies or innovative therapies for diseases that had not previously been treated successfully, the approval process frequently proved long and costly. Many companies struggled financially through the 1980s waiting for an FDA determination.

As the industry matured, cooperation between product developers and government regulators improved. Steps in the approval process became more predictable, and a shift in technology

was also noted: The primary products of the 1980s involved the use of recombinant DNA proteins without further alterations. During the early 1990s researchers turned their attention to more obscure applications and to products requiring more extensive genetic modification.

In the 1990s FDA granted approvals for vaccines against rabies, tetanus toxoids, and pertussis. According to government statements, vaccines were one of the most effective and cheapest ways to eradicate some diseases. Accordingly, the National Institute of Health's Office of Financial Management reported that funding for vaccine research and development rose 65 percent from 1993 to 1999. Concern about health care costs during the early 1990s focused the national spotlight on the pharmaceutical industry and questions were raised about the high cost of biological products.

Definition

The definition of a biologic has changed over time. In the US, the Public Health Services Act (PHSA) of 1999 defines a biological product as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine, or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment or cure of a disease or condition of human beings." [4] The statute's definition of "biologic," is fairly broad. The inclusion of the term "analogous products" makes the definition particularly broad since the basis for determining analogous products is not provided by the statute.

Biological products, like other drugs, are used for the treatment, prevention, or cure of disease in humans. In contrast to chemically synthesized small-molecular-weight drugs, which have a well-defined structure and can be thoroughly characterized, biological products are generally derived from living material—human, animal, or microorganism—are complex in structure, and thus are usually not fully characterized.

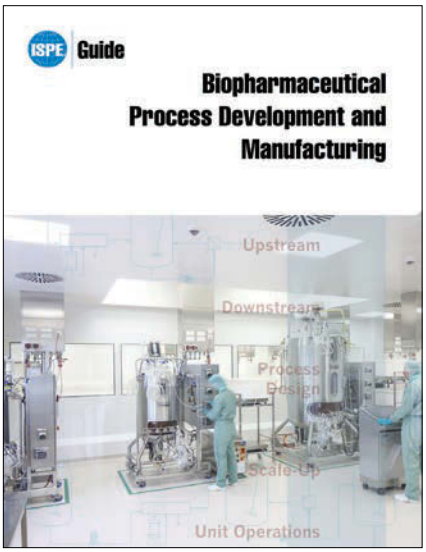
Biological products can be composed of sugars, proteins, or nucleic acids, or a combination of these substances. They may also be living entities, such as cells and tissues. Biologics are made from a variety of natural resources—human, animal, and microorganism—and may be produced by biotechnology methods.

Most biologics, however, are complex mixtures that are not easily identified or characterized. Biological products differ from conventional drugs in that they tend to be heat sensitive and susceptible to microbial contamination. This requires sterile processes to be applied from initial manufacturing steps.

The categories of therapeutic biological products regulated by the FDA's Center for Drug Evaluation and Research (CDER)—under the Federal Food Drug and Cosmetics Act (FDCA) and/or the PHSA, as appropriate—include the following:

- Monoclonal antibodies for *in vivo* use.
- Most proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g., thrombolytics), and other novel proteins, except for those that are specifically assigned to the CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, humans, or microorganisms, and recombinant versions of these products. Exceptions to this rule are coagulation factors (both recombinant and human plasma–derived).
- Immunomodulators (nonvaccine and nonallergenic products intended to treat disease by inhibiting or down-regulating a preexisting, pathological immune response).

Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells *in vivo*.



GMP for Biological Products

The manufacturing process for a biological product is different from the process for small-molecule drugs because in many cases there is limited ability to identify the clinically active component(s) of a complex biological product; such products are often defined by their manufacturing processes.

Changes in the manufacturing process, equipment, or facilities could result in changes in the biological product itself and sometimes require additional clinical studies to demonstrate the product's safety, identity, purity, and potency. Traditional drug products usually consist of pure chemical substances that are easily analyzed after manufacture.

Since there is a significant difference in how biological products are made, the production is monitored by the agency from the early stages to assure the final product turns out as expected. For this reason, in the manufacture of biological products, full adherence to good manufacturing practice (GMP) is necessary for all production steps, beginning with those from which the drug substances are produced.

Principle

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The ways in which therapeutic biological products are produced, controlled, and administered make some particular precautions necessary. Unlike small-molecule medicinal products, which are produced using chemical and physical techniques capable of a high degree of consistency, the production of therapeutic biological products involves biological processes and materials, such as cultivation of cells or extraction of substances from living organisms, including human, animal, and plant tissues. Propagation of microorganisms in embryos or animals, growth of microorganism strains and eukaryotic cells, and hybridoma techniques are also involved. These biological processes may display inherent variability, so that the range and nature of byproducts are variable.

Materials used in these cultivation processes provide good substrates for growth of microbial contaminants. Control of therapeutic biological products usually involves biological analytical techniques that have a greater variability than physicochemical determinations. In-process controls, therefore, take on a great importance in the manufacture of therapeutic biological products. Therapeutic biological products manufactured by these methods include vaccines, immune sera, immunoglobulins (including monoclonal antibodies), antigens, hormones, cytokines, allergens, enzymes, and other products of fermentation (including products derived from recombinant DNA).

Personnel

All personnel employed in areas where biological medicinal products are manufactured, including those concerned with cleaning, maintenance, or quality control, should receive additional training specific to the products manufactured and to their work.

Personnel should be given relevant information and training in hygiene and microbiology. Employees responsible for production

and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology, and veterinary medicine, together with sufficient practical experience to enable them to exercise their management function for the process concerned.

The immunological status of personnel may have to be taken into consideration for product safety. All employees engaged in production, maintenance, testing, and animal care should have regular health checks and be vaccinated when necessary with appropriate specific vaccines. .

Apart from the obvious problem of exposure of staff to infectious agents, potent toxins, or allergens, it is necessary to avoid the risk of contamination of a production batch with infectious agents. Any changes in the immunological status of personnel that could adversely affect the quality of the product should preclude their work in the production area.

Facility and Equipment

The degree of environmental control of particulate and microbial contamination of the production premise should be adapted to the product and the production step, bearing in mind that the level of contamination of the starting materials and the risk to the finished product. The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis, and the use of closed systems.

The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination. In principle, dedicated facilities should be used for the handling of live organisms used in production of tuberculin products, such as the bacille Calmette-Guerin (BCG) tuberculosis vaccine. Dedicated facilities should also be used for the handling of *Bacillus anthraces*, *Clostridium botulinum*, and *Clostridium tetani* until the inactivation process is accomplished.

Production on a campaign basis may be acceptable for other spore-forming organisms, provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time. Simultaneous production in the same area using closed systems of biofermenters may be acceptable for products such as monoclonal antibodies and products prepared by recombinant DNA techniques. Processing steps after harvesting may be carried out simultaneously in the same production area, provided that adequate precautions are taken to prevent cross-contamination.

For inactivated vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification. Positive-pressure areas should be used to process sterile products, but negative pressure in specific areas at point of exposure to pathogens is acceptable for containment reasons. Where negative-pressure areas or safety cabinets are used for aseptic processing of pathogens, they should be surrounded by a positive-pressure sterile zone.

Air-filtration units should be specific to the processing area concerned, and air recirculation should not occur from areas handling live pathogenic organisms. The layout and design of production areas and equipment should permit effective cleaning and decontamination (e.g., by fumigation, vaporized hydrogen peroxide). The adequacy of cleaning and decontamination procedures should be validated.

Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing. Pipework systems, valves, and vent filters should be properly designed to facilitate cleaning and sterilization. The use of "clean-in-place" and "sterilize-in-place" systems should be encouraged. Valves on fermentation vessels should be completely steam sterilizable.

Air-vent filters should be hydrophobic and validated for their scheduled life span. Primary containment should be designed and tested to demonstrate freedom from leakage risk. Effluents which may contain pathogenic microorganisms should be effectively decontaminated. Due to the variability of biological products or processes, some additives or ingredients (e.g., buffers) have to be measured or weighed during the production process. In these cases, small stocks of these substances may be kept in the production area. Seed lots and cell banks (master cell bank and working cell bank) used for the production of biological products should be stored separately from other materials. Access should be restricted to authorized personnel.

Animal Cell Substrates

The selection of an appropriate cell substrate for use in the production of biological drug products has been a recurring focus of attention and anxiety for at least the past 50 years. The reasons for that are not difficult to understand because the central issue has always been: "Is the product manufactured in a given cell substrate going to be safe to use in humans?"

Phenotypic Characteristics

A large number of phenotypic characteristics of animal cells have been described in the literature. Of those, three characteristics have been particularly important in the assessment of cells grown *in vitro* that might be considered as substrates for the production of biological products. These include:

1. Life potential
2. Tumorigenic potential
3. Chromosomal complement

With regard to life potential, cells grown *in vitro* may be divided into two large general classes: those with a finite life potential, such as human diploid cells, and those with an apparent infinite life potential, such as cells derived from tumor tissue.

When cells grown *in vitro* are assessed for their ability to produce tumors in animal test systems, they again may be divided into two general classes: those that have the ability to produce tumors, and those that do not display the characteristic. However, it is important to note that the results of any tumorigenicity assay depend very heavily on the sensitivity of the assay system itself. A variety of such assays have been developed over the past 50 years, and a number of more recent systems are able to detect the tumorigenic potential of inoculated cells that had been scored as negative in earlier systems.

The chromosomal complement of cells grown *in vitro* also may be divided into two general classes: diploid cells and heteroploid cells. Diploid cells contain the normal number of chromosomes for species from the cells were derived, whereas heteroploid cells contain an abnormal number of chromosomes and also have numerous structural abnormalities.

Production

Specifications for biological starting materials need additional documentation on the source, origin, method of manufacture, and controls applied—particularly microbiological controls. Specifications are routinely required for intermediate and bulk biological medicinal products.

Standard operating procedures should be available and maintained up to date for all manufacturing operations. The source of cells (laboratory and/or culture collection) from which the cell sub-

strate was derived should be stated. Information obtained directly from the source laboratory is preferred.

Starting Materials

The source, origin, and suitability of starting materials for biological products should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests. When sterilization of starting materials is required, it should be carried out by heat. When necessary, other appropriate methods may be used for inactivation of biological materials (e.g., irradiation).

Seed Lot and Cell Bank System

To prevent the unwanted drift of properties that might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture, or propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.

The number of generations between the seed lot or cell bank and the finished product should be consistent with the marketing authorization protocol. Scale-up of the process should not change this fundamental relationship. Seed lots and cell banks should be adequately characterized and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Seed lots and cell banks should be established, stored, and used in such a way as to minimize the risks of contamination or alteration. Establishing the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot, the cell bank, and personnel.

When establishing the seed lot and cell bank, no other living or infectious material (e.g., virus, cell lines, or cell strains) should be handled simultaneously in the same area or by the same persons. Evidence of the stability and recovery of the seeds and cell should be documented.

Stored containers should be hermetically sealed, clearly labelled, and kept at an appropriate temperature. An inventory should be kept and controlled. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken should be recorded and documented.

Only authorized personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled and documented. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination and mix-ups. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimize the risks of total loss.

All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned to the stock.

Operating Principles

The growth-promoting properties of culture media should be demonstrated. Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling take place.

Centrifugation and blending of products can lead to aerosol formation, and containment of such activities to prevent transfer of live microorganisms is necessary. If possible, media should be sterilized *in situ*. In-line sterilizing filters for routine addition of gases, media, acids or alkaline, defoaming agents, etc., to fermenters should be used where possible.

Careful consideration should be given to validation of any necessary virus removal or inactivation. In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by nontreated products.

A wide variety of equipment is used for chromatography; such equipment should be dedicated to the purification of one product and should be sterilized or sanitized between batches. Use of the same equipment at different stages of processing should be discouraged. Acceptance criteria, life span, and sanitation and/or sterilization method(s) of columns should be defined and documented.

Labeling

All biological products should be clearly identified by labels. The labels used must remain permanently attached to the containers under all storage conditions, and an area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labeling, then it should be in a labeled package. The information given on the label on the container and the label on the package should be approved and compliant with regulatory requirement(s). The label on the container should show:

- Name of the drug product
- List of active ingredients and the amount of each present
- Batch or final lot number assigned by the manufacturer

- Expiration date
- Recommended storage conditions
- Direction for use and warning and precautions that may be necessary
- Name and address of the manufacturer or the company

The package label should show at least the nature and amount of any preservative or additive in the product.

The package leaflet should provide instructions for the use of the product, and mention any contraindications* or potential adverse reactions.

Storage and Handling

Biological products at licensed establishments should be protected at all times against improper storage and handling. Completed product should be kept under proper temperature requirements (e.g., refrigeration at 35–45 °F [2–7 °C]), unless the inherent nature of the product makes storage at a different temperature advisable. All biological products to be shipped and or delivered should be securely packaged and packed. ◂

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* A specific situation in which a drug, procedure, or surgery should not be used because it may be harmful to th e patient.


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REDUCTION OF HUMAN ERROR IN HYBRID FACILITIES WITH SINGLE-USE EQUIPMENT

Dave Wolton, Aaron Hubbell, and Declan O' Sullivan

This article presents a useful guide to help prevent human error in hybrid facilities. It seeks to understand why the industry developed current practices, what human errors are being made, what has changed in the last 5 years and how future factories could operate. Will the new equipment and new approaches lead to safer, more reliable and repeatable factories?

Authors' note: In this article, "hybrid" refers to facilities that use both stainless steel equipment and single-use equipment to produce product.

Introduction

The argument for single-use technologies for producing pharmaceutical products has been made many times over the last 20 years. It can safely be said that the technology is now here to stay. This means that focus has changed from "Can it be used?" to "How can it be made more reliable, cheaper, and robust?" and now to "How does it affect the safety of therapeutic products and people?"

Operational excellence experts are focusing on improving the implementation of this technology; this in turn has an effect not only upon the choice of equipment, but also its design and the design of the facility that drives worker interaction with the technologies.

How Did We Get Here?

Before going into problems that have surfaced over the last few years, it is worth outlining why we are where we are:

Pillow-shaped (2D) bags first came into widespread use with the advent of blood bags, which showed they could not only be robust, but also keep sterility under quite harsh conditions. It was only a matter of time before these bags began to be used for other biological material, media being the next logical step. Cube-shaped (3D) bags rapidly followed, with an increase in size (see Figure 1). It then became apparent that intermediate product could also be safely stored, and by the mid- to late-1990s intermediate products of about 200 liters (L) were being stored in 3D bags.

Attach or Customize?

In the 1990s/2000s sterility was assured by either fitting the filters to the bags before irradiation (customization) or by tubing welding (limited initially to small-bore tubing). Technology was not available or suitable that would have allowed for filters to be separated from the bags on a routine basis. This ended up driving the market more towards customization.

Flexibility in design is often a key driver for implementing disposable systems. The upside of flexibility is that every user gets the opportunity to start with a blank piece of paper and be as creative as they wish with the design of what are often very standard applications. The downside is that each design effectively becomes a prototype when the numbers produced for and used by each individual user are added, compared to the standard blood bags mentioned earlier. Additionally, without robust planning and disciplined changeover processes, the flexibility that designers enjoy often turns into operational complexity and subsequent errors for operational staff. Processes with multiple decision points, options, and vague guidance for equipment setup all contribute significantly to human error.

Size is another key factor. Until recently 200L/500L bags have been as large as many companies would go, which required in larger and larger tote storage areas. Even at the 500L scale, the weight of a full tote approaches the fringes of mobility by human force only. This is starting to change rapidly, however. Up to 5,000L bags are now available, and 2,000L is being seen as normal. Movement is no longer an easy option due to size, weight, and momentum issues.

The result is highly customized unique products for each end user. This has led to issues around handling, worker interfaces, human error, and subsequent failure; these will be discussed later in the article.

Human Error

This article concentrates on human error in assembly of the bag at the supplier, during transport, and in use. It also seeks to help reduce human error by incorporating thoughtful design. Strictly speaking, human error in a design that leads to failure on site is not caused by the end user; it is, however, caused by the designer.

New Technologies

Advances in technology have helped our industry increase throughput and become more productive, yet we must exercise some forethought in the possible work practices and behaviors that technologies—particularly automation—will create in workers. While allowing increased capabilities, new technologies can:

- Increase operational demands as systems and equipment are driven harder

- Cause systems to break down in new and different ways
- Force operators to figure out real-word solutions and practices to deal with technology
- Create opportunities for new types of errors

No human-free plant exists; people must always be present to some degree. A human is the only "system" able to manage the interfaces between various systems and technologies in the modern manufacturing environment.

Automation deserves special mention for its role in either preventing or causing human error. Computerized aids and automation are trusted in the same ways that coworkers are trusted: Highly reliable aids build high degrees of trust, while low-reliability aids degrade trust. Initial assumptions of "the computer must be right" erode over time as workers gain experience with the system and its ability to provide guidance and make decisions.

Human error based on over- or under-trusting automation (i.e., assuming the automation is correct when it fact it is incorrect and vice versa) is driven largely by workers' experience with the process, the automation's degree of reliability, and the transparency of the technology. Opaque systems are especially troublesome when displays communicate only status or mode but not actual system behavior and/or action. An example of valuable automation is processing product through a chromatography skid. Procedures such as bag filling require caution, however.

Operator interfaces displaying information that raises the operator's engagement tend to help reduce errors. Should errors occur in this environment, the operator is better prepared to troubleshoot and resolve problems.

System owners must apply careful thought to the design of automation and interfaces; they should also support work practices, procedures, visual aids, and training that support their human workers as they strive to keep the various systems integrated and in balance.

Problems and Solutions

As reliability and efficiency begin to trump flexibility, what problems are surfacing and how are they being resolved?

Handling Equipment in the Stores Area

Companies that implement single use tend to learn through bitter experience that it is essential to train stores personnel, use detailed work practices, and handle considerations by providing custom-made transport containers (Figure 2). This keeps the bioprocess bags integral and allows bags, tubing, and other consumables to flow to manufacturing areas only when needed and not sooner. This lesson, however, is often not transferred to new builds or new product introductions, and is mostly retrofitted. This level of detail is often lost in even the most detailed tech-transfer programs, where the focus is often concentrated on the higher upfront capital investment parts of a process.

Figure 1 Large-scale disposable process solution storage tote and defined tubing routing

This is starting to change. Projects can seek to mitigate these problems during the design phase, and not wait for investigations to prompt action.

Bag Design Reduces Mishandling Risks

Another issue is designing the bag set to avoid damage if at all possible. Over time the design of bag sets and associated tubing have become more

complex and unwieldy. What seems like a user-friendly system on paper or at bench scale often becomes exactly the opposite at larger scale, causing the end user to wrestle with meters of tubing, clamps, or filters. Not surprisingly, the end user often loses these wrestling matches, resulting in errors, frustration, or breaches in tubing and bag integrity. Simple equipment set mock-ups in the proposed manufacturing space can identify many usability issues proactively, as can involving operators and other end users when defining final configurations.

During a recent workshop, for example, end users were asked: Would they mind switching away from pinch clamps—which were known to damage the bag during handling and in transit—and instead use reusable clamps that did not come with the tubing/bags? The end users did not see this as a problem. It stopped the possibility that they might damage the bag membrane, and also made fabrication cheaper and quicker (since at the moment all the clamps must be individually wrapped in bubble wrap to mitigate the problem). In addition, positioning the clamps during manufacture could lead to problems during use, especially when making complex manifolds. The underlying question here is "Does the installation of the clamps by the operators at the user plant contribute to or reduce the process risk?"

It is only recently that sterile connector technology has become cheap, reliable, and (almost) foolproof enough to allow filters to be supplied separately. It can be argued that welder technology could have been used, but operations people would counter that the technology was not fast or reliable enough, which explains why it was rarely used for this application.

Contemporary bags at some manufacturing sites have been significantly simplified, reducing the likelihood of damage to the bag during transit, making it easier for the end user to handle, and diminishing opportunities for error.

Simplifying the bag designs (such as removing clamps) will make the bags simpler to manufacture and help enable mass production.

Self-Filling Bags and Bag Hoists

With 2D bags, unattended bag filling was not a big issue. The advent of larger and larger scale 3D bags, however, required operator presence to continually readjust the bag and stop folds from developing. In the worst-case scenario, bags could rupture if folds decreased the working volume sufficiently. Suppliers began to look for solutions that did not require the bag to be adjusted. This was achieved by a revised folding technique or by hoisting the bag into place. If these new designs are employed, the chance of rupture during filling is reduced.

Technical solutions for preventing folds and tears can be made even more effective by developing robust and standard work practices and guidance for operators in the field: Hands-on training and opportunities to practice operations in low-consequence conditions, clear and easily understood instructions and procedures, and visual work instructions (including photos or cartoons of "good" vs. "bad" bag installations) greatly increase the reliability and repeatability of technical solutions.

Figure 2 Custom-designed ergonomic storage and transport cart for membranes that protects contents and minimizes number of times disposable systems have to be handled

Skids with Pinch Valves

The need for automation has increased as suppliers have targeted areas like ultrafiltation, virus filtration and chromatography with single-use concepts. This has advantages and disadvantages. Automation eliminates certain classes of error, but increases opportunities for other types. For example, extensive automation can free an operator from operational tasks, which then places the operator in the role of system monitor. A consequence of this shift in operator role may be an increased likelihood of multitasking and distraction, which then increases the risk of missed or misinterpreted trouble signals. One strength of single use is that it is simple and visual (it is easy to tell if a tube is full or not), therefore care is needed in adding automation only where it is necessary.

Figure 3 Example of 3D Modeling

sign stage, where media solutions are encased in lightproof totes to minimize degradation of light-sensitive media and maximise potential media hold duration.

Even with the prechecks mistakes can occur, especially if the area has a lot of totes used in rapid succession, like chromatography. In many facilities, this mistake will be difficult to mitigate against as the buffer is made well away from where it is used. Organizational questions will need to be considered in such situations, such as "What is the appropriate staffing level in this area?" Efforts to reduce headcount in operational areas frequently place additional pressures on workers and force multitasking and other behaviors that increase error risk.

Improved Film Robustness

Following recent issues with the physical strength of certain films, some suppliers have focused more on improving their offerings. This will lead to reduced numbers of bags leaking due to rough handling.

The Advent of Static Totes

Increases in scale have driven the requirement to employ larger totes, which by the nature of their size and weight (particularly when full) have required a move away from smaller, more ergonomic systems. Once a tote becomes static, it requires a number of new approaches that help mitigate against human error.

Adding the Wrong Thing

Adding the wrong thing to a process will usually result in a failed batch. This is why a lot of effort is normally expended in making this as difficult as possible. In large stainless steel plants, hard piping, fixed (sometimes dedicated) tanks, recipe-driven programs, and transfer panels all help to mitigate the risk. In large-scale single-use facilities, these safeguards often don't exist and have been replaced with pre-addition checks like conductivity sampling.

Simple visual checks of media solutions can often be difficult to perform at large scale unless carefully considered during the design stage. With new facility design, and because large bags need to be static, it is possible to start to eliminate some issues that have historically been part of day-to-day disposable system operations. Large-scale systems require careful, reproducible, simple, and secure tubing routing to minimize the possibility of in-use of tubing and filter damage. As stainless steel systems have become more complex, their design has benefited (from an end-user point of view) through the use of 3D modeling. Given the size of large-scale disposable systems, it is possible to realize similar end-user benefits and eliminate some potential in-use errors through the use of the same 3D modeling methods. These 3D models can ensure that similar to fixed tanks, potential clashes can be identified and addressed either by simple solutions like tubing routing systems (see Figure 3), tubing supports, and filter supports or by changing the fixed equipment, which dovetails nicely with considering and designing 5S into production areas from the very start. If warranted, this can lead to automated transfers and can make work environments safer by eliminating trip hazards.

Human Error and Lead times

One of the current disadvantages of customized single-use equipment is very long lead times. As mentioned earlier, every user gets the opportunity to start with a blank piece of paper for their particular application. This can lead to multiple rounds of revisions and design tweaks, qualification of individual manufacture

of nonstandard parts and components, prototype lead times followed by potential updates to the design and finalization of manufacturing drawings, and placement of purchase orders, which starts the clock on standard delivery times.

In addition to business needs to minimize stock levels and potentially obsolete designs, strict inventory control is essential; even slight fluctuations in usage or identification of issues with particular production lots can bring large-scale manufacturing operations to a shuddering stop.

In summary, when dealing with inventory systems, human error has caused significant issues due to the current long lead times of customized single-use items. This needs to be highlighted during training sessions, along with developing mitigation strategies.

What Else Can Be Done?

There is an initiative underway to standardize assemblies used across the industry, thus allowing these assemblies to be kept in stock at the supplier. This doesn't mean that there will be a one-size-fits-all set of assemblies available from your local disposables supplier—that would require every manufacturing facility to have a similar design. What it does mean is that the components that make up the unique assembly that you have always dreamed of can be made from a prequalified set of standard components and subassemblies, which can be combined to create standardized end products.

This helps eliminate errors by pulling from a standard set of mass-scale production, where robust components, standardized procedures, and work instructions minimize the variability and level of training required when changing to a new disposable assembly, and reduce the potential for errors as a result of changes or unfamiliarity with systems. This standardization will not be able to cover all applications forever, however; there will be always a need to introduce new components to ensure that systems continue to evolve and improve as technology matures.

A critical component of the maturation process is incorporating the evolved work practices developed by operations staff into standardized processes, procedures, and automated control systems. Workers will always develop pragmatic work practices as they learn how to make diverse systems and technologies function in the real world. System owners and designers must tap into these real world lessons and convert tribal knowledge into standard processes. The key is to do this in a controlled manner to ensure that the scope of qualification requirements and lead times are minimized.

Summary

A key driver for the use of disposables was their ability to be configured by the end user "at will" and implemented quickly with minimal cost. As these items are now in routine use, a number of unforeseen issues have surfaced, and end users are now questioning how they work with these items to ensure that human error is minimized while at the same time they protect the inherent simplicity of their use.

Focus Areas to Reduce Errors

- Enhanced training programs.
  - It is envisaged that the training will expand knowledge and help users take full advantage of the flexibility of single use technology.
- Standardization
- Error proofing
  - Defined tubing routes
  - Automation
  - Purpose-built equipment (trollies, etc.)
  - Self-filling systems
  - Simplified designs (less chance of damage during transit and use)
  - Designing facilities for static operation

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TOLERANCE INTERVAL ALTERNATIVE TO ASTM E2709/E2810 METHODOLOGY

Providing assurance of passing the USP UDU Test <905>

James Bergum

This article presents a comparison of the ASTM E2709/E2810 and tolerance interval method.

The United States Pharmacopeia (USP) uniformity of dosage unit (UDU) <905> test is a market standard. Based on the following statements in the USP General Notices[1] and Requirements and the US Food and Drug Administration (FDA) "Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Production and Process Controls,"[2] there is a need for statistical methods that can be used to release lots of pharmaceutical products.

The USP General Notices states the following about compendial standards:

> *At times, compendial standards take on the character of statistical procedures, with multiple units involved and perhaps a sequential procedural design to allow the user to determine that the tested article meets or does not meet the standard. The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia.*[1]

The FDA stated in response to why the Stratified In-Process Dosage Unit Sampling and Assessment Draft guidance[3] was withdrawn:

> *Section VII (Routine Manufacturing Batch Testing Methods) acceptance criteria designated to the Standard Criteria Method and the Marginal Criteria Method were based upon the limits published in the United States Pharmacopeia (USP) General Chapter <905> "Uniformity of Dosage Units." However, the procedures and acceptance criteria in USP <905> are not a statistical sampling plan and so the results of the procedures should not be extrapolated to larger populations. Therefore, because the procedure and acceptance criteria prescribed in section VII provided only limited statistical assurance that batches of drug products met appropriate specifications and statistical quality control criteria, FDA no longer supports their use for batch release.*[2]

Therefore, a statistical methodology was desired that would ensure that a lot could meet the USP UDU test. One method to provide this assurance was developed[4-6] that resulted in the following standards: ASTM E2709,[7] "Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure" and ASTM E2810,[8] "Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units." ASTM E2709 is referenced in the FDA Validation guidance. An overview of the ASTM E2709/E2810 methodology is given in a later section of this article. In addition, an alternative methodology to ASTM E2709/E2810 is presented based on tolerance intervals that can provide the same statements with respect to confidence levels and the probability of passing the USP UDU test. A comparison of the ASTM E2709/E2810 and tolerance interval method is also presented.

USP UDU Test

The USP UDU test[9] is described in Table A (assumes symmetric potency limits about 100% label claim). The test consists of two stages, with criteria in each stage. If stage 1 criteria are not met based on 10 dosage units, 20 additional dosage units are tested and compared to the stage 2 criteria. There is an "indifference" zone, meaning that if $\bar{X}$ falls between 98.5 and 101.5% label claim (LC), then the first term in the acceptance value is 0 since $M = \bar{X}$.

Sampling Plans

There is a wide body of literature on sampling. Sampling plans are used to provide blend samples or dosage units that will be tested for process understanding, process validation, or to support the release of manufactured lots. A sampling plan describes where (locations) and how the samples are taken from the blend or lot and the number of samples (blend amount or dosage units) taken from each location. There are three common sampling plans:

Simple random sampling

Simple random sampling gives each possible dosage unit an approximately equal probability of being chosen as a member of the samples to be tested. A true random sample from a lot of tablets could theoretically be obtained by identifying each dosage unit in

the lot and then by a completely random process, pick n dosage units. To obtain a true simple random sample is often nearly impossible or impractical for sampling a lot of dosage units. An example that is generally considered a simple random sample is taking a sample from a coating pan for content uniformity since the tablets have been continuously mixed up during the coating process.

Stratified sampling

One problem with simple random sampling is that, just by chance, the samples may not contain dosage units from segments of the lot of interest. For example, in process validation, the beginning and end of the lot may be of interest. So, although a simple random sample is statistically valid, one may not be satisfied with a sampling plan that does not include samples taken from the beginning or end of the lot. Stratified sampling plans partition the lot into "strata" (e.g., first 1/20, second 1/20, …, and final 1/20). The combination of strata must cover the entire lot. Then random sampling is performed within each stratum.

Systematic sampling

Systematic sampling is performed by taking a sample(s) at equal intervals throughout the lot typically based on the total number of dosage units or manufacturing time. The first sample location is determined at random, and then the remaining samples are taken at equal intervals. For example, using manufacturing time, suppose the manufacturing run takes 15 hours and the desired sample size is 30 dosage units. Then the time can be divided into 30 ½-hour intervals. A time is selected in the first interval at random, say 10 minutes. Then samples would be taken at 10 minutes, 40 minutes, 1 hour and 10 minutes, etc. In practice, the first and last samples may be taken from the beginning and end of the lot. Then the remaining 18 samples could be done using a random time in the second interval. This is typically acceptable as long as the starting point and subsequent sampling points do not fix the samples in such a way as to potentially miss important elements of the process.

The three sampling strategies describe how to select locations for sampling. Typically for both simple random and stratified sampling, only one dosage unit is tested from each location. In this article, this is called Sampling Plan 1. For systematic sampling plans, one dosage unit (or blend sample) could be tested from each location, which is Sampling Plan 1. However, more than one dosage unit (or more than one blend sample) could be tested from each location. In this article, an equal number of samples (greater than one) taken from each location is called Sampling Plan 2. Sampling Plan 2 allows the estimation of two sources of variation—between location and within location. The two sources of variation are estimated by splitting the total variance into each source using variance component analysis. The variance component analysis is useful to determine whether or not the location to location is significant as well as how much of the total variation is due to location to location.

Tolerance Interval Approach

The tolerance interval approach discussed below can be applied to dosage units collected using Sampling Plan 1. Tolerance interval methods that could be applied to Sampling Plan 2 would have to incorporate two sources of variability (between and within location). The interval would have to account for the number of locations and the percentage of total variation due to the between-location variability. The ASTM E2709/E2810 (discussed in the next section) can be applied using sampling plans 1 and 2.

Tolerance intervals are used to capture a specified proportion of a distribution (p) with a specified confidence level (%) of 100*(1 – α). One-sided tolerance intervals lower and upper end points are calculated as follows:

$$\text{Lower limit (LL)} = \bar{X} - k^*s \quad (1)$$

$$\text{Upper limit (UL)} = \bar{X} + k^*s \quad (2)$$

Where

$\bar{X}$ = sample mean
s = sample standard deviation
k = multiplier of the standard deviation based on the specified confidence level 100*(1 – α) and proportion of distribution (p)

For a one-sided lower tolerance interval, p proportion of the distribution falls above LL with 100*(1 – α) confidence, whereas for a one-sided upper tolerance interval, p proportion of the distribution falls below UL with 100*(1 – α) confidence.

Faulkenberry and Daley[10] showed that $k\sqrt{N}$ is the 1– α percentile of a noncentral t distribution, therefore

$$k = t^{-1}(1 - \alpha, N - 1, \Phi) / \sqrt{N} \quad (3)$$

where

N = sample size
100*(1 – α) = confidence level (%)
p = specified proportion of distribution
t^{-1} = inverse t distribution (confidence level, degrees of freedom, noncentrality parameter)
Φ (noncentrality parameter) = $-\sqrt{N}*Z_{(1-p)}$
$Z_{(1-p)}$ = inverse standard normal distribution at 1 – p quantile

Note that p is a quantile of the standard normal distribution that is contained in the noncentrality parameter (Φ) of the noncentral t distribution. Therefore, if Φ is known, then p can be determined by setting $\Phi = -\sqrt{N}*Z_{(1-p)}$ and solving for p.

Tolerance intervals are widely published in the literature.[11,12] One proposal for metered dose inhaler and dry powder inhaler products[13] used tolerance intervals for a two-tiered sequential testing procedure that controls the probability of the product delivering below a prespecified effective dose and the probability of the product delivering over a specified safety dose. The parametric two one-sided tolerance interval (PTOSTI) plan consists of two one-sided tests to ensure with 95% confidence that the percentages of tablets below 85% and above 115% LC are both less than 6.25%.

The tolerance interval approach proposed in this article uses a PTOSTI approach to determine the percentage of individual content uniformity (CU) results falling between 85% and 115% LC and then correlates this probability with the probability of passing the USP UDU test. The percentage of individual results falling between 85% and 115% is called "coverage" throughout the remainder of this article. Coverage is determined by constructing two one-sided tolerance intervals each based on using a 95% confidence level resulting in an overall confidence level of 90%. One confidence interval is used to determine the proportion of CU results greater than 115% LC (p_u) and the other to determine the proportion of CU results below 85% (p_l). Note that p_u and p_l replaces $1 - p$ in the noncentrality parameter since p is the proportion of the distribution falling above LL or below UL, and p_u and p_l are the proportions of the distribution falling below LL or above UL.

The reason for using 95% for each tolerance interval is that a 90% confidence level for a two-sided tolerance interval splits the 10% (100%–90%) into 5% on each side. So each side alone would be at a 95% confidence level. Using an overall 90% confidence level, the proportion below and above 85% and 115% as well as the total proportion outside and within 85% and 115% LC can be determined. For example, if 0.005 (p_l) and 0.009 (p_u) of the individual CU results are outside 85% and 115%, respectively, then 1.4% (i.e., 0.5% + 0.9%) are outside 85% and 115% LC and the coverage is 98.6% (i.e., 100.0%–1.4%).

The goal is to solve for p_u and p_l. Equations 1 and 2 can be solved for their respective k's (k_u for upper and k_l for lower). Note that values for k_u and k_l can also be found by substituting p_u and p_l for (1– p) in Φ from equation 3. Equating these two expressions for k for each endpoint separately gives the following:

$$(\text{UL} - \bar{X})/s = t^{-1}(1 - \alpha, N - 1, \Phi_u) / \sqrt{N} \quad (4)$$

$$(\bar{X} - \text{LL})/s = t^{-1}(1 - \alpha, N - 1, \Phi_l) / \sqrt{N} \quad (5)$$

Given $\bar{X}$, s, N, α, UL, and LL, the values for Φ_u and Φ_l can be determined by determining the noncentrality parameter in equations 4 and 5. An R function "delnct" was written by Henrik Spliid, Technical University of Denmark[14] (included in Appendix), to find the noncentrality parameters given the desired quantile = (UL – $\bar{X}$)/s or ($\bar{X}$-LL)/s, confidence level = 1 – α, and degrees of freedom = N.

Setting the found $\Phi_u = -\sqrt{N}*Z_{pu}$ and $\Phi_l = -\sqrt{N}*Z_pl$, the values of p_u and p_l can be determined. $100*(1 - (p_u + p_l))$ is the coverage. An R program to perform these calculations is shown in the Appendix on page 79.

Once the coverage is determined, it can be correlated with the probability of passing the USP UDU test based on an operating characteristic (OC) curve. Figure 1 shows the operating OC curve for passing the USP UDU test based on simulation. The vertical axis is the probability of passing the USP UDU test, and the horizontal axis is the coverage. A separate curve is shown for "true" lot means from 90%–100% LC. The OC curves for 104% and 102% are the same as 96% and 98%, respectively (i.e., the OC curves are the same for lot means the same distance from 100% LC).

The probability of passing USP UDU has a dependency on the true lot mean. Note that coverage of 95% correlates with only about a 50% probability of passing the USP UDU test for lot means between 96% and 104% LC. Figure 2 shows the same plot over a narrower range, including a reference line at 95% for the probability of passing the USP UDU test.

Notice in both Figures 1 and 2 that for a given coverage, the probability of passing the USP UDU test decreases as the lot mean decreases from 100%–97% but then increases as the lot mean decreases from 97%–90% LC. This potential bias in the USP UDU test has been discussed.[15]

Table B shows the lot means and coverage corresponding to a 95% probability of passing the USP UDU test. Note that a lot mean of 97% requires the highest coverage (98.58%) to pass the USP UDU test with at least a 95% probability. Therefore, if the coverage is at least 98.58, then there is at least a 95% probability of passing the USP UDU test for all lot means from 90%–110% LC. The 98.58% could serve as a statistically reasonable quality standard where any methodology that can assure coverage greater than 98.58% could be acceptable (assuming normality). For example, an alternative to the proposal given in this article would be to show that a two-sided tolerance interval using 98.58% coverage is completely contained between 85% and 115% LC.

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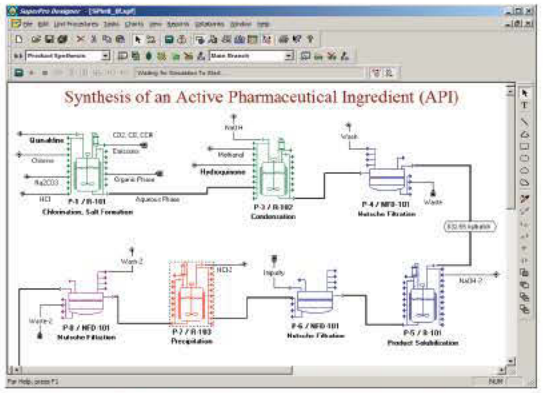

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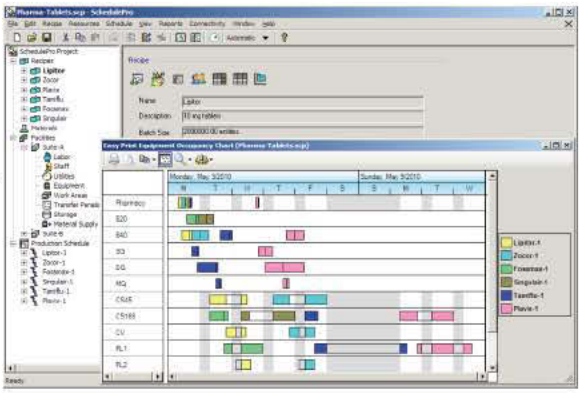

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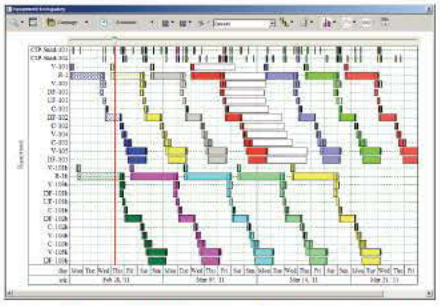

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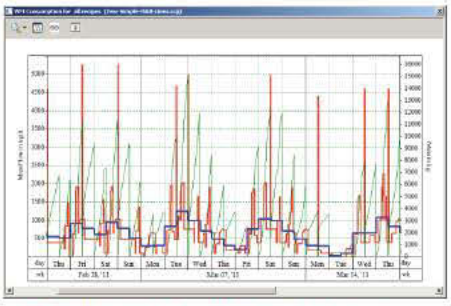

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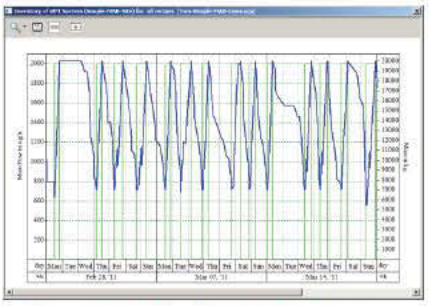

Managing inventories for input, intermediate, and output materials

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Figure 1 OC Curves for Passing USP UDU vs. Coverage (75%–100%)

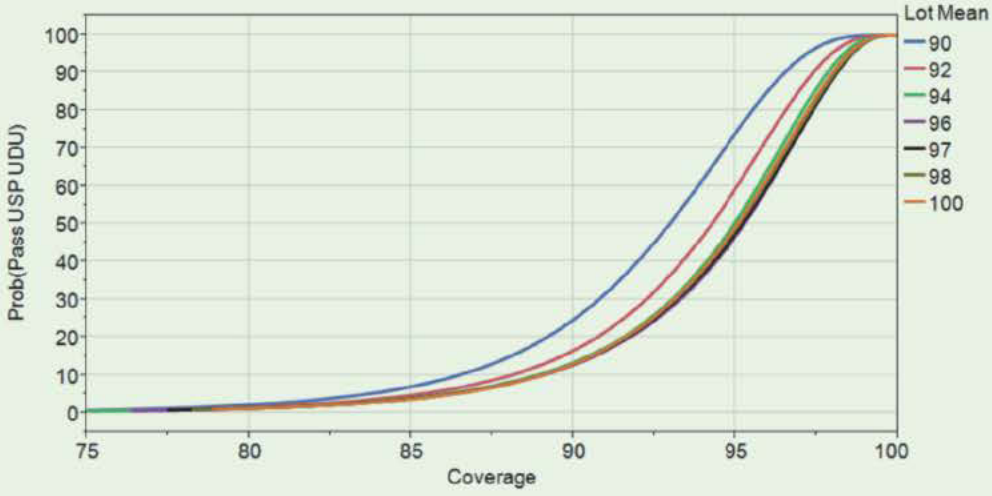
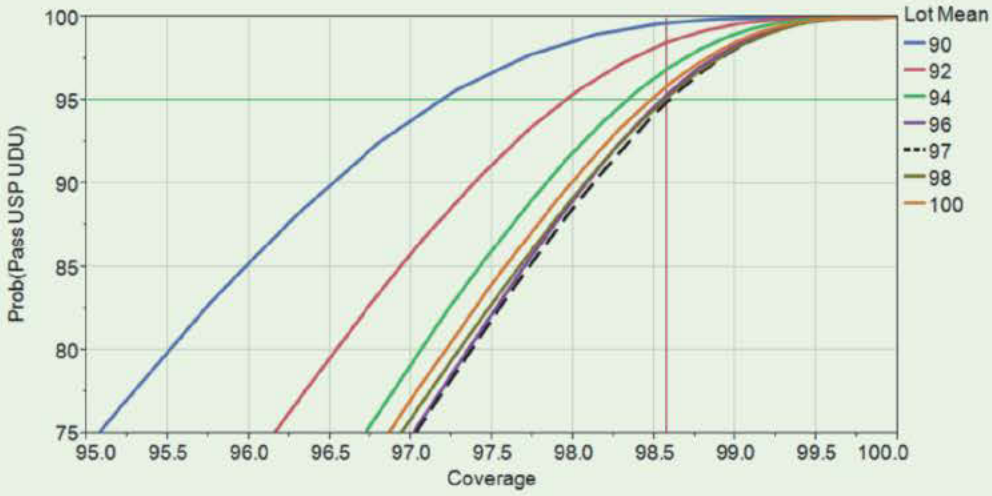


Figure 2 OC Curves for Passing USP UDU versus Coverage (95% –100%)



Overview of ASTM E2709/E2810 Approach

ASTM E2709/E2810 standards provide a methodology based on validation samples that can ensure that additional samples from the lot will pass the USP UDU test with a prespecified probability and confidence level. For example, if an ASTM E2709/E2810 acceptance limit is met, then a statement such as "With 90% confidence, there is at least a 95% chance that a sample from the lot will pass the USP UDU test" is true. ASTM E2709 provides the statistical aspects of the methodology. E2810 applies the general methodology of E2709 specifically to the USP UDU test.

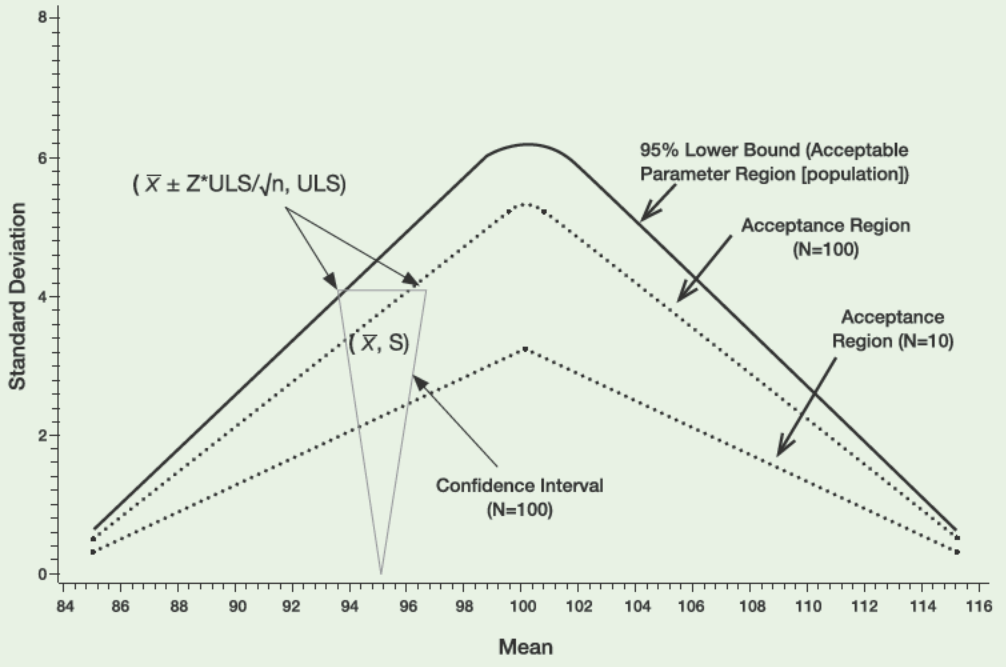
The procedure computes a lower bound on the probability of passing the UDU test based on statistical estimates made at a prescribed confidence level from a sample of dosage units. The method can be used to generate an acceptance limit table, which defines a set of sample means and standard deviations that assures passing the UDU test for a prescribed lower probability bound, confidence level, and sample size. If the limits in the acceptance table are met, then a sample tested using the USP test will pass with the prescribed lower bound probability, with the prescribed confidence level. For example, if the prescribed lower bound and confidence interval are 95% and 90%, respectively, then meeting the limit in the acceptance limit table ensures, with 90% confidence, that there is at least a 95% chance of passing the USP test.

Figure 3 provides a pictorial of the ASTM method. The y-axis and x-axis are the lot standard deviation and mean, respectively. The solid-line parabola-shaped curve (called the lower bound) represents combinations of lot means and standard deviations that have at least a 95% probability of passing the USP UDU test. Any points below the parabola have higher probabilities of passing the USP UDU test, since for any lot mean, the probability of passing the USP UDU test increases as the standard deviation decreases. The points on the lower bound were determined mathematically.[5]

The set of all points below the lower bound is called the "acceptable parameter" region. The lower bound only depends on the USP UDU test, fixed sample sizes, and criteria—no data is used to create it. The ASTM E2709/E2810 methodology uses sample results to determine if a lot can pass the USP UDU test. Based on

randomly sampling *N* dosage units from a lot, the mean, $\bar{X}$, and standard deviation, S, are calculated and shown in Figure 3. Based on the sample mean and standard deviation, a joint confidence region[16] is generated for the lot mean and standard deviation that is represented by the triangle. (Z is a standard normal critical value, and ULS is the upper confidence limit on the standard deviation.) If the 90% confidence region is completely contained under the lower bound, then with 90% confidence there is at least a 95% chance that the lot will pass the USP UDU test.

Figure 3 Pictorial of the ASTM E2709/E2810 Methodology



The two broken lines show the maximum standard deviation for each sample mean for *N* = 10 and *N* = 100 such that when the confidence region is generated for that combination of sample means and standard deviations, the entire triangle is below the lower bound. These sample means and standard deviations on the broken line for a given sample size are the entrees in the acceptance limit table. For the found sample mean, if the sample standard deviation is less than the standard deviation in the acceptance limit table, then with the desired confidence there is at least a 95% probability that the lot will meet the USP UDU test. The set of all means and standard deviations below the broken line forms the acceptance region for that sample size. As can be seen in Figure 3, the larger the sample size, the larger the acceptable standard deviation for a given sample mean. For example, a sample mean of 95% LC would have an upper limit on the sample standard deviation of about 2.2% LC for an *N* of 10 but increases to about 3.7 for an *N* of 100.

Approach Comparison

The ASTM E2709/E2810 and tolerance interval methods are compared in Figure 4 using OC curves for sample sizes *N* = 10, 30, 60, and 100. The x-axis is the "true" lot standard deviation. The y-axis is the probability of passing the acceptance limit table associated with either the ASTM or tolerance interval method or the USP UDU test. A reference line is drawn at the 95% probability of passing. These plots can be used to select a sample size. For example, in Figure 4a, if the true lot mean and standard deviation were 100% LC and 3.5%, respectively, then the probability of passing an acceptance limit table based on a sample size of 10 would only be about 60% and 35% for the tolerance interval and ASTM E2709/E2810, respectively. However, passing the acceptance limit tables based on a sample size of 30 would pass using either approach with well over a 95% probability. The ASTM E2709/E2810 OC curves get closer as the sample size increases.

Notice that for the same lot standard deviation, the tolerance interval method has a higher probability of passing the USP UDU test than the ASTM E2709/E2810 method.

For a confidence level of 90%, probability of passing the USP UDU test of 95%, and sample size, an acceptance limit table for the sample standard deviation can be constructed for both methods by fixing the sample mean and increasing the sample standard deviation from a low value, say 0.1, until either the probability of passing the USP UDU test is 95% using ASTM E2709/E2810 or the coverage limit of 98.58% (which corresponds to a 95% probability of passing the USP UDU test) is reached using the tolerance interval method. The standard deviation associated with meeting either of these probabilities is the entry in the acceptance limit table. Table C shows a portion of the acceptance limit tables for both methods with *N* = 10, 30, 60, and 100. An R program,[17], which can be found in the Appendix, was used to generate the complete acceptance limit table for the tolerance interval method.

Table D provides a comparison summary of the ASTM E2709/E2810 and tolerance interval approach.

As can be seen from the example, there are two reasons for the "conservative" nature of the ASTM E2709/E2810 method.

Figure 4a

OC Curves vs. Lot Standard Deviation for USP UDU, ASTM E2709/E2810, and Tolerance Interval Method
Lot Mean = 100% LC
***N* = 10, 30, 60, and 100**
All ASTM/tolerance interval tests based on 90% confidence level and 95% probability of passing USP UDU

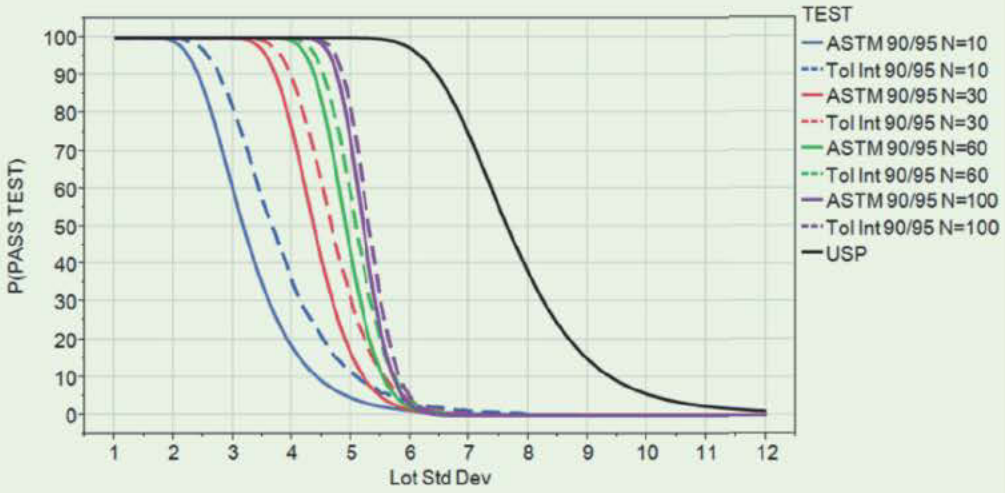
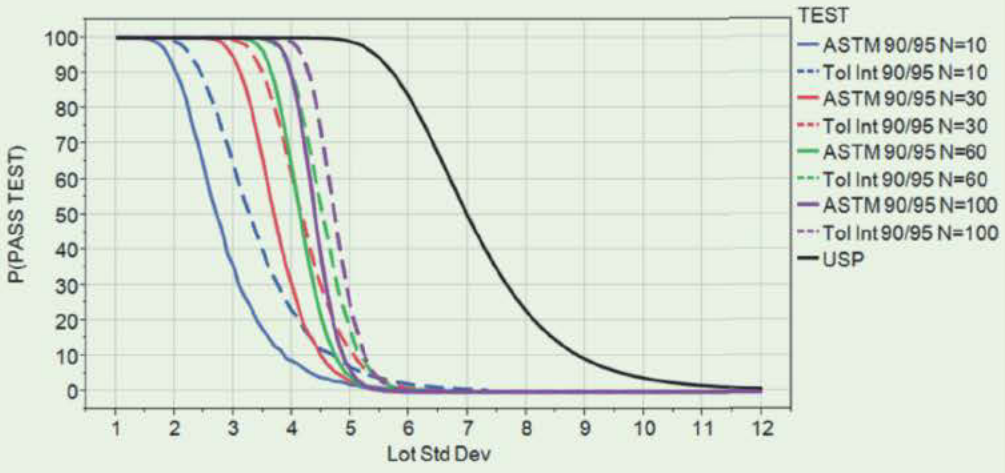


Figure 4b

OC Curves vs. Lot Standard Deviation for USP UDU, ASTM E2709/E2810, and Tolerance Interval Method
Lot Mean = 97% LC
***N* = 10, 30, 60, and 100**



▸ The triangular simultaneous confidence interval used in the ASTM E2709/E2810 method may not be the optimum confidence interval to use (see Figure 3). Note that in the example, the coverage using the lot mean and standard deviation from the joint confidence interval is 98.70% whereas the tolerance interval coverage is 98.95%. As Figure 5 shows, the probability of passing the USP UDU test increases about 2% as the coverage increases from 98.70%–98.95%.

▸ As noted above, the lower bound calculation is a mathematical calculation. So the probability of passing the USP UDU test is always less than or equal to the actual probability of passing the USP test. A comparison of the lower bound to the simulated "actual" probability of passing the USP UDU test showed that the lower bound is about 1%, 2%, and 3% lower than the simulated probability when the "actual" probability is 95%, 90%, and 80%, respectively. This difference can be seen in the example where the simulation result was 96.09%, which is about 1% above the lower bound of 95.06%.

Conclusion

ASTM E2709/E2810 and the tolerance interval methods can both be used to evaluate content uniformity data. Both methods can provide a desired degree of assurance that a sample from a lot will pass the USP UDU test. The tolerance interval method is a good alternative to the ASTM E2709/E2810 when using Sampling Plan 1; it generally results in higher acceptance limits on the sample standard deviation, especially at smaller sample sizes. ◂

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Figure 5 USP UDU OC Curve
Probability Passing USP UDU 75%–100% and Coverage 97%–100%

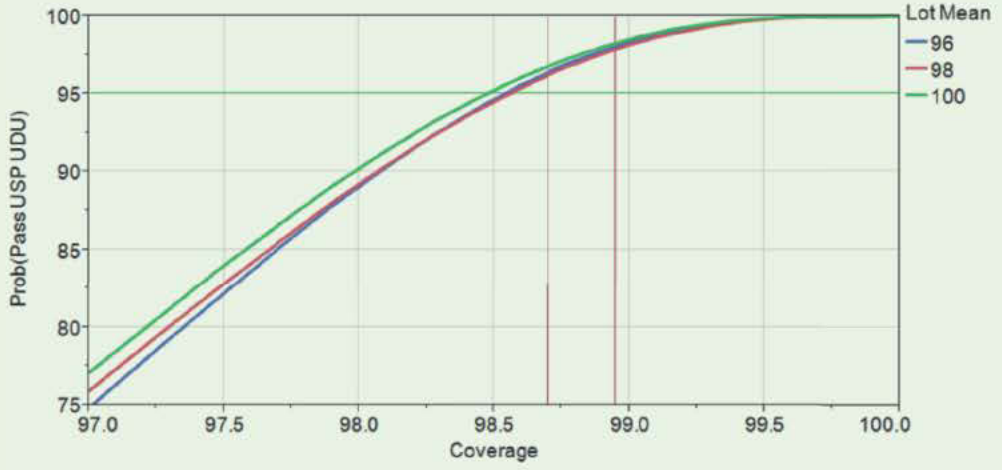

Table A USP UDU Test

All measurements of dosage units and criteria values are in percentage label claim (%LC). At each stage calculate the sample average $\overline{X}$ and the sample standard deviation s.

Stage	Number Tested	Pass stage if:
S_1	10	$AV^* = \lvert M - \overline{X} \rvert + 2.4s \le 15.0$, where M is defined below.
S_2	20	i) $AV^* = \lvert M - \overline{X} \rvert + 2.0s \le 15.0$ using all 30 results $(S_1 + S_2)$ ii) No dosage unit is outside the maximum allowed range of 0.75^*M to 1.25^*M.

M is defined as follows:

If T is less than or equal to 101.5%LC, and
(i) If $\overline{X}$ is less than 98.5%LC, then M = 98.5%LC.
(ii) If $\overline{X}$ is between 98.5 and 101.5%LC, then $M = \overline{X}$.
(iii) If $\overline{X}$ is greater than 101.5%LC, then M = 101.5%LC.

If T is greater than 101.5%LC, and
(i) If $\overline{X}$ is less than 98.5%LC, then M = 98.5%LC.
(ii) If $\overline{X}$ is between 98.5 and T, then $M = \overline{X}$.
(iii) If $\overline{X}$ is greater than T, then $M = T$.

T is the target content per dosage unit at the time of manufacture, expressed as percentage label claim. Unless otherwise specified in the individual monograph, T is 100.0%LC. *AV = Acceptance Value

Table B Simulation: Lot Mean vs. Coverage for Prob (Pass USP UDU) = 95%

Lot Mean	Coverage
96	98.54
97	98.58
98	98.55
100	98.47

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Table C	ASTM and Tolerance Interval Approach Acceptance Limit Tables (N = 10. 30. 60. 100) for the sample standard deviation (% LC)							
		N = 10		N = 30		N = 60		N = 100	
Sample Mean		ASTM	Tolerance Interval	ASTM	Tolerance Interval	ASTM	Tolerance Interval	ASTM	Tolerance Interval
100.0	100.0	3.211	3.587	4.479	4.656	5.002	5.079	5.279	5.310
100.2	99.8	3.172	3.585	4.429	4.654	4.955	5.076	5.238	5.307
100.4	99.6	3.134	3.579	4.377	4.646	4.905	5.068	5.192	5.298
100.6	99.4	3.095	3.568	4.325	4.633	4.851	5.054	5.141	5.284
100.8	99.2	3.057	3.554	4.272	4.614	4.795	5.034	5.086	5.263
101.0	99.0	3.018	3.536	4.219	4.591	4.737	5.009	5.028	5.237
101.2	98.8	2.979	3.514	4.165	4.563	4.678	4.979	4.968	5.206
101.4	98.6	2.941	3.488	4.111	4.530	4.619	4.943	4.906	5.169
101.6	98.4	2.902	3.458	4.057	4.492	4.559	4.902	4.843	5.127
101.8	98.2	2.863	3.425	4.004	4.450	4.498	4.857	4.779	5.079
102.0	98.0	2.824	3.389	3.949	4.404	4.438	4.807	4.715	5.028
102.2	97.8	2.786	3.350	3.896	4.354	4.377	4.753	4.651	4.971
102.4	97.6	2.747	3.308	3.841	4.301	4.317	4.695	4.587	4.911
102.6	97.4	2.708	3.265	3.787	4.244	4.256	4.634	4.523	4.848
102.8	97.2	2.669	3.219	3.733	4.185	4.196	4.570	4.458	4.781
103.0	97.0	2.631	3.171	3.679	4.124	4.135	4.503	4.394	4.711
103.2	96.8	2.592	3.122	3.625	4.061	4.074	4.434	4.329	4.639
103.4	96.6	2.553	3.072	3.571	3.996	4.013	4.364	4.265	4.566
103.6	96.4	2.514	3.021	3.517	3.930	3.952	4.292	4.200	4.491
103.8	96.2	2.475	2.969	3.462	3.863	3.891	4.219	4.135	4.415
104.0	96.0	2.436	2.917	3.408	3.795	3.831	4.145	4.071	4.337
104.2	95.8	2.397	2.865	3.354	3.727	3.770	4.071	4.006	4.260
104.4	95.6	2.358	2.812	3.299	3.659	3.708	3.997	3.941	4.182
104.6	95.4	2.320	2.759	3.245	3.590	3.647	3.922	3.876	4.103
104.8	95.2	2.281	2.707	3.191	3.521	3.586	3.846	3.811	4.025
105.0	95.0	2.242	2.654	3.136	3.452	3.525	3.771	3.747	3.946
105.2	94.8	2.203	2.600	3.082	3.383	3.464	3.696	3.682	3.867
105.4	94.6	2.164	2.547	3.027	3.314	3.403	3.620	3.617	3.788
105.6	94.4	2.125	2.494	2.973	3.245	3.342	3.545	3.552	3.709
105.8	94.2	2.086	2.441	2.919	3.176	3.281	3.470	3.487	3.630
106.0	94.0	2.047	2.388	2.864	3.107	3.220	3.394	3.422	3.552
106.2	93.8	2.008	2.335	2.810	3.038	3.158	3.319	3.357	3.473
106.4	93.6	1.969	2.282	2.755	2.969	3.097	3.243	3.292	3.394
106.6	93.4	1.930	2.229	2.701	2.900	3.036	3.168	3.227	3.315
106.8	93.2	1.891	2.176	2.646	2.831	2.975	3.092	3.161	3.236
107.0	93.0	1.852	2.123	2.592	2.762	2.913	3.017	3.096	3.157
107.2	92.8	1.813	2.070	2.537	2.693	2.852	2.941	3.031	3.078
107.4	92.6	1.774	2.017	2.482	2.624	2.791	2.866	2.966	2.999
107.6	92.4	1.735	1.964	2.428	2.555	2.729	2.791	2.901	2.920
107.8	92.2	1.696	1.910	2.373	2.486	2.668	2.715	2.836	2.841
108.0	92.0	1.657	1.857	2.319	2.417	2.607	2.640	2.771	2.762

Table D	Comparison Table—Tolerance Intervals vs. ASTM E2709/E2810	
Sampling Plan	N dosage units randomly (simple random sample or systematic using Sampling Plans 1) chosen from a lot. Each dosage unit tested for drug content. Results are expressed as % label claim (LC).	
Assumptions	Individual test results (CU) assumed to be generated by a normal distribution.	
Goal	Provide with 90% assurance (confidence level) that there is at least a 95% probability that the lot will pass the USP Uniformity of Dosage Units (UDU) test (Chapter <905>).	
	Methods	
	ASTM E2709/E2810	**Tolerance Interval**
Strategy	Construct a joint 90% confidence region for the "true" lot mean and standard deviation based on the sample mean and standard deviation. Calculate the lower bound on passing the USP UDU test using the point in the confidence region associated with the lowest probability of passing the USP UDU test. If the lower bound is at least 95%, then with 90% confidence, there is at least a 95% probability that samples from the lot will pass the USP UDU test.	Generate an operating characteristic (OC) curve for the USP UDU test with the y-axis denoting the probability of passing the USP UDU test and the x-axis denoting the coverage. Note: The OC curve is not dependent on collected data. The curve can be computed prior to data collection and used for any data set. OC curves are shown in Figures 1 and 2. Construct two one-sided tolerance intervals (a lower interval and upper interval each at the 95% confidence level to provide a 90% overall confidence level) to determine the coverage. Determine the probability of passing the USP UDU test by finding the point on the OC curve corresponding to the coverage obtained from the tolerance interval calculation. If the point on the OC curve is greater than 95%, then with 90% confidence, there is at least a 95% probability that samples from the lot will pass the USP UDU test.
Example	Suppose *N* = 100, sample mean = 99.0, and standard deviation = 5.020	
Comparisons: **Confidencevs Tolerance Interval**	Uses confidence interval to determine the "true" lot mean and standard deviation with the lowest probability of passing USP UDU Example: Point with lowest Prob (Passing UDU) is at a lot Mean = 97.892 & lot standard deviation = 5.6849 Although not part of the output, these values for the lot mean and standard deviation provides a **98.70%** coverage	Uses tolerance interval to determine percentage of individuals falling within 85-115%LC. R code given in the Appendix Example: Probability CU result falls below and above 85%LC and 115%LC are 0.78% and 0.28%, respectively or a total of 1.06% outside 85% to 115% LC. Therefore, the coverage is **98.95%**.
Comparisons: **Probability of Passing USP UDU**	The lowest probability point provides a lower bound on the probability of passing USP UDU of **95.06%**. Using the lowest probability point, the simulated probability of passing USP UDU is = **96.09%**.	Using the OC curve, the probability of passing the USP UDU test for a lot mean of 97%LC associated with a 98.95% coverage probability is **97.83**.
Acceptance Limit Tables	Both methods can provide acceptance limit tables that provide an upper limit on the sample standard deviation for a given sample mean. Acceptance limit tables for each method for *N* = 10, 30, 60, and 100 are given in Table 4.	
Comparisons Acceptance Limits	In the example, the acceptance limit is 5.028%LC.	In the example, the acceptance limit is 5.237% LC.
Comparisons Decision	Pass	Pass
Similarities	Easy to interpret. Can create look-up tables that are easy to use. Tables can be created prior to data collection. Can provide 90% assurance that is at least a 95% chance that a lot will pass the USP UDU test.	
Advantages	Can be used for Sampling Plan 2 that have multiple variance components (e.g., between and within location).	Actual probability of passing the USP UDU test is closer to the nominal 95%. Provides generally higher acceptance limits on the sample standard deviation.
Disadvantages	Actual probability of passing the USP UDU test is higher than the stated probability. (See below for causes.)	Standard deviation limits can be lower than ASTM E2709/E2810 if the sample mean is far away from target due to an increased confidence level at these points. Methodology for Sampling Plan 2 is in development.

Appendix: R Program to Generate Acceptance Limit Tables

```
setwd("C:/xxxxx")
# Input total confidence level (1- (upper and lower α's combined))
cilevel<-0.90
#Enter sample size
n<-30
# ******  No Edits Required Below Here *****
covlim<-98.58
smeanl<-seq(85.1, 100.0, by=0.1)
init<-rep(200,length(smeanl))
smeanu<-init-smeanl
# ******** delnct function Computes NCP ********
# ******** Given lot mean and standard deviation and target ***
delnct<-function(x,p,df,prec=1e-8) {
# Program by Henrik Spliid, Technical University of Denmark.
# Compute the t-noncentrality parameter for given x, p and df.
d1<-x
f1<-p-pt(x,df,d1)
d2<-d1-2
if (f1<=0) {d2<-d1+2}
f2<-p-pt(x,df,d2)
f3<-1
dold<- 0
d3diff<-1
while(abs(f3)>prec & d3diff > 0.00001){
d3 <- d1-f1*(d2-d1)/(f2-f1)
f3<-p-pt(x,df,d3)
if (abs(f2)>abs(f1)) {d2<-d3;f2<-f3}
else {d1<-d3;f1<-f3}
d3diff<-abs(dold-d3)
dold<-d3
}
delnct<-d3
delnct
}
# ************************** End Function ********************************************
# ************************** Generate Upper Limit on Sample Standard Deviation
********
sdinc<-round(0.001,digits=5)
slim<-rep(NA,length(smeanl))
i<-1
sd<-round(0.01, digits=2)
# ***** Fix Sample Mean ***************
for(mean in smeanl) {
s <- round(sd - sdinc, digits=5)
cov<-100
while(cov > covlim) {
s<-round(s + sdinc, digits=5)
invtup<-sqrt(n)*(115 - mean)/s
ncpup <- delnct(invtup, (1 + cilevel)/2, n-1)
zup <- -ncpup/sqrt(n)
prob115 <- 100*pnorm(zup)
invtlow<-sqrt(n)*(mean-85)/s
ncplow <- delnct(invtlow, (1+cilevel)/2, n-1)
zlow <- -ncplow/sqrt(n)
prob85 <- 100*pnorm(zlow)
totout<- prob115 + prob85
cov<-100 - totout
}
slim[i]<- round(s - sdinc,digits=5)
i<-i+1
}
table<-cbind(smeanl,smeanu,slim)
tablef<-data.frame(table)
names(tablef) <- c("Mean", "Mean", "SD Limit")
# ****  Print Table Stacked (i.e., one column) with mean and standard deviation ****
lmean<-cbind(smeanl,slim)
umeansorted<-sort(smeanu,decreasing = FALSE)
#umeansorted
limsorted<-sort(slim,decreasing = TRUE)
umean<-cbind(umeansorted,limsorted)
all<- rbind(lmean[1:149,],umean)
table2<-data.frame(all)
names(table2) <- c("Mean","SD Limit")
table2
write.csv(table2,file="Test Stacked.csv")
# *** Print Table in Five Pairs of Columns each with mean and standard deviation
****
table2a<-table2[1:50,]
table2b<-table2[51:100,]
table2c<-table2[101:150,]
table2d<-table2[151:200,]
table2e<-table2[201:250,]
table2f<-table2[251:300,]
newtable<-cbind(table2a,table2b,table2c,table2d,table2e,table2f)
newtable
write.csv(newtable,file="Test Table.csv")
```


About the Author

James Bergum is president of BergumSTATS, a company that provides statistical consulting to the pharmaceutical industry in the areas of chemistry, manufacturing, and controls. He holds a PhD in statistics from Montana State University and has over 30 years' experience in the pharmaceutical industry (Ayerst-Wyeth and Bristol-Myers Squibb) working primarily with formulation, process validation, process chemistry, stability, and analytical chemistry scientists. He developed statistically based acceptance limits for process validation that are referenced in FDA guidance for process validation. Bergum is a member of the American Statistical Association (40 years) and ASTM.

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PHARMACOVIGILANCE OPERATIONAL EXCELLENCE: A CASE STUDY

Mark Cupryk and Doina Morusca

This article describes a case study on how the principal elements of operational excellence were put to task by a dynamic, self-directed pharmacovigilance team to better ensure patient safety.

Patient-safety regulations, particularly in Europe, are evolving in complexity and robustness, consequently challenging marketing authorization holders (MAH) and their service providers to rapidly redesign their own drug-safety processes in order to maintain compliance. Even though the desired outcome is to possess better defined and robust pharmacovigilance (PV) processes, the actual challenge lies in designing and implementing the transformation when so many processes may require simultaneous modifications in a short period of time.

One established framework to achieve measurable long-term improvement, operational excellence (OE), can enable the MAH to transform their PV processes by rigorously aligning strategic objectives with the operational actions and vice versa. OE is increasingly being leveraged in transactional processes as compared to its familiar setting of manufacturing, so it is an ideal improvement framework for PV processes.

This article describes a particular case study on how the principal elements of OE were put to task by a self-directed PV team of a global pharmaceutical organization. The perception of the new European PV regulations being the most stringent, combined with an increased percentage of the organization's products being distributed and sold in a number of European countries, motivated the PV compliance objectives toward alignment with these specific regulations. The case study describes how the organization's strategy was tightly linked to PV operations through the plan-do-check-act (PDCA) cycle and also presents how much-needed metrics were established to enhance performance monitoring of each PV process.

What Is PV OE?

Dissimilar industries, and even diverse companies within the same industry, perceive OE differently. The pharmaceutical industry is no exception. In spite of this, one clear fact is that OE matters to these industries because it provides tangible results sustained over time and contributes to overall competitiveness.[1]

There are four critical themes common to the genetic makeup of successful companies leveraging OE:

1. Efforts are driven from an overall business strategy.
2. Use metrics to tie efforts to the strategy and track progress.
3. Structure the program so that people at all levels have a meaningful role.
4. Understand and use the right approach to address unique goals and challenges.

Successful companies have broad knowledge and ability to apply the right tool or approach based on the problem being solved. They combine Six Sigma, lean, theory of constraints, and other approaches into an overall program for improvement. And they don't usually employ a large staff whose sole responsibility is continuous improvement.[1]

Since each organization is unique, there is no set road map to follow on the OE journey. Moreover, the challenge is to address the existing processes, the network of existing service providers, and products already on the market. Such a transformation may require varying degrees of culture change since fundamentally important to OE is the mindset of continuous improvement, collaboration, and open communication.[2–3]

There are also numerous definitions for OE, but, for simplicity's sake, we use the following:

Operational excellence is an element of organizational leadership that stresses the application of a variety of principles, systems, and tools toward the sustainable improvement of key performance metrics.[4]

According to the World Health Organization (WHO), pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem.[5]

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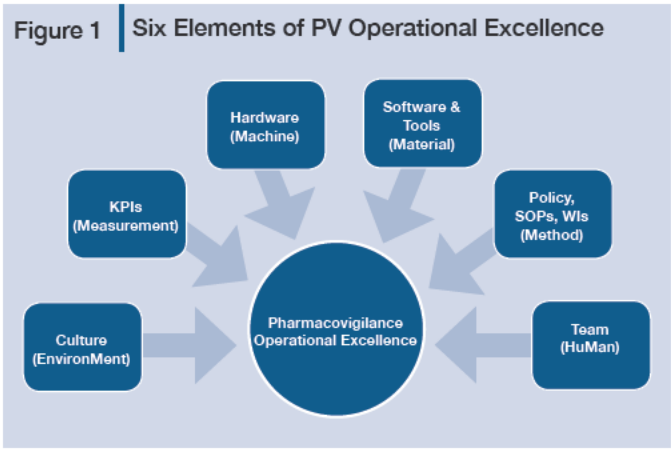
Figure 1 Six Elements of PV Operational Excellence



In distilling the two definitions, PV OE is positioned as "measurable drug-safety processes with a goal of continuous improvement."

Figure 1 shows the six elements that drive PV OE: culture; key performance indicators (KPIs); team; hardware; software and tools; policy, standard operating procedures (SOPs), and work instructions (WIs). Each is directly related to the "six Ms" of Six Sigma: Environ**M**ent, **M**easurement, **M**achine, **M**aterial, Hu**M**an, and **M**ethod, respectively. The six elements are commonly known as the probable roots for issue investigations, where one or more often contribute to potential variations of a process. In this context, the issues are typically analyzed to determine what kind of correction, corrective, and/or preventive action should be taken in the short and long term. Conversely, and often overlooked, these elements are the root causes for opportunities in implementing the continuous improvement of a process. In this positive light, they offer a constructive framework from which each element of a process can be evaluated and improved in the short and long term.

The PDCA Cycle

In the presented case study, as part of the outcome of its annual strategic review in Q4 2011, a global MAH decided to align its PV processes with the European Medicines Agency (EMA) good pharmacovigilance practices (GVPs) prior to these guidelines (listed in Table A) becoming effective. At the time, the GVPs were a relatively new layer of PV guidelines designed to increase patient safety and help foster improvement of PV at the operational level in the member states of the European Union (EU). Since the MAH was increasing the number of marketed medicinal products in the EU, it was a logical choice to ensure compliance to this level. In contrast, the US Food and Drug Administration (FDA) PV guidance documents (listed in Table B) were perceived as describing the FDA's current thinking on the specific subject but not necessarily required, while the EU modules, which are referred to as guidelines, were considered mandatory.

With so many existing process improvement methodologies such as organizational portfolio management maturity model (OPM3), lean management, Six Sigma, total quality management (Tqm), and quality by design, there is no single way to embark on the journey of PV OE. Conversely, these process improvement methodologies share many similarities, and, likewise, it appears that Six Sigma combined with lean management offer a superior approach with numerous tools to support their journey.[6] The PDCA cycle provides businesses, and their departments such as PV, with a cyclic methodology for continuous improvement toward OE.

In the presented case study, the established OE framework is depicted as two PDCA cycling gears propelling the MAH PV processes into increased efficiency and quality over time, as shown in Figure 2. The number of gears shown represent the number of critical monitoring cycles when applying PDCA at both strategic (larger gear) and operational (smaller gear) levels.

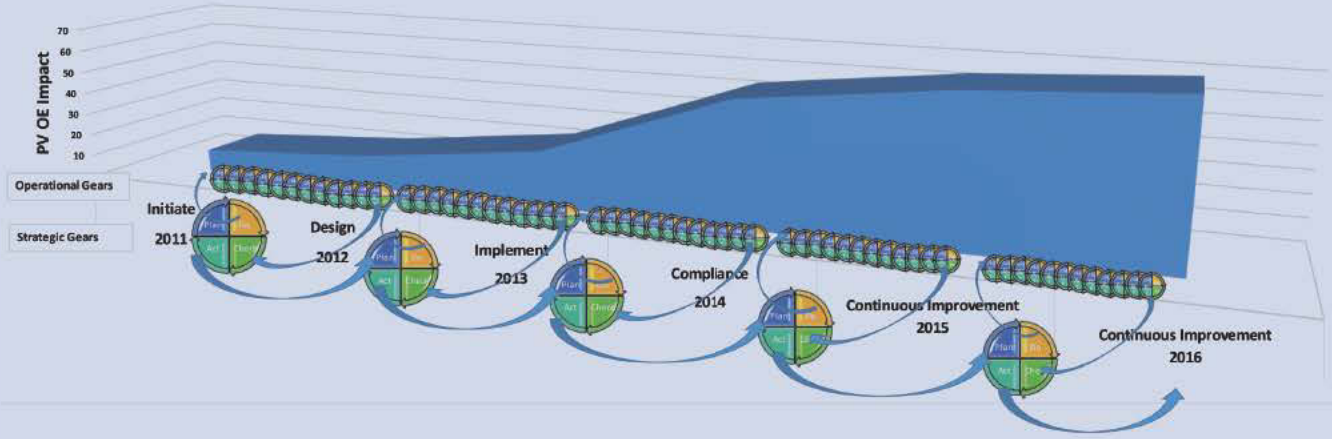
For example, the larger strategic PDCA gear rotates through a cycle over a longer period, annually, for example, to determine what strategic objectives must be completed, adapted, abandoned, or created across the different departments to successfully achieve the business mission.

Once the annual objectives are defined (PLAN phase) and communicated (DO phase), the objectives are converted into the operational tactics—i.e., the PLAN phase of the operational gear. The multiple smaller gears represent the recurring operational PDCA cycles to keep improving the various processes simultaneously.

At the end of the year, the overall operational progress and lessons learned are communicated back to the strategic team, rotating to the strategic gear to the CHECK phase, where the results of these multiple executions are verified against the initial objectives and amalgamated lessons are openly shared, leading to adjustments in the future strategy (ACT phase). These modifications are then used to realign the PLAN phase for following year's strategic objectives. Together, the dual PDCA cycles repeat themselves, adjusting to the strategic forces (environmental, internal, supplier, client, and competition) acting upon and within the organization.

For 2012, the MAH's strategic focus of the PLAN phase was the design of both required changes to the existing PV processes, such as auditing, individual case safety reporting, and literature surveillance, and any needed new processes, such as the post-authorization safety studies. In 2013, the strategy progressed to the implementation of the intended changes, while 2014 concentrated on measuring the actual compliance of the retrofitted processes. Finally, as of 2015, the focus is continuous improvement of each individual process.

Figure 2 PDCA Strategic and Operational Cycles along Operational Excellence Journey



Strategic and Operational PDCA Cycles

PLAN: Setting the Annual Strategic Objectives

To estimate the magnitude of the design improvement activities, a number of gap assessments were completed comparing expected activities identified in each of the 16 EMA GVP modules (listed in Table A) with the MAH's PV Standard Operating Procedures (SOPs), associated Work Instructions (WI), and other supporting tools. Each recognized gap was noted, along with the potential improvement actions to enhance the PV operational and quality processes. As process gap areas were reviewed and deliberated, opportunities regarding automation, the number and type of human resources, and the current technology were also considered.

The rollout of the effective GVP modules was forecasted by the EMA to occur during the period of 2012 to 2015; consequently, not all process gap assessments could be performed from the beginning of the realignment. Hence, the scope of the total effort was expected to increase as more of the EMA GVP requirements became available. To initiate the realignment, a charter was prepared identifying the various internal (project specific and departmental) and external stakeholders. An order of magnitude cost estimate to secure the required funding was prepared, and approved by the Chief Medical Officer, the project sponsor.

Once the funding was approved, a formal project implementation plan, including definite cost and time estimates for the known recommended realignment actions, was prepared. Communication requirements were clearly documented and validated by the director of PV, the appointed champion, who socialized the approach with the various department heads to secure buy-in. Each of the required future PV processes was assessed using the key elements of OE for compliance with the forthcoming regulatory guidelines. The critical PV OE design considerations are listed and categorized in Table C.

A risk register was created in order to identify, review, monitor, mitigate, and record risk-management activities. Some of the key risks identified and monitored included the potential for increased scope due to evolving regulatory requirements, insufficient internal resources to support the efforts, and PV service providers not complying with the regulations in the required time and/or to the appropriate level.

Perceived as the most substantial gap was the lack of a formal performance measurement system to monitor and control both individual and overall PV process performance, as well as how to address deviations from performance limits. For that reason, this element became the focal point of development for the PV team. Research on recent trends in metric systems was performed to understand the current thinking in the industry.

Noteworthy is ISPE's Quality Metrics program, which is aimed at assisting the industry in considering metrics aligned with the FDA six-system inspection, the product, the quality system, the process capability, and the culture. In addition to helping fulfill one OE's above-mentioned themes, its initial objective is to provide real-world experience with metrics definitions, data collection, and reporting burden for the benefit of both the industry and regulators.[7]

In spite of the EMA providing a robust foundation for PV processes, they have not yet recommended any related performance metrics. Consequently, the PV project team planned their own quality and timeliness metrics for each process primarily based on historical performance and other recommendations from the literature or subject-matter experts.

DO: Converting Strategic Objectives to Operational Actions
To convert the PV strategy to execution, actions with planned completion dates were established based on the perceived individual process risk to the business and the availability of regulatory guidelines.

An agile form of project management, as illustrated in the swimlane diagram in Figure 3, was the chosen operational delivery method, whereby the process owner was accountable for driving the required improvements. If there were issues impeding delivery, then the process owners were to report back to the operational team for further assistance. Hence, a "no news-good news" approach was instituted to minimize distractions and over-reporting.

The process owners and support members met biweekly to review progress and discuss any other process issues, risks, and changes. The qualified person for pharmacovigilance (QPPV) was ultimately responsible for ensuring the compliance of each PV process with the evolving regulatory requirements. Thus, the QPPV would share any newly released information from the EMA and other impacting regulatory agencies. All progress and future action items were recorded in the biweekly tracking report by the project manager and distributed to the operational team. The biweekly meetings served as an appropriate checkpoint for a transformation that was initially estimated to last approximately 2 years. It allowed the team to view the overall health of their project and identify where any additional support was required.

CHECK & ACT: Operational Monitoring and Controlling
To further communicate, monitor, and control the PV OE progress, a monthly update of the PV-related process work was prepared and distributed to the required stakeholders. The "PV Status Update" communication package included a summary of the process development progress to provide a clear snapshot of the entire program, as shown in Figure 4. Additional presentation slides provided supplementary details regarding the actual progress per PV process. Above all, at the executive level, the pragmatic summary slide provided the suitable visibility of scope, cost, and time variations as well as upcoming risks and changes in the team members. This monitoring step also allowed the project team to formally step back to CHECK and determine if they needed to ACT on future tactics.

CHECK & ACT: Strategic monitoring and controlling
In Q4 2012 and Q4 2013, a change request was prepared identifying any deviations and changes to the implementation plan needed for the upcoming year. For consistency, the change request was approved by the same people who had approved the initial implementation plan.

Similarly in Q4 2014, a closeout report identified the completed activities along with outstanding items that had been transferred to the operational team. This marked the turnover to PV operations to sustain continuous improvement efforts through the established feedback channels of the PDCA cycles.

Figure 3 | Operational Execution

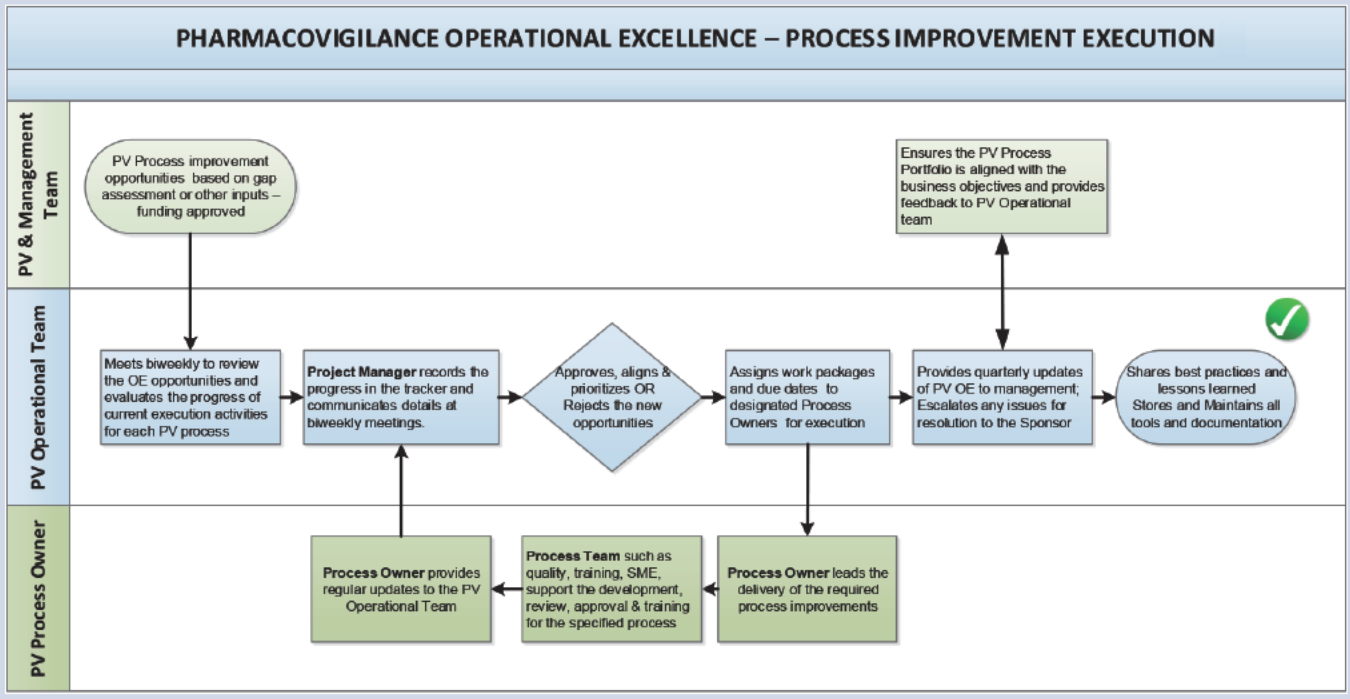


Figure 4 PV Operational Excellence Program Monthly Summary Example

Overall Program Status: Green

Stakeholder Representatives

Sponsor business unit:	Pharmacovigilance
Project Sponsor:	CMO
Project Owner:	Director

Current Project Team

QPPV, project manager, IT specialists, case reviewers, safety physicians, SDEA manager, quality director, director regulatory affairs, director (chair)

Objective

- Implement a compliant, effective and efficient pharmacovigilance system to align to the new EU legislation.
- Ensure partners and vendors are adapting to meet the changes in legislation so the compliance risk is level is mitigated across all organizational and geographic pharmacovigilance activities.
- Ensure current systems i.e. document management, training, CAPA and resources are sufficient in quality and quantity to manage the future pharmacovigilance system.

Benefit

- Maintain and alignment of regulatory compliance for global pharmacovigilance activities.
- Additional efficiencies and increased quality in current processes.

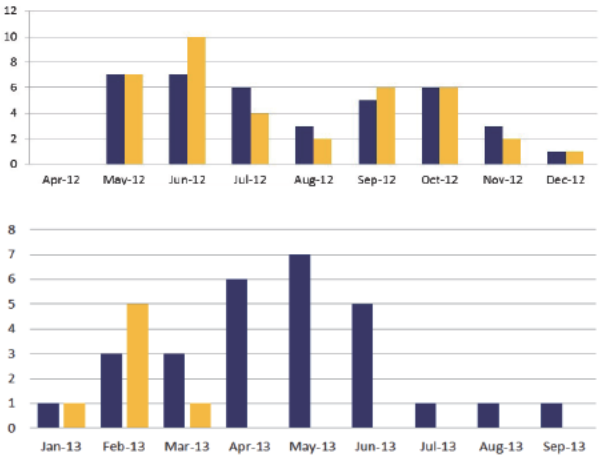
Key Monthly Accomplishments

Progress continued on the following activities:

- ✓ Plan for recruitment effort is still ongoing for compliance manager while the safety physician has been identified and secured
- ✓ The bulk variation submission process is defined and a plan has been prepared and approved
- ✓ PSMF is in place with required documents and the SOP is in review/approve stages
- ✓ CAPA work has impacted quality incident process so the process is being redefined and the work duration will be most likely extended.
- ✓ PASS framework has been established and is under review

Overall project progress since beginning: **67 %**
On track with forecasted completion

Plan vs. Actual Completed Deliverables



Past Key Issues/Risks

- Internal staff was over allocated and caused regular slippage of certain activities.
- New GVP modules increased scope and date of completion of project.
- Partners and/or vendors' lag in maintaining compliance may increase risk.

Changes

- No major scope changes but some activities' delivery dates were adjusted and the details are documented in the biweekly report.

Cost Plan vs. Actual

Met monthly forecast

Hence, the focus shifted from implementation to assessing how well the PV team could perform with their implemented processes and, equally important, how well the measurement system had been established. Another strategic review (CHECK & ACT cycle) will follow at the end of 2015, in order to determine what adjustments may be necessary for continuous improvement.

As part of the 2014 handoff, a more formal lessons-learned session, presented in Table D, was held by the operational team to candidly discuss and record the successes and improvement opportunities of previous years.

PV Measurement System Design and Build

In this section, the overall implementation of the measurement system for identifying, collecting, processing, presenting, and acting on PV process data is discussed. The PV audit process is framed as an example to demonstrate the similar design steps undertaken for each process.

PLAN: Measuring Performance

In the past, PV process reviews were performed on available metrics that had grown organically and so were not deliberate process indicators. A PV performance measurement system was considered a critical element for long-term improvement, not only because it was a stated quality-system requirement in the EMA's Module I, but because visibility would enable faster corrective responses to improve the multiple PV processes.

In establishing the design requirements for the measurement system, the PV team identified and selected 11 significant PV processes aligned with the key the EMA guideline modules.

An SOP was prepared distinguishing these 11 processes along with the metric expectations of timeliness and quality. A KPI dashboard, as shown in Figure 5, aimed to condense and communicate the health of each PV process. Each PV process was designed to have a number of indicators or metrics associated with its performance. In the case of the audit process, the individual metrics identified included percentage of late audits, number of critical findings, number of major findings, percentage of late reports, and percentage of late responses from auditees.

These metrics were summarized by an analytic value (e.g., "A1 PV Audit process") with a possible value of "on-target" or "warning." The direction of the trends of the analytics would be reviewed to diagnose the direction of process variability. Analytics would be monitored monthly, quarterly, or annually depending on the metrics that rolled into their total status. Any negative change in the analytics' trends would act as a signal to the reviewers to drill down to the metrics' level to understand the specifics of the process performance change.

Finally, since certain process KPIs were still in the development phase, these analytics were highlighted in gray to show that the process improvements were not yet effective.

According to Module IV in the EMA GVPs, PV audits include both PV system audits and audits of the quality system for PV activities. The overall description and objectives of PV systems and quality systems for PV activities are referred to in Module I, while the specific PV processes are described in each respective module. Module IV, Section IV.B, describes the general structures and processes that should be followed to identify the most appropriate PV audit engagements and the steps that can be

Figure 5 Dashboard of 11 PV Processes with Rolled-Up Analytic Indicators

KPI ID	Collect & Protect Data	Q1	Jan-14	Feb-14	Trend
A3	Literature Surveillance	Monthly	On-Target	On-Target	Same
A4	Individual Case Safety Reports	Monthly	Warning	On-Target	Up
A10	Product Information Maintenance & Safety Variation Submissions	Annually	Annually	Annually	NA
A11	Post-Authorization Safety Studies				

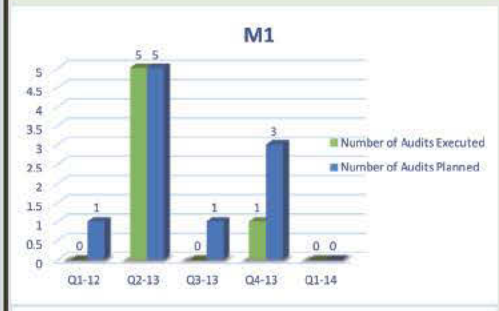
KPI ID	Manage & Minimize Safety Risk	Q1	Jan-14	Feb-14	Trend
A6	Signals	On-Target	Quarterly	Quarterly	NA
A8	Risk Management Plans (RMP) or Risk Evaluation and Mitigation Strategy (REMS)	Annually	Annually	Annually	NA

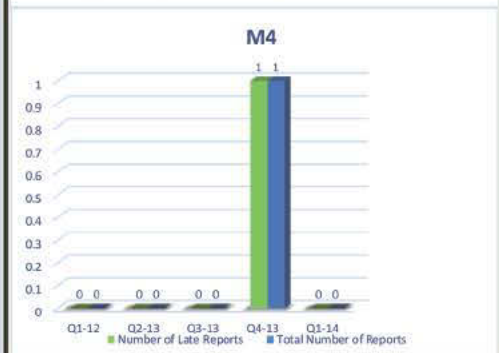
KPI ID	Communicate	Q1	Jan-14	Feb-14	Trend
A5	Safety Data Exchange Agreement	On-Target	Quarterly	Quarterly	NA
A7	Communications to agency and other stakeholders	Annually	Annually	Annually	NA
A9	Aggregate Safety Reports	Monthly	On-Target	On-Target	Same

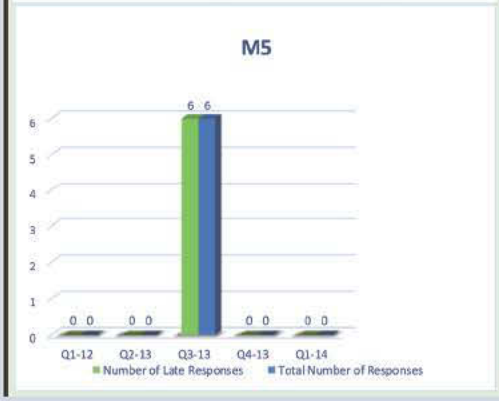
KPI ID	Ensure Compliance	Q1	Jan-14	Feb-14	Trend
A1	Pharmacovigilance Audits	On-Target	Quarterly	Quarterly	NA
A2	Corrective and Preventive Action				

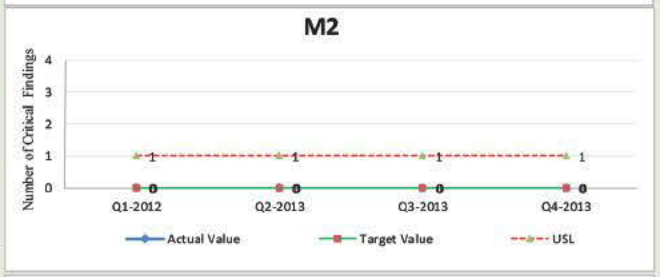
Figure 6 Dashboard of Key Performance Indicators for PV Audit Process

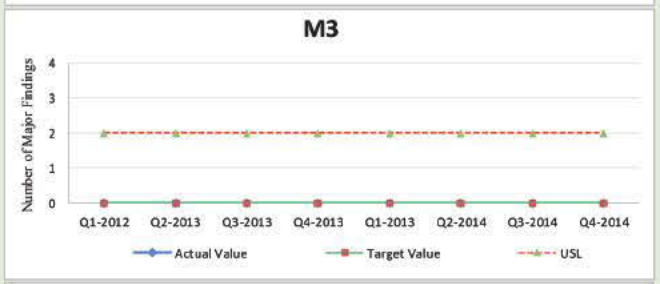
M1	Ratio of actual number of audits executed versus planned	On-Target
M2	Number of critical findings	On-Target
M3	Number of major findings	On-Target
M4	Ratio of actual number of late reports as per the defined time in SOP compared to the total number of reports	On-Target
M5	Ratio of actual number of late responses from auditee as per the defined time in SOP compared to the total number of responses	On-Target
A1	Audit Analytic	On-Target

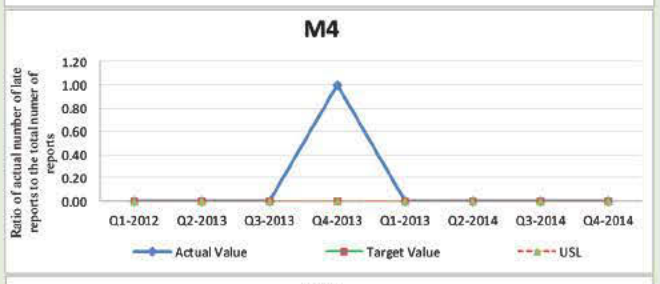


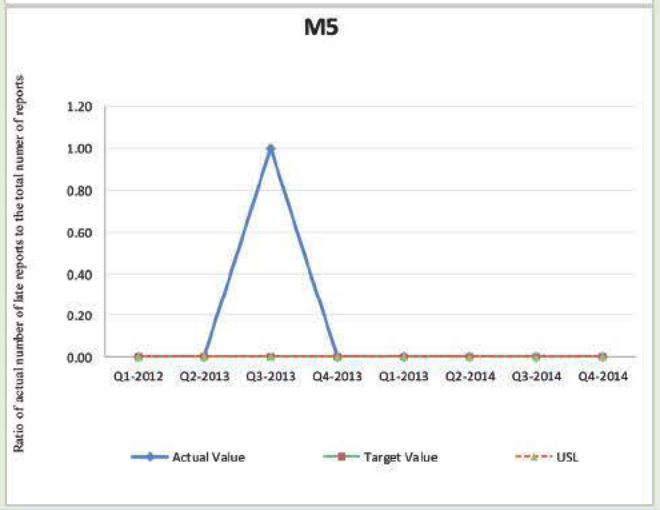












Compliance Status
M1 – For last 3 months planned 1 Audit and executed 0 M2 and M3 – no findings M4 – No reports M5 - No reports

Action Items
1. Confirm location and source to be used to count number of critical/major findings. 2. Discuss at OPS meeting when the planned audit will actually take place

undertaken by MAHs, competent authorities in member states, and the EMA to plan, conduct, and report upon an individual PV audit engagement. This section also provides an outline of the general quality-system and record-management practices for PV audit processes.[8]

In order to assess the compliance of the current PV audit process, the main steps in the audit SOP were evaluated directly through observation and also through the use of a suppliers, inputs, process, outputs, and customers (SIPOC) diagram, as shown in Table E. Any process steps requiring adjustments were revised until the process was endorsed by the PV team. Multiple operational working sessions served as not only an improvement discussion platform but also an excellent training forum and further challenged the understanding of the existing methods and tools.

Next, the team defined the voice of the customer (VOC)—i.e., exactly what they perceived as significant to the process based on EMA guidelines and historical performance. For example, as shown in Table F, PV audit-report approvals were perceived as often taking longer than required, so having a metric for the timeline for approval was "heard" as part of the VOC sessions. Then, these VOC requirements were translated into measurable targets or ratios; for example, 0 was initially targeted for the number of late reports compared to the total number of reports. This was a measurable audit process requirement identified as critical for PV, because the operational team chose to establish a strict target of no late reports. For certain processes, metrics were planned to be categorized further, with weights if perceived as necessary. In general, however, the identified metrics were presented as comparable in importance because it was not perceived as value added to define with further granularity and in the interest of saving time. The idea was to later use the annual review meeting and adjust the measurement system where deemed appropriate.

At this point, the upper and lower specification limits of process performance were also determined, including the expected follow-up actions such as escalation to management or investigations when the limits were exceeded.

Table A	EMA Good Pharmacovigilance Practices (GVP)—Modules		
Module No.	**Guideline Focus**	**Module No.**	**Guideline Focus**
Module I	Pharmacovigilance Systems and their Quality Systems	Module IX	Signal Management
Module II	Pharmacovigilance System Master File	Module X	Additional Monitoring
Module III	Pharmacovigilance Inspections	Module XI	Public Participation in Pharmacovigilance
Module IV	Pharmacovigilance Audits	Module XII	Continuous Pharmacovigilance, Ongoing Benefit-Risk Evaluation, Regulatory Action and Planning of Public Communication
Module V	Risk Management Systems	Module XIII	Incident Management (this module was later integrated into module XII)
Module VI	Management and Reporting of Adverse Reactions to Medicinal Products	Module XIV	International Cooperation
Module VII	Periodic Safety Update Reports (PSURs)	Module XV	Safety Communication
Module VIII	Post-Authorization Safety Studies (PASS)	Module XVI	Risk Minimization measures – selection of tools and effectiveness indicators

Finally, the anticipated collection and review frequency was scheduled in order to avoid a knee-jerk reaction to an insufficient set of data points. Monthly, quarterly, and annual collection periods were identified for different metrics of the PV processes. For example, the PV audit-process metrics would be collected, evaluated, and reported quarterly, since monthly was perceived as too frequent (i.e., there would be insufficient data) and annually was perceived as not having sufficient time to react to flagged issues.

As the entire measurement system was developed, it became apparent that many desired data points were either not captured by the PV operations team or were recorded in multiple redundant documents. Hence, part of the data-collection requirements involved identifying what the data source would be and where the electronic or paper source data file would be physically located. If source data was not available, then operational tools were prepared to collect the required data. In other instances, redundant data sources were amalgamated into one central location.

DO: Executing the Process

Once all the improvement components of the targeted PV audit process were in place, the retrofitted process was made effective and formal performance monitoring began in late 2013. Similarly, each process was activated when the required elements were endorsed by the PV team.

CHECK & ACT: Monitoring and Controlling the Process

As part of the design, a process-specific KPI dashboard had been prepared, such as the example for the PV audit process shown in Figure 6. The PV KPI dashboard was linked directly to the collected data and fulfilled multiple monitoring needs, such as:

- A quick view via the summary status of each KPI (on target or in warning) as shown in the top left-hand side.
- Current visibility through control charts of each actual KPI with their target and limits. In addition, statistical process control and trending was possible since the data was also presented over a specific time scale.
- Additional graphical information when a ratio was used as a metric, in order to ensure visibility of the magnitude of the numerator and denominator data.
- Descriptive data regarding the current compliance status along with the associated action items to help record and track what the outcome of each analysis required.

This information assisted the PV department to not only “check and act” on planning for the next quarterly cycle, but also helped determine which processes required further strategic improvement. This related operational opportunities back to the strategy with open communication and an “improvement” attitude.

Conclusion

The OE-minded PV team designed its PV process-improvement objectives over 2012 and implemented the majority of them in 2013. The project end date was regularly reassessed as more information became available on the actual requirements of the newly approved EMA modules.

In 2014, performance visibility of both transformed and new processes became possible via a new measurement system, which also provided monitoring and controlling capability of trends and nonconformances. During this period, the required adjustments to the PV processes were discussed, designed, and executed. In some cases, the metrics thresholds were changed and the frequency of data collection was questioned and adapted, if needed. The transformation was considered completed.

Table B	FDA PV Guidance Documents
	FDA Guidance Document
1.	Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs - Improving Human Subject Protection, January 2009
2.	FDA Guidance for Industry and Investigators: Enforcement of safety reporting requirements for INDs and BA/BE studies, April 2011
3.	FDA Reviewer Guidance for a Clinical Safety Review of a New Product Application and Preparing a Report on a Review, February 2005
4.	FDA Guidance for Industry: Pre-marketing Risk Assessment, March 2005
5.	FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005
6.	FDA Guidance for Industry: Development and Use of Risk Minimization Action Plans, March 2005
7.	FDA Guidance for Industry "Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report", August 1997
8.	Draft FDA Guidance for Industry: Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report), April 2013
9.	Draft FDA Guidance for Industry: Determining the extent of safety data collection needed in late stage premarket and post-approval clinical investigations, February 2012
10.	Draft FDA Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications, September 2009

Over 2015 and 2016 an emphasis on continuous improvement is anticipated as the processes appear to be aligned with current external and internal forces.

In this case study, the four themes of the PV OE journey were undoubtedly present, although not necessarily with the same degree of influence. The EMA alignment efforts deposited a catalyst for OE and allowed the PV team to better understand, further develop, and refine their own departmental processes. Since the PV team was already self-driven, collaborative, and transparent in their communications, it was a natural part of their culture to adapt and fuel the required changes to occur and continue the pursuit toward PV OE. The PDCA cycles of strategy and operations worked in conjunction to formally support the collaborative communications for OE.

Indeed, the six elements of PV OE were the levers of change impacting each PV process. Even though the level of pressure applied to each lever is unique for each organization, the elements are the root causes associated with opportunity actions to propel an organization toward OE. Therefore, identifying these accurately should bring about the expected outcomes. ◂

Table C	PV Operational Excellence—Design Considerations
PV OE Element	**Pharmacovigilance Operational Excellence Design Considerations**
Key Performance Indicators	What kind of official performance measurement system should be implemented since no measurement system had ever formally been designed and what measurements should be taken and from which data sources?
Team	What degree of outsourcing versus internal execution of PV related activities should be established to optimize cost and quality? Does the PV department have all the right people (Medical Physicians, Case analysts, Medical writers, administrative support, etc.) on the right seats of the PV bus? Will additional internal and/or external resources be needed to manage the forecasted improved processes t i.e. to set up and retrofit the processes and to run the corresponding operational activities?
Hardware	What kind of new hardware is needed and how should outsourcing data management be leveraged for compliance and efficiency?
Software & Tools	The current PV software tools are becoming obsolete, and significantly newer technology improvements are available to help support the PV processes. Is there an opportunity to procure new systems or upgrades to a more current infrastructure?
Standard Operating Procedures	How should the existing quality management system be leveraged or must new pharmacovigilance quality processes be implemented that address the quality specifics regarding patient and/or drug safety? Many PV procedures, work instructions and tools will need to be adapted, hence, how best to manage the review and approval cycle?
Culture	How can PV achieve a higher level of engagement from other departments such as regulatory affairs, medical affairs, labelling etc. since this appears to be a more visible requirement in the EMA PV Modules? How will shortfalls in resources be dealt with in terms of delays to project and securing other support? How long will it take to realistically achieve such an undertaking since PV still must continue to address its regular operational activities and now, must decide on how to evolve to an improved base line for operations?

Table D	Lessons Learned
Successes	**Improvement Opportunities**
1. Pro-active high performing PV team which went beyond their day to day to complete the activities. 2. Achieved global visibility and support as updates were communicated outside PV team on a regular basis. 3. Project Manager in place helped structure projects and monitor progress. 4. Helped the operational team to focus on PV objectives and increase their own understanding of PV processes. 5. Enabled the operational team to digest and establish the appropriate interpretation of the regulations. 6. Subject Matter Expert facilitated the accelerated development of SOPs and minimized rework. 7. Compliance was monitored continually by having SMEs and Quality personnel as members of project team. 8. Proactive leadership by the PV Director to ensure an appropriate operational balance between the day to day work and the alignment project activities.	1. The project took longer than expected due to the review and approval cycles involving a limited number of personnel, who were expected to maintain normal operations during the project implementation. It would not really have been possible to increase the review/approval resources, which are defined by job function. The aim was to maintain overall compliance of PV activities while completing the project deliverables, albeit, it took longer than initially planned. The operational team did increase the durations and communicate their forecasted dates as constraints were identified. In hindsight, since the project did extend longer than planned, it may have been possible to supplement with other support resources to keep the time variance to a minimum. 2. It was perceived that sometimes too many persons were present at the biweekly meetings. However, the meetings served to ensure alignment amongst the team and to support a common understanding of the process expectations by the EMA. Therefore the meetings also served as training for the entire team. Perhaps, the frequency could have been moved to monthly for certain team members. 3. It was unclear whether or not all the right stakeholders were receiving the right information at the right time. A communication plan had been developed from the start and targeted stakeholders were engaged and informed at the documented frequency and with the desired level of content. It may have been beneficial to share the communication plan further and perhaps consider other context or venues to distribute the project information.

Table E	Audit Process SIPOC			
Suppliers	**Inputs**	**Process**	**Outputs**	**Customers**
QA/PV	List of different types of audits	Define the types of audits	New List of types of audits	QA/PV
QA/PV	Defined types of audits and criteria for scheduling the audits	Determine the frequency of audits	Determined frequency of different types of audits	QA/Dir. PV/QPPV
QA/Dir. PV/QPPV	Determined frequency of different types of audits	Create a Schedule of the audit plan	Audit Plan Schedule	QA
QA	Audit Plan Schedule	Review and approve the scheduled audit plan	Audit Plan approved	QPPV
QPPV	Audit Plan approved	Maintain the list of scheduled and completed audits in PSMF	Updated List of scheduled and completed audits in PSMF	Admin
Admin	Updated List of scheduled and completed audits in PSMF	Conduct the audit	Audit conducted	QA/designee
QA/designee	Audit conducted	Draft the audit report	Drafted audit report	QA/designee
QA/designee	Drafted audit report	Review and approve the audit report	Audit r eport approved	QA/designee
QA/designee	Audit Report approved	Distribute audit report to auditee, Director PV, QPPV, deputy QPPV, Pharmacist and CMO	Distributed audit report to auditee, Director PV, QPPV, deputy QPPV, Pharmacist and CMO	QA/designee

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Table F	PV Audit Process Key Performance Indicator Requirements					
Critical to quality—KPI / **Voice of customer**	**Importance**	**Ratio of actual number of audits executed vs. planned (M1)**	**Number of critical findings (M2)**	**Number of major findings (M3)**	**Ratio of actual number of late reports compared to the total number of reports (M4)**	**Ratio of actual number of late responses from auditee compared to the total number of responses (M5)**
Ensure PV audits are completed in terms frequency per SOP	5	X				
Number of audit findings (critical and major)	5		X	X		
Appropriate time to achieve an audit report approval	5				X	
Final audit response time from the auditee	5					X
Frequency of data collection/reporting		Quarterly/quarterly	Quarterly/quarterly	Quarterly/quarterly	Quarterly/quarterly	Quarterly/quarterly
Target		1	0	0	0	0
Lower specification limit		0	N/A	N/A	N/A	N/A
Action on LSL		If actual ratio = 0 for **one quarter**, then discuss with QA. If actual ratio = 0 for **one year**, then escalate to management and discuss appropriate actions.	N/A	N/A	N/A	N/A
Upper specification limit		N/A	1	2	> 0	> 0
Action on USL		N/A	If actual number of findings ≥ 1, escalate to management	If actual number of findings ≥ 2, discuss at OPS meeting	If the number of late reports > 0, discuss at OPS meeting	If the number of late reports > 0, discuss at OPS meeting
Data type 1		Number of audits executed	Number of critical findings	Number of major findings	Audit report late	Final total audit response
Data type 1—source documents		PSMF_S	Audit reports	Audit reports	PSMF_Audit	PSMF_Audit
Data type 1—location of source document		PSMF—Section 8.3	PSMF— Section 8	PSMF—Section 8	PSMF—Section 8.3	PSMF—Section 8.3
Data type 2		Number of audits planned	N/A	N/A	Total number of reports	Total number of responses
Data type 2—source documents		PSMF_S	N/A	N/A	PSMF	PSMF
Data type 2—location of source document		PSMF—Documents	N/A	N/A	PSMF—Documents	PSMF—Documents

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- Bio Process Validation (T32)
- C&Q (T40)
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- Process Validation (T46)
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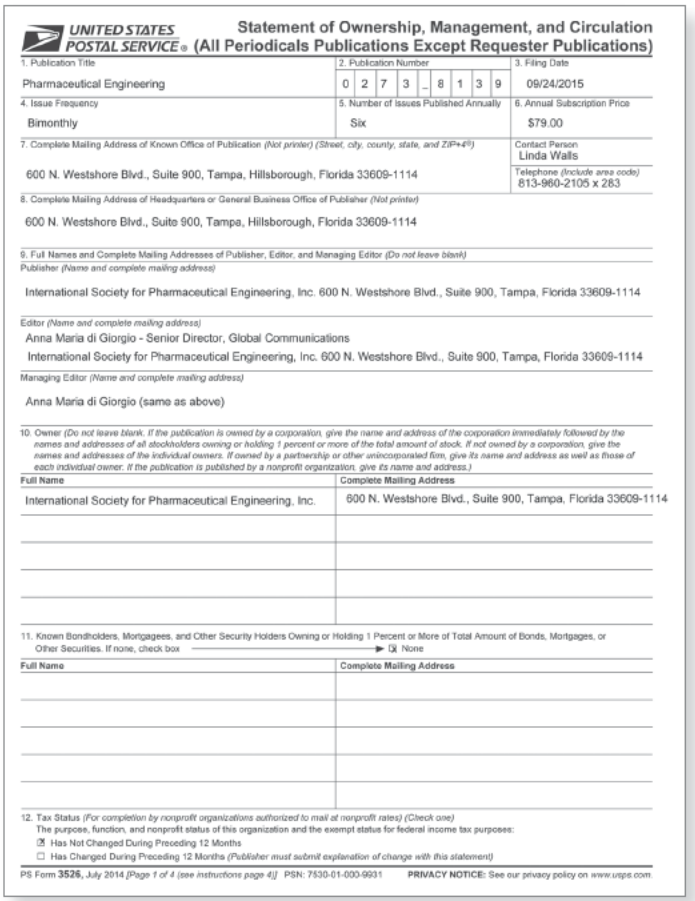

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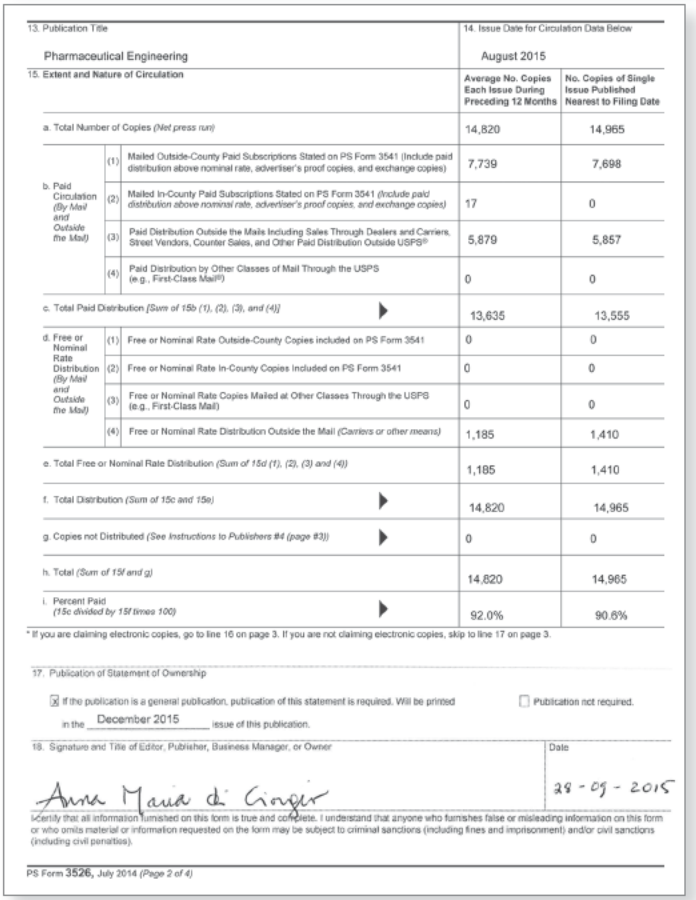

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MOORE'S LAW AND THE DEVELOPMENT OF BREAKTHROUGH BIOLOGICS

Scott Fotheringham, PhD, and James Hale

The power of exponential growth can be wondrous, especially for a businessman like Ron Walker. The 76-year-old Australian is one of the country's wealthiest property developers and knows how compound interest affects investments. But Walker learned the hard way that the natural world is no stranger to rapid growth, and it's not always benign.

In healthy tissue, cell number doubles every division. But the same is true of cancer cells, a fact Walker discovered in 2012 when he was diagnosed with melanoma, the deadliest of skin cancers.[1]

Nine months later this aberrant doubling had led to tumors in his lungs, brain, bones, and adrenal glands. He was given a few months to live.

Standard treatment for melanoma includes surgery, chemotherapy, and radiation.[2] But now, thanks to advances in molecular biology, immunology, improved cell lines, transgenic mice, and product processing, it can also be treated with biologics: targeted therapies that hold great promise.

Walker first received an infusion of Yervoy (Bristol–Myers Squibb), which led to a severe autoimmune reaction that prevented further treatment. He then enlisted in a Phase 1 trial for Keytruda (Merck). He flew to Los Angeles, received his first infusion, went home, and waited.

There's a lot of talk these days in pharmaceutical engineering circles about Moore's Law, the famous observation that computing power doubles every two years. It turns out that many of the innovations that have benefited biopharmaceutical engineering have occurred at a similar pace.

After 2008, the cost of sequencing DNA dropped faster than Moore's Law, mostly because the process has become a billion times faster since the first genome was sequenced in 1977.[3]

Structural proteomics determines the three-dimensional structure of gene products and allows the rational design of novel drug compounds. The efficiency of X-ray crystallography has improved a thousand-fold since the 1960s,[4] meaning that the number of 3D protein structures available for analysis has grown from under 4,000 to over 112,000 in the past 20 years.

Combinatorial chemistry has led to libraries of lead compounds that are several orders of magnitude larger than those of the early 1980s.[5] High-throughput screening has contributed to a 10-fold reduction in cost compared to 1995,[6] while computer algorithms that screen libraries using target biomolecule data have sped up the pace of drug design.

As John Cox, an executive vice president at Biogen, has pointed out, the increase in active pharmaceutical ingredient product titers and the decreased price per gram of production have combined to improve production efficiency 200,000-fold.[7]

These exponential advances have helped big pharma's bottom line. Between 2008 and 2013, sales of full-length monoclonals produced in mammalian cells doubled,[8] while annual sales of the top-six-selling-biologics quadrupled between 2004 and 2012.

The obverse of these huge improvements in sales, efficiency, and reduced costs is the observation dubbed Eroom's Law: The number of new drugs brought to market per billion dollars of R&D declined two-fold every 9 years between 1950 and 2012.[4] Part of this is due to the 10- to 100-fold increase in the cost of bringing a new product to market since the mid-1980s.[9]

With a record number of drug approvals last year, the trend may have reversed, but it's too soon to tell.[10] Eroom's Law has been mitigated by the FDA fast-track process for breakthrough therapies, which can see a drug pass from Phase 1 trials to market in a year. In addition, the increasing costs of drug research and development are being recouped, in part, by exorbitant increases of drug prices.

Within 18 months of receiving his first infusion of Keytruda, Ron Walker was free of cancer. For a disease that is almost always fatal, these exponential improvements in the science and technology behind drug R&D provide patients like Walker the hope of a miraculous cure. ◂

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