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EMBRACING INNOVATION IN PHARMACEUTICAL MANUFACTURING

John Cox on Disruptive Innovation | François Sallans on Quality's Cornerstone | Frances Zipp on Drug Shortages Prevention | Design Considerations for WFI Distilation System | 2015 IFPAC Symposium: Using Process Capability to Enhance Pharma Product Quality

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Embracing innovation means opening yourself up to disruptive innovation, according to John Cox, page 15. Quality and corporate culture go hand in hand, says François Sallans, page 13. ISPE's new tool for drug shortages prevention is phase 3 of the DSPP launched in 2014, Fran Zipp, page 22. Experts and newcomers weigh in on quality culture, pages 67-84. Notes from the 2015 IFPAC symposium, page 126.

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OCTOBER 2015

01 Rocky Mountain Chapter Fall Educational Event, Westminster, Colorado, US

07 Boston Area Chapter, Annual Product Show, Foxboro, Massachusetts, US

07 Nordic Affiliate, Advanced Aseptic Processing, Hilleroed, Denmark

07 San Diego Chapter, Clinical to Commercial Meeting, San Diego, California, US

07–08 ISPE/PQRI Process Validation Conference, Silver Spring, Maryland, US

12 DACH Affiliate, Wassersysteme in Der Pharmaproduktion, Weinheim, Germany

12–14 ISPE Manchester Training, Manchester, United Kingdom

13 Belgium Affiliate, GAMP Benelux COP Data Integrity, Zwijndrecht, Belgium

15 Nordic Affiliate, PAT (1 day), Copenhagen, Denmark

15 Turkey Affiliate, QbD for Pharma Products, Istanbul, Turkey

19 Carolina-South Atlantic Chapter, Manic Monday, Raleigh, North Carolina, US

19–20 ISPE Raleigh Training, Raleigh, North Carolina, US

19–23 ISPE Boston Training, Boston, Massachusetts, US

21 Nordic Affiliate, GAMP Event, Stockholm (Solna), Sweden

21 Spain Affiliate, Jornada de GAMP y Automatización, Barcelona, Spain

21 United Kingdom Affiliate, GAMP UK Forum at AstraZeneca, Macclesfield, United Kingdom

22 Spain Affiliate, Jornada de GAMP y Automatización, Madrid, Spain

22–23 Czech Republic/Slovakia Affiliate, Annual Conference: Containment Technology, Karolinka, Czech Republic

29 Carolina-South Atlantic Chapter, Oktoberfest, Cary, North Carolina, US

29 Midwest Chapter, Halloween and Get Pumped for Annual Meeting Party, Kansas City, Missouri, US

NOVEMBER 2015

08–11 ISPE Annual Meeting Philadelphia Marriott Downtown Philadelphia, Pennsylvania, US

09–10 ISPE Philadelphia Training, Philadelphia, Pennsylvania, US

12 Boston Area Chapter, Soft Skills: PowerPoint, Andover, Massachusetts, US

12–13 DACH Affiliate, Pharma 2025 Containment, Heidelberg, Germany

14–16 China Affiliate, Fall Conference, Shanghai, China

19 Belgium Affiliate, "Combo Products" Seminar, Mechelen, Belgium

26 Nordic Affiliate, Annual Conference: Quality Metrics/Risk Management, Stockholm, Sweden

26 United Kingdom Affiliate, Annual Conference: Using Risk Mgmt to Achieve Cost Efficiency Liverpool, United Kingdom

DECEMBER 2015

09–10 ISPE Tampa Training, Tampa, Florida, US

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

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Challenging the Gold Standard of Double-Blind Drug Trials

The Pharmaceutical Journal, 25 June 2015, Ingrid Torjesen

The infallibility of the double-blind randomized controlled trial has been challenged by researchers, who say results fail to reflect significant interactions between treatment and patient behavior. Writing in PLOS ONE, researchers argue that some treatments can be more effective when patients alter behavioral patterns, such as exercise levels or food intake. And the impact of behavioral effects varies according to how strongly the patient believes that they are receiving the active treatment.

They say that clinical trials with a single probability of treatment are inadequate for estimating the additional benefit that arises from such interactions and propose the use of two-by-two blind trials, which randomize both treatment and behavior by varying the probability of receiving active treatment across different participants. This allows the effects of treatment and behavior, and the interaction between them, to be assessed.

www.pharmaceutical-journal.com/news-and-analysis/news/challenging-the-gold-standard-of-double-blind-drug-trials/20068815.article

Margaret Hamburg Reflects on Six Years at FDA

JAMA, 16 June 2015, Rita Rubin

Margaret A. Hamburg, MD, the second woman nominated to be commissioner of the Food and Drug Administration (FDA), stepped down from the post in late March, just shy of six years on the job.

The agency's responsibilities grew within weeks of Hamburg assuming the post, when President Obama signed a law allowing the FDA to regulate tobacco products. The speed of approvals quickened during her tenure, with the FDA greenlighting 51 novel drugs and biologics in 2014, the most in almost 20 years, Hamburg wrote in a blog post on February 5 (http://1.usa.gov/19GX-Deu). Among the drugs approved in 2014 were four novel systemic antibiotics, only one less than the number approved the entire previous decade, she wrote.

jama.jamanetwork.com/article.aspx?articleid=2320313

What's in a Name? Contentious Fight over Biosimilars Coming to a Head

The Wall Street Journal/Pharmalot, 12 June 2015, Ed Silverman

A contentious debate over identifying biosimilars may finally be coming to a head. These drugs are designed to emulate expensive biologics and are forecast to save billions of dollars in U.S. health-care costs over the next decade. But finding the best approach for naming biosimilars has vexed regulators and divided drug makers amid sparring over patient safety and the potential for big profits.

The central question is whether biosimilars should be given the same name as biologics. Next week, the World Health Organization will hold the latest in a series of meetings to sort out the problem. The agency, which oversees the international naming system, recently recommended a compromise that has garnered some support, but whether a true consensus will emerge is unclear.

blogs.wsj.com/pharmalot/2015/06/12/whats-in-a-name-contentious-fight-over-biosimilars-coming-to-a-head/

NYT Op-Ed Slams 21st-Century Cures Act

The New York Times, 17 July 2015, Rita F. Redberg and Sanket S. Dhruva

The Food and Drug Administration (FDA) has been regulating the approval of medical devices since 1976, but its regulatory oversight has not kept pace with the increasing complexity of this technology. Many high-risk medical devices today are approved on the basis of just one clinical trial (as opposed to new medications, which usually require two trials). And only a small minority of clinical studies of medical devices are randomized, controlled and blinded – the gold standard for reliable evidence (and the benchmark to which studies of drugs are held).

Incredibly, legislation that the House of Representatives passed last week would severely weaken, not strengthen, the FDA's already ineffective regulatory scheme for medical devices. The device industry may stand to benefit from this legislation, but the health of the public does not.

www.nytimes.com/2015/07/17/opinion/the-fdas-medical-device-problem.html

Understanding the Dynamics of China's Medicine Regulatory Environment

Thomson Reuters, 17 July 2015, Magda Bujar

China's fast-growing pharmaceutical market has become a significant growth driver for multinational companies, with spending to hit $185 billion by 2018. Nevertheless, a number of challenging issues around China's regulatory procedures need to be addressed in order to decrease the drug lag of 4.5 years that Chinese patients currently face. Importantly, moves to improve this environment are underway.

In view of the challenges and changes occurring at a policy level and within the agency, and also recognizing that measuring the regulatory environment helps both companies in planning their strategy and agencies in managing review process expectations, the Centre for Innovation in Regulatory Science (CIRS) has recently released R&D Briefing 56 entitled "Understanding the Dynamics of China's Medicine Regulatory Environment."

lsconnect.thomsonreuters.com/understanding-the-dynamics-of-chinas-medicine-regulatory-environment

Hedge Funds, "Reverse Trolls" Crushing Biopharma Innovation

CNBC, 22 July 2015, Joseph Gulfo

Prior to September 2012, if your company was faced with a patent-infringement lawsuit brought by a patent troll (an entity that acquires patents just to seek cash payouts from other patent

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holders), your only recourse to invalidate the troll's nuisance patent was through the federal courts – a very costly and time-consuming effort.

In an attempt to increase efficiency and protect innovation, Congress passed the 2012 America Invents Act (AIA). It established "inter partes review" (IPR), a quick and easy way to get rid of nuisance patents. The results have been quite impressive with more than three-quarters of the patent claims challenged via IPR being invalidated upon further review. But, while the system has been very popular and effective for technology companies, two unintended consequences of the IPR law have given rise to practices that very much hurt biopharmaceutical innovation – "reverse trolls" and stock manipulation. You see, those acting in bad faith also have a legal right to file such challenges, and they do.

www.cnbc.com/2015/07/22/biopharma-hammered-by-hedge-funds-reverse-trolls-commentary.html

Opinion: A Prudent Course on Drug Approvals Is Best

Montreal Gazette, 23 July 2015, Allan Cassels

The newest report from Canada's brand name drug makers on access to new drugs has one key message: Compared with other countries, Canada goes slow and low. New drugs are slower to be covered by our provincial drug plans and the numbers of people who get access to new drugs are lower than in other countries. The report is undeniably negative: Canadians are suffering because our governments don't provide timely access to new medicines.

Canada is not wrong to be prudent in taking time to decide how, or whether, a new drug needs to be covered – a precautionary approach is just the smart way to go. Take, for example, the widely prescribed arthritis drug Vioxx, which caused as many as 60,000 excess heart attack deaths in North America, according to some estimates. Those Canadian provinces that were more restrictive in covering it probably had proportionally fewer deaths caused by the drug.

montrealgazette.com/health/opinion-a-prudent-course-on-drug-approvals-is-best

Why Pharma Must Change Its Model

Forbes, 30 July 2015, Bernard J. Tyson

A difficult feat to accomplish in business is to make dramatic change in the midst of current success. History is littered with companies that were once on top of the world and today are non-existent or merely footnotes because they were unable to make sustainable changes when times were good and yet change was required.

Last week, the Food and Drug Administration approved the first in a new class of drugs intended to treat high cholesterol, called PCSK9 inhibitors. Many experts are predicting it will prove to be the most expensive class of drugs ever. The companies developing these new products stand to make billions of dollars. By all appearances it stands to become the greatest financial success in the industry's history. In fact, the cost of these drugs threatens to undermine the health care system upon which the drug industry relies.

www.forbes.com/sites/matthewherper/2015/07/30/why-pharma-must-change-its-model/2

A Gene-Sequence Swap Using CRISPR to Cure Hemophilia

Hemophilia Federation of America, 24 July 2015

Sufferers of hemophilia live in a perpetual state of stress and anxiety: Their joints wear down prematurely and they have bleeding episodes that feel like they will never end. Their bodies lack the ability to make the clotting factor responsible for the coagulation of blood so any cut or bruise can turn into an emergency without immediate treatment.

Hemophilia A occurs in about 1 in 5,000 male births and almost half of severe cases are caused by identified "chromosomal inversions." In a chromosomal inversion, the order of the base pairs on the chromosome are reversed so the gene doesn't express properly and the sufferer lacks the blood coagulation factor VIII (F8) gene, which causes blood to clot in healthy people.

A Korean team led by the Director of the Center for Genome Engineering, Jin-Soo Kim, Institute for Basic Science (IBS), and Professor Dong-Wook Kim at Yonsei University has experimented with hemophilia A-derived induced pluripotent stem cells (iPSCs) and hemophilia mice and found a way to correct this inversion and reverse the clotting factor deficiency that causes hemophilia A.

www.hemophiliafed.org/news-stories/2015/07/a-gene-sequence-swap-using-crispr-to-cure-hemophilia/?utm_content=bufferf03b2&utm_medium=social&utm_source=twitter.com&utm_campaign=buffer

Much Ado about Something: Worries Are Growing About the Effects of Dealmaking among Generics Firms

The Economist, 2 May 2015

The plot is worthy of a Shakespearean comedy. Teva is in pursuit of Mylan. But Mylan dislikes its suitor and runs away to declare its love for Perrigo, while seeking a poison pill in case it is forced to marry Teva. Perrigo, though, rebuffs Mylan. With many suitors, Perrigo is holding out for a better offer – perhaps even from Teva itself. It may not be quite midsummer, but the unfolding drama featuring three generic-drug makers could well run until then.

This week Mylan, based in the Netherlands, rejected a $40 billion bid from Teva, of Israel, arguing that it "lacks industrial logic." To be on the safe side it has enacted a poison-pill defence against hostile takeover. Combining the world's largest generic-drug maker, Teva, with the third-largest, Mylan, would create a company with around $30 billion in annual revenues and, Teva says, $2 billion in cost savings. As part of its plan to escape Teva's clutches, Mylan has made three successive takeover offers to Perrigo, a smaller Irish rival, only to be spurned each time. Perrigo now seems likely to attract interest from other companies.

www.economist.com/news/business/21650151-worries-are-growing-about-effects-dealmaking-among-generics-firms-much-ado-about#Ac0oc4MfLpYL7Zym.99

Health Canada's New Rules for Homeopathic Products for Kids Should Apply to Adults, Expert Says

CBC News, 6 August 2015

Health Canada's crackdown on some natural health products for children should apply to products for all ages, a critic says. Last week, Health Canada announced it will toughen the rules for some products marketed to help children get over a cold or the flu. More than 10,000 natural health products, from herbal-based remedies to homeopathic treatments, were licensed by Health Canada last year alone. They are often sold next to conventional medicines. The regulator said it will no longer allow companies to make specific health claims on homeopathic products for cough, cold, and flu for children 12 and under, unless those claims are supported by scientific evidence. An investigation by CBC's *Marketplace* revealed how little scientific evidence is required by Health Canada to license homeopathic remedies.

Joe Schwarcz of McGill University's Office for Science and Society in Montréal, Québec, said Health Canada's proposed changes don't go far enough. "I don't think it makes any kind of sense to draw a line at age 12 and to require evidence for children's products but not to have the same criteria for products that are sold to adults," Schwarcz said. *Marketplace* asked Health Canada why all homeopathic products don't require scientific evidence.

www.cbc.ca/news/health/health-canada-s-new-rules-for-homeopathic-products-for-kids-should-apply-to-adults-expert-says-1.3181947 ◂

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CULTURE IS THE CORNERSTONE OF QUALITY

François Sallans
Vice President, Quality & Compliance and Chief Quality Officer, Johnson & Johnson

▸ A strong quality culture is best indicated by what is done when no one is looking. ◂

Delivering safe and efficacious products to patients and care-givers is the healthcare industry's greatest responsibility. The critical path to achieving this and fulfilling our responsibility is embedding quality in everything we do, and more importantly, into the thinking and actions of everyone in the system.

ISPE has been instrumental in harmonizing our understanding of what it takes to build and sustain a corporate culture that values and lives quality.

In its attempt to help end drug shortages, the ISPE Drug Shortage Prevention Plan (DSPP) proclaimed a quality culture as one that "encompasses an organization's practices, central values and philosophy as well as the concentration of all people and resources engaged in a never-ending quest for greater quality and service throughout every dimension of the organization. Quality culture describes the importance of cross-functional, organization-wide commitment to quality, allowing the company to make decisions that best benefit patients".

To help measure the maturity of a quality culture, the ISPE Quality Culture Team developed the "Six Dimensions of Cultural Excellence Framework".

Under this Framework, strong quality culture begins with management setting the tone at the top. Reaching employees and external business partners who act on a company's behalf with a clear message that conveys the company's commitment to deliver quality helps drive customer-focused thinking and decision making and quality performance. Delivering the message must be consistent, persistent, and relevant. This requires the leaders themselves to "walk the talk" and model the desired attitudes and behaviors.

Individual ownership of quality can only be achieved in an environment where transparency is welcome and protected. Giving people the opportunity to speak up anonymously, via a survey, without risk of retaliation or penalty gives management insight into what is working and which areas need attention. Another proven way for management to observe and collect feedback is to engage with employees in person.

In the attempt to measure quality culture, caution must be given to not drive the wrong behaviors by striving for a number. A strong quality culture is best indicated by what is done when no one is looking. While quality culture is not easily converted to a metric, companies can assess their quality culture maturity and continuous progress.

The spirit of continuous improvement is at the core of the work ISPE is leading to help manufacturers work in service for customers. The benefit industry and health authorities reap from operating a robust quality system and fostering a quality culture is the satisfaction that comes from fulfilling our shared mission – to help improve and safeguard the health and well-being of people.

Culture is the cornerstone of quality. ◂

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FUTURE FACTORIES FOR MANUFACTURING FLEXIBILITY

Scott Fotheringham, PhD

In the 1970s, Nucor, which had been a nuclear energy company, decided to pivot vertically into steel manufacturing. It transformed traditional production, lowering costs by using scrap metal and electric arc furnaces instead of the more expensive iron ore and blast furnaces on which companies like Bethlehem Steel relied. Nucor was so successful at capturing the lower end of the steel market, making rebar and other low-quality steel products with its mini-mills, that it disrupted the integrated steel mill industry. It eventually became the largest steel producer in the US.[1]

Disruptive Innovation

This example of disruptive innovation—the term coined by Clayton Christensen in *The Innovator's Dilemma* (1997)—serves as inspiration for the thinking and planning of John Cox, Executive Vice President of Pharmaceutical Operations and Technology at Biogen.

"I look at other industries, like steel, that have made huge shifts in their manufacturing processes," Cox says. "They went from batch mode to continuous mode, from large plants to mini-mills. The companies that embraced these innovations put themselves in a strategic position. I think the time is ripe for this type of disruptive innovation in bioprocessing."

> ▸ Right now there's a need to transform the throughput of large-scale plants to meet this demand. ◂

Cox is asking how pharmaceutical manufacturing, which is driven by capacity constraints, existing and to-be-built pipelines and the risks of sinking capital into future projects, can embrace innovations to provide the mass of drug product required by the booming market for monoclonal antibodies (mAb) and other biologics. It's a classic dilemma.

"Should our process engineers continue to improve technology's so-called sustaining innovations or, instead, as mini-mills did for Nucor, should we be investing in smaller, more flexible and agile technologies as we aim to meet market demand?" he asks. "We're at that kind of pivot point in our industry and Biogen is placing significant bets and investments around these new technologies to be ready for the future."

John Cox, Executive Vice President of Pharmaceutical Operations and Technology at Biogen.

Cox wants to see a new dominant design in pharmaceutical manufacturing, one that will come about through collaboration between academics, suppliers and industry engineers. He embraces a hybrid model of factory design, one that combines the flexibility and lower capital investment of portable, disposable systems with the high volume and throughput of stainless steel, to ensure production that will meet the needs of the types of patients that are the focus of R&D at Biogen. There is a need to improve production processing, particularly for biopharmaceuticals aimed at diseases such as Alzheimer's and multiple sclerosis (MS), so Biogen can supply the demand for metric tons of product annually.

"It's this scale of capacity capability from a single plant that will enable the products that this industry is embracing in biologics," he says. "Whether it's the cancer therapies (e.g., PD-1s), the PCSK9s or the Alzheimer's drugs that we and others are working on, we need this improved production.

"Right now there's a need to transform the throughput of large-scale plants to meet this demand. Our task is to figure out how to move from large-scale plants capable of producing kilogram quantities of product to ones capable of producing 10 tons of product annually."

The Evolution of Manufacturing Technologies

Cox points out that, since 1980, pharmaceutical product titers have followed a variation of Moore's Law, which holds that the number of transistors in an integrated circuit doubles every two years. Titers have increased 1000-fold from their levels in 1980 (0.01 g/L) with facilities now routinely hitting 10 g/L. While these increases are substantial, what is equally impressive is that the price per gram of product has fallen 200-fold in the past 35 years to a mere $50. Advancements in downstream processing have taken advantage of these high titers to bring about process yields of 3 g/L and more.

This rapid improvement in drug substance output has come about through an evolution of manufacturing technologies and factory design. These include the introduction of large-scale (20 kL) bioreactors and six-pack plants; the portable and ballroom concepts of design; single-use technologies to complement the traditional, fixed, stainless steel equipment; emerging contract manufacturers; and bioprocessing. Culture and purification improvements include significant increases in titers through high-titer yielding expression vectors, better parental cell lines and cell culturing (e.g., N-1 perfusion during seed train[4]), high-capacity purification and single-pass tangential flow filtration.

Simultaneously with these innovations, cost-cutting and streamlining saw the industry transform from one characterized by internal and domestic production, low utilization (an average of 54 percent) and significant inventories into one with outsourcing, global production, low inventories and high-capacity production. The accompanying quality issues and drug shortages that became common were, and continue to be, a concern. However, the good news is that pharmaceutical earnings are up almost 60 percent since 1990 and the pharmaceutical industry is expected to reach $1 trillion in sales by 2020. This new era is characterized by the burgeoning biologics sector, fed in large part by the market for large molecules (especially immune-oncology products), biosimilars, emerging markets and targeted niche drugs.

The Need for Production of Metric Tons While Maintaining Quality and Supply

Cox sees this transformational time for the industry as replete with challenges for people in operations, manufacturing and supply, particularly to meet this need for metric tons of product. While the dosages for Biogen's high-potency products like Avonex®, an interferon used for the treatment of MS, are in micrograms, dosages of mAbs tend to be in the range of milligrams. Couple this with the large, and growing, populations of patients with MS, Alzheimer's and various cancers and it is obvious why Cox is focused on the need for increased throughput.

"The industry is faced with the opportunity to think about capacity very differently," says Cox. "We're not treating handfuls of patients, or orphan drug numbers of patients, but millions of patients."

Biogen has 18 biopharmaceutical experimental therapeutics at various phases of clinical trials, including Daclizumab High-Yield Process, developed in collaboration with AbbVie Biotherapeutics, which has been filed with the FDA. It is for patients with relapsing-remitting MS. Aducanumab (BIIB037) is a monoclonal aimed at reducing amyloid plaques in Alzheimer's, which showed positive Phase 1-b trial results last March. Phase 2 results were disappointing, especially for the mid-range dose[5], but a Phase 3 trial has begun, with 1,350 patients for the five-year study. Anti-LINGO-1 (BIIB033) is in Phase 2 trials as an experimental re-myelinating mAb for MS patients.

A further factor influencing the need for metric tons of product is the need for high dosages to breech the blood-brain barrier for neurology products such as a mAb targeting amyloid plaques in Alzheimer's—higher doses are needed because a low percentage of the drug actually makes it to the brain.

The Question of Capacity

"There is a capacity need across the industry right now, not just for monoclonals, but for all large molecules, including recombinant and fusion proteins," Cox says. "Fortunately, the doubling of productivity that we've seen every few years applies to these products as well."

The launch volume of a drug product that the market requires depends on dosage, the number of potential patients and the production titer. As Andy Skibo points out elsewhere in this issue, launch volumes are difficult to predict and may vary by a factor of as much as 17.

This uncertainty when launching a new product means that companies need a flexible supply chain that can respond quickly to a wide range of possible production amounts. Until the required dosage of an experimental drug is identified and the production process (e.g., titer and production yield) is worked out, it is difficult to estimate the needed capacity.

"The way people have dealt with demand uncertainty is to build massive amounts of excess capacity," Cox says. "We went with massive amounts of stainless steel and, because of the uncertainty of both demand and the pipelines, we had significant

Biogen, with headquarters in Cambridge, Massachusetts, discovers, develops, manufactures and markets treatments for neurological, haematological and autoimmune diseases. It had revenues in 2014 of $9.7 billion.[2]

Its products on the market include the recombinant fusion proteins for hemophilia, ALPROLIX™ and ELOCTATE™. For relapsing forms of MS, there are two interferon products, AVONEX® and PLEGRIDY®, as well as TECFIDERA, the number one prescribed oral MS therapy in the U.S. More than 135,000 MS patients have been treated with TECFIDERA worldwide as of 2014. Monoclonal antibody products include GAZYVA®, indicated for chronic lymphocytic leukemia, which was the first product approved by the Food and Drug Administration (FDA) as a breakthrough therapy, and RITUXAN®, which is indicated for non-Hodgkin's lymphoma. These anti-CD20 mAbs are commercialized in collaboration with Genentech (Roche), earning Biogen $1.2 billion in revenues last year.

Biogen, like all of the industry, is adjusting to recent developments in pharmaceutical manufacturing[3] that include the globalization of markets and of production, patent expirations of blockbusters and the concomitant introductions of biosimilars and the design, development and testing of biopharmaceuticals targeted at specific diseases. These latter, breakthrough products, while promising to be incredibly valuable to the industry—not to mention to patients—bring up challenges for the industry, notably the need to increase factory output.

under-utilization across the industry. Then there'd be times when suddenly there'd be shortages because we hadn't built in advance and there'd be overbuilding. When capacity is not being used there are billions of dollars not being used. We ought to think of those billions in excess capacity as money that could be used in the healthcare system for more clinical trials."

On the other hand, when capacity is needed, a large-scale plant today can cost roughly $1 billion and take five years to design, build and license by the agencies for commercial product. Companies taking huge capital risks long before they know the product is going to get approved characterize the industry.

"You can't start building the plant after you have phase 3 results or else you'll be waiting two or three years to produce it," Cox says. "You have to take a huge risk and build rigid infrastructure, burying a large amount of investment capital in the ground."

Then, if the company finds out it needs four or eight or 17 times the amount of product, it simply won't be able to build the plants in time. Adding to the complexity of planning is the FDA fast-track approval process[6], especially for experimental drugs that might save lives of late-stage cancer patients, which can see a break-through product pass from Phase 1 to Phase 3 in a year.

"It's rare in this business for a plant to manufacture the product for which it was originally built," Cox says. "You have such un-certainty, at least historically, that it's incumbent on the people in supply and manufacturing to figure out how to reduce that capital risk investment while at the same time ensure supply certainty particularly for the kind of diseases we work with."

Designing plants and processes to be as efficient and nimble as possible can mitigate demand uncertainty.

"Using process sciences combined with process engineering capabilities has permitted our industry to respond to this type of demand uncertainty. For example, academics and some companies are starting to work more with continuous processing, using innovations like N-1 perfusion cell culture upstream. Also, if we can increase the productivity of a cell line four-fold through process science, the impact on our capital investment and our responsiveness would be enormous.

"These new technologies could disrupt manufacturing. We're doing the basic engineering research on this now because, in five years, we want to see these technologies in place. For those of us working in the engineering side of the business, we ought to be thinking and working as hard as we can to implement these technologies, processes and capabilities to be able to use capacity efficiently and get the maximum output."

Continued on page 20

GETTING INNOVATIVE, QUALITY MEDICINE TO PATIENTS, WHEREVER IT'S NEEDED

Lee Spach, Director, Global Supply Chain Hemophilia Franchise Lead and Adam Sherman, Director, Program Leadership and Management, Biogen

Lessons learned from building a large-scale humanitarian aid infrastructure to securely and reliably deliver medicine to some of the world's poorest countries

A year ago, Biogen and Swedish Orphan Biovitrum (Sobi) set out to make good on a promise – produce 1 billion international units (IUs) of hemophilia clotting factor for humanitarian aid purposes, the largest donation of its kind. The first 500 million IUs of the donation will be distributed by the World Federation of Hemophilia (WFH) over five years as part of their Humanitarian Aid program.

This fall, the WFH will deliver the first shipments to clinics in developing countries around the world, including, Senegal, Ghana and the Dominican Republic. Treatment centers are used to receiving donations on an unpredictable, ad-hoc basis. Now, these clinics will receive a predictable, steady supply of medicine. This not only expands patients' access to potentially life-saving hemophilia treatment, it creates a sustainable hu-manitarian aid model that can change the way hemophilia is treated in these countries.

However, achieving our goal has not been easy. A donation of this scale and scope hasn't been attempted before, largely because the infrastructure to manufacture, securely and reliably deliver, and distribute therapy in countries of need did not exist.

Assessing and Addressing the Challenge

When we began this journey, we immediately identified several challenges.

Commercial pharmaceutical distribution channels are highly regulated and clearly defined. But humanitarian aid channels are not. The medicines donated through humanitarian aid programs are often not approved for commercial sale in a country receiving the donation and may require additional importation steps. The complexity of production and delivery to patients through non-commercial channels is enormous, with each country presenting unique nuances, processes and requirements.

▸ We hope that the donation, unique in both scale and scope, serves as a catalyst for the expansion of the WFH's Humanitarian Aid program. ◂

Moreover, there is a heightened risk of diversion, tampering and theft that comes with donations of this kind, and in this case, a need for end-to-end cold storage in places where refrigeration isn't always available.

Delivering to Those Who Need It

Understanding the obstacles, we built an infrastructure to ensure the medicine would get to the people who need it.

To combat the risk of diversion, we created differentiated packaging and labeling for the vials and shipping cartons of the donated product. We also built a cloud-based system to enable secure tracking of donated product, allowing us to track, in real-time, the progress of our shipments from the warehouse to the treatment clinic.

We partnered with DHL's Global Humanitarian Aid and Relief division to establish a secure supply chain. Their rigorous inspection process in each country ensured safe arrival at the treatment clinics while our Global Security team expedited transport from tarmac to delivery vehicles through a unique auditing process that ensured cold storage and clear customs procedures.

Changing the Paradigm

The first shipments of clotting factor from this donation will arrive in approximately 20 countries this year. Over the next two years, the program is expected to more than double in size.

This effort has been a gratifying, uplifting and humbling experience, knowing its potential to be life changing for those who may receive donated therapies. We hope that the donation, unique in both scale and scope, serves as a catalyst for the expansion of the WFH's Humanitarian Aid program. WFH has been working for nearly 20 years to change the way hemophilia is treated in developing nations. We are proud to be working with them. We're also optimistic that this effort will serve as an inspiration for others in industry, advocacy and government to actively participate in improving medical care for people with hemophilia and as a model for Biogen to support and promote change for other, life-threatening diseases for which access to treatment may be a persistent public health challenge. ◂

HIRWA'S STORY

When nine month old Hirwa Mpano Virgile sustained an intracranial bleed in May of 2013, doctors knew he would not survive without immediate surgery. However, with just three vials of treatment in stock at the King Faysal Hospital in Kigali, Rwanda, he would require significantly more just to survive the surgery.

To receive the assistance they needed, the doctors requested a humanitarian aid donation from the World Federation of Hemophilia (WFH). The WFH, in turn, sent the treatment that the boy needed to get through his surgery and the subsequent recovery. The boy's father, Sylvestre Mulindabyuma, later wrote thanking everyone that helped save his son's life. Tragically however, as a result of the bleeding, the boy is now permanently blind, but the outcome might have been even worse had the WFH Humanitarian Aid Program not been there to lend a hand.

http://www1.wfh.org/docs/en/Programs/WFH_Humanitarian_Aid_2014.pdf

Continued from page 18

Cox believes that, moving forward, it won't be about who has the most stainless steel. Historically, companies have made decisions based on titers and calculated the number of liters of bioreactors they would need to meet the projected launch volumes.

"For years the idea was to get higher and higher titers," he says. "But the size of bioreactors and cell culture titers doesn't get at the real manufacturing objective, which is manufacturing throughput. The challenge for our process engineers has moved from getting high titers in these large bioreactors to how to process this much material. Our challenge has moved from one of production to one of purification."

Which circles back to the original question Cox posed: How are companies going to produce metric tons of biopharmaceuticals to meet demand?

Biogen's Future Factory Design—Flexibility in Manufacturing

Biogen's philosophy is that drug substance biologic manufacturing, scale up, technology transfers, managing redundancy and supply risk should be core competencies of the company.

""There are some others who don't consider these core competencies and they contract work out, but we like to do all this internally," says Cox. "We intend to stay at the forefront of this."

Cox understands that there may be times when a company underestimates the amount of product that is needed and has to go to a contract manufacturer. Meanwhile, CMOs are increasing their capacity right now, trying to respond to the demand for biologics. However, he prefers to reap the benefits of keeping internal control of supply and production.

"Take our work in Alzheimer's with Aducanumab®, and other products in our pipeline," he says. "These internal core competencies allow us to rapidly design and build a plant that will fit with the process science and engineering that we apply for that product. As a consequence we don't need to fit our processes into a contractor's facility. This puts us in a better position for launching a product. That way we maintain control of our destiny with a product that's significant for Biogen's future."

The result of this planning is multiple plants where Biogen engineers know they can run any number of the company's products using common platforms.

"We can validate and qualify them in each of our facilities. We can keep this redundancy and we can move products around to maximize utilization."

At the same time, Cox is aware of the risks that manufacturers open themselves up to in terms of quality and supply by aiming for this high capacity utilization.

"I know that groups like the ISPE are looking at how we change manufacturing, regulatory and quality to keep improving," he says. "There has to be a willingness in the industry to work with the FDA and other agencies on these new technologies to elevate quality, efficiencies and throughput. We take a hard look at how we follow and validate products, ensuring quality by using new tech in quality metrics and analytics."

The new factory model that Biogen is betting on is a hybrid dominant design that leverages a mixture of its existing plants and what it calls future factories. The latter, using disposable tanks and single-use purification, reduce cycle time, are portable and are cost-effective for small, clinical quantities of product. They are meant for early-phase production while allowing an increase in scale to meet demand variability. These are combined with stainless steel systems that are cost-effective for high volumes and throughput, have relatively low variable costs and represent sunk costs for many companies. Biogen combines its 2 kL bioreactors for high titer late-stage clinical and commercial production with its 15 kL bioreactors, on which it relies for high-demand products.

"There's a lot of debate in the industry about using disposables versus stainless steel," Cox says. "In terms of economics, it makes sense to use disposable for early stages of development, where you want to make a small amount of product to bring it through R&D to proof of concept. This gives us speed, is not a massive amount of capital investment and keeps us at the forefront of those technologies. It's an inexpensive way and means we aren't tying up a stainless steel plant to do it. Our plan for the production of monoclonals that are needed to supply large numbers of patients remains large-scale stainless steel.

"We still have to be investing in capacity, using disposable as well as building new stainless steel but, instead of building two or four new plants, we're going to build a plant that has a step change in terms of productivity. We then have a choice of being able to go rapidly from low to high utilization, depending on what's needed."

Biogen has plans to build another plant in Switzerland within three to five years that will maximize throughput up to five-fold compared to what a plant that size has produced historically. The new facility will incorporate Biogen's re-designed manufacturing, still focused around stainless steel and large-scale bioreactors, but rebalanced upstream and downstream with new technologies and equipment to improve productivity to the point where it will meet the goal of manufacturing metric tons of product annually.

"If we want to provide drugs to patients around the world, we have to have this capacity increase," he says. "It's extremely expensive to produce these biologics."

Cox see benefits of this hybrid-dominant design of plant beyond the bottom line. The capacity improvement and throughput capability of the company's plants leads to reduced costs, which in turn has allowed Biogen to announce a humanitarian aid donation program for hemophilia.

"It comes down to manufacturing, capacity, technology and our technical development capability that makes this kind of aid possible," Cox says. "We have a credo at Biogen: Caring deeply, working fearlessly and changing lives. All three are important and what we're doing with manufacturing will continue to help us live up to this credo."

John Cox knows he has to stay on his toes.

"Beyond the next five years, if our industry continues to move in this direction, the question I have for process engineers is, what's next?" ◂

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SIX DEGREES OF SHORTAGE PREVENTION: ISPE DEBUTS NEW GAP ANALYSIS TOOL

Frances (Fran) M. Zipp,
President of Lachman Consultant Services, Inc. and Member of ISPE Board of Directors

Serving as a member of the pharmaceutical industry is a privilege that brings with it significant personal responsibility. In recent years, preventing and mitigating drug shortages has become a critical concern for every pharmaceutical professional. ISPE is leading an international effort to understand, assess, and educate patients, providers, regulators, and manufacturers on this critical topic.

ISPE's most recent contribution in this key area has been the development of a new product based on its 2013 Drug Shortages Survey and 2014 Drug Shortages Prevention Plan (DSPP). The ISPE "Drug Shortage Assessment and Prevention Tool" focuses on prevention and practical application to help industry assess its preparedness for mitigating drug shortages. The tool was circulated to key constituents on 31 August 2015 for initial review and comment.

Background

The DSPP developed as a result of discussions with regulatory agencies centered on providing proposals to address the prevention of drug shortages. A key focus emerged from these conversations that was shared by both industry and regulatory agencies such as US Food and Drug Administration, Japan's Ministry of Health, Labour, and Welfare, and Health Canada: All agreed on the need to move from questioning key reasons for shortages to implementation of best practices. The DSPP, released in October 2014, was a global cross-industry effort.

To construct the Good Practice Tool, ISPE drew upon industry feedback from both the DSPP and its 2013 Drug Shortages Survey. The main objectives were as follows:

- Provide a holistic view of vulnerabilities within industry operations and supply chains
- Present recommendations for improvement
- Develop a framework by which industry could develop strategies and practices for each of the DSPP's six dimensions

Using the tool

The intent is for industry to use this tool as a means to achieve its desired state. It is essentially a gap analysis of current operations and the desired state for each of the DSPP's six dimensions:

- Corporate culture
- Robust quality system
- Metrics
- Business continuity planning
- Communication with authorities
- Building capability

The tool consists of a background followed by a series of questions designed to facilitate examination of corporate practices linked to drug shortages. Many of the questions cannot be answered with a simple yes or no; they require analysis that will help determine what ISPE refers to as "maturity level indicators." These are scored on a scale of 1 to 5, where 1 is the least mature and 5 is the most.

Once gaps are analyzed, the tool can help organizations assess their drug shortage preparedness, facilitate improvements, and increase supply reliability using a five-step process:

1. Commit to a shortage-prevention culture
2. Use the ISPE Good Practice Tool
3. Remediate
4. Embed as a part of the corporate culture
5. Engage with stakeholders (including regulatory authorities) to inform them of the changes implemented

Step 1 is self-explanatory: Without senior management commitment to address supply disruptions and improve supply chain robustness, the organization will struggle to reach its full potential in preventing shortages.

Step 2 is included in the Good Practice Tool, with questions designed to assess the gap between current operations and the desired state.

Step 3 uses the results from Step 2 to address vulnerabilities across the entire supply chain, from materials suppliers to contract manufacturing organizations.

Step 4 completes the internal assessment, with recommendations that should be integrated into corporate culture, including assessments from senior management that reflect success in achieving an uninterrupted supply of product.

Step 5 engages external stakeholders (e.g., suppliers, wholesalers, hospitals, regulatory authorities, etc.) in the improvement effort; this may include an update to the site master file.

Conclusion

ISPE's new "Drug Shortage Assessment and Prevention Tool" can initiate invaluable discussions aimed at helping organizations identify their limitations, whether it be in process, governance, or skills. It can also help companies can focus their resources to reduce vulnerability to supply disruptions. The ultimate responsibility for each of us in the pharmaceutical industry is to maintain a consistent supply of critical quality medicines to patients worldwide.

ISPE will release this tool at its November 2015 Annual Meeting in Philadelphia. We hope you will join us and learn firsthand how to move discussions to practical solutions. ISPE also plans to produce training and education materials on each of the elements as we continue our commitment to this critical topic. ◂

About the Author

Frances (Fran) M. Zipp is President of Lachman Consultant Services, Inc, a provider of compliance, regulatory, and technical consulting services to the pharmaceutical and related industries. She has a wealth of operational and management experience in the innovator and generic pharmaceutical industries.

Formerly she was group executive vice president and global head of quality for Teva Pharmaceutical Industries, Ltd., senior vice president of quality at Wyeth Pharmaceuticals, senior vice president of quality at Barr Pharmaceuticals, head of U.S. quality of Novartis (Ciba) and chief operating officer at AAPI Pharma Sciences Corp.

Zipp has been active in the pharmaceutical industrial and regulatory environment in the areas of quality metrics and drug shortages. She has worked closely with the FDA and international regulatory bodies, as well as with industry leaders to develop and advance strategies for improving the assurance of drug product quality and safety. In 2013, she was elected to the Board of Directors for ISPE. She received her bachelor's degree in chemistry and psychology from Duke University, North Carolina.

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GAMP AMERICAS CELEBRATES 15th BIRTHDAY

Mike Rutherford, GAMP Americas Chair 2012–Present, Vice-Chair 2009–2012, Secretary 2008–2009

It is hard to believe that Good Automated Manufacturing Practice (GAMP®) Americas is celebrating its 15th anniversary this year. I was not around for the formation of this amazing regional organization, but I have had the opportunity to be involved since 2002 as it grew and evolved to be part of the Global GAMP Community of Practice that has driven industry best practices around computer systems validation and compliance.

In the early 2000s, the increased US Food and Drug Administration (FDA) regulatory focus and emphasis on IT infrastructure and computer system validation, as well as Part 11, were very hot topics and played a key part in the growth of GAMP Americas and its integration with the Global GAMP organization. During this time, a number of GAMP Good Practice Guides (GPGs) were published with the direct involvement of members of GAMP Americas, including, but not limited to: *Validation of Process Control Systems* (2003), *A Risk-Based Approach to Electronic Records and Signatures* (Feb 2005), *Validation of Laboratory Computerized Systems* (Apr 2005), and *Global Information Systems Control and Compliance* (Nov 2005). In 2008, *GAMP 5* was written with the support of the various regional GAMP organizations, including GAMP Americas. This latest version of GAMP incorporated the numerous regulatory initiatives since *GAMP 4*, including cGMPs for the 21st Century, risk-based Part 11 guidance, and emerging standards such as ICH Q8, Q9, and Q10, and ASTM E2500, as well as the demand for more cost-effective and efficient approaches to computer system validation. Additional GPGs were also published, including *A Risk-Based Approach to Operation of GxP Computerized Systems – A Companion Volume to GAMP 5* (Jan 2010), *Manufacturing Execution Systems – A Strategic and Program Management Approach, and second editions of the Validation of Process Control Systems* (2011) and Validation of Laboratory Computerized Systems (2012). The latest GPG to be published by GAMP is *A Risk-Based Approach to Regulated Mobile Applications* (2014), bringing the total number of GPGs to 12 in just under 11 years, with several revisions to the various GPGs in the works right now.

So what is next for GAMP and, particularly, GAMP Americas? There are a number of emerging hot topics that GAMP Americas has engaged in through the sponsorship of global Special Interest Groups (SIGs), including the areas of the cloud, data integrity, and R&D/clinical. The cloud topic and the formation of the SIG was encouraged by the FDA and, in particular, Robert Tollefsen, since this was a topic they really saw moving forward quickly and wanted to understand the industry's perspective much better. The concepts of Infrastructure as a Service (IaaS), Platform as a Service (PaaS), and Software as a Service (SaaS) were quickly becoming ubiquitous IT terms, but no one really understood the compliance implications for our industry. The Cloud SIG has been working on several articles and technical documents on these topics, as well as Cloud Supplier Management and auditing since the industry has already embraced the cloud non-regulated activities. Economic realities dictate that using the cloud for regulated activities is inevitable, and it's actually a fact at many companies.

Data Integrity was highlighted in 2011 as the concept of "forensic inspections" became common for the FDA, and eventually other global regulatory agencies. Accuracy and reliability of the data used to support product release and product submissions was being questioned and in some cases found to be fraudulent. I, along with sev-

Members of the Global GAMP Community of Practice

eral members of GAMP Americas, was very fortunate to partner with Monica Cahilly, a data integrity SME consultant and champion, to begin to raise the awareness and understanding of data integrity issues. GAMP Americas, in conjunction with the Global GAMP leadership, approved the formation of a GAMP Data Integrity SIG. The SIG formation plans and launch were announced at the 2013 ISPE Annual Meeting during our Data Integrity Session, and the response was overwhelming. Before the first SIG meeting in January 2014, more than 50 ISPE members expressed interest in joining this new SIG – a very unusual response since SIGs are usually smaller task teams of eight to 15 people focused on the creation of best-practice guidance. This response forced us to rethink our approach and organizational structure for this SIG in order to meet our members' interests and the broad impact of this topic. The SIG has now grown to nearly 100 members, and interest continues to grow. This membership includes representatives from the FDA, the Medicines and Healthcare products Regulatory Agency (MHRA), and Health Canada, as well as an advisory board of leading industry and regulatory thought leaders. In its 18 months of existence, the GAMP SIG has chaired numerous conference sessions and generated a number of articles and technical documents on this topic that will soon be published by ISPE. Data Integrity, as seen from the recent ISPE/FDA/PQLI Quality Manufacturing Conference and the large number of global regulatory citations, is a truly hot topic and much broader than just information systems. GAMP is consequently working with the ISPE Knowledge Network Council and ISPE leaders to define a broader data integrity approach to leverage the knowledge and expertise of our ISPE Communities of Practice (COPs) and partnership with global regulatory agencies. We are really excited to see where this can go and the impact ISPE can have on this topic.

GAMP Americas has always championed expanding our focus beyond Good Manufacturing Practice (GMP) and into the rest of the GxP world. When GAMP started in the UK in the early 1990s, that was the focus because that was the primary pain point, but computer system validation and the topics we address are much broader than just GMP. GAMP Americas made an early conscious effort to recruit steering committee members who had clinical and R&D backgrounds so we could address Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) needs as well. That resulted in the formation of a global R&D/Clinical SIG several years ago. This SIG continues to address topics and generate articles on e-Clinical platforms, e-Data Privacy, risk-based monitoring systems, and applying *GAMP 5* to Agile – a system development methodology used very heavily in the clinical space. The SIG was a driving force in a joint conference with the Drug Information Association (DIA) in 2014 and is also partnering with the ISPE Investigational Products COP to broaden its reach and focus.

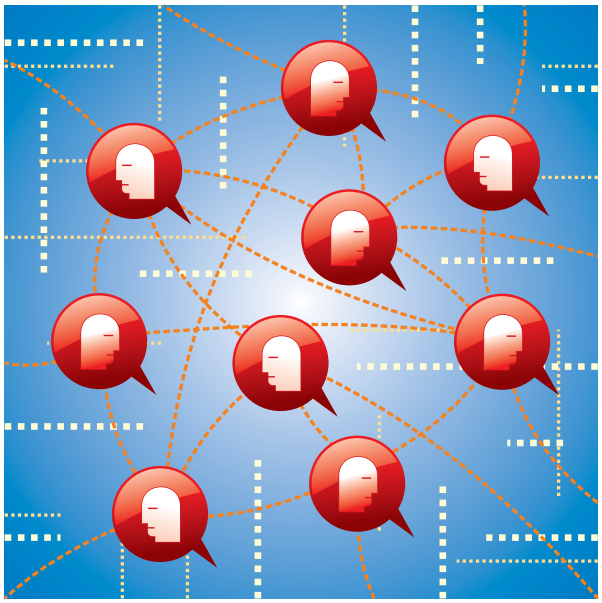
It has been 15 very busy and productive years for GAMP Americas. I have been very fortunate and proud to be involved in much of this activity, not to mention the honor of being the Chair of GAMP Americas during its 15th anniversary. I will also have the honor and privilege of being the Global Chair of GAMP in 2016 when it celebrates its 25th anniversary – now *that's* a milestone worth celebrating in true GAMP fashion. GAMP Americas has grown and changed a lot since its birth, but the dedication, commitment, vision, and enthusiasm of its members and leadership will always make it a productive and strong community. Thank you to all those who have made GAMP Americas what it is today and what it will be in another 15 years.

MUSINGS ON THE FORMATION OF GAMP AMERICAS

Randy Perez, GAMP Americas Chair 2003–2007, ISPE Chair 2011–2012, GAMP Global Chair 2013–2015

Throughout the 1990s, the pharmaceutical industry was struggling to come to terms with the relatively new concept of computer validation. Much of the thought leadership in the area was coming from the UK, where GAMP had formed early in that decade. In the US, that role was assumed, in large part, by the PhRMA Computerized System Validation Committee (CSVC), a working group that met regularly and sponsored training events and a small number of conferences. I joined that group in 1995, replacing current ISPE Board Member Fran Zipp as the Ciba-Geigy representative. However, that was not destined to be a long-term association, as a couple of years later PhRMA leadership decided that the organization should shift its focus to lobbying and disbanded its technical committees.

The ex-CSVC members found this to be problematic, as major issues like Part 11 and Y2K readiness were highly visible and very difficult to deal with in isolation. After a brief and unsatisfying attempt to work with the Parenteral Drug Association (PDA), we knew we had to find a new home. The UK-based GAMP committee at this time was under pressure from members working in multinational corporations to get their US colleagues on board with GAMP. Seeing an opportunity, Rory Budihandojo, who had been the Warner-Lambert representative to the CSVC, took the bull by the horns and contacted several ex-CSVC members about forming the first GAMP Americas Steering Committee. At the same time, he was working with Paul D'Eramo from Johnson & Johnson (J&J) to set up a local New Jersey one-day conference with a GAMP theme. This would become the first GAMP Americas Forum.



The forum concept, borrowed from our UK colleagues, was hosted by a company and typically attended by 50 to 75 interested individuals. It rapidly became obvious that the model would have to be different in the US, as 150 people registered for the inaugural event. The venue was moved from the J&J campus to the Somerset Marriott Hotel. Paul, recently moved from the FDA to the industry, had been one of our go-to guys at the Agency and showed us that he was still "the Man" as he arranged for J&J to graciously cover the costs of that first meeting. People were clearly hungering for this type of low-cost one-day conference where they could meet and talk with SMEs from the industry and the FDA and hear how other companies were dealing with complex and expensive topics.

So it was that the first GAMP Americas Steering Committee meeting occurred the night before the astoundingly successful first GAMP Americas Forum, chaired by Rory. The other officer positions were Vice Chair, which I filled, and Historian, which was filled by Kevin Martin. We had ideas for deliverables, including several for GPGs that were led by people from GAMP Americas, many of which were put into motion that night.

About a month after the first GAMP Americas meeting, the close partnership that the independent GAMP community had with ISPE was made even closer when GAMP accepted an offer to become an ISPE Technical Committee. This was a boon for both, as GAMP had a wealth of hot content to offer and ISPE had the venues and the organizational skills that an independent GAMP had no hope of matching.

In 2003, I took over leadership of a thriving GAMP Americas team from Rory, and I cannot express what an incredible job he did to get us off to such a flying start. That year, we initiated several more SIGs to work on new GPGs, including our first international SIGs. Possibly one of our most important actions, however, was to improve our communication and cement our long-term relationship with the FDA, as we invited Robert Tollefsen, National Computer Expert Investigator, to join our GAMP Americas Steering Committee. Along with Bob, who is still a member, we have made several friends in the Agency who graciously help us by participating on committees, speaking at conferences, reviewing documents, and responding to queries with their unique regulatory insights. It is a relationship that is highly beneficial to both ISPE and the FDA, providing a forum for discussion between SMEs of both organizations.

I am very proud to have had a hand in the formation of GAMP Americas and in the molding of its early work. While the organization has changed substantially in the 15 years since its birth, it has always remained a vibrant and productive community.

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ISPE TECHNICAL COMMUNITIES AT ISPE'S ANNUAL MEETING

ISPE Technical Communities provide special-interest online discussion forums where ISPE Members can ask questions, explore solutions, and share their knowledge with others in the field.

Technical communities allow industry, academia, and government representatives to collaborate and leverage resources for research, technology transfer, and other activities.

Technical communities are not stand-alone entities. They make up technical networks formed to link Member interests and job functions to create an output that supports the everyday needs of Members.

Each technical community is invested in creating knowledge resources, including delivering content for ISPE's 2015 Annual Meeting. These session topics are often generated from Member discussions in ISPE's online technical communities.

This year, technical communities are leading 38+ educational sessions and tracks within the six tracks at the Annual Meeting.

Here is a sample of sessions that have been created by ISPE technical communities to respond to industry hot topics and emerging trends. For a complete list, please visit the Annual Meeting website:

- Things Your Mother Didn't Tell You: Lessons Learned from Implementing Single-Use Technology in Scale-Up from Clinical to Commercial Manufacturing (Biotechnology)
- Pragmatic Approaches to Data Integrity (GAMP)
- Current Trends in Barrier and Aseptic Systems (Sterile Products Processing)
- Innovation Forum: Moving Beyond Paradigm Paralysis to Gain Control of the Quality Culture and Behavior of Your Manufacturing Workforce (Project Management)
- Patient-Unfriendly to Patient-Friendly, Compliance in CT, and Orphan Drugs (Investigational Products)
- The Latest OSD Regulation Requirements and Technologies for Pharma Operations (Oral Solid Dosage)
- Modification, Critical Utilities Maintenance Program, and System Optimization (Critical Utilities)
- Cross-Contamination: Dedication, Segregation, or Other? (Containment)
- Effective Integration of Environmental Health and Safety Requirements into Project Design Review (HVAC-Sustainable Facilities)

ISPE MEMBER LINH D. DO RECEIVES TAU BETA PI SCHOLARSHIP

ISPE Member Linh D. Do has received a Tau Beta Pi scholarship from the Fellowship Board of Tau Beta Pi, the Engineering Honor Society. Tau Beta Pi selected 261 Tau Beta Pi Scholars from 804 applicants for undergraduate study during the 2015-16 academic year. Most recipients will receive a cash award of $2,000 for their senior year of engineering study, and a few will receive $1,000 for one semester.

All Tau Beta Pi scholarships are awarded on the competitive criteria of high scholarship, campus leadership and service, and promise of future contributions to the engineering profession. All scholars are members of Tau Beta Pi.

Linh D. Do, an undergraduate student at San Jose State University, is one of the 50 scholarship recipients who are studying chemical engineering.

Tau Beta Pi is the Engineering Honor Society, founded at Lehigh University in 1885. It has collegiate chapters at 244 engineering colleges in the United States and active alumni chapters in 41 cities. It has initiated more than 564,000 members in its 130-year history and is the world's largest engineering society.

TRAINING NEW RECRUITS IN CHINA

As part of an ongoing collaboration between ISPE China and the Center for Drug Evaluation (CDE) of the China Food and Drug Administration (CFDA), ISPE China was invited to provide a half-day training to 34 newly recruited Chemistry, Manufacturing and Control (CMC) reviewers on June 24 at Peking University in Beijing. Jifeng Lei, Chair of ISPE China, and Charles Tong, PhD, former Chair of ISPE China, presented two sessions on Process Validation and Quality by Design (QbD) Principles and Application. Lei and Tong, who are ISPE-qualified trainers, adapted the training materials from the ISPE courses T46 and T43, respectively. Participants found the sessions interesting and useful in terms of elaborating important principles and illustrating their practical application with regard to QbD and process validation in a systematic approach. This successful collaboration demonstrates the CDE's recognition of ISPE's strength in knowledge management, development, and delivery of trainings on topics that are important to the industry and regulatory agencies.

Charles Tong explains QbD Principles and Application to a captive audience.

Jifeng Lei conducts a training session for a group of CMC reviewers.

GUIDANCE DOCUMENTS Slated for 2015

Sustainability Handbook

In current phrasing, "sustainability" refers to the wide range of measures considered necessary to help avert issues associated with climate change and an increasing world population. This handbook has been written around the premise that there is a viable path to achieving sustainability that responds to all of the precepts of the life sciences industry. Key objectives include providing a global pharmaceutical sustainability baseline for the life-sciences industry, as well as promoting the development of sustainability policies and guidelines that apply to specific organizational needs. Intended for use at the front end of projects, it is designed to provide information that will be useful to the project team in understanding sustainability criteria. This handbook is also provides information that may be useful in the development of new projects, e.g., Greenfield, Brownfield, or retrofits.

Operations Management Good Practice Guide

This Good Practice Guide is intended to offer a framework for the management of pharmaceutical operations, provide a structured description of processes and technologies within the pharmaceutical industry, and identify and develop industry good practices. It addresses all operations along the supply chain, from the selection of raw materials to the distribution of final product, and also covers how pharmaceutical systems can be organized and operated to guarantee the production, storage, and distribution of products while ensuring product quality throughout the supply chain. Industry professionals and stakeholders will have the opportunity to build and use a common language and learn how to use generic and specific tools while acquiring a deep understanding of the Operations Management processes and supporting technologies.

APPOINTMENTS

Chris Galione joins ISPE as Director of Sales, reporting to Susan Krys, Vice President of Program Development. Chris's responsibilities will include business development and the direction of all exhibit, sponsorship, and advertising sales for our North American, European and Asia-Pacific events.

Chris comes to ISPE from the American Association for the Advancement of Science (AAAS), where he was the Sales Director for its annual meeting and several smaller events throughout the year. At AAAS, Chris built and enhanced relationships between the association and the scientific research community, as well as worked closely with federal agencies such as the US Food and Drug Administration (FDA), the National Science Foundation (NSF), the Centers for Disease Control (CDC), and the National Institutes of Health (NIH).

Before AAAS, Chris ran a team responsible for all non-dues revenue for Biotechnology Industry Organization (BIO). There he was responsible for a $16-million annual revenue budget, while developing BIO's annual meeting.

Chris has fostered solid relationships with companies in the pharmaceutical industry and has a breadth of knowledge about their business and an understanding of how to create a successful strategic plan to engage the industry in support of a strong association.

Remeeza Shaikh joins ISPE as a CE Program Manager to partner with Marianne Bock in developing our education programs, reporting to Meredith Ellison, Director of Continuing Education. Rameeza previously worked for the Children's Hospital Association (CHA) in Washington as a Project Manager, where she served as the central point of contact for all activities related to the planning and executing of workshops, seminars and other professional development events.

Prior to working at the CHA, she was Coordinator, Programs & Professional Development, for the National Association of Elementary School Principals. Rameeza earned a Master's degree in English and an MBA from Strayer University. ◂

Is your project scope constantly changing?

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MEET YOUNG PROFESSIONAL MARK HEWSON

Mike McGrath

Sometimes projects don't turn out as originally planned. That is the case for Mark Hewson, who is in the process of completing his Master's thesis. The conversations he had with ISPE Members, among others, took his research in an unexpected direction. However, these conversations also revealed an area in which there is tremendous potential for career development gains for pharmaceutical engineers.

Mark Hewson is completing his Master's degree in techno-anthropology at Aalborg University, Department of Learning and Philosophy, in Denmark. He set out to examine the mechanisms that allow a novice pharmaceutical engineer to progress and be recognized as an expert in the industry. To move his research forward, Hewson, an ISPE Nordic Affiliate Student Member, reached out to fellow Members at ISPE events and even started a discussion on the ISPE LinkedIn page (www.linkedin.com/company/ispe).

"I tried to network with as many people as possible at events and get my question to them during the break times," says Hewson. "I found that I had to get people when I could because I never knew when I'd be able to get them again. People are very busy working on projects, which is a good thing for them, but it made it difficult to pin them down for an interview. But it was very useful, enlightening and helpful."

It was in those interviews that Hewson discovered a lack of clarity in the industry.

In setting out to define how an individual could move from being a novice to an expert, Hewson first had to define what a novice is, which was simple. He then had to define what an expert is before he could determine what it takes to move between the two.

That proved more difficult to define. "When I tried to dig deeper into this, I didn't get a consistent answer," says Hewson. "It appears to be largely dependent on the individual company concerned. This means that a subject matter expert (SME) for one company can be a complete novice for another company. How can I ask the original question when no one can really define what an expert is? So, my focus became how to define an expert in the industry."

According to Hewson, the ability to clearly define what it takes to be an SME could have wide-ranging benefits within the industry. The first definition would benefit the engineers themselves. "I see this as a way to encourage potential employees who see a structure for promotion and development," he says.

ISPE Members' input takes Mark Hewson's research in a new direction.

The second definition would benefit companies, both through recruitment of a broader range of talent and by establishing a competitive advantage. "By doing this, I think they're going to attract potential employees who might have overlooked the industry, because if employees can't see how their skills might be used, or a career path for them, they might look elsewhere," says Hewson. "I think it's also a tool when bidding for a contract. Companies can say 'We've got this way of proving our expertise; have our competitors got this?' I think customers will have more faith in the skills as they apply to the contract. So, it could be a competitive plus for companies to develop something."

After he submits his thesis in August, Hewson says that he would be open to continuing his research via the PhD route or participating in the development of industry-accepted definitions of SME skillsets.

Just as the ISO has set standards for quality, Hewson sees something similar applying to SMEs in pharmaceutical engineering. "I would like to see some kind of structure or framework in place that pharmaceutical engineering companies can develop," he says. "Even if it varies from company to company, it could fall into a larger framework that allows for some kind of support or validation of skills in the workplace."

Despite the change of direction, the experience has been good for Hewson. "I have attended network events and spoken to participants on a range of issues such as sustainability, chemistry – a whole range of subject matter. It has been quite enlightening and very informative."

Hewson intends to present his findings to ISPE committees in Denmark and Scandinavia, who have shown interest in his research. Anyone wishing to contact Mark Hewson regarding his research can reach him via his LinkedIn page (dk.linkedin.com/pub/mark-hewson/2a/139/636).

DPT Enhances Flexibility and Efficiencies at San Antonio Facility

DPT Labs, 8 July 2015

DPT Laboratories, a contract development and manufacturing organization (CDMO) specializing in semi-solids and liquids, has implemented a new order execution strategy that will enhance operations at its San Antonio, Texas, facility.

The new strategy entails a realignment and augmentation of resources to support three critical areas at DPT: 1) high-speed bottle production, 2) aerosols/foams filling and packaging, and 3) traditional semi-solids and liquids production. One of three DPT Centers of Excellence, the San Antonio facility was purpose-built to support semi-solid and liquid development and manufacturing solutions. This new strategy represents the next step for the company's existing operational platform.

leon-nanodrugs GmbH Raises EUR 18.5 Million in Series A Financing

B3C Newswire, 27 July 27 2015

leon nanodrugs GmbH today announced that it completed the first closing of its Series A preferred stock offering at EUR 18.5 million. The financing was led by TVM Capital Life Science, based in Munich and Montreal, with participation from Signet Healthcare Partners (USA), LifeCare Partners (Switzerland), CD-Venture (Germany), Albany Private Equity Holding (Australia), and a non-disclosed Family Office from Germany. Dr. Hubert Birner, Managing Partner, and Stefan Fischer, General Partner & CFO, TVM Capital Life Science, James Gale, Managing Director, Signet Healthcare Partners, Dr. Gerhard Ries, Managing Partner, LifeCare Partners, Dr. Frank Mathias, CEO, Medigene AG, and Dr. Bernd Baumstümmler, CEO, Instillo Group, will be joining the Board of Directors.

leon-nanodrugs was founded by a group of experienced drug development professionals in mid-2011. The company focuses on the reformulation of approved or promising small molecule and protein drug candidates based on its patented and award winning MJR-nanotechnology platform. leon-nanodrugs develops novel oral and parenteral formulations by using GMP (Good Manufacturing Practice) compliant nanotechnology to improve bioavailability, solubility as well as dissolution rates. leon-nanodrugs will use the proceeds of this Series A financing to expand its profitable service business and to enter into high margin co-development deals with pharmaceutical partners.

DSM Sinochem Pharmaceuticals Supports International Report on the Fight Against Antimicrobial Resistance

DSM Sinochem Pharmaceuticals, 22 July 2015

A frequently overlooked cause of Antimicrobial Resistance (AMR) is environmental pollution related to the production of antibiotic intermediates and Active Pharmaceutical Ingredients (API) for antibiotic drugs, according to a report by US-based organization "SumOfUs." This global movement brings together consumers, investors and activists who campaign for a more sustainable global economy. Based on 200+ independent sources, the report by SumOfUs reveals how the production of antibiotics has become a major contributor to AMR through environmental pollution. The organization calls on the global API-producing and API-using industry to clean up their production and supply chain in order to fight against this global health issue. DSM Sinochem Pharmaceuticals (DSP) echoes this call and fully supports the campaign.

Grifols, One of the World's Leading Experts for Blood Plasma Derivatives, Employs HERMA's 132M HC Wrap-Around Labelling Machine

Grifols, 16 July 2015

One of the world's largest suppliers of plasma-derived products, Grifols has recently built a new logistics center at an Irish location. The company, which is headquartered in Barcelona, Spain, chose HERMA and their Spanish sales partner SINEL SYSTEMS to implement a labelling solution at the new site. The task required finesse: It involves the precise labelling of cylindrical infusion bottles and the printing of variable information on these labels. The labels feature a small attached plastic loop that can be folded back later to serve as a hook in the hospital. In close cooperation, HERMA and SINEL SYSTEMS designed a labelling system that is based on the standard labelling machine 132M HC and does not require any complex special design. According to Grifols' specifications, further components were added to the machine, such as a laser printer that produces a color change on the labels and a camera system that checks the printed labels. Grifols is happy with the solution and its implementation.

Bavarian Nordic Announces that the Oxford Vaccines Group Has Initiated a Phase 2 Study of the Ebola Prime-Boost Vaccine Regimen Combining MVA-BN® Filo and Janssen's AdVac® Technology

Bavarian Nordic A/S, 15 July 2015

Bavarian Nordic A/S (OMX: BAVA, OTC: BVNRY) announced today that the Oxford Vaccines Group has initiated a Phase 2 clinical study of the Ebola prime-boost vaccine regimen that combines Bavarian Nordic's MVA-BN® Filo vaccine with the Ad26. ZEBOV vaccine from the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen). The first volunteers have received their initial vaccine dose.

Preliminary data from the first-in-human Phase 1 study, presented by Janssen in May to a US Food and Drug Administration Advisory Committee, indicated that the prime-boost vaccine regimen is immunogenic, regardless of the order of vaccine administration, and only provoked temporary reactions normally expected from vaccination. The Phase 2 study, to take place in the UK and France, is a randomized, placebo-controlled, multicenter trial evaluating the safety, tolerability and immunogenicity of the heterologous prime-boost regimen (Ad26.ZEBOV and MVA-BN-Filo) sponsored by Crucell Holland B.V., one of the Janssen Pharmaceutical Companies.

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Birgit Breitmoser
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Vetter Launches Vetter-Ject® – A New Syringe Closure System for Highly-Sensitive Compounds

B3C Newswire, 15 July 2015

Vetter today has announced the release of Vetter-Ject®, a novel closure system for prefilled syringes. By this closure part a baked-in siliconization of an integrated needle syringe can be realized. That allows the use in highly-sensitive compounds such as biologics. The tamper-evident closure system, combined with an integrated staked needle, supports the product integrity of Vetter-Ject®. At the development of Vetter-Ject® particular emphasis was laid on the usability. The system has already earned two prestigious international prizes.

Today, pharmaceutical and biotech companies are increasingly developing drugs that incorporate sensitive and complex compounds. To best administer these drugs to the patient requires an injection system that can be used flexibly while being safe and simple to handle. Vetter-Ject® is such a system. Consisting of a needle hub and a needle shield, the new syringe closure system is partly produced by means of a 2-component injection molding process of polypropylene and thermoplastic elastomer.

ECA Foundation Announces New Board Structure

ECA Foundation, 14 July 2015

On 10 June 2015 the ECA Foundation Advisory Board set the course for the future with a new board structure. While the ECA Foundation Board so far comprised 10 professionals from industry and authorities, the Board is now headed by the new Executive Team with three members: the Chairman, the Vice-Chairman and the Director Regulatory Affairs. In addition to this team the ECA now has an Extended Board. In this Board the various ECA Interest and Working Groups are represented by their Chairmen. This new structure recognizes and strengthens the Groups' increasing importance and allows them to be directly involved in defining and planning ECA activities. With every new ECA Group established its Chairman will also automatically become member of the Extended Board. In addition to the Executive Board and Extended Board there are also two new Advisory Committees. To avoid any conflicts of interest for their members, though, neither of them is part of the ECA Foundation legal structure.

Connecting Industrial Outstations Inexpensively and Securely

Siemens, 13 July 2015

With the new CP 1243-8 IRC communication processor, Siemens enables telecontrol applications based on the Sinaut ST7 telecontrol protocol. The new communication processor makes it possible to connect Simatic S7-1200 controllers as outstations (remote terminal units/RTUs) to higher-level ST7 stations with minimum effort and low costs. The solution is suitable for use in new and existing systems. Redundancy and comprehensive security functions ensure high availability and security. Key applications for the CP 1243-8 IRC are distributed at plants in the fields of drinking water supply and distribution, sewer networks, and rain overflow tanks. In addition, the communication processors can be used for environmental monitoring and as local transport and distribution grids for district heating and electrical energy networks.

Project HOPE Appoints Dr. Thomas Kenyon New President and CEO

Project HOPE, 10 July 2015

The Project HOPE Board of Directors announced today the selection of Thomas A. Kenyon, M.D., M.P.H., as the new President and CEO of the international health and humanitarian organization effective 1 October 2015. Dr. Kenyon joins Project HOPE after more than two decades with the Centers for Disease Control and Prevention (CDC), most recently as Director of its Center for Global Health. He was a key member of the U.S. government team that coordinated the White House's mobilization against Ebola, one of the most devastating public health emergencies in recent years. He is also a veteran of the worldwide fight against HIV/AIDS.

Dr. Kenyon has represented the CDC across U.S. government agencies, the White House, Ministries of Health, the World Health Organization and other multilateral organizations, philanthropic foundations and the private sector. He was the Principal Deputy Global AIDS Coordinator and Chief Medical Officer for PEPFAR (the President's Emergency Plan for AIDS Relief) at the U.S. Department of State. He also has first-hand knowledge of Project HOPE's mission, having served as a Director for Project HOPE in Swaziland from 1987–1992 and as a Consultant Pediatrician for a HOPE program in Grenada, West Indies, for two years in the mid-1980s. His public health expertise will also be valuable to Health Affairs, the nation's leading health policy journal, which is published by Project HOPE.

SATO Establishes SATO Healthcare Australia

Sato, 6 August 2015

SATO, a leading global provider of Auto-ID solutions that empower workforces and streamline operations, today announced the establishment of SATO Healthcare Australia Pty Ltd.

With the acquisition of Magellan Technology in 2013, the SATO Group nearly tripled its healthcare segment revenue in Australia. The newly established SATO Healthcare Australia will consolidate the healthcare business of the SATO Group in Australia. It will particularly focus on serving healthcare accounts in Australia and patient safety solutions featuring Auto-ID technology and the unique PJM RFID Technology to meet the needs of the growing healthcare market.

First Standard Cartridge Valve from Bürkert

Bürkert, 4 August 2015

Due to the increasing importance of space considerations, fluid performance and energy saving potentials, customized solutions are constantly becoming more complex, accompanied by higher component requirements. The new cartridge valve (Type 6164) from Bürkert simplifies pneumatic piloting controls through optimal integration of a pilot valve in block solutions and plastic injection moulded components. Due to its uncompromising reliability, above-average service life and efficient performance, this valve is setting new standards.

OMRON to Acquire a US-based Motion Control Company

OMRON, 30 July 2015

Following a resolution at a meeting of its Board of Directors held today, OMRON Corporation (Headquarters: Kyoto, Japan; President & CEO: Yoshihito Yamada) announced its entry into a stock purchase agreement to acquire a 100% stake in Delta Tau Data Systems, Inc. of California (hereinafter referred to as "DT"), which will result in DT becoming a member of the OMRON Group. The acquisition is subject to customary conditions to closing. OMRON expects the acquisition to close around early September 2015.

With headquarters in Chatsworth, California, DT is a control device company in the United States. This acquisition is part of OMRON's strategy to promote its development of factory automation technology and strengthen its sales capability in the control device business. Through the acquisition of DT, OMRON aims to reinforce its technology development and engineering capabilities in the field of motion control designed to drive manufacturing equipment. Merging products and technologies of both companies will also enable delivery of optimized motion control solutions globally through combined distribution networks.

Advanced Clinical Adds Senior Vice President, Consulting Services

Advanced Clinical, 6 August 2015

Advanced Clinical, a full-service global CRO, functional outsourcing, and strategic staffing solutions provider, today announced the addition of Bill McGuckin, Senior Vice President, Consulting Services, to the organization.

Mr. McGuckin brings over 12 years of consultative sales and leadership experience to Advanced, and will be responsible for the development, strategy, and delivery of Advanced Clinical's Quality Consulting Services. Prior to joining Advanced, Bill was Vice President of Life Science and Technology at a technology solutions provider where he transitioned his team into the most profitable business unit and recipient of the profitable growth award for year-over-year revenue and profit growth. He has held numerous leadership positions and has been recognized as a perennial top performer for his strategic thinking, cultivation of leaders, and innovative sales techniques.

Pentair Acquires Pigeon Point Systems to Expand Its Schroff Product Portfolio for Monitoring Systems

Pentair, 4 August 2015

Pentair announces the acquisition of Pigeon Point Systems, a producer of high-quality management components, focusing on open modular platforms as AdvancedTCA, MicroTCA, CompactPCI and VPX. By combining Pigeon Point Systems products with Pentair's broad range of Schroff products, Pentair will be able to provide an expanded product portfolio, increase presence globally and broader technical expertise to serve Pentair customers and their ever increasing needs in embedded computing and reliable system monitoring and control. ◂

NOVO NORDISK TO DOUBLE WORKFORCE IN NORTH CAROLINA

Novo Nordisk recently announced plans to invest $2 billion over five years in new production facilities to be located in Clayton, North Carolina, and Måløv, Denmark. These facilities are needed to meet the increasing global demand for diabetes medications.

The new North Carolina plant will produce active pharmaceutical ingredients (APIs) for an oral semaglutide, which is going into phase 3a development, as well as a range of current and future GLP-1 and insulin products. The investment is expected to double employment in the North Carolina plant to 1,400 jobs and add 100 new jobs to the plant in Denmark.

"With the new plant in Clayton and continuous investments in our current API production plants in Kalundborg, Denmark, we will have sufficient API capacity for diabetes products well into the next decade," says Henrik Wulff, Executive Vice President and Head of Product Supply at Novo Nordisk.

"We decided to place the new API facilities in the U.S. for strategic reasons," adds Wulff. "The U.S. is by far our largest market, and there are many logistical and economic advantages to having a larger part of our manufacturing in our main market. After a thorough evaluation of multiple sites and an extensive vetting process, Clayton ended up being our preferred location. We already have a large and very professional organization there and an excellent collaboration with city, local and state leadership, and we appreciate the incentives they have secured in connection with this investment."

The final design and cost of the new facilities will be presented to Novo Nordisk's Board of Directors in 2016, and the facilities are scheduled to be operational by 2020.

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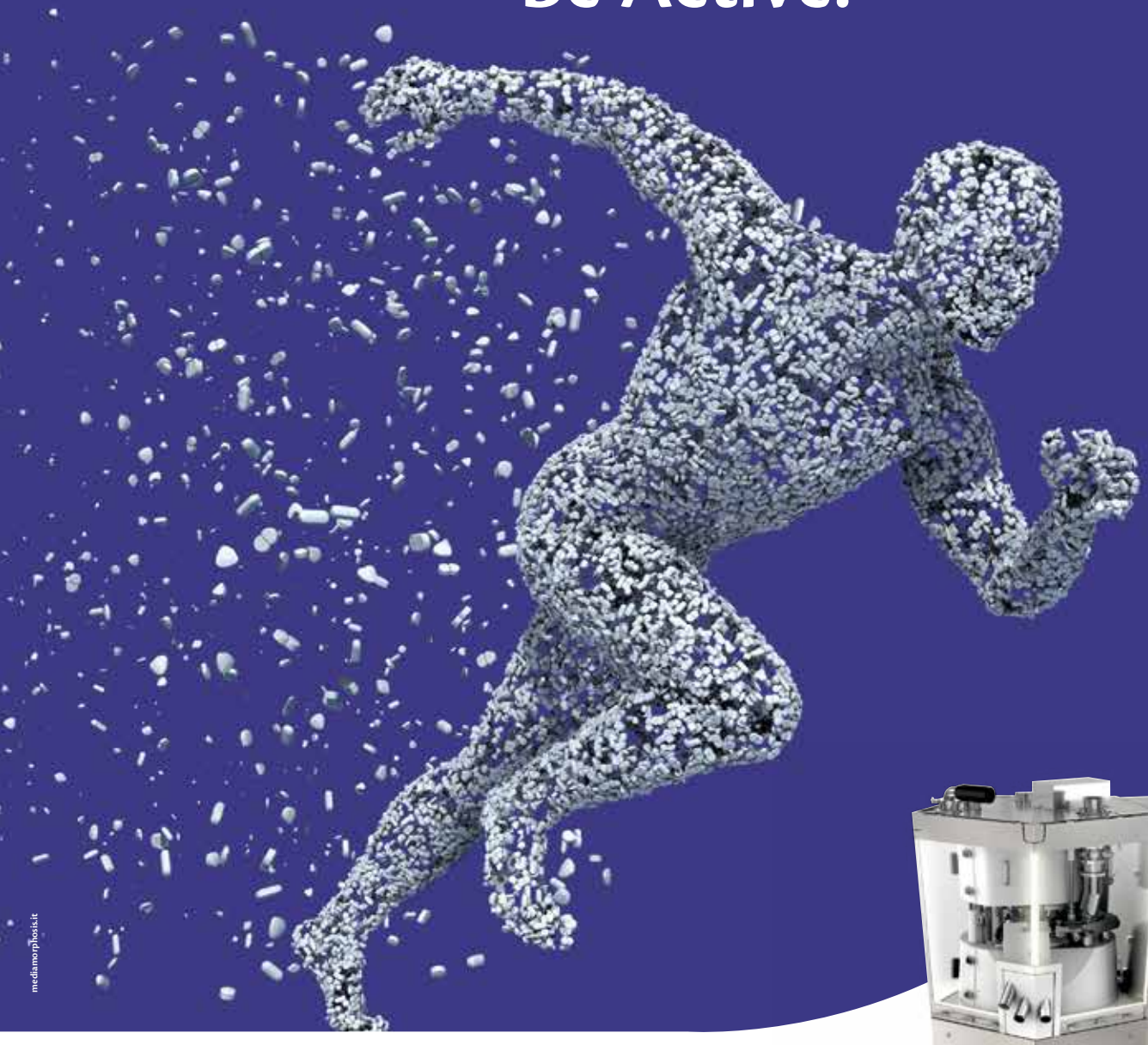

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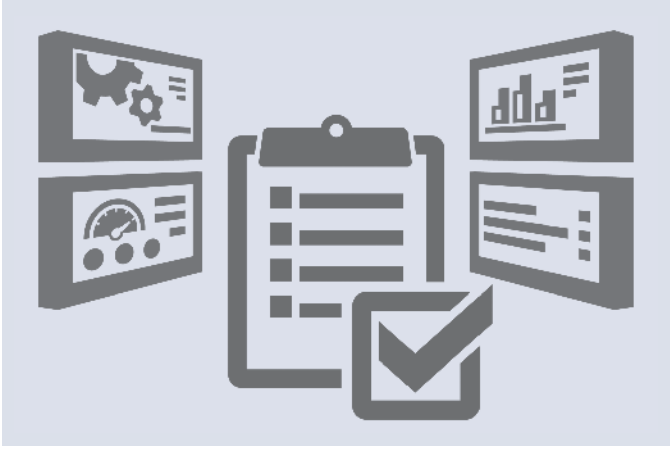
PERFORMANCE CHARACTERISTICS AND ALTERNATIVE APPROACHES FOR THE ASTM E2709/2810 (CUDAL) METHOD FOR ENSURING THAT A PRODUCT MEETS USP <905> UNIFORMITY OF DOSAGE UNITS

Plinio A. De los Santos, Lori B. Pfahler, Kim Erland Vukovinsky, Jia Liu and Brent Harrington

This article presents the methodology of ASTM 2810 and demonstrates the method's conservative nature. Additionally, alternative methodologies to ASTM 2810 are illustrated and their performance is compared to the USP <905> criteria.



Background

Over the past decade or so, much has been written and discussed about pharmaceutical drug product content uniformity testing. The discussions have focused primarily on the 2003 US Food and Drug Administration (FDA) Draft Guidance for Industry, Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment,[1] the International Conference on Harmonisation (ICH) uniformity of dosage (UDU) test or USP <905>,[2] the original 2004 and subsequent proposals for Large N lot release,[3] and CuDAL (ASTM E2709/2810).[4,5] In 2013, the FDA withdrew the 2003 stratified sampling draft guidance document citing, amongst other concerns, a lack of confidence in dosage unit results passing USP <905> Uniformity of Dosage Units. The United States Pharmacopeia (USP) *General Notices* state: "The standards in the relevant monograph, general chapter(s), and *General Notices* apply at any time in the life of the article from production to expiration" and "The similarity of these standards to statistical procedures seems 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." The interpretation of these statements, and in light of the withdrawn draft guidance, applied to dosage unit uniformity results has led to a renewed interest in determining dosage unit uniformity sampling plans and acceptance criteria that ensure a high probability of passing USP <905>. One such methodology, ASTM 2810, assures that future samples will indeed have a high probability of passing the USP <905> criteria and provides a statistical confidence in this event. This paper briefly examines the methodology of ASTM 2810 and demonstrates the performance of alternative methodologies compared to the USP <905> criteria. It also addresses the balance between the risk of nonconformance and the associated costs of increased testing.

The Issue in USP Tests and Solution Presented By ASTM 2810

Governance of the USP dictates that products must meet USP test criteria whenever tested. This can present a compliance issue if a lot of product tested at release just meets the acceptance criteria of the USP test and is released to the market. The lot may not pass a future surveillance USP test in this circumstance. As a result, regulators have been seeking greater rigor in development and manufacturing process requirements to ensure a high probability of passing USP tests from production through expiry.

To ensure a high pass rate for a USP test, the question of how many tests a product may be subjected to should be considered; the product testing encompasses both an individual lot and every lot produced from the particular manufacturing process. As a metaphor, imagine tossing a coin: There is a 50% chance of getting heads with one toss, but the probability of achieving heads for ten consecutive tosses is 0.1% (0.5^{10}). Now, assume that a product has a 99% chance of passing one time, then, if tested 10 times, it has a 90% total pass rate (0.99^{10}). But if the lot has a 95% chance of passing a single test, the total pass rate from 10 independent tests is 60% (0.95^{10}). The goal for the manufacturer is to assure a high quality product, noting that, a product with an impeccable ability to pass USP, say 99.9%, would only pass 100 tests 90% of the time and 1,000 tests 37% of the time. Even the best product has a chance to fail; this scenario illustrates the increased risk for the manufacturer when the product is tested at release and multiple times while on the market. Statistical knowledge will need to be applied to understand if the failure is random or unique.

In 2010 and 2011, two ASTM standards were approved that provide an approach to assuring confidence that a lot of product will pass a future USP test. ASTM E2709 provides the general framework of the approach, and ASTM E2810 provides the approach applied to USP <905>.[4, 5] The ASTM E2709/2810 method, oth-

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erwise known as Content Uniformity and Dissolution Acceptance Limits (CuDAL), is referred to in this article as ASTM or ASTM 2810. It is a well-known procedure that is used in the pharmaceutical industry for estimating the probability that a manufactured product lot will pass a multi-stage test, such as the USP tests for UDU (or content uniformity) and dissolution. Historically, this method was applied by many in the industry to establish criteria for Process Validation Stage 2 or Process Performance Qualification (PPQ).[6] PPQ is a predefined study with the goal of demonstrating that the commercial facility (equipment and utilities) and the commercial manufacturing process (personnel, control procedures and components) perform as expected based on the process design activities conducted in Stage 1 (process design).

The assurance provided by the ASTM 2810 method is achieved by calculating a C% confidence region on the average and standard deviation estimated from the UDU sample. The extremes of this confidence region are compared to a lower bound, LB%, on the probability of passing USP <905>. If the confidence region is within the lower bound, LB, then the sample, and hence the lot, has demonstrated the necessary confidence for the market.

As mentioned in the ASTM standard, there are other methods that could be employed to assure quality on the market. This paper overviews potential alternative solutions and compares their performance.

Interpretation and Performance Characteristics of ASTM 2810

The interpretation of passing an ASTM 2810 plan conducted at C% confidence with a lower probability bound of LB% is the following: "With C% confidence, there is at least LB% probability that a future sample taken from the batch will meet the UDU test." This statement, abbreviated C%/LB%, is powerful and provides strong evidence of high quality to regulators, manufacturers, and ultimately patients. It is important to understand how this statement is created and what the benefits and costs are of utilizing these plans in PPQ and routine release testing.

The statistical statement provided by an ASTM 2810 plan is accomplished by determining the worst-case mean and standard deviation as defined by the joint confidence region for both parameters at the selected confidence level (C%). An example of this region is shown in Figure 1 as the area inside the blue triangle. Figure 1 shows an example where the sample average is equal to 98.6 % Label Claim (%LC) and the standard deviation equals 4.73 %LC for 100 dosage units tested. This plan was conducted at 95% confidence with a 95%LB. The upper-left corner (worst-case mean and standard deviation for the batch) of the joint confidence region is just touching the estimated 95% LB. It is important to note that nearly all the other possible means and standard deviations in the confidence region will provide much more than 95% chance of passing a future USP test. In fact, most of the area of the triangular region falls in the contour, indicating a 99% to greater than 99.99% chance of passing the USP test.

Simulations were used to determine how well the ASTM 2810 plans perform. The simulations were conducted to determine whether the probability of passing is accurately estimated at the worst-case mean and standard deviation. It was found that the ASTM plan is conservative due to the methods used to analytically calculate the lower bound and confidence region. As a result, there is a difference in the actual pass rate for future USP tests based on simulation and the stated probability of the ASTM 2810 plan. For the plan used in Figure 1, there is actually a 96% probability that the worst-case mean and standard deviation will pass a future USP test rather than the specified LB of 95%. (The worst-case corner of the confidence region is on the 96% pass contour.) The bias becomes larger as the standard deviation increases and as the mean is farther from the target of 100%LC. This bias between the actual pass probability and the lower bound calculation in ASTM 2810 is noted in Bergum and Li (2007).[7]

While the ASTM method is a statistically valid approach, it is conservative. Here, "conservative" means the ASTM approach will not pass many inherently acceptable lots with sample sizes of 10 or 30, conventionally used for UDU lot release testing. For example, when taking a sample of size 30, a process with a true mean of 100%LC, a standard deviation of 5% will pass the USP <905> test approximately 100% of the time but would only pass a 95%/95% ASTM 2810 plan 7.7% of the time. (See Table A.) If the ASTM approach is used, a much larger sample must be tested so that the confidence region size is not substantially large. There are other statistical approaches that provide a more reasonable assurance and are efficient in testing, which should be considered. This point is mentioned in the ASTM standard and further demonstrated in this paper. Tolerance interval approaches have been considered in the past[8, 9, 10] and shown as acceptable in assuring quality. Tolerance-interval-based approaches are also evaluated in this paper.

Alternatives Considered

The statistical approaches evaluated in this paper fall into one of two categories:

1. Joint confidence regions that are compared against the lower bound probability of passing the UDU test. The actual lower bound probability used during the evaluation was estimated by a procedure described by Bergum and Li (2007).[7] A joint confidence region is an extension of the confidence interval concept with respect to two or more unknown parameters. The joint confidence regions considered during this evaluation are:

   - "ASTM" region, or Lindgren's[11] confidence region as described in ASTM E2709/2810 and implemented in the CuDAL Statistical Analysis System (SAS) program validated

through the PhRMA Chemistry, Manufacturing, and Control (CMC) Statistics Expert Team.

- "MOOD" region, or Mood's[12] confidence region. Initially proposed precise confidence region for the mean and variance. Although this confidence region is exact, it is not optimal with respect to its expected coverage area (roughly of trapezoidal shape). It is highly dependent on the normality assumption.
- "LRT" region: The likelihood ratio confidence region,[13] which is based on the likelihood ratio test statistic, has an asymptotically smaller expected area than the ASTM method.
- "LSRX2" and "LSRF" regions: These are large-sample regions,[13] with either chi-square (LSRX2) or F (LSRF) distribution plug-ins, which approximate confidence regions based on maximum likelihood estimation. These are more robust to departures from normality and more appropriate to use when the sample size is relatively large.
- "MACR" region: The minimum-area joint confidence region[14] is an equivalent confidence region with a higher asymptotic improvement in the confidence bands.
- "HT2" region: is a Hoteling T^2-based[15, 16] confidence region. The confidence region is constructed using the Hoteling T^2 distribution ellipse of parameters from simulation replicates.

These regions are compared in Figure 2 and show that the ASTM method yields a triangular shape region and that the MOOD method yields a trapezoidal shape region, while the other joint confidence region methods yield an approximate ellipsoid region. A detailed description of the joint confidence-based methods is provided in Appendix A.

2. Methods in which a normal tolerance interval is compared against assumed limits associated with the USP test. A tolerance interval is constructed to provide a probability that the interval contains at least a desired proportion of the population. The normal tolerance interval calculations considered are:

- "NTL" region: This is the standard two-sided tolerance interval based on a normal distribution to control the center of the distribution. Individual UDU results are assessed against the 85.0 to 115.0 limits, under the assumption that the UDU target is 100.0%.

- "AV" region: This requires that the USP <905> acceptance value (AV) be assessed against a 15.0% upper limit. The k value in the AV equation is adjusted based on the sample size taken using a one-sided tolerance interval with a selected confidence and coverage.

A detailed description of the above two tolerance-interval-based methods is provided in Appendix B.

Performance of the Alternatives: Comparison and Discussion

Operating characteristic (OC) curves are often used to illustrate the performance of a sampling plan and associated acceptance criteria and compare the expected probability of passing the plan against a critical metric from the acceptance criteria. These curves could be used to compare the performance of different plans even if the criteria, sample size, and statistical approach used are different. The probability of lot acceptance is typically placed on the y-axis and a calculation relevant to the acceptance test is placed on the x-axis. For the UDU test, the x-axis is often the percent relative standard deviation (%RSD) or the standard deviation (SD). If the y-axis value on the OC curve is near 100%, this indicates a high probability of passing a lot, and, conversely, if the y-axis value is near 0%, this indicates a low probability of passing a lot using the sampling plan.

OC curves were generated to compare the various methods under specific simulated scenarios. For each method, the following simulation parameters were considered:

- Batch sample sizes ("n") of 10, 30, and 60.
- Normally distributed batch data with a means of 96%LC or 100%LC and SD ranging from 0.5 to 8.0 %LC with 1,000 replicates generated for each case.
- A 95% level (%C) for calculating both the confidence regions and the tolerance intervals.
- A 95%LB probability of passing USP <905>, as described in ASTM Standards E2709-104 and E2810-115, in simulating the joint confidence region plans.
- A 95% population coverage between 85% and 115% product %LC in creating the normal tolerance interval plans.

Figure 3 provides a comparison of the alternatives' sampling plans and associated acceptance criteria for each of the parameters above. It also includes the OC curves for the USP <905> test (black lines) and serves as a performance reference of the UDU test against the other alternatives. Figure 3 also shows:

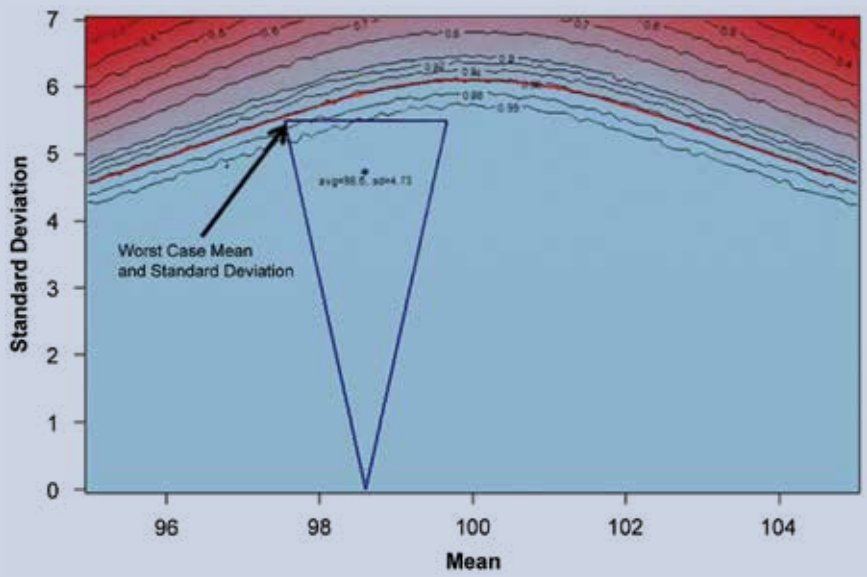
1. Increasing the sample sizes from 10 to 60 increases the power to detect changes in variability across methods. This is illustrated by the increased steepness of the curves as the sample size is increased.
2. As batch means move away from a 100%LC target to 96%LC, each method illustrated an increased conservatism. This is illustrated by the smaller SD required to achieve the same probability of passing the test for batch means of 96%LC vs. 100%LC. (That is to say, as you move away from the target mean, a smaller SD is required to maintain the same conformance rate or probability of passing.)
3. For all the parameters studied, the joint confidence region plans (ASTM, HT2, LRT, LSRF LSRX2, MACR, and MOOD) tend to be more conservative than the tolerance-interval-based plans and the USP test. This is illustrated in each of the six panes of Figure 3. Curves farther to the left are said to be more conservative due to the lower probability of passing the test (y-axis) for corresponding SD (x-axis). The degree of conservatism of the joint confidence region plans will change based on the choice of the lower bound.
4. There is more differentiation between the OC curves from the joint confidence region plans with changes in the sample size than with the evaluated offset of the batch means (i.e., change in batch mean from 100 to 96%LC).
   a. As the sample size increases with a fixed confidence level, the OC curves from the joint confidence region tend to overlap, which suggests signs of potential convergence. For example:
      i. At the lowest sample size (n = 10), the OC curves across the various joint confidence regions are very spread out.
      ii. At the highest sample size (n = 60), the OC curves for the various joint confidence regions appear to be clustered.
5. Regardless of the sample size, the ASTM and MOOD confidence regions were consistently among the most conservative OC curves (located towards the left).
6. The performance of the tolerance-interval-based plans with respect to the USP test is described below:
   a. The AV approach was substantially more conservative than the USP criteria when the sample size was small (≤ 30). As the sample size was increased, the AV method behaved more similarly to the USP test than any of other methods evaluated.
   b. The OC curves for the NTL criteria based on individual UDU results were consistently more conservative than the USP test but less so than the joint confidence region methods, across the sample size and means compared.

Based on the comparisons made above, the NTL 95%/95% criteria (i.e., with 95% confidence level/95% population coverage) based on individual UDU results exhibit a compromise (i.e., middle ground) performance relative to both the USP and the 95% confidence-region-based sampling plans. The NTL-based plans

have the advantage of providing a meaningful, practical statement while maintaining a sound statistical foundation. For example: 95% of dosage units reside within 85%–115%LC (coverage) with 95% confidence. Also, these plans are easy to communicate, implement, and adjust.

The AV 95%/95% could also be a practical method for implementation; however, this method is only recommended for sample sizes of 30 or less. Due to the proximity of the AV 95%/95% OC curve to the USP test at higher sample sizes, this plan would not provide the required protection for passing the USP criteria. To improve the performance when using the AV plan with larger sample sizes, it would be necessary to adjust either the confidence or coverage levels. (See Table B.)

Figure 1 Contour Plot of Probability to Pass USP <905>



An example joint confidence region (using ASTM 2709) is displayed as blue triangle (n = 100, sample average = 98.6 %LC and SD = 4.73 %LC). The red line at 0.96 probability contour represents the 95% probability bound determined using the ASTM 2709/2810 standards.

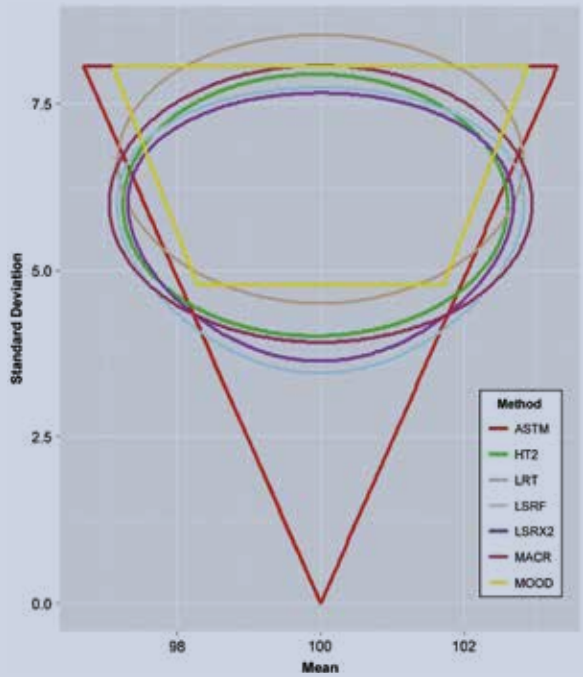
Future work could consider the assessment of alternative estimation approaches for the UDU test (for example, Bayesian methods) and a development of a risk-based framework to help with the selection of a suitable sampling plan and acceptance criteria for UDU. This work could also include the estimation of statistically based limits on the standard deviation and on the RSD, which potentially show that the process variability is within strict tolerances and the process is under a reasonable level of control and able to yield uniform results.

Conclusions

Both joint confidence-region-based plans and normal tolerance-interval-based plans are suitable for ensuring that the UDU test criteria will be met, as they all provide assurance to a level tighter than the USP test. Additionally, as the joint confidence region plans incorporate confidence statements on the mean and SD, they tend to be more conservative relative to the USP test. All pertinent test parameters (confidence, coverage, probability to pass) for each plan can be adjusted.

Table A provides an example adjustment and the resulting probability to pass the ASTM and NTL test plan criteria. Changing the parameters indeed changes the performance of the test plans, but what constitutes an appropriate plan choice? How should a plan be selected?

Figure 2 Comparison of Joint Confidence Regions



All confidence regions depicted above were constructed using a 95% confidence level, batch sample size of 30, batch mean of 100, and batch SD of 6.

Figure 3 OC Curves for Simulation Results at the 95% Confidence Level

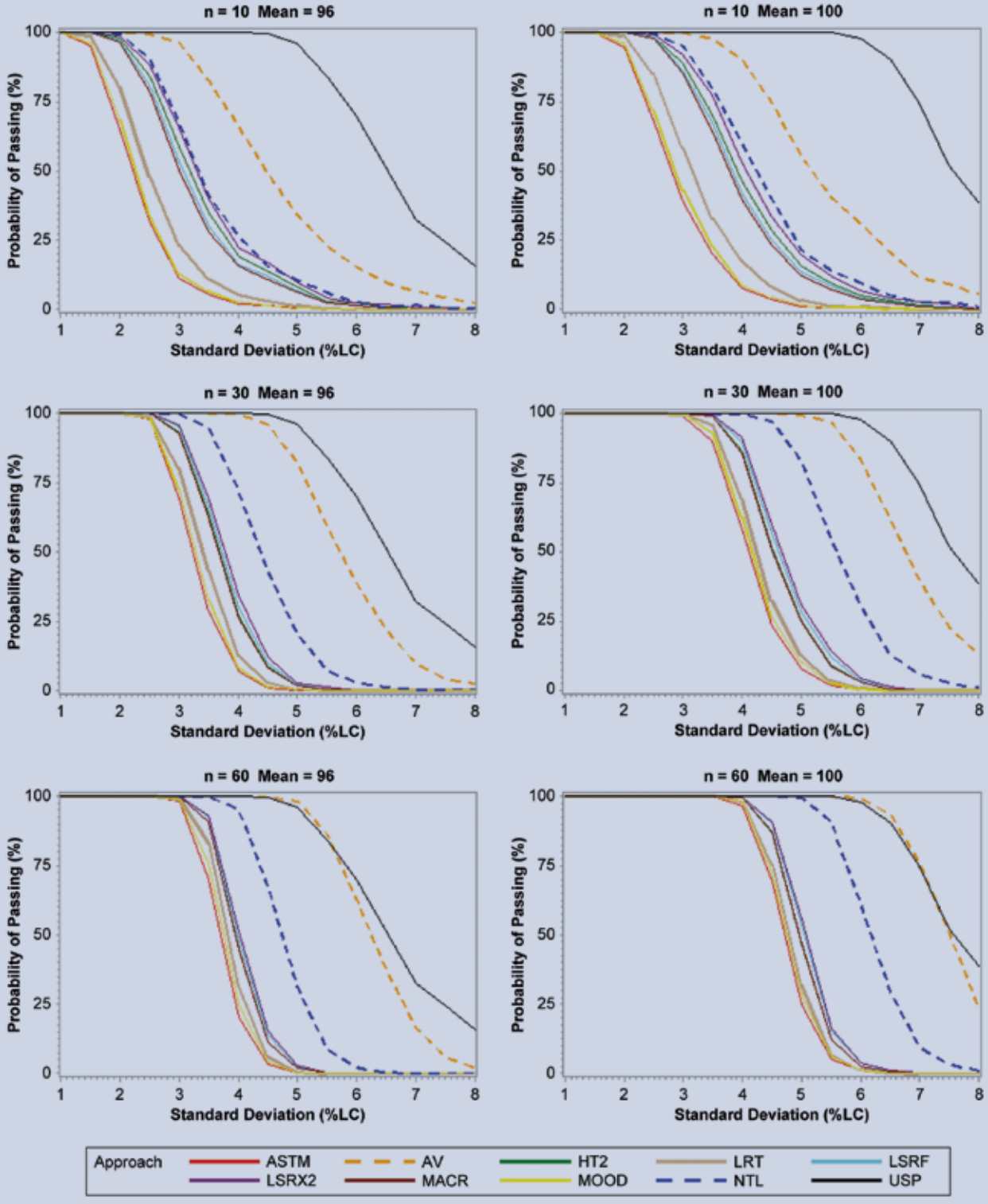


Table A Probability Estimate Comparison between USP <905>, ASTM, and NTL Plans for Batch Mean Potency of 100% and Sample Size of 30

Sigma	Probability to Pass USP <905> (%)	Probability to Pass ASTM (%) by Confidence/Lower Bound				Probability to Pass NTL (%) by Confidence/Coverage	
		95/95	95/50	50/95	50/50	95/95	50/95
2	100.0	100.0	100.0	100.0	100.0	100	100.0
3	100.0	99.4	100.0	100.0	100.0	100	100.0
4	100.0	58.3	95.5	99.6	100.0	99.9	100.0
5	100.0	7.7	46.0	67.2	98.1	83.0	99.7
6	97.8	0.4	7.9	21.6	72.4	31.0	89.6
7	74.7	0.0	0.5	2.8	27.1	5.8	50.4

Table B Alternative AV Plans for Sample Sizes between 40 and 100

n	Confidence Level (%)	Allowed Coverage Range	Tolerance Interval Multiplier Range
40	95	96 to 99	2.251 to 2.941
	96	96 to 99	2.288 to 2.986
	97	96 to 98	2.334 to 2.706
	98	95 to 98	2.265 to 2.776
	99	94 to 98	2.249 to 2.893
50	95	97 to 99	2.340 to 2.862
	96	96 to 99	2.220 to 2.901
	97	96 to 99	2.259 to 2.950
	98	96 to 98	2.313 to 2.682
	99	95 to 98	2.269 to 2.781
60	95	97 to 99	2.293 to 2.807
	96	97 to 99	2.322 to 2.841
	97	97 to 99	2.359 to 2.884
	98	96 to 99	2.254 to 2.943
	99	96 to 98	2.331 to 2.702
70	95	97 to 99	2.257 to 2.765
	96	97 to 99	2.284 to 2.796
	97	97 to 99	2.317 to 2.835
	98	97 to 99	2.362 to 2.888
	99	96 to 99	2.279 to 2.974
80	95	97 to 99	2.229 to 2.733
	96	97 to 99	2.254 to 2.761
	97	97 to 99	2.284 to 2.797
	98	97 to 99	2.326 to 2.845
	99	96 to 99	2.239 to 2.924
90	95	98 to 99	2.400 to 2.706
	96	97 to 99	2.229 to 2.733
	97	97 to 99	2.258 to 2.766
	98	97 to 99	2.296 to 2.811
	99	97 to 99	2.358 to 2.883
100	95	98 to 99	2.380 to 2.684
	96	98 to 99	2.403 to 2.709
	97	97 to 99	2.236 to 2.740
	98	97 to 99	2.272 to 2.782
	99	97 to 99	2.330 to 2.850

Table constructed to satisfy the criteria $K(95,95,n = 30) \leq K(c,p,n > 30) \leq K(95,95,n = 10)$. This is $2.220 \leq K(c,p,n > 30) \leq 2.991$.

Table C Selected One-sided Normal Tolerance Interval Multipliers

1-a	n	p	K
0.95	10	0.9052	2.400
		0.95	2.911
	30	0.9286	2.000
		0.95	2.220
	60	0.95	2.022

Table D Selected Two-sided Normal Tolerance Interval Multipliers

1-a/2	p	n	K
0.95	0.95	10	3.407
	30	30	2.556
	60	60	2.335

To comprehend the complexity of this choice, it is important to acknowledge that most small-molecule products have true process or population SD between 1% and 5%LC with safety and efficacy having been demonstrated through clinical studies and laboratory experiments. The ability to produce a product to a particular SD could be impacted by the technology required to achieve all of the desired product attributes.

As provided in Table A, if a manufacturer produced lots from a process with a true SD of 5%, then, on average, each lot would pass the USP test approximately 100% of the time yet pass ASTM 95%/95% and NTL 95%/95% approximately 7.7% and 83% of the time respectively. The most conservative plan may not be the most appropriate; a safe and efficacious product manufactured at an SD of 5%LC should pass when tested. This is a clear example of where excessive tightening of the requirements might create patient risk by increasing costs, creating product shortages, and

potentially preventing products from being marketed. Instead, the choice and application of the plan should be considered within the total quality system to ensure a safe and efficacious product at the most advantageous cost to the consumer.

Regardless of the statistical method utilized to gage product acceptability to USP <905>, specific sampling plans and acceptance criteria should be balanced by assessing the appropriate risk levels and available resources prior to their implementation. It is recommended that the manufacturer develop a strategy with goals that will ensure safety and efficacy and not unduly increase the cost to the patient or risk market shortages. The goal could apply to most products, with potentially some requirements tightened due to clinical need or loosened due to process capability, without loss to product safety or efficacy.

Finally, the strategy could be implemented within the three-stage process validation guidance. That is:

1. Continue to improve the process in development until Process Validation Stage 1, Quality by Design (QbD), product goals have been reached. Establish appropriate process controls in Stage 1 to aid Stage 2 and Stage 3 process monitoring and the ability to detect any changes.

2. Transfer the product to manufacturing during Process Validation Stage 2, where a larger sample size could be considered to estimate the SD and provide a baseline for process performance. This larger sample size will permit a stronger demonstration of the quality developed in Stage 1.

3. Then, during Process Validation Stage 3, or routine manufacturing, quality is ensured through the process engineering and process controls, where a smaller sample size is all that is required.

Appendix A: Description of Confidence Regions

A confidence region is an extension of the confidence interval concept with respect to two or more unknown parameters. This is constructed in such a way that if multiple sets of results were gathered repetitively and the confidence region were calculated for each set, on average a certain proportion would include the true values of the various parameter estimates associated with the confidence region.

There are a variety of methods for constructing joint confidence sets for mean μ and standard deviation σ, and the ones considered during this evaluation are described below. For all of these cases, a random set $\mathrm{R}(X_1, X_2, \cdots, X_n)$ will be considered such that:

$$\Pr((\mu, \sigma^2) \in \mathrm{R}(X_1, X_2, \cdots, X_n)) = 1-\alpha. \quad [1]$$

1. ASTM: The Lindgren confidence region is described in the ASTM standard E2709[4] and was implemented in the CuDAL SAS program validated through PhRMA.[7] This joint region is characterized by the following equations:

$$\mu \le \bar{X} \pm Z_{(1+\sqrt{1-\alpha})/2}\left(\frac{\sigma}{\sqrt{n}}\right) \quad [2]$$

$$\sigma \le \sqrt{\frac{S^2(n-1)}{\chi^2_{n-1,1-\sqrt{1-\alpha}}}} \quad [3]$$

2. MOOD, or the Mood confidence region: Assume that $X_1, X_2, \cdots, X_n$ are iid random samples from a normal distribution with mean μ and standard deviation σ. Then $\bar{X} = \frac{1}{n}\sum_{i=1}^{n} X_i \sim N\left(\mu, \frac{1}{n}\sigma^2\right)$ and $S^2 \sim \frac{\sigma^2}{n-1}\chi^2_{n-1}$, where $S^2 = \frac{1}{n-1}\sum_{i=1}^{n}(X_i - \bar{X})^2$. Based on Cochran's theorem, $\bar{X}$ and S^2 are independent. Mood (1950) proposed a 100(1- α)% exact confidence region for μ and σ^2, which is defined by:

$$\mathrm{R}(X_1, X_2, \cdots, X_n) = \{(\mu, \sigma 2):$$
$$\mu \le \bar{X} \pm Z_{1-\alpha_1/2}\left(\frac{\sigma}{\sqrt{n}}\right), \sqrt{\frac{S^2(n-1)}{\chi^2_{n-1,1-\alpha_2/2}}} \le \sigma \le \sqrt{\frac{S^2(n-1)}{\chi^2_{n-1,\alpha_2/2}}}\} \quad [4]$$

where 1- $\alpha = (1-\alpha_1)(1-\alpha_2)$, Z_1-$\alpha_1/2$) is the upper $\alpha_1/2$ percentile of a standard normal distribution, $\chi^2_{n-1,}\,\alpha_2/2$ and $\chi^2_{n-1,1-\alpha_2/2}$ are the lower and upper $\alpha_2/2$ percentile of a χ^2_{n-1} distribution respectively. The Mood exact procedure, although exact, is not optimal with regard to expected area and relies on the normality assumption.

3. LRT: Likelihood-ratio-based confidence region: $f(X \mid \theta)$ is the pdf of $X_1, X_2, \cdots, X_n$, and the likelihood function is defined as:

$$\mathrm{Ln}(\theta | x_{1,\ldots,} x_n) = f(X|\theta) = \prod_{i=1}^{n} f(x_i|\theta) \quad [5]$$

The likelihood ratio test (LRT) statistic for testing H_0: $(\mu, \sigma^2) = (\mu_0, \sigma_0{}^2)$ is:

$$R_n(\mu_0, \sigma_0^2) = \frac{L_n(\mu_0, \sigma_0^2)}{L_n(\hat{\mu}, \hat{\sigma}^2)} \quad [6]$$

where $\hat{\mu}$ and $\hat{\sigma}^2$ denote the maximum likelihood estimates (MLEs) of μ and σ^2. For large n, $-2\log R_n(\mu_0, \sigma_0{}^2)$ approximately follows χ^2_2 distribution, then an approximate 100(1- α)% confidence region for μ and σ^2 is:

$$\mathrm{R}(X_1, X_2, \cdots, X_n) = \{(\mu, \sigma 2): -2\log Rn(\mu, \sigma 2) < \chi^2_{2.1-\alpha}\} \quad [7]$$

Since the MLE for μ is $\bar{X}$ and the MLE for σ^2 is S^2, then:

$$-2\log R_n(\mu,\sigma^2) = n\log\left(\frac{\sigma^2}{S^2}\right) + \frac{nS^2}{\sigma^2} + \frac{n(\bar{X}-\mu)^2}{\sigma^2} - n. \quad [8]$$

So the likelihood-ratio-based confidence region for μ and σ^2 is

$$n\log\left(\frac{\sigma^2}{S^2}\right) + \frac{nS^2}{\sigma^2} + \frac{n(\bar{X}-\mu)^2}{\sigma^2} - n \le \chi^2_{2,1-\alpha} \quad [9]$$

Which is the same as:

$$n\left(-\log\left(\frac{S^2}{\sigma^2}\right) + \frac{S^2}{\sigma^2} + \frac{(\bar{X}-\mu)^2}{\sigma^2} - 1\right) \le \chi^2_{2,1-\alpha} \quad [10]$$

The likelihood ratio procedure is widely applicable, but its equation does not have a closed form solution. Given the computational complexity of the method, iterative search methods were implemented during the method performance evaluation.

The likelihood ratio equation can be approximated by the following power series, which is a Taylor series expansion of the logarithmic function under the assumption that $0 < \frac{S^2}{\sigma^2} \le 2$:

$$\log\left(\frac{S^2}{\sigma^2}\right) = \sum_{i=1}^{\infty} \frac{(-1)^{i-1}\left(\frac{S^2}{\sigma^2}-1\right)^i}{i} \approx \left(\frac{S^2}{\sigma^2}-1\right) - \frac{\left(\frac{S^2}{\sigma^2}-1\right)^2}{2} \quad [11]$$

The equation simplifies to the expression that happens to be one of the large-sample region methods described below:

$$\frac{n}{\sigma^2}(\bar{X}-\mu)^2 + \frac{n}{2\sigma^4}(S^2-\sigma^2)^2 \le \chi^2_{2,1-\alpha} \quad [12]$$

Arnold and Shavelle[13] showed that the likelihood ratio test procedure provides a higher confidence that the true parameter pair (mean and SD) would lie within the confidence region, as compared to the large-sample regions, especially when the sample size was small; however, they also concluded that for cases when the normality assumption was to be doubted in favor of a t-distribution alternative, the large-sample regions were recommended.

4. LSRX and LSRF: The large-sample approximate regions with plug-in values: Based on the central limit theory, $(\bar{X}-\mu) \dot{\sim} N(0, \frac{1}{n}\sigma^2)$ as $n \to \infty$, thus $\frac{n}{\sigma^2}(\bar{X}-\mu)^2 \dot{\sim} \chi^2_1$. And as $n \to \infty, S^2$ converges in probability to σ^2, which means $\sqrt{n}(S^2-\sigma^2) \dot{\sim} N(0, 2\sigma^4)$, thus $\frac{n}{2\sigma^4}(S^2-\sigma^2)^2 \dot{\sim} \chi^2_1$, As $\bar{X}$ and $S^2$are independent (Cochran's theorem):

$$\frac{n}{\sigma^2}(\bar{X}-\mu)^2 + \frac{n}{2\sigma^4}(S^2-\sigma^2)^2 \dot{\sim} \chi^2_2 \quad [13]$$

Since S^2 is a consistent estimator of σ^2 for any variable X_i, further approximation can be applied to [13] by replacing σ^2 with S^2. Then:

$$\frac{n}{S^2}(\bar{X}-\mu)^2 + \frac{n}{2S^4}(S^2-\sigma^2)^2 \dot{\sim} \chi^2_2 \quad [14]$$

Since the above equation is an ellipse, the perimeter of the ellipse (i.e., $t = 0$ to 2π) could be calculated with the following equations:

$$\hat{\mu} = \left(S\sqrt{\frac{\chi^2_{2,1-\alpha}}{n}}\right)\cos(t) + \bar{X}, \hat{\sigma} = \sqrt{\left(S^2\sqrt{\frac{2\chi^2_{2,1-\alpha}}{n}}\right)\sin(t) + S^2} \quad [15]$$

In Arnold and Shavelle[13], another modification was used on equation 14 when changing from χ^2_2 to 2F_(2,n-2), and $2F_{2,n-2}$, and $kF_{k,n-k} \ge \chi^2_k$. Then [14] changes to:

$$\frac{n}{S^2}(\bar{X}-\mu)^2 + \frac{n}{2S^4}(S^2-\sigma^2)^2 \dot{\sim} 2F_{2,n-2} \quad [16]$$

Since this is an ellipse, the perimeter of the ellipse (i.e., $t = 0$ to 2π) could be calculated with the following equations:

$$\hat{\mu} = \left(S\sqrt{\frac{2F_{2,n-2,1-\alpha}}{n}}\right)\cos(t) + \bar{X}, \hat{\sigma} = \sqrt{\left(S^2\sqrt{\frac{4F_{2,n-2,1-\alpha}}{n}}\right)\sin(t) + S^2} \quad [17]$$

As indicated earlier, when the sample size is large enough and the normality assumption cannot be satisfied, it is more reasonable to use the large-sample properties to approximate the confidence regions for μ and σ^2; however, if the sample size is not sufficiently large, the replacement of σ^2 by S^2 may be less accurate.w

5. MACR, or the minimum-area joint confidence region: Frey et al.[14] proposed a minimum-area joint confidence region for μ and σ from the normal distribution. Let $Z_i = \frac{X_i-\mu}{\sigma}, i = 1, \cdots, n$, then $Z_1, Z_2, \cdots, Z_i$ are iid random samples from the standard normal distribution. Define $\bar{Z} = \frac{1}{n}\sum_{i=1}^{n} Z_i$ and $S_z^2 = \frac{1}{n-1}\sum_{i=1}^{n}(Z_i-\bar{Z})^2$, where $\bar{Z}$ is independent of S_z^2. Then the joint probability density function for $\bar{Z}$ and S_z is:

$$f_{\bar{Z},S_z}(\bar{z},s_z) = \frac{(n-1)^{(n-1)/2}s_z^{n-2}\exp\left(-\frac{(n-1)s_z^2}{2}\right)\sqrt{\frac{n}{2\pi}}\exp\left(-\frac{n\bar{z}^2}{2}\right)}{\Gamma\left(\frac{n-1}{2}\right)2^{(n-3)/2}}, s_z > 0 \quad [18]$$

Let $A = -\bar{Z}/S_Z$ and $B = 1/S_Z$, then the joint probability density function for A and B is:

$$f_{A,B}(a,b) = \frac{(n-1)^{\frac{n-1}{2}}(1/b)^{n+1}\exp\left(-(n-1)/(2b^2)\right)\sqrt{\frac{n}{2\pi}}\exp\left(-\frac{na^2}{2b^2}\right)}{\Gamma\left(\frac{n-1}{2}\right)2^{(n-3)/2}}, b > 0 \quad [19]$$

Frey et al.[14] state that a minimum-area joint confidence region must have the form $\{(\mu, \sigma): f_{A,B}(a,b) \geq c\}$ for some constant, c, which is equivalent to the form $\{(\mu,\sigma): -\log f_{A,B}(a,b) \leq -\log c\}$. Combining equation 19, the minimum-area joint confidence region is determined by the statistic R, which is:

$$R_{n\,1-a} = (n+1)\log B + (n-1+nA^2)/(2B^2) - (n-1)/2 \quad [20]$$

Values for R based on different confidence levels and sample sizes were listed in Table 1 in Frey et al.[12] After performing a power transformation, this region is characterized by the following asymptotically elliptical equation, centered at (A = 0, B = 1):

$$R_{n,1-\alpha} = n\left((B-1)^2 + (A^2/2)\right) \quad [21]$$

Consider $B = 1/S$ and $A = -\bar{x}/S$, the equation 21 can be rewritten as:

$$1 = \frac{n}{S^2 R_{n,1-\alpha}}\left((S-1)^2 + \frac{(\bar{x}-0)^2}{2}\right) \quad [22]$$

From equation 22, the upper perimeter of the minimum-area confidence region (i.e., $t = 0$ to π, centered at $\bar{X}$ and S) could be calculated with the following equation sequence:

$$\hat{\mu} = \left(\sqrt{\frac{2S^2 R_{n,1-\alpha}}{n}}\right)\cos(t) + \bar{X}, \hat{\sigma} = \left(\sqrt{\frac{S^2 R_{n,1-\alpha}}{n}}\right)\sin(t) + S \quad [23]$$

6. HT2, or Hoteling T^2-based confidence region: Suppose that the UDU results for a batch is ND(μ, σ) and that we generate from that population a matrix with "r" rows and "n" columns. Also, for each row of that matrix, suppose we take the "n" samples and obtain a sample mean and standard deviation. Then we will have two vectors of size "r": one vector with the sample means "m" and the sample SD "s." If we were to characterize the bivariate distribution of the above vectors based on a Hoteling T^2 distribution, the prediction interval ellipse could be estimated by the following equation:

$$\frac{r}{S_m^2 S_s^2 - \mathrm{Cov}(m,s)^2}\left(\begin{matrix} S_s^2(\bar{X}_m-\mu)^2 + S_m^2(\bar{X}_s-\sigma)^2 \\ -2\,\mathrm{Cov}(m,s)(\bar{X}_m-\mu)(\bar{X}_s-\sigma)\end{matrix}\right) \leq \frac{2(r+1)(r-1)}{(r-2)}F_{2,n-2,1-\alpha} \quad [24]$$

Based on the geometric interpretation of the ellipse, its perimeter could be calculated with the following equations:

$$\hat{\mu} = x\cos(\theta) - y\sin(\theta) + \bar{X}_m, \hat{\sigma} = y\cos(\theta) + x\sin(\theta) + \bar{X}_s \quad [25]$$

where

$$x = \left(\sqrt{\frac{(S_m^2 S_s^2 - Cov(m,s)^2)2(r+1)(r-1)F_{2,n-2,1-\alpha}}{S_s^2\, r(r-2)}}\right)cos(t)$$

$$y = \left(\sqrt{\frac{(S_m^2 S_s^2 - Cov(m,s)^2)2(r+1)(r-1)F_{2,n-2,1-\alpha}}{S_m^2\, r(r-2)}}\right)sin(t)$$

$$t = 0\ to\ 2\pi$$

$$\theta = (1/2)\,tan^{-1}\left(\frac{2\,Cov(m,s)}{S_m^2 - S_s^2}\right)$$

Assuming that $\mathrm{Cov}(m,s) = 0$, based on the assumption that the sample mean and the variance are independent random variables, the ellipse perimeter calculation simplifies to the equations below. These assumptions were used during the evaluation of this confidence region.

$$\hat{\mu} = \left(S_m\sqrt{\frac{2(r+1)(r-1)F_{2,n-2,1-\alpha}}{r(r-2)}}\right)\cos(t) + \bar{X}_m,$$

$$\hat{\sigma} = \left(S_s\sqrt{\frac{2(r+1)(r-1)F_{2,n-2,1-\alpha}}{r(r-2)}}\right)\sin(t) + \bar{X}_s, \text{ for: } t = 0 \text{ to } 2\pi \quad [26]$$

Appendix B: Tolerance-Interval-Based Methods

1. AV, or acceptance-value-based criteria: The procedure is expected to evaluate acceptance values that provide a "1-α" confidence of covering at least a proportion "p" of the population, with an estimated probability "θ" of satisfying the UDU test, as follows:

   a. Consider that: (i) a sample of size "n" is taken from a batch, and that a mean "$\bar{X}$" and standard deviation "s" is computed; (ii) the actual batch UDU results are IND $(=\bar{x}, \sigma=s)$ and that the UDU target is 100%.

   b. Use the batch UDU results distributional parameters to generate a "r" x "n" matrix of results. For each of the "r" rows of the matrix, compute an acceptance value as follows:

$$AV_i = |M - \bar{X}_i| + \left(K_{1-\alpha,p,n}\right)(s_i),$$
$$\text{for } M = Min[Max(98.5, \bar{X}_i), 101.5] \text{ and i} = 1 \text{ to r} \quad [27]$$

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where "$K_{1-\alpha,p,n}$" is a one-sided normal tolerance limit multiplier such that, with a sample size "n" is able to provide a "1-α" confidence of covering at least a proportion "p" of the population, "$\bar{X}_i$" refers to the sample mean, and "s_i" refers to the sample standard deviation for batch "i."

Some specific one-sided normal tolerance limit multiplier values are listed in Table C. As expected, the multiplier decreases if the sample size increases (for the same level of confidence and population coverage) or if the confidence level decreases (for the same coverage and sample size levels).

c. Obtain the proportion "θ" of AV results falling inside the 15.0, which provides a probability of satisfying the UDU test. The acceptance limit of 15.0 could be potentially tightened if one requires more conservative criteria.

2. NTL, or normal tolerance limit criteria based on individual UDU results: This criteria requires that two-sided normal tolerance intervals of the UDU results fall within the 85.0% to 115.0%LC. If we were to assume that a sample of size "n" is taken from a batch "i," then a two-sided normal tolerance interval would be computed as:

$$LTL_i = \bar{X}_i - (K_{1-\alpha/2,p,n})(s_i)\,,\ UTL_i = \bar{X}_i + (K_{1-\alpha/2,p,n})(s_i) \quad [28]$$

where "$K_{1-\alpha/2,p,n}$" is a normal tolerance interval multiplier such that, with a sample size of "n" is able to provide a "1-α/2" confidence of covering at least a proportion "p" of the population, "$\bar{X}_i$" refers to the sample mean and "S_i" refers to the sample SD for batch "i."

Some specific two-sided normal tolerance interval multiplier values are listed in Table D. As expected, the multiplier decreases if the sample size increases (for the same level of confidence and population coverage) or if the confidence level decreases (for the same coverage and sample size levels).

As in the case of the AV-based method, we could obtain the proportion "θ" of tolerance interval estimates from simulated batches (generated from an assumed normal distribution) that fall inside the 85.0% to 115.0% limits and that could provide an estimate of the probability of satisfying the UDU test. ◂

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ORGANIZATIONS

ICH

ICH Releases Q7 Q&A on GMP for API[1]

The International Conference on Harmonisation (ICH) has published the ICH Q7 *Questions & Answers on the Good Manufacturing Practice (GMP) Guide for Active Pharmaceutical Ingredients* (API). PIC/S contributed to this Q&A document, which provides interpretation to GMP for APIs since the implementation of the ICH Q7 Guideline. The ICH Q7 Guideline was originally based on a PIC/S draft guideline on API and adopted by PIC/S in 2001 and then integrated as part two of the PIC/S GMP Guide in 2007.

Update from ICH Steering Committee, Fukuoka, Japan, June 2015[2]

The ICH Steering Committee (SC) and its Expert Working Groups met in Fukuoka, Japan, from 5–10 June 2015. The SC agreed on the key issues relating to the reform of ICH in terms of the Articles of Association, funding model, and membership. An important part of the reform effort is establishing a formal organization with a new approach to membership, governance, and shared funding among ICH members. The new ICH association, under Swiss law, is expected to be established over the coming months with the aim of being operational by 2016.

Twelve working groups met in Fukuoka and achieved important progress with regard to their respective objectives. The Q&A document on the *Q7 Guideline on Good Manufacturing Practices for Active Pharmaceutical Ingredients (API)* was signed off at Step 4 in Fukuoka and is thus ready for implementation in the ICH regions. In addition, two documents – the draft addendum to *M7 Guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* and the draft addendum to *E6 on Good Clinical Practice* – have reached Step 2b and will be submitted for public consultation.

AFRICA

Tanzania

TFDA Adopts the EAC Harmonized Guidelines on Evaluation and Registration of Medicines[3]

Tanzania Food and Drugs Authority (TFDA) has adopted the East African Community (EAC) harmonized guidelines on Medicines Evaluation and Registration (MER). These guidelines contain the common technical document as well as the common criteria to be used for the evaluation and registration of medicinal product dossiers in the region.

This adoption follows Decision EAC/CM29/Decision 36 to approve the EAC harmonized guidelines on medicines evaluation and registration by the 29th Ordinary Meeting of the Council of Ministers on 20 September 2014. The Council also agreed that 1 January 2015 is the effective date for the domestication and implementation of the harmonized guidelines at the EAC Partner States' level.

AUSTRALIA

TGA Provides Update on GMP Clearance Application Process Improvements[4]

The Therapeutic Goods Administration (TGA) has experienced a significant increase in the number of GMP Clearance applications. In 2014-15, a total of 5,384 GMP Clearance applications were received. This compares with 4,222 applications in 2013-14 and 2,418 in 2010-11. This has created a backlog of applications and extended processing times. To address this, the TGA is focusing on reducing the largest part of the backlog, namely applications for manufacturers located in countries with which Australia has Mutual Recognition Agreement (MRA) applications.

ASIA

China

CFDA Issues Three Appendixes to Good Manufacturing Practice for Medical Devices[5]

In order to strengthen the supervision and management of medical devices, improve enterprises' quality management level, and ensure the safety and effectiveness of medical devices, the CFDA recently formulated and issued Announcement on Promulgation of Good Manufacturing Practice for Medical Devices Appendix for Sterile Medical Devices, the *Announcement on Promulgation of Good Manufacturing Practice for Medical Devices Appendix for Implantable Medical Devices, and the Announcement on Promulgation of Good Manufacturing Practice for Medical Devices Appendix for In Vitro Diagnosis Reagents* in accordance with the Regulations for the Supervision and Administration of Medical Devices and the Administrative Measures for the Supervision of Medical Device Manufacturing.

The three appendixes, which include special requirements for the Good Manufacturing Practice of sterile medical devices, implantable medical devices, and in vitro diagnosis reagents, will come into effect as of 1 October 2015.

CFDA Issues Measures for Unannounced Inspection of Drugs and Medical Devices[6]

The CFDA recently issued the *Measures for Unannounced Inspection of Drugs and Medical Devices*, which will be implemented as of 1 September 2015. The measures comprise 35 articles in five chapters, including general provisions, initiating, inspection, handling, and supplementary provisions.

CFDA Issues Good Supply Practice for Pharmaceutical Products[7]

The Good Supply Practice for Pharmaceutical Products (CFDA Order No. 13) was adopted at the executive meeting of the

CFDA on 18 May 2015 and was recently promulgated. It went into effect as of the date of promulgation.

The 2015 Edition of Chinese Pharmacopoeia to Enhance the Overall Level of China's Drug Quality[8]

The 2015 edition of *Chinese Pharmacopoeia* was recently adopted at the plenary session of the Executive Committee of the Tenth Chinese Pharmacopoeia Commission. On 5 June 2015, the CFDA promulgated the 2015 edition of *Chinese Pharmacopoeia*, which will go into effect on 1 December 2015. The promulgation of the new edition of *Chinese Pharmacopoeia* marks the promotion of the level of China's drug use, production, and supervision. It will drive the overall improvement of drug quality and play a significant role in ensuring drug safety and effectiveness.

India

India Moves Towards Regulating Medical Devices[9]

In an effort to boost international confidence in medical devices manufactured by Indian firms, the Indian government is creating the National Medical Device Authority under the Department of Pharmaceuticals to begin the process of regulating medical devices.

Japan

PMDA International Strategic Plan 2015[10]

The Pharmaceuticals and Medical Devices Agency (PMDA) has shortened the review period for medical products to the world's top standard through its first and second Mid-term Plan Periods (Fiscal Year 2004 to 2013). In order to respond to domestic and global expectations, the PMDA has developed and announced its strategic plan entitled "PMDA International Strategic Plan 2015." Below are the key international actions set forth in the "PMDA International Strategic Plan 2015."

1. 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.
2. 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.
3. Cooperate with overseas regulatory authorities for the expansion of harmonization activities (such as the ICH and the International Medical Device Regulators Forum) and work-sharing (such as GMP/QMS inspections).

Malaysia

Malaysia Issues Guideline on Good Pharmaceutical Trade Practice[11]

Good Pharmaceutical Trade Practice for Private Sector is intended to ensure best trade practices across pharmaceutical distribution chains. All pharmaceutical trade practices should be in line with existing laws and regulations, and this guideline will address the finer details not spelled out under current legislation.

EUROPE

European Union

EMA Publication of Safety Reports for Nationally Authorized Medicines Will Support Timely and Harmonized Implementation of Safety Measures in EU Member States[12]

The European Medicines Agency (EMA) has started to publish the outcomes of single assessments of periodic safety update reports (PSURs) for active substances contained only in nationally authorized medicines. This initiative aims to support the harmonized implementation of safety measures for medicines with the same active substance across European Union (EU) Member States. All pharmaceutical companies holding marketing authorizations for medicines at the national level are advised to regularly monitor the published information to check for outcomes relevant to their products.

Launch of Two-Month Public Consultations on Revised Guidelines on Accelerated Assessment and Conditional Marketing Authorization[13]

The EMA has revised its guidelines on the implementation of accelerated assessment and conditional marketing authorization, two key tools in the European legislation to accelerate patients' access to medicines that address unmet medical needs. The public consultations on the revised guidelines are open until 30 September 2015.

EMA Releases "Quick Response (QR) Codes in the Labelling and Package Leaflet of Centrally Authorized Medicinal Products"[14]

With the availability of new communication technologies, it has become apparent that patients/users of medicinal products may benefit from information provided in electronic format. In this context, there has been an increased demand by applicants to the centralized procedure to include quick response (QR) codes in the labelling and/or package leaflet of medicinal products as an additional way of providing information to patients and health-care professionals. This document outlines the requirements for use of QR codes in this context.

EMA to Encourage Use of Scientific Advice for Post-Authorization Safety Studies[15]

The EMA is launching a 12-month pilot to encourage companies to seek scientific advice for post-authorization safety studies for medicines. This voluntary, optional procedure will help to improve the design of studies meant to collect further information on a medicine's safety once it is on the market. This pilot will build on the expertise of the Agency's Pharmacovigilance Risk Assessment Committee (PRAC).

EMA Launches Two-Month Public Consultations on Revised Guidelines on Accelerated Assessment and Conditional Marketing Authorization[16]

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FDA, European Commission and EMA Reinforce Collaboration to Advance Medicine Development and Evaluation[17]

Senior leaders from the US Food and Drug Administration (FDA), the EC and the EMA, aiming to enhance trust in the quality, safety, and efficacy of medicines, reviewed their ongoing cooperative activities and discussed strategic priorities for the next two years at their regular bilateral meeting held on 19 June 2015. Over the years, the EMA and FDA have significantly increased their level of collaboration and sharing of information to advance regulatory excellence worldwide. There are now daily interactions, most of them structured around scientific and regulatory working groups, or "clusters." The focus of the cluster reviews during this bilateral was pharmacovigilance, biosimilars, pediatrics, and veterinary medicines.

Looking ahead, the EMA, the EC and the FDA decided to establish a new cluster on patient engagement to share experience and best practices regarding the involvement of patients in the development, evaluation, and post-authorization activities related to medicines. Participants also agreed that communication on the ongoing successful cooperation should be enhanced and that efforts to support communication activities and align core messages should be strengthened. They also agreed to further strengthen their collaboration in inspections and data integrity, safety monitoring of medicines, biosimilars, pediatric medicines, rare diseases, and timely access to new medicines and veterinary medicines. This will help EU regulators and the FDA increase efficiency on a global level and avoid duplication.

Finland

Fimea Meets 2014 Performance Target[18]

The Ministry of Social Affairs and Health's statement on the Finnish Medicines Agency's (Fimea's) final accounts reports that Fimea has engaged in efficient cooperation, been active, and carried out assignments to an extremely high standard. Fimea met its 2014 performance targets and scored 4+ on a scale of 1 to 5. The year 2014 was Fimea's best to date.

National OTC Medicines Program Now Available in English and Swedish[19]

Fimea has published English and Swedish translations of the national over-the-counter (OTC) medicines program on its web-

site. The program discusses self-medication in Finland from the perspective of the related objectives and requirements and assesses the factors affecting OTC medicine selection. It lays down related principles and focuses on the possibilities offered by medicinal products with a marketing authorization as a component of self-care.

Switzerland

EU and Swiss regulators sign confidentiality arrangement [20]

The EMA's and the EC's Directorate General for Health and Food Safety have agreed with the Swiss Agency for Therapeutic Products (Swissmedic) and the Swiss Federal Department of Home Affairs (FDHA) to share non-public information on the safety, quality, and efficacy of medicines, already authorized or under review, both in Switzerland and the EU, in order to enhance public health protection.

The arrangement supports efforts by European and Swiss regulators to improve the oversight of medicines for human and animal health. The arrangement builds on the previous cooperation of the EMA and Swissmedic during the 2009/2010 H1N1 pandemic and on the Mutual Recognition Agreement signed in 2002. The arrangement came into effect on 10 July 2015; it is valid for five years and may be renewed.

United Kingdom

MHRA Launches Inspectorate Blog [21]

Keeping stakeholders informed of the latest changes in regulatory thinking, guidance, and requirements is crucial to the mission of the Medicines & Healthcare Products Regulatory Agency (MHRA). It allows the MHRA to provide stakeholders with advice and support, promote innovation, and ultimately protect public health. To this end, the MHRA has started an Inspectorate Blog – a new and exciting way to communicate. Upcoming topics are expected to include (GxP), compliance management approaches, data integrity, preventing drug shortages, significant findings from inspections, supporting innovation

and work with the MHRA Innovation Office, and upcoming learning opportunities.

GMP Data Integrity: A New Look at an Old Topic [22]
One of the top global issues reported in the pharmaceutical media over the past two years has been data integrity. Regulatory actions resulting from data integrity failures have led to the withdrawal of supply across multiple markets, product recall, and serious reputational damage for those companies concerned. However this hot topic is not a new requirement, as basic data-integrity principles are already described in international good manufacturing practice guidance. The MHRA is taking a three-part look at this issue in its new Inspectorate Blog.

Review Finds MHRA Can Lead the Way for Global Regulatory Reforms[23]
According to the findings of a Triennial Review of the agency, published 21 July 2015, the government agency that regulates medicines and medical devices to ensure their quality, safety, and efficacy can place the UK at the forefront of a global drive to improve public health. The MHRA is already a leading national regulator at both pan-European and global levels but can go further and deeper in leading the international community to implement reform.

NORTH AMERICA

Canada

Health Canada Publishes "Guidance on Medical Device Compliance and Enforcement (GUI-0073)" [24]
This document outlines the strategy and provides guidance for the medical device industry on Health Canada's compliance and enforcement activities. This version of the document includes updated Web links and the incorporation of changes to the establishment licensing provisions that occurred recently due to a cost-recovery initiative.

Regulations Amending the Food and Drug Regulations (Shortages and Discontinuation of Sale of Drugs) [25]
Drug shortages and discontinuations are an immediate, pressing challenge to patient safety in Canada. Under the present voluntary reporting system, Canadians and those responsible for the provision of their health care are not being adequately informed of drug shortages and discontinuations and thus are not able to make well-informed, timely mitigation decisions. The Food and Drug Regulations currently have no provisions addressing drug shortages. They do contain a provision that requires companies with a market-approved drug that has been assigned a drug identification number (DIN) to notify Health Canada within 30 days of discontinuation of the sale of that drug. However, that provision does not specify the information to be provided as part of a notification.

In order to address these issues, the government of Canada is proposing a mandatory drug-shortage-and-discontinuation reporting system that would provide patients, practitioners, and other health-care stakeholders with reliable and trustworthy information in a timely fashion, as well as a more accurate picture of which drugs are actively being sold on the Canadian market.

United States

The Drug Supply Chain Security Act Implementation: Product Tracing Requirements for Dispensers – Compliance Policy; Guidance for Industry [26]
The FDA announced the availability of a guidance for the industry entitled *DSCSA Implementation: Product Tracing Requirements for Dispensers – Compliance Policy*. This guidance announces the FDA's intention with regard to the enforcement of certain product tracing requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) added by the Drug Supply Chain Security Act (DSCSA). The FDA does not intend to take action against dispensers who, prior to 1 November 2015, accepted ownership of products without receiving product tracing information, prior to or at the time of a transaction, or do not capture and maintain the product tracing information, as required by the FD&C Act.

FDA Issues Rule on Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products[27]

The FDA is amending its regulations to implement certain drug-shortage provisions of the FD&C Act, as amended by the Food and Drug Administration Safety and Innovation Act. The rule requires that all applicants of covered approved drugs or biological products – including certain applicants of blood or blood components for transfusion and all manufacturers of covered drugs marketed without an approved application – notify the FDA electronically of a permanent discontinuance or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in supply (or a significant disruption in supply of blood or blood components) of the product in the United States.

FDA Releases "Analytical Procedures and Methods Validation for Drugs and Biologics Guidance for Industry"[28]

The guidance entitled *Analytical Procedures and Methods Validation for Drugs and Biologics Guidance for Industry* discusses how to submit analytical procedures and methods validation data to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products. It supersedes the draft by the same name that was published on 19 February 2014 and replaces the 2000 draft guidance for the industry entitled *Analytical Procedures and Methods Validation* and the 1987 FDA guidance for industry entitled *Submitting Samples and Analytical Data for Methods Validation*.

FDA Issues Guidance – "Request for Quality Metrics Guidance for Industry"[29]

Quality metrics are used throughout the pharmaceutical industry to monitor quality control systems and processes and drive continuous improvement efforts in drug manufacturing. These metrics can also be used by the FDA to help develop compliance and inspection policies and practices, such as risk-based inspection scheduling of drug manufacturers; to improve the FDA's ability to predict and, therefore, possibly mitigate, future drug shortages; and to encourage the pharmaceutical industry to implement state-of-the-art, innovative quality management systems for pharmaceutical manufacturing. This guidance includes an explanation of how the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) intend to collect

data and use quality metrics to help ensure that their policies and practices continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry.

The FDA understands that establishments involved in the manufacture, preparation, propagation, or processing of human drugs, including oversight to ensure quality, currently use quality metrics as part of the process validation life cycle and pharmaceutical quality system (PQS) assessment. This guidance outlines the FDA's authority to require owners and operators of such establishments to provide, upon request, records and information that the FDA may inspect and describes an initial set of requests it intends to make to certain owners and operators. The FDA intends to make its requests at the time this guidance is finalized and provide notice in the Federal Register. In order to receive public comment on these requests, this draft guidance describes the data that the FDA plans to request, the uses it intends to make of the requested data, and the quality metrics it intends to calculate.

openFDA: The First Year in Perspective[30]
On 22 May 2015, Taha Kass-Hout, MD, MS, gave an update on the openFDA project at the Big Data in Biomedicine conference at Stanford University.

His talk, coming a year after the first APIs were launched at openFDA, covered the progress that has been made with the project so far. Based on the three pillars of Open Data, Open Source, and Open Community, the openFDA project has spawned dozens of apps, thousands of community members, and millions of API calls. The video of this presentation can be viewed at https://open.fda.gov/update/first-year-in-perspective.

FDA Proposes to Revoke Two Biological Regulations[31]
The FDA has proposed to remove two regulations that prescribe procedures for its review and classification of biological products licensed before 1 July 1972. The FDA took this action because the two regulations are obsolete and no longer necessary in light of other statutory and regulatory authorities established since 1972 that allow it to evaluate and monitor the safety and effectiveness of all biological products. In addition, other statutory and regulatory authorities authorize the FDA to revoke a license for products because they are not safe and effective or misbranded. The FDA took this action as part of its retrospective review of its regulations to promote improvement and innovation.

FDA Releases Report: "FDA Science Moving Forward"[32]
The report entitled *FDA Science Moving Forward* details how the FDA has accelerated efforts to develop new approaches to engaging in synergistic collaborations both intramurally and with other government agencies, academia, industry, patient organizations, professional societies, and other stakeholders. The FDA discusses its efforts to attract, develop, and retain top scientific talent and enhance scientific training and continuing-education opportunities for its staff. In the final section of the report, it highlights examples of its scientific accomplishments, organized according to the eight priority areas that the FDA identified in its Strategic Plan.

SOUTH AMERICA

Fostering Cooperation and Strengthening Medical Product Regulatory Systems in the Americas[33]
The FDA's, Office of International Programs (OIP) is announcing the availability of grant funds for the support of a single-source cooperative agreement to the Pan American Health Organization (PAHO) for fostering cooperation and strengthening medical product regulatory systems in the Americas. The goal of the cooperative agreement is to build upon existing cooperation between OIP/FDA and PAHO to foster regulatory collaboration and strengthen regulatory capacity throughout the Americas.

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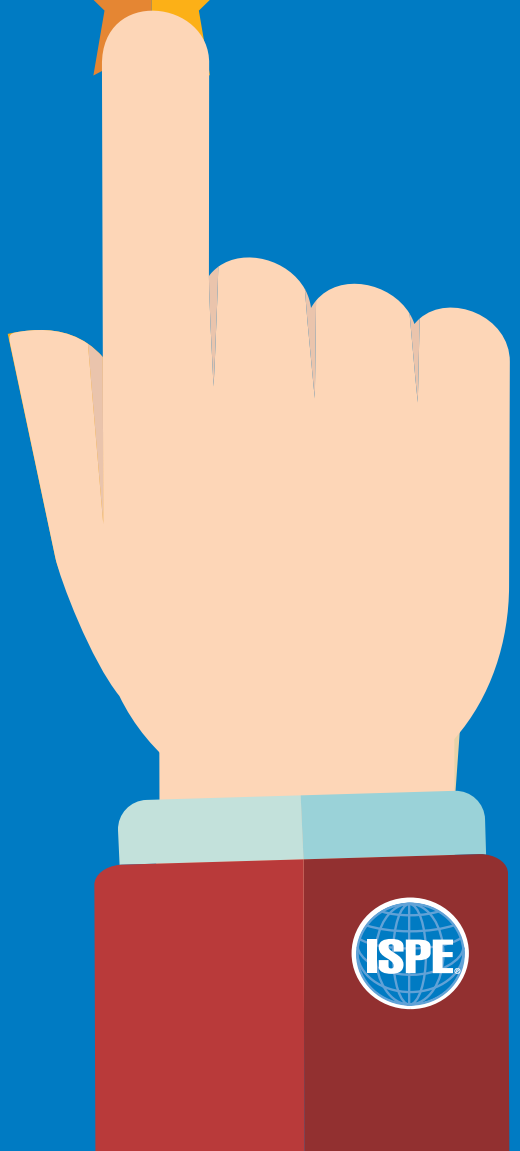
QUARTERLY REPORT
QUALITY CULTURE
October 2015

Quality by Design



QUALITY BY DESIGN

James Hale and Scott Fotheringham, PhD

Editor's note: Unless indicated otherwise, all quotations are the result of personal interviews or correspondence

Inside Apple's notoriously secretive lab on its Cupertino, California, campus, quality is an attribute that is not discussed; it just exists. It is what drives the computer manufacturer to obsess over materials, fit and function.

Born from the love of perfection that company cofounder Steve Jobs and design chief Jonathan Ive developed separately, an ocean apart, the devotion to quality processes stemmed from Jobs's relationship with Joseph Juran, formed while Jobs was leading NeXT Computer. Along with legendary designer Paul Rand—who developed iconic logos for IBM, UPS and others—and investor Ross Perot, Juran was one of a handful of renowned advisors Jobs turned to as he struggled to reassert his identity after his ouster from Apple in 1985. As his former company floundered under the leadership of John Scully, Jobs sought to create a product that would be set apart by beautiful design and remarkable functionality.

By turning to Juran—a Romanian-born engineer—Jobs embraced one of the gurus of modern quality management. During a stint with Western Electric, Juran had developed a theory that everyone involved in the manufacture of a product played a critical role in its success. Expressed in his 1951 book, *Quality Control Handbook*, his theory is credited with adding the human factor to the focus on quality in manufacturing, which had its roots in Frederick Winslow Taylor's work on productivity in the early 1900s and Walter Shewhart, who developed a theory of statistical control of manufacturing processes.

The 1996 PBS documentary *An Immigrant's Gift* told the story of Juran's life and groundbreaking work. As part of the project, director Jack Schatz asked Jobs to describe the importance that Juran's influence had on his thinking while he was trying to repeat his initial Apple success at NeXT. Jobs said that Juran showed him the importance of approaching business practices scientifically and questioning why they are done the way they are rather than following the traditional way of simply repeating what had been done before.

Photo courtesy of Matthew Yohe.

"That single shift is everything," Jobs said. [1]

Along with Iowa native William Edwards Deming (see "Quality's Midwife"), a Shewhart acolyte who had also passed through Western Electric, Juran played a major role in rebuilding and reshaping Japan's industrial system in the 1950s, moving the devastated country into a new era of manufacturing excellence.

Turning Theory Into Gold

Deming was the first to take his work to Japan, arriving in 1947 as part of a team of Americans assigned to develop a national census. Once there, his work in translating Shewhart's theories into practical approaches to control and management attracted the attention of the Japanese Union of Scientists and Engineers (JUSE). In 1950, the organization retained Deming to teach a series of classes in statistical control. Among his students was Akio

Morita, co-founder of the fledgling Tokyo Telecommunications Engineering Corporation, which would change its name to Sony five years later. Deming's focus in these lectures was the relation between quality controls, reduced expenses and increased market share. It was a lesson that Morita took to heart.

When Deming refused to accept royalties from the publication of his lectures in Japan, the board members of JUSE decided to create an award in his name—a prize that remains the most widely recognized and revered in the field of quality.

In 1952, JUSE extended the invitation to Juran to conduct a similar series of lectures, focusing on middle and senior management. Among the corporations that sent representatives were the Takeda Pharmaceutical Company, which had been operating in Japan since the 18th century, the chemical engineering giant Showa Denko, which had won the first Deming Prize in 1951, and Nippon Kögaku, which later changed its name to Nikon Corporation, after its most well-known product line.

The combined effects on Japanese manufacturing and engineering—and, by extension, the rest of the business world—are difficult to overstate.

Within 20 years, Japan was recognized as the pacesetter for implementing quality measures into all spheres of manufacturing, but particularly automobile manufacturing—a realm where the U.S. "Big Three" (General Motors, Ford and Chrysler) had previously been unassailed.

"By the 1970s, Americans were going over to Japan to take a look at how they were manufacturing," says Tripp Babbitt, a management consultant at the 95 Method in Fishers, Indiana, and a member of the Deming Institute. "Can you imagine an American manufacturer opening up their operation to Japanese visitors who wanted to see how things ran?"

Babbitt says Deming's influence was most strongly felt at Toyota, "but it was not limited to Toyota. It was much broader in steel, consumer products, watches, electronics and many more."

The Quality Boom

By the 1980s, the decline in Western manufacturing fortunes had reached crisis proportions, and quality proponents like Juran, Deming and Armand Feigenbaum began to be sought out by companies as well established as Ford and as nascent as NeXT. Deming's 1982 book *Quality, Productivity and Competitive Position* became required reading by corporate executives, who began to espouse the importance of total quality management (TQM) a set of management principles inspired by Feigenbaum's book Total Quality Control along with the work of Kaoru Ishikawa, a JUSE member who had championed the concept of quality circles among Japan's major industries and translated the works of Deming and Juran.

The most public display of the adoption of quality procedures and standards among the manufacturing sector was the sudden display of ISO certification, which became as ubiquitous in the early '90s as publicly displayed URLs were a decade later. Giant signs proclaimed that various organizations had met standards criteria set by the Swiss-based International Organization for Standardization. Formed in 1947, and built on the model of the International Federation of the National Standardizing Associations, which had been founded in the 1920s and suspended in 1942.

The rebirth of the organization in the years following World War II made perfect sense since the concept of standards certification was to level the field between countries, and assure other businesses and consumers that products had been manufactured to the same exacting metrics, using similar processes.

The ubiquity of ISO certification began in 1987, in parallel with the publication of ISO 9000, which codified the eight management principles that form the pillars of quality standards and contained three "models," including ISO 9001—which applies to organizations that design, develop or service new products. Today, more than one million companies around the world hold ISO 9001 certification.

ISO 9001 arrived just in time to bolster the sagging fortunes of America's most important industry.

After suffering record losses, and losing market share to foreign competitors, Ford recruited Deming to study its processes, and by 1986 the company had not only turned around its slumping sales figures, it had surpassed rival GM for the first time in six decades. Ford chairman Donald Petersen attributed the company's turnaround directly to Deming's teachings and told the industry bible *Autoweek Magazine* that Ford was building a "quality culture." [2] An ISO rating was just the thing to prove it was true.

After his return to Apple, and the company's improbable, inexorable rise from near bankruptcy in 1997 to the world's most valuable company—and the first U.S. company to be valued at more than $700 billion—Jobs also trumpeted an enterprise-wide culture of quality.

Growing a Culture

Success breeds imitation, and today, the adoption and nurturing of a quality culture is viewed as a business necessity. Seventy-five percent of senior executives surveyed by Forbes Insights and ASQ in April 2014 said their organizations had a culture of quality, and 20 percent said their quality programs were world class or state of the art. Among the key findings, according to Quality Progress, ASQ's official publication:

- Knowing your market—and, most importantly, your customers—are key to fuelling an organization's commitment to quality;
- Incentive programs tied to quality metrics and focusing on innovation and risk-taking allow organizations to nurture a culture of quality;
- Leadership is critical in setting the tone for an organization's culture of quality; and
- Leaders must provide examples and ensure that the principles of quality are understood and communicated throughout the organization.

Many organizations today embrace quality at the top levels, says Jordan Freed, director of performance excellence at Curtiss-Wright Controls Defense Solutions, whose products are found throughout the U.S. military. "More often than not," he says, "the senior executives get it, and place a high level of importance on it. The further up you go in an organization, the more connected they are to their customers. Reliable performance is essential to customers; it comes from quality systems."

Where you encounter problems, he says, is when middle management—often more concerned on a short-term basis with profit and loss—does not buy in or the quality staff is undersized. Quality is a long-term process, he says, and keeping an eye on overall goals is critical.

He says that in regulated industries like pharmaceuticals the head of quality is often also responsible for regulatory compliance. "Regulatory bodies are one of the stakeholders that pharma companies have to please. If you don't have a quality system that is responsible to compliance, you won't succeed in business."

Joseph FitzGibbon, president of Orion Canada, which consults on issues of quality with organizations throughout North America, says that support and involvement throughout the management chain is essential for quality principles to be effective.

"The present ISO 9001:2008 standard calls for a management representative to champion a QMS (quality management system) within the organization," FitzGibbon says. "This person does not have to be a member of top management, but—for purposes of ISO 9001—does have to have a direct line to top management. It requires the involvement of top management to ensure that ownership of the QMS does not center around a single individual. This requires that QMS processes are established and maintained, that reporting of QMS performance and the promotion of customer requirements across the organization can now be assigned to any role or split between many roles. These roles must be clearly defined."

FitzGibbon says that discipline, consistency and limiting variation in how things are done are all essential elements to ensure quality. "Some people doing day-to-day work say, 'I don't need procedures; I know what I'm doing,' but with the turnover of workers you need those procedures to ensure consistency"

Return On Investment

The need for consistency is something that is echoed by Christopher Kincer, president of Lexington, Kentucky-based ISO Experts. "If you look at successful organizations," he says, "they've reduced or eliminated variation in their processes. To be consistent, you want processes that are consistent. Identify what is variation and deal with it."

Integration is another important factor, adds FitzGibbon. "Way back, a number of organizations considered (QMS) a parallel system to what they were already doing. There's more integration now with ISO 13485, which is focused on medical devices and regulatory requirements. Many of them are doing the same things you need to run a successful business. For example, 'Do we have enough resources to do the work?' 'Are the people sufficiently trained to do the work?' 'Do we have backup if these critical suppliers go out of business?' ISO 13485 sets this out as a requirement. It needs to be documented, and it's subject to audits."

"If you have an effective quality leader who is bringing this to the organization, that is the most cost-effective way of meeting the objectives of the business," says Freed. "The goal of a quality program is to prevent failure. How do you measure the total cost of quality? If you consider quality across an entire organization, you can allocate the cost of quality control into four buckets: the prevention of quality problems, through things like good design, training, good manufacturing processes; the cost of assessment, of screening out problems; the cost of internal failures; and the cost of external failures, such as product recalls. As you move through these buckets, it gets more and more expensive to address failure."

Despite the proven link between quality measures and the reduction of risk and associated costs of failure, Kincer says: "You'd be amazed at how many multimillion-dollar companies have not identified their objectives when it comes to quality. These are basic quality principles that many organizations don't take into account. They may deal with customer complaints in a non-

systematic way; not looking at the root causes of issues. They're wasting time. If they'd look at the problem in a systemic manner, look at the root causes, the problem wouldn't happen again."

Kincer says it all comes back to principles that Deming espoused: "Plan what you're going to do. Do it by following your plan. Then, check to make sure what you did was successful in meeting your objectives. If it was, then you have a happy customer. If it wasn't, you need to act and fix the problem.

"A company that is manufacturing a product or providing a service needs to ask, 'What is the customer ordering from me and what am I doing to provide that?' Any type of industry—no matter where you are in the supply chain—has to have a process where they are going to take something and turn it into something that you're going to sell. ISO 9000 dictates that you need to document the process. This allows you to meet the desired output. It has to be measurable. When you document or measure something, you can reduce variation."

Does this apply to pharmaceutical engineering and manufacturing? Absolutely, says Kincer. "If a company is not doing this, it's missing a great opportunity to improve performance, improve employee morale, and improve internal and external customer satisfaction."

He says systems must be simple to implement and easy to maintain. "I look at what a person is doing. I look at a process. We try to create a document that is easy to follow and effective in achieving the objectives."

> What is the customer ordering from me and what am I doing to provide that?

Without that level of simplicity and a long-term commitment to quality, experts say the results will be inconsistent, undermining the entire effort.

That is something that Steve Jobs and Jony Ive ensured was part of Apple's DNA. After the overwhelming success of the iPod and iPhone—when their company was moving from the break of insolvency to the top of the world—they did not take their foot off the gas, and they did not forsake their devotion to simplicity, consistency and quality for something less.

"When times are good, it's easy to ask, 'Why do we need all this quality stuff?' says Freed. "But manufacturing processes shift with time. It takes continual effort to maintain consistent quality."

Quality's Midwife

"W. Edwards Deming's influence is everywhere," says Babbitt. "His work is everywhere, or we see organizations moving naturally toward his philosophy."

Born in Sioux City, Iowa in 1900, Deming trained as an electrical engineer, but gravitated toward mathematical physics. His most significant early work was the development of scientific sampling, which continues to be used to extrapolate census and labor statistics in the U.S.

At 27, Deming encountered Walter Shewhart, a physicist, engineer and statistician who worked at Bell Telephone Laboratories and was developing a theory of statistical measures that would be published in his 1931 book, *Economic Control of Quality of Manufactured Product*. Shewhart's work pointed out the importance of reducing variation in a manufacturing process and the understanding that continual process adjustment in reaction to non-conformance actually increased variation and degraded quality. Consistency was key.

Deming saw that Shewhart's theory could be applied not only to manufacturing processes, but also to the processes by which enterprises are led and managed. He honed his expansion of Shewhart's ideas by editing a series of the older researcher's lectures into a 1939 book called *Statistical Method from the Viewpoint of Quality Control*.

It was Deming's own lectures—particularly one he delivered at Tokyo's Hakone Convention Center in August 1950—that changed the course of Japan's, and eventually the rest of the world's, manufacturing processes. Calling his theory "statistical product quality administration," he espoused four main principles:

- Better design of products to improve service;w
- Higher level of uniform product quality;
- Improvement of product testing in the workplace and in research centers; and
- Greater sales through side markets.

It was a case of the ideal prescription at the perfect time. Japan's industrial sector was crawling out of the wreckage of the war years and the devastation of two atomic explosions, and its senior managers were eager to find a way to jump-start their businesses.

Despite Deming's success in Japan, he was not widely recognized in his native country until the Ford Motor Company hired

him in the '80s to help turn around their fortunes. By then, he was well into his career teaching statistics at New York University, and on his way to working out his last great contributions to management theory: the System of Profound Knowledge and 14 Points for Management—which were published in *The New Economics for Industry, Government, Education* just prior to his death in 1993.

Babbitt, while admittedly biased, says Deming's philosophy continues to be relevant for manufacturers in all areas, but he warns that patience is required. "It's a challenge to adopt Deming's philosophy, especially in larger organizations that are tied to the stock market. Their decisions are oriented around stock prices and reports, and their thinking only goes out 90 days. You need to look longer term to make longer term decisions about your organizational systems." ■

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GOOD BUSINESS IS GOOD QUALITY

At Bristol-Myers Squibb, A Culture of Quality Starts at the Top

Scott Fotheringham, PhD

For people in Bristol-Myers Squibb's manufacturing organization, delivering on the company's mission "to discover, develop and deliver innovative medicines that help patients prevail over serious diseases" has never been more significant.

As the New York-based BMS sharpened its R&D focus around fewer and more serious disease areas, getting it "right first time" on the manufacturing floor has become even more important to the company – and to the patients who depend on its medicines.

"This industry has traditionally equated the concept of quality with being compliant with regulatory authorities," says Donna Gulbinski, BMS's senior vice-president of global quality, who is responsible for the quality and testing of commercial products. "At BMS, we've been focused on accelerating a culture of quality that transcends compliance. We know that driving right first time, reliability and predictability in manufacturing directly contributes to getting our medicines to the patients who need them faster. Every action of every employee counts."

For BMS, strengthening a culture of quality starts at the top.

"Our Leadership Team has established a strong focus on developing and maintaining a culture of quality throughout the company," says Ricardo Zayas, the company's vice president of pharmaceutical operations.

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Bristol-Myers Squibb

That focus is reinforced by a governance structure and resources, and is entrenched in the company's commitment to "fostering the continuous, proactive improvement of our production and process capabilities… (to uphold) the highest standards of quality for BMS medicines."

To support the concept of a quality culture and mindset, BMS has adopted five key elements:

- aligned vision and expectations;
- quality objectives linked to company goals;
- management reviews;
- quality unit independence; and
- transparency and openness, so that significant events can be escalated.

The company has also embraced the tenets of lean manufacturing, continuous improvement and the emphasis on the elimination of waste, theories that were developed at the Toyota Motor Company in the decades following World War II. Gulbinski says BMS has developed a deep understanding of lean quality and the relationship between eliminating waste and improving quality.

"Good business is good quality," she says. "The lean quality motto of 'right first time' is key for us."

The company started implementing the tenets of lean manufacturing at just a couple of its sites, including one in Ireland, where the company was able to more closely understand and learn how to maximize its efforts.

"When we were ready to roll it out more broadly, we were much more familiar with aspects of lean quality, and that made the rest of the rollout better. We had a proven standard and time-tested technology," says Zayas.

The rollout was not without some resistance, he admits, adding that change always takes time to accept.

"It's a different way of doing things, but once employees understand that it's a better way to work, a more organized way to work, they adopt into it. When people learn the benefits of well-planned work, they're grateful and they like it. In the pharma industry, we plan production processes well—for example, every bottle we fill, every tablet we make. But we're not great at planning lab operations, which require a demand-and-supply schedule, and that people know what's needed tomorrow and also what the work schedule will be six to 12 months from now."

Zayas says the big advantage of adopting a culture of quality within the pharmaceutical sector is the focus on prevention.

"There needs to be a significant shift in the paradigm of our industry. With programs like product robustness, reliability excellence, process engineering, and equipment and operational excellence, it can take a lot of convincing leaders in pharma that these things are necessary. Well, guess what—if you have a good program in each of those areas you're going to be focusing more on prevention. You're going to have less total cost of quality and fewer back orders that represent lost revenue, because they're usually driven by deviations in your processes."

As Gulbinski explains, driving this kind of change begins with a strong presence on the shop floor, where operational excellence (lean quality) begins and ends. BMS helps to ensure buy-in with visual boards that express data like quality and safety performance to employees on the floor.

"If you want people to care, enabling them to understand how their work impacts the bigger picture really helps," she says. "What are we making today? What stage of manufacturing are we at? What issues do we have? What's our history look like? How are we doing against our targets? We hold daily huddles to discuss what's happening on the floor."

Another important component of the Toyota-led quality assurance movement that BMS has adopted is the Gemba Walk—one of the key lean principles.

"Walking around is a big part of what we do," says Zayas. "I do this when I visit sites, and more importantly, our site and area management people do this in a formal way."

"It starts with front-line supervisors," echoes Gulbinski.

One of those front-line BMS managers was Andrew Espejo, who is now an executive director of strategy on Zayas's team. For a number of years, Espejo was a general manager at BMS's Mount Vernon, Indiana, manufacturing facility, which is being transferred to AstraZeneca as part of the sale of BMS's diabetes drug business to the UK-based company.


Espejo

Espejo says the process was essential. "The most important thing for me was that they see us, and we hear them. From the Gemba Walks we implemented a ground-up 5S program (another primary methodology developed in Japan to ensure manufacturing quality). We were 30 miles from a major Toyota plant where many of our colleagues came from, so we decided to leverage what they knew about lean. It was truly amazing. We empowered the operators, gave them budgets and guidance about the strategy."

"In addition, during my tenure, I met with all of the colleagues at the Mount Vernon plant," says Espejo. "It took me nine months to complete. I called them 10-on-1's and I'd ask two questions, 'What do you like about working here? What things can we improve on? and I let the conversation go from there."

'We also spoke about quality and safety at town hall meetings every month." Said Espejo. Consistent messaging was a key element to instilling a quality culture."

Another important concept that is central throughout Bristol-Myers Squibb is keeping patients at the center of everything.

"When I met with new employees, I told them, 'What you do here, every single day, you're ensuring quality for our patients, who could be your family (who consume pharmaceutical products), friends, your community members.' It's about the patient—you, your parents, brothers, sisters—who takes a prescription medicine. (I'd tell them) 'You have their health in your hands when you come to work.' That's how you change the quality mindset from one of just compliance; you bring it to the human level."

Espejo says that—while BMS's business objectives were foremost—the human element of quality is a significant part of what resonated with employees.

"We didn't focus on cost. The cost savings emerged but we focused on the potential impact on patients. We have quality products going to patients, and that's the most important thing

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we do. It's hard not to stress the human element because that's who we are. We have the processes in place, but people run the processes."

One of the things that stays with him from his time in Mount Vernon is a line adapted from the Rascal Flatts song "Every Day."

Says Espejo: "We coined the phrase, 'every day you help save a life.' When we did our site strategy engagement sessions we would close the sessions with videos of our people talking about what they do and what it means to their life… If you don't focus on people, on the patients we work for, quality gets lost in the compliance mire. When people make the connection to themselves, their loved ones, to patients – it brings it home: 'I'm not just making widgets. People are relying on the quality of the products I make help treat serious diseases.'"

Making that connection, says Espejo, was a huge part of ensuring that the culture of quality replaced the culture of compliance at BMS.

Zayas says that implementing that kind of transition throughout the industry represents a challenge, but it's possible if pharmaceutical manufacturers are committed to the change.

"It's like reprogramming a massive network," he concludes. "You've got to commit to these programs, provide the necessary resources for people to implement them and help them. A lot of support is required because it's a lot of work. But, once you turn that corner, you turn into a powerhouse operation because you don't have the events that create lost revenue.

"The change at BMS has been dramatic. We've turned that corner where our employees realize the focus is on prevention, not on reaction," concluded Zayas. ■

WALKING THE QUALITY CULTURE TALK

Acting Responsibly; Earning Customer Trust Every Step of the Way

François Sallans
Vice President, Quality & Compliance and Chief Quality Officer, Johnson & Johnson

Regardless of industry, every organization has a culture. The degree to which quality is embedded in an organization's culture can mean the difference between success and failure. In some industries, such as healthcare, quality is more than a competitive advantage, it is a social responsibility.

Patients and caregivers expect, moreover, deserve safe and efficacious products that are available on demand. The concept is simple, but it requires a quality system that connects products, plants, people, processes and policies seamlessly and consistently and a strong quality culture to enable and sustain continuous improvement.

Despite many companies' efforts to operate in a state of compliance and to consistently produce high quality products, and despite regulators' efforts, patients contend with drug shortages that in some cases can be life-threatening. The ISPE Drug Shortage Prevention Plan (DSPP) suggests that preventing supply disruptions requires a robust quality system that integrates quality end-to-end and focuses on continuous improvement. The DSPP clearly defines a quality culture as one that "encompasses an organization's practices, central values and philosophy as well as the concentration of all people and resources engaged in a never-ending quest for greater quality and service throughout every dimension of the organization. Quality culture describes the importance of cross-functional, organization-wide commitment to quality, allowing the company to make decisions that best benefit patients."

Patients and caregivers expect, moreover, deserve safe and efficacious products that are available on demand.

To complement the DSPP, ISPE is developing the ISPE Drug Shortage Assessment and Prevention Tool, which will be published in November 2015 at the ISPE annual meeting in Philadelphia, PA. The tool is being designed to help companies evaluate the six dimensions of the DSPP, starting with the maturity of their quality culture as the enabler of the other five dimensions: Robust Quality Systems, Metrics, Business Continuity Planning, Communication with Authorities, and Building Capability.

In 2014, the ISPE Quality Culture Team was formed to develop a response to the question of whether it was possible to measure or quantify the impact of culture on the quality outcomes that matter to patients. The result was the "Six Dimensions of Cultural Excellence Framework" (Figure 1) that the team introduced at the ISPE Quality Metrics Summit in April 2015. This framework serves as a guide for companies to monitor the maturity of their quality culture.

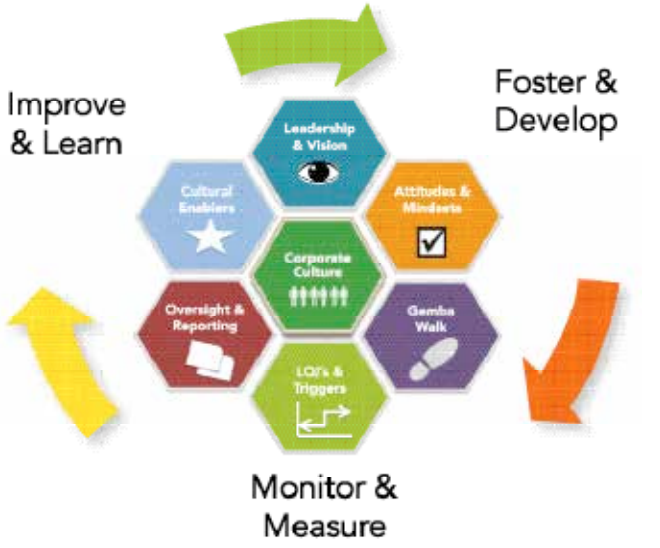

Figure 1: The ISPE Six Dimensions of Cultural Excellence Framework

The framework manifests into quality culture excellence when leaders set the tone at the top with a clear vision that espouses a company's commitment to deliver quality. To be effective, the vision is to be communicated, understood, and acted upon by every employee and external business partners, including supplier and contractors. Messaging must be consistent, persistent, and relevant. Leaders themselves must "walk the talk" and model the desired attitudes and behaviors. Management must also appropriately resource quality in personnel and in ongoing improvements to equipment and physical facilities.

Internalizing individual ownership of quality can only be achieved in an environment where transparency is welcomed and protected. Uniting people through an emotional appeal helps to create this mindset; but it requires an ongoing effort to embed behaviors until they become second nature. One way to evaluate the degree to which people are adopting a mindset and behaviors is through surveys. Giving people the opportunity to speak up anonymously without risk of retaliation or penalty gives management insight into what is working and which areas need attention.

Another proven way for management to observe and collect feedback is to engage with employees in person. By simply connecting with employees in their work space and assuring them that speaking up is safe, trust is engendered. Regular visits to the shop floor, offices, R&D laboratories, and customer engagements provide meaningful opportunities to observe, assess, listen and coach.

A top to bottom review of quality performance and resources across the R&D, supply chain, and commercial continuum is essential to guarantee the effectiveness and the sustainability of the quality system. Alerts when quality is at risk allow for prompt, proactive escalation and remediation. This requires an organization to:

- Establish a set of relevant key performance indicators (KPI) and quality culture metrics that clearly link the desired behaviors espoused in the vision to the critical quality outcomes for the product and the patient
- Ensure these measures are clearly understood by all and current progress against targets is visible/accessible to all
- Embed leading and lagging indicators to promote the desired behaviors and outcomes and monitor triggers that alert the existence (or potential) for non-desirable behaviors and outcomes

While quality culture is not easily converted to a metric, caution must be given to not inadvertently drive the wrong behaviors by striving for a number. The focus should not be on 'looking good,' which could lead to not reporting issues, but rather focus on 'being good.' A strong quality culture is best indicated by what is done when no one is looking.

Visibility, transparency and management oversight are fundamental elements of the quality culture and assure sustainability of quality performance. Transparent, systematic oversight and review of quality objectives helps deliver individual and company goals and objectives and external business partner service level agreements. A management review process must be established and operated consistently at all the levels of the organization (from the shop floor and plants to the C- suite). This process provides a comprehensive review of the quality performance, trends, actions as well as resource requirements to appropriately operate the quality system. Management oversight and monitoring is capital to guarantee the effectiveness and the sustainability of the quality system and to deliver the right quality performance.

Management awareness is essential, the culture of transparency and the expectation for escalation of significant events must be enforced and communicated through a specific company policy and other formal processes for action-orientated oversight and reporting against the triggers and metrics must be in place.

It is essential for companies to have the same level of oversight, reporting and transparency applied to both internal and external partners. This culture of transparency and awareness has to be shared and established with external partners and supported by adequate quality agreements and contracts.

Clear and common objectives supported by a uniform performance evaluation and appraisal system provide the structure to promote a quality culture. Sustaining quality requires continuous improvement. Listening throughout the organization and to customers enables an organization to learn and improve.

Among the characteristics of quality culture enablers, knowledge management and capability building are of great importance. Knowledge management processes must be in place to support the effective sharing of insights and learning across the organization. This includes processes to enable knowledge flow across external organizational boundaries and formal organizational development processes to build the capabilities necessary to foster a learning organization (e.g., proactive problem solving, transparency, accelerated team-based learning, enabling change and continual improvement)

Quality is more than an academic thesis; the ability to deliver quality consistently is a proven measure of one's reputation and success. The growing demand for quality will require manufacturers to step up their efforts to strengthen their quality cultures today.

THE CULTURE OF QUALITY AT Johnson & Johnson

At Johnson & Johnson we are taking a holistic approach to quality. From our operating model to how we think and act, quality is built in to our culture. In 1943, Robert Wood Johnson, then Chairman of the Board of Johnson & Johnson, memorialized our commitment to quality in Our Credo. The document outlines our responsibilities to our stakeholders with the overarching message that "…everything we do must be of high quality." Our Credo is displayed prominently in our offices throughout the world to remind us that caring for peoples' health is our greatest responsibility.

Aligning to Our Credo is Our Aspiration, which states that by caring, one person at a time, we aspire to help billions of people live longer, healthier, happier lives. We are privileged to work in an industry whose fundamental role is to help people live healthier

lives. Our Credo unites the people of Johnson & Johnson in this mission.

Cascading from Our Credo and Our Aspiration are strategic principles and growth drivers. The pursuit of growth drivers is guided by the Leadership Imperatives, a tool by which every employee's performance is evaluated. The Leadership Imperatives are proof that we recognize that how we achieve results is as important as the results themselves.

In furtherance of Our Credo, the Johnson & Johnson Quality & Compliance organization, led by the Johnson & Johnson Chief Quality Officer, developed our Quality Policy, Quality Policy Framework, and Quality Policy Standards. These tools define the requirements that our operating companies must achieve in how we design, make and deliver our products. These tools cascade down to more detailed technical documents and procedures that require each company to have processes that include monitoring, escalation, correction, and accountability, resulting in a system of continuous improvement.

As part of our quality system, we organized our structure to implement these quality requirements across the Johnson & Johnson Family of Companies. Johnson & Johnson operates in different segments: consumer, consumer medical devices, pharmaceuticals, and medical devices. Segment level Chief Quality Officers are responsible for developing strategies, providing oversight and delivering quality results end-to-end for the segments.

■ Our goal is to make Johnson & Johnson the company of choice for high-performing, quality-minded professionals. ■

Underpinning a quality culture is regulatory compliance. Our independent, internal audits are conducted on a regular cycle. Results, current status, and progress are all reported to business leaders and to the management of each Johnson & Johnson Company to help them support their sites' efforts to achieve compliance in a timely manner. Compliance is a companion to quality; it should not be mistaken as a measure for quality.

A Management Review Process allows management of the individual companies to seek continuous quality improvement by regularly reviewing the suitability, adequacy, and effectiveness of their respective quality systems. We also recognize that systems are run by people. Internalization of quality ingrains quality into the culture. Employees are challenged to demonstrate how they own quality in meaningful, measurable, and sustainable ways.

Since it is often true that what gets measured gets done, employees' performance is in part evaluated on how they maintain quality, compliance and accountability through actions and deliverables. We value our people who deliver quality by offering targeted personal and professional development programs. Every year, employees are given the opportunity to express their perception of how well we fulfill Our Credo responsibilities in the Global Credo Survey. Leaders share the results with their teams and identify areas of opportunity for task forces to develop solutions. Our goal is to make Johnson & Johnson the company of choice for high-performing, quality-minded professionals.

Ensuring customers have a positive experience at every intersection is the ultimate measure of quality. To better understand the customer perspective, our Global Customer Experience program enables us to listen to and validate customer feedback. When we enable our customers to succeed and live better we benefit too. Every day we work to convert transactions into relationships.

Quality is expected, but it can never be assumed, so every day we strive to instill our values, fulfill requirements and earn customer trust. ■

A YOUNG PROFESSIONAL'S TAKE ON QUALITY

An Interview with Robert Landertinger, A Co-Chair, ISPE Young Professionals Committee

Mike McGrath

Pharmaceutical Engineering spoke to Robert Landertinger, Technical Marketing Manager at Sartorius Stedim Biotech and Co-Chair of the ISPE Young Professionals Committee, about quality culture and the ISPE Drug Shortages Prevention Plan.

Tell me a little bit about yourself and your involvement in ISPE.

My father fell ill early, giving me the desire to help him and others. I was a very curious and creative child, and when my parents gave me my first microscope I realized the endless possibility to discover the wonders of our world. I analyzed the details of all the living things I found and then tried to help these creatures grow healthier by constructing new feeding sites. My next move was to study biopocess engineering at the University of Applied Sciences in Berlin, where the combination of biology and engineering gave me my first view of biotechnology. As a student I also worked in a biotechnology startup that provides various array services and houses one of the world largest clone libraries. Today I work at Sartorius, a company that provides single-use technologies and engineering services for the pharmaceutical industry.

I've been involved with ISPE since August 2013, when I attended the Annual Meeting in Washington. Since then I've helped identify and develop young professional leaders around the world. The biggest achievements have been the Ireland, Belgium, France, Nordic, and DACH Affiliates.

What, if any, quality concerns have been raised in the YP Committee?

The committee gives young professionals the navigation tools that we need to begin our journey in the pharmaceutical industry. Young professionals often don't see all of the complexities that arise because we are new to the industry. We are trying to learn about quality and understand how everyone works together to implement it. From this point of view, there is an overwhelming complexity in understanding what affects quality and what needs to be done to maintain a defined quality level in a big organization.

When you look at this complexity, what difference is there between what you learned in school and what you've experienced during your first 5 years in the industry?

The biggest difference is the level of detail, which is higher when working in the industry. In school all topics were addressed at a basic level, and bioprocess engineering classes focused on the manufacturing side of the industry. When you start to work you begin to understand that manufacturing is only one piece of the puzzle—it has to fit with quality, marketing, and other groups within an organization to produce lifesaving medicines for the people who need them the most.

The complexity of what I am learning now is really only possible through ISPE. Their Good Practice Guides—from project management to facilities and manufacturing to biopharmaceutical process development and manufacturing guidelines—provide the information on how to implement all of this knowledge. This is something you simply can't know when you're in school. My active involvement at ISPE also helps me learn industry best practices much faster, and allows me to connect with peers who have expertise in other areas.

When you were at university, did you think about quality? What did it mean to you?

At university we learned that quality was an important topic in drug manufacturing, but we did not delve deeply into it. Now I've learned that quality and continuous improvement cover all organizations in the pharmaceutical industry—not just manufacturing. That really expanded my view. I've had the opportunity to visit various manufacturers' sites, too, and it's truly amazing how they implement quality at different times. Quality for me is fulfilling customer and regulatory requirements; it's achieved by generating and following written procedures.

How is it implemented at Sartorius?

At Sartorius we follow the continuous-improvement process, because our technologies are used to produce biopharmaceuticals. This approach is supported by process capability assessments and monitoring as well as quality risk assessments. As a supplier, it is essential that we communicate intensively with the biopharmaceutical industry and understand their regulatory environment. Our quality people have to meet with drug manufacturers' quality people.

What do you mean by that?

If we're producing a single-use bag, for example, we have certain quality standards that we have to meet, not only in manufacturing a good product but also in addressing quality concerns about the product itself. One example is the concern of particle presence, which needs to be avoided in single-use technology. We have to have to fulfill certain quality standards so that our customers can meet their own product quality standards.

How do you see quality culture evolving over time? What do you see as opportunities?

The greatest opportunity—and I think this is the core of the ISPE—is connecting knowledge. That means continuous improvement and verification, not just doing a validation of certain standards but really getting into the verification process of something that is happening continuously. The focus is not only on direct manufacturing issues but on quality at a broader level and in the different business units of an organization. Even the quality culture on which we are working today with the Drug Shortages Prevention Tool will not be the end. As everyone implements this in their strategies, we'll learn new things and be able to develop these tools further.

From your perspective, what's the biggest obstacle to quality culture in an organization?

I think the biggest obstacle is always lack of clear communication. With the Drug Shortages Prevention Plan, for example, we learned that it's not just about an organization having a drug shortages prevention plan in place; it's also about communication with authorities—both local and international. Through ISPE we are able to agree on the same technical language, which also helps establish good communication and quality culture in our industry.

What have you learned in the first 5 years that you never even touched on in school?

The topic with the biggest learning curve was—and is—the complexity of communication with regulatory authorities. Being able to communicate clearly with the regulator during an audit can define a positive or a negative outcome. When I came into this industry I was surprised to learn that there's a trend toward talking openly with regulators. It isn't only about achieving business goals for the organization, and it's not just regulators putting guidelines in place for everyone to follow. It's about putting patients first.

What do you see yourself doing in the future?

In 10 to 15 years, young professionals will be the leaders in the industry, and I think we will offer some fresh perspective. I see myself as being an inspiring leader in our industry. I will drive innovation and improvement through my curiosity and creativity. I can see connecting to university students and teaching them the basic principles of the pharmaceutical industry.

Within ISPE, I see myself developing new platforms so we can collaborate more effectively across different regions of the world and between peers and experts. An ISPE member from Chicago once told me that the combined knowledge of the ISPE members makes us the best pharmaceutical university of the world in real time, a place where we share the knowledge that will give us the best possible medicines. In the future, I want to make this vision a reality. Today I want to be part of the innovation to drive the needed changes. ■

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TWO GROUND-BREAKING PRODUCTS COULD BE THE WAVE OF THE FUTURE FOR BÜRKERT FLUID CONTROL SYSTEMS

Mike McGrath

Decades before the expression became part of our everyday language, Christian Bürkert had an idea of what it was like to "go with the flow." Now, almost 70 years after its founding, the company bearing his surname remains fascinated with anything that flows, be it liquid or gas. And with the introduction of a pair of ground-breaking new products, Bürkert Fluid Control Systems appears ready to make sure that those liquids and gases continue to flow with ease.

Founded in 1946, Bürkert Fluid Control Systems is today one of the world's leading manufacturers of measurement, control, and regulating systems for fluids and gases. The company boasts an impressive portfolio of products and solutions, including solenoid valves, process and control valves, extended to pneumatic actuators and sensors. They cover all aspects of the fluid control circuit: measuring, controlling, and regulating. And its products have been used in a broad spectrum of industries and applications, from pharmaceuticals to cosmetics and from aerospace engineering to dairies and breweries.

"We, as a company, believe that the solutions and technologies we offer in one industry can be offered in other industries as well," says John van Loon, Segment Manager Hygienic, at Bürkert. "For example, we could have a Clean in Place (CIP) application in the pharmaceutical industry. Yet CIP is also seen in cosmetics and food and beverage. It may be slightly different from process design and regulations point of view, but for the products and system solutions we use for these applications, it's basically the same. We can make slight changes and then use the same solutions and systems in other industries. That's how we grow our business."

More Than Just Equipment Vendor

Although Bürkert offers more than 30,000 products, the company prides itself on being more than a standard supplier. And according to van Loon, it's about applications, not products. "When we look at an application from our customers, we look at their needs, and from these we select a solution," he says. "It can be one component, but it can also be a combination of stock components assembled together. Or maybe even a step further: a solution developed specifically for a customer for their application so they can have a much better use of our technology and can offer added value to their customer."

Based in Ingelfingen, Germany, the company is still 100-percent family-owned and designs, develops, manufactures, and sells its own components. It serves its international clientele through a network of 35 wholly-owned subsidiaries located in 36 countries around the globe. In addition, Bürkert has five of what the company calls "systemhauses" located in China, the United States, and Germany.

Listening To Market Needs

While Bürkert develops, designs, manufactures, and sells its own components, it understands that, in many cases, the market requires much more than that. That's where the Bürkert systemhaus comes in. The systemhaus approach allows customers to focus on their core business while Bürkert handles the fluid control systems. The systemhaus teams develop customized solutions for extremely complex and sophisticated production processes. Customers can specify the processes they need help with, or are looking to improve, or even bring Bürkert in to help design the process from the start.

"We had one customer in Denmark who asked for a gas control application on a media preparation system," says van Loon. "It faced issues with contamination of its system due to foaming in the pocket links. With the technologies we have in-house, we were able to give the customer a pressure control unit that was also completely cleanable. That's simply not on the market. It was developed because this customer came to us, knowing they can ask us for this service, and said 'We have these issues; do you have some kind of solution to help us out?'"

Bürkert sees itself as different from the competition in its willingness and ability to listen carefully to customer needs and find solutions. As a company, it also strives to recognize changes in the markets and regulations so that it can develop new products and technologies to answer these evolving requirements.

The company has, in the past two months, proven its ability to respond to evolving market requirements with the release of two new products whose development was driven by a close analysis of market needs.

FLOWave – A Revolutionary Flow Measurement Concept

Flow metering systems are used throughout the pharmaceutical industry. However, the technologies used in all current flow metering devices have their own challenges and weaknesses, not the least of which are the sensor elements within the tube. Inherently, this means that in a typical flow metering system, there is potential for issues, such as pressure drops and cleaning issues. So, Bürkert set out to design an improved system.

Companies in the pharmaceutical industry, like many others, also need to reduce the carbon footprints of their plants, out of a concern for the environment as well as a means to reduce energy costs. "We devel-

oped, with new technology, a flow sensor called FLOWave," says van Loon. "This device is a standard pharmaceutical tube where the measurement is done on the outside of the tube. The advantage is that we can now have a flowmeter in line that doesn't have any pressure drop, which will affect the energy level of your plant. If you reduce all of these pressure drops, it affects the overall cost of energy."

The FLOWave deviceuses Surface Acoustic Wave (SAW) technology for inline measurement of the flow rate in tubes. With this principle, there is no need for any sensor elements in the measurement tube that come into contact with the medium; this eliminates pressure drops, leakage problems, dead spaces, and replacement parts. In addition, with FLOWave, the measurement is independent of the flow direction. Bürkert says that this makes FLOWave very suitable for applications where the highest standards of hygiene and cleanability of systems are required – in other words, a solid fit for the pharmaceutical industry.

Tube Valve Body Third Generation

Similarly, diaphragm valves are used widely within the pharmaceutical industry. Typically, these are made from a block of steel that has been forged, cast or machined into shape prior to adding a diaphragm and an actuator. In a hygienic pharmaceutical application, customers must heat their systems with steam for a certain amount of time to clean and sterilize them, which is quite an expensive process. Bürkert set out to reduce the mass of the system, thereby decreasing the amount of material to be heated and reducing overall energy costs.

"We have been using hydroforming technology to make diaphragm valves for more than 10 years," says van Loon. "But until now, the design was not suitable for pharmaceutical applications, where you need a perfect hygienic design and cleanable, surface-finished materials that comply with all kinds of standards. We improved the design, way of manufacturing and materials and this evolved to a new series of tube valve bodies using the same pharmaceutical tube that our customer is using in its systems already for years, and we made a valve of it, which has much less weight."

For the hydroforming process, a stainless-steel tube in pharmaceutical quality is filled with a water-oil emulsion and then charged with a high inner pressure. In this process, the tube is formed into a valve body and simultaneously joined permanently to a support flange. Afterwards, the support flange and tube are connected via laser welding to ensure the cleanability and stability of the product. A special annealing process to increase resistance follows. In the final step, precision surfaces of the highest quality are generated. The result is an innovative product in which a medium only comes into contact with a pharmaceutical-compatible tube and diaphragm. Target applications of the new tube valve body are in the demanding pharmaceutical, biopharmaceutical, cosmetics, and food and beverage industry markets. From a technical, economic, and ecological perspective, the valve bodies satisfy the current requirements and regulations of these markets.

Van Loon explains that, compared to a typical product, "a two-inch forged body weighs 2.8 kilograms, while this new body weighs only 702 grams; that's a reduction of 75 percent. This means less mass and less energy to heat it. The heat time is also much faster, but what's very important is the cool down time is much shorter as well. We learned that by using less material, the heating and cooling times can be reduced times by a factor of two, which increases the process efficiency of this customer. Process efficiency means cost reduction." ◂

Bürkert Fluid Control Systems and ISPE

Pharmaceutical Engineering readers and ISPE Members will likely be familiar with the Bürkert name, as the company is an ardent supporter. "We have been working with ISPE for quite some time," says van Loon. "It provides us with a good platform for networking, gathering market information, and evaluating new trends. We also attend events and do a lot of tabletops at ISPE shows, from India to the US to Europe and other countries."

Readers can find out more about Bürkert at the 2015 ISPE Annual Meeting in Philadelphia, Pennsylvania (Booth 225) or by visiting www.burkert.com/en.

AIR FILTRATION CHALLENGES AND ANSWERS FOR DRY HEAT STERILIZATION TUNNELS

Marc Schmidt, Lothar Gail and Hugo Hemel

Dry-heat sterilization/depyrogenation may well be one of the most critical steps in the sterile manufacturing process. This paper analyzes the main challenges of high-temperature HEPA filter design and describes a new development that addresses these challenges, promising a more reliable operation and longer life.

Dry-Heat Sterilization and Depyrogenation*

Production of sterile medicine has to be carried out in a controlled environment to minimize the risk of product contamination. Regulatory guidance provides information on the area classification required for the various stages of manufacture, thereby preventing severe harm or life-threatening health risks to patients. (*Dry-heat depyrogenation is used throughout to refer to both dry-heat sterilization and dry-heat depyrogenation.)

Sterilization

Sterilization is a process that removes living microorganisms, including their dormancy, from materials and objects. The achieved state is called "sterile."

Depyrogenation

Depyrogenation is a process that removes biological pyrogens from materials and objects. Pyrogens in this sense are substances that cause fever when injected into the body. Of particular interest is the removal of bacterial endotoxins (for example, liposaccharides of the bacterial cell membrane with relatively high temperate resistance), but virus pyrogens and fungal pyrogens also have to be removed.

Dry-heat sterilization and depyrogenation are process steps used for the primary containers to ensure that they are sterile and pyrogen-free before they are aseptically filled and closed, as required by the US Food and Drug Administration (FDA) regulation 21 CFR Part 211.94. For many products, terminal sterilization of the finished filled container is not possible. Therefore, before it is filled, glassware must be sterilized and depyrogenated.

One of the most common methods of achieving sterilization and depyrogenation is through the use of a depyrogenation oven or tunnel; the process requires ensuring that the primary container reaches, and is held at, a high temperature for a defined period of time. Typically a temperature of over 121°C is used to sterilize – that is to say, kill any living organisms; depyrogenation requires higher temperatures in the region of 200°C to 350°C. Depyrogenation is used to reduce endotoxins. Because of the increasing demand for pyrogen-free sterile packaging and fast, safe, and efficient processing, dry-heat depyrogenation is a critical step in the sterile medicine filling process.

Pyrogen-free primary containers were originally required merely for the filling of large-volume containers, but it has now become a requirement for all sterile filling.[1] Regulatory authorities require the depyrogenation processes to be validated to demonstrate that a predefined performance is consistently met by the process; the FDA, for example, requires "that the endotoxic substance has been inactivated to not more than 1/1,000 of the original amount (3 log cycle reduction)."[2] This demand contributed decisively to the development of safe, fast, and efficient dry-heat sterilization processes, including unidirectional airflow with HEPA filtration.

The Protecting Role of HEPA Filtration

HEPA filtration is used to control the quality of air used for the ovens and tunnels, providing protection from particulate and microbial contamination.

However, the quality of the air supplied relies on the installed filter integrity as well as the seals from the filter media to the filter frame, and the frame to the equipment filter housing these needs to be essentially leak-free; leakage will reduce the quality of the air supplied by the system.

The dry-heat depyrogenation of glassware typically follows a three-step approach: infeed, heating, and cooling. (See Figure 1.) Dry-heat depyrogenation systems are typically located in, and supplied from, a Good Manufacturing Practice (GMP) grade C/D area and feed into a grade A area. (Note: Grades used refer to Volume 4, Annex 1; see Table A.) The regulations require grade A conditions for the whole glassware transportation line between washing and filling; therefore, in these areas any air admitted has to pass through a HEPA filter.[3]

The heating process, taking place in the "hot zone," makes high demands on HEPA filters at temperatures up to 350°C. But even in the "cooling zone," the installed HEPA filters have to withstand temperatures between 200°C and 250°C in the case of

sterilizable cooling sections. Challenges in terms of filter durability and efficiency have to be met to guarantee the sterility of the containers leaving the sterilization tunnel.

Challenges To Be Met

Various studies have shown that performance improvement issues dominate the priority list of the pharmaceutical industry. Challenges related to reducing time to market, increasing manufacturing throughput, quality requirements on cleanliness, complying with applicable regulations, and reducing costs are of high concern. The performance of a dry-heat depyrogenation tunnel has a direct influence on all these critical issues.

The degree to which a depyrogenation tunnel is able to retain the quality of the treated glassware in an effective, efficient, and repeatable manner is dependent on the performance of the HEPA filtration.[4]

Unidirectional airflow with HEPA filtration is the most common approach used to address the various challenges of dry-heat depyrogenation.[5] Final filtration of the circulated air stream enables a faster and more simultaneous heating up of the glassware. However, the air filter must withstand integrity challenges caused by large variations in operating temperature during heating and cooling (i.e., system start-up and shutdown). Process contamination and the resulting unscheduled downtime from the bypass of unfiltered air, leaks, or shedding of particles has to be prevented. Limiting particle shedding can be particularly critical in cases of temperature fluctuations that arise from emergency shutdowns or the interruption of power supply. In addition, the heating and cooling rates of HEPA filters need to be carefully controlled, as excessive heating/cooling rates can cause filters to shed particulates.

Controlling the challenges during exposure to high temperatures and frequent heating and cooling cycles for a HEPA filter is not an easy job. Grade A conditions are being stipulated and must be demonstrated.

High-Temperature HEPA Filtration

Considerations for Selecting the Right Solution

Several characteristic requirements for high-temperature HEPA filters can be identified that directly influence the productivity of a depyrogenation tunnel. From various in-depth interviews conducted with tunnel manufacturers and pharmaceutical end users, three HEPA filter requirements have been found most critical in especially the hot zone of a sterilization tunnel: high stiffness (to reduce flexing of the filter, which would reduce its life), durability of construction (for long operational filter life), and efficiency performance.

High stiffness and durability of construction should assure that the integrity of the HEPA filter is retained during elevated temperatures for the life of the filter. Filter design and material selection should be such that degradation does not occur and thermal expansion and contraction do not create stress cracks. Integrity breaches, caused by stress cracks, should be avoided at all times as these might result in bypass, particle shedding, and process contamination. It should be noted that, although the scope of this article is on the impact of the applied separators and sealant, particles may also shed from the filter media itself when the binding agent burns off and glass fibers are released. New filters are usually leak tested after they have been installed cold; then they are "burned in" through an initial heating cycle to ensure that any volatile content is removed and the media reaches a stable condition.

Compliant efficient performance that meets the vendor specifications for the HEPA filter should be confirmed through the filter test certificate and be maintained through its operational life. A stable downstream efficiency is to be retained during multiple heating and cooling cycles, whereby the particle counts are compliant with the Grade A specifications as shown in Table A.

Available Solutions To The Challenges

Historically, the number of options available (to tunnel manufacturers and pharmaceutical end users) for HEPA filters that can withstand temperatures up to 350°C has been limited. This section will compare two high-temperature HEPA filter options, with information on selection considerations.

The first option (A) is a filter design, which has served the pharmaceutical industry for many years. This filter type does, however, possess some generally known deficits, directly attributable to its construction and the components used. The second filter option (B) is a new design, which promises better long-term durability.

Option A: HEPA Filter with Ceramic Sealant and Aluminum Separators

The most commonly used filter option for sterilization tunnels comes with a ceramic sealant and fiberglass filter medium. (See Figure 2.) The medium is folded around aluminum separators, which, in turn, are placed in parallel in a stainless steel frame.

Because ceramic material is used to seal the aluminum-separated media pack to the frame, this filter type is sensitive to the formation of stress cracks. The cracks occur between the ceramic glue and the filter frame due to internal stresses created by process-driven temperature cycles. (See Figure 3.) In order to try to absorb the movement of the filter components during elevated temperature stages, the filter is equipped with a compensation mat located directly under the sealant.

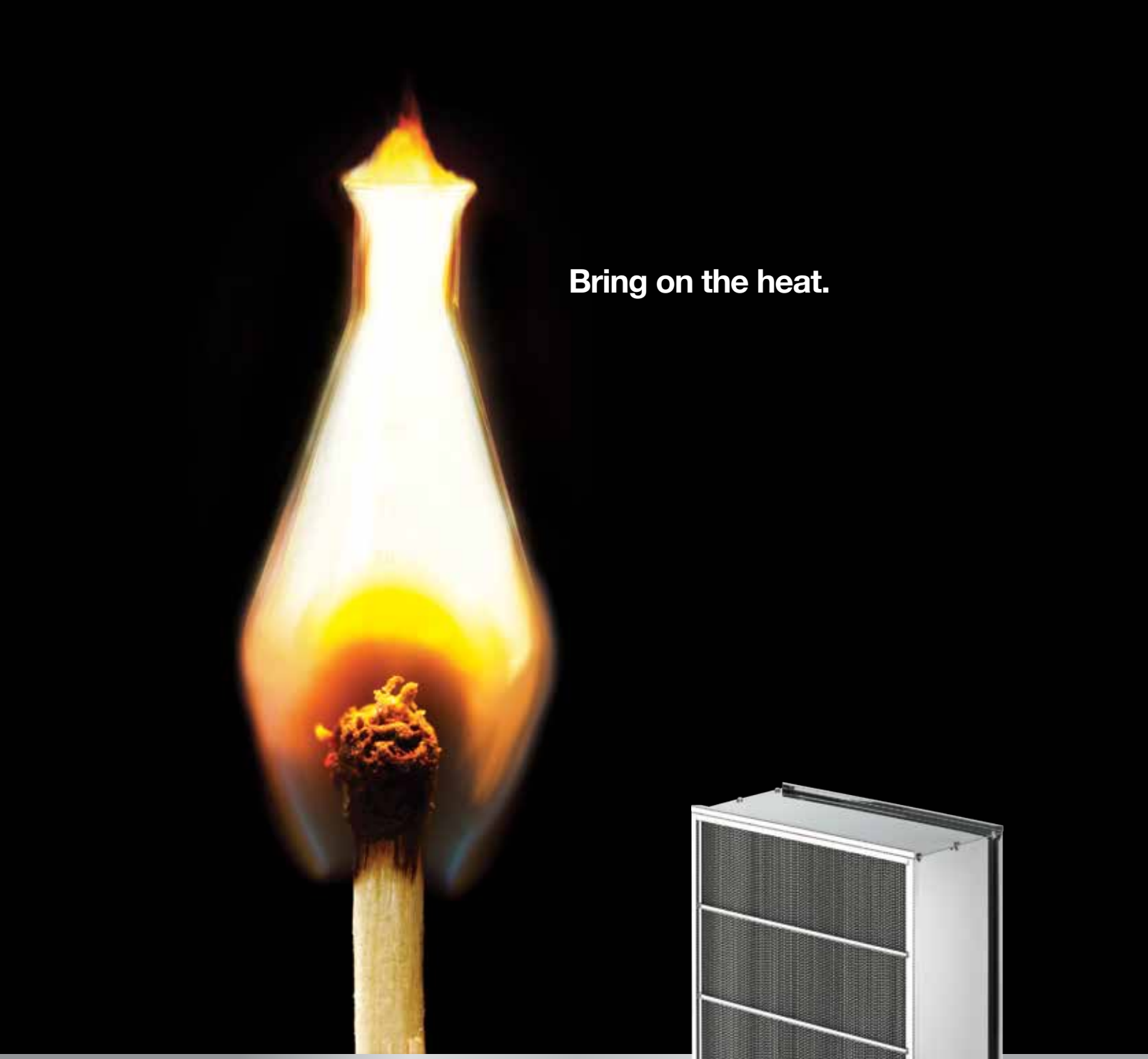

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Table A Environmental control requirements in regulations

ISO Class	USP particles/ ft^3	US FDA In Operation limit Particles/m^3	GMP Grades	EU and PIC/S				Active Air Action Limits cfu/ m^3
				In Operation limit (particles/m^3)		At Rest limit (particles/m^3)		
	≥ 0.5µm	≥ 0.5µm		≥ 0.5µm	≥ 0.5µm	≥ 0.5µm	≥ 0.5µm	
ISO5	100	3,520	A	3,520	20	3,520	20	< 1
ISO6	1,000	35,200	N/D	35,200	290	3,520	29	7
ISO7	10,000	352,000	B	352,000	2900	3,520	29	10
ISO8	100,000	3,520,000	C	3,520,000	29,000	352,000	2900	100
ISO 9	1,000,000	35,200,000	N/D	N/A	N/A	N/A	N/A	N/D
N/A	N/A	N/A	D	N/A	N/A	3,520,000	29,000	200

The stress cracks can cause leaks that result in the bypass of unfiltered air. Particle emission may be created when the edges of a sealant crack rub each other due to normal airflow-induced vibration of the filter assembly. Such shedding into the tunnel can be exacerbated during even small temperature fluctuations[6], potentially resulting in contamination of the process.

The air filter industry has worked together with the tunnel manufacturing industry to look for an alternative solution to reduce the risk of stress cracks. This has resulted in a so-called "dynamic seal," in which spacers are positioned on the "clean air side" of the installed filter. With this countermeasure, filtered air (which can include bypass air and particles released by the filter) is taken from the high-pressure hot zone of the tunnel and directed to the lower-pressure areas outside the hot zone, reducing the risk of contamination in the hot zone of the tunnel. Although this technique seems to reduce the problem, it is not a structural solution to the intrinsic issue with the filter design itself: For a long-term solution, the issue should be solved at the source. The same is true for installing a fine mesh immediately downstream of the (clean) filter outlet; the efficiency of such a mesh is limited by the mesh size – though it does provide mechanical protection to the more delicate filter media and will protect clean glass containers on the conveyor belt from being contaminated by larger particles released from the installed filter and applied gasket.

Option B: HEPA Filter with Elastic Fiberglass Sealant and Stainless Steel Separators

Similar to filter design A, filter design B comes with a stainless steel frame and a fiberglass media pack. It is free of silicone or other elastomers. The important differences are in the applied separator and sealant material.

Filter design B, as shown in Figure 4, is equipped with corrugated stainless steel separators and stainless steel support bars and stays. This construction gives a high overall durability and is less prone to oxidation, which is stimulated by high temperatures and might also occur on the aluminum spacers if the filters are not stored in the correct environment. The risk of oxidized particles shedding off the separators on the air leaving side is eliminated. The separators are placed in a staggered position to increase the media pack stiffness and to prevent the separators from nesting. Applying integrated stainless steel stiffener plates and stays prevents the winding of the bottom of the pleats.

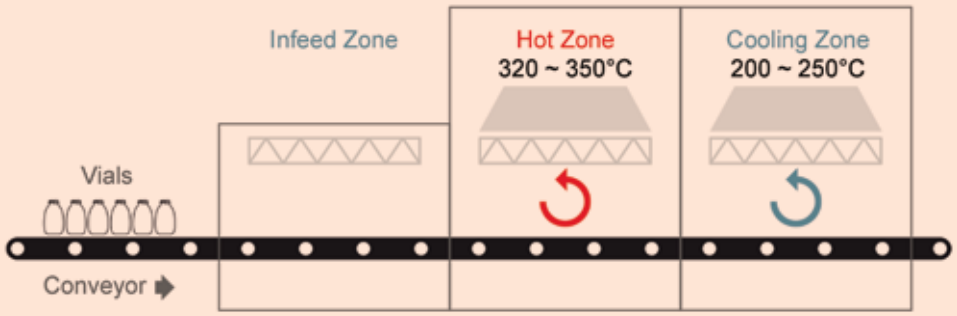
In addition to stainless steel separators and stiffeners, filter design B includes a compressed and elastic fiberglass sealant between the filter pack and the stainless steel frame, in contrast to the vulnerable ceramic sealant of filter design A. With the inclusion of a compressed and elastic fiberglass sealant, the HEPA filter is better able to compensate for the forces from heat stretching of components preventing the risk of integrity breaches from the stress cracks of ceramic sealant.

As an alternative to filter design B, there is also a filter design available on the market in which a ceramic frame and fiberglass strands are applied to reduce differences in thermal expansion. However, this filter design is only available in an 84 mm depth configuration, whereas the majority of dry-heat sterilization installations today are based on HEPA filter configurations in a depth of 150 mm or 290 mm. Both filter designs A and B qualify for these installations, which is the reason why this article is focused on a direct comparison between these filter types only.

Demonstrated Performance of New Filter Design

This section elaborates on the results of various tests that have been conducted on the performance of high-temperature HEPA filter design B. First, the outcome of a heat cycle test is presented to demonstrate the stiffness and durability of construction. Second, results of a laboratory particle shedding test are presented that allow a comparison of filter design B with filter design A. The filtration efficiency performance of filter design B was confirmed

Figure 1 Schematic representation of a sterilization tunnel



during a field test in a dry-heat sterilization tunnel. The described tests were conducted with air filters in either 150 mm or 290 mm depth – the test states which depth.

Stiffness and Durability Of Construction

Heat Cycle Test

To demonstrate the durability of HEPA filter design B, a heat cycle test was set up before burn-in to assess sensitivity to damage of the filter construction under high-temperature fluctuations. Twenty consecutive test cycles were executed at a nominal airflow rate of 2,100 m^3/h. The test was conducted to demonstrate reliability of the design over a number of heat-up and cool-down cycles; stress cracking of the ceramic sealant typically occurs early in the filter life. Each cycle had a duration of four hours, during which the filter was exposed to a temperature increase from 40°C to 350°C within 1.5 hours and then kept there for one hour before cooling back to 40°C within about four hours. (See Figure 5.)

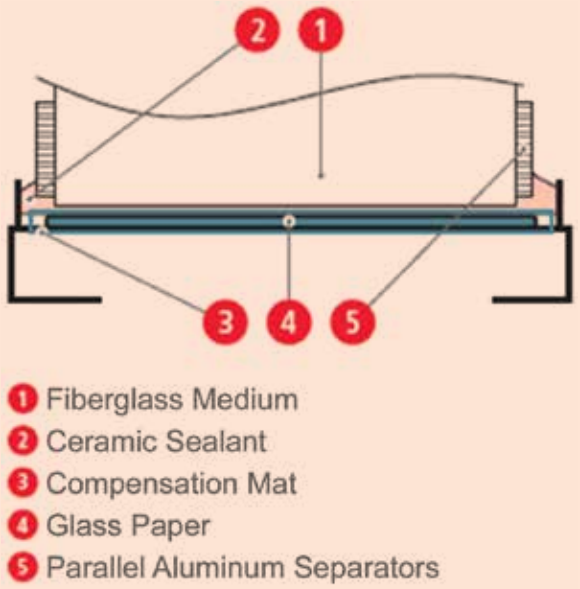
The results showed insignificant differences between pre-test and post-test values for both filtration efficiency and pressure drop. (See Table B.) No damage was observed on the media, and no stress cracks were found in the sealant. Although a tempering color did appear on the stainless steel parts due to heating, it had no effect on the actual performance. (See Figure 6.) Filter design B with compressed and elastic fiberglass sealant and stainless steel separators proved its durability of construction.

Proven Performance On Efficiency

Particle Shedding Test

Particle shedding caused by the high-temperature HEPA filter in operation should be prevented at all times. Any uncontrolled release of particles can result in process contamination that might negatively affect air quality and could lead to loss of production batches as well as undesired downtime and recalls.

Figure 2 Filter design A



To determine the filtration efficiency performance of filter design B vs. filter design A at high temperatures, and therefore indicate if particle shedding is present, comparative particle measurement tests were executed with a set-up as shown in Figure 7.

Prior to the test, both filter designs were burned in at 400°C for one hour. Filter design B (with stainless steel separators and fiberglass sealant) and filter design A (with aluminum separators and ceramic sealant) at dimensions of 610 × 610 × 150 mm were then installed in a high-temperature recirculation test unit. At a nominal airflow of 1,440 m^3/h, the temperature was gradually increased from ambient to 350°C by 3.5°C/minute. The typical rate of increase recommended for filters containing ceramics is in

Table B Pressure drop and efficiency before and after heat-cycle test

Test	Pre-test	Post-test
Filter Dimensions	610 × 610 × 290 mm	
Pressure Drop (Pa)	231	232
Efficiency at 0.3 µm (%)	99.99	99.99

Measured at ambient temperature.

the range of 1.5°C/minute; however, equipment limitations often have figures aligned with those used for this test. The temperature was stabilized at 350°C, after which it was reduced again to the ambient level.

During each phase and different temperature, particles of size ≥ 0.3 µm were counted downstream by means of a laser particle counter. A four-meter-long sampling tube consisting of a stainless steel/polytetrafluoroethylene (PTFE) tube was attached downstream of the air filters. By passing through the tube, the air was cooled sufficiently to supply the particle counter. Doing that, the increase in air volume over nominal room air was considered. Neither air filter was challenged upstream by an aerosol. The filtration efficiency target, measured downstream, was set at ≥ 99.99% for ≥ 0.3 µm particles.

Figure 8 shows a typical result of such a test. Although the number of particles counted downstream increased during heat stretching, the number of ≥ 0.3 µm particles counted for filter design B clearly stayed below the target of 99.99%. In contrast, the particles counted downstream for filter design A largely exceeded the target. The peak in counted particles occurred directly after the cooling down began. This was largely due to the integrity breaches that resulted from the air filter's construction with aluminum separators cast into the ceramic sealant, an issue that was explained earlier. Filter design B did not show integrity breaches and therefore limited particle shedding.

From the particle shedding test, it can be concluded that a high-temperature HEPA filter in design B offers a better and more consistent filtration efficiency performance when exposed to heating and cooling.

An additional benefit of filter design B is that it allows for a speedy temperature control. In contrast to filter design A, tempering during burn-in including longsome relaxation times is not required. With filter design B, heating up to 350°C is possible at a rate of 5°C/minute compared to a recommended rate of 1.5°C/minute for filter design A. Filter design B therefore improves the operational readiness of the tunnel. It should be noted that the actual burn-in procedure should always follow the instructions of the equipment and filter supplier.

Field Test In Dry-Heat Sterilization Tunnel

In order to assess how filter design B would perform in practice and see if the beneficial outcome from the laboratory particle shedding test would be confirmed in practice, filter design B was installed in the hot zone of an existing sterilization tunnel at a pharmaceutical equipment manufacturing company for a field test.

The primary purpose of the field test was to verify the air cleanliness in the tunnel and see if the particle concentration would meet the acceptance criteria for ISO Class 5, as prescribed by internal procedures for steady state operation.

Three different tests were performed. First, the high-temperature HEPA filter of design B was installed in the sterilization tunnel (Figure 9) and tested prior to burn-in. The air filter was then burned in overnight and retested the next day when the system was cold, and the particle counts were repeated at the same locations. Finally, the high-temperature HEPA filter was challenged with a polyalphaolefin (PAO) aerosol of 17 million particles (> 0.3 µm)/ft^3 of air. A filter scan was performed with a TSI Model 9310 particle counter downstream of the air filter in the hot zone. The surface was scanned 125 mm above the conveyor by an isokinetic probe. The tests were conducted under ambient conditions at one minute for each of the nine sample locations in the hot zone.

ISPE's Heating, Ventilation, and Air Conditioning (HVAC) Community of Practice (COP) as well as Sustainable Facilities COP have published a paper worth reading about particulate monitoring.[7]

All three tests passed the requirements. The detailed results of the two tests performed after burn-in are summarized in Table C.

With the installation of a high-temperature HEPA filter in design B, the hot zone of the sterilization tunnel met ISO Class 5 conditions in all three test cases.

Filter design A is vulnerable to stress cracks between the ceramic sealant and the frame. In contrast, filter design B is more robust retaining its integrity and limits particle shedding by its inherent flexibility allowing expansion and contraction during heating and cooling phase as well as during temperature fluctuations during tunnel operation.

Introducing A New Filter Design

When an alternative filter design is introduced, pharmaceutical manufacturers require evidence that the design provides an improvement over existing equipment. The testing here demonstrates that critical performance factors have been improved by the HEPA filter in design B. Confidence in the design is demonstrated by manufacturers of sterilization tunnels, who are prepared to supply tunnels using this filter technology.

Figure 3 Photograph of a stress crack in filter design A

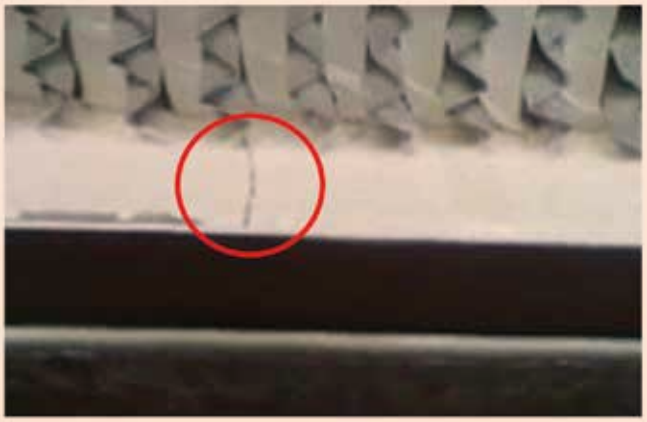


Figure 4 Filter design B

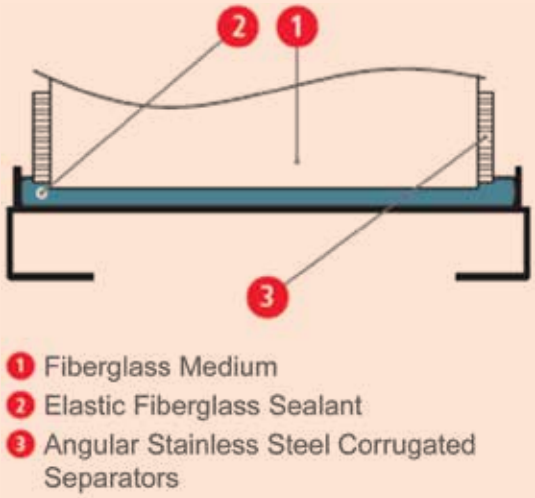
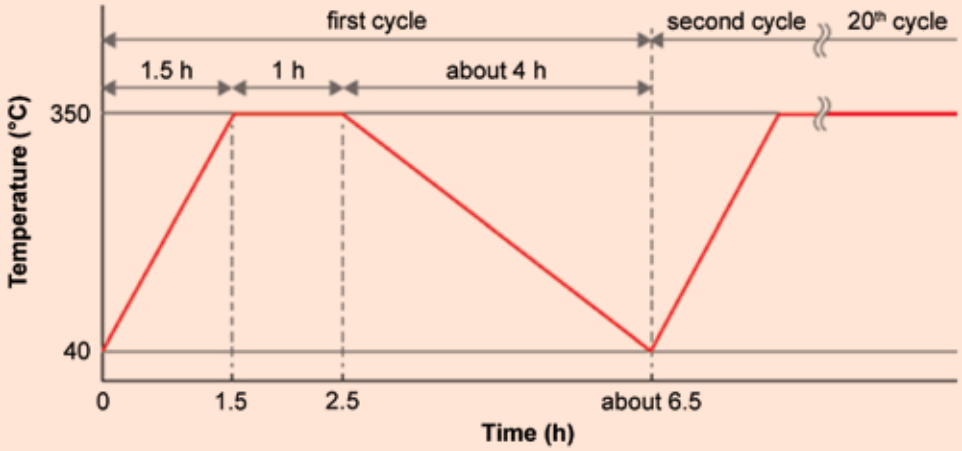


Figure 5 Heat-cycle test procedure



Conclusion

The temperature cycling during the start-up and shutdown of depyrogenation tunnels provides a significant challenge to a HEPA filter, and the life of the filter is usually limited by the number of cycles it can withstand successfully.

Filter design A, with ceramic sealant and aluminum separators, has served the pharmaceutical industry for many years. Nevertheless, this design does possess some generally known weaknesses that can, over time, lead to a loss of integrity from stress cracks between the sealant and the frame, resulting in increased risk of process contamination and premature filter replacement.

Multiple heat-cycle tests have demonstrated that filter design B, with compressed and elastic fiberglass sealant and stainless steel separators, offers more robust construction. From a comparative particle shedding test between filter designs A and B, one may conclude that design B offers more consistent filtration efficiency performance. Because of the absence of stress cracks, particle shedding is minimized. The beneficial results were confirmed during a field test in an existing sterilization tunnel, where the high-temperature HEPA filter in design B met the ISO Class 5 particle limit requirements before and after burn-in.

Figure 6 Photographs of undamaged filter design B before (a) and after (b) heat-cycle test

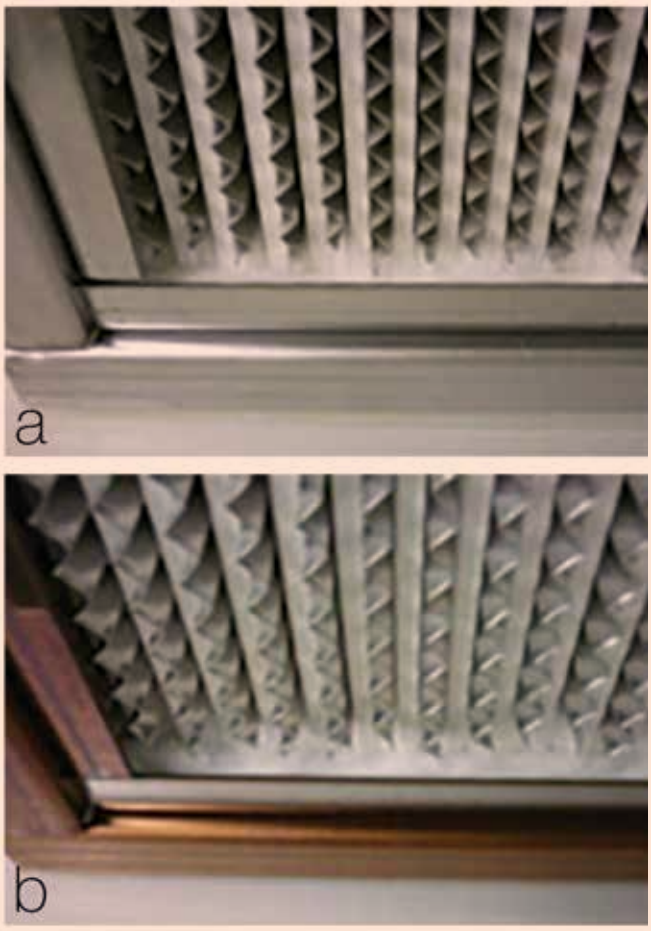


Figure 8 Efficiency performance during heating and cooling

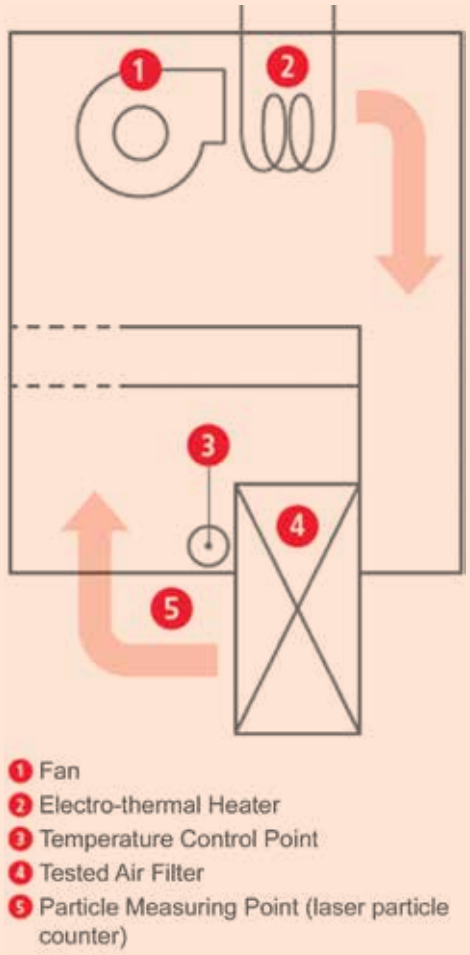


Figure 7 Particle shedding test set-up

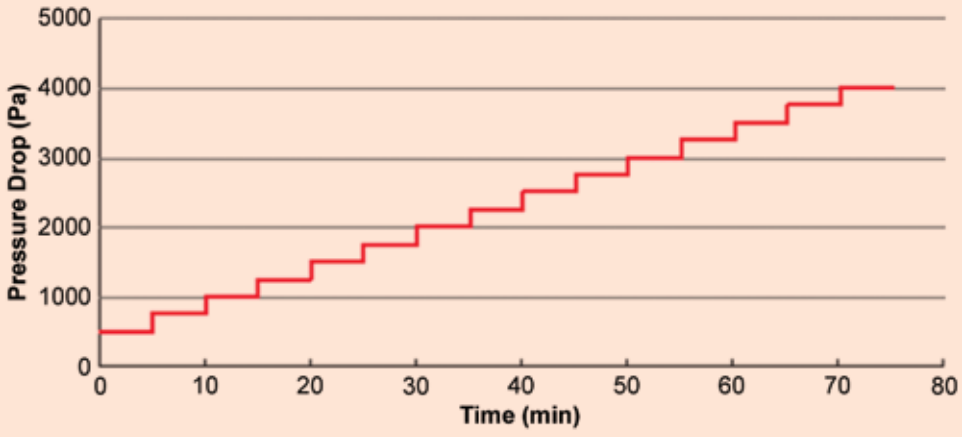


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Figure 9 Photograph of the hot and cooling zones of the sterilization tunnel with probe marks

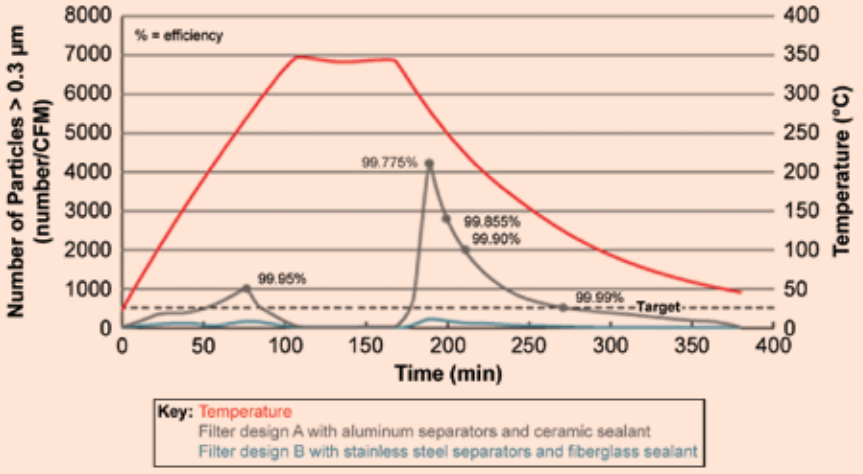

Figure 10 View into sterilization tunnel

Table C	Post-burned in sample test results				
Location		**Measured particle concentration (particles/ft^3 of air)**			
		0.3 µm	**0.5 µm**	**1.0 µm**	**5.0 µm**
Hot zone	A-1	25	4		
Hot zone	A-2	24	5	3	
Hot zone	A-3	17	5	3	
Hot zone	B-1	20	4	1	
Hot zone	B-2	28	5	2	
Hot zone	B-3	25	1		
Hot zone	C-1	23	6	2	
Hot zone	C-2	19	6	1	1
Hot zone	C-3	6			
Challenged with 17 million PAO particles/ft^3					
Location		**Measured particle concentration (particles/cf of air)**			
		0.3 µm	**0.5 µm**	**1.0 µm**	**5.0 µm**
Hot zone	A-1	34	4	1	
Hot zone	A-2	61	8	1	
Hot zone	A-3	137	29	2	
Hot zone	B-1	73	14	2	
Hot zone	B-2	58	7	2	
Hot zone	B-3	135	35	5	
Hot zone	C-1	30	6		
Hot zone	C-2	36	7		
Hot zone	C-3	80	20	4	
Particle Limits According to ISO 14644-1:1999					
		0.3 µm	**0.5 µm**	**1.0 µm**	**5.0 µm**
ISO Class 5 limit		289	100	24	≤ 1
Conclusion: Filter Design B Meets ISO Class 5 Conditions					

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DESIGN CONSIDERATIONS FOR WFI DISTILLATION SYSTEMS FOR IMPROVING QUALITY, PROJECT PERFORMANCE AND EQUIPMENT LIFE CYCLE COST REDUCTION

Juha Mattila and Mika Pärkkä

This article presents and discusses a number of key requirements and design, quality, and engineering considerations that have high importance in end-user usability, cost control and end-product quality that help manage risks in Water for Injection production and processes.

Water for Injection (WFI) production is a critical part of any parenteral drug process. There are several factors that need to be considered when selecting WFI production methods, such as capacity, future needs, storage, and quality control. This article discusses, among other things: concentrating on the end-user perspective when designing WFI distillation systems, evaluating different possible configurations, the latest available technologies, setting criteria and overall requirements, and the implications with regard to pharmaceutical production processes.

Distillation Technologies

This article also discusses design considerations from the perspective of different distillation methods. It focuses on the requirements of the European Union, but these methods can be applied to North America as well. The methods specifically in question are multiple-effect distillation and vapor compression distillation. In general, both of these are considered common technologies, but for clarity it is beneficial to highlight some major differences between them. Vapor compression technology was originally designed for desalination processing.

The process utilizes preheating and heat recovery along with the core, which uses the latent heat of steam by superheating vaporized feed water via the compressor, providing energy efficiency as well. The compressor operates by using electrical energy between approximately 15 kW to 20 kW per hour per produced 1,000 kg/h of WFI water. Multiple-effect water still (MWS) uses general plant heating steam for heating in the first stage of the process, after preheating the feed water by condensers evaporating the pure steam to WFI. Next in the process, preheaters and several column stages (there are typically six to eight columns for today's energy-efficiency requirements) vaporize pure steam and generate WFI. One major difference in these two technologies is the processing temperature. Vapor compression technology typically distillates in lower temperatures (for example, +105°C) and ends with room-temperature WFI (between +25°C and 35°C), where the multiple-effect water-distillation process utilizes nearly the maximum temperature provided by the heating steam (typically between +150°C and +170°C, depending on the used plant steam pressure) and ends with WFI (typically between +85°C and 95°C). More specific comparisons between these two technologies can be found in several *Pharmaceutical Engineering* articles covering this topic. See the schematic-diagram examples for typical WFI water pretreatment, WFI generation, and WFI storage systems (figures 1 to 3).

Determining the Daily and Maximum WFI Quantity

The daily quantity of WFI or pure steam required for any parenteral drug process typically plays a significant role in the overall manufacturing process. If a high volume of water is continuously needed, the entire manufacturing process may depend on the kind of equipment used and the available storage capacity. In instances of the occasional use of water, the necessity of equipment may be less, especially if the required amount of WFI in bulk can be obtained from outside sources. In cases where a minimal amount of WFI, such as 1,000 liters per week, is needed, in-house control of WFI production may still be preferred or probably cost less than purchasing it.

Knowing the WFI usage will allow for optimal design of the process. This knowledge will help to determine the proper size of the WFI holding tanks, holding time, and energy required to maintain temperatures (especially in the most common situation of WFI storage at temperatures of +80°C or higher) to ensure the availability of a consistent supply of WFI for the facility. It is essential to monitor the operating interval, counting back to the capacity needs in the process, how many shifts per day, and immediate peak needs.

System with WFI Production against Back Pressure

One safety precaution to ensure the quality of the WFI in the tank is to use a nitrogen blanket at slight overpressure. This measure minimizes the possibility of having air pockets as a source of contamination in the vessel. The challenge for the WFI distillation equipment is overcoming the positive pressure that is present in the WFI tank. If the WFI distillation equipment has the possibility to naturally produce WFI at a positive pressure, this can eliminate having to add a distillate transfer pump, tank, valves, and other instrumentation, which may complicate, add cost, and create a risk of contaminating the supply system. Most WFI equipment either relies on gravity feed, meaning the outlet needs to be higher than the WFI tank inlet, or requires a WFI pump. The multiple-effect distillation process can, however, be designed to push distillate up to five meters of H2O (0.5 bar) of back pressure naturally and without the use of an additional pump. This can eliminate having to raise the unit or condenser and does not require an additional pump in the system.

Define the available floor space and room height, bearing in mind the required service clearances around the system. Equipment should be designed so that there is service clearance from at least two sides of the equipment. Ensure the route for transporting the equipment onsite.

No one wants surprises when building a new facility or expanding/renovating. In order to avoid unexpected setbacks, study the entire route before bringing in the new equipment. It is always easier to break old equipment into small parts; new equipment often requires a similar process but in reverse. It is also important to remember that this equipment may be heavy, especially when full of water. This needs to be taken into consideration when calculating the floor load design and plans. The equipment area requirements and any maintenance clearances need to be considered when repairing or replacing components. Anything brought in-house may have the benefit of being tested as a whole – including all functions, sensors, and calibration.

Any equipment that is physically disconnected from wiring may require recalibration. Be sure to consider this in the Site Acceptance Testing (SAT) or onsite validation cost. Having documented proof that sensors and analyzers were tested and verified at the supplier's facility before delivery at Factory Acceptance Testing (FAT) and not disconnected after that can significantly reduce the onsite SAT and qualification timeline and cost. The cost of modification at the supplier's facility compared to onsite work is estimated at only 1:3.

Following the ASME BPE Standard

The ASME Bioprocessing Equipment (BPE) standard is an excellent tool for designing a sanitary process. The content is specific to material selection, types of applicable components, piping dimensions, types of connections, surface finishes, mechanical assemblies, and cleanability and process applications in general. The intention of the standard is to help with designing new equipment but also not to limit any new technologies in case they are novel and not noted in the specification. It's important to understand that there are always a number of required physical properties or methods that cannot be applied simultaneously and rule each other out in some cases. It is encouraged and beneficial to demand a statement from the vendor and see where the expectations, requirements, and available offerings meet and agree.

Some examples might help to explain this:

One such example is welding a pipe branch with 2D maximum dead leg using orbital welding. This may not be possible in the case of small-diameter pipes, such as outside diameter (OD) ½ inch and OD ¾ inch, since the 2D branch length is less than 20 millimeters, which is typically required to fit into an orbital weld machine clamp. This is acknowledged in the ASME BPE as not being an absolute requirement. However, this may still be achieved by using hand welding; the dead leg minimum requirement can be reached but by using hand welding instead of the generally preferred orbital welding. Surface roughness is better in orbital welding than in hand welding; that's why it is preferred.

Pipe bending vs. number of welds is also an interesting point of discussion. Even with the best of the bending machines, some of the inner surface finish is lost in an elbow bend; what is achieved, however, is not having two welds in the pipe. This is a far better alternative than adding to the number of welds or components in the process piping. Any other excess connections, such as clamps or flanges, may be avoided in the same way.

Drainability of equipment: It is not required to slope a pipeline that is 250 millimeters long or less. In other words, sloping is required for pipeline runs that are longer than 250 millimeters. Especially with large-diameter pipes, this may typically be achieved by forced sloping against tubing physical properties if bending vessel connections or adding sloping parts to flange joints is not feasible. However, this is not allowed due to the risk of weld leaks and pressure vessel safety, so this rule can conflict with the ASME Pressure Vessel Code, which always takes priority.

There are many more examples of design considerations based on ASME BPE. While some direct assumptions may not be possible based on the ASME BPE standard, prioritizing the features that are the most desirable or appropriate for the processes and applications is important.

WFI Hot or Cold Loop or Storage

When comparing WFI production equipment to the required storage temperature in a cold loop (+20 °C to 30 °C) or hot loop (+80 °C or higher), there is a difference in the energy consumption and the selection of the type of WFI production equipment. The benefit of a low-temperature output WFI system, such as a vapor compression system, is lower energy consumption. This type of system is not widely available for all applications. The hot-loop and tank WFI applications benefit from WFI supplied at an already high-temperature output of +85°C or even higher that is produced by multiple-effect distillation. Low-temperature output distillation systems are typically intended for immediate use without storage, and these systems require periodic sanitization at high temperatures to reduce bioburden.

Establish a solid and realistic calculation for the equipment based on realistic utility costs, performance values, and available quantities and conditions. Always compare apples to apples.

The best way to estimate these utility costs is by cooperating with utility design engineers and end users of the equipment. Knowing

Table A Multiple-effect WFI distillation: fixed-capacity running cost vs. proportional-capacity control

	Without PCC	With PCC
Number of start-ups and stops per day (estimate)	4	2
Number of operating days per year (d/year)	250	250
Start-up and sanitization time (min)	20	20
Cooling phase to shut down time (min)	15	15
Start-up running hours per year (h/year)	333	167
Total start-ups and stops per year (h/year)	583	292
Feed water reject ($/year)	20,393	10,197
Plant steam start-up heating ($/year)	7,169	2,895
Cooling water start-up and shutdown cooling ($/year)	0	0
Fixed plant steam pressure (bar)	5.5	4
Distillate/reject distillate capacity (l/h)	8,000	8,000
Feed water consumption (to reject) (l/h)	9,200	9,200
Plant steam consumption (kg/h)	1,393	1,125
Cooling water consumption (l/h)	0	0
Start-up and shutdown costs per year ($/year)	**27,563**	**13,092**
Annual savings with proportional capacity control ($/year)		**14,471**
Running cost savings during equipment life cycle ($/15 years)		**217,065**

the goal truly helps in making the right decision about the type of equipment needed for the facility today and in the event of a future expansion. Be sure to include the realistic washing, cleaning, and service and maintenance costs at realistic intervals. In addition to the running costs, the service costs play a significant role in the entire life cycle. There is always a risk of malfunction when it comes to complex processes and numerous moving parts; critical part maintenance and replacement costs can be significant, and production downtime is very expensive.

Temperature of Feed Water and Cooling Water

For multiple-effect units, feed-water temperature has a major impact on the required flow rates of cooling water. Additionally, it is required to consider the size of heat exchangers in order to work with higher-temperature cooling water. For example, inlet temperatures can be up to +35°C in southern regions compared to +5°C to 10°C in the northern regions. The higher inlet temperatures of feed water and cooling water to the WFI system lead to a smaller temperature differential in the cooling water available for heat transfer. This impacts the flow rate of cooling water, as colder water has more temperature differential. It's important to consider whether the cooling water supply temperature has seasonal variations, as this may cause other considerations for the capability of controlling the process under different conditions.

Multiple-effect distillation systems need to be evaluated to determine how many effects are optimal for utility use as well as the overall energy consumption of the respective vapor compression system. Individual and project-specific parameters should define the most appropriate system. Include the round-table review of the entire life-cycle cost of equipment, which encompasses energy consumption over the target operational life of equipment (typically 15 to 20 years), service costs, and investment cost.

In today's world of increasing energy costs and sustainability concerns, it is advised to look at multiple-effect distillation units with enough columns, or any other means of heat recovery, to save in heating- and cooling-water costs. In an MWS, for example, six to eight effects typically means that little to no cooling water is needed to produce WFI and save the most in heating costs, as an increasing number of effects significantly reduces the consumption of heating steam.

How the WFI Distillation System Integrates With the Storage Tank and Loop

Communication signals between the WFI tank and the distillation equipment can provide a proportionally controlled capacity. This means that the distillation equipment can automatically adjust to the current demand of WFI consumption based on the direct demand (level of the WFI storage tank). To achieve proportional capacity control, the water still needs to be equipped with a proportional control valve or valves for plant steam and feed-water control, utility measuring instrumentation, as well as a PLC control sequence for running the operation automatically. Feed water can

also be controlled by motor inverter control. Eliminating the starts and stops of the WFI still also reduces the time and energy spent on the running up, cooling down, or sanitization period of the units as per the current capacity needs. It may be difficult to think of these savings in numbers, but there is a way: Simply evaluate the number and duration of running cycles and peaks of WFI consumptions put in the simple spreadsheet of a daily schedule. Instead of five daily starts and stops, there may only be two, for example, as the distillation capacity is adjusted according to consumption. It is surprising how much time, energy, and money can be spent annually on ramping up and down the system. It can easily be proved that the payback time of proportional capacity control that has been implemented in a new or existing WFI distillation unit is short enough to justify investment. (See Table A.)

Expand Existing Production or Build a New Facility?

A new facility gives more freedom in equipment and process design in comparison to upgrading or expanding existing production capacity. With existing equipment, the impact of existing validation-procedure requirements on the upgrade process must be considered; having to redefine validation procedures due to major equipment upgrades can be time-consuming as well as resource-consuming.

When a completely new facility and equipment are being designed, it is recommended to discuss with management any expansion plans that may help prepare for increased capacity, such as reserving extra space for additional equipment or sizing the unit so that there is extra space for future use. A backup plan in terms of ensuring available capacity using duplicated processing units or dividing capacity over two or more units can be worth the investment in true 24/7 operating production facilities that allow minimal or no downtime. Duplicating equipment is a big investment, but it may be just a fraction of lost production capacity in a situation where there is prolonged downtime. Dividing the WFI production capacity from one big central unit to two smaller units may increase the investment cost but never by a factor of two. This solution can guarantee the minimum of half-capacity at all times and provide flexibility for planned downtime arrangements, such as periodic preventive equipment maintenance.

Along with the redundancy scenario considerations, it is important to acknowledge that a simpler system is better and more reliable. Do not fall into the trap of over-engineering that can compromise the reliability of the system and have negative implications on the quality of production. Unnecessarily complicated processes require more maintenance, more spare parts, more validation, more testing, and more documentation and can lead to an increased number of welds, connections, and ports that can compromise the WFI process.

If pure steam is required, consider whether an independent unit is needed or should the distillation unit be equipped with a pure steam generator operation, simultaneous steam generation, or a simple pure steam outlet port. One has to remember that a pure steam generator operation isolates the rest of the unit and produces only pure steam at the time of use. Simultaneous operations are typically not designed for central autoclave pure steam supply but for other smaller needs.

A combination-type unit means that the WFI is still equipped with a significantly bigger first column followed by a number of smaller distillation columns to be able to run steam generation for larger steam header systems with distillation simultaneously and without risk of process fluctuations.

Typical Utility Connections

The following utilities are typical for distillation systems:

- Feed water to unit (ambient temperature, sufficient supply pressure)
- Cooling water (supply pressure and temperatures according to open- or closed-loop system)
- Plant steam supply (typically three to eight bars, depending on the system)
- Atmospheric drain connection for blowdown and other reject waters
- Plant steam condensate return to heating system
- Three-phase electrical connection
- One-phase electrical connection (typically in case of additional peripheral devices)
- Ethernet connection wiring from the unit's control system to the facility BMS system for data collection and remote start/stop
- Dry contact wiring for possible handshake signals (for example, from the pretreatment system or WFI storage tank)

With multiple-effect water distillation systems, the steam utility line size may be bigger compared to a vapor compression steam connection. On the other hand, the electrical-connection power requirement for cable and main fuse size for a vapor compression system is significantly bigger. Multiple-effect systems require three-phase electricity merely for the feed-water pump and control system, while a vapor compression system requires high electrical power for its compressor. Cooling-water connection size and need depends directly on the cooling-water loop temperatures available, as well as the number of effects applied to the MWS or the cooling-water needs of the vapor compressor.

Efficacy of High Temperature and Particle Separation of WFI Process

The greatest means of risk mitigation with high-temperature distillation systems that employ separation of impurities is the safety they provide from contamination by microorganisms or their particles. Just as important is the removal of nanometer- or smaller-size particles that could affect patients when they are injected into the body. Microbial contamination in WFI cannot be detected by any sensor during on-line production. Conductivity of water can be one indicator of WFI quality and low conductivity to indicate sufficient quality of WFI, along with periodical off-line sampling for endotoxins. However, overlooking the highest risk of microbial contamination by small particulate presence in WFI can cause risks affiliated with patient safety – and especially with patients who have an infection or who are undergoing treatments that lower their resistance. Therefore, any considerations of not having sufficient microbial-controlled WFI production should be ruled out.

F_0 of WFI Process

Heat is an effective means of microbial control. Heat sterilizes the water through the different stages of the heat distillation process, starting with heating up the feed water in the condenser, going through column pre-heaters in each stage and finally ending in the first column, which operates with plant steam and exposes incoming water to the highest temperature. Following the route of feed water to flash vaporization and condensing to final distillate takes place in each column, ending at the condenser outlet, typically at +95°C to 99°C for the MWS. Typical maximum operating pressure for plant steam is eight bar, and this respectively equals to a temperature of +175°C. The WFI processing temperature or the exposure temperature of feed water and WFI throughout the process of MWSs is typically between +143°C and 175°C. In comparison, the typical operating temperature in processing WFI with vapor compression technology is significantly lower: between +100°C and +105°C. This means that in a multiple-effect distillation process, the F_0 exceeds the equal sterilization batch exposure time significantly, where the vapor compression distillation process does not reach $F_0 = 15$ at any stage of the process. Water dwell time in this process is too short, and the temperature too low.

Since the exposure time of water passing through the equipment is measured in seconds instead of minutes, the high temperature in exposure is critically important to achieving acceptable sterility levels that ensure a Sterility Assurance Level (SAL) of 10^{-6}.

This is a key element for safety of any such production, and calculating the F_0 value for the WFI system is critical. The heat exposure of water is not only estimated in the highest temperature of the first column but the F_0 accumulates in every part of the process where the exposure temperature exceeds +100°C.

The F_0 accumulation is exponential, and this shows when looking at water exposure in the WFI process at higher temperatures than the reference point of +121.1°C. For example, in the first column

Table B	Time/temperature correlation
Exposure Temperature (°C)	Exposure Time Required to Reach F_0 = 15
100	1,932.37 min
110	193.24 min
120	19.32 min
130	1.93 min
140	11.59 s
150	1.16 s
160	0.12 s
170	0.01 s

the feed-water temperature can rise to +170°C when running at eight bar of plant steam pressure. To achieve the same F_0 at +160°C that equals to 15 minutes at +121.1°C, only 0.12 s is required. See the time/temperature correlation table for reference (Table B).

Importance of Gas Separation

Gases affect the conductivity of water significantly, and removing non-condensable gases from the feed water is necessary in order to reach an acceptable quality of WFI.

Gases are present in natural waters, and the content varies significantly from one place to another. The most common gases are carbon dioxide, nitrogen, and oxygen. Of these three, carbon dioxide is the most difficult to remove since it has the highest solubility in water. Nitrogen and oxygen are present mostly as free N^2 or O^2, and removing them is fairly easy. Dissolved CO^2 is more difficult to remove and requires additional treatment. Softening, or reverse osmosis/de-ionization (RO/DI), do not remove gases efficiently enough.

Generally speaking, there are two ways to remove dissolved gases: vacuum, which requires the use of an additional gas separator or increasing temperature and surface area. This can take place in the pre-heaters and gas separator in the first column of an MWS. The gas separator consists simply of a spray nozzle that gives the warm feed water of the surface area needed to separate the gas. This drives the gases out of the water and into the atmosphere through a gas vent. These are totally integrated in the still and thus eliminate the need for additional equipment. Gas removal in an MWS can be further enhanced by adding a gas vent to the distillate collection line coming from the pre-heaters. These are usually enough to ensure adequate gas removal.

Feed Water Quality Considerations

Even though it is possible to produce good-quality WFI directly from softened water, the old principle "The cleaner in, the cleaner out" is still valid. Distillation is an excellent method for removing impurities from water, but it can't remove everything. On the other hand, there is no single method that can remove everything at once.

When it comes to the MWS, there are a few impurities in feed water that require special attention. Chlorides are particularly harmful to stainless steel at elevated temperatures, but they are easy to remove during pretreatment. If problems occur with chlorides, it is almost always occasional. Hardness causes scaling, but it is rarely present with water softening. RO/DI remove silica and hardness, just like other ionic impurities, from feed water. Generally speaking, scaling can be reduced even if some impurities remain in the feed water by ensuring an even distribution of feed water to the evaporator to keep all heat-exchanger tubes continuously wet. Behavior of the still is also more predictable when feed-water distribution works well.

In a cold system, there is always a risk of growth in the purification unit and downstream of it. High temperature that yields high F_0, though the contact time is short, is effective against any bacterial growth. Obviously this advantage is difficult to get in colder systems.

An MWS is less effective at removing total organic carbon (TOC), but it can be removed from feed water using activated carbon. Gases usually do not need special treatment; the integrated gas separator of the MWS is adequate for removing gases unless the feed water gas content is exceptionally high.

Good quality feed water is a typical general requirement (< 5 µS/cm). For example, using softened water instead of RO or DI water always leads to two things: 1) More frequent cleaning intervals of process contact surfaces and 2) An increased amount of blowdown from the distillation process and gas removal to be able to produce sufficient quality WFI. Typical blowdown ratio of a distillation system is 5% to 15%, and with softened water the amount can easily get up to 30%, which means an increase of 100% or more in the reject water amount. Such increases of rejects clearly reduce the efficacy of WFI production. In addition, an endotoxin load to the still may increase. This means a higher risk of carryover of endotoxins to WFI, although an MWS is generally very effective at removing them.

Conductivity Is Not Enough

Conductivity is an excellent way to continuously monitor distillate quality because it is simple, reliable, and sensitive. However, it is not sufficient because it indicates only the presence of ionic impurities and is not selective. If conductivity increases, other means are required in order to determine the cause. In addition, it does not detect endotoxins, bacterial growth, or TOC, all of which are important for WFI quality and have been defined in the

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Figure 1 Purified water generation – thermal sanitization

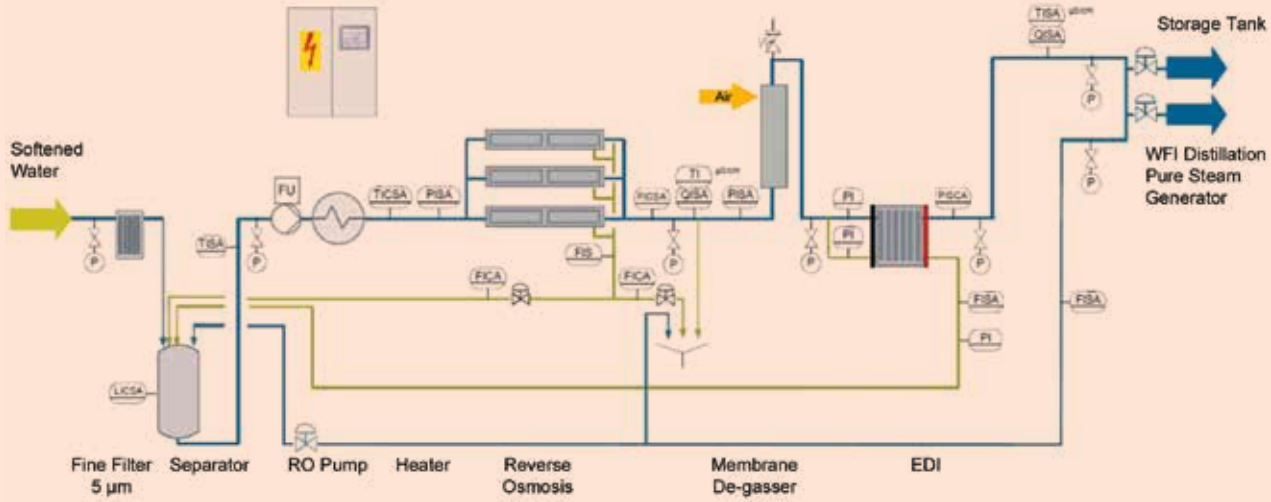
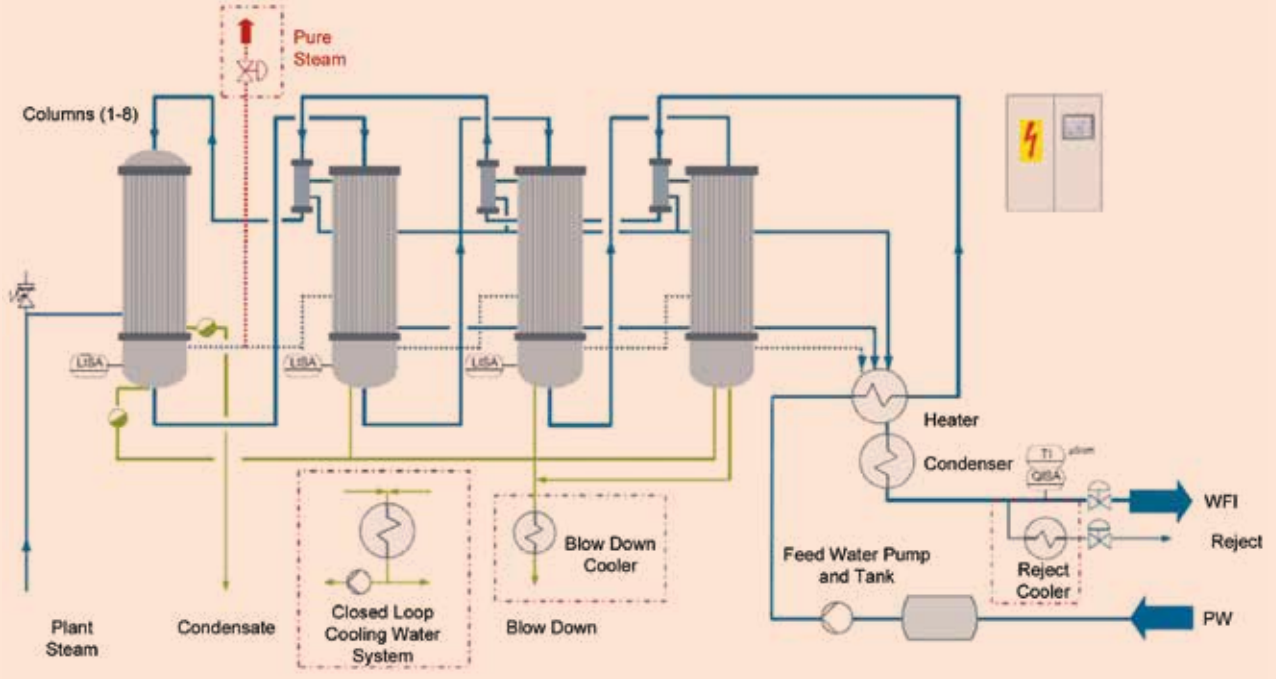


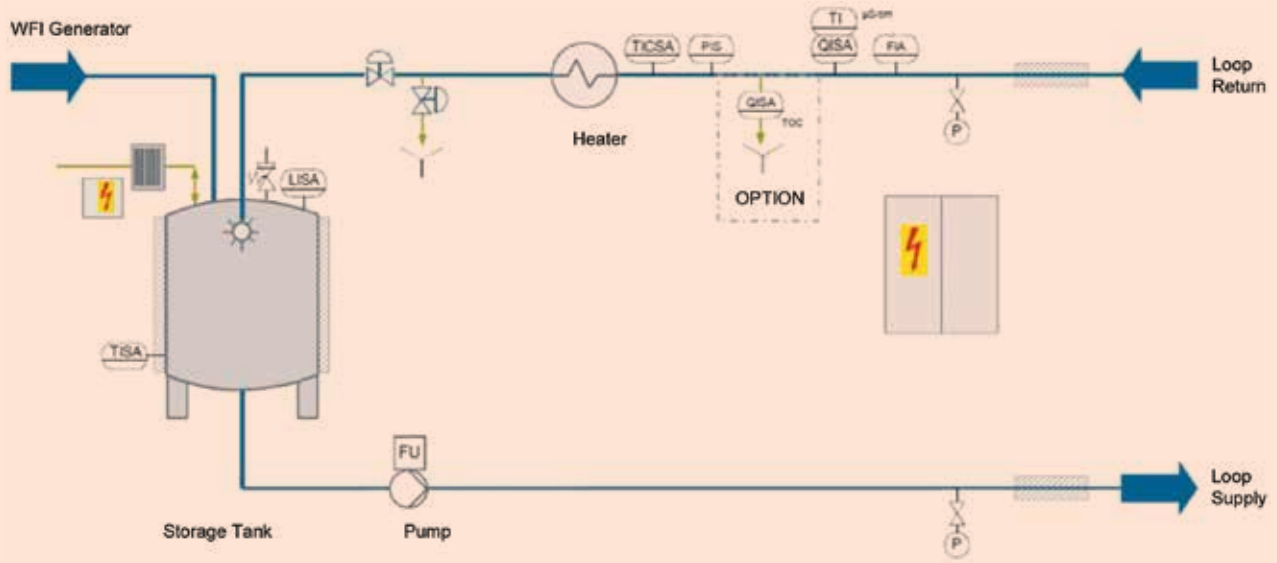
Figure 2 WFI generation – multiple-effect water still



pharmacopeias. Continuous TOC monitoring in WFI systems is normal practice, and it can be added to a still as well. When the purification and mo nitoring systems are maintained properly, an acceptable TOC level in distillate can be reached and monitored easily. Naturally, care must be taken with maintenance and the calibration of the analyzer, particularly because the levels are low.

Detecting endotoxins on-line is not possible with current technology. Yet endotoxins are one of the most critical and likely impurities in water, so it is a top priority to remove them from WFI. An MWS is known to have a very good ability to remove endotoxins continuously. A four-log reduction can be shown routinely, and higher reductions have been reached in tests. This

Figure 3 WFI storage and distribution – continuously hot



topic has been discussed thoroughly over the years, so we will not put more emphasis on it here.

Detecting bacterial growth on-line is possible using current technology, but it is not yet a common occurrence. Limit of determination can also be a concern. Bacterial growth is not directly related to TOC either. This emphasizes the importance of having a reliable method for eliminating it, and this has been discussed above. In addition, growth in a still after the columns is highly unlikely because the lowest temperature inside the WFI pipes is the same as the distillate outlet temperature. As a result, the risk for growth in the WFI line downstream of the still is also highly reduced. The risk for growth in the feed-water lines of an MWS can be reduced with a sanitization sequence. Feed-water lines can be sanitized if desired.

In conclusion, there are many factors that affect the design process, and they need to be evaluated to achieve the desirable result. Risk mitigation and product quality must never be compromised, but weighing different alternatives and possibilities objectively will help to find the most suitable solution.

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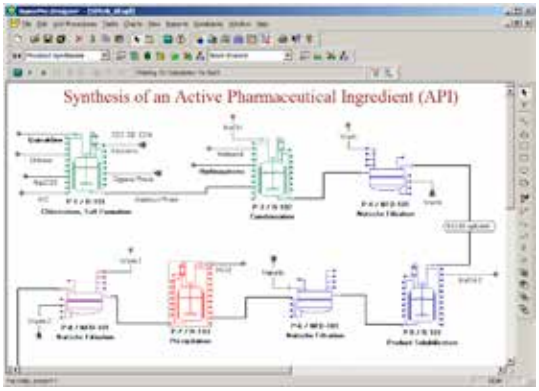

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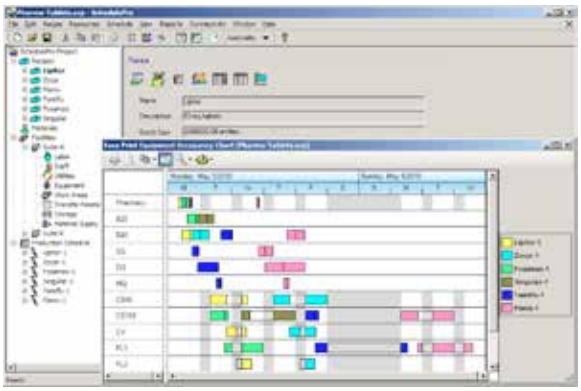

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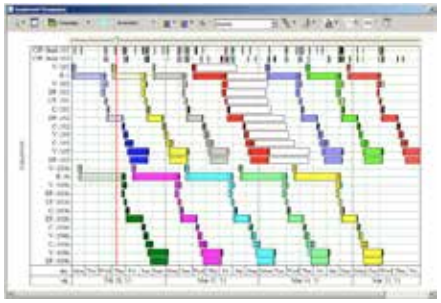

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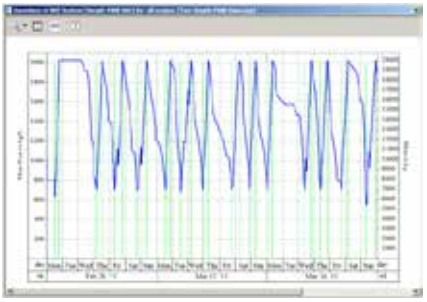

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AUTOMATED WASHING PRINCIPLES AND COMMON MISTAKES

Olivier Van Houtte, Paul Lopolito and Marcel Dion

This article will explain how some key process parameters, such as time, temperature, chemistry, coverage, and mechanical action, can affect the performance of an automated washing system. It will also discuss best practices for selecting appropriate chemistries and loading accessories and how to avoid common mistakes when using automated washing systems.

Automated washing systems are often used for critical cleaning and drying applications in research, pharmaceutical, and biopharmaceutical manufacturing facilities. Typical applications include the cleaning of laboratory glassware and parts from equipment used in the manufacturing processes of parenteral (injectable), oral liquid, and solid dosage drugs. A good understanding of basic principles of washing can help with making the best use of automated washing systems as well as avoiding typical mistakes that can lead to inconsistent cleaning performance, lower productivity, and higher operation and maintenance costs. Such knowledge represents an important step toward operational excellence.

Some key process parameters, such as time, temperature, chemistry, coverage, and mechanical action, can affect the performance of an automated washing system. Best practices from over three decades of cleaning and automated washing experience will be shared for selecting appropriate chemistries and loading accessories. Finally, ways to avoid common mistakes when using automated washing systems will be discussed.

Applications

Applications that are considered here include the cleaning and drying of various laboratory glassware used in research facilities; cages, racks, and other items commonly used in laboratory animal research environments; and components that come in contact with the manufacturing process of drugs in pharmaceutical and biopharmaceutical setups. Automated washing systems can be used to address the cleaning of parts from filling lines, packaging lines, stainless steel drums, fermentation containers, freeze dryer trays, tablet punches and dies, vials, and ampoules and change parts from blistering, packaging, and counting equipment. This article focuses on automated washing; however, a lot of the information can also be applied to manual cleaning.

Basic Washing Principles: TACCTS

A common acronym used in the industry to remember the factors to be considered in establishing an effective cleaning program is TACT (temperature, action, chemistry, time), but a more fitting acronym is TACCTS, which includes coverage and soil.

Soil

Cleaning parameters need to be established based on the effective removal of residue on the surface, so soil, and understanding the nature of it, should be considered first, even though it is the last letter in the acronym. Common questions such as:

- What is the nature of the soil?
- Is it organic in nature (such as fats, oils, waxes, blood, organic acids, sugars, and protein)?
- Is it inorganic in nature (such as minerals, carbonates, and metal oxides)?
- Does it contain both organic and inorganic components?

These are important questions to ask when deciding whether to use alkaline or acid cleaning agents or both chemistries in series.

What is the quantity of soil on the surface? A light or thin coating may be much easier to clean than a heavy or thick coating. What is the condition of the soil on the surface? An air-dried soil may be much easier to clean than a baked-on residue. A rougher surface is generally more difficult to clean than a smooth, nonporous surface.

Temperature

The critical parameter of temperature can apply to the pre-wash phase, detergent wash phase, and rinse phases. The temperature of the pre-wash phase may vary based on the nature of the soil. A high temperature, around 180°F (82°C), is recommended for fats, oils, and greases, while a moderate temperature, around 150°F (65°C), is recommended for minerals. A pre-wash temperature around ambient is helpful for proteins and sugars. A typical temperature range for a detergent wash is between 140°F and 180°F (60°C and 82°C). The graph in Figure 2 displays the effectiveness of different cleaning temperatures in the removal of wax/petrolatum soil.[1]

As the temperature reaches the melting point of the wax, around 140°F (60°C), the soil is easily removed from the surface. Lower temperatures, from ambient to 140°F (60°C), can be used for the wash phase depending on the soil and cleaning chemistries. Lower-temperature cleaning, if possible, is desirable in order to lower energy consumption and reduce the time spent on preheating the water. Hot rinses following the wash phase can reduce drying time. Overall, optimizing temperatures at every stage of the process may result in shorter cycle times.

Figure 1 (a and b). Typical dirty laboratory glassware

Figure 2 Effect of cleaning temperature

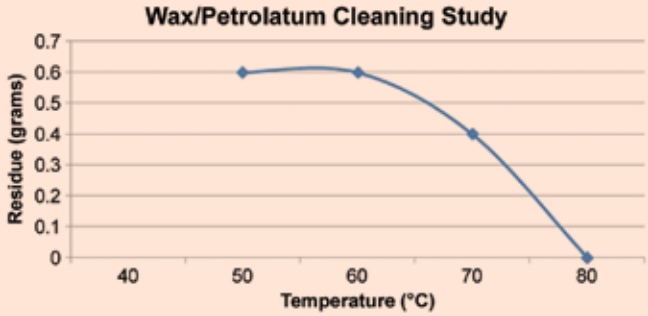
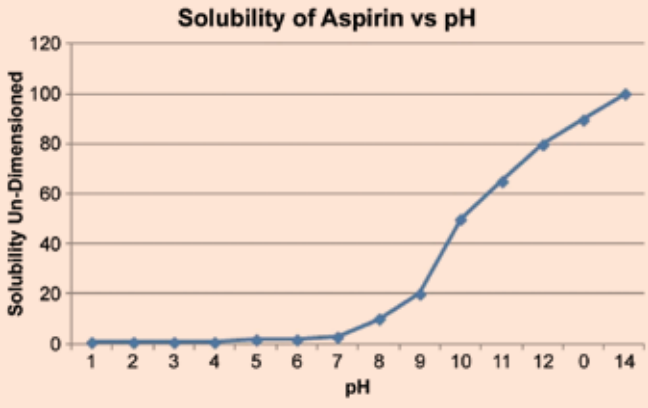


Figure 3 Effect of pH on solubility



Mechanical (Action)

Action or force applied to the surface through a dynamic spray device, such as a revolving spray arm or fixed spray devices such as a spindle, will help dislodge residues mainly through direct impingement and cascading flow. Monitoring the pressure from the recirculation pump to the spray devices ensures consistent operation. Routine inspection of the spray devices and spindles is important to ensure that they are free from debris. Cleaning items such as tubing and hoses requires flow velocity of about 1.5 m/s to ensure turbulence along the inner diameter and prevent air entrapment.[2]

Chemistry

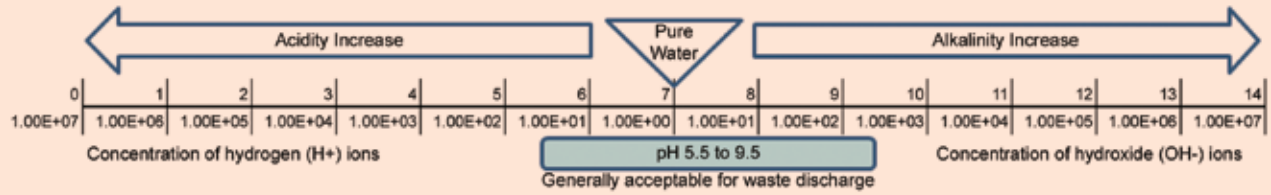
Several properties of cleaning agents can be manipulated in formulations in order to improve efficacy. The pH of a solution is an important chemical property that can influence the solubility of the soil in the cleaning agent. Figure 3 displays the solubility of aspirin; as the pH increases, the solubility drastically increases.[3] It is also important to assess material compatibility to avoid deterioration of the items being cleaned.

The pH scale ranges from 0 to 14, with 0 being the most acid and 14 being the most alkaline. A pH of 7 is a true neutral. As a side note, a pH range from 5.5 to 9.5 is generally acceptable for waste discharged; however, you should confirm with local municipal discharge regulations.4 The pH scale is logarithmic, as indicated in Figure 4. Alkaline and acid cleaning agents (high and low pH cleaning agents) can break soil down into smaller, more reactive components through hydrolysis. These smaller components are then more susceptible to other cleaning mechanisms present, such as solubility.

To continue with chemistry properties of cleaning agents, the role of surfactants in formulated cleaning agents needs to be discussed. Surfactants can improve many functions of cleaning, such as the wetting characteristics of the cleaning agent. Surfactants reduce the surface tension of liquids, which helps in displacing particles, penetrating soil, and addressing irregularities on target surfaces. If the cleaning agent cannot come into contact with the soil, then it is not going to be effective at removing the residue to acceptable limits. Figure 5 displays the impact of reducing the surface tension with surfactants.

The droplet on the left contains no surfactant, and the water beads on the surface. The images in the middle and to the right contain different surfactants and display different wetting and better coverage of the droplet to the surface. Surfactants also contain hydrophobic and hydrophilic ends, which bind and trap water-insoluble residues in micelles or bubbles, known as “emulsification.” Dispersants can also be added to cleaning agents to prevent the aggregation of particles. Chelating agents help bind and break down inorganic components within the soil that may interfere with the role of surfactants or other components within the cleaning-agent formulation. Figure 6 illustrates wetting properties of surfactants within the cleaning-agent formulation.[5]

Figure 4 pH Scale



The brown circles are soil within a groove of an irregular surface. The water, as depicted by the dotted line, is not able to wet or penetrate the groove on the surface, so the soil is not in contact with water; therefore, the residue is going to be more difficult to clean. The cleaning agent with surfactant wets more of the surface irregularities and will be more efficient at cleaning this soil.

Coverage

One of the most critical principles is coverage. Despite using the best cleaning chemistry and optimum cleaning temperature, if the cleaning chemistry doesn't come in contact with the soil, then the soil will not be removed and subsequently rinsed from the surface. Coverage is very important, and it can lead to consistent cleaning performance or consistent failures in automated cleaning. The cleaning chemistry should reach all internal and external surfaces. Items of concern may be those with small openings, cannulated items, and hoses. Understanding the items to be cleaned and the load configuration within the washer is an important part of standardizing the loading configuration and ensuring coverage. Sophisticated accessories and/or customized rack design are available to eliminate coverage issues. Riboflavin, or vitamin D, can be prepared in water at 0.2 grams/liter and applied to the surface, inspected with an ultraviolet (UV) light (at 565 nm) and then rinsed off the surface and re-inspected with the UV light to highlight areas with coverage issues.[1] The roughness and material of the surface to be cleaned can also influence coverage.

Time

Similar to the cleaning parameter of temperature, time can apply to the pre-wash, wash, post-wash rinse, second wash, post-second-wash rinses, final rinse, and dry time of an automated wash cycle. The length of time may be based on the amount of soil, the condition of the soil, and temperature. Generally, increasing temperature of the wash step allows for reducing cleaning time. Increasing cleaning concentration (still within the recommended use dilution) can also reduce cleaning time. General recommendations or rules are a one- to two-minute pre-rinse, followed by a five- to 10-minute wash and then one-minute rinses. Process analytical technology tools, such as conductivity and total organic carbon (TOC) (maybe even Ultra High Performance Liquid Chromatography, or UHPLC),[6] can be incorporated in-line or off-line for continuous monitoring of the final rinse to complete the cycle.[7]

Washing Functions

A typical washing cycle includes five phases: pre-wash, wash, rinse, final rinse, and drying. Each of these phases will have an effect on the overall cleaning results. The following are some of the parameters that must be considered to ensure the optimal performance of a washing system.

Pre-Wash

This is the first cycle phase and allows for removing the soil. For this phase, using lower-quality water is generally acceptable, which can help reduce operating costs. City water is commonly used; pure water is not required for this treatment. The idea here is to allow for the water to saturate the soil, which can typically be achieved in one minute or so. It is recommended to use cold or ambient-temperature water to prevent protein-based soils from being baked on surfaces, warm water for mineral-based soils, and very hot water for fats, oils, and greases.

Wash

The next step is called the wash phase. It is intended to thoroughly remove all remaining dirt particles on processed items. During this phase, a predefined amount of detergent is automatically injected into the washer chamber. Typical water temperature ranges from 140°F to 180°F (60°C to 82°C), while optimum cleaning results can be obtained at 150°F to 160°F (65°C to 71°C). It is important to select the right water temperature for the detergents in use in order to ensure that the detergents release their active ingredients and reach their optimal cleaning efficacy. Time and cleaning agent concentration are often adjusted based on the temperature and nature of the soil. Five to 10 minutes is typically enough to achieve acceptable cleaning results.

Rinse

The rinse phase follows the wash phase. At this stage, there should be no soil remaining on the parts. The rinse phase essentially allows for the removal of detergent residues. It is generally not necessary to use very hot water for this phase, unless sanitization at high temperature is required. When water is supplied to the washer at a lower temperature, rinsing at high temperature can increase the overall cycle time since a few minutes are usually required for the washer sump heating coils to heat up the water to the set point. It may not be necessary to use very high-quality

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water for this phase, and one or two rinses of one to two minutes each are typically sufficient to obtain the desired results. Since the water used for the rinse phase is recirculated in the chamber, longer rinses would simply redeposit residues on the load items. Extending the rinse time generally does not improve rinsing efficacy since the same "dirty" water is recirculated for the set time before being drained. A better approach consists of repeating the rinse phase using fresh water.

Final Rinse

This phase removes all remaining residues and is usually performed at a higher temperature to accelerate the subsequent drying phase. High-quality water, such as reverse osmosis (RO) or Water for Injection (WFI), is often used for this phase. The pure water is typically heated to around 122°F (50°C) and sprayed on the load items, preventing spotting and stains on glassware and parts. In most cases, one or two rinses are sufficient to remove all remaining detergent residues. At this stage, single-pass rinses are preferred over recirculated rinses because this method has the advantage of reducing the level of residues more rapidly than the usual recirculated rinsing. With this option, residues that are removed from the surface of load items are not redeposited on the glassware or parts because a continuous flow of fresh water is distributed inside and outside the items. It is always a good practice to measure the final rinse water quality using standard online conductivity or TOC monitoring systems. These process analytical technology (PAT) tools can help to achieve Quality by Design (QbD) goals and provide ongoing assurance over the life cycle of the cleaning process.[7]

Drying

The last phase consists of drying load items. It eliminates moisture on the load, chamber, accessories, and piping. The air temperature can reach up to 240°F (115°C) but may be limited to lower levels for heat-sensitive items such as plastic ware. It is important to force the air inside components to accelerate drying and position items to facilitate draining. Standing water or pooling is drying's worst enemy so it is critical that items be properly positioned on the loading rack.

Common Mistakes

The following is a list of common mistakes that result from a lack of understanding of the principles described above, a description of the outcomes, and ideas/suggestions as to how these mistakes can be avoided.

Figure 5 Effect of surfactants

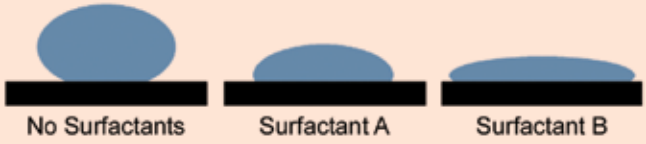
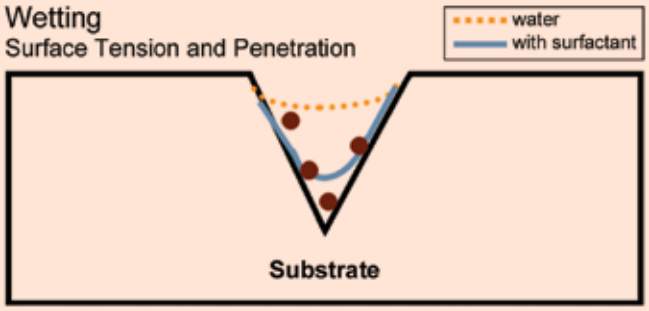


Figure 6 Effect of surfactants



Mistakes:

1. ***Using hot water in the pre-wash phase to clean protein-based soil.***
   Result: Soil is cooked on surfaces, making it more difficult to remove during the subsequent wash phase.
   Solution: Select cold water for the pre-wash phase.

2. ***Using cold or hot tap water in the wash phase to clean oily or grease/fat-type soils.***
   Result: Soil is not removed from surfaces, or an extremely long cycle time is required.
   Solution: Select very hot water for the pre-wash and wash phases.

3. ***Washing with a water temperature that is outside of the operating range of the chemicals being used.***
   Result: Soil is not removed from surfaces, or an extremely long cycle time is required.
   Solution: Check the operating range on chemical container labels and adjust the temperature accordingly.

4. ***Performing the final rinse with cold water.***
   Result: A very long drying time is required.
   Solution: Adjust the temperature of the final rinse phase as high as possible.

5. ***Using chemical(s) with the wrong pH.***
Result: A very long wash time or improper cleaning.
Solution: Use alkaline chemicals for protein and organic soils and acidic chemicals for inorganic, mineral-based soils.

6. ***Using acidic or alkaline detergents to clean aluminum containers or pH-sensitive load items.***
Result: Containers or load items will degrade/deteriorate rapidly.
Solution: Use neutral pH chemistry for these types of materials.

7. ***Trying to clean heavily soiled and dried load items with a low detergent concentration.***
Result: Wash time may have to be significantly extended.
Solution: Increase the detergent concentration until a reasonable result/time ratio is reached.

8. ***Using chemistries that create foam in the chamber.***
Result: Foam creates cavitation in the pump, resulting in lower pressure and possible damage to the pump. The presence of foam can also increase the volume of rinse water needed as well as cause issues with sensors and probe readings.
Solution: Use chemicals and wash temperatures recommended by the manufacturer or non-foaming detergents.

9. ***Setting long time for rinse phases.***
Result: A longer total cycle time.
Solution: If rinse water is recirculated, increasing time does not improve rinsing efficiency. It is recommended to shorten the rinse time and add rinse phases if required.

10. ***Setting high temperature for all rinse phases.***
Result: A longer total cycle time.
Solution: Higher temperatures do not typically improve rinsing efficacy. Reducing the temperature shortens rinse phases and reduces the stress on equipment. However, the final rinse should be heated to accelerate drying. There may be a need for achieving some level of thermal disinfection, for example: cages in the laboratory animal research industry.[8] In this case, heating only the last rinse phase is a common practice.

11. ***Using low-quality water for all phases.***
Result: Poor cleaning performance, spotting due to mineral deposits, higher detergent usage
Solution:

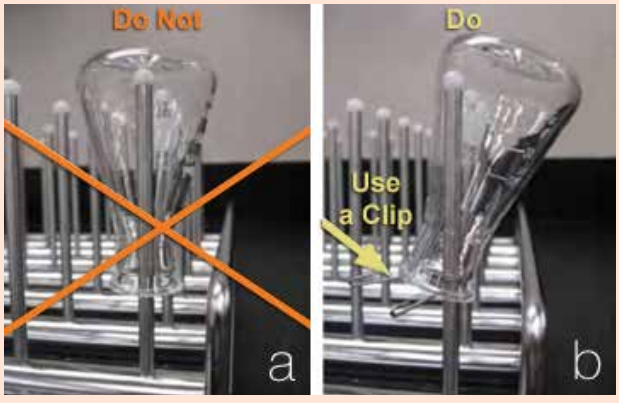
- Follow the washer supplier's recommendations for water quality.
- Adjust detergent concentration based on water hardness. Hard water is likely to require a higher concentration of chemicals to achieve acceptable results.

Figure 7 Example of the washer manufacturer's recommendation chart

Glassware Processing Capacity

Accessory	Volumetric Flasks	Erlenmeyer Flasks	Graduated Cylinders	Beakers	Carboys and Bottles
M-2 Spindle Header	500 ml to 2,000 ml	500 ml to 6,000 ml	500 ml to 2,000 ml	---	4 L to 20 L
M-5 Spindle Header	500 ml to 2,000 ml	500 ml to 6,000 ml	500 ml to 2,000 ml	---	500 ml to 20 L
M-8 Spindle Header	500 ml to 2,000 ml	500 ml to 1,500 ml	250 ml to 2,000 ml	---	500 ml to 4 L
M-18 Spindle Header	10 ml to 250 ml	250 ml to 400 ml	50 ml to 100 ml	---	200 ml to 400 ml
M-32 Spindle Header	100 ml to 250 ml	250 ml to 400 ml	50 ml to 100 ml	---	200 ml to 400 ml

Figure 8 (a and b). Examples of laboratory glassware on spindle racks



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- Use mineral-free water, at least for the final rinse phase (RO, deionized, distilled, WFI).
- Incorporate a formulated acid cleaning agent second wash following a post-primary-wash water rinse.

12. Using the wrong accessory for the application.
Result: Inadequate coverage and poor cleaning performance.
Solution: Follow the washer supplier's recommendations for the selection of accessories. See Figure 7 as an example. Perform riboflavin coverage testing to confirm that there is sufficient coverage of the glassware and parts.

13. Positioning load items incorrectly.
Result: Inadequate coverage and poor cleaning performance.
Solution: Follow the washer supplier's recommendations for the positioning of components on accessories. See examples in figures 8 and 9. Perform riboflavin coverage testing to confirm that there is sufficient coverage of the glassware and parts.

14. Overloading baskets and accessories.
Result: Limited coverage will produce inconsistent cleaning results. (See Figure 10.)
Solution: Avoid overloading, position items to prevent overlap, and run more cycles if necessary.

Conclusion

Mistakes can be avoided by understanding and applying basic principles of cleaning, by following the manufacturer's recommendations for loading items to be processed and by ensuring that equipment is properly maintained. The effectiveness of the automated cleaning of laboratory glassware, animal cages and racks, and components used in the drug manufacturing process is very much influenced by the cleaning parameters used: temperature, mechanical (action), chemistry, coverage, time, and factors such as the nature and condition of the soil (TACCTS). Setting these parameters properly will ensure consistent cleaning results, increase productivity, and lower operation and maintenance costs.

Figure 9 Examples of fully loaded wash rack

Figure 10 Example of poorly loaded basket

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ONLINE WATER BIOBURDEN ANALYZERS: A CASE STUDY FOR THE EXTENSION OF PURIFIED WATER HOLD TIMES

Members of the Online Water Bioburden Analyzer (OBWA) Work Group

This article presents the use of online water bioburden analyzers, a biological auto-fluorescence enhanced particle counter, to continuously monitor a pharmaceutical purified water system. We describe the applications and business benefits of this new class of water analyzers.

Introduction

Continued development and implementation of an online water bioburden analyzer (OWBA) offers the potential to improve the management of the pharmaceutical water system, and reduce costs, through a better understanding of water quality.

The installation of a system provides a reduction in compendial water testing and improved process control. The overall concept of an OWBA is comparable to an online total organic carbon (TOC) system, i.e., an online analyzer that provides real-time bioburden monitoring data and instantaneous process control feedback capability. The OWBA can be seen as a risk-reduction tool, providing business benefits through the following measures:

- **Labor Reduction (Resource Allocations)**
  - Decreased frequency of sampling and laboratory-based testing
  - System optimization
- **Product Quality and Process Understanding**
  - Reduced bioburden investigations related to water system excursions
  - Increased process understanding and product safety through real-time monitoring
  - Improved responsiveness to microbiological excursions
  - Increased confidence in water release from higher-level monitoring
- **Energy Savings**
  - Less-frequent heat sanitization cycles through continuous verification of system performance
  - Reduced operating temperatures of hot-water systems

The OWBA Work Group Focus

In an effort to accelerate the implementation of an OWBA, a collaborative work group was formed comprising representatives from several companies within the pharmaceutical/biopharmaceutical industry. By leveraging lessons learned through the assessment and implementation of various rapid microbiological methods (RMM) and process analytical technologies (PAT) across the healthcare and consumer-products industries, the primary goal of this work group is to provide guidance regarding the development and application of OWBA systems that would be broadly accepted by the industry and regulators.

The implementation lessons of an OWBA are shared from the experiences of the work-group members. The implementation of the OWBA at a manufacturing site should involve a feasibility study to compare microbial levels, as measured by traditional colony forming units (CFU), to the online measured auto-fluorescence unit (AFU) of the OWBA. The challenges of correlating the CFU with the AFU are daunting as the majority of microorganisms in our environment are not culturable and, therefore, undetectable with traditional plate-count methods; however, such comparisons provide an understanding of the technology and aid in the definition of control levels for the AFU measured by the OWBA. It is unreasonable to expect an exact agreement of the AFU and CFU given that the targets of detection for each technology are very different. In fact, the AFU, being based on molecular detection, may result in a higher numberical value when directly compared to the CFU, which is dependent on the observation of microorganisms' growth. A higher AFU number does not mean that the water system is out of control; nor does it imply that there is more risk for contamination.

Purified water systems that show periodic counts can provide a practical demonstration of the ability of OWBA systems to monitor and detect microbial contamination levels. However, a resulting AFU may not correlate directly with growth identified within traditional water system monitoring; this can result in a shift in the organizational understanding of the definition of alternative alert and action levels.

Green Initiatives

Environmental awareness is becoming more common in pharmaceutical companies. Energy usage of HVAC, heat (steam), and water systems is the second-largest cost (after labor costs) for many facilities. The duration, frequency, and effectiveness of heat- and chemical-sanitization cycles of a water system are based on historical monitoring data and system validation. Based on the large amount of additional data generated by an OBWA, sanitization cycles could be optimized and operating temperatures reduced, resulting in significant energy savings. Furthermore, the water hold times for storage tanks may be extended based on continuous bioburden monitoring, resulting in water and energy cost savings.

Extended water hold times based on measured water quality rather than demonstrated hold times has the opportunity to impact both the dumping of usable water as well as decreased energy costs associated with water manufacturing. For a Midwest

manufacturing facility, the production costs for purified water and Water for Injection (WFI) are $160 per 10,000 l and $350 per 10,000 l, respectively; this is a conservative estimate for the generation of pharmaceutical waters. The validated hold time at the facility is four days for a 9,000 l purified water system. The annual cost for water generation for a smaller loop is more than $13,000; increasing the hold time by two days would result in a 30-percent yearly savings for water generation.

Purified Water Hold Time Case Study

Pharmaceutical-grade water, both purified and WFI, is the largest raw material in the pharmaceutical industry, and a large amount of water that is prepared is never used as it is held up to the validated hold time. The hold times are created using a conservative risk assessment based on historical or limited data sets rather than process understanding. The OWBA has provided the opportunity to continuously sample water loops and demonstrate that the water system is in a state of control.

The purified water system that was evaluated for this experiment had a validated hold time of four days; there was a need to extend the hold time to seven days to support a water system upgrade. This would avoid the cost of having to stop production or bring in purified water by truck. The testing protocol was to monitor the water system with an OWBA (Instant BioScan RMS ON-90) continuously for seven days and confirm the results with laboratory sampling.

Data Handling

One of the unexpected challenges was the large amount of data the shift to online data from single daily sampling. The RMS ON-90 has a sample flow rate of 30 ml/minute and is set up to generate a data point every 3.3 minutes based on a 100 ml volume. This results in more than 400 data points daily, with periodic variations each day. Rather than attempt to compare large data sets to a single point, it was determined that setting a threshold based on routine operation would provide a baseline understanding of the water system that could be compared to the hold time study. The baseline measurement was determined as 178 AFU, based on the highest value of the daily average counts plus three times the standard deviation on monitoring prior to the hold time study. (See Figure 1.)

Figure1 **Twenty-four hour monitoring of the purified water prior to the hold time study. The large peak at 1,500 to 1,600 hours represents the daily heat sanitization for the water loop. The heat sanitization was not used during the hold time study.**

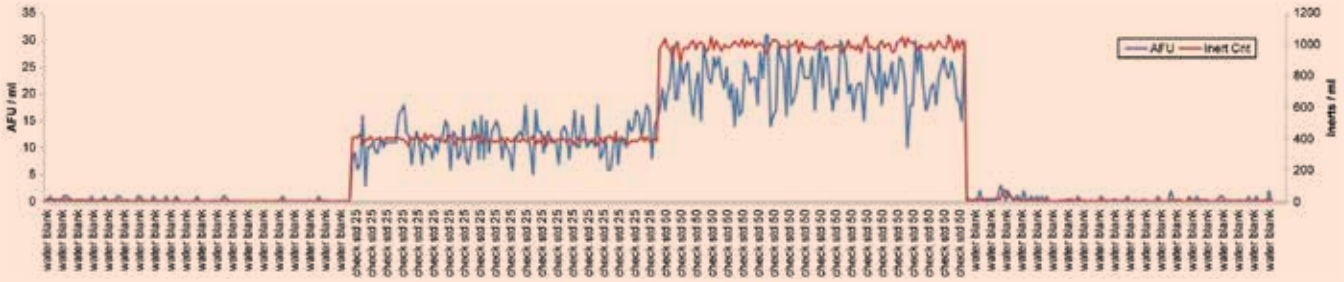

Table A **Daily averages and online water limits of the ON-90 and the laboratory sample results for comparison. The water system was within acceptance limits for the seven-day hold time.**

	Online Water Monitor		Laboratory Based Testing	
Day	**Average AFU/100 ml** (n = 434 data points)	**Daily Variation (Average + 3 Standard Deviations)**	**Laboratory Assay CFU / 100 ml**	**Within Limits** (Target < 600 CFU/100 ml)
1	1.2	6	1	Yes
2	1.5	7	0	Yes
3	2.0	9	0	Yes
4	1.9	9	0	Yes
5	3.4	16	3	Yes
6	2.0	11	2	Yes
7	1.4	12	0	Yes

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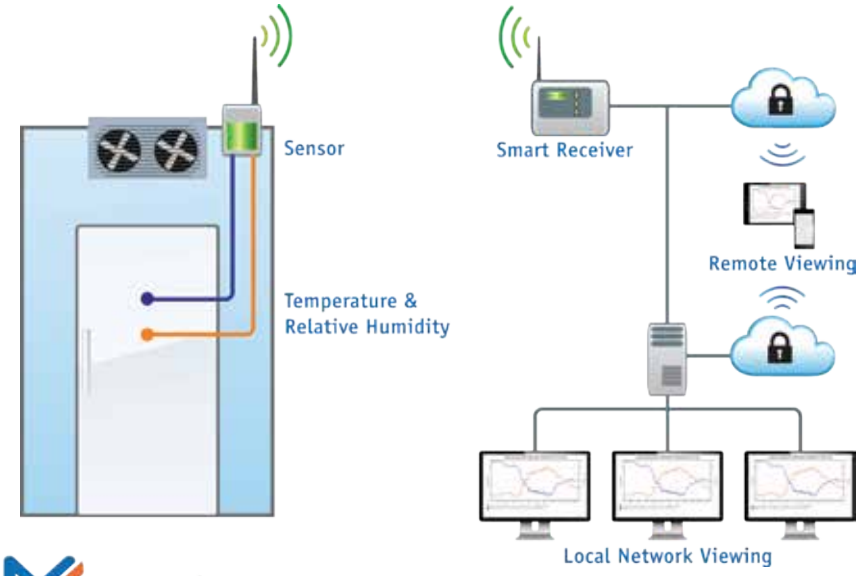

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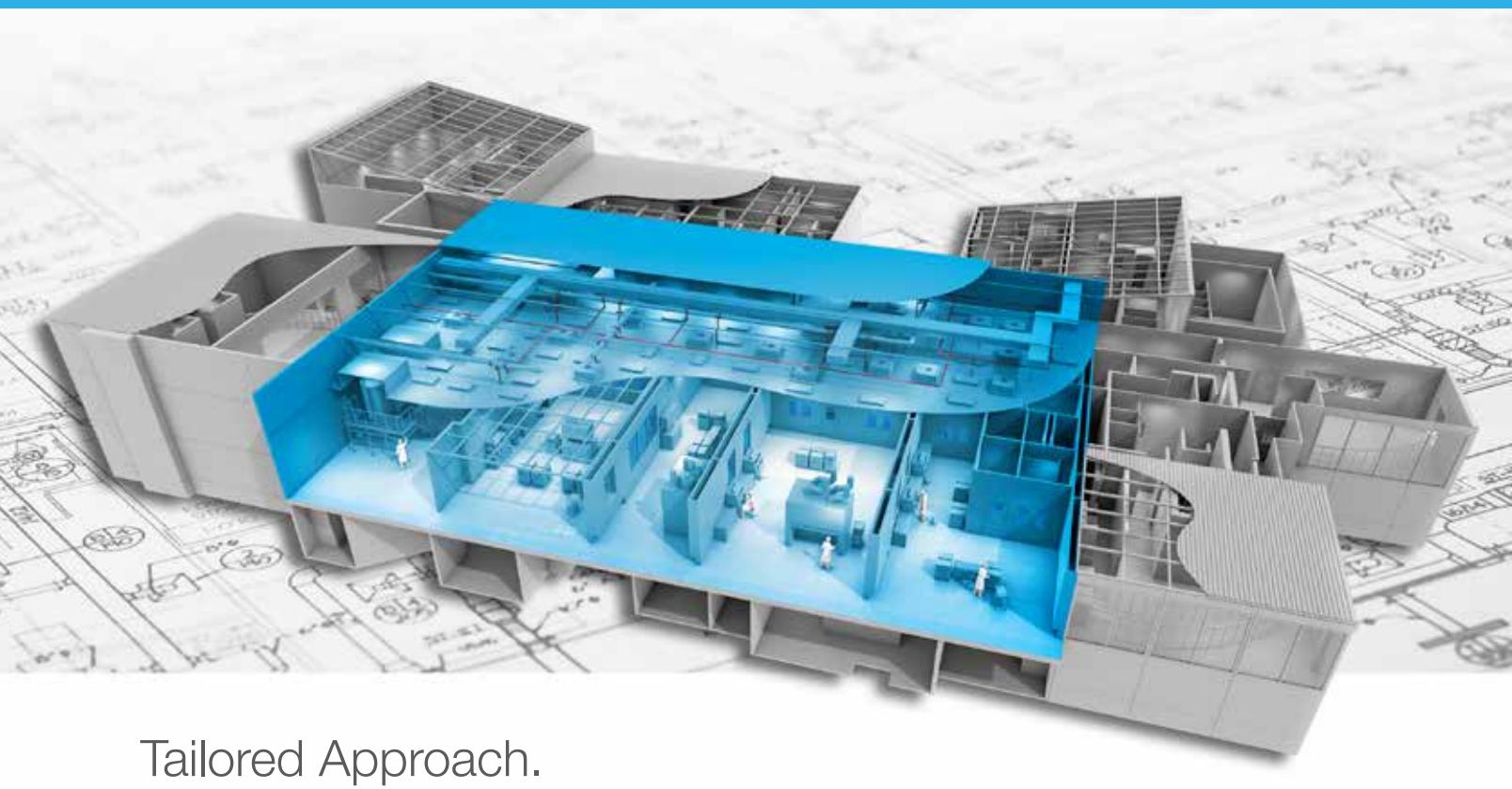

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Results

The results of the seven-day experiment demonstrate that the water system was not impacted by the extended hold times and did not exceed the AFU established during the validated cycle time. The purified water system maintained control during the hold study; there was no loss of control of the during the seven-day study, which provided confidence that no loss of control of the water system occurred. The results of the hold study can be found in Table A.

There were some observations made during the execution of this study that warrant further discussion: The daily heat sanitization of the water loop caused a large increase in the AFU counts; there is debate about whether this was due to microbubbles that formed as the water cooled in the transfer line or an increase in the number of dislodged biofilm/metallic plastic particles during the sanitization cycle. (See Figure 1.)

OWBA System Suitability Demonstration

The need to provide periodic suitability testing with check standards was performed manually using a commercially available fluorescent bead. The challenge of preparing very low particle solutions was mitigated by preparing check standards at higher levels. Bead solutions at approximately 25 and 50 AFU/ml were prepared using 18 M-Ohm water and introduced using the sample mode were performed; the results can be found in Table B and Figure 2.

Another observation is the transient spikes observed in the data; there is no assignable cause for the variation in the data. There was no verifiable pattern to the frequency or intensity of the spikes and no correlation to either the laboratory grab samples or the water system operations. The OWBA system used in the study did not have a sample capture device, so further investigation was not possible. This indicates the need to develop a sample capture device that would enable the unit to divert a sample of water for further investigation.

The daily manual sampling of the water system was typically performed midday; spikes in the OWBA system periodically occurred during this time frame as well. As an example, Figure 3 shows a

Figure 2 **One second data sampling graph of the check standards; the blue line is the AFU/ml (left vertical axis) and the red line is the inert/ml (right vertical axis). The data demonstrates the response of the unit and the minimal flush time required for steady state measurement.**

Table B **Results of triplicate measurements of 20 ml samples (60 ml total) with a 10 ml flush.**

Sample ID	AFU/ml	Recovery (%)
Blank	2	---
Check Standard – 25	26	104
Check Standard – 50	38	76

Figure 3 **Day 1: Twenty-four-hour monitoring of the purified water study during the extended hold time study.**

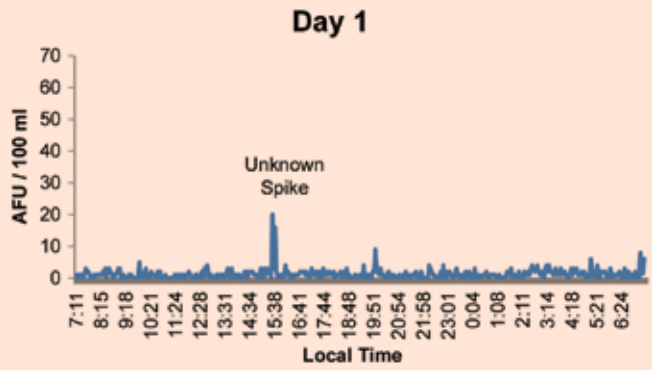

Figure 4 **Day 7: Twenty-four-hour monitoring of the purified water study during the extended hold time study.**

spike of 16 AFU at 15:41 hours, and no CFU were observed in the laboratory-tested samples. Figures 3 and 4 of the online monitoring demonstrate the low level of AFU during monitoring and also the periodic spikes that can occur. There was a coincidental spike on days 1 and 7 at exactly 15:41 hours; no assignable cause could be identified.

Investigating the root cause of each transient spike observed in the large set of data provided by an OWBA is challenging and may have diminishing returns. The power of an OWBA system lies in its ability to capture large amounts of data in real time to be able to differentiate normal from abnormal water system operation. As such, setting appropriate control limits with consideration for transient spikes should be made.

Conclusions

The OWBA provides confidence that the purified water system can successfully monitor a purified water loop for four and seven days providing documented assurance that the water system maintains control and that the water is fit for use. The laboratory testing of the water system for bioburden provides a comparison of the OWBA system data. The large amount of data and very granular reporting provide a high density of data that challenges water system owners interpret data and set control limits; there is a risk of trying to assign cause for transient events or perturbations.

The business benefit for the site to increase its water hold time is $9,000 annually per tank; based on two tanks, the return on investment for the unit is approximately three years.

The OWBA work group continues to drive the development and implementation of the systems across manufacturing facilities. The continued challenge for the implementation of the OWBA is the availability of calibrated standards and sample capture devices.

Members of the OBWA Work Group:

Hans-Joachim Anders (Novartis)
Frederic B. Ayers (Eli Lilly)
Jay Bolden (Eli Lilly)
Deb Gessell-Lee (Baxter)
Joe Johnston (Fresenius)
Neil Lewis (P&G)
Jeanne Mateffy (Amgen)
Cynthia Martindale (Amgen)
Jeffrey Weber (Pfizer)

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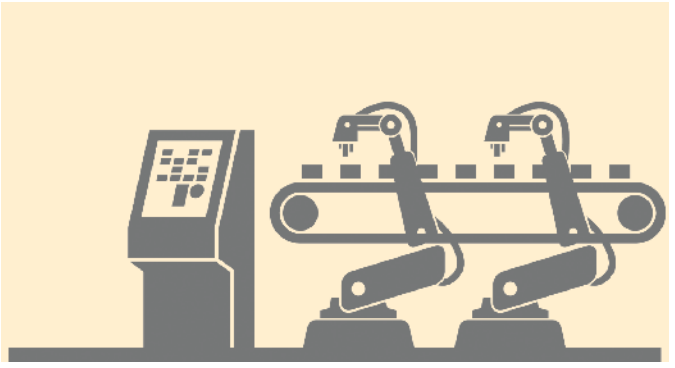
SYMPOSIUM SUMMARY REPORT: USING PROCESS CAPABILITY TO ENHANCE PHARMACEUTICAL PRODUCT QUALITY

Daniel Y. Peng, Arne Zilian, Johna Norton, Martin G. VanTrieste, Jason J. Orloff, Paul Stojanovski, George Millili, Alex Viehmann, Karthik Iyer and Lawrence X. Yu

This report summarizes speaker and audience interplay and the main points of the 2015 IFPAC symposium "Using Process Capability to Enhance Pharmaceutical Product Quality."

The views presented in this article do not necessarily reflect those of the US Food and Drug Administration.



Abstract

The symposium "Using Process Capability to Enhance Pharmaceutical Product Quality" was held on 27 January 2015 during the annual meeting of the 29th International Forum on Process Analytical Chemistry (IFPAC) in Arlington, Virginia. Presentations from both the innovator and generic pharmaceutical industries and the US Food and Drug Administration (FDA) are summarized here, stressing the following main points: (1) drug product specifications (acceptance criteria) should be based on patient needs (safety and efficacy), and process capability should not be used as a tool to drive tighter acceptance criteria; (2) it is important to differentiate what is the acceptable variability and unintended variability, and a risk-based approach commensurate with the risk to the patient should be used to decide appropriate actions if the process capability and/or other tools detect statistical signals and prioritize the continual improvements; (3) case studies, from both the innovator (small molecules and biotechnology) and generic pharmaceutical industries, demonstrate that process capability indices can be used to detect signals early, implement continual improvements, and prevent failure, thereby driving operational excellence and ensuring superior product quality; and (4) the pharmaceutical manufacturing sector needs to shift from a "compliance-driven" mindset and foster a culture of continual improvement and quality-driven principles. This paradigm shift promises to transform the pharmaceutical industry from a tradition of reactive troubleshooting to a new era of proactive failure reduction and prevention.

Introduction

More than 90 professionals from worldwide innovator and generic pharmaceutical companies, academia, and regulatory agencies attended this symposium. The symposium's overarching theme was process capability as a tool to enhance pharmaceutical product quality. The concept of process capability is not new; it was first introduced by the Western Electric Company in the *Statistical Quality Control Handbook* in 1956[1] and has been used in many industry sectors.[2] The process capability index compares the variability of a process quality measure against product specification limits (acceptance criteria) and to ascertain if the process is stable and capable. The speakers shared case studies, practical experiences from diverse industrial settings, and the benefits and challenges of using process capability tools tdo improve product quality. This report summarizes speaker and audience interplay, stressing the main points of the symposium and supplementing discussions from the previous IFPAC annual meeting.[3]

Opening Remarks

On behalf of the symposium co-chairs (George Millili, Alex Viehmann, Karthik Iyer, and Lawrence Yu), Daniel Y. Peng, PhD (Quality Assessment Lead, Office of Process and Facility (OPF), Office of Pharmaceutical Quality (OPQ)/CDER/FDA) gave a brief introduction. He used target shooting as an analogy for a pharmaceutical manufacturing process, whereby "precision" describes the spread (variability) of shots that hit some position on the target board and "accuracy" measures the bias of the mean (of shot positions) toward the target center point. It is also important to note that the size of the target board itself is predefined regardless of the shooter's variability. Likewise, as emphasized in International Conference on Harmonisation (ICH) Q6A,[4] the drug product specification (acceptance criteria) should be based on the patient needs (safety and efficacy) and not on the capability of the process. In many cases, pharmaceutical companies are setting the acceptance criteria based on safety and efficacy. However, in the past, some acceptance criteria are set based on the observed variability without consideration for the actual impact on the patient. This practice might unintentionally allow for a manufacturer with poor manufacturing and process controls to have wider acceptance criteria than that of good manufacturers who implement stringent process controls. Peng argued that a more meaningful approach would be for pharmaceutical manufacturing and regulatory scientists to agree on specification limits (acceptance criteria) that are defined by patient needs (safety and efficacy). With such acceptance criteria in place, process capability can be a great tool to transform the pharmaceutical manufacturing sector from

an outdated "compliance-driven" reactive mindset to a proactive approach to reducing and preventing failure.

Detecting and Responding to Unintended Variability

Arne Zilian, PhD (Operational Excellence Platinum Champion, Manufacturing Science and Technology, Technical Operations, Novartis Pharma AG, Basel, Switzerland) addressed the need to detect and respond to unintended variability. In transitioning from development into routine commercial manufacturing, the process is likely to encounter additional sources of variation that were not previously detected or encountered. It is important to appreciate that some variability will be acceptable if the variability has negligible impact on patient safety and/or drug product efficacy. On the other hand, continual improvement activities should be prioritized to address unintended variability that can affect patient safety and/or drug product efficacy. Zilian emphasized the inevitable need to balance between overreaction to individual events and the failure to detect unintended variability.[5,6] He then shared a case study to demonstrate how the risk of failure is evaluated based on process capability and an understanding of the variability. Even though the Individual chart (I-chart) (Figure 1) of the product assay detected some special cause variability based on Nelson Rule No. 2 (nine points in a row in a single side of Zone C or beyond),[7] the root cause of the variability was due to the changes in laboratory reference standard. The process capability index is still satisfactory (Cpk = 2.66) (Figure 2). Because there is no immediate concern for product quality, the variability is accepted and there is no need

Figure 1 Individual chart (I-chart) of the product assay

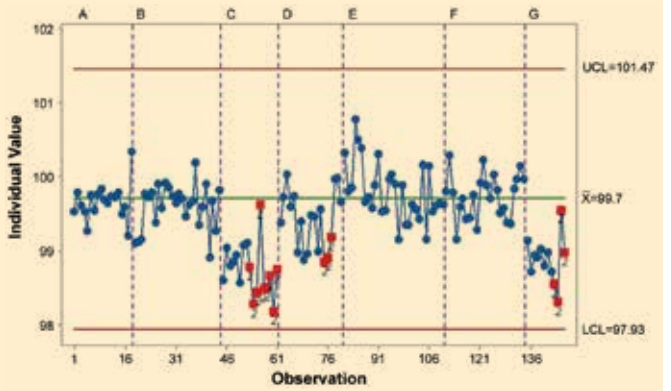
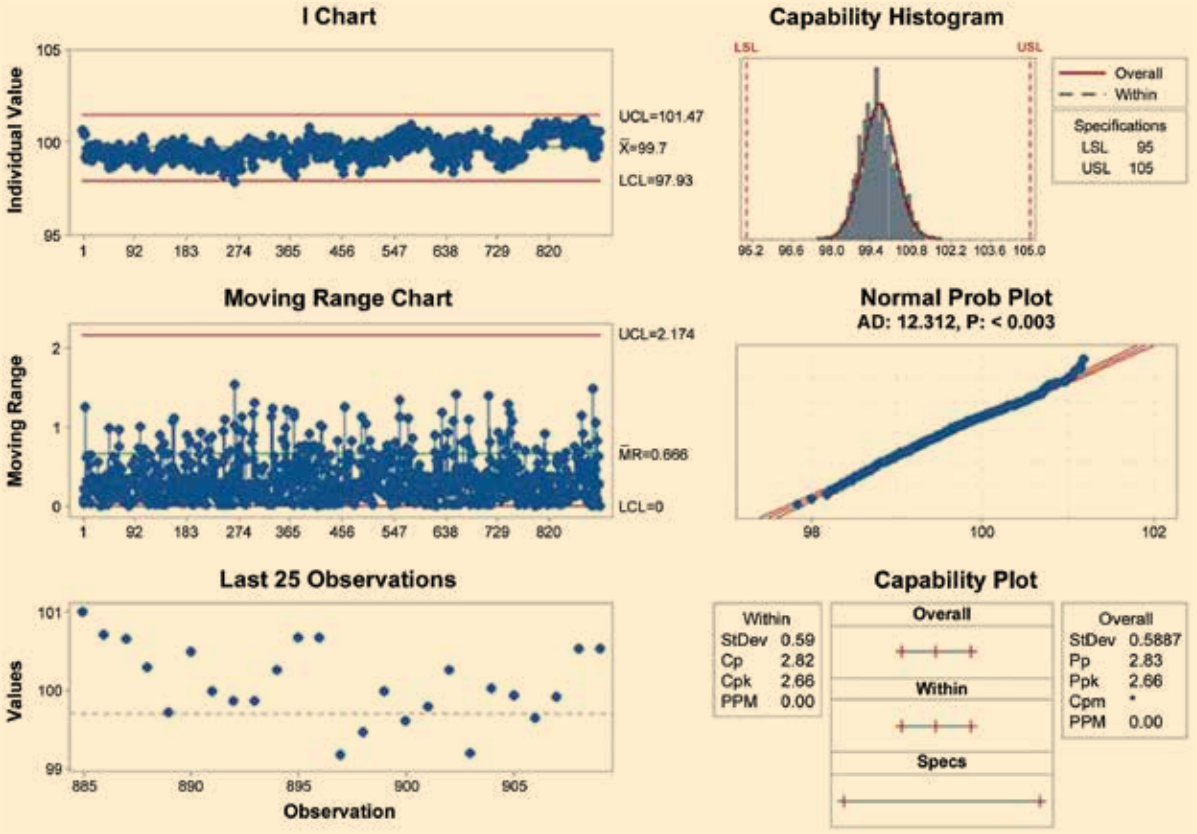


Figure 2 Six-pack process capability analysis of the product assay data



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to respond to the statistical signals in this example. Hypothetically, however, if the excursions are large enough and recurring, investigations, corrective action, and preventive action (CAPA) may be necessary due to the risk to the patient.

Process Capability in 21st-Century Pharmaceutical Manufacturing

Johna Norton (Vice President, Global Quality Assurance, API Manufacturing, Product Research and Development, Eli Lilly and Company, Indianapolis, Indiana) emphasized that reliable product quality is a key focus of 21st-century pharmaceutical manufacturers globally[8], and she discussed Eli Lilly's experiences in achieving robust process capability during commercial manufacture. The key building blocks of achieving this goal include the application of the best available science and technology, combined with effective control and quality systems, and a "continual improvement mindset" to drive robust daily operations. Norton shared several examples of process capability improvements by using product and process performance monitoring tools. Through these proactive failure preventions and continual improvements, the injury rate (to the operators), deviation rate, and backlog were decreased by 40% to 90% and productivity was significantly increased. Norton further discussed some strategies to achieve effective process capability and performance: (1) a culture of scientific excellence and continual improvement; (2) the technical capabilities of people and equipment; (3) management support and expectation; (4) a well-designed and funded IT infrastructure for data analysis and handling; and (5) a quality management system. She concluded that achieving effective process capability will greatly aid to achieve a deep understanding of product and processes and a sustainable supply of quality products because the issues are prevented through the continual improvement efforts.

The Quality Journey – From Good to Great

Martin VanTrieste (Senior Vice President, Quality, Amgen Inc., Thousand Oaks, California) gave a motivational presentation about pharmaceutical manufactures going from "good to great" by focusing on robust designs, robust manufacturing processes, and product quality. He emphasized that firms have to move away from seeing quality as a means of achieving compliance and should instead regard quality as a competitive advantage. He discussed the use of systems to identify, monitor, track, and control unwanted variation using process capabilities. He also shared several case studies, highlighting CAPAs initiated since 2007 to address the product quality attributes with low process capability (< 1.33). At the end of 2013, 74% of 891 parameters were performing at a Six Sigma level, and 21% were performing between Three and Six Sigma levels. The remaining 5% had CAPAs open to continually improve performance. Through this program, the cumulative saving is near $400 million, the product cycle time has been reduced by 64%, and the product scrap rate has been reduced by 92%.

Process Capability – The Balance of Performance and Compliance

Jason J. Orloff (Principal ChE and Statistical Consultant, PharmStat, Madison, Wisconsin) gave a presentation on keeping a balanced perspective between compliance and performance regarding process capability as a continual improvement tool. He first highlighted that wave after wave of quality initiatives from other industries have failed to take root in the pharmaceutical industry, perhaps reflecting that the pharmaceutical industry has its own distinct quality culture. Compared to the high volumes, low risks, and low costs of cellphones, car parts, and computer chips, the pharmaceutical product profile is typified by medium volumes, high costs, and high risks. The pharmaceutical quality culture is a dynamic, self-correcting system that must navigate both compliance and performance. A maximally efficient, agile, and flexible pharmaceutical manufacturing sector could be achieved with minimal regulatory oversight by formalizing systems of performance and ensuring that the balance between compliance and performance is maintained. Process capability is an indicator where compliance and performance may converge. Of course, it is important to note that process capability should not be used as a compliance tool to drive tighter specification; rather, it should be a self-audit tool for continual improvement to achieve "greater performance." Orloff then shared case studies to demonstrate his positions. The process capability of the critical quality attributes (CQAs) of products A and B at plants 1 and 2 were obtained, and the data was used as a tool to rank order the potential risk of product failure. The continual improvement efforts were then prioritized based on risk to the patient. This process capability strategy greatly improves the effectiveness and efficiency of the continual improvement efforts.

Cpk < 1.33…Now What? Process Capability – A Quality Tool

Paul Stojanovski (Vice President, Product and Process Robustness, Global Quality, Teva Pharmaceuticals Toronto, Ontario, Canada) shared the company's experience in using process capability as a quality tool from a commercial quality perspective. In the pharmaceutical industry, process capability is increasingly being used as a proactive monitoring tool for product and process performance and an investigational tool to help determine the root causes of product quality issues. Stojanovski discussed a process flow for actions to be taken when Cpk values are less than 1.33, along with considerations for out-of-trend (OOT) or out-of-specification (OOS) events. Two case studies were presented, one involving assay data for an immediate-release tablet and the other involving dissolution data for an extended-release tablet, to describe data collection, data evaluation, and decision-making processes. Relevant information included the identification of the appropriate CQAs, critical material attributes (CMAs), and critical process parameters (CPPs) in accordance with an understanding of product and process during the product

development stage. The batch data on CQAs are collected from commercial batch manufacturing, and a process capability analysis of CQAs is then performed. Risk mitigation (remediation) and other actions can then be initiated based on the potential impact of the OOT/OOS events and the risk to the patient. The effectiveness of CAPA is verified through continued process verification (CPV). Furthermore, available commercial batch data can be used to link process performance to annual product review and establish a proactive product control system to prevent product failure. The case studies demonstrated continual improvements in process that not only enhanced product quality but also benefited business and, most importantly, patient services.

Using Process Capability to Enhance Pharmaceutical Product Quality

Peng gave an overview of using process capability to enhance pharmaceutical product quality. He introduced the definition for and calculation formula of the four process capability indices according to the ASTM E2281 standard guide[9] and discussed the difference between process capability indices (Cp and Cpk) and process performance indices (Pp and Ppk). He noted that process performance indices account for overall variability in a system and do not presume a state of statistical control. Process performance indices address how a process **has performed** but cannot forecast future batch failure rates. On the other hand, process capability indices only account for inherent variability (noise) associated with a stable process, representing how well a given process **could perform** when all special causes of the observed variability have been eliminated. The difference between Ppk and Cpk indicates the degree to which a process has not reached the statistical control state (stable state) and to which continual improvement opportunities exist. Shewhart control charts are often used to evaluate whether a process reaches a stable state and to estimate the inherent process variability.[3, 10] Peng briefly discussed different types of control charts and used examples to illustrate the applications in monitoring pharmaceutical product CQAs, manufacture site performance, and the corporate level of the overall "culture of quality" associated with pharmaceutical production. In such a culture, product manufacturers take full responsibility for the quality of their products and strive for continual improvement, to achieve "greater performance" such that the compliance with regulatory expectations would naturally follow. Finally, Peng summarized the benefits of using process capability: (1) it considers not only process mean and variability but also these in relation to product specifications (acceptance criteria) that are established based on patient needs (safety and efficacy); (2) it is quantitative and action enabling; (3) it can be applied across sectors (brand, generic, over the counter (OTC), and biotech products); and (4) it requires no additional testing since the commercial batch data are available at the manufacture site per current regulations.

PANEL DISCUSSION

Audience: The calculation of process capability indices is directly related to the width of the specifications (acceptance criteria) and inversely proportional to the process variability. But companies with good processes are nevertheless often asked to tighten specifications. Can the panel comment on this dilemma?

Panel: As several speakers have emphasized, acceptance criteria should be established based on patient safety and efficacy needs, whereas trends in process performance and process capability are useful for identifying continual improvement opportunities. Statistical process control (SPC) tools serve as a pre-alert system allowing for CAPA to take place before the process actually produces OOS products. The Agency acknowledges that, in the past, it was usual and customary to set acceptance criteria based on process capability (the variability observed in the data). This practice unintentionally allowed manufacturers with poor manufacturing and process controls to operate with relatively wider specifications compared to good manufacturing and controls with tighter specifications. Now, under the 21st-century modern pharmaceutical manufacture initiatives, the Agency is taking steps to link quality to patient outcomes, encouraging applicants to use scientific data of safety and efficacy to justify the proposed specifications (acceptance criteria).

Do data have to be normally distributed to use process capability indices?

This question has been discussed frequently and was also discussed in detail at the IFPAC 2014 process capability symposium.3 In general, the answer is "Yes." Data normality is one of the prerequisites for using process capability indices (Cpk) to estimate future batch failure rates. However, when the data are not normally distributed, remedies such as data transformation, distribution fit, or reference interval calculation (also known as the percentile method) can be used. The ISO 21747 guidance document provides further details.[11] It is a good practice to graph raw data (in a histogram, for example) to visualize and probe the distribution curve. There are two other prerequisites for using process capability indices (Cp/Cpk) to forecast future batch failure rates: (1) a sufficient number of the subgroups must be included, and (2) the process must be in a state of statistical control, which means that all special causes of variability have been eliminated from the system.[9]

Will one Cpk number drive unintended consequences?

It is important to understand the three prerequisites for using process capability indices: (1) Is a sufficient number of the subgroups included? 2) Are data normally distributed or can they be

transformed into normal distribution? 3) Is the process in a state of statistical control? Have all special causes been eliminated from the system?

In addition, some measure of the sampling error should be calculated whenever these indices are reported. For example, the lower 95% confidence bound since these statistics give the user some idea of the uncertainty of these indices at a given sample size. A "rational subgroup" may also be important, within which the variations are assumed to be due to common causes only, but the variations between rational subgroups are assumed to be due to special causes. The sampling plan for collecting subgroup observations should be designed to minimize the variation of observations within a subgroup and to maximize variation between subgroups, thereby giving the best chance for the within-subgroup variation to reflect only inherent process variation.7

Furthermore, Cpk is just one part of the overall picture. Product quality should be built on enhanced product and process design, understanding, and control. Operational excellence requires a holistic approach, reflecting a culture of scientific excellence and a mindset of continual improvement and including an efficient and effective quality management system. It is also important to note that the ultimate goal is to achieve high-quality products rather than chase a high Cpk number.

We agree that process capability is a valuable tool; however, can the panel comment on how to get the necessary workload resources and IT support?

Strategic planning and a risk-based approach to prioritizing continual improvement activities are important. Initially, a program can focus on a small list of key products and identify key CQAs. Once a continual improvement project demonstrates the scientific merits and business benefits, further projects can be rationalized so that resources and IT support could follow successful showcase results.

Can we use other tools (Monte Carlo simulation, for example) to estimate probability during development?

Scientists are encouraged to use any scientific tools that can help to achieve successful commercial manufacturing. We understand that, during the early-development stage, material-sparing

approaches can result in limited batch experience. The process in general has not reached the "statistical control" state due to the deliberate changes during formulation, process and analytical method development and optimization. It is highly likely that the formulations, manufacturing processes, equipment, and scale may significantly evolve during different phases of product development. However, it is important to understand and gain estimation whether the designed product and process can approximately achieve the desired target. If the quality attributes obtained from the initially designed product and process are totally off the target, fundamental changes in design may be necessary. Without knowing this, rushing into technology transfer and process qualification could slow down instead of speed up the commercialization process and waste resources. Pharmaceutical scientists should use their scientific discretion to choose appropriate tools (the preliminary process performance index, process capability index, Monte Carlo simulation, or process robustness contour plot, for example) to estimate potential risks and prioritize commercialization efforts.

Summary

Key conclusions from the symposium may be summarized as follows: (1) Drug product specifications (acceptance criteria) should be based on patient needs (safety and efficacy), and process capability should not be used as a compliance tool to drive tighter acceptance criteria. (2) It is important to differentiate between acceptable variability and unintended variability. A risk-based approach should be used to decide appropriate actions if process capability or other tools detect a statistical signal and to prioritize continual improvements. (3) Case studies from both the innovator (small molecules and biotechnology) and generic pharmaceutical industries demonstrate that process capability indices can be a valuable tool for driving operational excellence and ensuring the delivery of superior product quality. Early detection, failure prevention, and continual improvements are essential. (4) We can expect great rewards within the pharmaceutical manufacturing sector as its outdated "compliance" mindset is replaced by a culture that is fully dedicated to product quality.

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Johna Norton is Vice President, Global Quality, for API Manufacturing, Product Research and Development, and Puerto Rico for Eli Lilly and Company. Norton joined Eli Lilly and Company in 1990 as an Analytical Chemist and has subsequently held various positions in quality assurance and quality control (QA/QC) at its facilities in Indiana, Ireland, and Puerto Rico. In 2012, she assumed her current responsibilities for providing quality oversight and direction for the company's API Manufacturing network and the Product Research and Development organization. Norton holds a Bachelor's degree in chemistry and a Master's degree in analytical chemistry.

Martin G. VanTrieste is Senior Vice President, Quality, at Amgen. He is responsible for all aspects of quality assurance, quality control, compliance, operational excellence, and environment, health and safety as well as training. Prior to joining Amgen, VanTrieste was Vice President, Worldwide Quality, for Bayer HealthCare's Biological Products Division and Vice President, Quality Assurance, for the Hospital Products Division at Abbott Laboratories. While at Abbott Laboratories, he held various positions in Quality, Operations, and Research and Development. He started his career at Abbott in 1983 after obtaining his Pharmacy degree from Temple University School of Pharmacy. He has been actively involved with various professional and trade organizations, including United States Pharmacopeia (USP), Pharmaceutical Quality Research Institute (PQRI), Pharmaceutical Research and Manufacturers of America (PhRMA), and AdvaMed, and he is the Chair Elect of the Parenteral Drug Association (PDA). He is the founder and first Chairman of Rx-360 and is currently on its Board of Directors. In 2012, PharmaVoice named VanTrieste one of the 100 most inspiring people in the pharmaceutical industry, calling him "a man with a mission."

Jason J. Orloff is a Principal Statistical Consultant at PharmStat and an international consultant specializing in applied statistics and experimental design for pharmaceutical and biopharmaceutical development, quality assurance, quality control, validation, and production under the CGXPs. He is a contributing author to ISPE's PQLI® *Guide Part 4: Process Performance and Product Quality Monitoring System* and to PDA's Technical Report 59 on "Utilization of Statistical Methods for Production and Business Processes"; he has also written articles for the *Journal of Pharmaceutical Technology*. He has over 10 years' experience in manufacturing, quality, and regulatory affairs in the pharmaceutical industry. Areas of expertise include PAT, OOS, SQC, SPC, assay validation, and setting specification criteria. A chemical engineer with real-life expertise at applying statistics in a highly regulated environment, Orloff is able to work effectively across all levels of an organization as well as make high-level concepts accessible to a variety of audiences. He has worked with a wide variety of companies, including pharmaceuticals, parenterals, biotechnology, fine chemicals, medical devices, food, and nanotechnology. He holds a Bachelor of Science degree in chemical engineering from the University of Wisconsin–Madison and a Master of Science degree in applied statistics from DePaul University.

Paul Stojanovski is Vice President, Process and Product Robustness, for Teva Pharmaceuticals. He graduated with a BS from the University of Toronto as a specialist in chemistry and biochemistry and is a member of the Association of the Chemical Profession of Ontario, Canada. Stojanovski has worked in the pharmaceutical industry for over 25 years in the areas of QC, QA, compliance, and operations, and, more recently, as part of global quality for process and product robustness. His current assignment is to develop and implement a proactive product control system at each of Teva's manufacturing plants.

George Millili, PhD, is currently Senior Principal Technical Advisor at Genentech (a member of the Roche Group) in the Compliance and External Collaboration department, where he is responsible for external collaboration for the Americas. Prior to this position, Millili was Director of Pharmaceutical Commercialization Development at Merck and was responsible for Merck's Technical Operations groups in Latin America and Puerto Rico. Before that, he was Senior Director of Pharmaceutical Technology Services for GPSG, a division of Johnson & Johnson, where he led a group responsible for new product introduction, packaging development, marketed product support, and validation of new and existing technologies. Prior to that, he was Executive Director for Worldwide Manufacturing Technology at Dupont Merck Pharmaceuticals. Millili's areas of interest are product development, scale-up, and technology transfer of pharmaceutical products. He has a Bachelor's degree in pharmacy from Temple University and a Doctorate in pharmaceutics from the Philadelphia College of Pharmacy and Sciences. He has been an active Member of ISPE throughout the years and is currently Chair of the Global PQLI technical committee and a member of several other committees in the association. Millili also recently co-led an industry-wide team that developed and published an ISPE PQLI® Guide on Process Performance and Product Quality Monitoring Systems.

Alex Viehmann is a statistician for the Quality Intelligence Branch in the Office of Surveillance, OPQ/CDER/US FDA. His primary role is to provide statistical support for pre-market review, field investigators, and compliance officers with items related to applied statistics. He is also active in policy development with regard to sampling, test method evaluation, and statistical quality control. Viehmann holds a Bachelor of Science in economics and statistics from the University of Maryland at College Park.

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Lawrence X. Yu, PhD, is Deputy Director, Office of Pharmaceutical Quality (OPQ), US FDA, providing executive leadership and technical direction to a multidisciplinary staff of over 1,000 medical, scientific, and professional support employees engaged in all matters related to the regulation of pharmaceutical quality, including submission review, manufacturing facility assessment, and surveillance of pharmaceutical quality and facility for new, generic, and biotechnology drugs. Yu is a fellow and the past section Chair of the American Association of Pharmaceutical Scientists and an Associate Editor of the *AAPS Journal*. He has authored/co-authored over 130 papers, presented over 100 abstracts, and given over 200 invited presentations. Please address all correspondence about this article to: lawrence.yu@fda.hhs.gov.

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TOBACCO IN THE SERVICE OF PHARMACOLOGY

James Hale and
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For there is nothing either good or bad, but thinking makes it so.

Shakespeare

One of the challenging concepts of Buddhism is that things are inherently empty – devoid of meaning and value – until we invest them with these qualities. We tend to believe that something is true or false, admired or hated, and that these are immutable qualities. Shakespeare echoed this when he had Hamlet say to Rosencrantz, "for there is nothing either good or bad, but thinking makes it so."

But what about tobacco? We could be forgiven for believing that tobacco is the exception that proves the rule – that it is one thing that is universally reviled. How could this plant be anything but bad? Worldwide, one billion people smoke tobacco, lung cancer is, by far, the leading cause of cancer deaths (about 27 percent), 80 percent of which are a direct result of smoking. Many additional cancers of the GI tract can be attributed to smokeless tobacco products. Can any good come from tobacco?

Few plants have been as closely associated with humans and for so long. Leaves of the wild plant were smoked 8,000 years ago. Its cousin, *Nicotiana tabacum*, is one of the oldest plants grown purposely by humans, with evidence of cultivation in Mexico as long ago as 1400 BCE. Columbus came across indigenous people smoking tobacco in Cuba, and Hernández de Boncalo took seeds to Europe in 1559. Nicotine from tobacco was used in the 17th century – and continues to be by some organic farmers – as the first plant-derived pesticide.

Which brings us to beneficial pharmaceutical uses of the plant. Plant-derived nicotine is extracted and purified for use in nicotine replacement therapy to help addicts recover from smoking addiction. But it is biotechnology that is revolutionizing the pharmaceutical industry, and tobacco is poised to contribute.

In 1982, tobacco became the first transgenic plant, when a variety was transformed to antibiotic resistance using *A. tumefaciens*. Since then, transgenic tobacco varieties have been created with traits for pathogen resistance, herbicide tolerance, pest resistance, drought and cold resistance, and bioremediation. Due to these advances in biotechnology, we are now seeing the development of plant-derived monoclonal antibodies (mAbs), complex biologics that provide unparalleled specificity and targeting as pharmaceuticals. These biologics have been used for rheumatoid arthritis, transplant rejection, and some cancers.

Historically, mAbs have been produced using mammalian cell lines. But questions about the ability to scale production in mammalian cells have led to alternative systems, including plant-based manufacturing protocols. Enter, once again, *Nicotiana*.

Plant expression systems have the advantage of being more adaptable, quicker to develop, and less expensive to scale up than their mammalian counterparts. Production can take as little as eight weeks. To date, only one biopharmaceutical extracted from a transgenic plant has been approved – Elelyso (Pfizer and Protalix), for the treatment of Gaucher's disease – though many more are in the pipeline, including drugs such as PlantForm's biosimilar Herceptin®, an mAb extracted from transgenic tobacco plants for use in the treatment of breast cancer. Other tobacco-based biologics are being tested for use in emergency situations, including infection with HIV, West Nile virus, and Ebola.

Ebola, as we saw last year, is an interesting case for the pharmaceutical industry. The 2014 outbreak in West Africa highlighted how ill prepared we are for such an epidemic. With neither vaccine nor other tested treatment available at the time (rVSV-ZEBOV is currently being tested by Merck), health authorities turned to experimental drugs. One of these, ZMapp, is a biologic cocktail (developed by Mapp Biopharmaceutical from research it conducted with the Public Health Agency of Canada, Kentucky BioProcessing, and the National Institute of Allergy and Infectious Disease) designed to provide passive immunity against the Ebola virus. It consists of three human-mouse chimeric mAbs synthesized in Nicotiana benthamiana by Kentucky BioProcessing, a Reynolds America subsidiary. Of the ten Ebola patients treated with ZMapp eight survived. There were only that many doses because, at this point, it takes 6,000 pounds of tobacco to make even a few dozen doses. To scale this in anticipation of a future epidemic, more research and development is needed.

It may be that tobacco, so long a public health menace, may soon be a source of life-saving biopharmaceuticals. ◂

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