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Sustainable Manufacturing

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ISPE 2017 Article of the Year

An Interview with GSK's Roger Connor

Conference Highlights: ISPE Europe Pharma 4.0

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SUSTAINABILITY AND THE WAY FORWARD

Anna Maria di Giorgio
Editor in Chief

This issue highlights a variety of voices and points of view on matters ranging from sustainability to serialization, Pharma 4.0 to viral contamination, and EMA's new location to game theory.

In our cover story, Scott Fotheringham, PhD, interviews industry insiders to get their take on the sustainable use and reuse of water in pharmaceutical manufacturing plants.

Our editorials continue to provide food for thought: Board Chair Tim Howard reflects on achievements during the first quarter of 2018, International YP Chair Caroline Rocks shares her experiences with travel as professional development, and Pharmaceutical Engineering Committee (PEC) member Nissan Cohen argues for zero liquid discharge and a sustainable approach to water wastage and effluents in biopharmaceutical production.

Our first feature is the 2017 Roger F. Sherwood Article of the Year Award, "A Holistic Production Model: From Industry 4.0 to Pharma 4.0," from the July-August 2017 issue of this magazine. The article is the first in the award's history in which the judges' decision was unanimous. This speaks to the strategic thinking showcased in the article: equal parts innovation, pragmatism, and measurable goals. Heartfelt congratulations to the authors: Prof. Dr. Cristoph Herwig, Christian Wölbeling, and Thomas Zimmer, PhD.

Our second feature is my interview with Roger Connor, President, Global Manufacturing Supply, GlaxoSmithKline, whose keynote at ISPE's 2017 Annual Meeting & Expo made the case for bringing "outsiders" into pharma to jump-start innovative thinking in manufacturing. Jim Breen adds a sidebar about "embracing innovation" and why building facilities of the future is the only way forward.

Technical articles run the gamut from regulatory compliance to product development. Arjun Guha Thakurta presents a case study on India's experience with serialization; Brent Harrington and his team discuss the analytical target profile; Thomas R. Spearman and Daniel C. Carroll evaluate terminal HEPA filter maintenance programs in parenteral manufacturing plants; and Anne Stokes, PhD, discusses a risk-managed approach for managing potential virus and TSE contamination in cGMP biopharmaceutical facilities.

Risk-taking, original thinking, and solid technical information abound in this issue; I hope you find its articles relevant to the work you do. We aim to please, but if you have a differing point of view, let us know. We want to pursue conversations, even the difficult ones, in the pages of *Pharmaceutical Engineering.*

And here is one such conversation, albeit one-sided: This is my last issue as Editor in Chief, and I would like to say thank you to the members of the Pharmaceutical Engineering Committee and the legion of collaborators, authors, and reviewers who have helped make *Pharmaceutical Engineering* the standout magazine it is today. I have learned a great deal from each of you, and I don't think I have ever met a more passionate group of engineers, or one whose members contribute so much time to supporting one another as well as the industry. I bow my head to you all. ‹›

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Pharmaceutical Engineering inspires engineers and regulators around the world with engaging and useful articles. From technical articles that provide practical how-to advice to thought-provoking features on current issues, *Pharmaceutical Engineering* offers readers a global picture of the profession and the industry.

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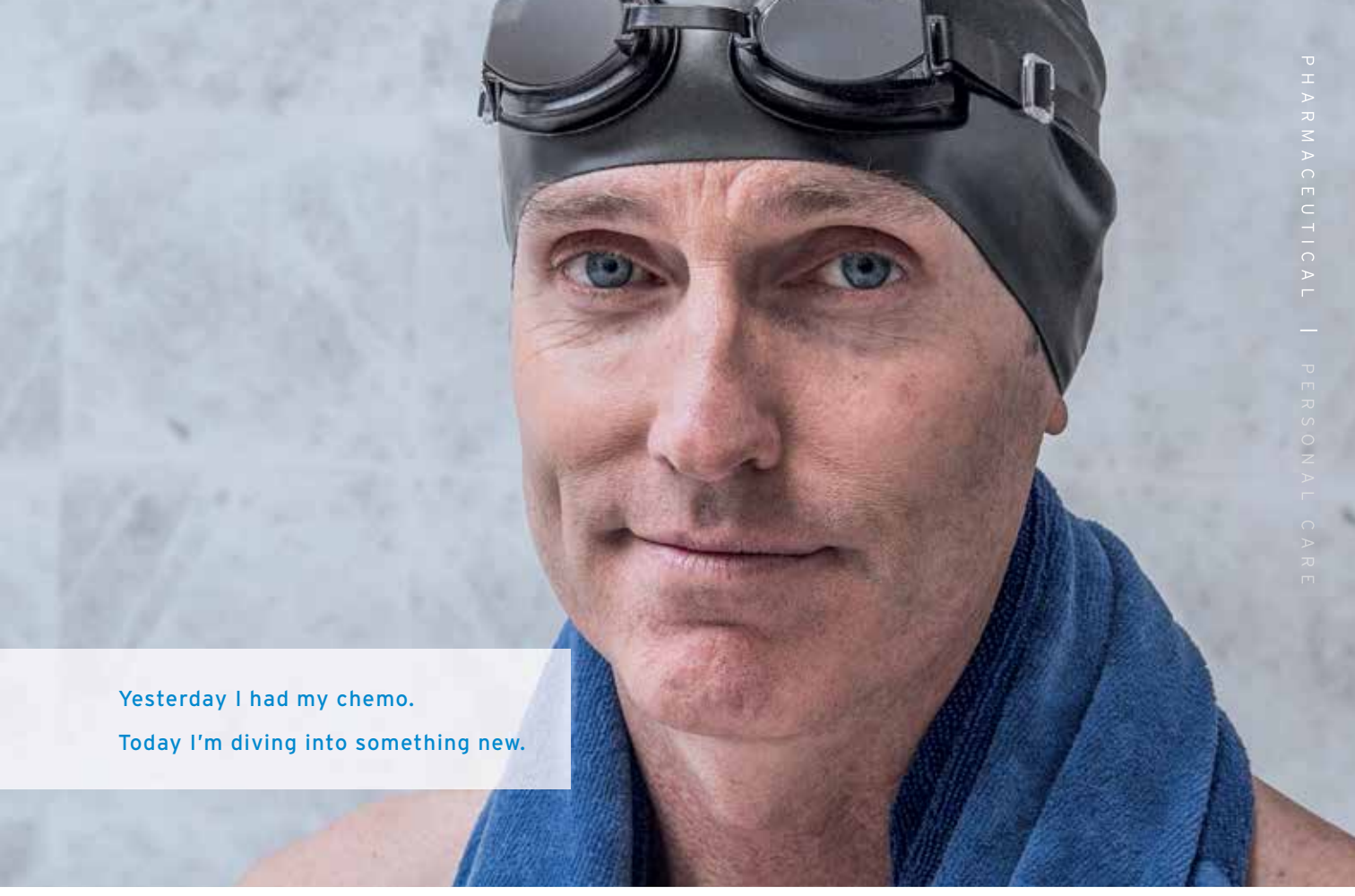
Pharmaceutical Engineering welcomes readers' comments. Letters must include the writer's full name, address, organization, and years of ISPE membership. If published, letters may be edited for length and clarity.



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FIRST QUARTER UPDATE

Tim Howard

Fellow members, it is my pleasure to provide a short update on some of ISPE's accomplishments, its strategic plan, and ongoing activities.

CHAPTER CONFERENCES

First, I would like to congratulate the following chapters that have recently or soon will convene their annual vendor exhibit or technology conferences. If you haven't attended one of these events, I encourage you to do so. Each provides great networking and educational opportunities.

- 01 February: Delaware Valley Chapter 28th Symposium & Exhibition
- 15 February: Rocky Mountain Chapter 2018 Vendor Show
- 02 March: San Francisco/Bay Area Chapter 27th Annual Vendor Night
- 13 March: CaSA 25th Life Sciences and Technology Conference

WOMEN IN PHARMA

Kudos to the Women in Pharma (WiP) Community of Practice (CoP), which continues to generate great interest and momentum. WiP is a forum for women in the pharmaceutical industry designed to foster connection and collaboration to promote career advancement and work-life balance. WiP also provides opportunities for speaking engagements, education sessions, technical presentations, and panel discussions.

Since its inception, WiP has created an online community, organized networking dinners at ISPE Annual Meetings, and led technical sessions at ISPE conferences. Look for opportunities to connect with this CoP through your local chapter, at an upcoming conference, or via the CoP online community portal.

STRATEGIC PLAN

One highlight of our strategic plan is "Driving Efficient Manufacturing Operations." We are acting on this through the following programs and initiatives:

Biotechnology

Training courses offered in the United States and Europe include overviews of biotech processing, facility design, and process validation. Our December 2017 biotech conference in San Francisco was well received; we expect similar success at this year's conference, 3–5 December in San Francisco. ISPE Europe will also host a biotechnology conference in Lyon, France, 20–21 September.

Business results

Our forums, guidances, and trainings are designed to facilitate meaningful exchanges between members, companies, regulators, suppliers, and other organizations The 2018 Facility of the Future conference began the year on a high note, providing a great mix of lessons learned, disruptive technologies, and innovation. The conference also hosted an extended roundtable discussion and networking focused on driving more efficient operations. The Aseptic Manufacturing Conference, 6–7 March in Reston, Virginia, will focus on robotics, sterility assurance, disposables, upgrading legacy facilities, and a new half-day track on highly potent and toxic products. The conference also continues its tradition of providing great regulator interaction. For more information, visit the conference page on the ISPE website: https://www.ispe.org/conferences/2018-aseptic.

Leadership in regulation

Our newly formed Regulatory Steering Committee meets every two weeks to stay abreast of global regulatory topics aligned with ISPE concerns and priorities, and identify those where ISPE can lead and contribute to the dialogue.

Foundational training

In addition to the biotechnology courses mentioned above, we have a robust set of training courses planned. Our subject matter experts also provide custom in-house training. You can see the list of courses available on the Training page: https://www.ispe.org/training

Guidance Documents portal

Launched in January, this permits free online access to a library of nearly 20 Good Practice Guides; this is another way the ISPE gives you the guidance you need to succeed in our industry.

ISPE FOUNDATION

The ISPE Foundation is becoming a significant asset for our members, affiliates, chapters, and industry. Although much remains to be done, we have officially established the foundation and started fund-raising. Our Board of Directors holds regular meetings, with an extended session planned for the 2018 Europe Annual Conference, 19–21 March in Rome, Italy. While focused on long-term maturity, the foundation's short-term goals of providing scholarships and education grants are well aligned with ISPE's founding vision: to perpetuate education in our industry.

That's my wrap-up of the first quarter of 2018. Looking forward to Q2! ‹›

Timothy P. Howard, CPIP, PE, Vice President at Commissioning Agents, Inc., and President of its wholly owned subsidiary Coactive, Inc., is Chair of the ISPE International Board of Directors. He has been an ISPE member since 1993.

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THE VALUE OF TRAVEL, THE BENEFITS OF DIVERSITY

Caroline Rocks

I was inspired to write this editorial after attending the YP and Student Brunch at the 2017 ISPE Annual Meeting & Expo, where Kelly Keen, a member of the ISPE Board of Directors, shared her story. In particular, she emphasized that traveling had been an invaluable part of her career. Her story resonated with me.

Unlike a lot of YPs, I didn't study or work abroad in my early career, or take a year off after graduation to travel. I considered myself a little bit of a homebird, and secured my first job in the same city in which I had studied: Dublin, Ireland.

The first opportunity to travel in my career was factory acceptance testing of process equipment in Europe. More recently, I was able to travel outside of Europe, visiting manufacturing facilities in India, Malaysia, and the United States.

I expected that my skills as an engineer would develop as I gained experience. What surprised me was that by traveling abroad as part of my job (rather than just on vacation), I was pushed outside of my comfort zone and I gained new skills, both professional and personal. Every small aspect of travel has increased my confidence and my independence.

ADAPTABILITY

Like every other traveler, I have experienced delays, gotten lost, dealt with language barriers, had flights canceled, and arrived to overbooked hotels. These experiences have strengthened my adaptability and resourcefulness both on the road and at home. I now find it much easier to adapt to changing circumstances and environments; I've become more resourceful and am a better problem solver.

Traveling requires you to pay attention to many details beyond your work. You must be organized and mindful of your safety, all the while representing yourself and your organization in a positive light. For me, this doesn't just include planning flights, transportation, and accommodations; I research my destination to learn about cultural differences in dress or behavior. I also adapt menus wherever I land to beat jet lag, and incorporate basic workouts so I stay on track for the busy schedule that awaits.

APPRECIATING DIVERSITY

It is tremendously rewarding to work with colleagues from all over the world in cultures and climates so different from mine to achieve the same goals. Travel has taught me cultural understanding and sensitivity, which are vital in today's global pharmaceutical industry. In truth, though, when I consulted with my international counterparts while writing this editorial, we exchanged stories of our cultural faux pas—for which we have (fortunately) forgiven ourselves. I have seen how other cultures conduct business, and as a result have learned new ideas, solutions, and ways to approach problems.

BUILDING MY NETWORK

Along with business travel this year, I went to my first international ISPE conferences: the Europe Annual Conference in Barcelona, Spain, and the Annual Meeting & Expo in San Diego, California. It was my first meeting with international ISPE YPs and members, and the first time I'd attended a large-scale international ISPE event.

YP and Student Brunch, ISPE 2017 Annual Meeting & Expo

Networking at these events pushed me outside my comfort zone, as networking styles differ across cultures. I appreciated how many ISPE members took the initial step to approach me and introduce themselves before asking about my background and accomplishments. Taking their lead, I became more comfortable introducing myself to someone new. I returned from both conferences having broadened my network and forged meaningful connections.

STRENGTHENING COLLEGIALITY

I continue to find it invaluable to explore new parts of the world. It has been humbling, terrifying, and exciting all at the same time. Here are a couple of things I do that help me connect with new international colleagues on a personal level.

- Often when you meet a person for the first time you exchange names only, and they can be difficult to remember. I ask to see their badge, then repeat their name back to them, which helps me remember it when we cross paths again. There have been lots of ice-breaking laughs when I struggle to pronounce new and unfamiliar names.
- Another strategy is to understand a little of the local language. Learning a few words like "thank you" or "how are you?" or telling a story about an experience you once had in the country has really helped me forge relationships and strengthen our teamwork to achieve business goals. ‹›

Have you any experiences or business travel trips to share? Join the conversation on the YP Community page: http://cop.ispe.org/yp.

To join our YP Community, select it during your registration process or update your existing account on ispe.org. It's that easy! This is the place where all the local chapters and affiliates share details and photos of their events so you can get new ideas and guidance for your own group. I also blog here on a regular basis to provide updates on the work of the International YP Committee.

Caroline Rocks is a Senior Process Engineer at Mylan, Dublin, and 2017–2018 International YP Chair

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REINING IN CONSUMPTION
for sustainable manufacturing

The word "sustainability" is both overused and abused: We hear about sustainable development in a sustainable economy that uses sustainable packaging for a sustainable future. But it's an important concept, especially for the pharmaceutical industry as it transitions from manufacturing in stainless steel facilities to single-use technology (SUT) in much smaller plants. This shift has revolutionized pharmaceutical manufacturing and is producing results that go far beyond the financial. Corporate examples that measure results using the triple bottom line* can help us define and understand sustainability more clearly.

Derek Mullins, Senior Manager, Corporate Facilities and Engineering at Amgen, described the results he's seen. "The process change from large fixed stainless steel facilities to smaller single-use systems has allowed us to rethink how we design and operate these plants," he said. "It's also led to significant environmental benefits in terms of energy and water consumption."

Amgen's biologics plant in Singapore, opened in 2014, is only one-quarter the size of other facilities that produce the same volume of drug substance. "The big benefit is flexibility," Mullins continued. "We can configure a plant like this to make more products, in smaller batches.

"The capital costs are less than for a stainless steel plant, time to build is shorter, and the equipment can be run parallel with the facility. You can actually start building the facility while you're still specifying, designing, and procuring the manufacturing equipment. For a large facility, the equipment is built in as the building is constructed."

Mullins found that energy and water savings went hand in hand with these benefits. By shrinking core manufacturing capability, ancillaries got smaller. The purified water system is smaller, as is the steam-in-place system, since the need for steam is reduced. Mullins calculates that when the Amgen facility is compared to a stainless steel facility producing a similar amount of product, it uses 69% less energy, consumes 45% less water, and emits 69% less carbon dioxide (CO_2).

Since a heating, ventilation, and air-conditioning (HVAC) system and its associated utilities account for more than 60% of the energy used at a traditional facility, this is where Amgen sees the greatest rewards. "We were sensible in sizing the equipment and built it to the size we needed, taking the Singapore climate into consideration," Mullins said. "Had we been cautious, we would have oversized everything and put in the standard HVAC design, with large boiler systems and large reverse osmosis plants. If we had, the facility would have been as inefficient as a stainless plant."

—continued on page 12

WE ARE IN THE MIDDLE OF A REVOLUTION IN DATA-BASED TECH THAT AFFECTS THE WAY AND THE SCALE AT WHICH WE WORK

* A concept that expands the financial bottom line to include a company's degree of social responsibility, economic value, and environmental impact.

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THE CASE FOR SUSTAINABILITY

Pharmaceutical manufacturing relies on resources such as energy and water that can be expensive and generate costly amounts of waste. Companies that minimize waste while using natural resources and energy efficiently can see benefits.

"There is increased interest in the benefits of continuity in most of its forms—continuous manufacturing and processing, generally—which inevitably leads to smaller, more technologically controllable facilities," said Robert Bowen, an architect and director of facilities integration in the United Kingdom (UK). He specializes in the design and development of sustainable pharmaceutical facilities in the UK and the rest of Europe.

"We are in the middle of a revolution in data-based tech that affects the way and the scale at which we work. It offers the potential for increased throughput with significantly reduced footprint and huge significance in terms of ownership and capability. These are the fundamentals of sustainability in this industry."

Governments, market regulators, investors, and industry groups are mandating, promoting, and otherwise encouraging corporate sustainability practices in pharmaceutical manufacturing.[1] Many companies already recognize the benefits of limiting greenhouse gas emissions, reducing energy and water use, using waste to generate electricity or heat, and decreasing or recycling waste. These advantages were apparent to Ethicon's facility in Puerto Rico, the 2016 winner of ISPE's Facility of the Year Award for Sustainability.[2] The following year, two other pharmaceutical corporations were named winners of the Presidential Green Chemistry Challenge awards: Merck, for its sustainable manufacturing processes, and Amgen, for greener reaction conditions to improve solid-phase peptide synthesis.[3]

Innovation in sustainable facility design, construction, and maintenance are another industry focus. Many companies, including Genzyme, GlaxoSmithKline (GSK), Alexion, Johnson & Johnson, and Pfizer have embraced LEED† certification for new construction and building renovations.[4] Others have adopted similar environmental assessment methods such as BREEAM,† or national methods, which often require a defined level of classification to obtain a permit, such as CASBEE† in Japan and Green Mark† in Singapore.

Companies are also harvesting green energy sources such as wind and solar. GSK, Novartis, Janssen, and DePuy Synthes collaborated to build and maintain wind turbines that could generate electricity and reduce CO_2 emissions at their facilities in Cork, Ireland.[5] The Janssen facility in Titusville, New Jersey, which received LEED Gold certification, generates almost 85% of its electricity from a giant array of solar panels.[6] AstraZeneca, Biogen, Novo Nordisk, and Johnson & Johnson belong to RE100, an industry initiative comprised of companies committed to sourcing 100% of their electricity from renewable sources.[7]

Johann Bonnet, Vice President, Business Development, Pharma & Cosmetics at Veolia Water Technologies, believes that a robust focus on corporate sustainability in four areas benefits pharmaceutical manufacturers:

- Regulatory compliance: A sustainability strategy that focuses on managing risks associated with water use, energy consumption, and waste can prevent FDA warning letters.
- Design: Including environmental footprint reduction to reduce life cycle costs in the design of plastic products (such as medical devices, inhalers, and packaging) can curb unnecessary waste and provide a source of reusable materials.
- Innovation: Original thinking can reduce waste and boost profitability—by reusing solvents as secondary raw material, for example.
- Spending: Scale down investments in infrastructure; rent, share, or outsource manufacturing facilities instead.

CONSERVING AND REUSING WATER

Access to a good source of clean water is a main area of concern in pharmaceutical manufacturing. In addition to being potable, pharmaceutical water must comply with international laws, pharmacopoeia, and regulatory guidelines.

"Legislation is there and companies have sustainability policies, but what drives them to consider water efficiency is economics," said Nik Krpan, president of Cheme Engineering, a consultancy based near Toronto, Canada, that offers process engineering services to the biopharmaceutical industry. "It depends on the jurisdiction. At some sites in the developing world there is little or no municipal infrastructure for drinking water or sewage treatment. In these cases, facilities need to be prepared to treat their own waste, which provides an incentive to do so in an economically feasible way. They can implement groundwater recharge, greenwater harvesting and recharge, rainwater harvesting, and reclamation of water. Here we see this as sustainability, but there it's a necessity and sometimes legally mandated."

Bonnet and Veolia work with companies in Europe, including Roche, Bristol Myers-Squibb, AstraZeneca, and Pfizer. They have undertaken projects that include the construction of a sewage-treatment plant to reduce the environmental footprint, biogas production, chemical use minimization, water-use management, electricity cogeneration that reduces carbon emissions, as well as water reuse and purification.

"The biggest consumers of water are boilers and coolers, and the payback on these systems can be significant," Bonnet said. "Changing from an open-loop to closed-loop system increases efficiency. Water can be recycled, since the grade of water does not need to be as high as for process. The goal is not [necessarily] to recover all the water, but companies are looking at what makes sense in terms of economics and the environment."

In North America, the incentive to conserve water is caused by the rising cost for water and sewage services, which is increasing two to three times faster than for other utilities.[8] "The situation in North America is caused by a history of under-recapitalization of municipal infrastructure and now we are playing catch-up," Krpan said. "Because there's a lack of appetite to increase taxes, local governments increase water rates instead."

Nissan Cohen, owner of Start-Up Business Development and a specialist who consults on industrial water issues, says that "North American companies could realize cost savings by paying more attention to water." He likes to refer to the four Rs of sustainability—reduce, recycle, reuse, and *reclaim.* He says that 25%–35% percent of the water that goes down the drain should be reclaimed. "For a US company that dumps 100,000 gallons of water a day, that's about $800 down the drain every day. I estimate that the industry is

† LEED: Leadership in Energy and Environmental Design, a green building rating system developed by the United States Green Building Council

BREEAM: Building Research Establishment Environmental Assessment Method, a system that determines a building's social, economic, and environmental sustainability performance

CASBEE: Comprehensive Assessment System for Built Environment Efficiency, the green building management system in Japan

Green Mark: an initiative launched in 2005 by the Singapore Building and Construction Authority to encourage and reward an environmentally friendly and sustainable built environment

wasting a lot more than $50 million per year on water."

Krpan believes the trend for manufacturing facilities is to reuse water, despite an esthetic stumbling block. "There is an 'ick factor' to reusing water for human consumption," he says, "so generally reclamation at pharma sites involves using it in cooler towers or boiler feeds, or for nonproduction uses such as gray water." In some cases it is used for aquifer recharge.

One country that has overcome the distaste for reusing water is Singapore. While the densely populated island imports some of its drinking water from Malaysia, its Public Utilities Board (PUB) reclaims its branded NEWater from sewage wastewater, using a three-step purification process of microfiltration, reverse osmosis, and disinfection with UV light. NEWater supplies 40% of the country's needs.[9]

"Water is a constrained resource in Singapore," said Amgen's Mullins, whose facility in the country relies on NEWater for industrial uses, such as cooling water, that don't require potable water. "The local PUB regulations are tight and they expect large water users like us to put in place sensible water management processes to conserve water."

Where possible, Amgen uses recovered water for its cooling towers instead of using drinking water. In a region where potable water is scarce, the company also collects condensate from the HVAC cooling coils. This is a significant source in a tropical climate, amounting to about 24 cubic meters of water per day, which contributes to significant water savings. Amgen believes it can further improve the water intensity of this facility and the company has its sights on its facilities around the world, even in regions where water is plentiful.

"We always ask ourselves if it's OK to use drinking water in a cooling tower," Mullins said. "We recover water in all our plants and use reverse osmosis so it can be reused, or collect clean condensate. An example is our eight-story building in Cambridge, Massachusetts, where we collect cooling condensate from all the air handlers and it gets recycled into the cooling towers."

ZERO LIQUID DISCHARGE

"I like to show companies where the water is and where it goes, what are the costs, and how they can reclaim and reuse this water and, in so doing, become better corporate citizens," Cohen said. He's an advocate of zero liquid discharge (ZLD), a process that purifies and recycles wastewater, leaving behind solid waste that can be recovered, incinerated, or disposed of (see his editorial on page 16) "I absolutely recommend that companies reclaim water. Water can be taken back to source water if the conductivity is low enough; depending on the results, it can be used for irrigation outside, for sanitary applications in urinals and toilets, or in cooling towers for AC systems."

Many effluent waters can also be reclaimed and reused elsewhere at the facility, he says. The simplest example is to feed gray water into an external irrigation system.

One place where ZLD makes sense is India, where seasonal rains make it difficult to find sources of clean water. The Indian Pharmacopoeia mandates that municipalities chlorinate water to make it potable for pharmaceutical applications, but during monsoon season water comes in at such a rate that it outstrips the 20-minute contact time required to purify the water.

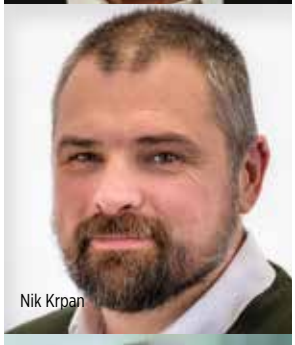
"Pharmaceutical companies are adding chlorine to the water, but it's not doing anything, especially during monsoon season," said Cohen, who recently visited the country. "The amount of pathogens, microbials, and organics in the water cannot be treated properly. I recommended to the Indian Pharmacopoeia

THE PROCESS CHANGE FROM LARGE FIXED STAINLESS STEEL FACILITIES TO SMALLER SINGLE-USE SYSTEMS HAS ALLOWED US TO RETHINK HOW WE DESIGN AND OPERATE THESE PLANTS


Johann Bonnet


Rob Bowen


Nissan Cohen


Nik Krpan


Derek Mullins

THE BIGGEST CONSUMERS OF WATER ARE BOILERS AND COOLERS, AND THE PAYBACK ON THESE SYSTEMS CAN BE SIGNIFICANT

that they change from chlorine dioxide to any purifying agent that would be effective on the front end, such as ozone. Ozone oxidizes bacteria, pathogens, and organics efficiently and is 36 times more effective than chlorine.

"If you can clean it up on the front end, you can reuse the water. Ozone can reduce bacteria and other pathogens to zero, which is important. The water can be reused in cooling towers or makeup water for the source water. The quality of the treated water is actually better than the source water coming in. Why isn't it being reused? Ozone generators are used extensively to clean up water and waste in the bottled water industry," Cohen continued. "The bottled water has to have an ozone residual to prevent bacterial growth and maintain its shelf life of two years. Not many pharma companies are using it, though."

HOW DOES PHARMA COMPARE?

"When you consider that the cement industry was the first worldwide adopter of a sustainability policy in the early part of this century,[10] the pharmaceutical industry has been late in the game," Bowen said. "That was a part of the driver for ISPE to publish its *Sustainability Handbook*."

Bowen, who is the global Co-Chair of the ISPE HVAC and Sustainable Facilities community of practice, and Nicholas Haycocks, Senior QA Specialist at Amgen, recognized the need for a sustainability guide for the pharmaceutical industry. They led the task team that produced the handbook in 2015,[11] which provides a global perspective on legislation, regulation, and policy development. Among the topics it covers are the design and engineering of sustainable energy processes, HVAC systems, electricity and utilities, waste management, and water use. Bowen is positive about what companies are doing.

"Some companies are extremely proactive in their response to sustainability, both in terms of climate change and the recognition that the supply chain and operation can provide significant returns when a sustainable policy is adopted," he said. "These accrue through manufacturing efficiencies, operational benefits, and staff welfare gains. Sometimes this awareness has been influenced, from a board perspective, by early adopters.

"It tends to show most when there is the opportunity for a new plant and the chance to showcase. The EU Directive about climate change goals is 15 years old, and its expectations about tougher building standards and aggressive time targets are well embedded in the culture. In some ways that takes the onus off the companies, as they have to comply."

In the European Union, there is usually a separation between legislation concerning buildings, and legislation dealing with processes and equipment. For buildings, architects and building engineers (e.g., mechanical/HVAC, electrical, civil/structural) have mandated targets, even for retrofits. "Companies have little choice but to follow," Bowen said. "Of course, there is a latitude divide at play. If you have sun all year, it's relatively easy to take advantage of solar power. That is, it's easier in Texas than in Ireland. In straight build terms, a small retrofit in an older building is less likely to be built to sustainable standards, unless legislated, than a new build.

"In terms of legislation dealing with processes and equipment, the pressure is on only where there is a company commitment. Big pharma is in the vanguard here as well, as they have the investment opportunities and most have taken a board commitment to investigate green options. Where these have been adopted, the benefits have become clear and self-sustainable. Likewise, in the drive for improved production methods and the use of datatech, the potential efficiencies of continuous manufacturing are beginning to show great gains that support sustainability and carbon reduction through plant-size reduction, asset reduction, reduced energy, and material usage."

Bowen returns to the triple bottom line. "There are intangibles that drive our interests, other than the pure cost to sustainability. We strive for simpler, more sustainable operations, more satisfied employees, and a greater return on investment. It is a case of practicing what you preach—creating a manufacturing and operational environment that supports health, increases life expectancy, well-being, and a better environment. The pharmaceutical industry is the grunt end of the health care industry and only works if it's sustainable. The health care industry only works if it cares about its environment and its patients, for whom it is there to improve things and to provide cures." ‹›

—Scott Fotheringham, PhD

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ZERO LIQUID DISCHARGE

Reducing water wastage and effluents in biopharmaceutical production

Nissan Cohen

The biopharmaceutical industry, blessed with excellent water resources, has developed exacting specifications for the many types of water used in the manufacture of pharmaceutical products. Unfortunately, little attention has been given to losses from wastewater, reject water, and effluent that is sent to drain.

This could be a looming problem. According to a UNESCO report,[1] the worldwide need for potable water is expected to grow by 400% over the next 50 years. This increase will be generated by population growth, industrialization—especially in emerging economies, and rising demand for better drinking water.*

Unfortunately, accessible drinking-quality water will remain finite at 0.3% of the planet's total water mass.† Without a comprehensive water program that emphasizes recycle, reuse, reclaim, and reduce, the biopharmaceutical industry could face growing water shortages and rising costs.

As a result, many pharmaceutical companies are considering ways to minimize their liquid discharge. Some have adopted a zero-liquid-discharge (ZLD) program for their facilities. ZLD is a closed-loop cycle that minimizes or eliminates discharge of any liquid effluent by recycling and treating all wastewater.

Because of the large investment required, however, ZLD remains a long-term goal for many organizations. With some thought and easy engineering fixes, however, companies can attain at least minimal liquid discharge by setting interim goals that help recycle, reclaim, reduce, and reuse current water operations.

GETTING STARTED

Here are some questions that can help you determine how to move forward:

- Where does the water come from and where does it go?
- What modules use water and dispel directly to drain?
- What is the quality of the water being discharged?
- What costs are associated with the treatment of the water before and after disposal?
- What are we doing to minimize liquid discharge?

Each site will have different answers to these questions, but there are universal issues all should consider: Water is the most important excipient used in pharmaceutical production. All water is purchased, usually from a municipality or water company. Water that is not used (or is deemed unusable) is sent to drain. Every site pays sewer fees for discharge, which goes to a wastewater treatment plant (WWTP). Many pharmaceutical companies must also purchase sewer permits for biological oxygen demand (BOD), chemical oxygen demand (COD), and effluent. These permits cost money, and if the site exceeds its rated allowable limits, the local WWTP authority will assess a fine for the overage. Add up each of these expenses and you can see that water is quite expensive.

ASSESSING WATER USAGE

Source water from the municipality can be used for all applications in the plant, including purified water and water for injection (WFI). Water used in the production area often requires both wastage and secondary steps for water treatment. This may include rinsing of chemicals, surfactants, acids, and bases using clean-in-place (CIP) systems, rinsing operation streams for microbial destruction, or autoclaving detritus material from biological material harvesting. The rinsing operations alone may require hundreds to thousands of gallons of water, all of which is sent to drain—or to acid waste neutralization and then to drain. Other operations and modules in the water-purification train also generate waste, with the effluent directed to sewers. But much can be reclaimed and reused in other applications around the site.

Here are some conservation possibilities:

- Softener reject, combined with source water, can be directed for cooling tower makeup.
- R/O reject water can generate an average 20%–25% of the total makeup: that's 20–25 gallons of reject for every 100 gallons of water used in R/O membrane systems; some systems approach 50%. This water can be recycled and reused within the building or complex.
- Continuous electrodeionization reject can be fed directly to the break tank in pretreatment, or blended with source water at the beginning of the pretreatment skid or train.
- CIP rinse water can be measured to determine its conductivity; depending on the results, the water can be sent back to the pretreatment break tank or directed downstream to acid waste neutralization.
- Gray water can be fed to the external irrigation system.
- Many dishwasher and washing equipment effluents can also be directed to irrigation systems.
- HVAC condensate can be repurposed for irrigation or sanitary applications.
- One of the biggest wastes—flushing point-of-use devices before sampling—sends a tremendous amount of excellent water directly to drain. Adding a diverter valve on the drain pipe can redirect the water to R/O or ion-exchange feed.
- Condition-based backwashing of pretreatment beds (e.g., sand filters, multimedia filters, and carbon beds) can significantly reduce water usage and effluent to drain.
- Spillage from filling operations that use purified water or WFI can be reprocessed for pretreatment, irrigation, or used for sanitary/hygienic applications (toilets, urinals, etc.).
- Sanitary fixtures may be updated to include

* Around 748 million people do not have access to an improved source of drinking water.

† While almost 2% of the water on the planet is drinkable, most of that total is confined to ice, glaciers, and year-round snow pack.

no-flow urinals, dual-flush toilets, ultra-low-flow fixtures, etc.

- When purchasing new equipment, consider the possibilities for water savings. Equipment manufacturers often build in mechanisms for recirculation and reuse. Some vapor-compression distillation units, for example, have onboard recycle and reuse mechanisms. Others may have low-flow options that can be employed when the machine is idle.

WASTEWATER TREATMENT

Oxidation wastewater treatments use ozone and/or hydrogen peroxide to oxidize organics, biologics, and carbon-based detritus in the water and convert them to carbon dioxide (CO_2). Photochemical oxidation adds ultraviolet light to the process, elevating the oxidation to an activated state and increasing it multifold to destroy or treat nonbiodegradable organic contaminants. Photochemical oxidation breaks down and oxidizes BOD and COD molecules, forming CO_2 and water in the effluent stream.

Many biotechnology facilities, which use autoclaves to destroy microbial material left after harvesting, dump the autoclaved material down the drain with the wastewater. This increases the BOD in the drainage water and effluent to the wastewater treatment plant. If photochemical oxidation were used, microbial material could be oxidized and eliminated in a few minutes, producing only CO_2. This could eliminate the need for a BOD permit, as the water treated with photochemical oxidation treatment is pristine, and could be recycled to any process purification module for reuse.

CONCLUSION

The need for potable-quality water will increase 400% over the next 50 years, while accessible water resources will remain at only 0.3% of total water mass of the planet.

The pharmaceutical industry should work toward a ZLD goal, recycling and reusing water from all operations, waste streams, rinsing operations, regeneration cycles, back flushing, and sanitization schemes.

Decreasing BOD and COD burden in wastewater by using ozone, hydrogen peroxide, and photochemical oxidation techniques may eliminate the need for costly WWTP permits.

Pharmaceutical facilities should reuse, recycle, reclaim, and reduce water use whenever possible. The bottom line savings can be immense over 5-, 10-, and 20-year periods of controlled, limited, and, ultimately, zero liquid discharge. ‹›

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Nissan Cohen, an ISPE member since 1994, is a worldwide expert in total organic carbon, high purity, ultrapure, reclaim-and-recycle water systems, with profound expertise in instrumentation, automation, and organic contamination oxidation systems using ozone, UV, ion exchange, and catalysts.

Also in this section

ISPE EUROPE PHARMA 4.0 CONFERENCE: A FIRST-PERSON REPORT

From November 23 to 24, over 230 participants from 19 countries gathered in Verona—located in Italy's high-tech corridor—for a conference focused on the challenges and opportunities of Pharma 4.0. Organized by ISPE Italy and the Pharma 4.0 Special Interest Group (SIG) at the at Villa Quaranta Hotel, the event featured high-profile speakers from ISPE working groups as well as innovation leaders from pharmaceutical companies, contract manufacturing organizations, equipment vendors, consulting firms, and academia. Topics included end-to-end integration, data integrity and analytics, automation, and the workforce of the future.

It was a conference of firsts: the first time ISPE brought the transformative concept of Industry 4.0 in the highly regulated world of pharmaceutical operations to a European audience, the first time ISPE held an affiliate-supported conference in Italy, and the first time an ISPE Europe conference included content developed by Young Professionals (YPs).

While Pharma 4.0 has been called a new industrial revolution, its implementation will more likely resemble an evolution in which digitization and automation meet a very complex product portfolio with long life cycles. So it is important to achieve a common understanding of readiness and maturity, starting with enablers and components defined in ICH Q10: Pharmaceutical Quality System. It is also important to develop business cases to be certain the right products are identified, such as full automation.

Digitization, an important component of Pharma 4.0, will connect everything, creating new levels of transparency and speed. This will enable faster decision-making, and provide in-line and in-time control over business, operations, and quality. Of course, digitization will also require higher levels of security, since connected systems heighten vulnerability.

The Pharma 4.0 SIG is working on pharma-specific maturity models, as well as those already defined in other industries, via its five subgroups:

1. Holistic manufacturing control strategy based on ICH Q 10: Pharma 4.0 road map
2. Pharma-specific impact and maturity model
3. Process mapping and data integrity by design
4. Automation and continuous process verification
5. Plug and play automation

To help participants understand these concepts more thoroughly, a group of Young Professionals developed and presented a role-playing workshop. Using a series of virtual businesses, organizers asked the audience to determine each one's Pharma 4.0 readiness factor and identify what was needed from each segment of the business to achieve it. (See YP article on page 20.)

Attendees agreed that two factors were required for successful implementation: First, management must consider Pharma 4.0 a strategic value and create a corporate culture to nurture its growth. Second, management must decide what "Workforce 4.0" might look like.

ISPE is already working on this topic; you'll read about it in future issues of *Pharmaceutical Engineering*. ISPE is also helping companies and universities define skillsets and job profiles for future employees.

ISPE thanks the Italy Affiliate for its tremendous support in organizing the conference.

—Thomas Zimmer, PhD, Vice President, ISPE European Operations

YP WORKSHOP: A STRATEGIC I4.0 ROAD MAP

Which road map to Industry 4.0 (I4.0) should the pharma industry follow? We explored this question during the YP workshop held during the Verona conference, leveraging "gamification" (a learning technique that incorporates game elements) to determine a strategy for the journey.

A road map describes a path that goes from point A to point B—but we all know that a straight line is rarely a feasible option. There are also multiple points of origin that can yield different approaches, perspectives, and objectives, each with potential conflicts and contradictions. In our case this means engineering, information and operational technology (IT/OT), supply chain, quality, regulatory, etc. The biggest challenge is to ensure a holistic perspective aligned with a company's business or end goal.

The Industry 4.0 journey, shown in Figure 1, has similar strategic and tactical approaches.

ROLE-PLAYING

Participants were asked to develop a five-year I4.0 strategic road map, using four case studies from the pharmaceutical industry: an API manufacturer, an OTC and pharma health care company, a pharmaceutical logistics company, and a "big pharma" company. Each scenario was given a specific company profile, DNA, and a vision proposition, linked intentionally to Industry 4.0 solutions.

Participants were then divided into groups and assigned one of six business roles: R&D, engineering, manufacturing and supply chain, quality assurance and regulatory affairs, business unit and marketing, and business and operations/automation (IT/OT).

Each group named a CEO and a digital transformational lead, then had to agree on initiatives and investments that would bring value to their company. The objective was to identify at least two transformation initiatives per function in each of the business roles. At the end of the exercise, each group presented their road map. The process took just under 20 minutes.

The road map presented by "DermaCaring," a fictitious over-the-counter (OTC) and pharmaceutical health care company, is shown in Figure 2.

DERMACARING SCENARIO

The OTC and pharma personal care sector provides patients with drug therapies for skin diseases such as cancer, psoriasis, and dermatosis. DermaCaring's strength lies in a cutting-edge center of excellence in biotechnology and dermatology research. Finished goods are manufactured by third-party suppliers around the world.

DermaCaring's vision and five-year goal was to implement a complete change in the drug-to-patient model. Their aim was not only to handle last-mile distribution, but to deliver the right medicine in the right quantity with real-time production. To achieve this transformational change, the DermaCaring team identified a key enabler: innovative mobile equipment for on-site diagnosis that works by taking skin samples. The equipment would be able to adjust the drug formula composition and produce the exact quantity needed by the patient. The team suggested it be placed in local pharmacies.

As the discussion started, each DermaCaring team member described the first steps for their business role or function. The digital transformational lead guided and connected the proposals from each of the six business functions, looking at correlation and timing. Figure 2 illustrates DermaCaring's road map.

The main finding from this exercise is that I4.0 solutions were identified along with the usual business project activities and steps, converging toward the final innovative drug-to-patient model.

Outstanding I4.0 technologies or enablers included:

- Cognitive capabilities, virtualization, and digital networking of the equipment (IT/OT)
- Adaptive process analytical technologies to meet ad hoc formula development, plus fast-prototyping of concepts in partnership with the original equipment manufacturer (R&D and engineering)

PARTICIPANT FEEDBACK

Participant feedback indicated that we reached our goal. Here are some of the comments we received:

> *Refreshing session, good setup to unleash creativity and interactivity, reasonable results doable even in 15 min. Good opportunity to dive a bit deeper with peers rather than just small talk.*

> *The workshop of the Young Professionals fitted perfectly well into the discussion about the Pharma 4.0 needs. It emphasized the cross-functional cooperation needed to tackle the challenges of the future and allowed participants to apply some of the learnings from previous sessions. And observing the intense discussions of the individual workshop groups during their assignment, participants had fun, too.*

We would like to thank all the participants and organizers for letting us participate in this event.

PARTICIPANT EVALUATIONS

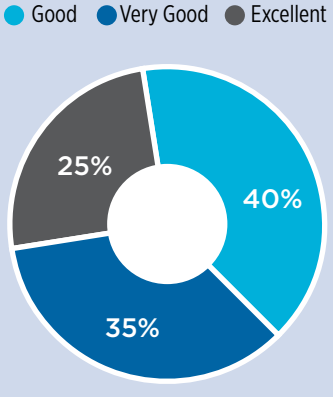


FIGURE 1: INDUSTRY 4.0 ROAD MAP

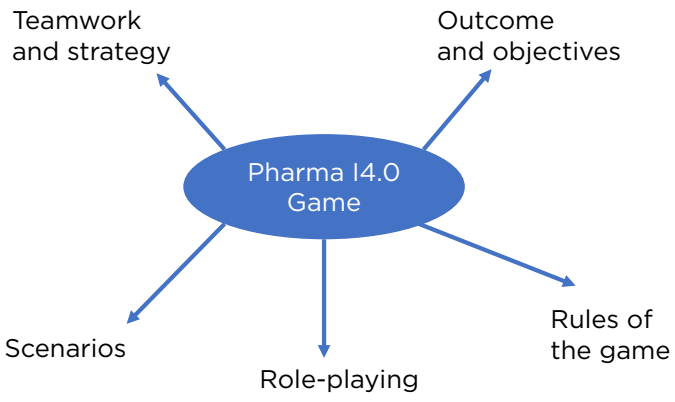


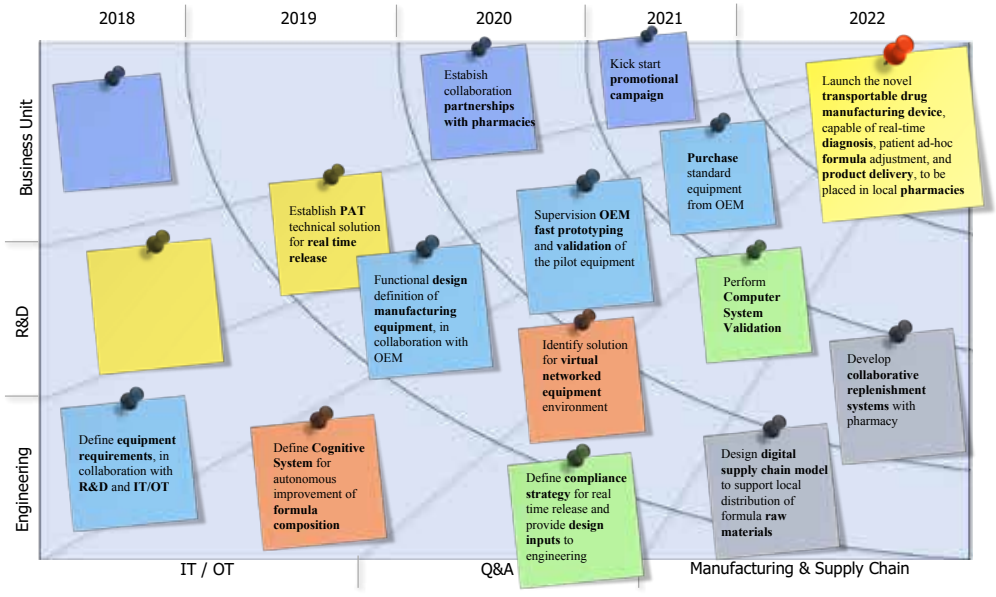
FIGURE 2: DERMACARING

Company Description
OTC & Pharmaceutical Personal Care Company

Profile
Pharmaceutical research and biotechnology company

DNA
- Modern biotechnology and dermatology research center of excellence
- Internal drug formulae development process
- Externalized manufacturing and finished goods packaging leveraging TPMs
- Seeking collaboration with original equipment manufacturers

Vision
Change paradigm of manufacturing and drug-to-patient model. The aim is to reach each patient locally, provide on-site diagnosis, real-time production and delivery of ad hoc drugs through innovative equipment to be placed in local pharmacies



- Digitalization and the collaborative relationship, and raw materials replenishment directly to pharmacies (supply chain)

WRAPPING UP

Thorough planning is key for a transformational challenge like the one I4.0 demands, and all stakeholders must be considered from the very start. Maintaining the right focus and motivation, as well as designing and executing the strategy can only be achieved with the commitment of all stakeholders, not just senior management. We recognize this is an idea that could be misunderstood: Different teams working on different ideas could produce different results, couldn't they? In fact, having different teams work together in a coordinated effort toward the same goal, complementing one another, would end in just one result.

We also believe it is senior management's role to take responsibility for involving all stakeholders, keeping them motivated and focused on the big picture. Any project, regardless of size, has an objective; I4.0 is no different. ‹›

—Juan José Alba Gil, Oliver Ingold, Abdelghani Meqdad, and Federico Poli

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TAPPING THE NETWORK
Meet YP Thorsten Böhle

We all know the saying: There's no reason to reinvent the wheel. It is likely that someone else has already come up with a workable solution to your particular challenge. We also know the quickest way to conquer challenges is to find that person, learn about their solution, and then do the same thing. Finding that person, however, is not always easy.

Members of the pharmaceutical industry need look no further than ISPE, according to Young Professional (YP) Thorsten Böhle. As the YP Chair for the ISPE DACH (Germany, Austria, Switzerland) Affiliate, Böhle is in a position to help members find the solutions that they seek.

Born and raised near Kassel, Germany, Böhle studied at the University of Kassel, where in 2007 he received his master's degree in electrical engineering. That same year, he started his first job as an automation engineer with B. Braun Melsungen AG. Böhle says that one of the reasons he gravitated toward pharmaceuticals is the industry's high level of regulation. "You need to focus on defining and managing stable processes, and this can create a lot of complexity," he says. "I enjoy working with many people from different backgrounds and in a global environment. And of course, the outcome is that you produce medicines for patients to be healthy again."

He moved to Basel, Switzerland in 2011, and joined F. Hoffmann-La Roche AG, where he is project engineer for process automation. In mid-2016, Böhle seized an opportunity at Roche and took on the position of subproject manager for automation and MES in a new late-stage development and commercial launch facility for oral solid dosage forms.

"I started in August last year and the team has grown to 16 people who are involved in every detail of the project," he says. "This facility is designed for the launch of new innovative Roche products, which have special requirements on the production equipment like containment and cleaning-in-place functionalities. We have a high demand at Roche for this kind of production facility, so it has a lot of attention from our global customers and production organization."


Thorsten Böhle

In his free time, he enjoys the outdoors with his spouse (also a Roche employee) and their two daughters, aged 4 and 2. He also organizes Alpine tours for the mountain and ski section of the Roche Sports Club.

ONBOARD WITH DACH

Böhle's introduction to ISPE came somewhat by chance in 2011 when a colleague at his former employer B. Braun had a copy of *Pharmaceutical Engineering* on his desk. "Before that time, I didn't know what ISPE was about, but the magazine gave me a broad idea of the variety of activities that ISPE offers," he says.

He followed that up by attending a DACH workshop on data integrity. "For the project I lead, we need to ensure that our systems are compliant with the latest regulatory requirements, e.g., electronic production data is stored long term where there is no risk of loss," says Böhle. "This workshop was very interesting for me and it showed me that when you have different parties together—from other pharmaceutical companies, vendors, or regulatory agencies—it is beneficial. There is a lot of experience inside the ISPE network, and I realized at this workshop that we don't have to reinvent the wheel every time. Sometimes you only have to look to the left or to the right, and see that there are quick solutions that are already rolled out at other companies."

Böhle got to know Marcel Staudt, the Affiliate's former Chair, and Gunter Baumgartner, the current Chair, as well as Board member Robert Landertinger. The three introduced him to the idea of developing a YP network within DACH, and the request piqued his interest. He became involved and is now the Chair of the YP group.

"We defined a core team, which has now grown to 17 people, and we meet biweekly, on Monday evenings, to determine our next steps and strategies for enlarging our YP network," says Böhle. "The network is strong and growing, with about 40 members in the group now, and we have planned a lot of activities for the upcoming year.

"Our next big challenge is to attract more students. We want to get in touch with other YP networks within ISPE, like the Boston Area and South Carolina–Atlantic Chapters, to find out how they generate such big numbers within their organizations. We are hoping to find best practices and lessons learned, and then maybe we can go in the same direction," he notes—in yet another example of not reinventing the wheel. ‹›

—Mike McGrath

REGULATORY UPDATE

ISPE Regulatory Volunteer Operations: Part 2

In my last column,[1] I introduced the Regulatory Steering Committee, which was convened to provide guidance and oversight for ISPE's regulatory committees and initiatives. This column focuses on the committees and groups that carry out this important work in accordance with the ISPE Strategic Plan.

RQHC

Formerly the Regulatory and Compliance Committee, the Regulatory Quality Harmonization Committee is comprised of a management team called "RQHC Global" and regional focus groups (RFGs).

RQHC Global supports the RFGs by coordinating regional initiatives and ensuring a global approach is taken where needed. It also coordinates ISPE responses to new and draft regulatory documents by selecting documents for comment, identifying subject matter experts within the Society to develop ISPE's response, and overseeing the comment process to ensure it remains transparent and aligned with members' interests. In addition, RQHC Global supports ISPE education by developing regulatory/quality tracks and panels at ISPE's international conferences and Annual Meeting.

RQHC's current RFGs are Asia-Pacific, Europe/Middle East/Africa, and North America, with plans to reestablish a group in Latin America. The RFGs are tasked with maintaining ISPE's currency in global regulatory environments, establishing and growing regulatory relationships in their regions, and advancing ISPE's visibility with key regulators. RFGs assemble task teams as needed to explore potential regulatory, quality, and compliance opportunities, and recommend approaches for ISPE's involvement or response. RFGs also arrange informal meetings with regulators to identify areas of concern in which ISPE may be able to provide expertise.

RQHC MANDATE

Facilitate industry-wide clarity of new applicable regulations on regulatory matters relevant to ISPE's attention and expertise, advising on impacts and resolving towards solutions, seeking harmonization of regulatory expectations where desired and possible.

PRODUCT QUALITY LIFE CYCLE IMPLEMENTATION COMMITTEE

ISPE's PQLI® initiative was established to provide guidance on the implementation concepts described in ICH guidelines Q8, Q9, Q10, and Q11. To this end, the committee has published four Good Practice Guides to provide global solutions for these challenges. It helps ensure product quality throughout the product life cycle, with a view to continuous product improvement. The committee also addresses significant new regulatory-focused topics and issues that affect both small and large molecules, across dosage forms.

PQLI technical subteams are working on the following topics:

Expedited Programs for Patients

Expedited therapy designation has resulted in numerous approvals contingent upon post-approval commitments, including clinical studies, stability, and managing global supply chain to assure medicinal product availability. Uncertainty around implementation of elements of product-control strategies has created perceived risk to firms pursuing accelerated development submissions as well as life cycle management post approval, with the potential of impeding timely access to novel medicinal products. This team is engaging industry and regulators for open discussion of the challenges of entering accelerated development programs, developing best practices to enable improvements in future submissions to benefit both industry and regulators.

Clinically Relevant Specification (Patient-Focused Quality Standards)

This subteam is developing strategies and practical solutions for establishing appropriate product-quality standards focused on patient safety and efficacy. Its scope includes understanding patient needs, appropriately designing product quality profiles, deep understanding of the formulation and manufacturing process, and establishing appropriate specification, which links to patient safety and efficacy. Focusing on drug substance and drug product impurity specification as a first step, the group will gradually expand to other critical quality attributes and more advanced therapeutics, including biotech products.

Continuous Manufacturing

Created to coordinate regulatory and scientific efforts, the Continuous Manufacturing team provided comments for the US Food and Drug Administration (FDA) docket "Submission of Proposed Recommendations for Industry on Developing Continuous Manufacturing of Solid Dosage Drug Products in Pharmaceutical Manufacturing." The comments offered ISPE's view of desired content in future FDA or international guidance on continuous manufacturing for solid oral dosage forms. The team also plans to produce implementation papers.

Knowledge Management

This team is researching how the pharmaceutical industry is leveraging knowledge management, an ICH Q10 enabler. It intends to share case studies and develop industry best-practice guidance.

Process Capability

Both FDA and the pharmaceutical industry have advocated recently that process capability become more mainstream. Formed in 2015, this team is dedicated to advancing the use of process capabilities in the pharmaceutical and biotech industries. Members have written two articles. "Role of Process Capability in Monitoring Product Quality," a concept paper, is available on the ISPE website.[3] More recently, team members developed a process capability maturity model tailored to our industry that was published in the January-February 2018 issue of *Pharmaceutical Engineering*.[4] This model should help life sciences executives set up process capabilities programs within their own organizations and compare them to those of peer companies.

Process Validation

The Process validation (PV) team has spent the last seven years working to advance implementation

of the life cycle approach to process validation by addressing its most difficult aspects. The team has issued eight discussion papers, with topics that include determining and justifying the number of PV batches, developing CPV monitoring plans, implementing the life cycle approach at contract manufacturing sites, and applying the life cycle approach to both biotech manufacturing and packaging validation. These are available on the ISPE website at: https://www.ispe.org/other-publications/papers.

The team has held nine conferences, including the recent Process Validation Conference, which focused on continued and ongoing PV plan development, and the Statistics in Process Validation Conference, which focused on statistics in support of all stages of the PV life cycle. Team members have also contributed to a three-day training course on implementation of the life cycle approach to PV which covers PV-related aspects of product development, the validation exercise, and ongoing process verification following PV. Over the past year, they have compiled a comprehensive PV Good Practice Guide, which is slated for publication in 2018.

ISPE REGULATORY INITIATIVE TEAMS

Initiative teams are convened to address broad topics that are regulator driven or regulatory focused.

Quality Metrics

The Quality Metrics/Advancing Pharmaceutical Quality team was created in 2013 following an FDA request for ISPE's views on measures of product quality, site quality operations, and systems performance. The team's resulting activities have enabled ISPE to provide objective, data-driven input to the FDA, European Medicines Agency, and other regulators on standardized metrics reporting. The team partnered with McKinsey and Co. from 2014–2015 to conduct the industry's first quality metrics pilot program. The results,* along with industry input obtained at ISPE summits and conference sessions lead by the team, informed ISPE's comments on FDA draft guidances "Request for Quality Metrics"[5] and "Submission of Quality Metrics Data,"[6] as well as the "Quality Metrics Technical Conformance Guide—Technical Specifications Document; Availability."[7] The pilot data continue to provide a valuable source for additional analysis in response to FDA requests.

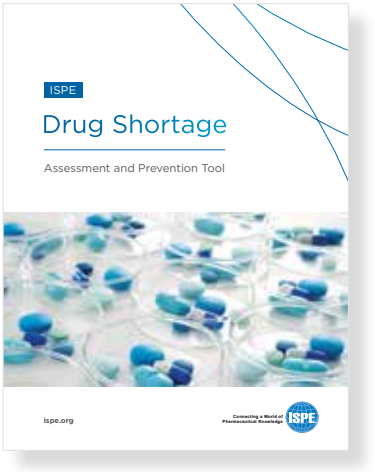
Building on pilot data that identified relationships between organizational culture and quality outcomes, the Cultural Excellence subteam examined the influence of an organization's culture as an enabler of quality outcomes. In 2016 the subteam published the "Cultural Excellence Report,"† which was presented in conjunction with a two-day conference on the topic. The conference and report offered original approaches, practices, and practical tools to promote behavioral change that will ultimately benefit patients and businesses.

In 2017, the team held two industry workshops for knowledge exchange on quality metrics that were designed to advance industry/regulator dialogue beyond written feedback to face-to-face conversations on achieving the FDA's vision of a "maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."[2] The team is now expanding its focus from the agency's proposed reportable metrics program to the integration of culture, operations, and operational excellence for a complementary approach to advancing the state of pharmaceutical quality to benefit industry, regulators, and patients alike. This innovative work will be highlighted in a *Pharmaceutical Engineering* Special Report on Quality Metrics in the September-October 2018 issue.

Drug Shortages Initiative

For nearly a decade ISPE has facilitated communication between the industry and health authorities on the subject of drug shortages. The Drug Shortages Initiative team is committed to promoting programs and tools to assure the continuous availability of quality pharmaceuticals to patients. The team also promotes drug shortages prevention through ISPE's Facility of the Year Awards program by recognizing companies that have strengthened their ability to prevent drug shortages or minimize their effects on patients.

In 2013 the team launched a comprehensive survey to gather data on the technical, scientific, manufacturing, quality, and compliance issues that have resulted in drug shortages. Results were



published in the "Report on ISPE Drug Shortages Survey."‡ Follow-up publications included the "Drug Shortages Prevention Plan,"‡ which detailed recommendations for avoiding or mitigating drug shortages, and the "Drug Shortage Assessment and Prevention Tool,"‡ a system for actioning the prevention plan.

In 2017 the team collaborated with the Pew Charitable Trusts to publish "Drug Shortages: An Exploration of the Relationship between US Market Forces and Sterile Injectable Pharmaceutical Products."‡

For more information on any of the groups, contact Carol Winfield, ISPE Director of Regulatory Operations, at cwinfield@ispe.org.

— Carol Winfield,
ISPE Director of Regulatory Operations

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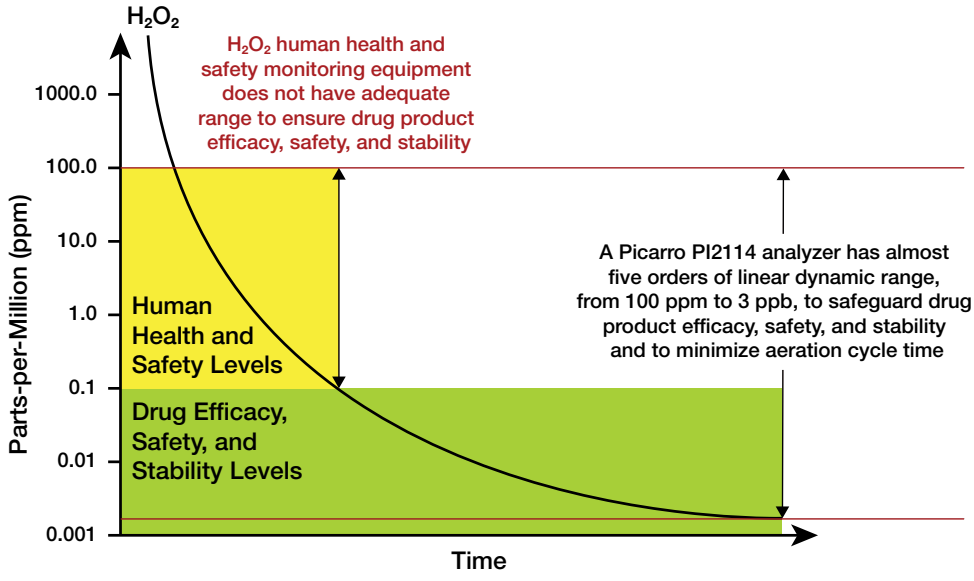
* Available free for ISPE members at https://www.ispe.org/initiatives/quality-metrics/publications-tools

† Available free for ISPE members at https://www.ispe.org/news/cultural-excellence-report

‡ Available free for ISPE members at https://ispe.org/initiatives/drug-shortages/publications-tools

Picarro Ensures Ultra-Low Residual H_2O_2 Levels for High-Potency API, Biologics, and Aseptic Fill-Finish



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COST-SAVING FEATURES

- **No wet chemicals or consumables**
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Picarro analyzers measure hydrogen peroxide as low as 3 ppb to help avoid oxidation and safeguard drug stability. Major pharmaceutical, CMO, and isolator companies use them in high-potency API and biologics manufacturing and in aseptic fill and finish.

The Picarro PI2114 analyzer is fast and easy to use. It doesn't need chemicals or consumables. And it requires infrequent calibration and maintenance to minimize operating costs.

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GXP CONFERENCE IN MOSCOW

Memorandum of intent creates ISPE affiliate in Eurasia

In October 2017, for the first time in its history, ISPE participated in an educational conference at Moscow's GXP Institute, part of the Russian Federation's Ministry of Trade and Industry. Past Chair Mike Arnold welcomed the audience via videoconference, and Richard Denk from the ISPE DACH Affiliate delivered the keynote address on aseptic processing and upcoming regulation.

The highlight of the conference occurred when ISPE Vice President of European Operations Thomas Zimmer, PhD, signed a memorandum of intent on behalf of ISPE CEO and President John Bournas, to establish an ISPE Eurasian Economic Union (EAEU) Affiliate.

An ISPE EAEU Affiliate would provide great opportunities to the pharmaceutical community of the union countries, Alexander Sharonov, Director of the new affiliate, told the Russian State Institute of Drugs and Good Practices. "[I]t is the access to the latest technologies and professional knowledge. … Such expertise and the best world experience in the sphere of pharmaceutical engineering are being developed particularly in the ISPE association, which unites more than 18,000 members from more than 90 countries of the world."[1]

"We want the professionals working in Russia to be aware [of] and enjoy the same opportunities as foreign colleagues," added Sergei Tsyb, Deputy Minister of Industry and Trade of the Russian Federation. "ISPE is a nonprofit organization that conducts many educational programs, issues manuals and scientific materials on the design, construction, and operation of pharmaceutical production. Thus, we help our specialists to be at the same educational and professional level with foreign colleagues."[1]

The idea of an EAEU Affiliate was first proposed in July 2017, when a delegation of Russian pharmaceutical industry professionals and regulators met with ISPE in Bethesda, Maryland, to discuss the creation of an EAEU Affiliate. The EAEU is an international organization for regional economic integration whose member states are the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, the Kyrgyz Republic, and the Russian Federation. ‹›

—Thomas Zimmer, VP ISPE European Operations

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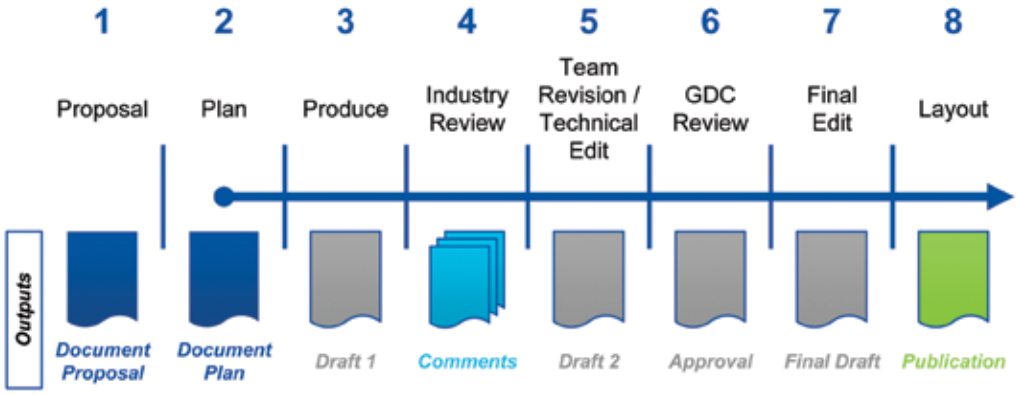
AN ISPE EAEU AFFILIATE WOULD PROVIDE GREAT OPPORTUNITIES TO THE PHARMACEUTICAL COMMUNITY OF THE UNION COUNTRIES

BUILDING COMMUNITY

RIDD Team: Create, Structure, and Deliver Knowledge



SPE is committed to increasing the value of membership. To make sure we are delivering on that promise, we launched strategic development teams to take a hard look at our operations. One of those teams is the Rapid Information Development and Delivery (RIDD) team, a subcommittee of the Guidance Document Committee (GDC).

The RIDD team was created to improve how we create, structure, and deliver knowledge to ISPE members. Initially focused on the Guidance Document development process, the team reviewed publication data from the last five years and found that only one-third of the documents, from proposal to publication, were completed in less than two years. They realized that we needed a modular approach to content development that could deliver critical information to members in a timely fashion. They also recommended that we identify and reduce redundancy within the materials.

RIDD is also helping to build a new information development architecture that will improve the knowledge-development and distribution process, and allow authors and reviewers to operate at a much higher capacity than they do today.

Dr. Trish Melton, MIME Solutions Limited, leads the RIDD team, which has identified two initial goals: First, streamline the guidance document development process to accelerate new and in-process projects. Second, develop a knowledge framework to organize and deliver information.

GOAL ONE: STREAMLINE

The current guidance document development process has eight stages; the RIDD team is focused on stages 1–5.

In addition, applying lean principles to project planning will produce more tightly defined topics and less scope creep. An improved onboarding process will include a workflow diagram and a collection of templates, examples, and tips. Other improvements under development are defining author and reviewer roles more clearly and assigning mentors and technical editors earlier in the process.

The team will roll out the improved and streamlined process in the first half of 2018.

GOAL TWO: ORGANIZE AND DELIVER

The difficult work of identifying duplication, rationalizing content, and creating subtopics is about to begin. The new knowledge management framework will become an essential tool for comparison and retrieval. The team will also develop a plan to convert current knowledge assets—guidance documents, white papers, etc.—to the new framework, developing a lean process to align with the framework, and running a pilot.

It's a lot of work, but the benefits should be unparalleled. In conjunction with the new Guidance Document portal, members can expect to get the right knowledge to the right person at the right time.

— Konyika Nealy, Senior Director of Guidance Documents and Knowledge Networks

Our library of 24 Good Practice Guides is now available free to ISPE members. Visit the new ISPE Guidance Documents portal:

https://guidance-docs.ispe.org

TO TEMP OR NOT TO TEMP?

Short-term opportunities can kick-start your career

David G. Smith

Organizations often augment their workforces to address temporary work requirements. These appointments can range from long-term consulting engagements for complex projects to short-term coverage for employee absences. Over the years, I have spoken with many leaders who began their careers as temporary employees. Many credit those opportunities as career kick-starts, which helped them develop relationships and experiences that were essential to landing full-time roles.

Before applying for a temporary assignment, do your homework. Talk to others about which agencies they used, then check out those websites to learn about benefit options, how they operate, and the kinds of organizations they support. I highly recommend working with agencies that have deep experience within your field. This ensures they will have multiple employment options as well as the knowledge to represent you well when speaking with hiring managers.

If you are targeting a specific company, it is important to note that they may use multiple staffing organizations. While this can be tricky to navigate, leverage your network to see if someone can help you identify a potential list.

Once you engage with an agency, you will want to be ready. You will likely receive questions regarding your pay, shift, commute, travel, and other requirements. (Review my column in the July-August 2017 issue for tips on phone interviewing.) Remember that recruiters work best with candidates who communicate their interests clearly.

Here are some questions I recommend you ask a recruiter before you commit to working with his or her agency:

1. Do I have to pay a fee?
2. Will you contact me about opportunities, or should I apply directly to those that interest me?
3. If the latter, where can I find them?
4. Will you contact me before sharing my résumé with another company or hiring manager?
5. Can you explain the decision-making criteria for the role, who will be involved, and what the next steps are? (Note: This can vary considerably from role to role, even within the same agency.)
6. How can I learn more about the benefits you offer? (Note: The answer can vary by client.)

IS IT THE RIGHT FIT?

Temporary positions can give you critical experience, help develop relationships, and better understand how an organization operates. For candidates that lack internship or other related experiences, temporary positions can be great bridge to full-time positions. If you can impress the company with your quality work, you will have an advantage over other candidates who lack your track record, connections, and personal knowledge of the company's processes.

Temporary positions can also be good for candidates who not sure about which position would be the best long-term fit; these jobs offer a chance to test the water without long-term commitment. Their short-term nature, however, means you'll need to be agile and adaptable to succeed: Your learning curve will be steep and access to information may be limited. The assignment may require specific coverage hours and dates, and sometimes, a full-time employee may have to approve your work.

There also are some real differences in how companies engage with temporary workers. While you'll work on a company campus, your employer is the agency that recruited you. Understanding the rules of engagement and your responsibility for complying with them are the keys to your success. A process-specific question, for example, would likely go to the company supervisor, but a question about taking time off would go to the agency. These topics are usually covered through the offer process and/or orientation prior to the beginning of an assignment.

TEMP-TO-HIRE CONSIDERATIONS

While positions billed as temp-to-hire may become a path to a full-time employment, it is never guaranteed. Before accepting such a position, here are some questions you should ask:

- Is this position temp to hire—or just temporary?
- What is this organization's track record of hiring others who were in a similar position?
- How long must I be a temporary employee before I can be evaluated for a full-time position?
- What process must I follow to be considered for a full-time position?

The answers to these questions vary by organization. In most cases, companies require temporary employees to go through the same evaluation and application process as other applicants.

To maximize your chances of full-time hire, take note of the following tried-and-true guidelines:

- Show up and do great work.
- Relationships matter.
- Learn quickly.
- Communicate your desire to become an employee, but don't be a pest.
- Apply for positions that match your qualifications.

I hope this advice helps you evaluate your opportunity. The right temporary assignment could be a great way to gain valuable experience and launch your career. ‹›

Have other questions? Send me a note at david.g.smith@biogen.com and I will try to answer it in a future column.

David G. Smith is Talent Acquisition Lead, PO&T North America, Biogen.

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Pharmaceutical Water and Pure Steam Systems

LetzM-WFI (patent pending)

- Production of WFI by non-distillation methods
  Ph. Eur. WFI monograph (0169)
  according to the questions and answers paper
  of the EUROPEAN MEDICINES AGENCY

- Ozonation for pre-treatment and ceramic-ultrafiltration

ISPE 2017 ARTICLE OF THE YEAR

A HOLISTIC APPROACH TO PRODUCTION CONTROL

FROM INDUSTRY 4.0 TO PHARMA 4.0

Prof. Dr. Christoph Herwig, Christian Wölbeling, and Thomas Zimmer, PhD

This article presents the work of the newly formed ISPE Holistic Production Control Strategy Working Group, which has identified and summarized the need for a redefined control strategy implementation methodology.

PROBLEM STATEMENT

The current submission-based control strategy plays a key role in ensuring that critical quality attributes (CQAs) are met, and the quality target product profile (QTPP) is realized. It does not, however, consider GMP, facilities, utilities, equipment, and other production-specific controls to mitigate risk and ensure an effective, reliable, and stable production process. In addition, the effect of unknown process parameters, raw material attributes, and impurities usually are not sufficiently addressed in the control strategy lifecycle management—it is often impossible to predict such variations for a production lifecycle already in development.

Transforming today's development-based control strategy to commercial manufacturing by technology transfer and scale requires a best practice methodology that would change the current control strategy into a holistic production control strategy (HPCS).

This would create a flexible and robust production process with well-documented lifecycle management that could be applied to existing production operations as well as facilities of the future, from design concept to detailed design, and from implementation up to commissioning, qualification, and daily operations.

Speaking at the ISPE EU Annual Conference in Frankfurt in March 2016, Ian Thrussell, Expert Inspector at the World Health Organization, identified additional requirements: "The transformation in the design and the execution of the control strategy has to follow a 'data integrity by design' approach."

Data integrity by design is a structured risk-based approach that applies critical thinking to create process maps, process data maps, and data flows to design the production process in a flexible and robust manner. Professionals miss an opportunity for success when they don't apply two key cross-functional factors: a process-oriented approach, and communication skills. Additionally, business process descriptions or process charts/maps and process data maps are not always developed and applied properly.

Critical thinking during the design, creation, and execution of the shop floor production process ensures repeatable, robust, and right-first-time execution of the commercial production process. The parameter space must be adapted throughout the product lifecycle, beyond the original design space and the submission-based control strategy.

ICH is currently drafting the Q12, "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" Guideline, which will specify the post-approval change management of the product control strategy, and enable the application of new, robust, and flexible product and production-process monitoring plans and controls like continuous process verification (CPV).

FIGURE 1: ICH Q10—PHARMACEUTICAL QUALITY SYSTEM

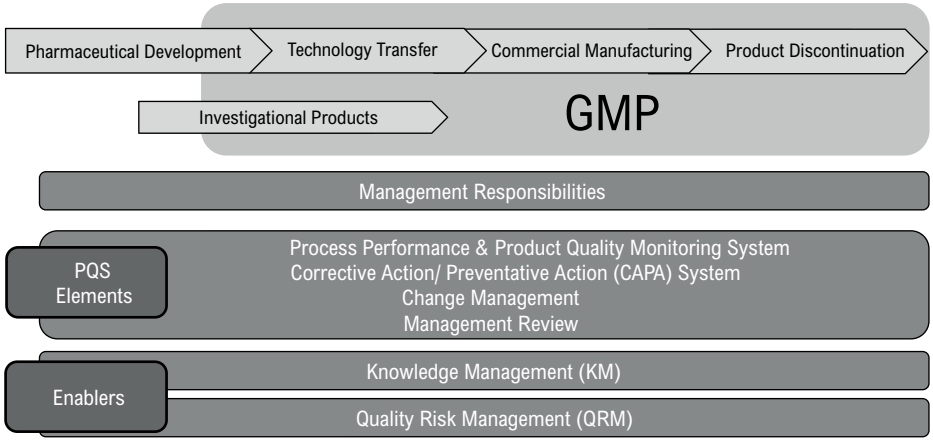
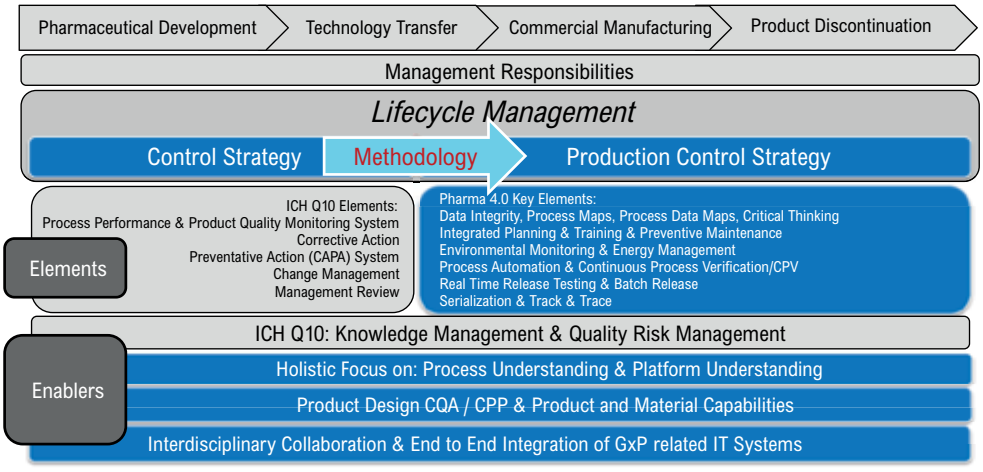


FIGURE 2: FROM ICH Q10 TO PHARMA 4.0—HOLISTIC PRODUCTION CONTROL



All these concepts are currently isolated from each other, however. A new "holistic" production control strategy could be based on existing ICH-defined concepts, incorporate new elements and enablers that address challenges from digitalization and big data management, and include all activities throughout the value chain and the product lifecycle.

THE CHALLENGE: IMPLEMENTING ICH Q10 IN PRODUCTION

This information was presented at the 2016 Facilities of the Future Conference, 14–15 November 2016, Bethesda, Maryland, US

The proposed approach is based on the ICH Q10 view of the PQS product lifecycle and control strategy.

Figure 1 shows the original ICH Q10 visualization of the PQS. This concept is based on key principles (enablers) and control strategy design tools (elements) used throughout the pharmaceutical production lifecycle. ICH Q10 states that "these elements should be applied appropriately and proportionally to each lifecycle stage recognizing opportunities to identify areas for continual improvement."

Using this as a basis, the HPCS working group developed a concrete and practical corresponding picture to detail this approach in production.

Figure 2 shows enablers and elements, which are critical success factors for designing and executing a stable yet flexible and robust HPCS in commercial manufacturing.

The physical and operational design of the pharmaceutical equipment, facilities, logistics, and operational concepts (including work instructions, automation, and equipment) shall be based on business process descriptions, process maps, process data maps reflecting production experience, and best practices. Early collaboration from all pharmaceutical departments—quality assurance, quality control, process development, manufacturing operations, engineering, automation, and information technology (IT)—is required to design a robust, flexible, right-first-time facility that operates at the expected quality level to ensure that the CQAs are met and the QTPP is realized. A data integrity by design principle can also be implemented by applying a risk-based approach based on critical thinking.

While current ICH Q8 and Q10 definitions of control strategy remain valid, facilities of the future will have a high level of automation applying the newest technologies. Pharmaceutical production based on Industry 4.0* factory design will become "Pharma 4.0" when applied to GMP compliance, validation, and GAMP® requirements. HPCS encompasses best practice design methodology from the submission control strategy documentation to the master production control record, up to and including Pharma 4.0 documentation

Holistic Production Control Strategy

- Is a set of enablers and elements that provides a holistic view of production to ensure a flexible, agile, sustainable, and reliable pharmaceutical production that mitigates the risk to patients, products, processes, and the business.
- Covers products and materials designed for fully automated processes. It requires an educated workforce to manage integrated processes and data flows as well as modern platforms, machines, and facilities designed for digitalization and automation.
- Supports business processes with integrated GxP IT systems along the supply chain.
- Requires management to establish and foster an adequate framework and organizational culture for Pharma 4.0.

* Often called the fourth industrial revolution, Industry 4.0 is the digitization of manufacturing, including "big data," connectivity, analytics, the Industrial Internet of Things, and digital-to-physical transfer.

and requirements. This leverages the benefits from the new operational excellence opportunities of Pharma 4.0. A new "Workforce 4.0" will also be required to interact with the complex and intelligent equipment.

APPROACHING THE PROBLEM

Control strategy best practice methodology is outlined in the ISPE PQLI® Guides. HPCS implementation requires a cross-divisional approach and methodology that includes product and production data lifecycle management. This is not yet completely well established in all organizations.

HPCS enablers

ICH Q10 identifies knowledge management and quality risk management as two major enablers throughout the pharmaceutical lifecycle and the bases for HPCS design and execution. Product design—including identification of CQAs, critical process parameters (CPPs), and critical material attributes—is another key enabler for product and material capabilities.

Holistic process and platform understanding needs cross-organizational interdisciplinary collaboration from all departments and stakeholders combined with integration of all GxP-related IT systems to enable data integrity. Enhanced data science approaches in production must become the foundation for decision-making to operate in automated environments, implement process analytical technology (PAT) in its holistic definition, and allow modern advanced technologies like continuous manufacturing.

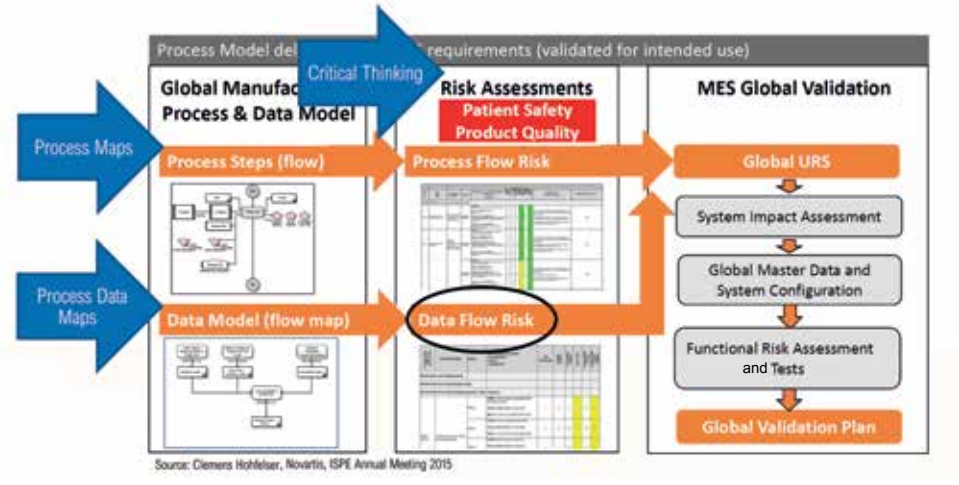
HPCS elements

By applying a design process based on process maps and underlying process data maps, Pharma 4.0 will ensure data integrity by design.

Data integrity is much more than ensuring a good audit trail: It is about

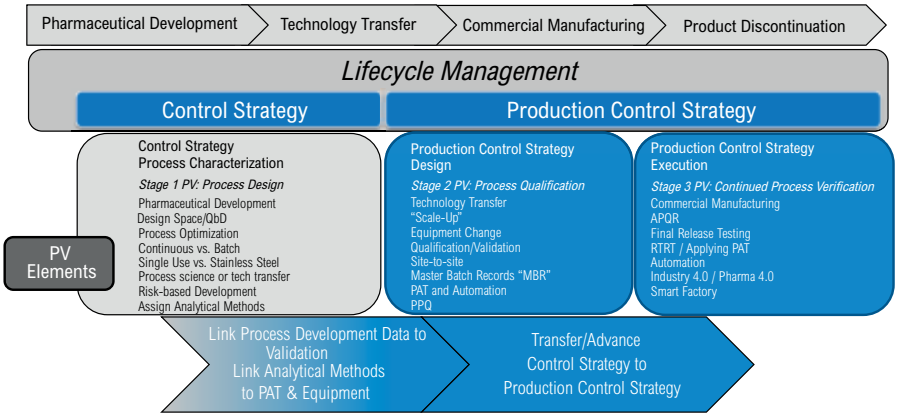
FIGURE 3: UNDERSTANDING THE SCOPE OF THE HPCS

FIGURE 4: ASSESSMENT OF KEY GLOBAL MANUFACTURING PROCESSES



Source: Clemens Hohfelser, "Data Integrity in Manufacturing Execution ... A Process Oriented Approach." Presented at the ISPE 2015 Annual Meeting, 8–11 November 2015, Philadelphia, Pennsylvania, US. Reprinted with permission.

FIGURE 5: THREE-STAGE PHARMA 4.0 PROCESS VALIDATION



Source: ISPE Biotech Special Interest Group

FIGURE 6: INTERDISCIPLINARY COLLABORATION

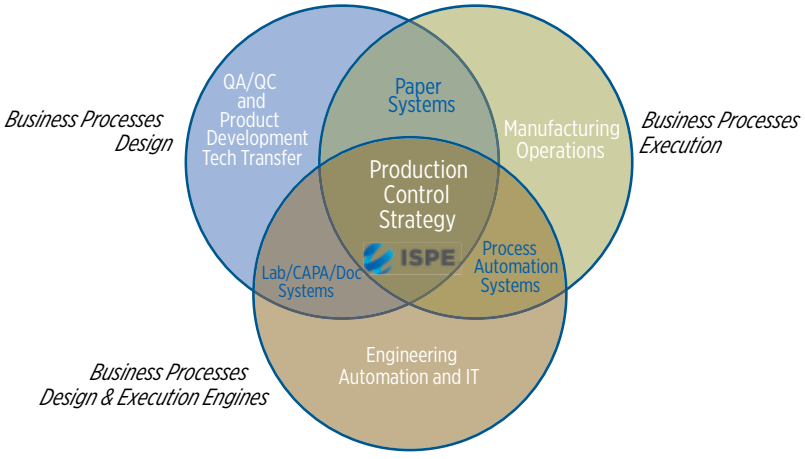
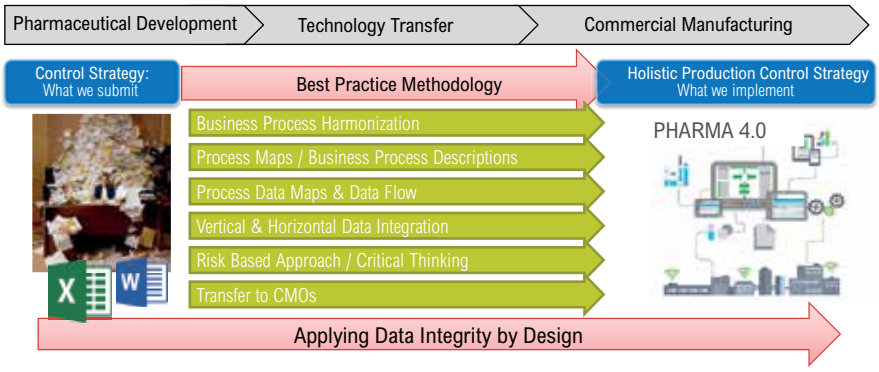


FIGURE 7: HPCS BEST PRACTICE IMPLEMENTATION



quality of data, the right content, and respecting the ALCOA+ principles.† Auxiliary materials and excipients, for example, could have the same name and quality-specific reference number across the global network of a company to avoid mix-ups and misunderstandings. Critical thinking is needed to design a robust, repeatable, but still flexible production process. This includes thorough data science approaches and architectures. When establishing a quality risk map using ICH Q9, for example, one of the most important steps is risk identification, which requires experience, a balanced view on risk, and the ability to imagine what can go wrong. Hence, prior knowledge should be available in a structured form.

Integration of all supporting computerized systems is key, both vertically and horizontally across systems, as well as throughout the product lifecycle and the value chain. This includes physical data interfaces, process automation to support CPV (by applying modern technologies like PAT), and predictive process controls to establish real time release testing (RTRT). Big pharma companies that recognize this need have started to establish a one-source "data lake" for system integration, plus fast real-time and ad hoc reporting for management decisions.

Preventive maintenance to enhance performance and minimize downtimes could be integrated into a process planning procedure that optimizes the collaboration of all production-related equipment, operators, and their training, as well as environmental monitoring, including energy consumption. A "ready-to-run" visual shows all conditions required to start production: Is the employee qualified? Has he/she undergone updated SOP training? Has the machine, room, and equipment clearance been done? Are all maintenance cycles in compliance with internal SOPs? Has the product dossier been updated with the latest corrective/preventive actions and change management?

Environmental monitoring and energy management are similar to preventive maintenance, and should be integral parts of a release to start production. Integrated energy management will ensure that all processes have sufficient electricity and backup. Even seconds of downtime can destroy a batch. All other infrastructure system malfunctions could be defined as relevant for quality and compliance, and integrated into the supervision process.

Automation and CPV usually apply only to their bespoke products. Products more than 10 years old are often not suitable for automated processes, as they depend largely on unwritten operator knowledge of both the process and the interaction between equipment and environmental conditions. The strategic target of a development project, therefore, could be pharmaceutical processes with automated PAT-related controls when CPV is applied.

Real-time and batch releases in a Pharma 4.0 world would be harmonized so that batch and document release are synchronized; this would prevent holding the real-time release of a process until all documents had been reviewed.

Other commercial and regulatory requirements like mass serialization and track and trace against counterfeit products are also key elements of HPCS. As the product code and security number are now considered compliance relevant they must be an integral part of the whole supply chain; this also prevents false positives. Even a high-quality product can hold up the supply chain if its serialization numbers are not correct.

These are all generic key elements of Industry 4.0 applied specifically as Pharma 4.0. In general, all GxP-related IT systems such as enterprise resource planning, enterprise content/documents management, and enterprise quality management could be integrated in one enterprise manufacturing intelligence system.

HPCS in a Nutshell

Potential cost savings are enormous. Regulatory guidelines are in place to leverage this potential, but examples to put them into practice are still missing. At the same time, regulatory authorities and inspectors increasingly apply requirements for quality risk management and safe production for pharmaceutical products. The trend to mega-digitization—the Industrial Internet of Things or Industry 4.0—offers the opportunity to realize these potentials. This is more than just the next wave of hot topics; it will lead to one of history's biggest paradigm changes for pharmaceutical manufacturing.

To create a successful cross-functional approach to these new concepts, the pharmaceutical industry must align with its main stakeholders: regulators, investors, manufacturing leaders, and key suppliers. An ISPE SIG is studying how best to transition commercial manufacturing from current control strategies to an HPCS using a Pharma 4.0 framework.

Three main areas need attention:

Leadership: Senior management understanding, ownership, and responsibility for cross-functional stakeholder management.

Capabilities: Cross-divisional knowledge, understanding, and collaboration.

Toolbox: Identify, implement, and train methods and best practices to implement an advanced HPCS.

PHARMA 4.0: HPCS

The holistic view of the production control strategy consists of four key areas where enablers and elements are applied. Regulatory requirements and guidelines provide overall governance (Figure 3):

1. Manufacturing process work instructions

The master production control record is still the key regulatory element for the description of the manufacturing process. Processes that follow the paradigm of a flexible execution need a flexible control strategy. In addition, the elements of preventive maintenance and optimized process planning influence the production process flow.

2. Quality and compliance

ICH and FDA process validation guidelines help establish flexible production processes, including the CPV and ongoing process verification; these

† See Special Report on Data Integrity, *Pharmaceutical Engineering* 36, no. 2 (March-April 2016): 39 -67.

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enable close monitoring and control of CQAs and CPPs. Combining data integrity and data lifecycle management approaches with practical knowledge management processes is still a challenge in the industry.

In a Pharma 4.0 world, however, the concept of quality assurance must be adapted to cross-functional business processes and must redefine the tasks and responsibilities of systems, cross-functional process owners, and content owners in the various business functions.

3. Performance

To ensure a cost-efficient production process, data must be evaluated, analyzed, and used to optimize the process. Quality metrics will be applied to measure the efficiency of the overall production process. Enabling flexible processes can also shorten production lead time.

In a Pharma 4.0 world, operational excellence goals should be redefined. If targets continue to be "solo-ed" the total optimum will never be reached. This management challenge is supported by knowledge from senior experts and knowledge management tools.

4. Integration: Plug and produce

The HPCS-enabled smart factory will be integrated horizontally and vertically by standard interfaces, which will ease integration of prequalified equipment. This is already established in the semiconductor and other industries. Integration for plug-in compatibility should also comply with data integrity requirements (such as audit trail); data security; seamless integration of online, in-line, and at-line PAT instrumentation process control; and RTRT or packaging serialization and track and trace. Future integration concepts should follow this plug-and-produce concept to reduce costs and enable flexible production solutions and provide a cost-efficient lifecycle management interface.

In Pharma 4.0 the industry needs globally defined technical standards such as GAMP or ISO as well as standards for product quality profiles and technical suitability for automated processes. Some materials should be removed from developer material lists as unsuitable for technical processes (e.g., for high physicochemical variability).

Products made for small batches and personalized medicine need other standards than a mass product for large populations.

HPCS IN PROCESS VALIDATION

The ISPE Process Science Working Group, part of the Biotech Special Interest Group (SIG), enhanced the ICH PQS lifecycle picture and applied it to the three stages of process validation (Figure 5). This shows the evolution of the control strategy to the HPCS across the three process validation stages.

WORKFORCE 4.0

An HPCS needs interdisciplinary collaboration of all organizational business units responsible for the production process, technology, and quality. Per ICH Q10, this also includes management, since they are responsible for quality and HPCS compliance. We call this Workforce 4.0.

SUMMARY

There is a huge potential in applying Industry 4.0 technologies along the end-to-end supply chain. Regulatory prerequisites for this approach are already in place. While the industry may still be hesitant to implement these technologies and change well-established, qualified, and validated production processes, development of the ICH Q12 "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" Guideline will enhance the regulatory basis for this approach.

The goal of the Pharma 4.0 SIG and its Holistic Production Control Strategy and Plug and Produce Subgroups is to provide best practice implementation methodologies, approaches, and practical examples on how to apply the technologies and integration approaches and to improve quality by well-understood and -controlled processes. With these in place, data integrity, quality, compliance, and predictive production processes will be the reward. ‹›

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IN CONVERSATION: BRINGING THE OUTSIDE IN

"When a factory is needed in the future, what could it look like, and how should we think and work differently to build it?" This is a question that Roger Connor, President, Global Manufacturing Supply, GlaxoSmithKline, considers frequently. I had the privilege of meeting him during the ISPE 2017 Annual Meeting & Expo. This is an abridged and edited version of our conversation.

Roger Connor

How do you define innovation? How do you develop that value within an organization, from the ground up?

It's all about people and the "leadership shadow" that they cast. At the top of the house you have to welcome innovation, recognize it, and demand it. Right across the organization, you want every one of your leaders to believe it's their role to innovate, to spot things that can improve. So, as well as the big innovation plays—the headline projects—you need to recognize all the smaller things that get done.

Line managers are some of the most important people in our factories. They set the tone and culture for the company. If they set a certain expectation of a team and encourage innovation, that's where the successful ideas come from.

Do you think it is easier outside of North America? Is there a cultural difference across continents?

Western countries can be more focused on trying to solve things themselves. I see a greater hunger in Asia to go and learn from others. They're not embarrassed to "steal with pride," as we call it, to find a best practice in another sector and apply it. If you get into a mindset of "Well, it's not invented here, so we'll have to find a solution," that is just waste.

I was going to ask about the impact on manufacturing operations of trying to solve things yourself, but you summarized it with one word.

It's complete and utter waste. I'd much rather ask our teams to learn first—to go and see what others have done. That's the behavior we should reward. If we encourage people to go out and learn, we'll get a massive return. This also allows us to move rapidly onto the next problem, and the next one after that.

What are the industries from which pharma can learn the most, and what do they bring to the table?

The obvious one is aerospace, which is very highly regulated, as we are. It has deviations, it has quality control issues, and still the industry manages to have one of the best safety records of any sector in terms of avoiding catastrophic failures. Some of the areas we can learn from in aerospace include material science and preventive/predictive maintenance. So, aerospace really interests me.

Another is the automotive industry. The sector has had to innovate to survive as profit margins have been squeezed and competition has grown. The industry is going through radical change in terms of new technology. We can learn from this and recruit some great talent too.

How easy is it to do that?

It's very easy to attract people to health care from outside our sector. At GSK, for example, what attracts people most is our mission and values. It's an opportunity to apply their technical skill set in an area where they feel they can really make a difference.

What is it that they bring to the table, in terms of values and traits, that bodes well for the future and future hiring?

They come in to the sector with a real hunger for continuous improvement. They believe that everyone has a responsibility to create value every day, whether it is to make a product safer or make it cheaper. I love that infectious desire to improve.

When managing a global operation, do you look at it as a whole or as a series of necessarily diverse parts that address distinct needs across geographies? Is a holistic vision possible?

I look at both. There are elements, I believe, in an organization our size that need to be looked at holistically. For example, you want everyone to buy into your mission and goals as a global company. And everybody needs to understand the important role they personally play.

On the other hand, within our global manufacturing organization (I have more than 70 factories and 30,000 employees), we have quite specific skills, competencies, and disciplines that are essential to our operating environment. Our people need to engage fully with these. They also need to feel they can influence their immediate work area to make things better. And you have to let that happen.

So it's a mixture: You set some very clear global rules and standards, and then, within that framework, let the positive aspects of local culture shine through.

In a complex operational environment, how do you make compliance easier for employees?

We ensure compliance through our training, our procedures, our oversight, and our process design. All these things add up to creating a compliance-based culture. But we have to make it easier for people to do the right thing every time. That starts with simplifying our SOPs (standard operating procedures). They can be complex, not visual enough. I want them to be incredibly intuitive for our operators, so there's no room for misinterpretation or omissions. Equipment design and technology can also help here. We need to hardwire the right way of working into our machinery to reduce the scope for operator error.

What is needed for sustainable manufacturing to become embedded in an organization's overall culture and management?

I think this goes back to a continuous improvement culture and really asking yourself each day, whether as a leader or an individual: "What have I learned? And tomorrow, what will I do better?"

YOU SET SOME VERY CLEAR GLOBAL RULES AND STANDARDS, AND THEN, WITHIN THAT FRAMEWORK, LET THE POSITIVE ASPECTS OF LOCAL CULTURE SHINE THROUGH

We have tried and, I think, have successfully created a "production system" environment at GSK, a defined way for our teams to operate, inspired by the automotive industry. We're in year six of fostering that production system mindset across the organization. I think sustainable manufacturing depends on creating this environment—one where teams manage their own performance, solve problems together, and learn from their mistakes. You need standard ways of working—for leaders and operators—to make this work. The result is a very powerful dynamic that delivers sustained performance improvement.

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EMBRACING INNOVATION

James Breen

ISPE has identified facilities of the future (FOF) as a priority in its strategic plan, and is paying particular attention to helping members and corporations understand the skills they will need to advance and maintain a competitive edge. These "musts" are key to facilities of our future (FOF) programs:

- Manufacturing facilities must be able to respond to the rapid changes in technology.
- They must meet global customer demands and expectations.
- They must be agile and flexible enough to produce multiple products, often simultaneously.
- They must manufacture products at the highest quality standards at all times.

Over the past few years ISPE has mobilized its global resources to develop programs, conferences, and training that reflect viewpoints from regulators, academia, owners, equipment vendors, and service providers on the FOF trends in manufacturing.

In 2016, ISPE added FOF as a seventh category in its Facility of the Year Awards (FOYA). These prestigious honors recognize global teams that exhibit the highest caliber of innovation and technological ingenuity in pharmaceutical engineering projects. In 2017 Lilly was recognized for its Puerto Rico/Indianapolis Continuous Oral Solid Dosage project, garnering category wins for Facility of the Future and Process Innovation. The company was named Overall Winner on 31 October at the 2017 ISPE Annual Meeting & Expo Membership and Awards Breakfast in San Diego, California, a recognition that demonstrates the value and importance of this topic within the pharmaceutical industry.

FOF was a key theme in the ISPE Annual Meeting keynote presentations, as well. Enno de Boer of McKinsey discussed "Digital Manufacturing: The Next Frontier of Innovation" and its impact on pharmaceuticals and other industries. FOF will also be a key topic at the 2018 ISPE Europe Annual Meeting this March.

Roger Connor, President Global Manufacturing and Supply, GlaxoSmithKline, another keynote speaker at the 2017 Annual Meeting, encouraged attendees to embrace innovation and the manufacturing process of the future. "If we do," he said, "not only will we deliver for the person at the end of the supply chain, we will become an example for all other industries. Maybe someday they'll call *us* for help and inspiration."

The Global Pharmaceutical Manufacturing Leadership Forum (GPMLF), comprising some 50 industry leaders from top pharmaceutical companies around the world, works with ISPE and regulatory agencies on critical issues facing the industry. GPMLF is also focused on FOF, leading discussions and providing information to the pharmaceutical industry on how to handle new technologies and how to prepare workers to participate in this transformation.

THE LIFE SCIENCES CAN ALSO LEARN LESSONS FROM OTHER INDUSTRIES, AND CAN USE THAT INFORMATION TO CATALYZE THE DEVELOPMENT OF NEW FOF CONCEPTS

The life sciences can also learn lessons from other industries, and can use that information to catalyze the development of new FOF concepts. Aerospace, for example, is an industry that is as regulated as ours and is one from one which we can leverage best practices.

The speed of change and developments in technology are causing organizations in all industries to rethink their business models. Industry 4.0, the Internet of Things, 3D printing, digital transformations, machine learning, virtual reality, artificial intelligence, robotics, and virtual reality are some of the challenges facing industries and organizations around the world.

While these changes will no doubt be disruptive, they will also create new opportunities for people working in the industry. The workforce of the future must understand these trends and know how to use developing technology. Both ISPE and GPMLF have identified the workforce of the future as a strategic priority; both organizations have made commitments to help prepare their members and employees for the future.

It's an exciting time for the pharmaceutical industry. ‹›

If you have comments on how ISPE can better address the topic of Facilities of the Future, please reach out to me: jbreen4@its.jnj.com.

James Breen is Vice President, Lead Biologics Expansion, Janssen Pharmaceutical; Vice Chair, ISPE Board of Directors; and Vice Chairman, GPMLF. He has been an ISPE member since 2000.

It's a long-term process.

It's a gradual process. It's easy to issue instructions and standards. You can do that in weeks. But to inspire people—head and heart—they need to understand and buy into the vision and what you want them to do. This starts with identifying the "change agents" within your facilities—influential individuals who get it and can bring people with them.

What are the benefits for patients?

First, the quality of the product continues to improve. Second, patients can rely on you to keep your products in supply. The third is competitiveness: You drive the cost of goods down for your products and they become more affordable.

Patient benefit is a big motivator for me and the people in my organization. We talk a lot about the person at the end of our supply chain.

Let's shift gears and talk about gene therapy and its impact on pharmaceutical manufacturing.

It's going to be totally game-changing. Remember GSK launched the first approved cell and gene therapy, Strimvelis, in Europe. This is a seriously impactful cell and gene therapy that we've brought to market. It is totally different from anything we have made before. So while the clinical trial supply chain and commercial supply chain are different for a normal pharmaceutical product, for cell and gene therapy they are exactly the same.

These products can have an incredibly short shelf life. That means your manufacturing facility has to be co-located with your treatment facility, or at least be very close. Your laboratory also becomes your factory. For GSK, that has meant forging some strong external partnerships.

Can you talk about creating the right conditions for developing cell and gene therapy?

Absolutely. We're a big presence in the UK, and we have been talking to the government about what will make the UK the go-to location for cell and gene therapy development and manufacturing. There are a number of critical factors: links to academia, to encourage research; the availability of specialist skills and labor; and a favorable fiscal environment to attract investment. Put these things together and you will attract cell and gene therapy companies.

With Brexit looming, that last point might prove difficult.

To be honest, at GSK we don't see Brexit as driving our choice of location for manufacturing. By far the most important factor is access to the skills and capabilities we need. There are going to be challenges with Brexit, such as the importation of product and retesting. We'll have to direct some resources to address that.

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Looking to the future, from a manufacturing perspective, what are the top three obstacles the industry faces?

As an industry, we are risk averse. We need to take some chances on new technologies and really swing behind them, put our best brains on them, and make them work. There'll be bumps along the road, so we need to be courageous and place some bets on big technology. That's one.

Two, in our industry we tend to work in silos. We have to work in partnership more with R&D and commercial teams, sharing business goals. It's not enough to speak from a manufacturing perspective only. We need to work together to deliver a strategy and goals that we all believe in and want to make a success.

As a sector, our thinking can also be siloed. When GSK forged a partnership with the McLaren Formula One racing team to help improve our business, it made a huge difference. We weren't sure what to expect at the start, so we had to believe. We created a joint team to look at performance in our packaging areas for potential improvements. The idea was to use the race mentality. First, we had to define what "winning" looked like for us: "A day when no one is hurt, a day when we don't have any defects." Then problem-solve to achieve this goal, like a Formula One team. We got improvement within days, thanks to the completely fresh perspective they brought.

The third obstacle is our sector's tendency to focus on bigger, long-term-change projects rather than short-term improvements that can deliver quick wins. We need both. One of the benefits of having a consumer health care business within GSK is that this encourages the pace of change and execution associated with FMCG (fast-moving consumer goods), delivering results more quickly. Rapid results also create energy and confidence in your organization. ‹›

—Anna Maria di Giorgio

BREAKING BARRIERS TO BIOSIMILARS

James Strachan

Sitting Down With … Richard Markus, Vice President of Global Development, Amgen, USA

Richard Markus

How did you get your start in pharma?

I've always been interested in science, especially biology, but my first job after college actually involved statistical programming in the pharma industry. As I learned more about the industry, my interest in it—and particularly in clinical research—grew. So my next step was to go back to school and earn my MD and PhD, with the expectation of going back to the field of drug development as a physician. I started working at Amgen around 11 years ago as a physician scientist. I worked with a fantastic team to develop a bone-targeting agent (XGEVA; denosumab) for cancer patients, which was in phase II trials at the time. It was a very large effort involving multiple studies in patients with different cancers, so it was an exciting way to start my career.

But then you moved into biosimilars …

Right. My roles progressed until I had the opportunity to help start Amgen's biosimilars business—an entirely new division for the company. Back then, there wasn't much clarity on how to develop biosimilars; the regulatory environment was still evolving (and it still is today). Indeed, biosimilars represented a whole new class of product; they are not innovator drug products and certainly not chemical generics. It was a once in a lifetime opportunity to be involved in the creation of a whole new type of product.

How has biosimilar development changed?

Earlier biosimilars were based on smaller and generally simpler products, but in the last couple of years biosimilars have been involved in much more complex antibody treatments. They are not just more complex because of

their size, but because they consist of multiple parts with different functionality or activity. For example, one part may bind the primary target on the tumor, while another binds T cells or the immune system—the combination is what provides activity, and each different part of the biosimilar must have no clinically meaningful differences in function or activity compared with the originator. Technology advances in the last two decades have not only enabled us to manufacture such complex biologics, but also to evaluate them with high confidence. And that's allowed us to expand our biosimilar pipeline from three products to ten.

What have been the biggest highlights of the division so far?

I am really proud of our work with trastuzumab—a biosimilar that we are developing with Allergan. The collaboration with Allergan began very early in our program and focuses on oncology products. We are both mature companies in terms of our goals; we know who we are and what we want to contribute, which makes for a successful partnership. It's important for us both to have a high-quality product, and to have the clinical data to confirm and support the level of similarity, because it gives patients and physicians the confidence to make an informed decision about the drugs they want to use. Trastuzumab is currently in review in Europe and the US for market authorization and we are looking forward to the anticipated approval.

And what about personal highlights?

The biggest highlight for me has been working with fellow scientists at Amgen. Many companies outsource much of their biosimilars work, as they don't have the capacity to do it themselves. We have built our biosimilars

THINK (BIO)PRINT

Erik Gatenholm, CEO of Cellink, USA.

Great strides are being made in bioprinting, and the end result could revolutionize pharmaceutical development and testing.

In the November [2017] issue, *The Medicine Maker* discussed the far future of healthcare and drug development. From my perspective, the ideal future would give everybody access to healthcare, and would enable everybody to live a long, healthy life. Three-dimensional printing and artificial intelligence were two key technologies discussed last month, but another technology that will certainly have an important role in the future of medicine is bioprinting. The possibilities of bioprinting are potentially endless. My company specializes in "bioinks" and I like to tell people that, if you collected all of the tissues being printed by our customers, you'd almost be able to build an entire human body! Other companies are printing other tissues, such as cancer tumors, which can be useful in drug development.

Like most shifts in the industry, bioprinting will come to the forefront incrementally, rather than with a single big breakthrough. With each passing year, we gain more knowledge about how cells react and work with the latest bioprinting technology. With that data analysis, we can build better models, which help us further understand new areas, which help us build better models, and so on. Bioprinting is heading in a few different directions, with R&D groups and academic researchers wanting to experiment and play around with the possibilities. The next market step will be to break into specific industries. Toxicology and drug discovery are obvious areas where bioprinting could be a real benefit—think of how commercial drug development might change if companies could test candidate molecules in human models early on. And it could also affect personalized medicine.

Beyond that, the far future potential that we all have in our minds is organ transplants. There's a great deal of research and technological evolution that needs to be done to reach that point, however, and we need a few champion institutions to help push it forward. With the current organ donor system, there will never be a surplus—rather there will always be a waiting list. And we can never unleash the potential for research institutes to test theories with human organs. Bioprinting could pave the way for human organs for transplant and research—eventually. The big questions then will revolve around regulation. The industry will be massive, but will it be controlled by a pharma patent perspective or by more general regulations? How do we decide who gets priority and when, if they're widely available? It's important for companies operating in the space to keep an open dialogue with regulatory bodies to make them aware of the various processes so these questions can be brought up and answered alongside the evolving technology.

It's a very exciting stage for bioprinting right now—and it's only going to get more exciting in the years to come. Currently, the industry and regulators are amassing a tremendous amount of fundamental knowledge and it won't be long before smart decisions start being made. We need some good, solid, successful applications to move things forward. It has been the same with the 3D printing of metals and plastics—everybody knew that it could deliver fantastic benefits, but it has taken time for everyone to figure out how 3D-printed parts can be best used. We just need to decide how bioprinting can genuinely bring benefits to pharma development and patients. ‹›

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business with the same laboratories, manufacturing facilities, and the same group of scientists who I've been working with for years, which has been a great pleasure.

I think I am very fortunate in my role. I still get the fun of working with scientists and data—and making decisions about the program and the molecules themselves. I also interact directly with regulators, who have been really well engaged with the field from the very beginning. Working with regulators is very rewarding; I like to think we have made a meaningful contribution to shaping the field and helping patients.

If you could change one thing about the biosimilars field, what would it be?

There was actually a recent change in the biosimilars field which we are pleased with, and which we will continue to support. In the US, the Centers for Medicaid and Medicare Services (CMS) reversed a policy for biosimilars that used blended billing and reimbursement codes that ultimately followed a generics reimbursement paradigm. As a manufacturer of innovative biologics and biosimilars, we are pleased that CMS put patient needs first and will now ensure that each biosimilar product will have its own billing code and individualized reimbursement rate. This will facilitate efforts to support product traceability and ultimately foster a more competitive biologics market.

In the generics world, there have been many shortages of critical chemotherapies, partly because of how policies have played out in terms of incentivizing (or disincentivizing) certain methods. I think it is important that we actually learn from those issues and make different choices for biosimilars. We need to be able to ensure consistent quality with continuous competition—both in the short term and long term.

The challenge is creating sustainability for healthcare assistance—particularly in oncology—because patients are often treated with two or three product combinations at a time, which is expensive (and a cost that is endured through second and third line treatments as well). It's great that we can help save lives, but to maximize the number of lives we can save, the cost of drugs needs to be addressed, and healthy competition is the solution.

All of this said, the biosimilar payment environment in the US is still evolving, but Amgen supports a "level playing field" for how reference products and biosimilars are paid for. ‹›

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INDIAN SERIALIZATION MANDATE AND THE US SUPPLY CHAIN

Arjun Guha Thakurta

India is a worldwide leader in drug manufacturing, producing 10% of global pharmaceuticals, with 2016–2017 exports valued at $16.4 billion.[1] Indian generic manufacturers generate 20% of all global exports and more than 80% of antiretroviral drugs in the developing world.[7] India's pharmaceutical market is projected to reach $55 billion by 2020.[2]

Given the strength and importance of the country's pharmaceutical sector, it is essential that Indian exporters adapt to comply with stringent new global regulatory requirements for serialization and traceability. These have been enacted by countries around the world to support the manufacture and distribution of safe, high-quality drugs.

This challenge will be felt keenly in the United States, since India supplies roughly 30% of its generics market. While there are approximately 546 manufacturing units in India that supply product only to the United States,[1] many are only at the early stages of implementing serialization. Some were not ready to meet the US Drug Supply Chain Security Act (DSCSA) mandate for item-level serialization, which became effective last November.[5] This is one reason that the ISPE Serialization Workshop in May 2017 highlighted the Indian generic medication supply shortage in a discussion with participants from the US Food and Drug Administration's (FDA) Office of Drug Security, Integrity, and Recalls. On 30 June 2017 the agency modified its draft guidance and issued a one-year nonenforcement period until November 2018 to give manufacturers additional time and avoid supply disruptions.[8]

In addition to serialization, harmonized standards between the United States and India will also help ensure an uninterrupted flow of safe medicinal products. For these reasons, CONVAL Group, consultants to worldwide pharmaceutical companies on compliance and quality issues, and RxGPS, the alliance for global pharmaceutical serialization, provide information and recommendations to bodies such as GS1 India,* Pharmexcil, National Informatics Center (NIC), Directorate General of Foreign Trade (DGFT), Ministry of Commerce, Drug Controller General of India, and several Indian

* GS1 is a nonprofit organization that develops and maintains global standards for barcodes and other unique identifiers. According to its website, GS1 India works with industry and government agencies "to enable compliance with regulatory requirements and global best practices." For more information, see http://gs1india.org.

FIGURE 1: COMPARISON OF US AND DGFT REQUIREMENTS

Packaging Levels	US DSCSA	India DGFT
Pallet, partial, and mixed case Meant for transport/logistics (tertiary)	• No DSCSA requirement • US supply chain requirement—SSCC	**Tertiary**: GTIN 14, expiry date, batch number, and SSCC
Homogenous case Intended for logistics and sale Contains inner packs and/or quantities of lowest unit of sale (tertiary/secondary)	• GTIN 14 (NDC encoded) • Expiry date • Batch number • Unique serial number	**Tertiary**: GTIN 14, expiry date, batch number, and SSCC **Secondary**: GTIN 14, expiry date, batch number, and unique serial number
Inner pack (secondary) Packaging level containing multiple lowest unit of sales. Used for convenience and handling	• No DSCSA requirement	**Secondary**: GTIN 14, expiry date, batch number, and unique serial number
Lowest unit of sale (for sale to pharmacy). Bottle, blister carton, large vials, cartons of vials, etc. (secondary/primary)	• GTIN 14 (NDC encoded) • Expiry date • Batch number • Unique serial number	Saleable packs concept undefined according to India DGFT mandate
Primary level (for sale to consumer). Packaging in direct contact w/medicine: e.g., strip, vial	• None (if not lowest unit of sale)	**Primary**: GTIN 14, expiry date, batch number, unique serial number (optional)

Source: Amerisource Bergen

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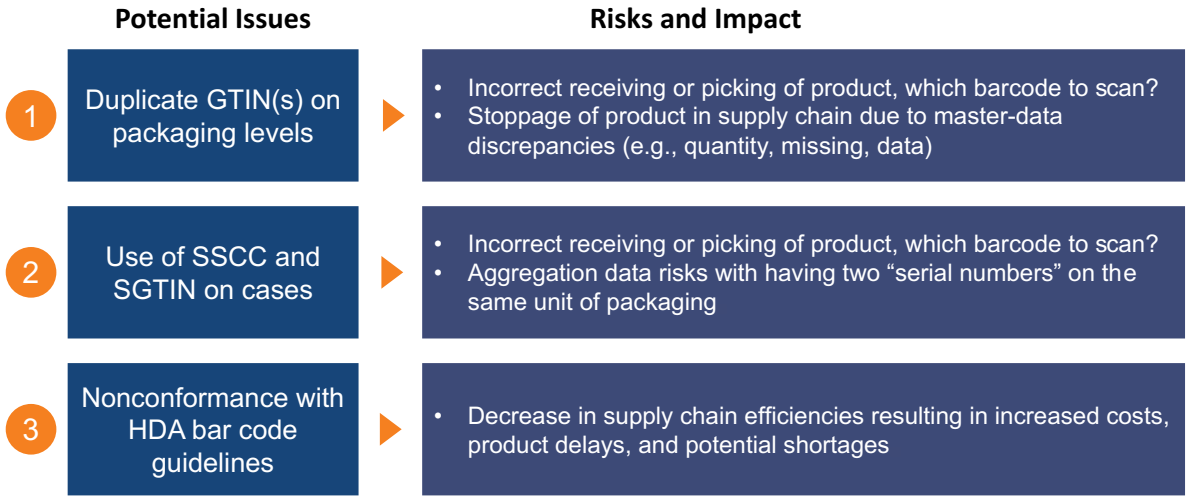
FIGURE 2: US MARKET IMPORTS—ISSUES, RISKS, AND IMPACTS



Source: Amerisource Bergen

pharmaceutical associations that implement, regulate, and enforce India's mandate for serialization for all exports of medicinal products. These efforts are directed toward aligning India's serialization regulation with the GS1 global standard[3] and with DSCSA mandates in the United States (Figure 1).

There are four key areas of risk that threaten Indian pharmaceutical exports and the US supply chain: scope, collaboration, automation, and reporting.

SCOPE

Every pharmaceutical exporter of medicinal products that we've talked to has indicated that its serialization program has overshot the scope, its budget, and timeline. This affects departments that include artwork, supply chain, new product launch, target-market-specific regulations, shop-floor production, quality assurance, information technology, and engineering. At the same time, new international regulations continue to evolve, with recent additions from China, Egypt, Jordan, Russia, Saudi Arabia, South Africa, and South Korea. This is important because organizations that have developed an internal serialization program are now extending them beyond the walls of the company, since they partner with dozens or hundreds of contract manufacturers around the world.

The risks of inadequate scoping include limited time to develop a complete, properly funded serialization program that complies with evolving regulations, and managing with limited resources to meet these challenges.

Limited time

Approaching deadlines for new serialization regulations leave limited time for compliance. This could lead to loss of market share and supply chain interruptions, with patients paying the price if drug shortages accrue. Because the few global vendors that provide compliant solutions are already overbooked, the average time of a line delivery can be as long as 8–9 months. Average time for qualification of each serialization line is approximately 8–9 weeks. IT integration for reporting requires additional time. The key to compliance, therefore, is linked to an early start of a serialization program.

Ever-changing scope

The extent of a company's serialization program depends on different and changing country regulations that require software upgrades, new installations, or new equipment. These additional efforts increase serialization program costs and alter schedules. This happened when both China and Brazil put their regulations on hold while they updated them. Meanwhile, companies had already invested to meet the compliance mandates. These moving targets make it difficult for management to set up a fixed schedule and budget. As a consequence, budget and timelines must be tracked and updated regularly. This effort should be company-wide, ongoing, and consider new directives issued from regulators.

Lack of skilled resources

Resources that can handle complex serialization programs and understand the end-to-end life cycle of data and its integrity are in short supply. Detailed technical knowledge and experience in serialization hardware and software configurations, artwork, a comprehensive tracking list of finished product stock keeping units (SKUs) and their delivery schedules, packaging orientation, IT infrastructure, site-server and data-exchange-reporting cloud solutions are some key competency areas. Generally, multiple vendors are involved at various levels of the solution.

Less-skilled resources can cause damage or add risks. The major risk of insufficient or inadequately trained resources is that track-and-trace solutions will continue to be commercialized without key understandings of configuration management, Electronic Product Code Information Services (EPCIS)[†] reports, and reconciliation due to inadequate testing.

[†] A global GS1 standard that allows different applications to create and share electronic product code data, creating a framework that permits all trading partners to know the status of any given item.

COLLABORATION

The serialization world has become a fragmented network with diverse country-specific mandates, some of which are not even aligned with GS1 global standards. Some countries have issued serialization mandates without performing a regulatory risk assessment to check the effect of new regulations on a globally integrated supply chain.

Similarly, many serialization solution vendors failed to perform standard feasibility studies, which led to vendor blocking and dedicated data exchange. Consider, for example, a facility that hosts multiple vendor-specific site servers. If vendor A installs eight lines and their proprietary site server to manage those lines, vendor B then installs six *more* lines and *their* site server. The Open Serialization Communication Standard (Open-SCS) Working Group[6] created the interoperability standard for industrial automation in which users, vendors, and consortia collaborate to create secure and reliable data transfer standards for multivendor, multiplatform programs like this.

Inadequate collaboration has resulted in a higher cost and variable implementation schedules across supply chains. Downstream supply chain partners, including wholesalers, dispensers, and patients, are currently not even aware of or trained to understand what needs to be done.

AUTOMATION

Track-and-trace systems follow a five-level model: line-level equipment performing serialization coding-inspection-confirmation (levels 1 and 2); site-level server for serial number issuance and reconciliation (level 3); enterprise resource planning (ERP) systems, and manufacturing execution systems (MES) for product data exchange, e.g., process order, product ID, batch number, and expiration date (level 4); and applications—generally cloud-based—for reporting and data exchange with health authorities, wholesalers, and others (level 5).

Developing these systems involves a multivendor system landscape that is fairly new to the pharmaceutical industry, especially in developing countries. The setup of these systems is complex, posing risks if something goes wrong. Accountability and responsibility issues arise when there are technical problems.

INDIA IS A WORLDWIDE LEADER IN DRUG MANUFACTURING, PRODUCING 10% OF GLOBAL PHARMACEUTICALS

In developing countries, new serialization vendors are mushrooming, despite their lack of experience with good automated manufacturing practices (GAMP®) standards. Many do not follow the software development life cycle approach, and testing is rudimentary. They are unable to manage configuration changes and modular developments, and frequently change the base version of the software to incorporate new functionalities. They also do not understand the critical requirements of 21CFR211.68[‡] and other regulatory requirements that are essential for assuring data integrity and a robust serialization solution.

Data exchange and reporting carry their own risks and, in case of supply interruptions, can disrupt availability across wide geographic areas.

REPORTING

Every country has its own reporting mandate and ways of exchanging data. In India, all serialization data is reported to the Drugs Authentication and Verification Application (DAVA), a national portal that is maintained by the NIC.

Data repositories such as this, which host sensitive business information, need robust security to thwart unauthorized access and breaches to protect sensitive business information. Security holes can render the portal vulnerable to hackers, who tend to target the most vulnerable data repository.

In addition to security concerns, the dynamic reporting requirements of level 5, which enable diverse, multicountry reporting with the use of standard software tools, carry the risk of error and scope creep. The location that has had, or currently has, physical possession of the product must have accurate master data, transactional data, and event data related to the product to assure real-time point-of-dispense verification. Any software error in this database can directly affect patient safety. Scope creep occurs when a new regulation leads to a technical upgrade of already commercialized serialization lines, which in turn can require configuration changes to hardware and software, which introduce other new risks. This adds additional effort, time, and cost to the program.

Until now, few countries have successfully achieved live productive environments with established country reporting and downstream supply chain integration. The effect of the real-life portal load and stress is unknown to most implementation programs currently underway.

INDIAN SERIALIZATION

Export requirements

In 2011, India's Directorate General for Foreign Trade (DGFT) began to issue public notices informing manufacturers that as of 1 April 2016 all drug formulations for export must be serialized at the primary, secondary, and tertiary packaging levels.[1] While primary level serialization is currently optional, dummy serial numbers need to be recorded in the portal for export to countries that have no mandatory serialization requirement.

Drug formulations must be identified with a 2D barcode encoding a 14-digit global trade item number (GTIN), batch number, expiration date, and unique serial number. Drugs can be exported only if both the tertiary and secondary packaging carry bar coding as applicable and the relevant data is uploaded to DAVA. Verification occurs at each packaging level as defined by DAVA reporting guidelines.[4]

[‡] US Code of Federal Regulations Title 21, Part 211, Section 211.68, "Automatic, mechanical, and electronic equipment."

FIGURE 3: INCONSISTENT LABELING CREATES CONFUSION

- Multiple GTINs on homogenous cases
- SSCC and GTINs on same homogenous cases (nonlogistics units)
- Mix or combination of GS1 India-issued GTINs and US-issued GTINs on homogenous cases
- Same GTIN on multiple levels of packaging

Primary level (optional)

Packaging in direct contact with the product and meant for sale to consumers (e.g., medicine strips, vials, single-therapy kits, or items packed in mono cartons). It carries a 2D barcode as per GS1 standards. Authentication uses the 14-digit GTIN and serial number on the label.

Secondary level

Secondary packs such as folding boxes and mono cartons. It carries a 2D bar code, with the GTIN, batch number, expiration date, and serial number indicated on the pack.

Tertiary level

The highest level of packaging, this can be a shipper case (intermediate pack) or a palletized unit containing several shipper cases destined for transport as individual units. The label carries a 1D barcode with embedded GTIN, batch number, expiration date, and serial shipping container code (SSCC).

Within this level are homogenous cases that contain inner packs at the lowest unit of sale (tertiary or secondary), and heterogeneous cases that contain different products.

DAVA PORTAL

The root cause of many of the problems with Indian serialization regulations is that they apply to exports, but not to products for domestic consumption. In theory, Indian exports must adhere to the importing country serialization mandate. Indian regulations,[9] however, state that:

> *In case, the Government of the importing country has mandated a specific requirement, the exporter has the option of adhering to the same and in such a case, it would not be necessary to comply with the stipulation under sub para (i) to (iv) of Para 2 of this Public Notice and if an exporter is seeking to avail such exemption from bar coding prescribed by the Government of India as above,* ***the exporter is given the option to move an application to the Pharmaceuticals Export Promotion Council of India (Pharmexcil) for this purpose, clearly specifying the nature of such an exemption in the interest of the exports from the country****. Pharmexcil shall dispose of such applications on case to case basis with prior approval of Government.* ***However, the tertiary level of packaging will have additional printing of barcode as per Para 2 (i) (c) of this Public Notice in addition to importing country's requirement, if any.*** [emphases added]

Many pharmaceutical and merchant exporters don't understand how to interpret this mandate, especially if they're exporting to the United States. The confusion about requirements for the Indian mandate and the US HDA and DSCSA shipper case label requirements have caused major logistical disruptions for wholesalers and distributors.

Another concern is that Indian exporters are required to create dummy serial numbers for primary packs in the Indian DAVA portal. RxGPS and the US FDA have serious concerns about the generation and use of such dummy serial numbers, as they are tantamount to fake serial numbers, which defeats the core principle of fighting counterfeits.

The Indian regulation for reporting aggregation—a requirement for countries that do not have their own serialization regulations and do not apply directly to the US market—mandates the use of GTIN-independent serial numbers. These must be unique to the company, but are not required to follow the GS1 standard of SGTIN (GTIN + serial number), which is the serialized numeric identifier (SNI) per FDA guidance for prescription drug packages.

Currently, all global vendors are aligned with the GS1 EPCIS standard that considers SGTIN as the SNI, which is globally accepted. Changing a standard feature of any serialization unit poses a risk to data integrity. This can lead to incorrect generation of EPCIS reports, present an unmanageable technical requirement, and creates the potential for supply disruption.

IMPLEMENTATION BLACK HOLES

The lack of harmonized regulations between the DGFT and importing countries has led to confusion about export product labeling. We have seen multiple GTINs on homogenous cases, SSCC and GTINs on the same case, a combination of GS1 India-issued GTINs and US-issued GTINs on a homogenous case, and the same GTIN on multiple levels of packaging.

US market challenges

These problems will affect the US supply chain. Having duplicate GTINs on packaging levels can lead to errors, since it is unclear which barcode should be scanned. GTIN discrepancies can cause a product to be returned. Combining the SSCC and GTIN—which puts two serial numbers on the same unit of packaging on the same homogenous case—can lead to aggregation errors. Nonconformance with Healthcare Distribution Alliance bar code guidelines can decrease supply chain efficiency, resulting in increased costs, product delays, and potential drug shortages (Figure 2 and Figure 3).

RECOMMENDATIONS

Given the limited time for compliance, the variable scope due to differing regulations from country to country, and the lack of qualified resources to help develop a serialization program, we suggest the following:

Start your serialization program early. Keep in mind that new regulations will continue to challenge implementation of your schedule and will affect your budget. Your priorities will change over time. Standardize your process and how you collect, store, and share data. Harmonize your implementation plan, taking into account all possible scenarios, and leverage specialized consulting help if in-house expertise is not sufficient.

Collaborate with regulators and industry groups. GS1 and RxGPS should engage early with regulators. Consulting companies and solution providers should unite under ISPE to develop a serialization working group. The DGFT should harmonize its implementation with that of the US DSCSA and the European Union's Falsified Medicines Directive (FMD). Create custom unified deliverables to reduce maintenance of master data and validation efforts. The solution should be designed from the bottom up, from line level to the cloud, without retrofitting of regulations to a commercialized solution, which carries the risk of undetected errors.

Collaborate on automation. Indian serialization vendors should enroll with Open-SCS to make sure that they are aligned with global standards. Indian pharmaceutical companies and exporters should watch for vendor blocking. Custom solutions require enhanced validation efforts. Serial number management and exchange should be part of the overall program. Do not consider line level as a hardware problem alone; instead, qualify it as a hybrid computerized system.

Collaborate on reporting. Pharmaceutical companies supporting the US supply chain should consolidate their site and production-line reporting, obtain exemption from Pharmexcil for correct DAVA portal reporting, and set up correct master data sets, including GTINs. Full aggregation reporting requirements should be based on clear regulations. Consider nondeterministic random serial numbers for the FMD and implement this concurrently.

If these recommendations are considered, we are hopeful that Indian pharmaceutical manufacturers will meet the compliance deadlines that are fast approaching. We would like to see US importers of pharmaceutical supplies closely monitor contract manufacturers that use locally developed serialization solutions, since the manufacturers are at high risk of not meeting DSCSA requirements and compliance deadlines. The selection of globally reputable serialization vendors will fast-track the implementation schedule and harmonize its standards to meet the requirements of the DSCSA.

We have less than a year to succeed. ‹›

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DEFINING THE ANALYTICAL TARGET PROFILE

Brent Harrington, Kimber Barnett, Stephen Chesnut, Neil Clayton, Michael Cohen, Janice Ensing, Timothy Graul, Melissa Hanna-Brown, and James Morgado

Analytical target profile criteria for judging the quality of results generated by analytical methods are framed in an optimization paradigm by illustrating the ATP criteria as a loss function. In the case where specifications are based on quality arguments and process capability, a probability-defined loss function is useful for providing a direct measurement of risk for making incorrect inferences. Three ATP criteria from recent literature are compared.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q8: "Pharmaceutical Development," defines the quality target product profile (QTPP) as the basis of pharmaceutical product development. The QTPP is intended to define quality criteria appropriate for the intent of the product: purity, sterility, stability, route of administration, dosage form, bioavailability, and strength.[1] Similarly, quantitative analytical methods, the measurement system in pharmaceutical development, require a clear indication of the quality of results generated by the method.

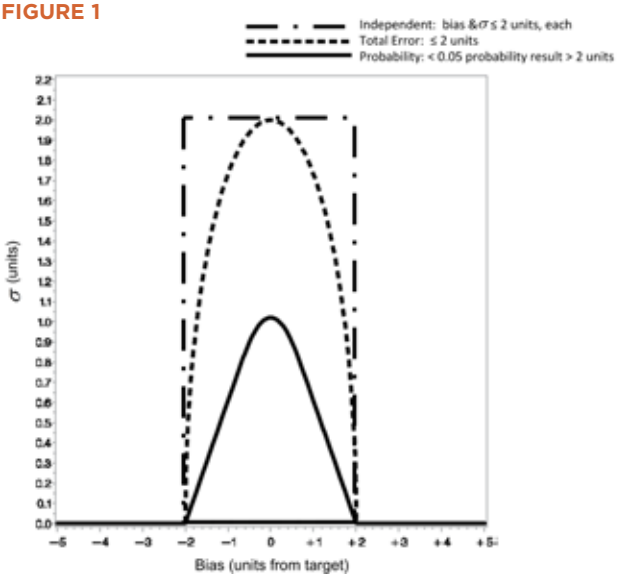
Analogous to the QTPP, an analytical target profile (ATP) can be a tool to define a priori quality criteria for results generated by analytical methods. The ATP is not a necessary method validation criterion; ICH Q2 discusses the analytical method characteristics that should be considered during procedure validation: accuracy, precision, specificity, detection limit, quantitation limit, linearity, and range.[2] Each attribute should be measured as appropriate, dependent upon the purpose of the method.

As described in ICH Q2[2] and other complementary compendia guidance,* a method appropriate for its intended purpose should demonstrate adherence to predefined criteria. Historically, criteria have been defined in a validation protocol and are used to infer method validation upon successful execution and demonstrated adherence to the stated criteria. Although imperative to method performance, these attributes do not provide a direct measure of the analytical method ability to generate a test result.[3]

Predefined method criteria should also be linked to the product specifications with which the method is associated. Pharmaceutical specifications are commonly based on regulatory requirements and process capability. In these cases, specifications do not delineate the point at which clinical significance begins or ends. When specifications are established in this way and method variability is constrained to reasonable levels (the current practice), the main risk of making a wrong decision based on test data resides with the suppliers, in the form of false out-of-specification results.

* United States Pharmacopeia, European Pharmacopoeia, and Japanese Pharmacopoeia

FIGURE 1



Identifying required analytical method output in terms of the final result provides a pragmatic target for development and intended use.[3] This article illustrates an approach for defining a quality criterion that translates the deviation from a target risk into a verifiable performance measure.

DERIVATION

Validating a method to ICH Q2 attributes of accuracy and precision demonstrates the degree of certainty in results generated by the method. Importantly, accuracy and precision serve as performance measures that can be translated into a pragmatic metric that provides understanding of decision risk concerning a test result.

Joint mathematical formulation of the accuracy and precision criteria is an important consideration. As detailed in recent works,[3–8] the idea is to define a quality statement through a function so that an increase in a defined risk (as stated in the quality metric or ATP) is incurred with deviations of either accuracy or precision from their target values. Applying a loss function with measures of accuracy and precision as the coefficients achieves this goal.

LOSS FUNCTIONS

A loss function maps values of variables into a relationship with defined cost. In this paper, we define cost as the risk of not meeting a defined criterion in

the loss function. A parabolic loss function† is often applied because it produces a progressively increasing cost as deviations from the target increase. Two such functions illustrated in recent works incorporate analytical method characteristics of accuracy and precision[5,9] and are provided below. The first defines "total error," the cost of deviating from target accuracy and precision as the sum of each of these measures ("target measurement uncertainty" is analogous).[10] The second loss function, "probability," is defined as the likelihood that an analytical test result resides outside an a priori–determined range.

A general expression for the expected deviation from target, *T*, given a measured value *Y* with accuracy $\{E(Y) = \mu\}$ and precision $\{Var(Y) = \sigma^2\}$, is provided as the total error in Equation 1—the square root of the expectation of the quadratic loss function $E[(Y - T)]^2$. (See sidebar on page 56 for the derivation.)

$$\text{Total error} = \{\mu, \sigma\} \mid \sqrt{(\mu - T)^2 + \sigma^2} \leq \lambda \quad (1)$$

Where

$(\mu - T)$ = accuracy (bias), difference between true method average (μ) and expected true content (T)

σ^2 = variability, true method variance

λ = maximum allowed loss (the square root of the sum of the two measures)

Alternatively, define the measured values (Y) as random variables distributed under an $N(\mu,\sigma^2)$ normal distribution with mean (μ) and variance (σ^2); a probability statement utilizing the normal density function is described in Equation 2 (probability). Probability loss is a representation of the ideas first published in *Pharmacopeial Forum*.[11]

$$\text{Probability} = \{\mu, \sigma\} \mid 1 - \int_{T-e}^{T+e} \phi(y: \mu, \sigma)\, dy < p \quad (2)$$

Where:

φ = normal distribution density function

y = measured analytical result

μ = true method average

σ = variability, true method precision measured as standard deviation (SD)

T = expected true content

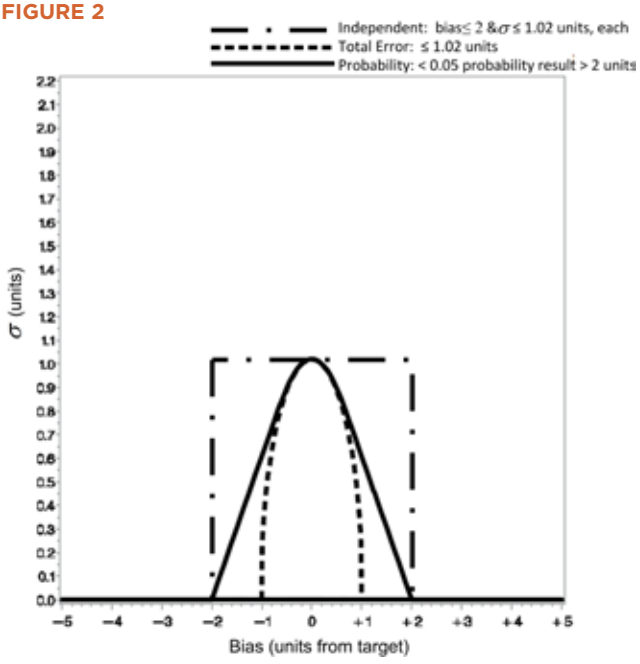
e = allowable range about the target

p = maximum allowed loss—a probability

Each of these equations defines a criterion that allows the joint assessment of the accuracy and precision of the analytical method. This relationship is readily seen in Equation 1 as the square root of the sum of the estimated accuracy $(\mu - T)^2$ and precision (σ^2) components. The sum of these components must be less than a stated limit (λ). Comparatively, the probability statement of Equation 2 defines acceptable accuracy and precision as a set $\{\mu,\sigma\}$ that limits results (y) deviating by more than $\pm e$ from the true value T. This limit is defined as probability p.

† The loss function is a metric that measures deviations from the target and produces a "loss or cost" for these deviations. The parabolic loss function does this in a progressively increasing manner; i.e., greater and greater loss for large deviations from the target.

FIGURE 2



For comparison with the two loss functions above, separately derived criteria for analytical method characteristics of accuracy (bias) in Equation 3 and precision in Equation 4 are provided. In this article, these separate and independently defined criteria will be termed as the "independent loss criteria."

$$\text{Accuracy (bias)} = (\mu - T) \leq b \quad (3)$$

$(\mu - T)$ = accuracy (bias), difference between true method average (μ) and expected true content (T)

b = maximum allowed bias

$$\text{Precision} = (\sigma) \leq s \quad (4)$$

Where:

σ = variability, true method precision as measured as SD

s = maximum allowed precision

LOSS FUNCTION INTERPRETATIONS

In practice, a quality limit would be defined as a practical limit for the analytical method that may be linked to the product specifications; for the example case provided in this article, a quality limit of two units is defined. The quality metric for each of the three loss functions is defined in Table A. Each of the defined loss functions restricts the range from target to be not more than two units. While all of these approaches are valid and may be applied at the supplier's discretion, there are practical differences between the approaches.

Figure 1 displays contour plots for the three loss functions defined in

FIGURE 3

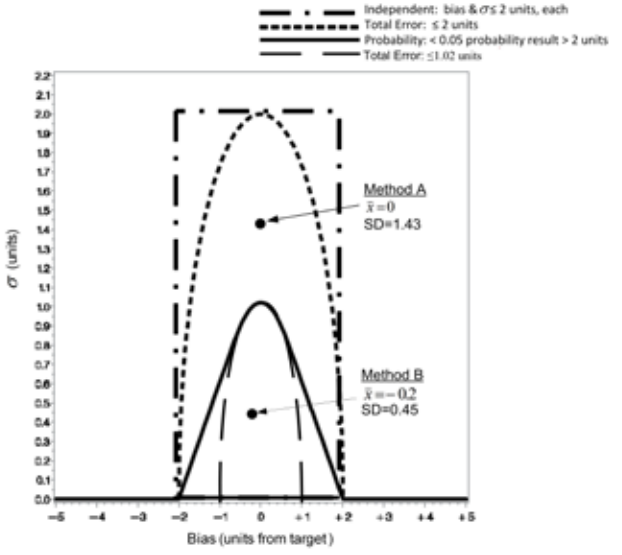
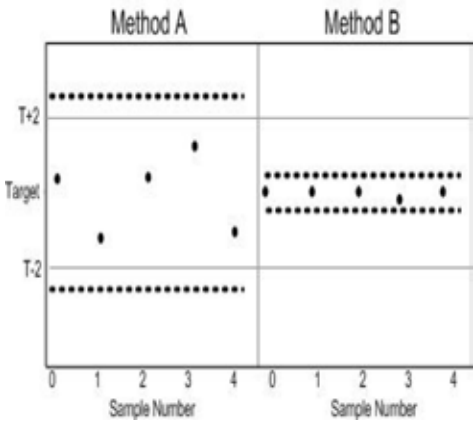


FIGURE 4



THE PROBABILITY LOSS IS A PRAGMATIC CRITERION USEFUL FOR DEFINING THE MAXIMUM RISK OF OBSERVED RESULTS RESIDING FARTHER THAN A PRESPECIFIED RANGE

Equations 1 to 4. The plots illustrate the relationship, as defined by the functions, of precision *(σ)* and accuracy (distance from target). The parabolic shape of the total error and probability loss functions is also displayed in Figure 1.

Obviously, a method with no bias (zero on the *x*-axis) can accommodate the largest variability. A method with measurable bias (not zero on the *x*-axis) must demonstrate reduced variability, decreasing to zero for ever-increasing bias to ensure the same loss limit. This is illustrated for the probability < 0.05 and total error ≤ 2 unit curves in Figure 1. When employing the independent loss approach, which sets separate limits for bias and precision, there is no trade-off between accuracy and precision. The independent loss approach implies that a method may have maximum allowable bias and imprecision simultaneously with no defined joint cost—as seen in the upper left and right corners of the black rectangle.

Characteristics of the loss functions clearly illustrate a difference in the maximum σ (*y*-axis) allowed for the quality metric limits defined. Defining the total error and independent limits to be ($\lambda \leq 2$) and ($b,s \leq 2$), respectively, allows for a much more liberal limit of variability than that defined by the probability loss quality limit in Figure 1 ($p < 0.05$ and $e = 2$). As defined for this example, the total error and independent limits allow an analytical method to produce results with much greater variability than a method that is controlled to the limits defined by the probability loss quality limit.

The quality metric criterion defined by the three loss functions is redefined below to account for this disparity in the allowable variability. An equitable comparison can be made by restricting the maximum σ of the total error or independent loss function to equal that of the probability loss function at the zero distance from the target value. By defining the λ in the total error loss function of Equation 1 as the ratio of the allowable range or loss (e.g., $e = 2$) by an appropriate z-score (1.96 for a 95% two-sided confidence of the normal distribution), the total error and probability loss functions are equivalent at a zero distance from target. Figure 2 displays such a refinement, for which we can now make a viable practical comparison of the risk of test results outside an a priori–defined range.

Based on the Figure 2 normalization, the quality metric limits (for which acceptance is judged) are redefined for each loss function as shown in Table B. The practical difference in the loss functions' performance can be seen in the risk of making incorrect decisions concerning experimental results. The risk of accepting a subpotent pharmaceutical product lot has been illustrated in previous work with the independent and probability loss functions.[5] Demonstrated here is a comparison of the three criteria against the following quality statement: There exists no more than 0.05 probability of a result being > 2 units from the true target content. This is the quality statement defined in the probability loss function of Equation 2 with $e = 2$ and $p = 0.05$.

TABLE A

Loss function quality limits against which a method is to be judged, Case 1: equal maximum allowance from target

Loss function	Quality limit
Total error	Total error ≤ 2 units *(λ)*
Probability	Probability < 0.05 *(p)* that individual results will reside > 2 units *(e)* from target *(T)*
Independent	Bias ≤ 2 units *(b)* and σ ≤ 2 units *(s)*

TABLE B

Loss function quality limits against which a method is to be judged, Case 2: equal maximum σ units at target

Loss function	Quality limit
Total error	Total error ≤ 1.02 units *(λ)*
Probability	Probability < 0.05 (p) that individual results will reside > 2 units *(e)* from target *(T)*
Independent	Bias ≤ 2 units *(b)* and ≤ 1.02 units *(s)*

Table C compares the three loss functions illustrated in Figure 2 in the ability to demonstrate a pragmatic decision concerning a result.

Table C illustrates theoretical analytical bias values in column 1 (true bias [μ]) ranging from 0 to 2.00, and the maximum variability (maximum allowable sigma [σ]) solution calculated from each loss function equation (columns 2, 3, and 4). From these two values, the probability of an assay value, assuming normal (true bias, maximum allowable σ) distribution, residing > 2 units of the true content is then calculated and reported (columns 5, 6, and 7).

The probability loss function restricts the maximum allowable σ to a level commensurate with the labeled bias amounts that maintain a constant probability; column 6 of Table C shows constant 5% probability for all rows (true bias) except for row 6, which shows 0.0% probability for a true bias at the stated limit. of 2%. In contrast, both the total error loss function and independent criterion fail to constrain the variability (maximum allowable σ) in a manner that maintains a constant probability; this is demonstrated in columns 5 and 7, respectively.

As illustrated in the example, the independent criterion allows a result to reside > 2 units from the true content a large percentage of the time, for even moderately biased methods (7.8% probability for a bias of 0.5; see column 7, second row in Table C). While smaller acceptance regions could be defined, the basic premise of increased loss (probability results outside defined limits) for methods that deviate from the target remains when using the independent approach for setting limits of accuracy and precision.

The total error loss function restricts the acceptable region (probability of 5%) more greatly than the probability loss function criterion in this illustration. The acceptable distance from the target (true bias) has been reduced to ±1.02 units in Figure 2, where the quality metric is defined by the total error function in this manner. The consequence is evident in column 5 of Table C for a method that incurs a true bias of 0.5 units or greater; the probability observed value more than 2 units from target is 4.8%, 3.5%, and 0% for methods with true biases of 0.5, 0.75, and ≥ 1.02. The total error approach is overly conservative for most pharmaceutical applications when applied in this manner.

In terms of practicality, the probability loss function clearly defines an appropriate quality metric for assessing an analytical method to produce results for which a risk-based decision can be made with a stated level of certainty. A method that meets the probability loss quality criterion in this example can be said to generate results within ±2 units of target at least 95% of the time. Neither the independent nor the total error loss functions make such a pragmatic risk-defined statement. In fact, the independent criterion allows values to be outside the target range of units, more liberally surpassing the stated quality limit of probability not more than 0.05. Using the total error loss function, depending upon how it is defined, could lead to either unnecessarily conservative criteria, as illustrated in Table C, or unnecessarily liberal criteria, as illustrated in Figure 1.

EXAMPLE

This example illustrates the practical inferences of using the differently defined ATP mentioned in this article. Defining an ATP criterion even prior to the analytical method development process sets a pragmatic minimal target for accuracy and precision that can be assessed periodically throughout the development of the method prior to verification or validation exercises. This may be achieved through several carefully planned and executed experiments that explore the method accuracy and precision. The following describes one experiment that examines a method's ability to provide repeatable sample recoveries.

ATP CAN BE A TOOL TO DEFINE A PRIORI QUALITY CRITERIA FOR RESULTS GENERATED BY ANALYTICAL METHODS

DERIVATION OF EQUATION 1

It is desirable to obtain values close to a target, *T*. A loss is experienced when deviations from the nominal target occur irrespective of the direction. The following quadratic loss function achieves this goal, for a random variable of interest, *Y*.

$$\text{Loss} = E[(Y-T)^2]$$

For a measured value *Y* with accuracy $\{E(Y) = \mu\}$ and precision $\{Var(Y) = \sigma^2\}$ the above loss function has the expected value derived below:

$$E[(Y-T)^2] = E[(Y-T)(Y-T)]$$

$$= E[(Y^2 - 2YT + T^2)]$$

$$= E(Y^2) - 2TE(Y) + T^2$$

Note: $Var(Y) = E(Y^2) - [E(Y)]^2 = \sigma^2$

So, by adding and subtracting $[E(Y)]^2$ to the above, we obtain the following:

$$E[(Y-T)^2] = E(Y^2) - 2TE(Y) + T^2 + \{[E(Y)]^2 - [E(Y)]^2\}$$

$$= \{E(Y^2) - [E(Y)]^2\} + [E(Y)]^2 - 2TE(Y) + T^2$$

$$= \sigma^2 + \mu^2 - 2T\mu + T^2$$

$$= \sigma^2 + (\mu - T)^2$$

Suppose, as an early development exercise, an analyst executes two methods to assess the sample preparation ease of use. She independently weighs and prepares five composite unit dosage samples from a single batch of material for each of two competing sample preparation techniques (Methods A and B) to assess the precision of the methods. Since the true value of the samples is not known, the average values $(\bar{x})$ are determined though separate extraction studies. The average $(\bar{x})$ from extraction studies and SD of the five composite samples for each method are illustrated against the ATP criteria in Figure 3 and described in the previous section. Because the point representing the ($\bar{x}$ and SD of Method A falls below the *TE* ≤ 2 criterion line, Method A would pass this criterion. However, since this point resides well above the *TE* ≤ 1.02 and the probability criteria (< 5% results > 2 units from target), Method A would fail these criteria. Conversely, Method B passes both the *TE* ≤ 1.02 and the probability criteria (< 5% results > 2 units from target).

ATP criteria provide a quality metric to further differentiate acceptable methods. Method B is expected to elicit samples with *TE* < 1.02, while Method A can be expected to deliver *TE* ≤ 2 units. The use of *TE* as a criterion does not directly identify the consequence of using either Method A or B. The probability loss criterion illustrated does, however. Since the $\bar{x}$ and SD of Method B resides below the probability loss criteria in Figure 3, Method B can be expected to produce results that are not more than ±2 units from the target with at least a 95% probability. The pragmatic consequence of accepting either Method A or B as an appropriate measurement system is illustrated in Figure 4.

Both methods may be appropriate in making reliable decisions based upon the samples; the difference in sample-to-sample variability, however, means a greater range in results with the use of Method A and thus a greater risk of decisions concerning the samples residing with the range of target ±2. The evidence is readily seen in a graph of the data as the spread of the samples derived from Method A is much greater than those prepared using Method B. As illustrated in Figure 3, Method B resides within the probability criterion that states not more than 5% of results reside greater than a distance ±2 of the target. This is evident by the inclusion of the 95% confidence bound for individual samples within *T* ±2 for Method B in Figure 4.

TABLE C

Maximum allowable σ and probability of a reported value > 2 units distance from true amount of pharmaceutical ingredient for total error loss, probability loss, and independent approaches at various levels of true bias

	Maximum allowable σ [a]			Probability observed value > 2 [b]		
TRUE BIAS	**Total error**	**Probability**	**Independent**	**Total error**	**Probability**	**Independent**
0.00	1.02	1.02	1.02	5.0%	5.0%	5.0%
0.50	0.89	0.90	1.02	4.8%	5.0%	7.8%
0.75	0.69	0.76	1.02	3.5%	5.0%	11.4%
1.00	0.20	0.61	1.02	0.0%	5.0%	16.5%
1.50	0.00	0.30	1.02	0.0%	5.0%	31.2%
2.00	0.00	0.00	1.02	0.0%	0.0%	50.0%

(a) Value of σ calculated from each loss function equation given the true bias in the table

(b) Probability: $1 - \int_{-2}^{2} \phi\,(y\text{: true bias, allowable } \sigma)\,dy$

CONCLUSION

ATP criteria for judging the quality of results generated by analytical methods have been framed in an optimization paradigm by defining the ATP criteria as a loss function. Two rigorously defined ATP statements to define quality criteria were illustrated in this manner, and compared to historically defined validation criteria. Each ATP statement defined a maximum criterion for deviations of results from a target. One defined this criterion in terms of total error: deviations from the target plus variability. The second defined the criterion as the probability a result resides further from a target than a defined allowance. A comparison of these two criteria and an independently defined criterion of accuracy and precision was made with respect to a decision-based judgment concerning the test results.

The probability loss is a pragmatic criterion useful for defining the maximum risk of observed results residing farther than a prespecified range. Other approaches may be valid and may be applied in line with the acceptable level of risk and at the discretion of the supplier. However, in the case where specifications are based on quality arguments and process capability, the probability loss approach is useful for providing a direct measurement of risk for making incorrect inferences. ‹›

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PARENTERAL HEPA FILTER PM INTERVAL

Thomas R. Spearman, PE, and Daniel C. Carroll, CMRP

This article shares a process used to evaluate terminal HEPA filter maintenance programs serving a parenteral manufacturing plant. The evaluation determines whether maintenance history data supports extending preventive maintenance frequency.

Terminal HEPA filters in HVAC applications serving Grade B, Grade C, Grade D, CNC, and unclassified areas are included in the evaluation. "Grade" is used throughout to refer to the EU GMP Annex 1[1] classifications of areas served by HEPA filters. Unidirectional airflow HEPA filters are excluded from the evaluation, since they have significantly higher failure rates than terminal HEPA filters.

HEPA* filter preventive maintenance (PM) tests the following attributes using a procedure based on the Institute of Environmental Sciences and Technology Standard IEST-RP-CC034: HEPA and ULPA† Filter Leak Tests:[2]

- Integrity: An aerosol challenge test. The acceptance criterion is that filter penetration is less than 0.01% of the upstream concentration.
- Airflow: A rate limits test. The acceptance criterion is that airflow is 10% above the air volume needed to provide the area with the minimum air changes per hour.
- Differential pressure: A static pressure-drop test. The acceptance criterion is that pressure drop is less than twice the initial pressure drop established at installation.

Failure modes analyzed in the evaluation are:

- Media leak: A leak in the filter medium itself, such as a pinhole.
- Housing leak: A leak in the housing that holds the filter, including a gasket leak.
- Media damage: A leak caused by touching or scraping the filter medium during testing, when protective grills are removed so that the filter medium can be scanned. Damage can occur during grill removal or replacement.
- Low airflow limit: Air volume necessary to produce minimum required air changes per hour:
  - Grade B areas: 20 air changes per hour
  - Grade C areas: 20 air changes per hour‡
  - Grade D areas: 15 air changes per hour
  - Grade D gown rooms: 20 air changes per hour
- High differential pressure: Exceeding twice the initial pressure drop established at installation.

* High-efficiency particulate air filter
† Ultra-low-penetration air filter
‡ FDA regulatory requirement; see reference 3

The air supply volume required to produce the minimum air change rates is calculated per filter and specified in cubic feet per minute or cubic meters per hour.

When the testing acceptance criterion is not met, a corrective action or preventive action (CAPA) event is originated. As part of the investigation, environmental monitoring data from the affected area is examined. From 1 July 2011 to 31 October 2015 (the time period covered by this article), no event investigations connected an environmental excursion to a HEPA filter failure. As a result, product quality was not affected.

HVAC SYSTEM OVERVIEW

Cleanroom HVAC systems supply high-quality filtered air low in microbial and particulate load to all processing areas, with temperature conditions that minimize microbial proliferation while maintaining operator comfort. Air-handling units that supply classified areas force air through prefilters, removing particles larger than 0.3 micrometers (µm) with an efficiency of 95%. After passing through supply ductwork, air is terminally filtered through HEPA filters with a minimum efficiency of 99.97% for particles greater than 0.3 µm for Grade C and D areas, and a minimum efficiency of 99.99% for particles greater than 0.3 µm for Grade B areas. HEPA filtration is not required for controlled not classified (CNC) and unclassified applications.

HVAC systems are designed to maintain cascading air pressure differentials between areas of differing classification (Grades B, C, and D). A minimum 0.04 inches of water column (10 Pascal) pressure differential is maintained between adjacent areas of lower grade. Grade C raw material sampling and dispensing suites are maintained negative to adjacent areas to facilitate containment. Air pressure differentials are continuously monitored, recorded, and alarmed.

TABLE A: HEPA FILTER FAILURES FROM 1 JULY 2011 TO 31 OCTOBER 2015

FAILURE MODE	FAILURES	
Media leak	69	1.4%
Housing leak	29	0.6%
Media damage	3	0.1%
Low air flow	2	0.0%
High differential pressure	0	0.0%

WEIBULL DISTRIBUTION

Developed in 1937 by the Swedish scientist and engineer Waloddi Weibull, the Weibull distribution is the leading method for fitting and analyzing equipment life-cycle data. Organizations such as the US military, Pratt & Whitney, and General Motors further developed the method.

The two-parameter Weibull distribution is widely used for life-data analysis. The Weibull cumulative distribution function (CDF), shown in the equation below, provides the probability of failure up to time t[4]

where:

$$F(t) = 1 - e^{-(\frac{t}{\eta})^{\beta}}$$

where:

$F(t)$ = fraction failing up to time t

t = failure time

e = natural logarithm base

η = characteristic life or scale parameter

β = slope or shape parameter

The complement of the CDF is reliability or the probability the failure will not occur up to time t. The reliability function is shown in the equation below.

$$R(t) = e^{-(\frac{t}{\eta})^{\beta}}$$

where:

$R(t)$ = fraction passing up to time t

t = failure time

e = natural logarithm base

η = characteristic life or scale parameter

β = slope or shape parameter

β (beta) shows the class of failure modes:

$\beta < 1.0$ indicates "infant mortality," a failure rate that decreases over time

$\beta = 1.0$ indicates random failure or failures independent of age

$\beta > 1.0$ indicates wear-out or increasing failure rate over time

The Weibull charts in this article have plotted the reliability function and are labeled "passing rate" on the vertical axis.

Figure 1 is the Weibull distribution plot for HEPA filters with a media leak failure mode. The plot consists of a horizontal scale illustrating the age to failure and the reliability function (1-CDF) on the vertical axis.

The η (eta) for this distribution is 11,100 days, indicating that 63.2% of the filter population will have failed due to a media leak by this point. The β (beta) is greater than 1, indicating a wear-out pattern.

The probability value estimate percentage (pve %) is greater than 10%, indicating that the mathematical model represents the data and is safe to use for life data.

FIGURE 1: WEIBULL DIAGRAM, MEDIA LEAKS

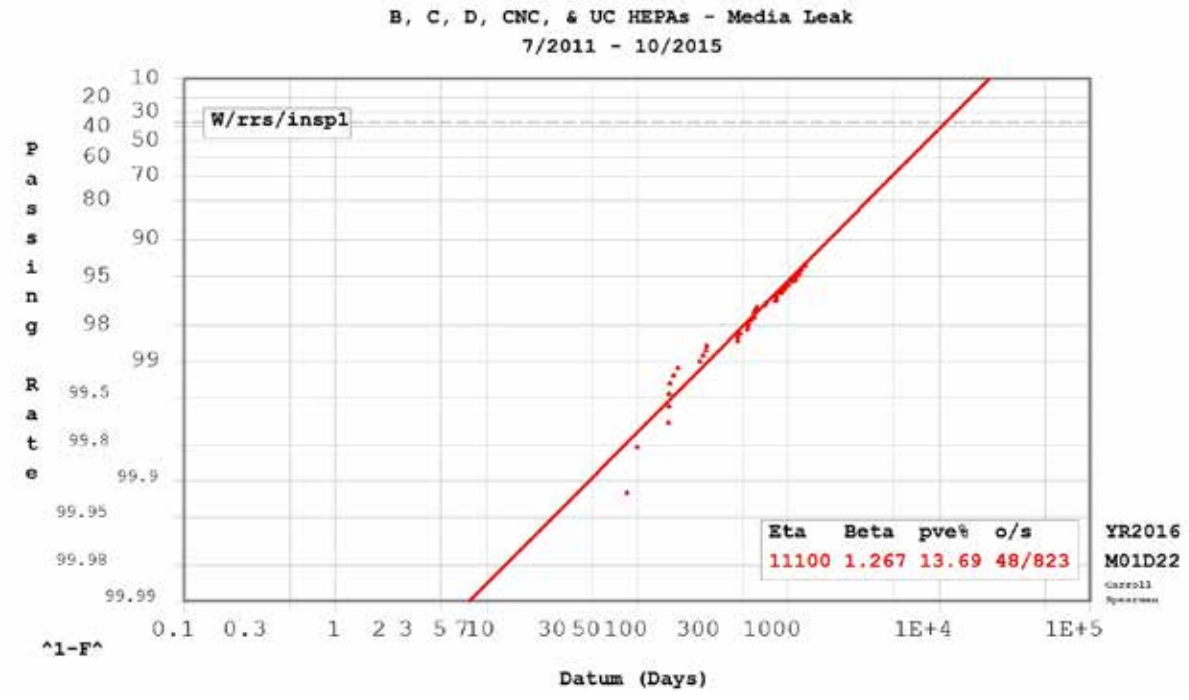
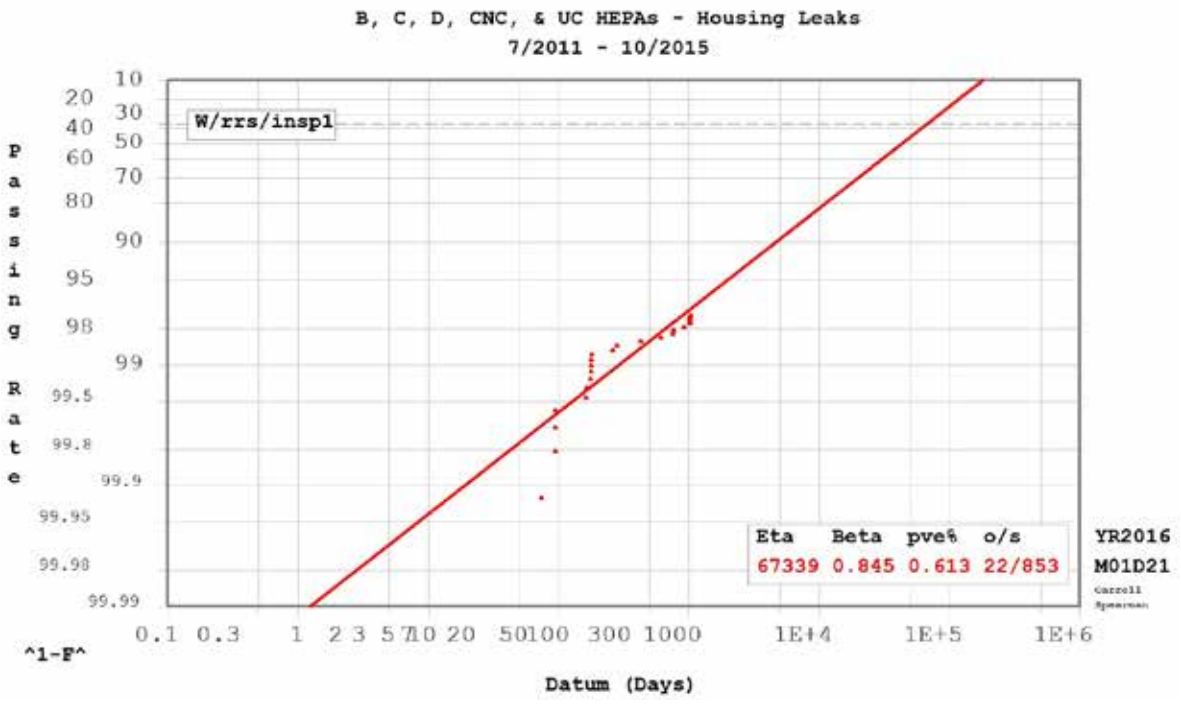


FIGURE 2: WEIBULL ANALYSIS, HOUSING LEAKS



THE WEIBULL DISTRIBUTION IS THE LEADING METHOD FOR FITTING AND ANALYZING EQUIPMENT LIFE-CYCLE DATA

The occurrences/suspensions (o/s) summarize the failure points plotted on the graph (occurrences) and those that are included in the model but not plotted (suspensions). Suspensions are units that failed by a different mode or have not failed at all and are "suspended." Although not directly plotted, suspension data affects the median rank of the data, which affects the vertical axis position.

To determine how long 98% of the filter population will survive a media leak, locate 98% on the vertical axis, find where it intersects with the Weibull line, then determine the life expectancy from the horizontal axis. In Figure 1, this occurs at 510 days.

RESULTS

Weibull distribution analyses were performed on HEPA filter PM work orders dating from 1 July 2011 to 31 October 2015, using the maintenance history for 804 HEPA filters. Each work order with a failed tolerance code was reviewed to determine the failure mode. Weibull analysis software was used to calculate the proposed intervals at the 90%, 95%, and 98% passing rates (Figures 1 and 2). Table A summarizes the number and percentage of failures during the time period by failure mode.

Table B, Table C, and Figure 1 summarize the Weibull analysis results for media leaks. Table B displays the data set by grade and as a complete group. The Weibull interval indicates the time period necessary to achieve the Weibull pass rate.

Table C shows proposed PM intervals at passing rates of 90%, 95%, and 98%. The criticality of the filter relative to the area classification determines the desired passing rate.

Table D, Table E, and Figure 2 summarize the Weibull analysis results for housing leaks. Table D summarizes the data set by grade and as a complete group.

TABLE B: WEIBULL ANALYSIS, MEDIA LEAKS

APPLICATION	WORK ORDERS	PM QUANTITY	β	PVE, %	WEIBULL		
					PASS RATE, %	INTERVAL	
						DAYS	YEARS
Grade B	1,654	183	1.238	80.08	98.7	265.1	0.7
Grade C	1,222	249	1.052	2.47	97.6	394.7	1.1
Grade D	1,166	218	1.135	39.67	99.2	457.9	1.3
CNC	732	147	1.708	69.53	98.8	471.2	1.3
Unclassified	31	7	1.000	n/a	100.0	n/a	n/a
All	4,805	804	1.267	13.69	98.60	385.4	1.2

TABLE C: WEIBULL ANALYSIS, MEDIA LEAKS, PROPOSED PM INTERVALS BY PASSING RATES

APPLICATION	PROPOSED PM INTERVAL					
	Days	Years	Days	Years	Days	Years
	98%		95%		90%	
Grade B	376.5	1.0	798.9	2.2	1,429	3.9
Grade C	331.1	0.9	803.0	2.2	1,592	4.4
Grade D	1,032.0	2.8	2,345.0	6.4	4,421	12.1
CNC	636.9	1.7	1,099.0	3.0	1,675	4.6
Unclassified	161.3	0.4	409.6	1.1	841.3	2.3
All	510	1.4	1,064.0	2.9	1,878	5.1

Table E summarizes the proposed intervals at passing rates of 90%, 95%, and 98%. The criticality of the filter relative to the area classification determines the desired passing rate.

Although a Weibull distribution was created for each classification, filter function is identical for each application. HEPA filters in all classification areas are installed, commissioned, qualified, and maintained similarly. The filter and housing design are the same, as are the failure mode and failure detection methods. A single population of HEPA filter failures, therefore, was used to determine future inspection frequencies.

Three failure modes not associated with time were ruled out. Media damage was excluded because it occurs during intrusive activity, when the protective grill is removed. It's important to note that testing HEPA filters too frequently risks unnecessary damage to the filter medium. During the period analyzed, filter damage during testing was documented three times.

Low airflow was excluded because it is a system adjustment issue, and high differential pressure has no failure data.

Media and housing leaks were the dominant failure modes and the only ones associated with time. Housing leaks, however, are considered an "infant mortality" failure mode: expected to decrease over time. The Weibull value also supports this. As a result, the proposed PM interval for housing leaks (Table E) is longer than the intervals proposed in the media-leak analysis (Table C) in all applications except for the Grade C.

Media-leak analysis, therefore, is used as a basis for recommended PM intervals. These results are applicable to other cleanrooms that have similar tests for HEPA filters.

DISCUSSION AND CONCLUSIONS

Using the data in Figure 1 and Table C, higher theoretical pass rates were selected for areas of higher classification, reflecting a risk-based approach. Since Grade B areas serve as background for the critical Grade A areas, a pass rate of > 98% was selected. Because the Grade C and D areas are used for such activities as equipment prep, formulation, vial washing, capping, and gowning, a pass rate of > 95% was selected.

Table F shows recommended PM intervals based on these theoretical pass rates, as well as labor and cost savings calculated using the following assumptions:

- The PM requires two people for execution
- The PM requires 1 hour per person
- The shop labor rate is $55 per hour

Total labor savings are estimated as 1,141 hours per year. Total financial savings are estimated as $62,755 per year.

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TABLE D: WEIBULL ANALYSIS, HOUSING LEAKS DATA SET

APPLICATION	WORK ORDERS	PM QUANTITY	β	PVE, %	WEIBULL		
					PASS RATE, %	INTERVAL	
						DAYS	YEARS
Grade B	1,654	183	0.791	100.00	99.9	54.02	0.1
Grade C	1,222	249	0.897	0.76	98.3	186.80	0.5
Grade D	1,166	218	1.000	n/a	100.0	n/a	n/a
CNC	732	147	0.649	32.35	99.5	1960	0.5
Unclassified	31	7	1.000	n/a	96.2	309.30	n/a
All	4,805	804	0.845	0.61	99.4	158.20	0.4

TABLE E: WEIBULL ANALYSIS, HOUSING LEAKS

	PROPOSED INTERVAL					
	Days	Years	Days	Years	Days	Years
PASS RATE	98%		95%		90%	
APPLICATION						
Grade B	2,416.0	6.6	7,850.0	21.5	19,508.0	53.4
Grade C	220.6	0.6	623.8	1.7	1,392.0	3.8
Grade D	5,716.0	15.7	14,512.0	39.8	2,9810.0	81.7
CNC	1,679.0	4.6	7,056.0	19.3	2,1394.0	58.6
Unclassified	161.3	0.4	409.6	1.1	841.3	2.3
All	663.5	1.8	2,000.0	5.5	4,689.0	12.8

TABLE F: RECOMMENDED PM INTERVAL AND SAVINGS SUMMARY

APPLICATION	GRADE B	GRADE C	GRADE D	CNC	UNCLASSIFIED
Population	183	249	218	147	7
Current PM interval	6 months	1 year	1 year	1 year	1 year
Recommended PM interval	1 year	2 years	2 years	After installation only	After installation only
Pass rate	> 98%	> 95%	> 98%	Not required	Not required
Labor savings, hours per year	366	249	218	294	14
Savings per year	$20,130	$13,695	$11,990	$16,170	$770

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MANAGING POTENTIAL VIRUS AND TSE CONTAMINATION

A Risk-Based Approach for cGMP Biopharm Manufacturing Facilities

Anne Stokes, PhD

Biopharmaceutical products manufactured from mammalian or microbial cells are inherently at risk of contamination from two major types of entities.

The first type consists of adventitious or endogenous viruses. Viruses are composed of a nucleic acid genome surrounded by a proteinaceous capsid, with or without a lipid envelope requiring a host cell for replication. Adventitious viruses are introduced to the manufacturing process unintentionally; endogenous viruses are already present in the cell line and may be part of the host genome.

The second type consists of transmissible spongiform encephalopathy agents (TSE, or prion diseases), which can be introduced into the manufacturing processes by contaminated ruminant (cattle or sheep) materials. TSEs are neurodegenerative disease-causing agents that contain no genetic material. TSEs affect humans and animals, and are characterized by the accumulation of an abnormal isoform of a cellular glycoprotein known as PrP, or prion protein. Prions are highly resistant to physicochemical inactivation procedures such as heat, ionization, ultraviolet light, microwaves, irradiation, and acid treatment. Reducing TSE infectivity risk relies on stringent methods such as treatment with a strong base and the elimination of animal-derived raw materials (ADRMs) from the manufacturing process.

Both viruses and TSEs pose a risk to the entire manufacturing facility.

VIRUSES

Virus safety assurance for biopharmaceuticals derived from cell lines of human, microbial, or animal origin is demonstrated by a threefold approach described in ICH,[1] FDA,[2-3] and EMEA[4] regulatory guidelines (Figure 1).* The key virus safety components are:

1. Selecting, assessing, tracing, and testing cell lines and raw materials (including media components) for the absence of viruses and limiting the use of ADRMs;
2. Testing the product for the absence of viruses at appropriate stages of production; and
3. For mammalian cells, assessing the capability of production processes to clear infectious viruses.

* ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; FDA: US Food and Drug Administration; EMEA: European Medicines Agency

TSEs

Bovine spongiform encephalopathy (and its link to variant Creutzfeldt-Jakob Disease,[6] which was first identified in the UK in 1996) has had a significant impact on the biopharmaceutical industry. As a result, international agencies—including those in Europe, the United States, and Japan—have published guidelines applicable to the management of TSE risk to minimize patient exposure via pharmaceutical products.[5,7,8]

While the risk of TSE propagation by mammalian cells is low,[9] measures to eliminate ADRMs must be enacted to mitigate potential exposure. If this is not possible, a comprehensive risk assessment based on species, tissue, country of origin, and manufacturing process used to produce the raw material or component[5] should demonstrate that there is no residual risk from TSE agents.

RISK-MANAGEMENT PROGRAM

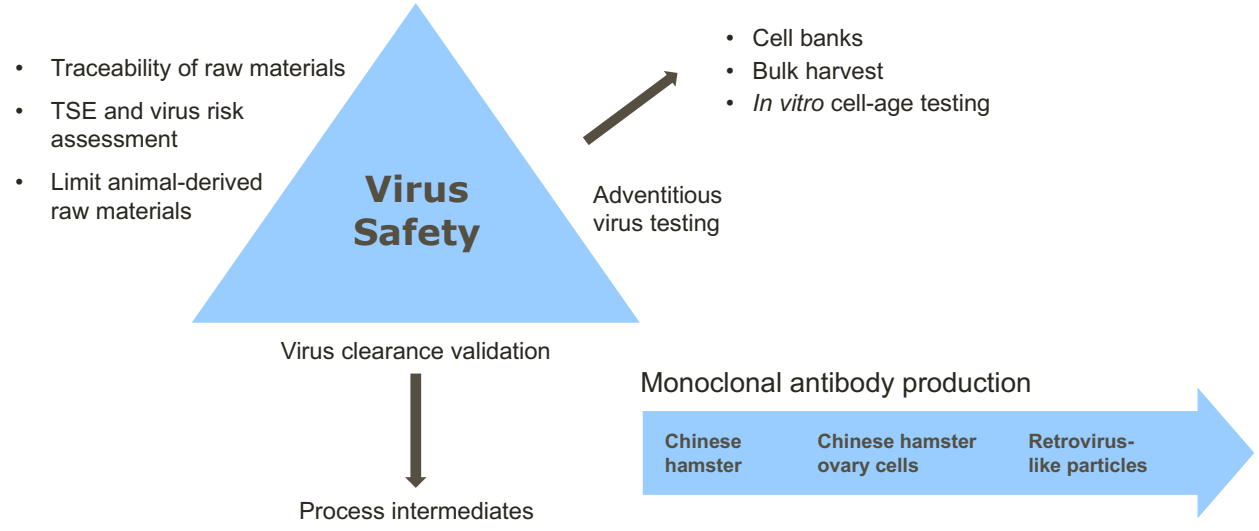
These and other quality and regulatory expectations can be managed through a comprehensive virus and TSE risk-management program and control strategy. Examples include the implementation of a current good manufacturing practice (cGMP) philosophy and personnel training that encompasses all the operations carried out in the manufacturing facility. Other considerations include:

- Facility controls such as ISO room classifications; heating, ventilation, and air-conditioning (HVAC) systems; laminar flow hood use; closed processing; process segregation; cleaning procedures; and pest control
- Equipment use and maintenance
- Equipment type, i.e., single use vs. stainless steel
- Personnel, waste and material flow strategies

This holistic approach to managing virus and TSE risk provides confidence that the clinical materials supplied to patients are free from the risk of contamination.

BOTH VIRUSES AND TSEs POSE A RISK TO THE ENTIRE MANUFACTURING FACILITY

FIGURE 1: THE VIRUS SAFETY TRIANGLE



CONTROL FRAMEWORK

The risk of virus contamination in manufacturing facilities is also low, but when it occurs, the impact is severe. Examples of facility contamination recorded in the literature[10–12] describe economic losses sustained in facility recovery after an incident, and patient hardship caused by loss or interruption of drug supply.

Viruses can infect mammalian production cells such as Chinese hamster ovary cells[13] and NSO cells (derived from a non-secreting murine myeloma). Biopharmaceuticals derived from *Escherichia coli* are also at risk from endogenous[14] and adventitious bacteriophages.[15] Viruses of yeast—both retroviral-like elements such as Ty1[†16] and double-stranded RNA viruses—may be transmitted during mating, but do not appear to produce particles that are infectious via an extracellular route.

The control of risk is governed by ICH Q9 guidelines[17] applied to areas with the potential for TSE and virus contamination (Figure 2). These areas include raw material and component sourcing, transport, and receipt; movement of materials into the manufacturing facility; buffer and media makeup; and GMP manufacturing operations. Requirements for virus and TSE control are also outlined by regulatory authorities and requirements in internal policies, procedures, and controls—including facility audits.

In virus and TSE risk assessments, each manufacturing step is reviewed for the risk of contamination from personnel, material, and environmental sources. Risk values of probability and occurrence are assigned both before and after mitigation actions are taken. Segregation strategies and general risk-mitigation steps are also reviewed.

RAW MATERIALS AND COMPONENTS

The main sources of risk for virus contamination are ADRMs or animal-derived ingredients (ADIs). TSE contamination may arise from tissues or secretions of animals—primarily ruminants—susceptible to prion diseases used to prepare cell banks or medicinal product. Primary ADIs or ADRMs may be included as active substances, excipients, or adjuvants (fetal bovine serum, sheep-wool-derived cholesterol, or milk-derived galactose). Secondary or tertiary ADIs include recombinant proteins (e.g., insulin) manufactured in media that contain a ruminant material (such as milk) and/or are used as biopharmaceutical production media additives.

Ruminant substances (e.g., tallow) in product-contact materials (components, consumables, and equipment) must be controlled by identifying the species and tissue source, country of origin, and method of treatment during manufacture (alkaline hydrolysis and/or heat).

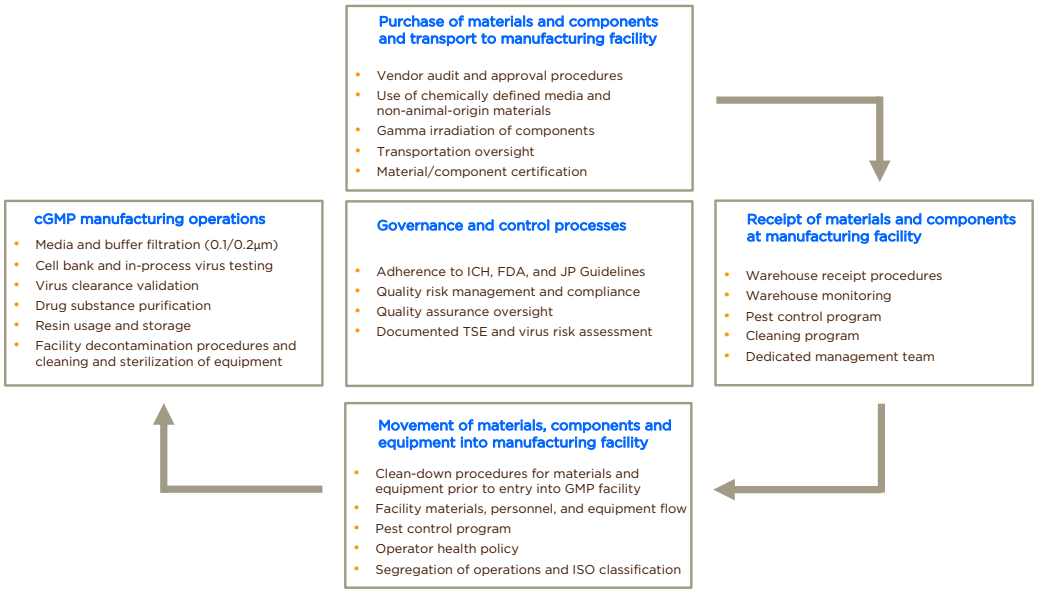
All materials must have supporting vendor documentation, such as a Certificate of Origin or European Directorate for the Quality of Medicines Certificate of Suitability.[‡] This applies to materials used in cell lines prior to the manufacture of cell banks, GMP cell banks, and raw and product-contact materials used throughout the product life cycle. Measures should also be in place to prevent exposing process-contact equipment and utilities to materials of human or animal origin.

Transportation from the vendor to the site of manufacture provides another element of risk that must be considered. Moving materials from the warehouse into the GMP core should be governed by strict procedures that

[†] Long-terminal repeat retrotransposon of the yeast species *Saccharomyces cerevisiae,* whose structure is similar to retroviruses

[‡] A process for periodic renewal of these certificates via vendor management programs should also be in place.

FIGURE 2: BIOPHARMACEUTICAL PRODUCTION AND MANAGEMENT OF POTENTIAL TSE AND VIRUS RISK



THE MAIN SOURCES OF RISK FOR VIRUS CONTAMINATION ARE ADRMs OR ADIs

include disinfectant; materials, personnel, and equipment flow segregation; ISO room classification; and operator health policy. Cell banks should only be released for manufacture after a TSE and virus risk assessment, appropriate virus testing and approval of a written report.

Each of these steps helps ensure that the origins of all animal-derived raw and starting materials used to develop cell lines and manufacture biopharmaceutical products have been investigated, and that potential contamination risks from TSE or viral agents have been fully defined and assessed.

MANUFACTURING FACILITY CONTROL

Manufacturing facility control incorporates GMP policies and procedures relevant to the facility operations as well as regulatory guidelines. HVAC systems aid in virus control by delivering terminal high-efficiency particulate (HEPA) filtered airflow to maintain segregation between zones, creating directional flow and differential pressures to provide the requisite number of air changes for classified rooms (ISO-5, ISO-7, ISO-8,). HVAC systems also prevent particulate material from migrating between processing areas and circulating or accumulating within rooms. Microbiological and particulate monitoring verifies the integrity of controlled environments and area classification requirements.

During purification operations, segregation through architectural design or by closed systems are important in pre- and post-virus-removal steps. A system of airlocks prevents cross-contamination during entry to and exit from rooms and areas. Pass-throughs are kept clean and free of debris. All cell lines are tested for virus and risk-assessed for TSE, then dispositioned prior to use as required by standard operating procedures. Procedural controls are in place in the event of a facility contamination or pest ingress. Mitigating actions can be triggered by a positive (or false positive) adventitious and/or endogenous virus test.

EQUIPMENT CONSIDERATIONS

As the industry moves toward closed processing, single-use bioreactors and chemically defined media (which must be free of ADIs) are also risk-reduction steps in TSE and virus control.

Single-use bioreactors (SUBs) permit fully closed processing and are disposable, providing compartmentalization that can greatly mitigate a contamination event. The control framework for successful implementation of SUBs includes addressing the critical nature of container closure integrity. *In situ* pressure-decay bag testing prior to use can detect leak sizes 300 micrometers (µm) and larger. Another critical concern for flexible containment systems is microbial ingress, which can occur with leaks as small as 10–22 µm. To prevent this, the SUB is maintained at positive pressure relative to the room.

Stainless steel bioreactors, equipment, and piping require changeover and cleaning to mitigate contamination. Process closure of the downstream manufacturing platform also increases operational flexibility, simplifies changeover, and reduces risk of virus contamination. Closure of existing stainless steel chromatography and tangential flow filtration skids by leveraging single-use interconnections creates a stainless steel–disposable hybrid solution, where many components are single-use gamma-irradiated tubing assemblies, filters, and bags.

PERSONNEL, MATERIALS, AND WASTE FLOWS

Personnel, materials, and waste flows are controlled via facility floor plans and room segregation. Access to GMP areas is limited to key staff and strictly monitored. GMP gowning and manufacturing operations, including manipulations, prevent introduction (or reintroduction) of viruses. All personnel entering processing areas must do so via designated gowning rooms and adhere to the requirements for that room. Persons with apparent illnesses are excluded from contact with raw materials, process intermediates, packaging materials, and the product until their conditions are corrected or they have been determined not to jeopardize product safety.

FACILITY CLEANING AND DISINFECTION

Stainless steel equipment is cleaned between uses and tested at product changeover. Soil- or contaminant-specific cleaning regimens must be verified or validated. All equipment and consumables introduced to the facility should be assessed for risk and exposed to disinfectants and cleaning agents that demonstrate the required removal and inactivation properties. In addition to other recommended contaminant-specific cleaning agents, 70% isopropyl alcohol—shown to have viricidal activity against retrovirus[18]—is used routinely for hand spraying and equipment wipe-down. For part washing, a combination of caustic washing agents and high temperature provide effective inactivation. A strict rodent and insect control policy must also be in place.

THIS HOLISTIC APPROACH TO MANAGING VIRUS AND TSE RISK PROVIDES CONFIDENCE THAT THE CLINICAL MATERIALS SUPPLIED TO PATIENTS ARE FREE FROM THE RISK OF CONTAMINATION

Sodium hydroxide (NaOH) is used as a sanitizing solution for column resins.[19] Even highly resistant non-enveloped viruses such as canine parvovirus and SV40[§] are inactivated by NaOH, and enveloped viruses (such as influenza) are also effectively removed.

VIRUS SAFETY TRIANGLE

Testing

Virus testing is a normal and routine part of biopharmaceutical manufacturing and quality control testing. According to ICH Q5A,[1] appropriate testing for viruses must be carried out on the master cell bank (MCB), and must include both *in vitro* and *in vivo* tests. *In vitro* tests are carried out on a batch basis. More extensive testing is performed on cells at the limit of *in vitro* cell age, which should be evaluated for endogenous viruses that may have been undetected in the MCB and working cell bank. *In vivo* tests are conducted in rodents and embryonated eggs.

Detection

The rapidly expanding field of molecular virology and associated methodologies has developed extensive tools to analyze materials at all points of the manufacturing process for the presence of virus. These new methods, which include broad-range polymerase chain reaction as well as mass spectrometry, microarrays, and massively parallel sequencing (also referred to as next-generation sequencing), can detect a broad range of viruses both known and unknown.[20] The advantages and disadvantages of these new methods and their ability to complement routine methods for virus detection form the basis of a continued dialogue between industry and regulatory agencies. Questions include whether nucleic acid detection is indicative of a complete genome or, more importantly, a live virus.

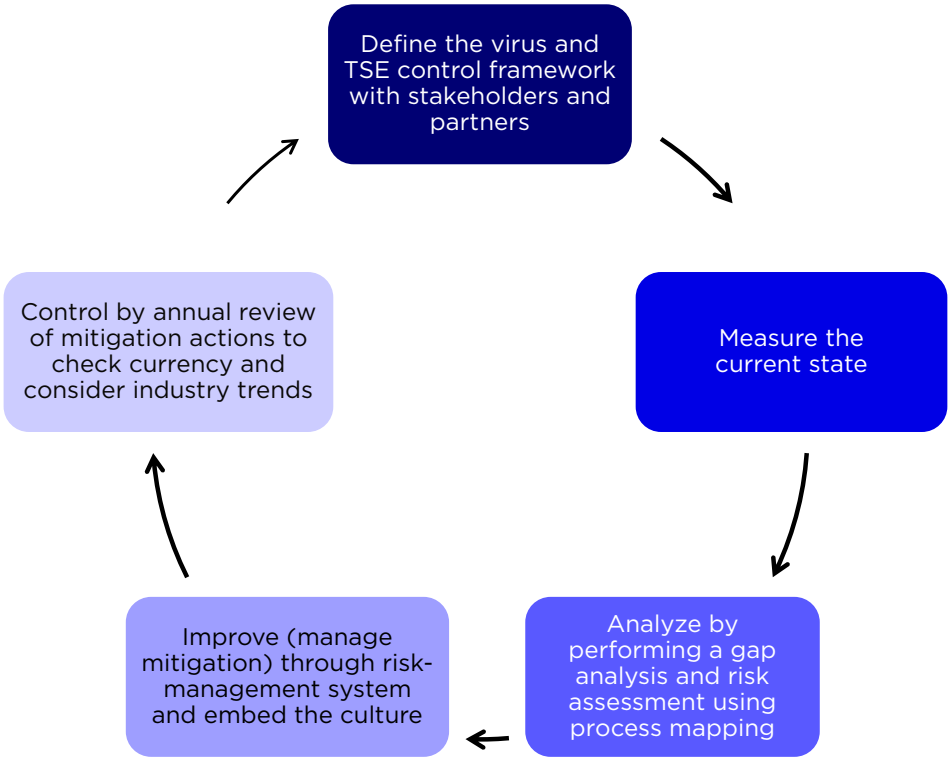
In cases of facility contamination there is no doubt that these methods offer a distinct advantage for rapid identification of the contaminant. Novel molecular methods also help reduce, refine, or replace live animals in biosafety testing. In addition, these new methods are increasingly being used to support the three-pronged approach to virus safety (i.e., the virus safety triangle), which has delivered safe products to patients over a considerable period of time.

Virus clearance validation

The third arm of the virus safety triangle is virus clearance validation (VCV). Typically carried out as part of the manufacturing process for clinical material, VCV requires a demonstration of clearance for two model viruses. Mechanisms of removal include partitioning or inactivation; the log reduction values are additive. For biologics license applications or marketing authorization application submissions, two additional model viruses are used. The aim is to obtain a clearance factor of < 1 virus-like particle in 10^6 doses of drug for both clinical and commercial material. A calculation is performed to determine the downstream load using the virus counts in the fermenter harvest. The amount of retrovirus present in fermenter harvests is measured ideally for three batches.

[§] Simian vacuolating virus 40, or Simian virus 40, is an oncogenic polyomavirus that induces cancers in laboratory animals and may also affect humans.

FIGURE 3: CONTINUOUS IMPROVEMENT SCHEMATIC FOR CONTROL OF TSE AND VIRUS RISK



RISK-MANAGEMENT CYCLE

TSE and virus control requires a continuous improvement cycle. First, the current state is measured; process mapping analysis then identifies gaps and indicates necessary mitigations via a risk-management system. An annual review of mitigation actions to check currency and industry trends helps define best practices and provides continuous control (Figure 3).

CONCLUSIONS

This article outlines the risks that viruses and TSE agents pose to the manufacture of biopharmaceuticals and describes a holistic control strategy that promotes the provision of safe medicines to patients. Because these agents differ significantly in their physicochemical properties, they present unique challenges and require different approaches to risk mitigation.[1,5] While raw material, component sourcing, vendor oversight, and certification controls are important, virus-risk reduction also relies on the application of both novel and routine methods of detection and virus clearance validation.

TSE control relies on documented risk assessments, including raw material sourcing, elimination of ADIs, and effective manufacturing controls such as alkaline hydrolysis and high heat extremes for product-contact materials, including tallow derivatives. While TSE clearance and detection methods are available, they are not routinely applied for biopharmaceutical manufacturing processes due to control of ruminant risk materials at source.

The control framework described here includes appropriate manufacturing facility design; HVAC system control; ISO room classification; architectural segregation; appropriate equipment types (stainless steel, single use, or hybrid); waste, materials, and personnel flows; cleaning and disinfection; pest control; and operator health policy. Internal and third-party control is governed by regulatory guidelines in addition to local policies and procedures monitored by quality assurance personnel.

Management of virus and TSE risk is a continuous process that involves gap analysis, improvement practices, and control measures. New control methods continue to be developed and implemented by the pharmaceutical industry. Gaps can be closed by adopting industry best practices and routine oversight of the operations by quality assurance and compliance personnel. This holistic approach, using a three-pronged strategy for virus control and a TSE risk-assessment process, provides confidence that the materials supplied to patients are safe and free from virus and TSE contamination. ‹›

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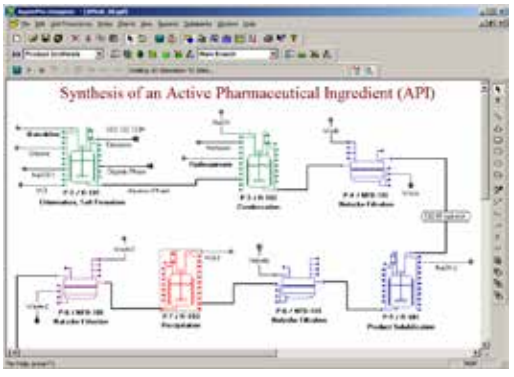

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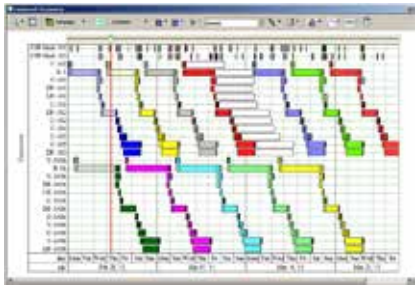

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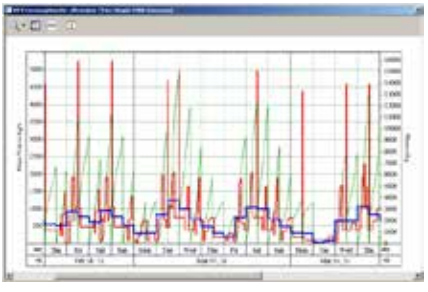

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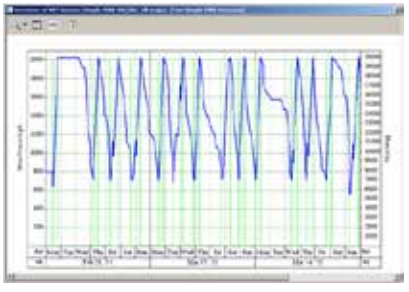

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EMA MOVES TO AMSTERDAM


René Nanninga

The United Kingdom's (UK) "Brexit" vote to leave the European Union (EU) by March 2019 has created challenges for the European pharmaceutical industry. Among the first important decisions resulting from the impending departure was where to relocate the European Medicines Agency (EMA), currently headquartered in London. On 20 November 2017, the EU's European Council resolved this concern when it chose Amsterdam from among the 19 cities vying for the coveted prize.

Amsterdam meets all the criteria put forth by the EU, including good access to the rest of Europe, adequate office space, and multilingual education for the children of agency staff. The city is a good choice, according to René Nanninga, chairman of the ISPE Netherlands Affiliate and Director, Engineering & Technical Support at Xendo BV, a biopharmaceuticals, medical devices, and health-care consultancy and project-management company in the Netherlands.

"Amsterdam is a practical choice, given its proximity to London," he said. "Critical to relocation will be enticing EMA personnel to continue to work with the agency. It will be possible to live in London and work in Amsterdam, at least during the transition phase." In fact, 65% of current EMA staff were willing to relocate to Amsterdam, a factor that may have garnered votes. "The standard of living is high in the Netherlands, and this is reflected in the willingness to move." The city also has an abundance of well-educated people capable of working at the EMA.

Amsterdam is easily accessed from the rest of Europe; Schiphol airport, one of the continent's major transportation hubs, is a 20-minute drive from the city center. The Netherlands has excellent universities, university hospitals, scientific research, and a thriving biotechnology community. The Medicines Evaluation Board in nearby Utrecht is an independent health authority that regulates the quality, efficacy, and safety of drugs in the Netherlands; the country also acts as a Reference Member State* (or Rapporteur) for many medicines.[1]

CONCERNS

Moving the EMA has the potential to disrupt European pharmaceutical manufacturing. Companies that have registered their products with the UK as the Reference Member State will have to think strategically about how, when, and to which European health authority to transfer their product procedures. Additionally, 60% of qualified persons for pharmacovigilance (QPPV) currently reside in the UK; EMA guidelines, however, state that a European QPPV must reside in the EU.[1] There is also some concern that the EMA's drug-approval process will be hampered by interruptions predicted as a result of the move.

"Whether approvals for new medicines will take longer entirely depends on whether the processes of the EMA will be interrupted," Nanninga said. He believes it will be an enormous achievement if the agency is able to maintain all its processes while onboarding 900 people in Amsterdam. "Will they be able to get continuity of people? Will they get onboard sufficient people in time to be introduced to the products, processes, and procedures to provide continuity. Programs might be delayed or rescheduled."

BENEFITS

Amsterdam's estimated economic windfall is $1 billion. The city will benefit from 900 new jobs, an influx of people attending meetings of scientific committees and advisory groups, and the potential transfer of pharmaceutical company offices from companies with offices currently in the UK.

"The agency will bring many highly educated people to live in or around Amsterdam," added Nanninga, "[plus] an additional 30,000 hotel nights per year—which will require the construction of at least one new hotel—as well as lots of foreign visitors. The economic impact will be phenomenal.

"While Brexit and the EMA relocation are two different issues, they are connected, and I think their impact on the pharmaceutical industry in the EU will be quite significant," he continued. "Global pharma firms like their headquarters to be close to the EMA, or at least to have an affiliate close by, as happened in the past in the UK. If they don't have a local office in the Netherlands now, I suspect they will." Nanninga also anticipates that the move will be a boost for Dutch pharmaceutical affiliates, since they will have greater access to EMA meetings and symposia. ‹›

—Scott Fotheringham, PhD

* A member state that evaluates marketing authorization application dossiers and prepares assessment reports on behalf of the Concerned Member States in mutual recognition (MR) and decentralized (DC) procedures.

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1. European Medicines Agency. Heads of Medicine Agencies. "Guideline on Good Pharmacovigilance Practices (GVP). Module I—Pharmacovigilance Systems and Their Quality Systems." EMA/541760/2011. 22 June 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129132.pdf

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