PHARMACEUTICAL ENGINEERING®

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THE SUMMER ISSUE — TECHNOLOGY

3D Printing and Bioprinting in Pharmaceutical Manufacturing

The Marriage of Pharma and Tech Yields Benefits for Patients

Biotechnology in Europe Special Interest Group

PLUS

2017 ISPE EU Conference Highlights

Applying QRM to Improve Sustainability of Pharma Manufacturing

Performance and Validation of Ozone Generation for Pharmaceutical Water Systems

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EDITOR'S VOICE

NEW TECHNOLOGY, AMBITION, AND PATIENT SAFETY

Anna Maria di Giorgio
Editor in chief

Technology is not new. Biotechnology is not new; it's new-ish. Yet when the two come together to look at how they can transform medicine, its creation, delivery, and access, well, that is new and can be extraordinary. Extraordinary enough that the FDA established the Emerging Technology Team (ETT) in the Office of Pharmaceutical Quality (OPQ) of the Center for Drug Evaluation and Research (CDER) in 2015.

Sau Lee, PhD, who chairs the team, explains the ETT's intentions and outlook in our cover story, "Just Getting Started: 3D Printing and Bioprinting in Pharmaceutical Manufacturing." In that story, author Scott Fotheringham, PhD, looks at 3D printing and bioprinting. He pursues still other technological advances in his feature "A Good Fit: The Marriage of Pharma and Tech Yields Benefits for Patients," discussing several pharma/tech alliances and their ambitions.

Our chapter profile highlights ambition, too. Mike McGrath spoke with the Great Lakes Chapter President Deborah Geyman about its recent financial struggles and how she sees brighter days ahead—did you know Great Lakes serves more than 800 members scattered across the six states surrounding Lake Erie and Lake Michigan? On this same topic of ambition, tenacity, and diligence, Mary Foss offers thoughtful advice to students entering the industry for the first time, and our regular columnist David Smith reveals the best way to "ace" a telephone interview.

Our technical authors look at patient safety from novel angles: applying QRM to reduce HVAC costs (Appleby, et al.), the benefits of ozone technology in water pharmaceutical systems (Cohen and Johnson), how to minimize and control microbiological contamination in water systems (Sandle), the reliability of sterility assurance tests (Stering), and a method for demonstrating content uniformity (Stepanic and Saeed).

All in all, we have a little bit of something for everyone in this issue, and I hope you enjoy it.

Happy summer and I look forward to seeing you at the 2017 ISPE Annual Meeting & Expo in San Diego, California.

PS: Remember to vote for your new Board of Directors—look for your electronic ballot via email by late July. ‹›

ISPE

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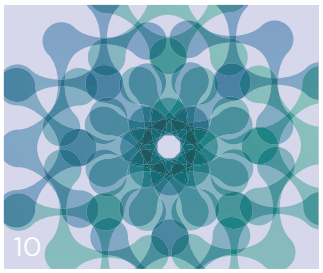

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ADVANCING INNOVATIVE TECHNOLOGIES

Mike Arnold, Senior Director at Pfizer, and Chair of ISPE's 2016-2017 International Board, Member since 1998

Over the past several years, I've presented on various topics aligned with "emerging technology" in our industry. I routinely concluded those presentations stating, "He who has technology wins!" At that time, of course, I was referring to pharmaceutical manufacturing companies.

It's now clear, however, that we are at the point where our patients are also well positioned to win. Few will argue that over the coming decade medicine will become more personalized as biotechnology evolves. In addition, patients will more routinely play a significant role throughout the supply chain, not only at its end.

While there is nothing more exhilarating than the prospect of affecting patients' lives for the better, no challenge is more daunting. In addition to manufacturing technologies, for example, there are technologies that support the conduct of clinical trials that are integral to our success in serving patients. The challenges associated with emergence of these technologies include global regulatory standards for use and acceptance. We must overcome these and other challenges if we are to be successful.

ISPE recognizes that helping the industry advance involves more than training its people in the basics of facilities and equipment, production systems, and quality systems. We intend to strengthen our position as the go-to organization for knowledge regarding designing, building, and operating pharmaceutical plants across all technology platforms. We will continue to respond head-on to developing industry issues by fostering knowledge exchange and related professional development to achieve results. As always, through our efforts, we hope to improve patients' access to quality medicines.

Key to our success is promoting member access to the regulatory agencies that help bring drugs and new technologies to market. At the ISPE/FDA/PQRI Quality Manufacturing Conference, held in Arlington, Virginia, from 5–7 June, more than 20 FDA representatives took time out of their week to interact with attendees, lead working sessions, and answer questions. The FDA regulatory panel held on the last day saw seven FDA staff answer questions on topics ranging from quality metrics to the mutual recognition agreement (MRA) and emerging technologies. The questions came from informed participants, and answers from the FDA were frank and straightforward. There are few associations that can offer such access to its members, and we feel privileged to be able to do so.

ISPE values its working relationship with regulators as we work to fulfill both regulatory and industry objectives. Our most recent decision—to rename the former ISPE Regulatory and Compliance Committee to Regulatory Quality Harmonization Committee (RQHC)—reflects our desire to partner with regulators in developing strategies that will promote global harmonization.

ISPE VALUES ITS WORKING RELATIONSHIP WITH REGULATORS AS WE WORK TO FULFILL BOTH REGULATORY AND INDUSTRY OBJECTIVES

Regulators around the world continue to address the inevitable pipeline of new pharmaceutical manufacturing technologies. This is a space where industry and regulators need to partner frequently and effectively. The FDA's Emerging Technology Team (ETT) in the Office of Pharmaceutical Quality (OPQ) of the Center for Drug Evaluation and Research (CDER) demonstrates the agency's focus in this space. And the spirit of collaboration that surrounds it, in both intention and action, is one we should all share.

More than half the year may be behind us, but what lies ahead is very exciting: ISPE's European and American biotechnology conferences, Process Validation and Process Validation Statistics Conferences, the 2017 Annual Meeting, the ISPE Biopharmaceutical Leadership Forum … and that's just the conferences! Our roster of training courses in North America and Europe provides timely access to insights on data integrity, C&Q, biotechnology manufacturing facilities, and GAMP® GxP process control. I hope you will take advantage of these opportunities to enrich yourselves, learn, and collaborate with your peers.

To support these and other global initiatives, the ISPE International Board of Directors has approved the establishment of the ISPE Foundation to support education, training, and research for the advancement of innovative technologies. The foundation will also address global challenges in the development, manufacture, and supply of quality pharmaceutical products for the benefit of patients around the world, and provide a platform to support our Chapters and Affiliates. We look forward to working closely with them to identify global initiatives that will promote our industry and benefit ISPE members industry-wide, regionally, and locally. ‹›

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2017 CALENDAR

Please refer to ispe.org/globalcalendar for the most up-to-date event listing and information

JULY

3–5 Brazil Affiliate
GAMP® 5 Training
São Paulo, Brazil

5 Argentina Affiliate
Proyecto Integrado Diseno Planta y HVAV 1ra Parte
Buenos Aires, Argentina

5–6 DACH Affiliate
Die Containment-Schnittstellen im Productfluss
Illertissen, Germany

6 Singapore Affiliate
Introduction to Biosafety Workshop
Thirsty Thursday
Singapore

San Francisco/Bay Area Chapter
YP Networking Event
Vacaville, California

11 Italy Affiliate
Summer Night 2017
25th Anniversary Celebration
Milan, Italy

12 Argentina Affiliate
Proyecto Integrado Diseno Planta y HVAV 2da Parte
Buenos Aires, Argentina

Greater Los Angeles Chapter
Technical Meeting
Los Angeles, California

13 San Diego Chapter
Therapeutic Thursday
San Diego, California

19 Brazil Affiliate
Good Engineering Practice Day
São Paulo

19–20 Brazil Affiliate
Commissioning and Qualification Training
São Paulo, Brazil

20 San Francisco/Bay Area Chapter
Fun Day
Napa, California

27 Brazil Affiliate
Signatures & Electronic Registers Training
São Paulo, Brazil

Great Lakes Chapter
Networking & Craft Beer Toasting
Cincinnati, Ohio

Pacific Northwest Chapter
Annual Golf Tournament
Mukilteo, Washington

San Diego Chapter
Facility Tour or Technical Meeting
San Diego, California

AUGUST

1 Brazil Affiliate
Concepts in Serialization Training
São Paulo, Brazil

7–8 CIP Design, Integration, and Chemicals–Updated! (T03)
ISPE Training Institute
Tampa, Florida

9 Brazil Affiliate
Validation of Computerized Lab Systems Training
São Paulo, Brazil

10 San Diego Chapter
Life Science Resource Fair (Vendor Night)
San Diego, California

11 San Diego Chapter
20th Annual Golf Tournament
Encinitas, California

11–12 Philippines Affiliate
Seminar on Quality Management Systems
Quezon City, Philippines

16 Greater Los Angeles Chapter
Technical Meeting
Los Angeles, California

17 San Francisco/Bay Area Chapter
Commuter Conference
San Francisco, California

17–18 Brazil Affiliate
Validation of Biotechnology Processes Training
São Paulo , Brazil

18 Rocky Mountain Chapter
Golf Tournament
Erie, Colorado

23–26 Singapore Affiliate
Conference and Exhibition 2017
Suntec City, Singapore

24 Brazil Affiliate
2017 Cold Chain Day
São Paulo, Brazil

Brazil Affiliate
Concepts & Validation Cloud Computing Training
São Paulo, Brazil

Pacific Northwest Chapter
Praxair Tour
Fife Air Separation Plant Tour
Fife, Washington

25 Midwest Chapter
Annual Golf Tournament

30 Brazil Affiliate
Sustainability Training
São Paulo, Brazil

SEPTEMBER

7–8 Commissioning & Qualification (T40)
ISPE Training Institute
Tampa, Florida

8 Singapore Affiliate
Go-Karting Challenge
Singapore

10 Nordic Affiliate
Critical Utilities CoP Network Meeting
Copenhagen , Denmark

Nordic Affiliate
Nordic PAT CoP Autumn Meeting
Malmo, Sweden

11–13 GAMP Data Integrity 21 CFR Part 11–New! (T50)
ISPE Training Institute
Tampa, Florida

12–13 Brazil Affiliate
Analysis of Risks in Pharma Conference
São Paulo, Brazil

12–14 2017 Process Validation Conference
Bethesda, Maryland

13 DACH Affiliate
DACH CoP GAMP D/A/Ch Forum mit Vortragen
Frankfurt, Germany

13–15 2017 Process Validation Statistics Conference
Bethesda, Maryland

14 Canada Affiliate
Bike & Hike

San Francisco/Bay Area Chapter
Dinner Meeting
San Francisco, California

14–15 Process Validation in Biotech Mfg. (T32)
ISPE Training Institute
Tampa, Florida

18–20 Brazil Affiliate
GAMP 5
São Paulo, Brazil

Quality Risk Management Workshop–Updated! (T42)
ISPE Training Institute
Tampa, Florida

21 Nordic Affiliate
Serialisation: The New Paradigm in Supply Chain
Copenhagen, Denmark

23 Greater Los Angeles Chapter
Golf Tournament
Los Angeles, California

25–26 Biotechnology Mfg. Facility Design–Updated! (T31)
Cleaning Validation Principles (T17)
Amsterdam, Netherlands

25–27 Basic GAMP 5, Annex 11/ Part 11–Updated! (T45)
Amsterdam, Netherlands

Process Validation–Updated! (T46)
ISPE Training Institute
Tampa, Florida

26 Brazil Affiliate
Update in Climatization & Clean Rooms
São Paulo, Brazil

26–27 2017 Europe Biotechnology Conference
Dublin, Ireland

27–28 Commissioning & Qualification (T40)
GAMP 5 GxP Compliance–Updated! (T21)
Sterile Pharma Mfg. Facility (T12)
Amsterdam, Netherlands

28 DACH Affiliate
Workshop: OSD-Produktion als Ultra-Fast-Track-Projekt
Ingelheim, Germany

San Diego Chapter
Facility Tour or Technical Meeting
San Diego, California

OCTOBER

2–3 Biotechnology Mfg. Processes (T24)
ISPE Training Institute
Tampa, Florida

4 Boston Area
Annual Product Show
Foxboro, Massachusetts

5 San Diego
Technical Meeting
San Diego, California

5–6 Technology Transfer (T19)
ISPE Training Institute
Tampa, Florida

9 DACH Affiliate
Workshop: New Ph. Eur. WFI Monograph
Penzberg, Germany

10 Belgium Affiliate
GAMP COP Benelux: Computerized Systems & Data
Wilrijk, Belgium

France
Conference IPIL: Externalisation
Lyon, France

12 San Francisco/Bay Area
Oktoberfest Social Event
San Francisco, California

12–13 GAMP 5 GxP–Updated! (T21)
ISPE Training Institute
Tampa, Florida

14 Nordic Affiliate
GAMP Networking Meeting
Copenhagen, Denmark

16–17 Canada Affiliate
Education and Product Symposium
Montreal, Canada

18 France Affiliate
Atelier de Réflexion
Operation Management
Paris, France

18–19 Poland Affiliate
YP and SME Global Systems and Data Integrity
Lodz, Poland

Brazil Affiliate
Annual Conference
São Paulo, Brazil

19 IChemE Singapore Awards
Singapore

France Affiliate
Atelier GAMP Francophone
IT Infrastructure
Paris, France

Rocky Mountain Chapter
Fall Educational Event

23–24 Biotechnology Mfg. Facility Design (T31)
Cleaning Validation (T17)
Pharma Water Generation USP WFI & PW–Updated! (T04)
Boston, Massachusetts

24–26 HVAC (T14)
Boston, Massachusetts

25–26 Pharma Water Storage/Qualification–Updated! (T23)
Pharmaceutical Facilities Management Training Course (T26)
Boston, Massachusetts

26 DACH
Workshop Pharma 4.0 Digital Transformation Ideation
Ismaning

29–1 Nov 2017 ISPE Annual Meeting & Expo
San Diego, California

30–1 Nov Singapore
Pharmaceutical GMP Course
Singapore, California

31 Brazil Affiliate
Validation of Electronic Spreadsheets
São Paulo, Brazil

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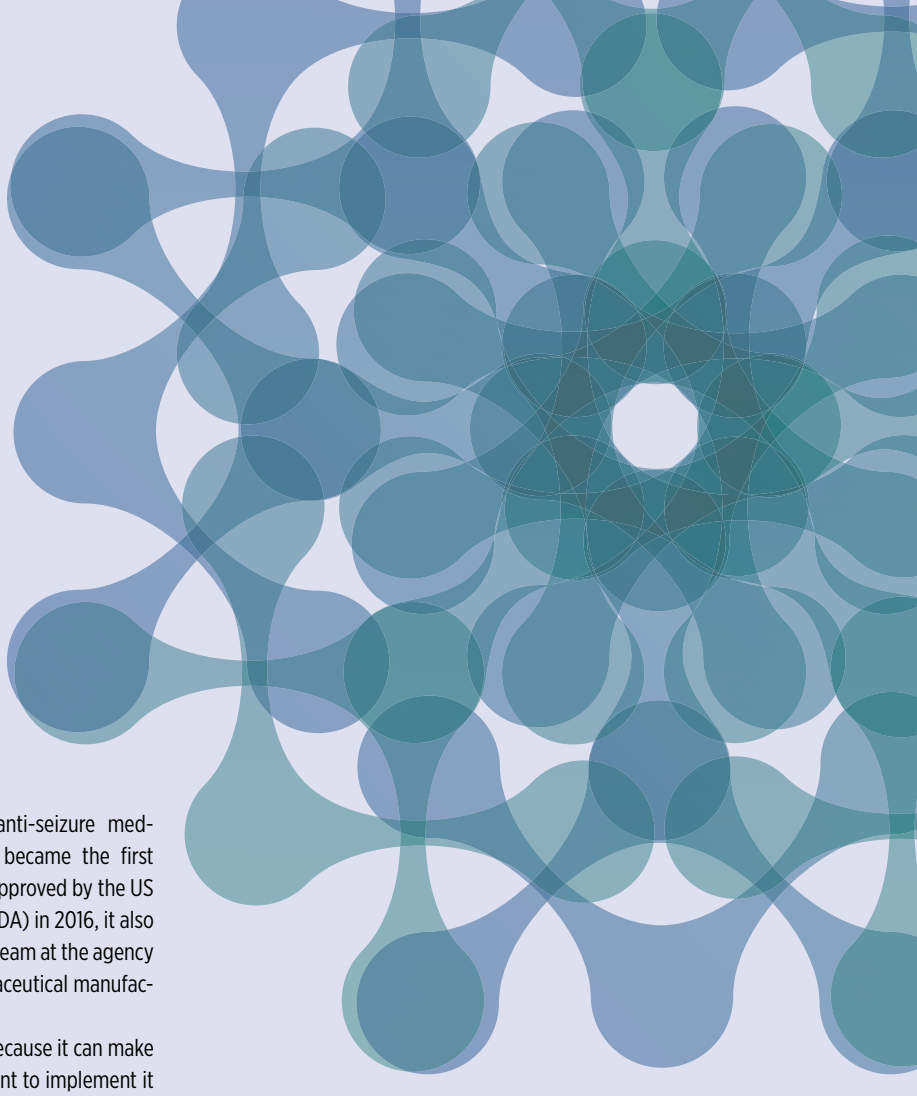
JUST GETTING STARTED

3D Printing and Bioprinting in Pharmaceutical Manufacturing



When Aprecia Pharmaceuticals' anti-seizure medication Spritam (levetiracetam) became the first 3D-printed* drug product to be approved by the US Food and Drug Administration (FDA) in 2016, it also became the first confirmed drug supported by a new team at the agency that encourages industry uptake of emerging pharmaceutical manufacturing technology.

"Industry is supportive of innovative technology because it can make manufacturing more efficient, yet they may be hesitant to implement it due to perceived regulatory uncertainty," said Sau (Larry) Lee, PhD and chair of the Emerging Technology Team (ETT) in the Office of Pharmaceutical Quality (OPQ) of the Center for Drug Evaluation and Research (CDER) at the FDA.

"While the regulatory process remains the same, what has changed is the industry's recognition of the FDA's willingness to accept the adoption of innovative technology. ETT provides a forum for industry to engage the agency, discuss their technology, and help reduce uncertainty.

"The challenge on the industry side is to determine which type of products will use these technologies," Lee continued. "Because the technology is new, industry sometimes needs additional clarity regarding the regulatory expectations. FDA can help them apply these technologies to pharmaceutical applications. We tell them what types of data we want to see and then it's up to the company to generate the appropriate data and to have an early engagement with regulators."

Staffed by representatives from all relevant CDER review and inspection programs, the ETT is meant to encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing where the FDA has limited review or inspection experience. Among the emerging technologies the team has addressed to date are continuous manufacturing, advanced analytics, aseptic filling closed systems, and 3D printed tablets like Spritam.

BEYOND MANUFACTURING TABLETS

3D printing and bioprinting have the potential to transform drug making beyond manufacturing tablets. The technology is also being used to create tissue and miniature cellular models, some of which can even mimic the biology of human organs.

"We will soon see the printing of cell-based diagnostics for the rapid screening of drug candidates and chemotherapeutic agents," said John Fisher, chair of the Fischell Department of Bioengineering at the University of Maryland and an expert in bioprinting. "This should reduce the need for animal studies or narrow down candidates to be tested in conventional ways, thus reducing costs."

Bioprinting is the process of creating cell patterns using 3D printing technologies to produce complex live tissues. While the technical challenges related to living cells and tissue construction make bioprinting more complex than nonbiological 3D printing, together they can be used to create surgical models, molds for titanium implants, prosthetics for amputees, dental crowns and bridges, cranial implants, and, hopefully one day, bone, heart valves, and even a functional heart. Bioprinting is faster and cheaper than previous technologies, with a prosthetic hand costing as little as $150.[1] The Ottawa Hospital, in partnership with the University of Ottawa, has opened a new medical 3D printing program—

* 3D printing, also known as additive manufacturing, refers to a group of processes and materials that can produce a three-dimensional solid object from a digital file by applying successive layers of material.

the first based in a Canadian hospital—that recently created 3D-printed prosthetic hands for two patients.

In addition to prosthetics and cellular networks, 3D printing and bioprinting will change how drug candidates are tested, how drugs are manufactured, the supply chain, and industry dependence on animal testing.

3D PRINTING AND BIOPRINTING HAVE THE POTENTIAL TO TRANSFORM DRUG MAKING

3D MANUFACTURING

Spritam is a good example of how 3D manufacturing has evolved and how it can enhance product characteristics. The drug is made by printing medication and binders layer by layer, without compression, punches, or dies.[3] This produces higher drug loading—up to 1,000 mg—than can be obtained by conventional manufacturing. The tablets also dissolve more quickly in the mouth, making it a boon for patients with dysphagia. But there's still another benefit:

"The tool-less making of tablets permits novel pill shapes, which can affect the absorption rate," said Peter Denmark, North American sales manager for EnvisionTEC, a manufacturer of 3D printers and materials. "It allows for patient-specific drugs for which the dosage can be calculated per patient per disease due to additive manufacturing."

Using conventional manufacturing, drug makers can produce up to 1.6 million tablets per hour, a number that far exceeds what a 3D printer can currently produce.[4] Thomas West, project director and manager of intellectual property at Aprecia Pharmaceuticals, doesn't see this as a limitation, however.

"The real purpose of 3D printing is to create products with unique functionality that cannot be achieved by high-speed compression tableting or other traditional manufacturing technologies," he said. "Over time, we expect 3D printing technology to evolve and gain efficiencies, but the focus will be on the unique functionality of the end product rather than a way to replace traditional manufacturing of standard tablets."

As an example, West points out that 3D printing technology can be used in a centralized manufacturing setup to make differentiated products, because those don't compete with traditional tablets.

BIOPRINTING EQUIPMENT

The simplest bioprinted tissue is a single layer, like skin. Organovo and Invetech partnered to develop the first 3D human tissue bioprinter in 2009. The sector has expanded greatly since then. One company embracing the technology is L'Oreal, which is working with Organovo to bioprint human skin to test cosmetics.[8]

"All of our customers are patterning cells and biomaterials to do new science or build useful products," said Danny Cabrera, CEO of BioBots, a biotechnology firm in Philadelphia, Pennsylvania, US. The company makes 3D bioprinters that can use ink containing human cells. "Some of our customers are building living tissues out of a patient's own cells, then using those tissues to test therapies and determine the best treatment for an individual. BioBots can build personalized living things out of cells and biomaterials."

A typical bioprinting system includes hardware, design software, and inks. The software translates files from 3D computer-aided engineering and design tools such as SketchUp, AutoDesk, or SolidWorks into printer instructions. The inks can be cell lines or chemical material such as collagen, gelatin, polyethylene glycol, or alginate—anything that can be extruded from a syringe.

Like EnvisionTEC, BioBots also works with pharmaceutical customers who use 3D bioprinters to make pills. "They're exploring how different solutions dissolve at different rates and how geometry controls dosing, down to the minute," said Cabrera. "Their goal is to personalize dosages and diffusion profiles for individual patients."

DRUG SHORTAGES AND RECALLS

The ETT sees a gap between the basic research and technology development conducted by universities and government agencies and its adoption by the private sector,[7] and uses a collaborative approach to bring the groups together.

"The ETT plays a leadership role in the OPQ quality assessment team for applications containing an emerging technology," said Lee. Team members evaluate ways that existing FDA guidance and policy may impact uptake of innovative technology. The ETT's long-term goals include modernizing pharmaceutical development and manufacturing, in large part to address the problem of product recalls and drug shortages.

"A lot of shortages and recalls are related to quality issues, either due to manufacturing processes or aging facilities," he explained. "The pharmaceutical industry tends to invest more in drug discovery than manufacturing. This means that manufacturing technology has not progressed as significantly. The FDA hopes to address this by promoting technology improvements that provide flexibility, robustness, and agility of pharmaceutical manufacturing. The goal is more reliable technology that reduces the likelihood of defects and errors."

Traditionally, the FDA only talks to a company once it has a drug candidate, but conversation with the ETT can start earlier because it focuses on technology. "The more they tell us about the drug product or substance the better," said Lee. "The level of detail we can provide in our comments will vary depending on the level of detail they provide."

The ETT approved Spritam, and was also instrumental in supporting approval for a switch from batch to continuous manufacturing for Janssen's HIV medication Prezista (darunavir). "FDA successfully worked to provide regulatory clarity to the applicants and reviewed their submissions in a timely manner," Lee said. "The ETT was only established two years ago, yet we get lots of requests, and have had a good response from industry."

In addition to conducting its own research, the FDA works with academia and industry to assess the use of these technologies to support product applications.[5] Last year the agency issued a draft guidance covering 3D printing protocols and devices.[6]

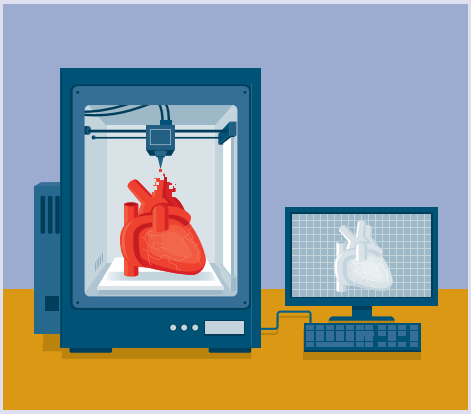
SUPPLY CHAIN

3D printing's effect on the supply chain will result in on-demand production, local manufacturing, and the creation of unique, individualized products. Dentists, for example, are already printing 3D crowns and bridges. In drug

making, 3D printing will enable low-volume production and increased speed to market.

"The supply chain will be shortened and become hyper local," EnvisionTEC's Denmark said. "Think of the compounding pharmacies having an additive machine in house to produce patient-specific pills. And for drug testing of new candidates, dosage can be changed on the fly, with less expense, locally."

The potential for localized and centralized manufacturing might, as many in the biotechnology sector advocate, keep aspects of drug manufacturing in the United States. "The overall value proposition for the differentiated dosage forms that 3D printing allows can support manufacturing in places like the US, as Aprecia does," said West. "This is instead of relying on asymmetry in labor costs from abroad."



Since 3D printing is in its infancy in the pharmaceutical industry, its unique value creation is not yet through cost reductions, but "through proprietary innovations in technology, which for us are US-based," said West. "The technology will improve in the commercial context as innovation continues."

At the same time, other parts of the supply chain, such as the sourcing of raw materials and the manufacture of active pharmaceutical ingredients (APIs), are not affected by 3D printing technology. One challenge for the industry is transforming APIs into materials that can be 3D printed.

ONE OF THE MOST EXCITING TECHNOLOGY DEVELOPMENTS IS "ORGANS-ON-CHIPS"

BIOPRINTED TISSUE AND MODEL ORGANS

Bioprinting tissue uses "inks" that include cellular matrix and support materials, as well as sacrificial material that is washed away after printing.[8] Fisher's lab at the University of Maryland collaborates with KeraNetics, a North Carolina–based biomaterials company, to bioprint purified keratin proteins that the company uses in its wound healing and tissue regeneration products.

Fisher's lab has also bioprinted placenta and other tissue models to study preeclampsia and the transport of pharmaceuticals from mothers to fetuses in utero. Other long-term potential uses include making miniature organs for drug testing. While experimental bioprinted heart valves have been produced[13] and the FDA recently approved cell-based cartilage regeneration, whole organ constructs of heart, liver, or other organs are still a distant goal.[9]

"These are interim steps in a long process," said Fisher. "You have to keep the market in mind. The mechanical heart valves and bovine heart valves work well. A tooth could be engineered, but will it be cheaper? What dentists are constructing now is viable and works."

He would like to see more collaboration with the pharmaceutical industry in the development of printable materials. "There is a need to develop more materials and more material systems," he said. "The pharmaceutical industry, with its ability to screen and develop molecules, could offer a wonderful synergy."

ORGANS-ON-CHIPS

One of the most exciting technology developments is "organs-on-chips": micro-engineered systems that mimic the functions of human biology. These living systems—about the size of a USB flash drive—are comprised of tiny channels lined with human cells to recreate the environment of an organ. One of the pioneers in commercializing organs-on-chips is Emulate Inc., a company developing examples for the lung, liver, intestine, kidney, and brain to be used in a lab-ready unit.

Emulate uses engineering principles to recreate the complex, dynamic cellular microenvironment in the living human body, including the flow of blood and air, as well as the mechanical forces that cause breathing and peristalsis. An example is Emulate's lung-on-a-chip, which has at its center a porous membrane. On one side are airway cells from the air sac. On the other are capillary cells. Each layer of cells is in contact with a microfluidic channel. Blood pumps through one channel in contact with the capillary cells; air passes through the other. Force on either side of the channel stretches and releases the cells to mimic the environment in the lung as we breathe.[10] When these lung cells are challenged with medicines, chemicals, or toxins, their responses can be measured and observed, in part because of the transparency of the chips that allows the workings of the cells to be witnessed.

Organs-on-chips might reduce the need for animal testing,[2] which, in addition to its ethical considerations, is expensive and doesn't always predict human biology accurately. They may also reduce the time spent on drug testing, which currently can take years, costs hundreds of millions of dollars, and involves thousands of patients in clinical trials.

Based in Boston, Emulate is a private company that began as part of the Wyss Institute of Harvard University, where organs-on-chips were pioneered by Donald Ingber, PhD. The FDA and other government agencies provided grant support to Wyss, and Emulate is carrying on this partnership.[11] In April, the FDA's Center for Food Safety and Applied Nutrition entered a collaborative agreement with Emulate to evaluate and qualify the company's organs-on-chips technology as a model to study potentially harmful compounds in food, cosmetics, and dietary supplements.[12] The FDA and Emulate will look first at the effects of these compounds on the liver, using Emulate's liver chip.

"Emulate collaborates with many stakeholders involved throughout the drug development process, including regulatory agencies," said Geraldine Hamilton, PhD, the company's president and chief scientific officer. "Our aim is to evaluate our organs-on-chips technology so its functionality aligns with the requirements of regulatory research and filings with FDA and other agencies.

"Within the pharmaceutical industry, we'd like to see organs-on-chips used throughout the drug-development process, including the discovery of new drug targets, understanding disease mechanisms, and determining the efficacy and safety of new drugs," added Hamilton. Emulate partners with

companies including Merck, which uses its lung-on-a-chip to study asthma, and Johnson & Johnson, which uses its liver and thrombosis chips to study toxicity and side effects associated with new drug candidates.

Paul Vulto, cofounder of Mimetas, a Dutch company that also makes organs-on-chips, thinks the chips offer complex predictive models that are more accurate to the human condition than traditional cell culture or animal models.

"Organs-on-chips aren't a monoculture," he said. "They're comprised of multiple layers of cells grown in 3D in a controlled co-culture, yet we can still handle them in large numbers and they're robot compatible. We're collaborating with the most innovative companies, but eventually the whole industry is going to do this because the old paradigm of simple 2D monocultures has proven to be not good enough."

The Mimetas Organoplate is a 384-well plate whose bottom layer holds microfluidic channels that join four wells. Cells can be grown in a gel-collagen structure, while growth medium is perfused alongside. This form of bioprinting produces 3D cell culture of organ-like growth. For example, a neurovascular unit contains three layers of cells: neurons, astrocytes, and blood vessels. The tissue shows brain activity and can be challenged with test compounds.

"Toxicology models are currently primarily used by the pharmaceutical industry as internal decision-making tools," Vulto said. "Once pharmaceutical companies have gathered sufficient evidence of the physiological relevance of these models, we can take this evidence to the FDA and the EMA. Regulatory agencies are important drivers of this technology in areas such as preclinical safety. It would be a great boost if some of these models get accepted."

WHEN IT COMES TO BIOFABRICATION, WE'RE JUST GETTING STARTED

PERSONALIZED MEDICINE

Like other proponents, Hamilton and Vulto predict that organs-on-chips will not only transform drug development and testing, but will be used to develop personalized medicine, using a patient's cells in the chip. An individualized organ-on-a-chip would then be used to find the best treatment option and avoid therapies that would be ineffective or cause harm.

"By combining organs-on-chips with an individual's cells, this emerging approach offers new possibilities to understand our own health and the way in which medicine is practiced," said Hamilton.

"Complex diseases, especially those that develop over a lifetime like cancer and Alzheimer's, are multifactorial," said Vulto. "These diseases are individual and are probably not going to be solved by a blockbuster drug that fits everyone. To find a good therapy you have to stratify patients and develop the right drugs for specific subtypes of the disease.

"We want to move into the clinic as a decision-making tool to select the right drug for each patient," said Vulto. "Currently this uses molecular techniques like microarray or gene sequencing. There is an unmet need for phenotypic models that are more complex for diseases for which we don't necessarily need to understand the mechanism. You can test if the tissue responds positively to the drug."

"These first-generation organs-on-chips are better mimics of the human body than cells grown in a dish and, in some cases, animals," said BioBots's Cabrera. "Can they be better? Of course, but we're nowhere near done. When it comes to biofabrication, we're just getting started."

—Scott Fotheringham, PhD

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ISPE.

Also in this section

2017 ISPE EUROPE ANNUAL CONFERENCE REACHES NEW HEIGHTS IN BARCELONA

The ISPE Europe Annual Conference drew more than 500 people to the Crown Plaza Hotel in downtown Barcelona from April 3–5. With 77 education sessions and 50 exhibitors, the gathering was described by at least one attendee as "the best and biggest conference ever." John Bournas, ISPE CEO and President, noted that the forum doubled previous ISPE Europe attendance records.

EXECUTIVE FORUM

The conference started with an executive forum, as usual. This year's theme of "Pharma 2025" explored the industry from different corporate perspectives: mid- and large-sized manufacturers, global engineering firms, and international consulting organizations.

Wolfram Carius, Executive Vice President, Bayer, said that new and promising technologies outside of a company's core focus often benefited from partnerships with other stakeholders to limit financial risk. Because managing complexity is an unavoidable challenge that will require special skills and capabilities for the workforce of the future, he also described human resources as a success factor for future pharma that goes beyond technology. Good engineering practice, he added, should especially be considered key.

Christian Bechon, CEO, LFB Group, said that good strategic planning should lead any investment decision. He highlighted the importance of location selection for new production sites, adding that technology, infrastructure, and sociopolitical choices are additional factors. It also became clear that traditional stainless steel equipment may have a future in certain product portfolios—not only in single use technology.

Juan Hernandez, President, Life Sciences and Advanced Manufacturing, Fluor Corp., gave an inspiring presentation on factories of the future from an engineer's perspective. Not only will aesthetics and art influence facility exteriors, he said, some technology will be movable—packed in containers and ready for plug and play. Imagine how this would affect knowledge and technology transfer in the future!

Paul Rutten, Partner, McKinsey & Company, discussed the role of lagging/leading indicators and FDA's metrics initiative in future pharma operations. New KPIs describing company culture and individual behaviors will be needed, especially for managers.

Christian Wölbeling, Senior Director Global Accounts, Werum IT Solutions, discussed the road from Industry 4.0 to Pharma 4.0, beginning with the ICH Q10 "new quality system." He explained the elements and enablers that should be considered in the fully integrated digital world of data integrity by design. Years of step-wise process remain to align the supply chain and achieve a holistic production control strategy. [Editor's note: For more on HPCS, see *Pharmaceutical Engineering* 37, no. 3 (May-June 2017): 44–49.]

François Sallans, VP Quality and Compliance and Chief Quality Officer, Johnson & Johnson, closed the day with an update on the continuing problem of drug shortages. This uphill battle needs both management awareness and political willingness to act, exemplified by ISPE's partnership with the Pew Charitable Trusts in the United States. In Europe, ISPE will continue to perform trainings with interested parties. Ultimately, he noted, it is a social responsibility for public health and safety to implement the countermeasures identified by industry associations and other stakeholders

KEYNOTES

Juan Andres, Global Head Technical Operations, Novartis, discussed future trends in medicines. As we live longer we contract more diseases, and this creates a demand for affordable medicines and individualized treatments tailored to our needs. The only response to this is innovation. He cited as an example a completely new approach to cystic fibrosis that can treat babies in utero.

Some manufacturing technologies, however—such as tableting and coating—experience little pressure for innovation. The main paradigm in this part of the pharma industry was "playing not to lose."

He compared innovation in the pharma industry to the technical revolutions that had occurred in other industries over the past 10 years—from iPhones to digital music streaming and Tesla cars. These changes were spurred by the "ability to supply." Pharma cannot offer innovation with limited supply, therefore we must supply in ways never done before. Quality, safety, and efficacy must be innovated at the same time. The new paradigm must be "play to win!"

Other points:

- Nowadays compliance and a robust supply chain are basic expectations. But these are not enough, as "legally driven" companies are not the most successful.
- Consultancy concepts of the past like just-in-time, Six Sigma, and lean production were "monistic" and not "holistic." One size does not fit all.
- Wise decisions are needed about where to invest: in core business. Don't get attached.
- Be careful with external spending and outsourcing, it can become a very complex and fragmented landscape to manage.

- The driver is the "individual optimum," which can lead to a "penny-wise and pound foolish" result.

In summary, he said "don't ignore new technology, invest and partner, reliability is not negotiable, and productivity serves affordability!"

Gert Moelgaard, Senior Consultant, Moelgaard Consulting, predicted a continuation of double-digit global pharma growth. The so-called 2011 "patent cliff" was an indication that pharma was no longer innovative. In the meantime, specialty drugs like Humira and Avastin will be part of our future, despite their high cost. Biosimilars and even orphan drugs have caught fire in big pharma.

The top 20 specialty drugs are injectables. Their challenges are smaller batches, shorter cycle times, operating efficiency, enhanced change-over times, and a higher pressure for time to market. The goal for manufacturing must be a completely automated filling process without any manual intervention; this also sets future expectations for regulators (Figure 1).

Pierre-Alain Ruffieux, Head of Global Quality and Compliance, Hoffman-La Roche, considered "culture first" when describing quality management in 2025. Robust compliance, reliable manufacturing, and a more harmonized regulatory environment would be the framework. For technology, he asked, "What hinders innovation? Are we able to attract the talent we need for the future? Will top engineers go to pharma?" Industry must find the answers to these questions.

Speed will be of the essence. There will be more players and more drug applications. Today the average time for a drug registration is nine years—it should be two! Unharmonized regulatory inspections lead to a very high inspection load with no added value. Because registration requirements for approval of new drugs differ from country to country, a multi-country launch of a new drug is extremely complex and costly. The same is valid for post-approval changes and the whole life cycle management of a drug.

Some good developments are the new United States–Europe Mutual Recognition Agreement, which finally will be activated 2019 after more than 20 years. ICH Q12 has the right concept of harmonized post-approval changes, but whether and when it will be implemented is uncertain. The definition of "established conditions" could be a major roadblock.

Robert Nass, Merck KgA, described major trends:

- Biologics/monoclonal antibodies (mAbs)/ biosimilars
- Advanced therapy medicinal products (ATMPs)/personalized medicines
- Emerging markets
- Digitalization

The demand for single-use technologies will increase, but the need for stainless steel factories will continue, triggered by the specific needs of products and product portfolios. The drive toward continuous processing will increase. There will also be a need for end-to-end solutions in the pharmaceutical value chain to bring affordable drugs to the market. Digital trends will spread in the pharmaceutical industry (Figure 2).

Among the industry's continuing management challenges, regulatory uncertainty remains the top concern. Harmonization of regulation is more than open. Regulatory relief will not come, as regulators worldwide are driven by public expectations of zero risk, therefore they will continue to apply procedures for risk minimization and safety improvement. All in all, complexity will not disappear, so industry must manage it.

The only way is to reduce unrewarded complexity in operations and in all processes. There is much improvement potential.

TRACK 1: FACILITIES OF THE FUTURE

The Facilities of the Future Track was very well attended and provided some of the conference's most interesting concepts and discussion. There was a special focus on facilities, serialization, and innovation; many questions focused on practical experiences and problems for which companies were seeking solutions.

In pharmaceutical manufacturing there is much focus on the latest facility projects and new technology solutions. There are only very few continuous manufacturing facilities in commercial operations, for example, but more coming within the next year or so. There were several short presentations on technical proposals for continuous manufacturing as well as a link between continuous manufacturing and Industry 4.0, which was inspiring.

The new EU requirements on serialization are

becoming a daily challenge in many companies that supply both European and the US markets. The EU is still organizing operations within production stakeholders MAO and CMO. Turkey provided very practical shop floor feedback on how to avoid mistakes, one of the very useful takeaways for many participants.

Finally, the innovation part of track 1 brought many interesting solutions on contract manufacturing sourcing, next-generation WFI systems, and the potential impact of the new EU Pharmacopoeia WFI monograph on future WFI installations. Regulators provided feedback on harmonization in regulatory requirements around the world. China gave feedback on CFDA findings regarding GMP for international and Chinese companies. These presentations sparked interesting discussions.

ISPE plans to repeat this track at the 2018 ISPE EU Annual Conference.

TRACK 2: ADVANCED ASEPTIC PROCESSING

Roland Guinet, former GMP Senior Inspector in the Agence Nationale de Sécurité du Médicament et des Produits de Santé, opened the session with an overview of the expected new regulation for sterile products in Europe. Starting from "what we already know," he highlighted potential improvements from EMA's EudraLex Volume 4, Annex 1: "Manufacture of Sterile Medicinal Products" and Annex 17: "Real Time Release Testing."

PhD Student Monika Stieglbauer explained how we can close the gap between bench and bedside by manufacturing individual multipeptide vaccines for cancer immunotherapy.

Patrick Baleriaux, CEO, Aseptic Technologies SA, demonstrated how ready-to-fill vials can easily fill very small quantities of autologous and autogenic therapies. These products are very sensitive and usually require cryogenic storage.

Elaine Strong, Lead Pharma Solutions, Piramal Healthcare, described the challenge of the containment in high-potency antibody drug conjugate manufacturing. These mAbs are significantly more potent than traditional cytotoxic products and all processes must be considered with a combined risk and compliance approach.

Lothar Germeroth, Senior Vice President, Managing Director, Juno Therapeutics, closed the day with a presentation that showed the timeline of innovative cell and gene therapy from development to the patient. Individual treatments are becoming a reality!

Michael Dieterle, Director, Boehringer Ingelheim, and Jan Schäfer, Manager, Process Engineering, Sartorius, discussed the implementation of a 2,000-liter commercial manufacturing workshop fitted with single-use technology, highlighting benefits, challenges, and solutions. Markus Keller, Senior Research Engineer and Biologist, Fraunhofer Institute, gave a glimpse of the future with GMP robots that can be used in a sterile environment. High technology combined with human-like movements opened new perspectives for human-less workshops.

Ruben Rizzo, International Sales Manager Projects, Skan, presented a new approach for the decontamination of isolators and restricted access barrier systems using vaporized hydrogen peroxide (H2O2) cycle technology.

Jean-Pascal Zambaux, General Manager, Disposable Lab, presented an innovative single-use isolator dedicated to small preparations of cytotoxic products with total GMP compliance.

Niels Guldager, Global Technology Partner, NNE, described the development of biotech facilities in China. Big laboratories installed huge high-tech production capacities in a giant "antibody technical park" while incorporating cGMP requirements for biotech products.

A workshop was organized to share perspectives about the development of robotics in the pharmaceutical industry. Participants divided in three groups to discuss pros and cons. Attendees then regrouped in the plenary session to present each group's findings and conduct a general discussion.

TRACK 3: DATA INTEGRITY

Data integrity management across global organizations, preparing for GMP inspections, and the new GAMP® guide for data integrity management were presented. Data integrity in clinical trials, the role of cloud solutions, and human factors in data integrity were also discussed.

TRACK 4: CLINICAL AND ATMP SUPPLY CHAIN

Following an overview of regulatory aspects, Roche and Sanofi presented risk-based distribution concepts. MHRA Regulator David Churchward discussed innovation. The session concluded with a discussion of technological solutions to support the supply chain of tomorrow. ‹›

MOU SUPPORTS PACKAGING MASS SERIALIZATION

ISPE and the Open-SCS Working Group of the OPC Foundation signed a memorandum of understanding at the 2017 Europe Annual Conference in Barcelona.

The OPC Foundation is a global not-for-profit organization that pursues interoperability in automation by creating and maintaining open specifications to standardize the communication of acquired process data, alarm and event records, historical data, and batch data to multivendor enterprise systems and between production devices.

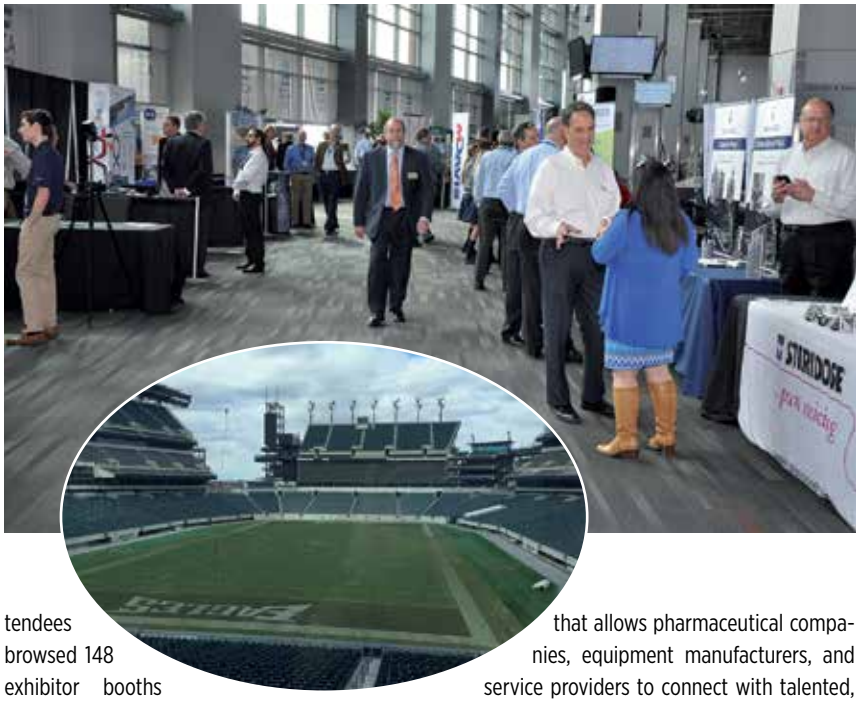
The agreement formalizes a collaborative relationship to promote a technical standard for system integration for health care packaging, serialization regulation compliance reporting, and mass tracking of serialization numbers.

This GAMP®-based implementation will define:

- The open packaging serialization global name space
- The packaging serialization user requirement specification for business and operations processes
- The packaging serialization system integration functional requirement specification (EPCIS framework), which will become a GS1 EPCIS standard application
- The packaging serialization OPC-UA companion specification with OPCF compliance certification
- Secondary goals include promotion of the Open-SCS serialization work by ISPE and promotion of the GAMP-based development and implementation by the foundation's Open-SCS Working Group.

DELAWARE VALLEY CHAPTER ANNUAL SYMPOSIUM AND EXHIBITION

Jenna Eicherly, Project Manager, Laporte Consultants and Vice President, Education Committee, Delaware Valley Chapter



The Delaware Valley Chapter is proud to host the longest-running vendor exhibition event in the ISPE community. The chapter held its highly anticipated Annual Symposium and Exhibition on 26 February, in Philadelphia, Pennsylvania. The event gave vendors an opportunity to demonstrate new technology and equipment; the 764 attendees from around the world got a chance to research these innovations and sample everything the chapter has to offer, from education sessions to networking to outreach to the next generation of scientists and engineers.

For the second year in a row the symposium was held at Lincoln Financial Field, home of the Philadelphia Eagles football team. Attendees could take two different stadium tours: The first was a behind-the-scenes look at the venue's press box, interview room, locker room, and football field. The second, titled "Go Green," showed why the arena is one of the greenest stadia in the world. The tour included a peek at their clean energy solutions, water/gas/electricity savings, and recycling and composting programs.

For the first time, the symposium opened with a keynote speech. The chapter hosted John Bournas, ISPE CEO and President. Bournas has been instrumental in developing the society's global initiatives, leveraging technology to extend ISPE's reach and expanding educational and training programs. He updated attendees on exciting news about ISPE as an organization.

After the keynote, the exhibition floor opened, and the symposium went into full swing. Attendees browsed 148 exhibitor booths to see what new equipment and ideas are available and watched technical presentations on the demonstration stage.

The exhibitions also included presentations by Future Cities, an exciting program that engages students in the sixth, seventh, and eighth grades to research, design, and build cities of the future using SimCity software.

The symposium offered six education sessions on two tracks:

1. Operational Risk
   - Supply Chain Risk: Andrew Skibo, MedImmune
   - Quality Risk: Lou Angelucci, Johnson & Johnson
   - Regulatory Risk: Gayle Lawson, CDER

2. Facilities
   - Facilities: Michael Blackton, Adaptimmune
   - Insights into Passivation and Rouge: Patrick Banes, AstroPak
   - Design and Construction Management: Bill O'Brien, Jared Craig, and Anthony Detweiler, Integrated Project Services

The career fair has become an increasingly popular symposium feature that allows pharmaceutical companies, equipment manufacturers, and service providers to connect with talented, qualified employment candidates.

After a long and fulfilling day, attendees were invited to unwind with an evening of networking and fun. Local rockers Tommy Conwell and the Young Rumblers were on hand to entertain the crowd.

Be sure to join us next year as we aim for the biggest and best symposium ever! ‹›

ISPE EUROPE'S BIOTECH PORTFOLIO

Tom Bannon, Michelangelo Canzoneri, Christoph Herwig, Miriam Monge, and Thomas Zimmer

The biotechnology sector is changing the pharmaceutical manufacturing environment: The trend toward personalized medicine is driving smaller batch sizes with higher production volumes. Digitization and integration of GXP computerized systems will leverage data and turn it into predictive control and knowledge. Highly potent products like cancer vaccines and antibody drug conjugates (ADCs) promise enormous potential, but are highly toxic, and require both product and operator protection.

As part of its global strategy, ISPE has pledged to boost its biotech capabilities. The Biotechnology Community of Practice (CoP), established in 2005, is one of 16 offered by the organization. The seven-member Biotechnology Strategy Steering Committee, chaired by Britt Petty and Co-Chaired by Andrew Skibo, was established in 2015 as part of the ISPE strategic plan for 2016–2019.

BIOTECHNOLOGY IN EUROPE SIG

In late 2015, adhering to its global strategy and coordinating closely with the Biotechnology Strategy Steering Committee, Biotechnology CoP, and European Affiliates, ISPE established the Biotechnology in Europe Special Interest Group (SIG) to help ISPE build capabilities and identify areas of opportunity in the European biotechnology manufacturing space (see sidebar).

The group's vision is to:

- Deliver solutions with tangible results and practical application to the European biopharmaceutical industry
- Increase patient access to medications and make biologics more affordable
- Foster global connectivity between biotechnology industry leaders, experts, and regulators
- Share, present, and document industry solutions to benefit ISPE Affiliates and their stakeholders
- Facilitate disruptive and incremental innovation in biologics development and manufacturing

The SIG identifies European areas of focus and works within the CoP to foster development of technical content and greater networking of biotech professionals in Europe. The SIG Chair coordinates closely with the CoP Chair.

Working groups

The SIG comprises four working groups:

Quality and Regulatory evaluates the effect of new regulation on operations: investment, cost of goods, and special expertise required for regulatory and quality management activities.

Process Science follows the new holistic production control strategy for biological products, the impact of Industry 4.0 and digitalization on biopharmaceutical production, and how computerized process simulation and modeling can shorten time to market.

Innovation explores new developments in platform technologies such as single-use technology, robotics, and 3D printing and how they can best be used in pharma.

Knowledge Management focuses on classifying product-related knowledge transfer, the workforce of the future, the education profile that will be required, capabilities and skillset needed on various levels of production, and quality management in future biotech production.

ISPE EUROPE BIOTECHNOLOGY

In the past two years, ISPE Europe has come to the forefront of the organization's effort to deliver solutions with tangible results and practical application for the biopharmaceutical industry. As part of its effort to connect biotechnology leaders, experts, and regulators, ISPE Europe hosted its first Conference on Biotechnology, "Reinventing Commercial Biomanufacturing," in Frankfurt, Germany, 24–25 October 2016. Phar-

Biotechnology in Europe SIG Members

Chair Michelangelo Canzoneri	Head of Technology and Innovation, Therapeutic Proteins, Sanofi, Germany, and Chair of the Europe Biotech SIG
Tom Bannon	Senior Process Engineer, PM Group, Ireland
Angelo Bernardis	Global Pharma Technology Manager, Amec Foster Wheeler, Italy
Andrew Brown	Allergan (formerly Actavis Biologics), Liverpool, UK: Manager, Downstream Process Development and Process Engineering
Richard Denk	Head Sales Containment, SKAN AG, Switzerland
Ylva Ek	Qualification Program Manager, Enterprise Solutions, GE Healthcare; Vice Chair of the ISPE Nordic Affiliate; member of the ISPE Biotechnology SIG and the EMEA Regulatory and Compliance Committee
David Estapé, PhD	Technology Manager, Global Life Sciences and Chemicals Business Unit, M+W Group, Germany
Niels Guldager, CPIP	Global Technology Partner, Biotech, NNE, Denmark
Christoph Herwig	Professor of biochemical engineering at the Vienna University of Technology, Austria
Eamon Judge	European Project Planning Leader, Global Facilities Delivery, Eli Lilly and Company, Ireland, and President of the ISPE Ireland Affiliate
Ralf Kretzschmar	Liquid Processing Equipment, Bioprocessing Equipment and water preparation systems, Bosch Pharma
René Labatut	Vice President, Global Head of Technology Innovation, Sanofi Pasteur, France
John Milne	Training Director at the National Institute for Bioprocessing Research and Training, Ireland
Miriam Monge	Director of Process Development Consultant Team, Director of Marketing Integrated Solutions, Sartorius Stedim, France
Frank Nygaard	CMC Project Director, Symphogen, Denmark
Kevin Page, PhD	Senior Good Manufacturing and Distribution Practice Inspector, MHRA, UK
Johanne Piriou	Expert Consultant, Aktehom, France
Annette Peceny, PhD	Senior Director CustomBiotech–BioPharma, Roche Diagnostics GmbH, Germany
Patrick Sagmeister	Co-founder and CTO, Exputec, Austria
Manfred Seifert	Head of Sales, Western Europe, Zeta Biopharma GmbH, Austria
Christian Wölbeling	Senior Director Global Accounts at Werum IT Solutions, Co-Chair of ISPE's Knowledge Network Council and GAMP MES SIG; member of the Pharma 4.0 SIG, Pharmaceutical Engineering Committee, and DACH Affiliate Board
Thomas Zimmer	ISPE Vice President of European Operations, Germany

maceutical Engineering presented highlights of the event in the January-February 2017 issue.

Dublin 2017

The 2017 Europe Conference on Biotechnology "Biotechnology Factories of the Future" will be held in Dublin, Ireland, 26–27 September. The conference will explore capacity constraints, innovative tools in knowledge management, process science, technological advancement, and future challenges in the biotechnology industry. (For registration and other details visit http://www.ispe.org/2017-europe-biotechnology-conference).

Keynote speaker Gerald Kierans, Director of Technical Services, Pfizer Pharmaceuticals, Grange Castle, Ireland, will address the capacity situation of contract manufacturing organizations (CMOs), contract research organizations, and analytical laboratories; the demand for key discipline expertise as the biotechnology industry expands and diversifies; and the technology platforms and product portfolios that may experience bottlenecks.

Dominic Carolan, CEO, National Institute for Bioprocessing Research and Training, Dublin, will address the human factor in this landscape: How should we train and educate people?

Richard Parker, Senior GMDP Inspector, Medicines and Healthcare Products Regulatory Agency (MHRA), UK, will provide insight into regulatory development for biopharmaceuticals.

Bjoern Philipp Kloke, Head of IVAC Technology Platform Engineering, and Martin Zindler, Software Architect, both at BioNTech AG, Frankfurt, will speak about individualized medicines in biologics.

Track 1: Technology, innovation, and factory of the future

Industry case studies will illustrate megatrends influencing new pharmaceutical plant construction:

- Biologics manufacturing "Industry 4.0": full automation, the elimination of human beings from the shop floor and movement of qualified people to production control strategies, process control, and quality oversight.
- Product portfolios will become more heavily weighted with biologicals, fusion proteins, and ADCs; originator products will be replaced with biosimilars and personalized medicine.
- Smaller batches and more complex product portfolios will increase the use of single-use technology to avoid lengthy cleaning validation and cleaning processes.
- Technology platforms will include active substances with higher toxicities that require full containment in manufacturing processes and open product handling.
- Continuous manufacturing will reduce time to market by excluding scale-up processes and related risks. Upstream and downstream technology platforms will benefit.

The track will include a panel discussion on Ireland as a market for biotech manufacturers and how Brexit could influence the production landscape.

Track 2: Process science, knowledge management, and regulatory

Topics will include enablers such as data science workflows to realize new production control ›

strategies, using diagnostic tools for process control in biologics production, and new ways to characterize extractables and leachables. Other sessions will explore quality management in this new environment, as well as the capabilities, skill sets, and education needed to establish the workforce of the future. Track 2 will also feature a panel discussion on regulatory challenges in biologics production.

For more information on the Biotechnology in Europe SIG, CoP, or Steering Committee, contact Michelangelo.Canzoneri@sanofi.com. ‹›

CAST YOUR BALLOT!

2017 Board of Directors Election

In late July 2017, ISPE members will have the opportunity to exercise their right to vote for their 2017 Board of Directors. Current ISPE members will receive electronic ballots by email from Intelliscan, Inc., ISPE's independent election partner. (Editor's note: Make sure to add "@intelliscaninc.net" to your safe senders list.) Members for whom an updated email address does not exist will receive a postcard with voting instructions. The election closes at 11:59 PM EDT on 13 September 2017. The Board Nominating Committee and Board Officer Nominating Committee vet candidates nominated by ISPE members.

ALIGNING ACTION WITH STRATEGIC DIRECTION

ISPE's board is composed of fifteen members (five officers and 10 directors) plus the society's CEO and President, who serves as a nonvoting ex officio member. Directors are elected to two-year terms and can serve up to two consecutive terms; officers make a five-year commitment to rotate through the executive roles of Secretary through Past Chair in one-year terms.

"As ISPE's main decision-making body, the Board establishes the society's vision and mission, articulates strategic priorities, and ensures that business operations are consistent with society policies, best practices, and relevant laws," said John Bournas, ISPE CEO and President.

A seat on the Board entails considerable responsibility, and candidates who seek election know that the demanding nomination process cannot be taken lightly. Members are encouraged to reacquaint themselves with the ISPE 2016-2019 Strategic Plan Summary (http://www.ispe.org/about-ispe/strategic-plan-summary.pdf) and to consider ISPE's business objectives when casting a ballot for their representatives. ‹›

ISPE eLearning

Expanded online training lets you study anytime, anywhere

ISPE's online training courses let you take ISPE's signature training—the type usually delivered over two to three days in a distant classroom—from your home or office. Courses leverage the expertise of our global membership to provide real-world solutions to help companies improve product quality, lower production costs, and increase process efficiency while understanding regulatory requirements. Our courses include assessments, a downloadable course presentation for note-taking, and links to regulatory information. Participants earn ISPE CEU's upon successful completion.

Visit Expanded Online Training (www.ispe.org/expanded-online-training-courses) and select "Demo" to see a preview of each course.

Airflow Pattern Visualization (AFPV)

Airflow pattern visualization provides a visual record of actual airflow patterns in a pharmaceutical facility. It is currently the most widely accepted method of demonstrating that airflow patterns in critical processing areas meet regulatory expectations. In addition, airflow pattern visualization allows multiple functional organizations to discover the effectiveness and significance of the airflow design and functionality, especially in critical areas. The course provides a unique opportunity to explore the requirements for airflow pattern visualization and to see different video examples of actual airflow pattern visualization results. The course provides a comparison of different types of airflow patterns, but focuses primarily on unidirectional airflow patterns in critical areas (ISO 5). The student will also learn how to avoid some of the problems that can occur when creating the visual recording how the results of airflow pattern visualization can be evaluated objectively.

Auditing for Medical Devices

This course provides you with the basic competencies required to effectively perform the auditor's assigned responsibilities by defining audits, explaining why audits are carried out, discussing the types and levels of audits and discussing what is required for preparing to audit medical devices.

Basic Principles of Computerized Systems Compliance: Apply the GAMP® 5 Guide—A Risk-Based Approach to Compliant GxP Computerized Systems

This course introduces participants to regulatory requirements for computerized systems in the pharmaceutical industry and explores tried, tested, and internationally recognized methods of meeting those requirements. GAMP guidance provides a pragmatic and effective framework for achieving computerized systems that are fit for intended use and meet current regulatory requirements, by building upon existing industry good practice in an efficient and effective manner.

Immediately apply the course learning objectives with an electronic download of the *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems Guide*.

Biotechnology Basics: Fundamental Principles of the Biotechnology Industry

Explore the history of the biotechnology industry and will learn the fundamental concepts of biotechnology science and learn basic terminology and how it is applied in the industry. The course will identify basic process science and unit operations for the manufacture of products and will describe the regulatory foundation that makes biological products different from traditional pharmaceutical products.

Calibration Management: A Robust, Cost-Effective Approach Using the GAMP® Good Practice Guide—A Risk-Based Approach to Calibration Management

Calibration is an essential element in ensuring compliance in the pharmaceutical and associated regulated life science industries. To ensure success, calibration should be managed effectively, by appropriately qualified and competent personnel. This online course provides guidance in setting up a calibration management system,

which will give a structured approach to instrument risk assessment, calibration program management, documentation, and corrective actions, essential to regulatory compliance.

Immediately apply the course learning objectives with an electronic download of the GAMP® Good Practice Guide: A Risk-Based Approach to Calibration Management

Cleaning Fundamentals for the Pharmaceutical Industry

Clean-in-place design integration and cleaning chemical selection are vital components of every pharmaceutical manufacturing process; indeed, all pharmaceutical companies employ some type of cleaning application every day. As a result, FDA inspections of cleaning processes have been occurring with greater frequency in today's highly regulated manufacturing environment. To achieve effective and easily validated cleaning methods is to gain a thorough understanding of cleaning methods. This course will provide an overview of clean-in-place (CIP) systems including design, integration, and selection of cleaning chemicals. Participants will discuss engineering concepts, principles, and integration of CIP systems, clean-out-of-place (COP) systems, or immersion parts washers. While there will be some discussion of manual cleaning practices, cleaning principles will be primarily introduced as they relate to the dynamics of CIP and COP technologies, with an emphasis on selecting the right cleaning chemistries for specific soil residues. Additional topics covered include a CIP technology review including examples of various pharmaceutical processes that illustrate how CIP technologies and hygienic design can improve cleanability. Other topics for discussion include CIP spray device selection criteria and dynamics of integrating CIP process piping into a pharmaceutical process.

Clinical Trial Materials: Applying Production, Quality Assurance, and Packaging Processes

In this course, you will receive a thorough overview of the clinical supply chain from beginning to end, including: designing appropriate packaging and labeling to match the study design, creating a plan of action to prepare the clinical trial material (CTM), and how to implement the plan and troubleshoot. The course also covers the logistics of distribution of the CTM to the clinical sites globally. Important tools, such as outsourcing vendors for packaging and labeling, interactive response technology, and randomizations will be covered to ensure familiarity with all the necessary concepts. Additional content will focus on the roles of the clinical project team and how they interact with the CTM group and the regulatory framework needed to stay abreast of regulatory changes.

Complying with Part 11: Risk Management

This course provides a practical introduction to the 21 CFR Part 11 regulations, which affects many aspects of computerized systems in the pharmaceutical industry. The course will present an overview of Part 11 expectations including FDA's current interpretation. This will be followed by a detailed analysis of Part 11 requirements, a discussion of electronic records and signatures, and key industry issues. The recently revised EU GMP Annex 11 and Chapter 4 (which have been adopted for international use by PIC/S) are also covered. As well as the

European and international expectations for electronic records and signatures, the general requirements for computer systems validation and compliance as described in Annex 11 will be explained in detail.

Containment Fundamentals

This course will focus on airborne contaminants and begin by discussing the definition, history, and rationale for the containment of compounds and processes. An exploration of different containment philosophies, methods of source containment, and a hierarchy of containment approaches will also be covered. After establishing the need for containment and presenting alternative methods, the course will focus on the importance of fully understanding a manufacturing process in all its dimensions (physical hardware, remedial containment provisions, facility considerations, operator interface, cleaning and decontamination, and other aspects) before optimal containment solutions may be developed and incorporated into the manufacturing processes. This course will also address plant operations ranging from pilot scale to commercial manufacturing.

Immediately apply the course learning objectives with an electronic download *Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment (Second Edition)*.

GEP: Risk and Cost Management

Effective project progress, monitoring, and control are not regulatory issues, but are necessary for the efficient operation of a company and part of good engineering practice (GEP). This course considers the entire range of pharmaceutical engineering activity and identifies key attributes of GEPs consisting of proven and accepted engineering methods, procedures, and practices that provide appropriate, cost-effective, and well-documented solutions to meet user requirements and comply with applicable regulations. GEP underpins activities of daily operations and forward planning of a pharmaceutical business; the adoption of GEP methodology can lead to a balance of expenditure and activity. The scope of GEP covers the complete life cycle of engineering from concept to retirement and provides a foundation required across the pharmaceutical industry upon which other areas, such as GxP, build. In addition, GEP documentation can be leveraged to support verification work. This course also utilizes benchmarking tools from company practices against what is considered industry good practice.

Immediately apply the course learning objectives with an electronic download of the *ISPE GPG: Good Engineering Practice*.

GMP Auditing for the Pharmaceutical Industry

Auditing is a critical function within a pharmaceutical company. It provides management with information about how effectively the company controls the quality of their processes and products. Auditors must perform their jobs competently to ensure their company's compliance with pharmaceutical US FDA GMP regulations and other quality standards like ICH Q10. Auditing for GMP is specifically designed to address the challenges of GMP auditing for the pharmaceutical industry and present the basic competencies required to effectively perform the auditor's assigned responsibilities and contribute to the improvement of auditor performance within a regulated industry. The course includes a supplemental module that provides guidance in preparing for regulatory GMP inspections and is designed to provide broad fundamental industry knowledge through a customized learning experience for individuals that want to expand their cGMP knowledge.

Maintenance: Reliability, Engineering, and Asset Management

Maintenance programs have long been recognized as critical to the success of the operations they support. Maintenance has the potential to affect both the quality of products and the compliance of pharmaceutical processes. This course provides a practical and consistent interpretation of the necessary elements of a pharmaceutical maintenance program, while offering maximum flexibility to enable widespread adaptation and encourage innovation to minimize the total cost of asset ownership. course leverages the content and templates from the ISPE Good Practice Guide: Maintenance to provide the tools for the development, implementation, and execution of cost-effective compliance for new or existing maintenance programs in a pharmaceutical manufacturing environment. In addition, the course promotes the concept that maintenance performed on any physical asset should only be performed if it addresses a potential failure mode. The course defines roles and responsibilities across cross-functional areas and recommends a systematic approach aimed at continuous improvement of maintenance operations.

Immediately apply the course learning objectives with an electronic download of the *ISPE Good Practice Guide: Maintenanc*e.

Operationalizing a Quality Metrics Program: Critical Success Factors

Metrics programs should be a core part of a company's Pharmaceutical Quality System. This online course is designed for every person who is involved in a metrics program, including operators and quality control personnel who contribute to generating the raw data, through to those involved in collecting, submitting and, most importantly, analyzing the data, drawing conclusions, and taking relevant and necessary actions to implement continual improvement projects.

Following the passage of the US FDA Safety and Innovation Act (FDASIA) of 2012, the FDA is considering the utilization of quality metrics as an input to its inspection models to determine inspection schedules for manufacturers, as well as to assist in the prediction of possible drug shortages. Metric data as well as other information available to the agency may assist with amendment of postmarket change reporting requirements and restructure the frequency and format of inspection. To that end, after receiving input from industry on which metrics manufacturers use and find effective to measure quality performance the FDA issued two draft guidances, one in 2015 and a revision in 2016.

This online course teaches the role of quality metrics within a company's key performance indicator program using the extensive experience ISPE gained from two extensive pilot programs undertaken in collaboration with McKinsey and Company and with participation from 28 companies and 83 sites. The participating companies and sites represented a wide range of technologies and included contract manufacturing organizations and laboratories, and drug substance manufacturing sites. ISPE used this vast breadth of experience and engagement with companies in regard to potential regulatory metrics—what they might be, how they could be collected and used.

The course includes an electronic download of the ISPE *Quality Metrics Initiative Wave 1 and Wave 2 Reports*.

Operations Management

For the purposes of this eLearning course, oper-

TIME TO CAST YOUR VOTE

2017 – 2018 ISPE INTERNATIONAL BOARD OF DIRECTORS ELECTION

Vote by 13 September 2017

You have the opportunity to choose representatives to fill open seats on ISPE's International Board of Directors.

ISPE®

It's an important position! The Board creates the Society's vision, establishes Society policies, and controls Society business.

Look for your electronic ballot via email* in **late July**.

Email will be sent by Intelliscan, Inc., our independent outside election partner. Please add @intelliscaninc.net** to your "safe sender" list to ensure you receive your official email ballot.*

ations are defined as the transformative process within a series of activities, along a value chain extending from supplier to customer. Operations management designs, operates, and improves supply chain systems for getting work done. The ISPE Good Practice Guide: Operations Management aims to provide the pharmaceutical industry with a knowledge base to promote the use of best practices and operational excellence within pharmaceutical operations management. Addressing operations along the supply chain, from the selection of raw materials through to the distribution of final product. For this training, operations are defined as the transformative process within a series of activities, along a value chain extending from supplier to customer. Operations Management designs, operates, and improves supply chain systems for getting work done.

Immediately apply the course learning objectives with an electronic download of the *ISPE Good Practice Guide: Operations Management.*

ISPE's eLearning offerings include online courses and webinars to help you expand your skills and knowledge from the comfort of your desk (www.ispe.org/elearning):

- General Industry Knowledge: These courses offer general industry knowledge while providing an industry overview, historical background and the basic building blocks to get you started and understand more advanced and specific industry topics

  (http://www.ispe.org/elearning/fundamental-industry-knowledge-online-courses#general)
- Fundamental Industry Knowledge Courses: ISPE's prerecorded courses, which were developed and reviewed by expert instructors and international regulatory advisors

  (http://www.ispe.org/elearning/fundamental-industry-knowledge-online-courses)
- GMP Courses: Learn the U.S. Food and Drug Administration's Systems-based GMP inspection approach (http://www.ispe.org/gmp-online-training-courses)
- Webinars: Prerecorded webinars for over 20 topic-specific areas (http://www.ispe.org/webinars)

NEW GUIDANCE DOCUMENTS AVAILABLE

NEW CONCEPT PAPERS

The Role of Process Capability in Monitoring Product Quality: Monitoring Requirements and Self-Audit Continuous Improvement Opportunities

Process capability is not a regulatory requirement, but it is a supporting tool that helps organizations understand how a particular process is behaving and therefore, may be used to support product quality. For example, maximizing this ratio reduces risk to the patient, reduces the risk of drug shortages, and enables companies to provide products more reliably to patients around the world. Improving capability requires prioritization and a comprehensive understanding of the most important sources of variability in the process, excipients, raw materials, components, equipment, and supply chain.

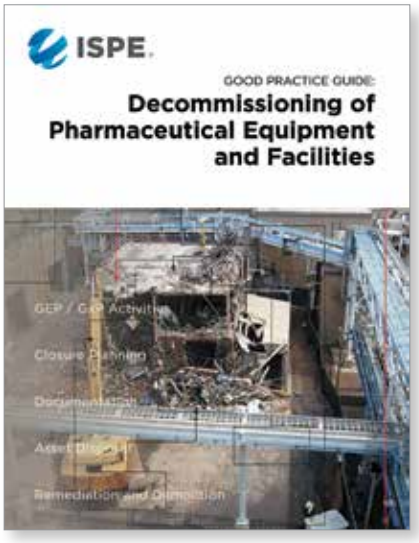
Through understanding of this variability, action plans aimed at controlling and reducing variability can be implemented. This concept paper explores key considerations and challenges associated with implementation of process capability indices within the pharmaceutical industry.

Data Privacy: A Compliance Blind Spot

Clinical computerized systems, such as clinical trial databases, frequently process personal data, and thus require compliance with data privacy regulations. Controls required by data privacy regulations include encryption and restricted access, along with informed consent. Challenges associated with data privacy regulation include minimal clear guidance on requirements, often unclear scope of data privacy, and complexities associated with global footprints.

This concept paper aims to highlight where data privacy regulations could apply, and the requirements for computerized system implementation arising from those regulations. The data privacy principles described in this paper are condensed into tangible and meaningful actions with respect to clinical systems implementation. Case studies are provided to show real world examples of how privacy principles and regulations affect clinical systems.

To read more, visit http://www.ispe.org/publications-guidance-documents/series#concept-papers.



NEW GUIDANCE DOCUMENT

Good Practice Guide on Decommissioning of Pharmaceutical Equipment and Facilities

"Decommissioning" is a general term for a process to remove something from active status. It may be a precursor to putting facilities/equipment into storage, repurposing, or demolition/disposal. There are many factors and requirements to consider in this process, including documentation, process management, environmental, health, and safety, compliance, financial, operational, maintenance, supporting contracts, and interfaces with other facilities and site utilities.

The *ISPE Good Practice Guide: Decommissioning of Pharmaceutical Equipment and Facilities* provides information on best practices to be used for the decommissioning and disposal of assets ranging from a single item to a whole facility. This Guide brings together a wealth of information from a wide range of professionals in the life sciences industry who have vast experience with site closures, from decommissioning of small plant items through to complete operational sites and product/equipment transfers. The Guide compiles practical information from past lessons learned, helping readers to avoid reinventing the wheel when it comes to decommissioning activities and supporting documentation.

The Guide aims to provide both definition and explanation of the process of decommissioning.

This Guide is intended to be a "one-stop-shop" for basic information required for the decommissioning of equipment and facilities.

For more information, or how to order, visit http://www.ispe.org/publications-guidance-documents/decommissioning-pharma-equipment-facilities. ‹›

APPOINTMENTS

Sr. Director of Guidance Documents and Knowledge Networks, Publications

Konyika Nealy oversees the development of ISPE's Guidance Documents and interfaces with ISPE's knowledge networks, including Communities of Practice and ad hoc groups formed to advance the organization's strategic goals. Before assuming her current role, Konyika was the vice president of quality assurance and validation for Pilgrim Quality Solutions, a developer of electronic quality management system software. Other previous assignments include associate director of quality and regulatory affairs for Cryo-Cell International, a cord blood bank, and regulatory affairs manager for Sirion Therapeutics, a privately held ophthalmic-focused biopharmaceutical company. She began her pharmaceutical career at Bausch and Lomb (now Valeant) in 1996 with a 12-year tenure in quality control and regulatory affairs. Konyika earned her bachelor's degree in microbiology and cell science from the University of Florida, a master's degree in public health from the University of South Florida, and has recently completed her doctoral degree in health science from Nova Southeastern University. She received her RAC certification in 2006. Konyika lives in Tampa, Florida, with her husband and three children.

Technical Writer/Editor, Publications

Nina Wang serves as the Technical Writer and Editor for ISPE's collection of Guidance Documents and supports the Guidance Document Committee and development teams. She brings over 14 years of experience in the biopharmaceutical, pharmaceutical, and diagnostic industries. She has extensive technical expertise in manufacturing support, validation, engineering, and process development from companies including Novartis, Grifols, Fluor, and Human Genome Sciences (now GlaxoSmithKline). Nina holds a bachelor's degree in chemical engineering from Northwestern University and a master's degree in biotechnology from Johns Hopkins University. She resides in the San Francisco Bay Area with her husband and two children. ‹›

TIPS FOR TRANSITIONING TO INDUSTRY

Mary Foss, Assistant Professor of Engineering Technology, Weber State University, Utah

Spencer Petersen, Assistant Professor, Department of Engineering Technology, Weber State University, Utah

Congratulations, Class of 2017! You have worked hard to become an engineer. Here are a few tips to smooth your transition to industry and allow you to become a contributing member of the pharmaceutical industry.

1. Establish a code of ethics

Hold yourself and your work to a standard where cutting corners, ignoring details, expediting a process, or doing a "good enough" job is not acceptable. You should aim to pay for yourself each year by providing a quality of work that creates significant savings for the company that employs you.

2. Dress professionally

Your work should stand out, not your attire. Avoid clothing that communicates personal or political preferences. When in doubt, ask someone you respect or the person who signs your paycheck.

3. Frictionless surfaces and unknowns

Most of the problems you've solved to this point yielded tidy solutions. You may even believe that a theoretical model is always preferred over an empirical one. For example, you can easily model the volume of a 10,000-gallon water-for-injection tank based on the water level. However, when the problem is a horizontal cylindrical tank with conical ends, constructed with a sanitary design that is sloped so it drains with gravity, and accounts for the surface tension of the water, things get much more complicated.

To solve the problem analytically you'd have to make so many assumptions that your answer would be useless. Regrettably, you can't put those semesters of calculus to use just yet. You can, however, use your ability to solve problems creatively, and apply your knowledge of science and engineering to determine when it's best to find a solution on paper and when you should collect data instead. By facing these challenges, you not only advance the field, but yourself as a professional.

4. Good, fast, and cheap

"Good, fast and cheap—you get to pick two." Although you aren't being paid by the hour, you are being paid to analyze problems quickly and effectively, determine an appropriate course of action, and hold to ethical standards. Your ability to balance these competing forces will improve as you gain experience; it should be something you seek to master.

5. Continuous improvement

There is no such thing as "good enough." No matter what you do there, there is always a way to do it better, improve the quality, or reduce the cost. Regarding your work with this attitude will serve you well throughout your career.

6. Get out of your chair

Too often engineers work where they are most comfortable—at their desk. There is often a barrier between engineering and operations for this very reason. Spend time studying your organization's operations. You will learn much from seeing the process and talking to those familiar with it.

7. Appreciate diversity

Your workforce is strong not because everyone thinks alike, but because everyone thinks differently. Research suggests that "progress depends as much on our collective differences as it does on our individual IQ scores."[1] Be aware of how others might see you, too, and realize that your colleagues may hold some unflattering beliefs about millennials.[2]

8. Earn the experience before the promotion

Remember that you're in your career for the long haul. Your salary is determined by what you can contribute, which improves only with time and experience. Focus on things you can control—such as your performance in your current position.

9. Become a leader

You may not be a manager, but you are a leader. Set an example built on respect for others and the belief that everyone wants to make a positive contribution.

10. Own it

You may start out doing a menial job. Own it. Learn everything you can about it. By doing this, you will become a valued employee and likely be deemed a candidate for promotion. ‹›

References

1. Page, Scott E. "The Difference: How the Power of Diversity Creates Better Groups, Firms, Schools, and Societies." Princeton University Press, 2007
2. Stein, Joel. "Millennials: The Me Me Me Generation." *Time*, 20 May 2013. http://time.com/247/millennials-the-me-me-me-generation .

ACING THE PHONE INTERVIEW

Hi David, I've had a few phone interviews recently, but I never go any further in the process. What am I doing wrong?

David G. Smith is Principle Recruiting Partner for Biogen's manufacturing, manufacturing sciences and quality organizations in the United Sates.

For most candidates, a phone interview is the first real point of contact with the company, and should be taken as seriously as an on-site interview. The casual nature of a phone call, however, can lead to some traps. Let's explore some tips and tactics.

PREPARATION

Take time to research the organization and ensure you have a good grasp of the job description. Know what is on your résumé; it will be the basis for many of the questions you receive. Be ready to explain your work history and to discuss specific experiences and skills. (Note: For more detailed interviewing recommendations, read my column in the May-June 2017 issue of Pharmaceutical Engineering.)

Conduct the interview in a location where you won't be distracted or interrupted. Choose a place in which you would typically work, such as a home office—a professional setting will help you rise to the occasion. Try to avoid a casual environment like your car or a park bench. Use a land line if possible. If you must use a mobile phone, make triple sure that you are in an area with good signal strength.

Prepare questions that you want to ask and prioritize them based on their importance to you. Stay away from any discussion of benefits, starting salary, and the like. If the process progresses, there will be time to address these.

Do a dry run with a friend to see if your set-up works. Get feedback on the quality of the connection, cadence of your voice, and energy level. Ask if there were any background noises or other distractions—phone microphones can pick up sounds you might not notice. It is also a good idea to practice referencing your résumé and other documents.

THE INTERVIEW

Your interview will probably last about 30 minutes, so be concise with your answers on basic questions about schedule requirements, travel, relocation, the reason for leaving your current position, and how quickly you could transition into the new role. The faster you can move through these, the more time you'll have to discuss your qualifications. Have examples ready to showcase your transferable skills and explain how you work through challenges.

A PHONE INTERVIEW SHOULD BE TAKEN AS SERIOUSLY AS AN ON-SITE INTERVIEW

Perhaps the most difficult question to ask yourself is how well you communicate. Do you sound excited about the opportunity? Have you done your homework? Are you authentic? Are you easy to speak with? Your recruiter will evaluate these qualities closely.

Here are some additional tips:

- Dress professionally. This can help you elevate the conversation and feel confident.
- Don't rely on a calendar invitation. Dates and time zones in email systems often fail to function properly. Confirm the date, time, duration, and phone number via email. Trust me—this one is important.
- If a hiring manager or recruiter calls you at an unplanned time for an impromptu phone interview, don't wing it. It is perfectly reasonable to say that you are not able speak freely and would like to schedule a time to connect. This will allow you to prepare appropriately and be at your best.
- If you have trouble projecting your voice on the phone, print the interviewer's LinkedIn picture and fix it at eye level to simulate speaking to a person.
- Sitting too long in one place can lower your energy level, which might be reflected in your voice. Try taking a brisk walk before your call to raise your energy.
- Take notes. Capture the questions you are asked. Mark your résumé to indicate areas of concern or value; you will need this information when preparing for future interviews. If the conversation touches on topics you want to discuss further, write them down.
- Use a headset. This will allow you to take notes and reference documents more easily.

Before the call ends, ask about next steps, timing, and who will contact you. If all goes well, an onsite meeting might be scheduled while you're still on the phone, so be prepared to talk about your availability—especially if travel would be required.

AFTER THE INTERVIEW

After you hang up, reflect on the conversation. What did you do well? Did you miss something in one of your responses? Did you feel comfortable in your environment? Assessing the interview can help you to understand how to improve your strategy next time.

Send a thank you note. Not only is this a great opportunity to thank the interviewer for taking the time to consider you, it is also a chance to reaffirm your interest in the position, add an important follow-up that you may have missed in an answer, attach a letter of recommendation, and emphasize your value statement. Keep it concise to ensure it is read. ‹›

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

FEATURE

A GOOD FIT

The Marriage of Pharma and Tech Yields Benefits for Patients

It is no wonder pharmaceutical companies are looking to enter new health care territory. In 2016 there were only 22 new drug approvals in the United States, returns on investment continue to fall,[1] and pricing pressures continued to mount. At the same time, the cost of bringing a new drug to market—a process that can take many years with no assurance of success—rose to over $2 billion.

To compensate for this uncertainty, drug makers are diversifying their portfolios by partnering with technology companies and embracing innovative products such as connected data-gathering medical devices and platforms that collect and analyze patient data.

It's a lucrative space, according to Rock Health, a venture fund focused on digital health that reported funding of $4.2 billion in 2016. The most funded categories are genomics and sequencing, analytics and big data, wearables and biosensing, telemedicine, and digital medical devices.[2] Drug makers hope these will help them amass more (and more accurate) patient adherence data, offer personalized treatment advice, manage chronic diseases better, provide medical alerts and reminders, and analyze data.

Novartis, considered a leader in the adoption of digital health technology, has formed partnerships with many technology firms to benefit both patients and the company.

"Smart technology, wearables, and sensors are increasing our ability to gather more robust data around patients' responses to medications, their adherence to prescribed regimens, and disease progression," said Vasant Narasimhan, MD, global head of drug development and CMO for Novartis. "The proliferation of connected sensors also enables health care companies to improve the measurement of clinical end points, which reduces the burden on patients by allowing us to measure those end points from the patient's home."

A vibrant segment of device development is inhalers that monitor use by patients with asthma and other respiratory diseases. Both AstraZeneca, maker of Symbicort, and GlaxoSmithKline, which pioneered its Ventolin inhaler in 1969, are developing these "smart inhalers." Generics manufacturer Teva Pharmaceuticals bought Gecko Health Innovations in 2015 to access its CareTRx platform for the management of respiratory diseases. By using a clip-on sensor that connects to its inhalers, CareTRx data analytics capability provides alerts to help patients manage their disease.

Novartis plans to launch a smart inhaler with an integrated sensor in 2019.[3] "Novartis is the first pharma company in respiratory medicine to offer a completely integrated and connected delivery device," said Narasimhan. The firm has partnered with Qualcomm to develop sensors for its Breezhaler, a wireless inhaler for patients with chronic obstructive pulmonary disease. Patients and their doctors will have access to real-time health and adherence data, transmitted wirelessly via mobile applications and the data cloud.

DIABETES MANAGEMENT

For diabetics, keeping track of blood glucose levels in hand-written logs can be onerous. Tech companies such as Livongo and Medtronic market glucose monitors that send data wirelessly to insulin pumps, where it is recorded for reference. The information can be uploaded and stored in the cloud, and mined for patterns that allow patients and their health care providers to better manage their disease. Medtronic also has an app that collects data from diabetics on their exercise and carbohydrate consumption. IBM Watson, a cognitive computing platform, analyzes the data to predict potential hypoglycemic events hours in advance, allowing patients to avoid harm.

Novo Nordisk, a major producer of insulin that began its partnership with IBM Watson Health in 2015, began to collaborate with software company Glooko in 2017 to develop a diabetes management app that will continuously monitor blood glucose levels. The data is sent to Watson to record the effects of insulin and measure drug adherence.[9–10]

Verily Life Sciences (formerly Google Life Sciences) began work with Alcon, Novartis's ophthalmic division, in 2014 to research "smart ocular devices." The companies are investigating two groundbreaking types of contact lenses: One could correct presbyopia, or age-related farsightedness. Another version is being

planned to monitor glucose levels in diabetics' tears.[4] Lens design allows tear fluid to reach embedded sensors that measure blood sugar levels. A microscopically thin wireless antenna will transmit the information to an external device.[7] Building on its expertise in miniature electronics, data analysis, and software development, Verily also launched Onduo, a joint venture with Sanofi, a leader in the global diabetes market, to create an as-yet-undefined management and treatment program for type 2 diabetes.[5]

BIOELECTRONICS

In addition to implanted devices such as pacemakers, which have been used for years to correct irregular heartbeats, deep-brain electrical stimulation has also been effective in the treatment of Parkinson's disease and severe depression. To help control appetite in those struggling with obesity, EnteroMedics has developed vBloc, a pacemaker-like device implanted under the skin that sends electrical signals to the vagus nerve, which helps control stomach emptying and tells the brain when the stomach feels full.[8]

Research is showing that bioelectronics stimulation can also treat chronic diseases such as diabetes, asthma, and arthritis without the use of chemicals or proteins. Galvani Bioelectronics is developing miniaturized electrical devices that will wrap around nerves to deliver these electrical impulses.

"Existing devices target large areas of tissue indiscriminately," said Kristoffer Famm, President of Galvani. "Our objective is to home in on specific groups of neurons within circuits. We believe that recent scientific advances have made it possible to create the potential to develop more precise bioelectronic medicines."

Famm says that these devices will affect individual nerve fibers or brain circuits to modulate the neural impulses controlling the body, repairing lost function and restoring health. "They could, for example, coax insulin from cells to treat diabetes, regulate food intake to treat obesity, and correct balances in smooth muscle tone to treat hypertension and pulmonary diseases."

CHALLENGES

The model for creating and marketing digital technology products can sometimes clash with pharmaceutical firms' traditional model, which involves spending years on R&D to develop a new drug, followed by regulatory approval, production, and marketing. In contrast, digital products typically undergo rounds of improvements and upgrades that continue after launch. While upfront costs are typically lower and development time shorter, the profit from digital devices is much smaller than for blockbuster drugs. The question of who controls patient data is an additional concern; pharmaceutical firms worry that technology companies are gaining access to large amounts of information about the behavior and outcomes of patients who use their drugs.[6]

Despite the challenges, Novartis remains bullish. "Our ambition is to harness these technologies to make the drug development process better, faster, and cheaper," said Narasimhan. "We're partnering with tech companies small and big at every step of the development chain, from identifying patients to redefining the role of trial sites, designing novel endpoints using sensors and wearables, and leveraging data to improve our operations.

"Enhancements in drug development like

these will only come to life through collaboration across the health care and technology spaces. It is crucial that we continue building ecosystems of collaborative science, and foster seed investments and partnerships with incubators for revolutionary enhancements to drug development. Partnering with best-in-class experts and leaders in other industries will be critical to successful scale-up of these technologies in the drug development arena." ‹›

—Scott Fotheringham, PhD

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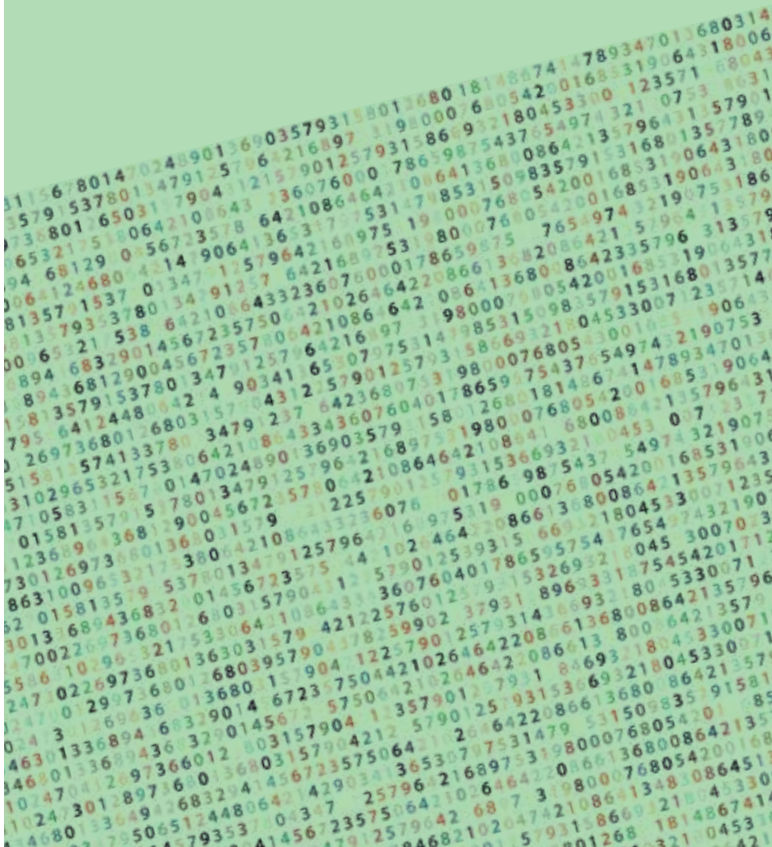

GREAT LAKES CHAPTER BRINGS TRAINING AND INFORMATION TO THE MIDWEST

The Great Lakes region in the American Midwest is home to several pharmaceutical hubs, giving ISPE's Great Lakes Chapter a deep potential membership pool. And this vast territory also presents the Chapter's greatest opportunity: to engage more than 800 members scattered across the six states surrounding Lake Erie and Lake Michigan—Ohio, Illinois, Indiana, Kentucky, Michigan, and Wisconsin.

Founded in 1994, the Great Lakes Chapter's membership is spread out across several cities, with pockets in Detroit and Kalamazoo (Michigan), Indianapolis (Indiana), Chicago (Illinois), and Lexington (Kentucky), plus a few smaller enclaves in southern Indiana and Wisconsin.

ISPE members often view social networking as an important aspect of membership., and Great Lakes Chapter President Deborah Geyman, Quality Principal Auditor for Zimmer Biomet, emphasizes its importance while acknowledging that it is a challenge for the Chapter. "With our geography, it is perhaps more problematic from the social standpoint than it is for other Chapters or Affiliates," says Geyman, who took over as President earlier this year. "For many members, driving four hours from Indianapolis to Chicago for cocktails after work is hard to justify. The bottom line is we need to have enough people within an area to pull off social events."

The same holds true when it comes to meetings for the Chapter's Board. "I have one [member] in Southern Indiana, another in the upper north side of Chicago, one on the far east side down in Indiana, and one in Cleveland," she explains. "So, all of my officers are at least two hours apart from each other." To compensate, many meetings take place via Skype.

A TOUGH ECONOMY

A trend that both Geyman and former President Joe Robinson, Midwest Regional Manager for Commissioning Agents, say has affected membership is tighter corporate budgets for association memberships and travel. "Things have changed over the last couple of years," says Robinson. "When I started with ISPE, everybody had money to go to everything; there wasn't a problem. But now the larger companies have been tightening the reins on the money being spent for things like this."

And while membership levels have remained somewhat steady over the last few years, the Chapter has been recovering from the impact of a few poorly attended events. Robinson describes one in the Kalamazoo area in 2013 when all arrangements had been made, but few attendees had confirmed one day prior to the event. "So we had to change our plans and it ended up costing the Chapter thousands of dollars because of all the guaranteed money for the venue. Since then, we have been really gun-shy."

As Robinson explains, he felt it was necessary to act to preserve the Chapter's strained finances. "I ratcheted down on the spending so we didn't run out of money," he says. "Then we renegotiated contracts for insurance and other things to get spending to a manageable rate."

Quick facts

Founded: 1994
Region: Great Lakes, US
Membership: 800+

Contacts

President
Deborah Geyman, Zimmer Biomet

Vice President
David McAlonan, AbbVie

Secretary
Cindy Bambini, CRB

Treasurer
Timothy Fry, the jdi group, Inc.

Past President
Joe Robinson, Commissioning Agents

Directors
Felicia Ford-Rice, PAREXEL Consulting
Robert Lennon, Dakswan Automation Systems, Inc.
Aaron Mertens, STERIS Life Sciences

Membership
Michael Carey, Gerflor USA

2017 EVENT

Geyman, however, remains optimistic that the Chapter has brighter days ahead. Some of that comes from her firm belief in ISPE. "Nobody can compare to ISPE for technical expertise, the availability of guidance documents, and community of practice tools," she says. "They always reach out to members and stay contemporary on expectations, reporting on various processes in the pharmaceutical industry from critical utilities to computer validation systems and process validation. ISPE has been the lifeblood of the pharmaceutical industry for many years.

"People like the strong technical information that ISPE provides," she continues. "We are looking at how we can improve engagement by bringing training and valuable information through the region in a cost-effective manner. We're quite excited about working with ISPE to bring the GAMP® Forum to our members."

Both Geyman and Robinson see the June 15 forum, held at the Lilly Manufacturing Quality Center in Indianapolis, in concert with the 2017 Indianapolis training event from June 12–14, as a potential springboard for renewed member engagement. A three-day training course introduces participants to regulatory requirements for computerized systems in the pharmaceutical industry and explores tried, tested, and internationally recognized methods of meeting those requirements. The one-day GAMP Forum is devoted to the newest concepts in data integrity. It will include discussions on trends as well as breakout sessions on establishing programs, conducting audits, and addressing data integrity challenges in key business areas. The forum will wrap up with a panel discussion with experts from the industry and the Global GAMP Data Integrity Special Interest Group.

"I think that this event has the potential to be the spark that has been needed for a while to get things kick-started," says Robinson. ‹›

—Mike McGrath

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Roger Connor
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Bringing the Outside In: How Inspiration from outside Pharma Can Transform Our Approach to Manufacturing

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APPLYING QRM TO IMPROVE SUSTAINABILITY OF PHARMA MANUFACTURING

Chris Appleby, Norm Goldschmidt, Randall Hansen, Nick Haycocks, Thomas McMenamin, and Derek Mullins

As economic pressures and legislated environmental protection measures continue to increase, the pharmaceutical industry is moving to control cost, reduce energy use, and become a better steward of the environment.

Within pharmaceutical manufacturing facilities, energy consumption due to the maintenance of environmental conditions through operation of heating, ventilation, and air-conditioning systems (HVAC) is typically the most significant energy user (often accounting for 50%–70% of the total energy consumption). Optimization and improvement initiatives in this area such as reducing the air change rates can provide some of the most significant opportunities for reduction in energy consumption, with the associated reductions in cost and carbon footprint.

The importance and nature of the products we manufacture bring into sharp focus the need to ensure that manufacturing operations maintain robust, scientifically sound principles of good manufacturing practice (GMP).

As energy costs and demands for carbon footprint reduction increase, it is critical we demonstrate the ability to appropriately control our manufacturing operations. Our patients and regulators must be assured that, regardless of these outside demands, our intent to avoid unacceptable risks to patient safety, product quality, and regulatory compliance remain steadfast.

The intent of this article is to provide discussion, guidance, and examples on the use of ICH Q9: "Quality Risk Management (QRM)" when reducing HVAC air change rates within manufacturing and supporting operations.

HISTORY

Typically during the design of new pharmaceutical manufacturing facilities and their associated HVAC systems, it has been simpler, cheaper, and more effective from a project timeline basis to focus on the process engineering and the development of the design space around the process. Environmental control is viewed as a secondary concern, and it is common practice to take a standardized, well-understood cleanroom solution (such as a formally classified area) and apply this to the scope of the project. While from both an engineering and quality perspective this may have been a wholly appropriate decision at the time, the chosen solution may not necessarily have been the most economic option.

This approach has resulted in a large number of areas having significantly higher air change rates than is required to maintain an environment complying with the regulations and product /process requirements.

The problem, we suggest, is the lack of a comprehensive understanding of the regulatory requirements and the science behind the provision of an effective design to provide appropriate effective environmental control via the HVAC system.

It is not unusual to see a minimum air change rate as one of the design criteria. Guidance values for air change rate are frequently misinterpreted as requirements. For example, the US Food and Drug Administration (FDA) guidance for sterile drug products suggests at least 20 air changes per hour (ACH) are typically acceptable to maintain ISO 8 (class 100,000) conditions during operations. This figure of 20 ACH is often quoted as a minimum ventilation rate for all cGMP facilities. Scientifically, depending on the particle challenge from the specific process and the efficacy of the HVAC design, the actual air change rate required may be as low as 6, 10, or as high as 30 ACH.

Qualitative assessments in evaluating cross-contamination risk often overstate the potential for airborne contamination, resulting in unnecessary 100% fresh air systems, HEPA filters, airlocks, and room-pressurization systems.

Today's manufacturing projects face new challenges for designing, implementing, and managing facilities. The desire is to provide effective and efficient cross-contamination prevention with the appropriate understanding, control and management of risk.

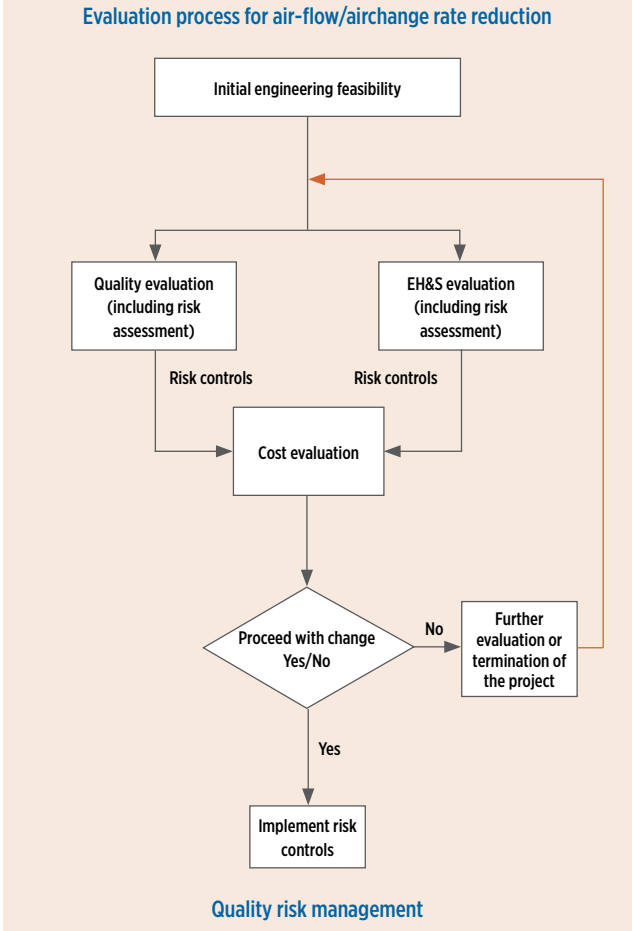
It is clear that an effective, proactive process of risk management is required to balance product quality with the constraints of cost, environmental pressure, and regulatory compliance.

USE OF QRM IN HVAC AIR CHANGE REDUCTION

To demonstrate control of risk in any situation, one must first understand the existing risks. Effective risk management, including risk mitigation, can then be determined and applied. ICH Q9 "Quality Risk Management (QRM)" provides us with "a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle."[1]

QRM is the appropriate process to use when developing the control processes to be used for cross-contamination prevention in facilities and manufacturing. It allows the definition of the risk, development and assessment of the efficacy of the controls to be effectively demonstrated to a regulator.

Figure 1: QRM evaluation process



Application of QRM process

Figure 1 is intended to provide a simple overview of the use of QRM in HVAC air-change rate reduction. As can be seen, three key factors for consideration of HVAC reduction are:

- Product quality
- Environmental health and safety (EH&S)
- Costs associated with making the proposed change

The title "Quality Risk Management" may imply only quality considerations would be evaluated, but QRM provides the framework to apply the principals of risk management to each key factor.

Product quality evaluation

If initial engineering identifies opportunities for reduction in areas where GMP products or materials are manufactured or stored, the impact of the proposed changes to quality, patient safety, and regulatory compliance must be assessed.

- Microbiological risk assessment and evaluation will be incorporated into the QRM exercise. If microbiological attributes are considered, involvement of relevant technical or subject matter experts are required.
- If the HVAC system is operating under GMP change control, modifications made to the HVAC system must be made in accordance with relevant change control procedures.
- If changes are identified during initial new facility design or upgrade proposals for existing facilities, the risk assessment of the design can be conducted during any stage of the process, though the optimum approach will be to do it early, revising it as necessary during the design development process. Technical and quality representatives should be consulted regarding the new design proposals. Quality approval is incorporated as part of the new or upgrade design phase (design qualification).

The QRM process, including review and communication, is designed to identify the risk control measures that, when implemented, adequately reduce risk to an acceptable level, so that the proposal can proceed. If the risks cannot be reduced to an acceptable level, the proposal cannot proceed.

EH&S evaluation

When opportunities for reduction are identified, EH&S risks should be identified, evaluated, and mitigated when necessary. It is recommended EH&S evaluations be incorporated, either directly or by reference, in the overall QRM conducted for proposed changes. The site- or project-specific person responsible for EH&S should be involved in the risk assessment and use applicable tools, such as HAZOP (hazard and operability analysis), as required. Examples of EH&S risks include the potential for higher than OEL levels of solvent (due to process requirements, or cleaning/sanitization regimes) resulting from reduced air change rates—and the associated reduction in fresh air supply.

The EH&S risk management process should identify risk control measures to sufficiently reduce risk and allow changes to proceed. If the risks cannot be reduced to an acceptable level, the proposal cannot proceed.

Cost evaluation

The third factor to consider as part of the airflow/air change rate reduction initiative is potential or actual costs associated with implementing the proposed change. Apart from initial cost saving estimates determined within the pre-evaluation phase, other costs must be considered in the overall evaluation of the airflow/rate change reduction initiative.

Associated costs for consideration include, but are not limited to:

- Reduction in energy costs
- Cost of implementation, including required equipment modification cost
- Ongoing maintenance costs
- Operational costs (e.g., additional facility cleaning, increased start-up time)
- Analytical support cost (e.g., requalification, changes to routine environmental monitoring)
- Cost of failure (e.g., system fails to maintain minimum requirements and product quality, patient safety, or delayed regulatory compliance)

EVALUATION OF HVAC REDUCTION

Requirements to modify each HVAC system should be accurately defined and fully understood. The most commonly used scientific basis for developing an appropriate HVAC system design is specifying air quality requirements for the products manufactured in the areas defined.

Typical considerations for air quality requirements include:

- Viable and nonviable particulates: expressed as total colony forming units per unit assessed or total particulate count per unit volume of air
- Relative humidity: as applicable per specific product or EH&S requirement
- Temperature: as applicable per specific product or EH&S requirement
- Pressure cascade: as applicable per GMP and / or EH&S requirement

Typically a conservative set of HVAC parameters are selected to achieve the air quality requirements during design. These airflows and set point parameters are then used as a basis for demonstration and qualification to verify the HVAC system meets the design requirements.

A perceived positive result of this overly conservative design approach is that the resulting manufacturing areas often operate several orders of magnitude "cleaner" than specified (or required). The initial (through higher capacity equipment, larger ductwork, etc.) and ongoing operational cost required to achieve and maintain these very high levels of performance are wasted, as the over specification is typically such that the resulting additional control is not needed to comfortably achieve the specified product quality attributes and associated regulatory compliance (Figure 2).

For new facilities the designer should be tasked with defining the appropriate air change rate; for existing manufacturing areas current operational conditions and airflow rates should be considered and a risk assessment conducted where the operational information shows that there are opportunities to optimize the operation. Examples of drivers for this change may include:

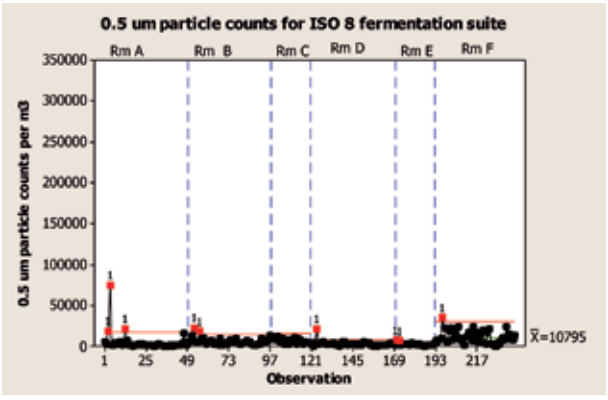
- Reduce energy consumption and associated costs
- Reduce noise
- Decrease lifecycle cost of the HVAC system
- Decrease site utility loads to avoid upgrade of utility generation capacity
- Improve understanding of quality and operational risks by reevaluation of the system

Prior to conducting a QRM exercise, it is recommended that the proposed change is pre-evaluated by the engineering department, with the potential benefits of the proposed change(s) quantified. This initial engineering feasibility study is conducted to determine if it is worth the investment required to conduct the QRM exercise.

A reduction in airflows or air change rates only can be considered if an appropriate risk assessment is conducted and approved. The approval should include site engineering, production, EH&S, and quality. The risk assessment should consider relevant and available data for the area and associated HVAC system, including operation and maintenance of room/area environmental parameters identified as critical to product quality and maintenance/production operator safety.

Where operating/maintenance data are not available, for example, in the design phase of new rooms/areas, this should be taken into account during the risk assessment, as unknown risks default to high. The outcome of the initial risk assessment may include actions to generate data, for example, proposed system-modeling (CFD) and/or baseline particulate monitoring. These data can then be used to reevaluate the risks associated with the proposed change or new design.

Figure 2: 12-month 0.5 Qm particle counts for sample ISO 8 fermentation suite



A sample of 0.5µm particle data from a fermentation are area classified as ISO 9 (in operation, ISO 8 at rest) is shown to left. Particle counts are may order of magnitude within the requirement for at rest, while the area is in fact in operation (class limit: 3,520,000 0.5 µm per cubic meter)

Special considerations

Rooms with special requirements, such as very low humidity or the need to recover quickly after room cleaning so production can resume, need additional evaluation to determine if air-change reduction is feasible.

Engineering evaluation process

As mentioned earlier, the first step in the evaluation of air-change reduction is to perform an engineering feasibility study and high-level estimate of possible operating cost savings and enabling costs. After the risk assessment step, the cost estimate should be updated to include the cost of mitigating measures and the cost vs. benefit reviewed again. Except for very simple, straightforward situations, there is often a "detailed design" phase when the proposed reduced air change rates are compared against the actual individual room requirements for air to maintain room conditions and pressurization, etc., system fan and control device turndown is analyzed, any equipment changes are determined, final new flow rates are calculated, and drawings are updated. Occasionally, tools such as airflow modeling are used for rooms where there are concerns about the ability to provide effective ventilation of critical parts of the room at reduced airflows. An updated estimate of implementation costs and projected operating cost savings is often done at this stage before a final decision is made to implement the changes.

Although each system and requirements are different, the evaluation stage and the later implementation stage can be greatly assisted through the development of a standardized process for evaluation, execution, and verification.

CONCLUSION

Reduction in air change rates for HVAC systems serving pharmaceutical facilities provides one of the most significant potential opportunities for energy reduction, with associated reduction of operating cost and carbon footprint. It also can provide benefit in terms of reduced equipment maintenance. When applied at the design stage for new facilities, additional benefits can be gained through lower initial capital cost of smaller equipment, including central utilities equipment such as boilers and chillers and

their associated distribution systems.

When analyzing proposed changes there are many aspects that must be considered, and robust processes are needed to ensure that these aspects are effectively assessed, and that the specific and general requirements of the end user are met. This is, after all, about ensuring that the required environment is maintained to support the manufacturing process.

Use of the QRM approach provides an effective method to ensure the requirements from all stakeholders in the process are identified and assessed. Applying the QRM process results in a good understanding of what is really required of the HVAC system supporting manufacturing operations. The knowledge gained by using the QRM process forms a sound basis for optimizing the HVAC (e.g., air change rates) while properly controlling risks to patients, product quality, and maintaining regulatory compliance. ‹›

Applying QRM to Air Change Reduction: An Example

The following is an example of an evaluation of room air change rates for potential reduction using QRM, providing more detail on engineering considerations.

BASIC ENGINEERING CONSIDERATIONS

When evaluating room air change rates, always remember that the airflow to a room must be adequate to:

- Maintain the room temperature and humidity at values sufficient to meet any product/process and occupant comfort requirements
- Maintain room airborne particle concentration levels below established limits for rooms with formal cleanroom classifications (e.g., Grade C, ISO 8)
- Dilute airborne particle concentrations below limits for occupant product exposure
- Dilute any vapors to concentrations below either occupant exposure or flammable vapor limits
- Provide make-up air to offset process-related room exhaust flows (e.g., dust collection exhaust)
- Maintain differential pressures between rooms/spaces to help limit the movement of airborne contaminants between spaces

High air change rate and control of particle movement

High room air change rates, when coupled with directional flow, can aid in controlling airborne particle movement. A Grade A unidirectional airflow area is an example, as is a down flow (e.g., weigh) booth. The air change rate in most pharmaceutical manufacturing rooms, however, is not nearly as high as in a Grade A area or a down flow booth and, at best, has a minor effect on particle movement. It is also worthwhile remembering that these areas that benefit from such high air change rates are proportionally smaller than the lower risk support areas within the facility. The benefits that can be achieved through reductions in these higher risk areas are also proportionally lower when compared with the execution level of difficulty.

GUIDANCE VALUES FOR AIR CHANGE RATE ARE FREQUENTLY MISINTERPRETED AS REQUIREMENTS

Reduced air change rates

The air change rate can either be reduced at all times, or only during off hours. Sometimes It might be possible to reduce the air change rate during occupied/production times combined with a further reduction during off hours.

Reducing the room's air change rate at all times generally involves a rebalancing of the flows to the new lower rates and adjustments to assure proper room pressure relationships, etc. This rebalancing can be done on HVAC systems that do as well as those that do not incorporate room level airflow control devices (i.e., automatic or remotely adjustable volume control/regulating devices such as variable volume boxes, mechanical constant volume regulators, or automatic room pressure controls at individual rooms).

Reducing airflows only during off hours can be more complicated than reducing the normal air change rate because of the dynamic nature of this approach (two operating modes). Issues such as how long the room takes to achieve the required normal operation parameters (e.g., temperature, humidity, air change rate, pressurization) when switching from reduced flow/off hours operation to normal operation must be addressed. Reducing room air changes during off hours is most likely to be successful when the HVAC system incorporates room level airflow controls because these control devices can usually be set up to maintain the proper room pressure relationships at both the normal and reduced flow rates. Control of the capacities of the main system fans to maintain a stable main duct pressure is also desirable so that the room level controls will not be over pressured and also to save fan energy.

Particle count and room air changes

There is a definite relationship between a room's air change rate and its airborne particle count whenever the particles are generated within the room. The particle count of air supplied to the room by the HVAC system is, however, a function of filtration, not room air changes.

The relationship between air change rates and room airborne particle counts can be approximated by the following relationship: $C_{ave} = C_{sa} + PGR/ACH$

Where:

C_{ave} = Average room airborne particulate count

C_{sa} = Particulate count of supply air

PGR = Particle generation rate due to room activities

ACH = Air changes per hour

When working with high efficiency filters such as H14 HEPA, or U15 ULPA,

the supply air particulate count is sufficiently low as to be considered negligible. Based on this, the main driver for air change rates is the rate of particle generation within the space. Areas of low activity will typically have considerably lower particle generation rates, and other controls such as gowning and cleaning will further impact particle generation.

Technical and regulatory considerations for rooms with a formal cleanroom classification

Classified rooms (e.g., EU Grade C, ISO 7) have defined limits for airborne particle concentrations and usually support the manufacture of sterile products or certain biological products. The room air change rate must be sufficient to dilute the room-generated airborne particles to meet the defined limits. Rooms designed with air change rates that were based on industry practice (i.e., "rules of thumb") have often been found to operate at a cleaner grade/class than needed. Experience with installations that have reduced air changes has shown that many such rooms can be operated at reduced air change rates and still stay comfortably within airborne particle count limits.

The EU GMP Annex 1 (sterile manufacturing)[3] no longer mentions air changes. The US FDA guideline for sterile drug products produced by aseptic processing notes that "for Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable."[2] Many rooms of lower grade/class should be able to operate below the 20 air change "limit" and still meet airborne particle count limits.

Facilities serving markets outside the US must often demonstrate not only that they meet particle count limits in the "operational" mode, but also in the "at-rest" mode (no people present), and that the particle count will achieve the at-rest level within a reasonable amount of time (e.g., 15–20 minutes) after production operations cease ("recovery" time).

A short recovery time is an indication of thorough (effective) ventilation of the room. It is the combination of the room air change rate and the type and placement of air introduction and air extract devices that determine how effective the HVAC is at ventilating a room for the removal of airborne contaminants. Good design of room air introduction and extract devices and their locations increases the ventilation effectiveness and generally allows the use of a lower air change rate to achieve a given level of control. An example is the choice of room supply air device. It is common to use "cleanroom" supply air devices ("diffusers") that, unlike diffusers used in offices, are designed to minimize the mixing of supply and ambient room air. Where there are not enough of these cleanroom diffusers in the room to provide good air distribution, there may be stagnant-air areas, resulting in a longer recovery time, even if the room meets the in-operation and at-rest particle limits. Sometimes a change (in lower grade/class rooms) to supply air diffusers designed for air mixing, such as the "swirl" type, will shorten the recovery time.

Experimental data from various ISO 7 and ISO 8 has shown that while air change rates have an impact on the ability of a system to recover particles from the room, the benefits of increasing the air changes can be limited, and sometimes provide no additional benefit.

Figure 3, "Sample recovery time from in operation to at rest for EU Grade C/ISO 7 room," shows that the recovery time actually improved when the airflow was reduced to below 30 ACH. This is believed to be due to a "sweet point" in the room's air distribution patterns at this airflow. A room with a poor recovery time may not be a good candidate for air change reduction unless changes can be made to improve the effectiveness of the ventilation.

Recovery testing measures the system's ability to recover airborne contamination from suspension, and is measured in minutes to reduce airborne particles from the in-operation to at-rest specification.

Classified rooms also have to meet defined limits for microbiological contamination. The HVAC system and room air changes do not directly control microbiological contamination, but have an indirect effect due to the control of total airborne particulates. It is possible, therefore, that a reduction in room air change rate could cause microbiological contamination to increase. In this case, the room ventilation (air change) was doing what it was supposed to do by diluting and removing airborne particles. If this increase in particles is noticeable, then it is quite possible that the higher air changes were, in effect, masking the real problem by dilution and removal of airborne particles. This situation may require restoration of the higher air change rate until the root cause of the microbiological contamination is identified and mitigated. If the increased micro "counts" measured after air change reduction are well below the actual quality/regulatory limits, a review might indicate that the new level is acceptable.

Figure 3: Sample recovery time from in operation to at rest for EU Grade C/ISO 7 room

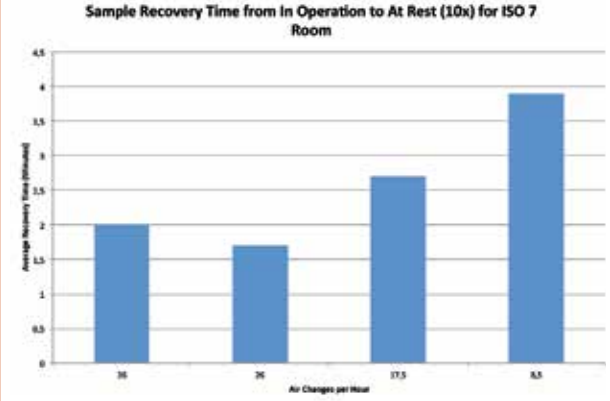
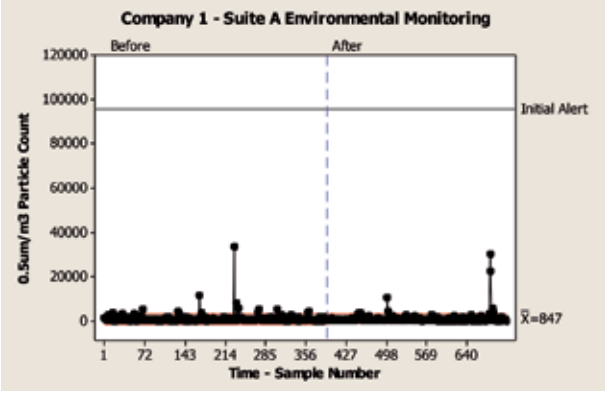


Figure 4: Company 1—Suite A environmental monitoring



Technical and regulatory considerations for rooms without a formal cleanroom classification: e.g., oral dosage, most active pharmaceutical ingredient manufacturing (API)

Individual manufacturing firms may have their own names or internal classifications for such areas (e.g., pharmaceutical, controlled not classified).

Rooms for the manufacture of nonsterile products are usually not required by regulation to have formal cleanroom classifications with defined airborne particle limits for US FDA and European Medicines Agency (EMA) regulated markets. Some other markets may have particle limit expectations (formal or informal).

For these rooms, there is no US FDA or EMA requirement for a minimum room air change rate. Some countries in other markets do have minimum air change requirements (often 10 changes per hour).

The air changes in nonclassified rooms do need to dilute airborne particles as they do in a classified room, but meeting occupational hygiene requirements to ensure a safe environment for people in the room often drives the room's air change rate more than quality concerns.

API manufacturing areas (traditional small molecule) use many chemicals and it is common for rooms to be rated hazardous due to the presence of potentially flammable vapors. The use of gases, such as nitrogen, that, if released, can displace the oxygen in a room is also common. These rooms can be candidates for air change reduction after evaluation of environmental health and safety considerations, such as whether reducing the air change rate would change the room to a higher hazard rating, increase operator exposure to hazardous substances, create the potential for oxygen deprivation, etc.

Laboratories are often designed to a minimum air change rate. Like API areas, for most laboratories, the concerns are greater for EH&S issues than quality. A lab's air change rate is often based on the assumption that fumes and vapors need to be diluted, either due to normal operations or as the result of a spill. For many labs, however, operations involving chemicals take place inside of fume hoods and not on the open bench-top and it is common to require that all lab occupants immediately exit the room in the case of a spill or similar event to minimize their exposure.

ANSI/AIHA Standard Z-9.5-2012 for Laboratory Ventilation states that "Numerous studies make it clear that the airflow rate is just one factor affecting contaminant levels in a room. Frequently, other factors have been shown to make a bigger difference than some changes in the airflow rate."[5] Evaluation of laboratories by a team including engineering and EH&S representatives with a good knowledge of the lab operations and substances used will indicate if the lab is a good candidate for reduction of air changes. This is only applicable in labs where the firm's requirements for a minimum air change rate are the determining factor in setting the air change rate.

Airlocks (both for classified and nonclassified applications)

Many airlocks are also gowning areas, which mean they have high intermittent internal particle generation. They also are transition spaces and, as such, need a short recovery time. Because of this, airlocks are often designed with a higher air change rate than the rooms they connect. Many airlocks are small and the financial savings from reducing air changes may also be small, making the change financially unattractive. Just like other spaces, however, if the airlock is comfortably within airborne particle limits and microbiological limits (where these apply), and has a good recovery time, there is potential for reducing the air changes.

Equipment considerations

Reducing the room air change rate will have an effect on the HVAC system's components, most notably fans and airflow control devices.

Today, many fans are controlled by a variable speed drive (e.g., VFD) making capacity reduction simple. Even so, there is a limit to how far you can reduce a fan's flow and still have it operate properly. If the fan is belt-driven and the flow reduction is significant, it may sometimes be advantageous to reduce the fan speed by changing the drive sheaves and belts, even when there is a VFD. In those cases where the fan is not able to operate properly at the reduced flow rate (often because it was oversized to begin with), the fan will limit the amount of the air change reduction, unless of course it is financially attractive to install a smaller fan or modify the existing fan.

One of the desirable effects of air change reduction is a significant reduction in fan power draw. This, of course, means the electric motor driving the fan will be operating significantly below its rated output. In general,

Figure 5: Particle recovery test results

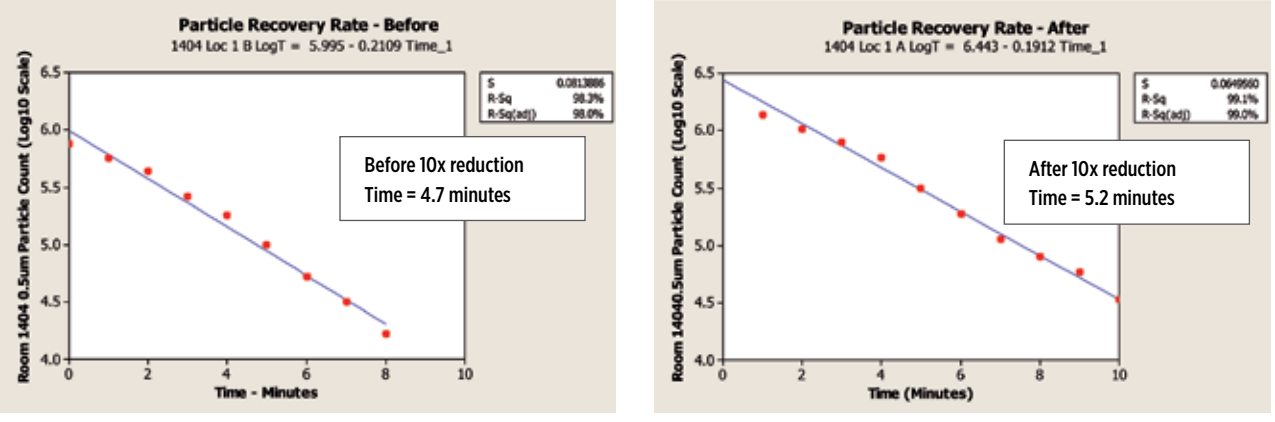
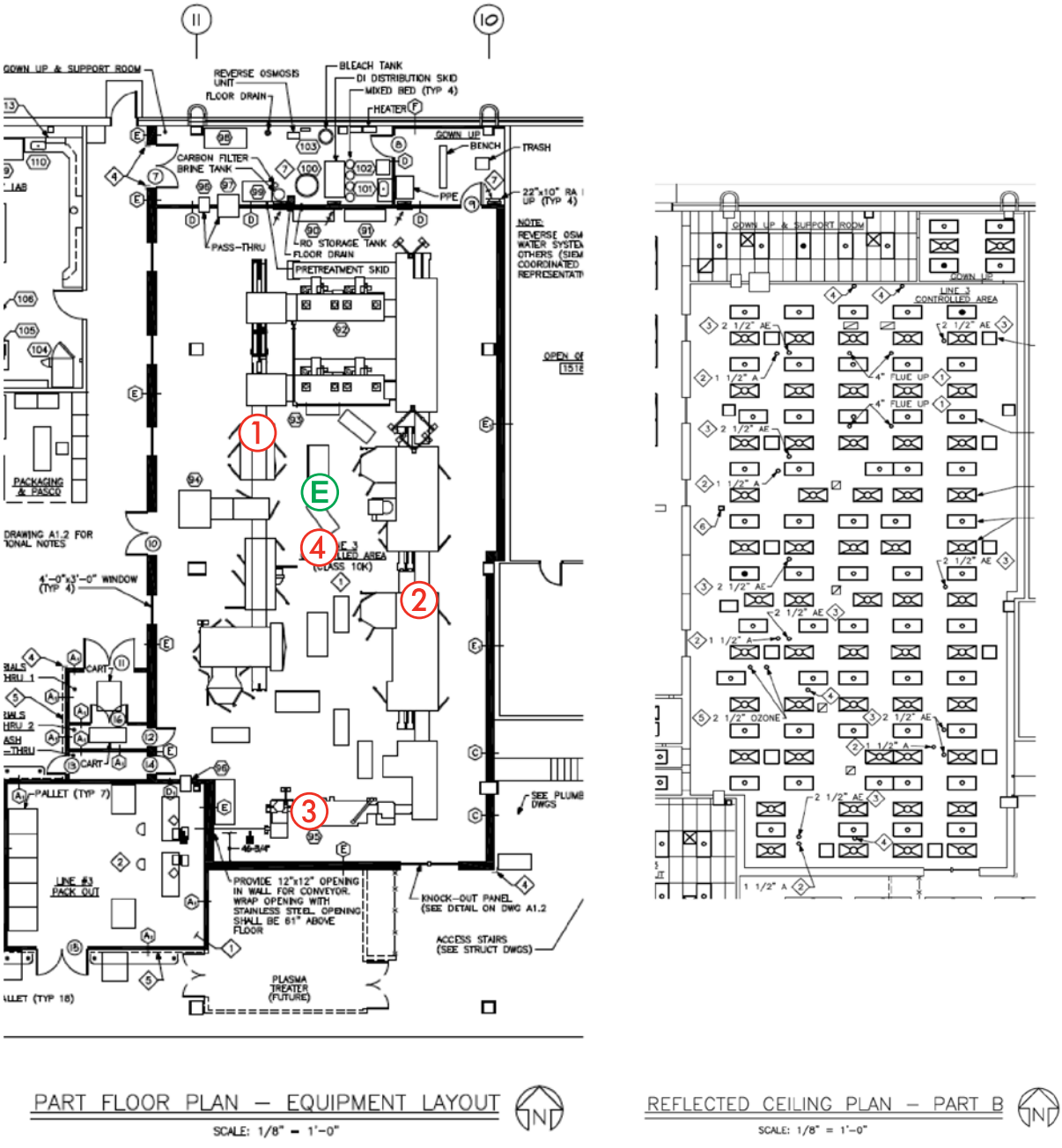


Figure 6: Conditions of test



Source: Genesis Engineering

retaining the original motor is fine, but sometimes it is advantageous to install a smaller motor if it will be operating so far below its rated output that its efficiency is significantly reduced. Operating a motor in the air stream at a poor efficiency causes additional losses through shedding the additional heat into the air stream. Reduction in this additional heat load will reduce cooling requirements on the system and subsequent electrical energy consumption.

Many HVAC systems have airflow measuring instruments installed in main ducts or in air handling units for monitoring or control. The minimum

Table A: Conditions of test, background info

Challenge	~4,000,000 parts per minute (at center of room 3 meters from position 1)
Position 1	Filler (line on west side of room)
Position 2	Stopper (line at east side of room)
Position 3	Capper (line at south side of room)
Position 4	Center of room (1 meter from challenge)

flow rate (velocity) must be considered, and in some cases changes to the measuring device type or reduction of the size of the duct it is installed in might be needed.

Reducing a room's air changes involves reducing airflow rates by adjusting dampers. Adjusting manual dampers is often successful as these can be closed almost to shutoff where necessary and fixed in position. Occasionally a manual damper could be so oversized that it will need to be replaced or partially blanked off. The main limitations with dampers are with control dampers, because they can't operate at the almost fully closed position and still provide proper control. Variable air volume boxes, mechanical constant volume regulators, and similar flow control devices all have upper and lower flow limits. The acceptable flow turndown of these devices will often limit the amount that air changes can be reduced unless it is sufficiently economically attractive to install smaller devices.

HVAC room air supply, return, and exhaust ductwork does not generally limit airflow reduction. Process exhaust flow rates (e.g., dust collection, lab fume hood exhaust) are not normally reduced due to reduction of a room's minimum air change rate and so this can limit room air change reduction. The amount of outside/fresh air handled by an HVAC system generally remains about the same after an air change reduction as it was before. Although the amount of outside/fresh air may not change, its percentage of the total air handled by the HVAC system will increase because the total airflow will decrease. In climates with cold winters, the winter "mixed-air" temperature needs to be checked to determine if preheating of the air will be needed.

Where HVAC is the dominant load on the facility's heating and cooling plant (e.g., chillers) and the application of air change reduction and other energy saving approaches is extensive, the ability of the central utilities equipment to operate efficiently at reduced loads should be evaluated.

Case Study 1

Company A achieved significant benefits in reduced energy cost through implementation of a data driven approach to optimization of air change rates in GMP manufacturing spaces.

They have accomplished this by using a science-based approach and a standardized process for evaluation, execution, and verification of candidate areas for optimization. Performance data from potential areas is analyzed to evaluate the potential opportunity for optimization of ventilation rates, whilst maintaining the key process parameters for the area within specification. In addition to the operational data analysis, the value of the opportunity is calculated, to ensure the cost of the resources required to execute the change makes business sense.

In one such example, HVAC ventilation rates to an ISO 8/Grade C area were reduced by 25% without impact to key area operating parameters.

Analysis of one-year operating data revealed that significant change could be made without impact to key parameters.

First, the area was evaluated for system and equipment constraints, and the maximum reduction calculated. Then the environmental monitoring data was evaluated and the process capability calculated. With this information, it was confirmed that the area was operating well within the required process requirements.

Recertification testing was executed immediately prior to execution of the optimization, and the tests repeated afterward to demonstrate compliance with the required parameters prior to release back to manufacturing. Airborne particle counts and particle recovery testing were included in the recertification.

The resulting retest revealed no notable change in the areas operating characteristics. Particle counts (0.5 µm/cubic meter) for the area before and after the test are shown in Figure 4 below. In addition, the results of particle recovery testing showed no significant change, with an average time for a 10x reduction (from in-operation class limit to at-rest) of 4.7 minutes before, and 5.2 minutes after (EudraLex guidance for such an area is the ability to recover from in operation to at rest of 15–20 minutes. See Figure 5 for particle recovery test results.

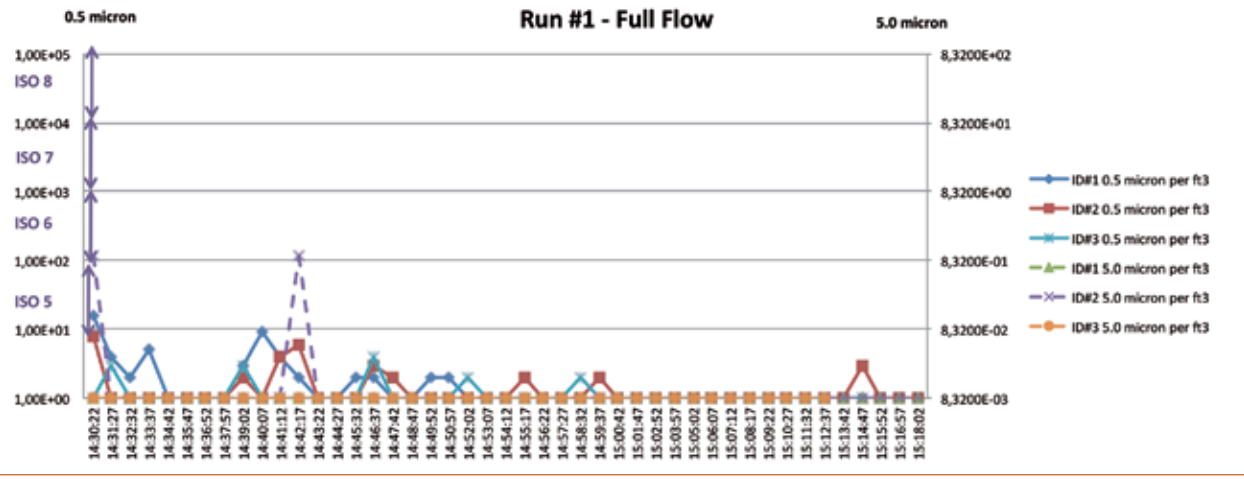
Energy reductions have been verified in direct fan power, and also in indirect energy such as cooling and reheat requirements. The cost benefits of such reductions have been evaluated at $7–$9 per square meter per ACH per year. This figure is consistent with similar optimization projects across peer facilities.

Case Study 2

OBJECTIVE

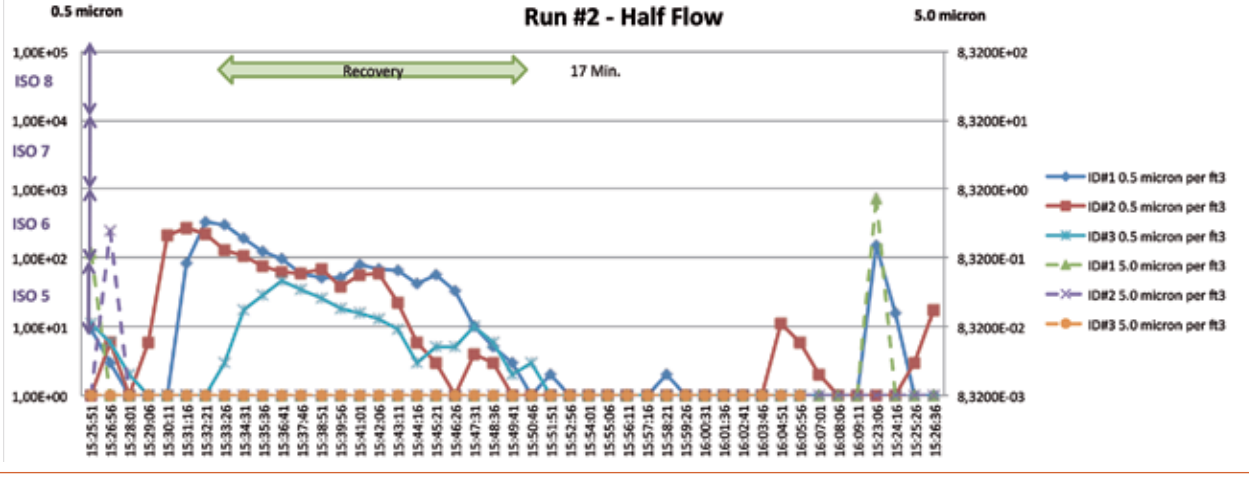
Company B designed an experiment to challenge design practices that utilize high air change rates to maintain particulate levels within classified spaces. The experiment utilized a newly completed sterile diagnostic product filling line, prior to commencing operations. For this reason, a surrogate

Figure 7: Run #1, full flow



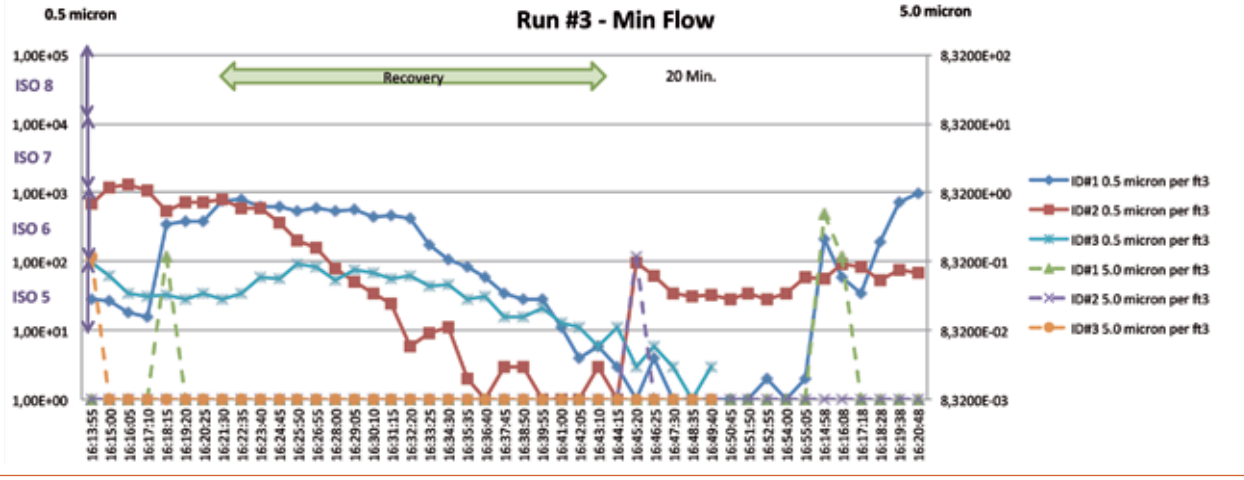
Results: Approximate class: 100; recovery time: N/A

Figure 8: Run #2, half flow



Results: Approximate class: 1,000; recovery time: 17 minutes

Figure 9: Run #3, min flow



Results: Approximate class: < 10,000; recovery time: 20 minutes

particulate source was used to simulate the maximum room occupancy. The surrogate emission rate was based on 200,000 0.5µm particles per minute for each occupant at double the expected occupancy.

The intent of the study was to produce sufficient independent data on the performance of subject rooms with regard to both particulate control and recover time at reduced air change rates to inform design and operational standards revision maintained by the quality unit.

TEST METHOD

Multipoint monitoring was undertaken at both return inlets and at area-of-concern (potential product contact) points throughout the subject room(s). The sampling parameters are based on experimental limitations and data-gathering requirements, and are not necessarily aligned with ISO 14644-3: [4]

- Number of sample locations: 4
- Airflow states: (3) Full flow (45 ACH), half flow (22.5 ACH), minimum flow (15 ACH)
- Particle size sampled: 0.5 µm
- Operational states:
  - In operation (until equilibrium particle count is reached)
    - Simulated using particulate challenge of 4.0 × 106 particles/minute via Laskin nozzle
  - At rest
    - De-energize particle generator and observe time to recover to 1% of average ambient particle concentration
- Sampling time per measurement: 1 cubic foot per minute (with this parameter you can see an increase and decrease of particles—readings shall be at intervals of less than once per minute)
- ISO class limit: 7
- Locations are near the "particle source" and locations equivalent to "filling," "stoppering," and "capping"

TEST CONDITIONS

Particle counter locations were selected near critical operations and were located without HEPAs directly above them. Particle counters were connected to isokinetic probes by 1.5-meter hoses. The particle generation was located as a single source near the center of the room (see Figure 6 and Table A).

RESULTS

The investigation found that the facility was able to maintain airborne particle count below class limits for class ISO 7 (previously known as Class 10,000) at all flow conditions against a particulate challenge of 4×10^6 particles per minute (Figures 7–9). The facility is easily able to maintain these same conditions at rest using the minimum tested ventilation rate of 15 ACH.

CONCLUSION

The test showed that the facility could reasonably be expected to be requalified successfully at lower airflows during operation and with a night setback scheme, without adverse impact to product quality. The facility now runs at half the original design airflow in operation, and one-third the original when idle! ‹›

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PERFORMANCE AND VALIDATION OF OZONE GENERATION FOR PHARMACEUTICAL WATER SYSTEMS

Nissan Cohen and Brian L. Johnson

Despite the advantages of ozone technology as a powerful commercially available oxidant and disinfectant, this technology has not been adopted broadly by the pharmaceutical industry. This article contains the rationale for applying ozone technology in a packaged system, which offers greater reliability and efficacy, using best practices that eliminate variables common in on-site integrated ozone systems. This approach is novel and innovative; it provides known results with new tools that quantify and estimate mass transfer efficiency, decrease the risk of misapplication, and increase success.

Virtually all users of pharmaceutical water systems pursue lower maintenance and operational costs, increased reliability, and improved life cycle management. Biopharmaceutical companies are looking for innovative methods and newer technology to increase throughput, quality, and uptime.

Ozone technology delivers the most powerful commercially available oxidant and disinfectant with few detrimental or detracting issues. Ozone sanitization and disinfection has been used for decades, and its adoption in pharmaceutical water systems has been increasing for several years, although it has not yet been adopted broadly in the industry.

When used in lieu of hot water or chemical sanitization for ambient-temperature purified-water systems, ozone prevents the accumulation of microbials and organics and requires less maintenance over the life cycle of the water system. In addition, at 24/7 administration ozone is:

- 85% less expensive than hot water sanitization five times a week
- 20% less expensive than once-weekly hot water sanitization
- Tens of thousands of dollars less than twice yearly chemical sanitization[1-2]

This paper emphasizes the need to understand this technology, its efficacy, and adoption into pharmaceutical water systems to address problems and limitations of legacy processes. This article also explores the efficacy of applying ozone technology in a "packaged" system using best practices. This approach eliminates variables common in on-site integrated ozone systems, and allows easier implementation at lower cost, with better and more predictable results.

BACKGROUND

Ozone (O_3) is triatomic oxygen, which oxidizes carbon compounds in water to carbon dioxide (CO_2) when sufficient ozone and time are provided. (Many complex organics oxidize to smaller complex compounds before oxidation to CO_2.) Since microbials, bacteria, pathogens, and endotoxins all contain carbon, ozone is an excellent biocide that destroys these organisms by oxidation.

There are three ways to produce ozone:

Electrolysis produces small amounts of ozone *in situ* from the water system. This method cannot adjust readily to dynamic conditions when loading requirements can change quickly.

UV production is a viable ozone-generating method but has limitations of cost, efficiency, and concentration; it is also energy inefficient when compared to other methods.

Corona discharge is the most efficient commercialized method for ozone production. It uses a reaction chamber with a dielectric barrier in which high voltage is applied to an oxygen feed gas to generate ozone. Modern corona discharge units are adjustable to throttle ozone production up or down under dynamic conditions when load and demands change. Most advanced corona discharge ozone generators use enriched oxygen from oxygen concentrators (usually +90% by weight) as the feed gas due to more efficient ozone production and lower overall operating costs.

OZONE EFFICIENCY

Ozone has a short half-life (the time required for the ozone concentration to dissipate to 50%). In 25 °C water, 50% of the ozone decays in approximately 15 minutes (Table A). Different temperatures and water chemistries influence this rate. Ozone reverts to oxygen more rapidly at higher temperatures, for example.

Table A: DO_3 half-life as a function of water temperature (pH 7)

°C	Minutes
15	30
20	20
25	15
30	12
35	8

Ozone's short half-life allows disinfection regimes to be calculated easily, according to the concentration required to achieve the desired effect: maintaining pristine systems devoid of microbials and organics. The sidebar on page 48 shows a simplified example of these calculations and how to assess the ozone needed for a given concentration.

AQUEOUS OZONE PROCESS

The aqueous ozone process consists of four steps:

1. Ozone generation
2. Mass transfer
3. Concentration and contact (residence) time
4. Process control

Ozone generation

As noted above, modern corona discharge ozone generators produce gas on-site, with control capability for increasing or decreasing output. They may include an air dryer or oxygen concentrator for feed gas preparation, as well as filtration, gas flow control, and gas concentration control.

Mass transfer

In the mass transfer process, ozone is dissolved in water. Ozone is more soluble in water than oxygen, although its solubility is dependent on the temperature, pressure, and other factors.

When designing an efficient mass-transfer process, bubble size is a critical parameter. Mitani et.al. stated "[T]he smaller the bubble size, the greater the mass transfer rate of gas. The larger surface area to volume ratio of very small bubbles provides an overall larger area for ozone mass transfer to occur."[3] The interaction of the bubbles with the water promote higher mass transfer efficiency (MTE), resulting in higher oxidation and disinfection efficiency due to the greater ozone diffusion in the water.[4] For best efficiency, bubbles should be 1 micrometer (µm) or smaller.

Larger bubbles reduce mass transfer and cause greater off-gassing of undissolved ozone, which translates into a loss of MTE. Bubbles coalesce, increase in size, and migrate to the upper surfaces of the water, accumulating in the head space of the tank or pipe. This off-gas must be collected, controlled, and decomposed to oxygen before it can be discharged.

A well-designed mass transfer system will create and manage the surface area for a reliable MTE ratio that is typically greater than 90%, which means that 90% of the ozone gas produced is transferred into solution. The gas-to-liquid ratio is paramount when calculating anticipated MTE of an ozone mass transfer system. An improperly sized and/or designed system can waste or fail to dissolve much of the ozone produced, causing inefficient and expensive operations.

Sizing

This is the amount of ozone the generator produces, based on the dosage needed to establish proper oxidation and disinfection.

Calculations for sizing an ozone generator and mass transfer system are based on temperature of the water, contact time (see below), ozone concentration and half-life, volume of water to be treated, and flow rates. Considerations must include MTE, which is the ratio of ozone dissolved, total ozone demand (including the decay rate), and concentration of oxidizable material in the water that will consume dissolved ozone.[5]

Correct sizing is critical as MTE, decay rate, and ozone demand can change rapidly with organic loading and process changes including water temperature and pH variations.[5] Pharmaceutical water quality and conditions tend to be less dynamic, but are susceptible to seasonal changes, enhancing the need for good sizing practices. These start with a proper mass calculation, acceptable process and safety margins, and sizing to account for dynamic operational ranges.

Definitions

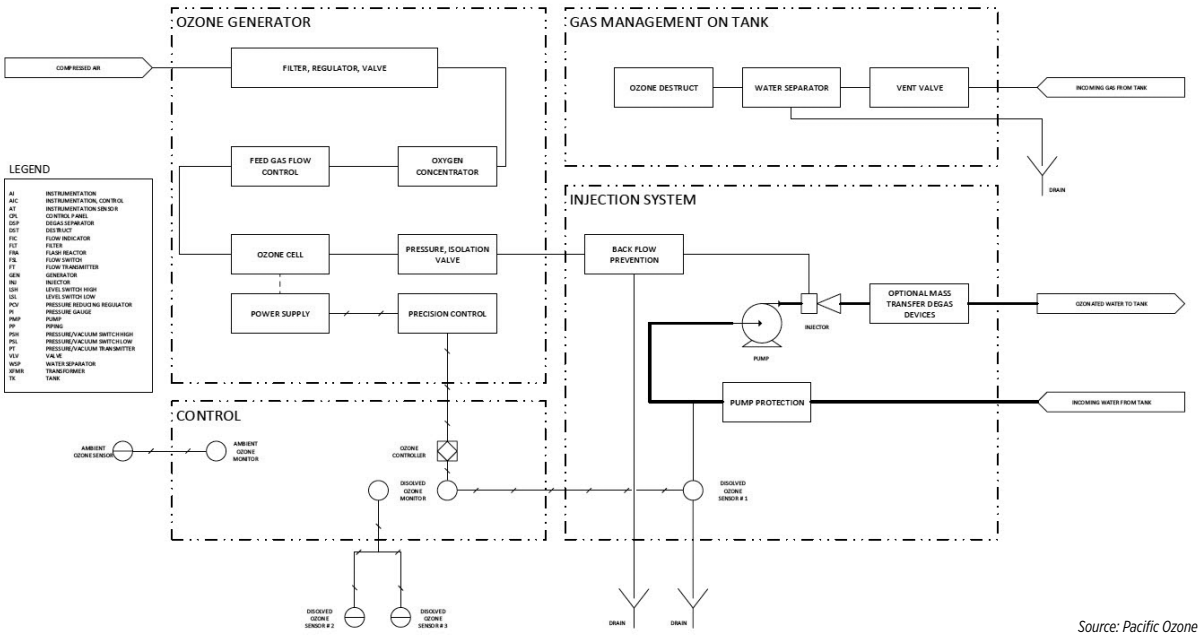
Sizing (mg/l): Amount of ozone delivered to a process

Mass transfer efficiency (MTE): percentage of ozone applied minus the immediate loss of consumption

Ozone demand (mg/l): Amount of ozone consumed by oxidizable material; must be determined empirically

Demand factors: Temperature, pH, organic content, etc.

Figure 1: Packaged ozone system process and instrumentation diagram



Source: Pacific Ozone

Concentration

The concentration of ozone dissolved in the water (DO_3) is expressed as a mass volume percent. DO_3 is dependent on MTE and the mixing of dissolved ozone with the volume of water. To meet oxidation and disinfection goals, the ozone solution must be mixed promptly with the surrounding water in the tank to deliver a homogenous single-phase solution.

Due to ozone's short half-life and the ongoing demand to oxidize organic material in the water, it is extremely important to replenish the ozone continuously to maintain a steady-state concentration. The sidebar on page 49 shows ozone solubility calculations using Henry's Law. At 45˚C, for example, ozone's shorter half-life results in rapid decay and less contact time with the organics in the water. This reduces the level and efficiency of oxidation unless the decay rate is overcome by adding more ozone to maintain a steady-state concentration. Conversely, in colder water ozone has a longer half-life—although its reaction can be slightly slower—and less ozone is needed to maintain the concentration.

Ambient-temperature waters are ideal for ozone disinfection and maintaining concentration. Ozone is more soluble at ambient temperatures than at warm or hot temperatures, and more ozone gas produced by the generator is transferred into the water. This increases the efficiency of the mass-transfer process and consistency of the disinfection process.

Contact time

Contact (or residence) time becomes a crucial parameter when trying to calculate concentration and time values following the MTE for any given water system. Concentration and time value is measured in milligrams of DO_3 per liter of water multiplied by the reaction time in minutes. This is an accepted methodology for measuring and validating disinfection, and for defining and designing an ozone system. A known MTE from a well-designed and verified system with uniform mixing, therefore, will ensure the water is in contact with the ozone long enough and at a concentration high enough to deliver reliable disinfection results.

Control

A well-designed ozone system must include the instruments necessary for control of the unstable and highly reactive gas. The technology required for good ozone process control includes instruments to measure DO_3 (with feedback control), ambient ozone (for safety and OSHA compliance), ozone

Compensating for ozone half-life

O_3 n/HL∝ = O_3 c

Where:

O_3n: Not compensated for half-life of ozone destruction, amount of ozone required to achieve and maintain desired ozone concentration,

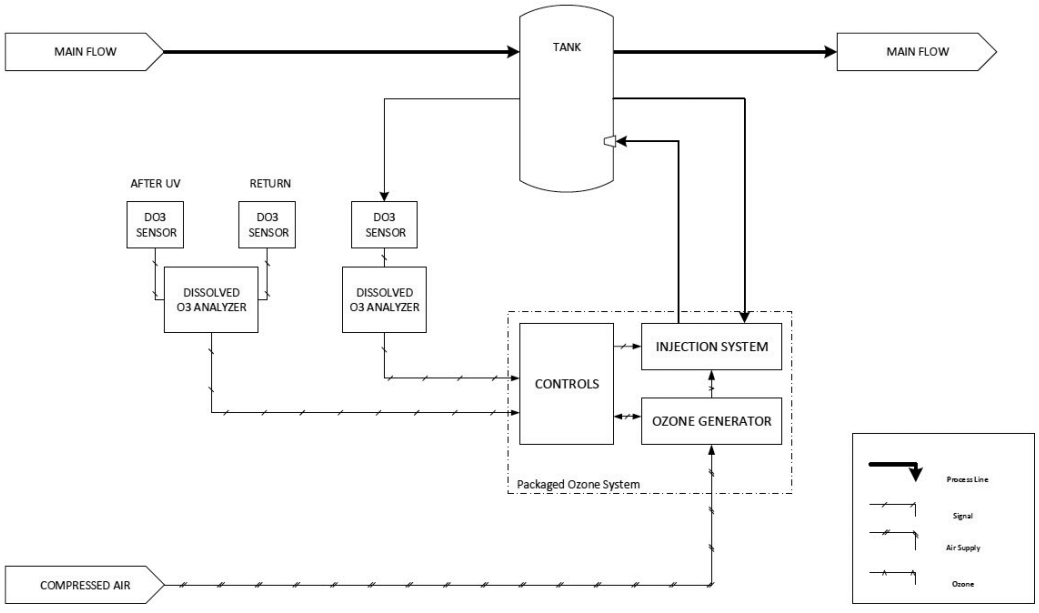
HL: Half-life of ozone according to the water temperature from the table above

O_3c: Compensated or actual amount of ozone required to be injected in order to maintain residual concentration at the actual water temperature.

Using the relationship and above data, in this case at 25˚C, 10 g / 0.25 hour = 40 g or four times more than without compensation for ozone destruction in water because of half-life.

Source: "How to Compensate for Half-Life of Ozone." © Absolute Ozone. www.absoluteozone.com. Reprinted with permission.

Figure 2: Packaged ozone system process flow diagram



Source: Pacific Ozone

gas production flow and pressure, and hydraulic parameters that influence mass transfer.

PACKAGED OZONE SYSTEMS

To configure and control the variables inherent in oxidation processes, packaged ozone systems can minimize the discrepancies associated with individual components and maximize the efficiency and ease of system validation. Components can be tested, integrated, and validated for all performance characteristics by the manufacturer using process analytical technology (PAT), since all measurement, testing, and feedback mechanisms are integrated. This enables monitoring and verification of all instrumentation and process parameters in real time, and offers immediate information on the process and its adherence to the user requirements specifications. The installation/operational qualification (IOQ) phase can easily be integrated; commissioning and qualification can be performed readily with continuous monitoring, using PAT for validation.

Typical components include an ozone generator, oxygen concentrator, venturi mixing device, mixing tank or vessel, ozone concentration monitor, ambient ozone monitor, various valves, and sometimes an ultraviolet (UV) lamp for ozone destruction (See Figures 1 and 2).

The ozone generator is the system's workhorse, using the corona discharge method to generate ozone from oxygen. The oxygen concentrator uses compressed air, which has an oxygen level of approximately 20% and increases the oxygen level to approximately 90% as feed gas to the corona discharge unit of the ozone generator.

The ozone gas is transferred into the water stream using a venturi or another microbubble device. This dissolves the ozone gas into the water and promotes the mass transfer process. A properly selected venturi, plus related piping and pump arrangements will ensure the gas-to-liquid ratio and bubble size to meet design requirements. A packaged ozone system also typically incorporates an injection assembly that may include a venturi, nozzles, shearing devices, and degas separators that define the pump characteristics required for the process.

The ozonated water is delivered to a tank or vessel to oxidize and destroy carbon-based organics in the water. Good mixing and fluid dynamics in the tank are integral and should also be part of the system design. Tank nozzles, connection locations, level, and flow conditions should all be considered. Flow-through characteristics within the vessel and a DO_3 monitor should ensure uniform mixing, tight control capabilities, and avoid short circuiting.

Precise DO_3 concentration control within the tank under all operating conditions is imperative to achieve expected destruction of organics and microbials.[6] DO_3 concentration monitors measure ozone concentration in

Solubility of ozone in fluids: Henry's Law

The maximum achievable balancing concentration of gas in fluids

$C_{Liquid} = C_{Gas} \times ß_{(Temperature)} \times P_{Gas}$

Where:

C_{Liquid}: Dissolved concentration in liquid

C_{Gas}: Gas concentration

ß: Bunsen coefficient (solubility), temperature dependent

P_{Gas}: Gas pressure

Source: MKS Instruments, Inc. "Plasma and Reactive Gas Solutions: Ozone Data & Conversion Tables." © 2004 MKS Instruments, Inc. www.mksinst.com. Reprinted with permission.

PACKAGED OZONE SYSTEMS CAN MINIMIZE THE DISCREPANCIES ASSOCIATED WITH INDIVIDUAL COMPONENTS

real time as either parts per million or parts per billion. Feedback control sends a signal to the ozone generator to adjust the gas output to maintain a targeted DO_3 concentration and microbial-free system. An ozone gas monitor for the airborne environment is installed to comply with OSHA standards (Figure 2).[7]

Advantages

Even the best biopharmaceutical water systems are dynamic, with seasonal and other influences that can cause chemistry and temperature changes that affect the growth and concentration of microbials and organic material. Despite fluctuations in the water quality, properly sized packaged ozone systems can maintain pristine conditions using science-based approaches for control, monitoring, and administration.[8] They can also be easily throttled for increased or decreased ozone production.

MTE ratios are straightforwardly calculated and ozone demand can be recalculated in real time when fluctuating water chemistry or loading occurs. When devising IOQ and range tests, ozone production can be adjusted and monitored to match intended output and concentration. Packaged ozone systems can be tested under wet conditions and thus commissioned and qualified, verified, validated, and used in PAT schemes. Packaged ozone systems replace uncertain or ill-defined output with a science-based, quantifiable output.

CONCLUSIONS

Calculations for ozone solubility and efficacy are dependent on water temperature, organic loading, half-life, concentration targets, tank or piping volume, and requested ozone residual. Packaged ozone systems can calculate and compensate for these factors, reduce implementation risk, and provide a better, lower-cost, and more reliable disinfection process for high-purity pharmaceutical water systems. The systems' immediate feedback, control mechanisms, and built-in safety features can alleviate onerous IOQ and validation procedures and adhere to PAT protocols. Since all data is recorded and available while complying with FDA's 21 CFR part 11, current good manufacturing practice compliance is discernible. ‹›

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DESIGN AND CONTROL OF PHARMACEUTICAL WATER SYSTEMS TO MINIMIZE MICROBIOLOGICAL CONTAMINATION

Tim Sandle, PhD

Water-borne microorganisms are ubiquitous and varied in their ability to survive and grow under different conditions. Therefore, an out-of-control water system can cause harm to the patient or adulterate pharmaceutical products. Purification of water is required to prevent interaction with drug substances or other ingredients in the product formulation. Water must also be microbiologically controlled and monitored.

Both chemical and physical water-purification methods are based on robust technology that can, in most cases, reduce the level of contaminants to fewer than one part per million (or $1{:}10^{-6}$). These methods have an assay sensitivity in the range of parts per billion ($1{:}10^{-9}$).

While chemical analysis usually generates answers quickly enough to ensure a rapid response to problems, microbiological assessment is often slower and less accurate. While rapid microbiological methods are gradually being implemented (such as ATP bioluminescence* or fluorescent DNA-specific dyes), most microbiological assessments of pharmaceutical-grade water rely on cultural methods.[1] This means bioburden results are not available until several days have elapsed,[2] placing considerable emphasis upon good design principles.

This article assesses some of the requirements for good design, together with the control measures necessary to maintain effective microbiological control in pharmaceutical facility water systems.

PHARMACEUTICAL-GRADE WATER

There are four grades of water in pharmaceutical production defined in the United States Pharmacopeia (USP) and/or European Pharmacopoeia (Ph. Eur.): potable (mains) water (USP), purified water (USP and Ph. Eur.), highly purified water (Ph. Eur.), and WFI, or water for injection (USP and Ph. Eur.). Potable water is the starting water for the other grades; it has no direct product contact. Each grade has microbial issues related to the method of production, degree of purification required, and process of storage and distribution.

Purified water, typically produced by reverse osmosis, is intended for use in formulations that are not intended to be sterile or apyrogenic (i.e., do not require an endotoxin specification). Uses include some oral and topical products, as well as the granulation processes for tablets and capsules. With such medications, the concern is with overall bioburden and the absence of "objectionable" microorganisms: those that pose potential patient harm, based on the route of administration.3 Purified water is also the feed for WFI and for pharmaceutical-grade clean steam. Highly purified water is intended for the preparation of ophthalmic, nasal/ear, cutaneous, and other medications, as required in the Ph. Eur. This grade of water requires both endotoxin (< 0.25 endotoxin units [EU] per milliliter [mL]) and bioburden control (< 10 colony forming units [CFU] per 100 mL).

WFI is the highest quality water used by the pharmaceutical industry; it is produced either by reverse osmosis or by distillation (according to both USP and Ph. Eur. since 2015). Bioburden and endotoxin control requirements are set out in the Ph. Eur. as < 10 CFU/100 mL (bioburden) and < 0.25 EU/mL (endotoxin). WFI is used for the preparation of parenteral medicines, dialysis, and irrigation solutions, as well as cleaning reagents in the highest-grade cleanrooms.

MICROBIOLOGICAL CONCERNS

Potable water from private water companies or municipalities is monitored to ensure that levels of chemical pollutants remain within established safety criteria, and screened for microorganisms including Escherichia coli, enterococci, *Pseudomonas aeruginosa*, and fecal coliforms.[4] In most locales the quality of the water supplied to the pharmaceutical facility is satisfactory. As a safeguard, however, many facilities elect to test the water for organisms like *E. coli* as a marker for fecal contamination. Onsite potable water is treated, softened, purified (according to the grade required), and distributed.

While most well-designed water systems can be maintained in a state of control, microbiological problems can develop. Microbial adherence is a consequence of the balance of attractive and repulsive physicochemical interactions between bacteria the surface. The primary issue is biofilm formation—slime-like microbiological communities that occur when microorganisms adhere to a surface (such as pipework with a poor flow rate).

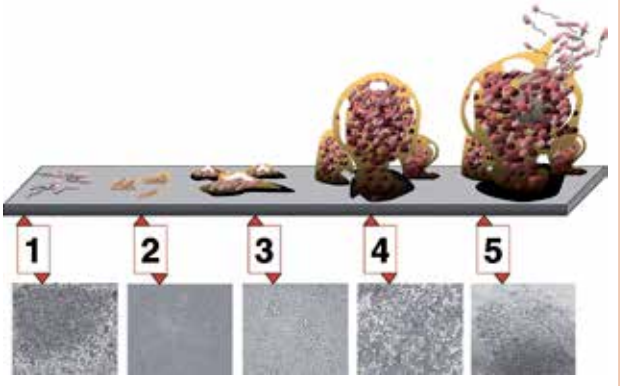
A biofilm develops because bacterial cells, once attached, secrete a polysaccharide known as glycocalyx (hydrated polymeric slimy

* Adenosine triphosphate (ATP) is a nucleotide found in all living organisms; ATP bioluminescence is used to monitor contamination.

matrices). The glycocalyx enables each bacterium to encapsulate itself on the surface; biofilm forms as these organisms accumulate. The steps involved in biofilm formation are (Figure 1):

1. Individual cells populate the surface (initial attachment)
2. Irreversible attachment
3. Extrapolymeric substances are produced and attachment becomes irreversible
4. Biofilm architecture develops and matures
5. Single cells (or clumps of cells) are released from the biofilm over time

Figure 1: Generalized biofilm formation

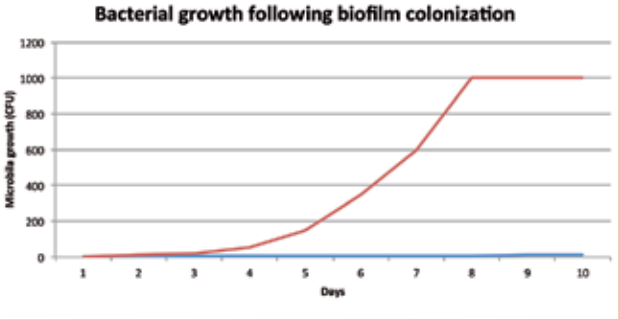


Source: D. Davis (CC BY 2.5 [http://creativecommons.org/licenses/by/2.5]), via Wikimedia Commons

This type of attachment occurs relatively slowly. Various factors affect the process, including the type of bacterium involved, the size of the bacterial population in the environment, and the duration of its growth phase.[5] In general, Gram-negative bacteria form biofilms more readily,[6] due in part to appendages on the bacterial cell (fimbriae) that allow such them to attach to surfaces more easily. Surface charge is another important phenomenon in relation to bacterial adherence.[7]

Microbial growth in a biofilm is often rapid at the point of source (Figure 2). The pattern from user outlines is often sporadic, however, because contamination is eluted from the biofilm at different rates over time.

Figure 2: Microbial numbers in a water system rise exponentially following biofilm formation



Biofilms are of particular concern with water systems, since Gram-negative bacteria constitute the majority of the bacterial populations found in aquatic environments. These types of organisms, moreover, also shed endotoxins, a component of the cell wall.[8]

Many stages of the water-purification process can create conditions which, although designed to reduce contaminants, paradoxically promote biofilm formation. An example is in-depth filtration through a matrix. As water percolates through the filter, microorganisms are adsorbed onto the matrix, where they form complex communities. Further on, the purification pathway can create a series of colonizable environmental niches of varying nutrient richness. At the end of the process, which essentially depletes nutrients to very low levels, an extreme environment is created.[9] This environment elicits extreme responses from any microorganisms present, making them difficult to eliminate.

For appropriately designed and maintained systems, purified water and WFI present low risks of microbial contamination. Whenever microorganisms are detected (and certainly when above specification), however, this creates a significant hazard.

GOOD DESIGN PRINCIPLES

While different phases of water generation can contribute to risks, there are a number of design and control steps that can reduce microbiological proliferation:[10]

Break tanks

Break tanks, which prevent water produced during production from reentering the water supply, are the first areas in which microbial colonization can occur. Microorganisms present in incoming potable water attach themselves to the sides and bottom of the tank, forming a biofilm. Samples taken from the tank usually meet the specification for potable water and give no immediate indication of the biomass that is accumulating. Regular maintenance and tank flushing are the main preventive measures.

Activated carbon beds

The bed matrix consists of finely divided charcoal, which is highly efficient at removing low-molecular-weight organic materials. It also oxidizes and removes additives such as chlorine. The vast surface area and accumulation of nutrients on the bed, combined with chlorine removal, can lead to rapid microorganism colonization and proliferation. Most of the organisms are Gram-negative bacteria and, should they undergo cell lysis, can be a source of endotoxins. An essential point of control over the entire water system is the ability to sanitize the beds regularly with hot water or steam, coupled with frequent replacement. Sanitization should begin at a higher frequency (such as weekly) for a new water system; this could be decreased over time (monthly) based on a microbial bioburden trend review. Six months to one year of data would be required to assess the bioburden pattern.

Water softeners

In areas with hard water, softeners are required to prevent interference with the deionizers and reverse osmosis systems. As water passes through the resin-filled columns, divalent calcium and magnesium cations are exchanged for sodium ions. The resin matrix provides an enormous surface area for potential microbial colonization, however. Sanitization and control measures such as ultraviolet light and chlorine are essential in maintaining water quality.

MICROORGANISMS PRESENT IN INCOMING POTABLE WATER ATTACH THEMSELVES TO THE SIDES AND BOTTOM OF THE TANK, FORMING A BIOFILM

Deionization devices

Standard deionization systems consist of charged resin columns. These may be separate for cation and anion removal, or may use a mixed-bed system. The advantage of deionization is that the columns require regeneration with 1 molarity (M) hydrochloric acid and 1M sodium hydroxide, both of which are strongly biocidal. If the regeneration frequency is high, the columns are maintained in a sanitized state. Unsanitized columns or those that are not regenerated for more than a couple of days present the same problems as activated charcoal beds, which is the risk of bacterial growth occurring.

Electrodeionization systems permit continuous column regeneration without the need to add regeneration agents. They are easy to maintain, but they also encourage bacterial growth. A reverse osmosis membrane will filter out bacteria, but growth can occur if not properly maintained. As fragments of the bacterial cell wall break off, endotoxins can easily pass through the membrane.

Storage and distribution systems

Poorly designed storage and distribution systems create opportunities for recolonization and, ultimately, product contamination. Colonization is often difficult to detect because biofilms release contamination slowly and randomly. (Microbial populations in water rarely indicate normal distribution, which means levels can appear and disappear over time before the overall trend can be discerned.)

Storage tanks

Water storage tanks are normally constructed from stainless steel. Where they are used, it is important to determine capacity, rate of use, and frequency of flushing and sanitizing the internal surfaces. Regular water turnover helps prevent contamination; slow turnover, on the other hand, presents a greater potential contamination risk. Storage tanks should be vented to manage water level fluctuations. To prevent microbial contamination from outside air, vents should be fitted with a hydrophobic air filter. Such filters are also used to avoid filter occlusion, which can create vacuum conditions and lead to tank implosion. Vent filter integrity testing should be performed regularly (e.g., once every 6 or 12 months).

Storage temperature

It is standard practice to store WFI in a recirculating stainless steel system, although on occasions polyvinylidene fluoride (PVDF) is used when very low mineral content water is needed. Recirculating systems that operate at temperatures of 65ºC to 80ºC are self-sanitizing, with the caveat that no cold spots below 65ºC form. Purified water systems can be hot or cold. Key aspects of cold water systems are discussed in more detail below.

Pipe and tank design

If they are poorly designed or improperly maintained, pipes and tanks are more likely than any other part of the water system to develop contamination. The general requirements for well-designed pipes are:

1. Smooth internal surfaces. Microorganisms adhere less well to smooth surfaces than to rough surfaces, therefore corrosion resistance and avoiding rouging (iron oxide formation) is important (as can be achieved by the electropolishing of stainless steel). Pipe joints and welds can also disrupt smoothness.
2. Continuous water movement in tanks and rapid flow in pipework; velocities in the range of 1–2 meters per second have been found to be satisfactory.[11] This minimizes opportunities for microorganisms to adhere to surfaces (and form biofilms). Where shear forces occur, microorganisms adhere poorly to surfaces. Where there is no water movement, there is no shear (shear increases with the speed of flow).
3. Avoid areas where water can remain stagnant:
   a. If a branch pipe is too long to allow the turbulence of the flowing main to disturb its contents, water may stagnate in "dead legs" (Figure 3). The principle is to always minimize the length of branch pipes.
   b. Water can also remain stagnant in valves, particularly at user points—and especially those that not in frequent and regular use. This can be counteracted by hygienic or "zero dead leg" valves which, although significantly better than the alternatives (say ball valves). This should not lead to a sense of false security, however, since they can harbor endotoxin-shedding biofilms. Having the correct sloping for drainage can also reduce contamination risk.
   c. Ring mains should be sloped ("drop") from point of origin to the point of return to ensure that systems are completely drainable.
4. Avoidance of leakage. Water leaks can cause bridging of water to the external environment through which bacteria may enter the system. Storage tanks should be equipped with filter on their air vents to prevent air-borne microbiological ingress. They may even be held under a "blanket" of an inert gas such as nitrogen.
5. High temperature storage and distribution. The risks of endotoxin-shedding biofilms despite the best attempts at control above are thought to be so consequential that the most manufacturers require

Figure 3: Poorly designed water distribution pipe with a dead leg

Image: Tim Sandle

the temperature of storage and distribution to be maintained higher than 65°C. Lower temperatures may also be acceptable, provided the manufacturer has adequate data to demonstrate that a lower temperature works as intended.

It should however be considered that 65°C is too high a temperature for most pharmaceutical formulation purposes. This means that user points are generally equipped with some form of cooling mechanism. It should be noted that heat exchangers used for this purpose may be a source of endotoxin and bacterial contamination and may thus cancel out many of the benefits of high temperature circulation.

6. The use of coated surfaces on pipes and in tanks, where appropriate (as not to pose a risk of leaching toxic substances) can help to address bio-fouling.[12]

Cold water systems

Systems for purified water typically use ozone, ultraviolet light, and in-line filters to maintain microbial quality instead of high temperature. Important points to consider are:

1. Ozone is used periodically for sanitization. It attacks the outer surfaces of microorganisms and destroys cell walls and membranes.
2. Ultraviolet light is not a sterilant, although it has some microbial reduction properties.[13] Efficiency depends on path length, speed of flow, and age of the light source. The most commonly used wavelength for microbial reduction in pharmaceutical water treatment systems is 254 nanometers (nm). Ultraviolet light is also very useful for catalyzing the breakdown of ozone or hydrogen peroxide used as sanitizing agents, although its efficacy is often diminished by poorly maintained or malfunctioning lamps.
3. Filters are ideal matrices for colonization; they need careful monitoring of pressure differentials and frequent sanitization or chan ging. If a biofilm has formed on a filter, sanitization will kill most microorganisms within the biofilm but will probably not remove the matrix, which may be rapidly recolonized. In addition, the presence of highly resistant "persister cells" within the population will remain unaffected and regrow.
4. Cold water systems generally use thermoplastic materials because they suffer less biofouling than stainless steel (at low temperatures). Plastic material used to construct pipework is typically polypropylene or PVDF.
5. Bends in pipework should be as gentle and as few as possible; tap points should be kept to a minimum. Any disruption to the smooth flow of water results in turbulence, which assists biofilm formation by creating more opportunities for circulating microorganisms to adhere to colonizable surfaces.

User points

Water points in production areas involve the transfer of water from the circulating water loop to the point of use via transfer piping (or tubing), which should be made of a suitable nontoxic material, such as polyvinyl chloride (PVC), chlorinated PVC, polypropylene, or PVDF. The transfer piping should be drained after use and changed regularly (such as every 24 hours); care must be taken to avoid splash-back from sinks or recontamination from aerosols. New tubing should be sanitized before fitting; it is also common for the tubing and outlet to be flushed prior to use (for a defined time or given volume of water). These measures are taken to avoid contamination of the water during the transfer process.

WHEN THINGS GO WRONG

Loss of water system control and microbial contamination can have a number of causes, including aging resin, aging filters, poorly maintained ultraviolet lights, improper maintenance, failure to achieve effective heat distribution, leaks (such as heat exchangers), dead legs, and water-system modifications (e.g., cutting through pipework).

Treating water systems

Several options are available for treating and improving water quality. The method chosen depends on what is causing the microbial deterioration, the source of the problem, the water quality required, the volume to be treated, and the type of distribution system. System design can influence the size of the microbial population and the ability to remove it. Dead legs, long pipework runs to taps, undrainable pipes, and U-bends can also create microbiological problems.

Four methods are routinely used to remove microbial contamination: heat, chemicals, filtration, or ultraviolet light. Contact time is important for each one.

Heat, as described earlier, can be used in the circulating loop of a hot-water system maintained at 65°C to 80°C (with ≥ 75°C being optimal). If this proves insufficient there should be the capacity to superheat the system (taking the temperature up to 121°C for one hour or longer).

Chemical treatment (e.g., ozone, chlorine, chlorine dioxide, hydrogen peroxide, peracetic acid, and sodium hydroxide) is applicable to raw mains water, but can also be used to treat distribution systems of water produced by distillation, deionization, and reverse osmosis. Concentration of the chemical used depends on the location of the water in the distribution system. Chlorination, for example, is generally effective if minimum levels of 0.2milligrams (mg) per liter (L) of free chlorine are attained. The contact time will vary with water temperature and pH; typical times for 0.2mg/L of free chlorine are between 30 and 60 minutes. Importantly, any chemical added must, at some point, be removed.

Membrane filtration using a 0.22 micrometer (µm) porosity filter is applicable where usage is moderate and continuous water circulation can be maintained (i.e., water is continually returned to the storage tank and

Figure 4: : Membrane filtration test

MOST OF THE ORGANISMS ARE GRAM-NEGATIVE BACTERIA, AND SHOULD THEY UNDERGO CELL LYSIS, CAN BE A SOURCE OF ENDOTOXINS

refiltered, except what is drawn off for use). While filtration works well in principle, it is relatively expensive for high throughputs because they need regular changing to prevent blockage and "grow-through." For this reason, using 0.22 µm filters to control contamination in water used for product manufacture is frowned upon. Filters should be used only prior to the distribution process.

Ultraviolet radiation (254 nm) is used to disinfect water of good optical clarity; it works particularly well in a recirculating system where water flows over a multiple lamp system. While contact times vary according to dose and flow rate, they are normally in the region of 1 to 10 seconds. This time is required to allow UV light to penetrate through the water and make contact with any bacteria present.

MICROBIOLOGICAL MONITORING

Frequent monitoring is important to verify microbiological control. This involves a bioburden assessment, typically using microbial count methods with membrane filtration, and a low-nutrient agar such as R2A as the method of choice (Figure 4). Where applicable, a *Limulus* amebocyte lysate test for bacterial endotoxin is also recommended. In both cases, action or alert limits must be based on validation data and must be set low enough to signal significant changes from normal operating conditions.

CONCLUSION

In pharmaceutical water-distribution systems, microbial adhesion will initiate biofilm formation, exacerbating contamination of water, reducing the aesthetic quality of potable water, increasing the corrosion rate of pipes, and reducing microbiological safety through increased survival of pathogens. Microbial control, therefore, is a matter of concern for engineers, production personnel, and microbiologists.

This article has outlined the microbiology of water systems and provided an overview of the design, control, and generation of pharmaceutical-grade water. While several aspects of design and control have been discussed, perhaps the two most important are to avoid standing water (which is invariably a source of contamination) and to have provisions for sanitization in place at each step of the water system. ‹›

Editor's note: Items 1–5 in the "Pipe and tank design" section of this article have been reprinted from *Pharmaceutical Microbiology: Essentials for Quality Assurance and Quality Control*, by Tim Sandle, Chapter 10: Assessment of Pharmaceutical Water Systems," page 120 (2015), with permission from Elsevier.

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RISK ASSESSMENT FOR THERMAL INFLUENCES ON FILTER AND CONTAINER CLOSURE INTEGRITY TESTING

Magnus Stering

Patient safety depends on the reliability of sterility-assurance tests. Sterilizing grade filter integrity testing (FIT)—diffusion and bubble point tests—and container-closure integrity testing (CCIT) of single-use bags (pressure-decay test) are therefore critical.

In the pharma-biotech industry, it is generally understood that environmental temperature drifts can influence FIT and CCIT test values. Using the ideal gas law as a rule of thumb, homogeneous temperature changes of 1°C inside the sample during the diffusion measurement phase can affect the diffusion test result by about 25% (see sidebar on page 59). Environmental temperature drifts can generate both false passed test results—which can put patients' lives in danger—and false failed test results, which may quarantine otherwise acceptable product and contribute to drug shortages. This is why stable temperature is a prerequisite for the abovementioned tests. Temperature changes do happen, nevertheless, due to factors such as laminar airflow and nearby steam-sterilizing autoclaves or freeze dryers. And post-use testing in a low-grade environment could also be subject to temperature variations. Wetting conditions are another concern, as liquid that is too cold or too warm will thermally equalize with the environment during the measurement phase. (Wetting liquid temperature will not be discussed extensively in this article.)

The effect of temperature change is complex, and cannot be explained by the ideal gas law alone. The influence on test results also depends on whether the sample is made of stainless steel (multiuse filter housing) or plastic, such as a polypropylene (PP) filter capsule or single-use bag in ethylene vinyl acetate, since different materials react differently to temperature changes depending on their thermal expansion factors and heat conductivity. Different test methods also yield different test results. The diffusion (also called forward-flow) and pressure-drop tests are, for instance, more affected by temperature variations than is the bubble point test (see sidebar on page 59).

This article shows experimental data on the thermal behavior of filter capsules in PP compared to multiuse filter housings in stainless steel when exposed to temperature changes during a diffusion test. The temperature changes generated during these trials were much greater than would be expected under normal conditions. Samples would not be put into water under normal conditions, either. This was necessary, though, to generate diffusion curves that clearly demonstrate the complexity of this behavior.

ENVIRONMENTAL TEMPERATURE DRIFTS CAN INFLUENCE FIT AND CCIT TEST VALUES

The purpose of this article is to increase understanding of thermal impact on FIT and CCIT, and to provide a tool for improved risk assessment, such as failure mode effects analysis (FMEA).

Materials

- Compressed air
- Hot and cold water
- A 10-liter bucket
- Axial fan heater (AEG, HS 204 ST 2000W)
- Reference temperature sensor (Sika Electronic TT31048)
- Filter-integrity tester
- Test tubing
- 10-inch stainless steel housing
- 10-inch filter cartridge (0.2 micrometers [µm])
- 10-inch filter capsule in PP (0.2 µm)
- 5-inch filter capsule in PP (Sartopore2 0.2 µm)

Remarks

The filter-integrity test device used for these trials measures diffusion according to the pressure-decay method, combined with a sample net volume determination (see DIN 58356 part 2). Other devices may use volume dosing. Regardless of measuring method, all flow-measuring devices are bound to the physics of the ideal gas law ($pV = nRT$). In addition, the behavior of the test sample when it is exposed to thermal variations is independent from the testing device.

Differences in behavior between devices based on software and safety parameters for detecting unstable conditions are still possible, however. This article does not intend to make any comparison between devices. The risk assessment suggested in this article should therefore take into account the device being used.

TRIALS

Test 1

A diffusion test under stable environmental conditions at an ambient room temperature of 22°C was performed on a 10-inch filter capsule. After 80 seconds of measurement the filter capsule was entirely submerged in a bucket with water at 30°C to generate a quick temperature increase (Figure 1). The diffusion curve showed can be seen in Figure 2.

Interpretation

During the first 80 seconds the temperature is stable. This generates a stable pressure drop per time unit, which is displayed as a stable diffusion rate.

When the PP capsule is placed in warm water, the capsule volume expands and its volume increases. This generates an approximately 15-second pressure drop per time (Δp/t) increase, which is interpreted as an increased diffusion rate by the integrity tester.

As PP does not conduct heat efficiently, heat transfer into the test gas is slow. When the heat transfer takes place, the pressure drop per time is reduced. The integrity tester interprets this as a reduction of the diffusion rate.

Between t = 80 seconds and t = 135 seconds, the diffusion value is above or equal to its initial value. During this lapse of 55 seconds there is no negative impact on the test value, meaning there is no risk for a false passed test result. After 55 seconds of heating, the test value is back to its initial value. Beyond t = 135 seconds (beyond 55 seconds of heating) the test value goes below its initial value, thus generating a risk for a false passed test result that could put patients at risk.

Definitions and abbreviations

CCIT: Container closure integrity testing; used for single-use bags and other means of containing medicinal and other products

False failed test result: A failing integrity test result for an integral sample

False passed test result: A conforming integrity test result for a defective sample

False negative: A term used in sterility testing for a test giving a sterile result although the sample is unsterile. This term must not be used for integrity testing results as confusion about the meaning may occur.

False positive: A term used in sterility testing for a test giving an unsterile result although the sample is sterile. This term must not be used for integrity testing results as confusion about the meaning may occur.

FIT: Filter integrity testing; used for sterilizing grade filters, typically with a pore size of 0.2 or 0.22 µm

Sample: Generic term for a filter capsule, a filter in a filter housing, single-use bag, or a vessel

Figure 1: 10-inch filter capsule with attached temperature sensor

Test 2

The same trial performed under identical thermal conditions on a filter cartridge inside a stainless steel housing resulted in a test abortion as soon as the filter housing was put into the bucket of warm water. This was due to a hard-coded algorithm used by the integrity tester to detect unstable environmental conditions; no graph could be displayed.

Interpretation

Table A shows that the thermal expansion of stainless steel is significantly smaller than that for PP. (The thermal expansion of a given material is typically inversely proportional to its melting temperature.) In combination with stainless steel's more efficient heat transfer, this generates a quick pressure increase inside the housing when it enters the warm water that exceeds the diffusive pressure drop. In fact, if the integrity tester used for these trials detects a pressure increase of 2 millibars (mbar)/10 seconds or more, the test is aborted with an error message.

Test 3

A diffusion test under stable environmental conditions at an ambient temperature of 22°C was performed on a 10-inch filter capsule. After 135 seconds of measurement the filter capsule was entirely submerged into a bucket of water at 17°C to generate a quick temperature decrease. The diffusion curve is shown in Figure 3.

›

Interpretation

When the PP capsule enters the cold water the capsule contracts and its volume is reduced. This slows down the pressure drop per time over approximately 15 seconds, which is interpreted as a reduction in the diffusion rate by the integrity tester.

As PP does not conduct heat efficiently, heat transfer from the test gas to the water is slow. When the heat transfer takes place, pressure drop per time is increased. The integrity tester interprets this as a diffusion rate increase.

Between t = 135 seconds and t < 178 seconds, the diffusion value is below its initial value. During this lapse of 43 seconds there is a negative effect on the test value, raising the possibility of a false passed test result that could put patients at risk. After 43 seconds of cooling the test value is back to its initial value. Beyond t = 180 seconds (beyond 43 seconds of cooling) the test value goes above its initial value, generating a risk for a false failed test result without any patient risk.

Test 4

A diffusion test under stable environmental conditions at an ambient temperature of 22°C was performed on a 5-inch PP capsule (with half the wall thickness of the 10-inch capsule). After 175 seconds of measurement the filter capsule was entirely submerged into a bucket with water at 17°C to generate a quick temperature decrease. The diffusion curve is shown in Figure 4.

Interpretation

The general shape of the diffusion curve is, as expected, identical to the previous trial with the 10-inch capsule.

Differences can be seen in the contraction phase, which is shorter, and the transition from contraction to heat transfer phase, which also goes faster, thus creating a sharp "knee" rather than a slow transition. The PP wall of the 5-inch capsule is indeed thinner than for the 10-inch capsule; outer wall surface-to-gas volume ratio is greater for the 5-inch capsule. Heat transfer from the test gas to the water is therefore faster for the 5-inch capsule; the more accentuated slope of the curve indicates this.

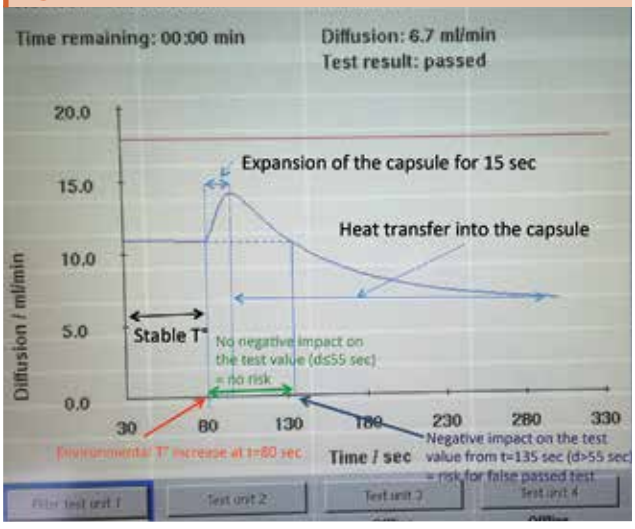
When the heat transfer takes place from the test gas to the water, the pressure drop per time increases. This is interpreted by the integrity tester as an increase of the diffusion rate and, in this particular case, a false failed test result.

Table A: Thermal expansion rates

Material	Linear coefficient α at 20°C (10^{-6} K^{-1})	Volumetric coefficient AV at 20°C (10^{-6} K^{-1})
Aluminum	23.1	69
Platinum	9	27
PP	150	450
PVC	52	156
Sitall*	0 ± 0.15	0 ± 0.45
Stainless steel	10.1 - 17.3	51.9
Steel†	11.0 - 13.0	33.0 - 39.0

* Average for –60°C to 60°C † Depends on composition

Figure 2: Test 1 diffusion curve



Test 5

A diffusion test under stable environmental conditions at an ambient room temperature of 22°C was performed on a 10-inch filter cartridge in a stainless steel housing. After 125 seconds of measurement, the filter capsule was entirely submerged into a bucket with water at 17°C to generate a quick temperature decrease (Figure 5).

Interpretation

The stainless steel housing contracts when it enters the cold water and its volume is reduced, but to a much smaller extent than the PP capsule because the thermal expansion coefficient of stainless steel is 9 times smaller than PP (Table A). In contrast to the PP capsule, therefore, the stainless steel housing does not generate any initial reduction of the measured diffusion when being cooled. The curve shows just a very short phase of slow diffusion increase as the temperature decrease of the test gas has a much greater impact than the volume reduction.

Because heat transfer is much faster for stainless steel than for PP, the air inside the housing close to the wall cools rapidly. The effect on the measured pressure drop per time gives a steep slope to the diffusion curve. When the air close to the wall has cooled, heat transfer is slower and pressure drop per time also slows. The integrity tester interprets this as reduction of the average diffusion rate.

Figures 6 and 7 summarize the behavior of these two samples. No diffusion graphs from putting stainless steel housing into hot water are available because the integrity tester interrupts the test as soon as it detects the pressure increase.

Test 6

A diffusion test under stable environmental conditions at an ambient temperature of 22°C was performed on a 10-inch filter capsule with a temperature sensor attached to the wall. After 176 seconds of measurement, one side of the capsule was exposed to a heating fan that generated a progressive temperature increase from 22°C to 71°C (Figure 8). Relative air humidity was between 40% and 60%. The difference between this trial and those that put the filter capsule in warm water is that the heat only comes from

Diffusion Test

The ideal gas law pV = nRT can be derived to:

$p_1 \times V_1 \div T_1 = p_2 \times V_2 \div T_2$

Where

p_1 = Pressure before the temperature change (e.g., 3,500 mbar absolute)

p_2 = Pressure after the temperature change

T_1 = Temperature of the test gas before the temperature change (e.g., 273 K)

T_2 = Temperature of the test gas after the temperature change (e.g., 272 K)

V_1 and V_2 = Net sample volume, considered as constant for stainless steel housings

Therefore

$p_1 \div T1 = p_2 \div T_2$

and

$p_1 \times T_2 \div T_1 = p_2$

Numerical application

3500 mbar × 272 K ÷ 273 K ≈ 3487 mbar

3487 mbar – 3500 mbar = –13 mbar

A typical pressure drop during the 5-minute diffusion test time is 50 mbar. The impact is then calculated as:

–13 ÷ 50 × 100% = –26%

The 26% pressure reduction from the temperature change results in a measured diffusion increase of 26%.

Diffusion vs. Bubble-Point Test

A diffusion test measures the drop from the specified test pressure in a known volume over a period of time. The pressure drop takes place because the test gas dissolves into the membrane wetting liquid and passes through the membrane without expelling the wetting liquid. The pressure drop is converted into diffusion, per DIN 58356 part 2:

$$\text{Diffusion} = \frac{p_1 \times V_{net}}{t \times p_{ref}} \times \ln \frac{p_1}{p_1 - \Delta p} \left[\text{ml/min}\right]$$

If there is an environmental temperature variation during the measurement phase beyond recommended limits (±1°C per 5 minutes), 5 minutes can be enough to allow a certain heat transfer to take place. Very short measurements would be less affected, due to thermal inertia, but could yield too-low pressure drops and not provide the required accuracy.

Bubble-point detection measures pressure drop in a known volume at higher and higher pressures. After each pressure increase there is a stabilization phase of about 6 seconds that compensates for an eventual thermal impact. Each pressure drop is converted into a flow value. The bubble-point detection then compares flow values at every pressure step. When an exponential increase takes place, it means that the wetting liquid has been expelled from the biggest pores. The differential pressure at which this takes place is the bubble-point value.

The bubble-point method consists of several short measurement steps with a short stabilization step in between, combined with a relative comparison between subsequent values. As a result, temperature variations are less important and could be demonstrated by a calculation similar to the diffusion. Should this be of interest, please contact the author.

Figure 3: Test 3 diffusion curve

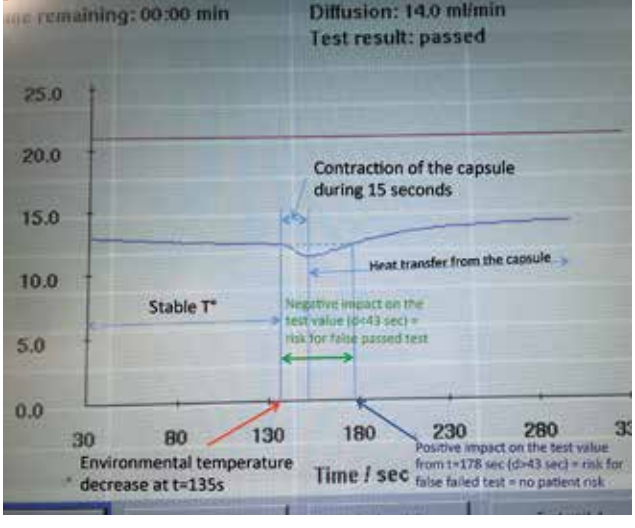
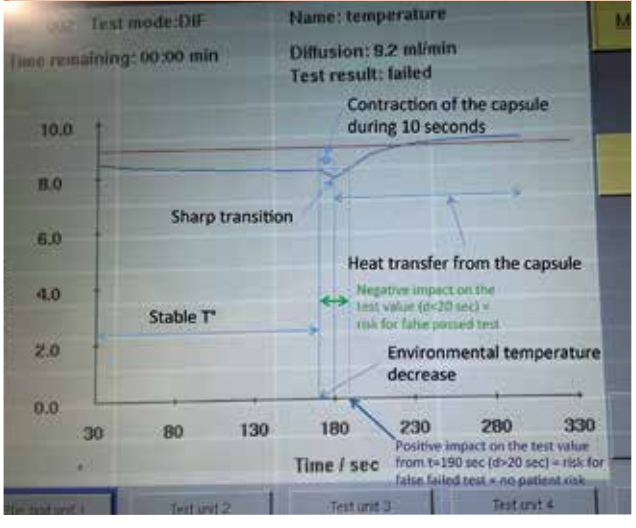


Figure 4: Test 4 diffusion curve



one side and is progressive. The humidity was also much lower, which influenced the heat transfer, and the temperature was higher, going up to 71°C.

Interpretation

With a continuous temperature increase from t = 176 seconds, there is a mix of volume increase and heat transfer until the end of the test, after the 15 seconds it takes for the heat to get through the PP wall of the filter capsule. This, combined with the poor conductivity of air inside the capsule, resulted in a much lower impact on the test result than was expected from the ideal gas law.

HEAT TRANSFER

Because air is a poor conductor of heat, there will be obvious horizontal temperature gradients inside the sample being subjected to the temperature change. Additionally, because hot air has a lower density than cold air, hot air will rise inside the sample and create vertical temperature gradients.

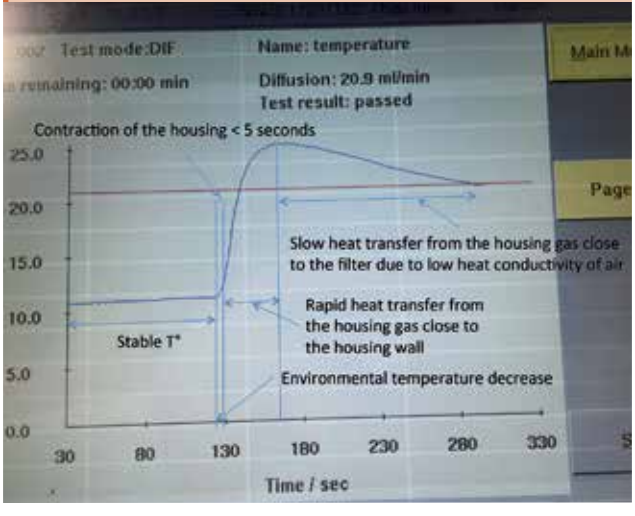
If the temperature change comes from only one side, heat transfer will generate temperature gradients as shown in Figure 9. The volume change will also be affected, because the sample will expand in an uneven way.

The effect on the test value due to expansion or retraction is dependent on the sample dimensions and net volume: Under identical environmental conditions a filter capsule with a small distance between the filter and the outer wall of the capsule will show a greater impact on the test value than a capsule of same dimensions with a large distance between the filter and the outer wall (Figure 10). The time-dependent function for volume change can be represented as f (t) ΔV (Figure 11). A sample encapsulated in a holder (e.g., single-use bag) between restraining plates further delays the heat transfer from the environment.

CONCLUSIONS AND DISCUSSION

Environmental temperature drifts may have an important effect on integrity test value and may generate false passed and false failed test results; the former can put patients' lives in danger, while the latter can contribute to drug shortages. Stable temperature is therefore a prerequisite for reliable integrity testing. Even when stable temperature is part of the standard operating procedure, however, temperature drifts can still occur.

Figure 5: Test 5 diffusion curve



STABLE TEMPERATURE IS A PREREQUISITE FOR RELIABLE INTEGRITY TESTING

Figures 6 and 7: Diffusion curves for PP and stainless steel

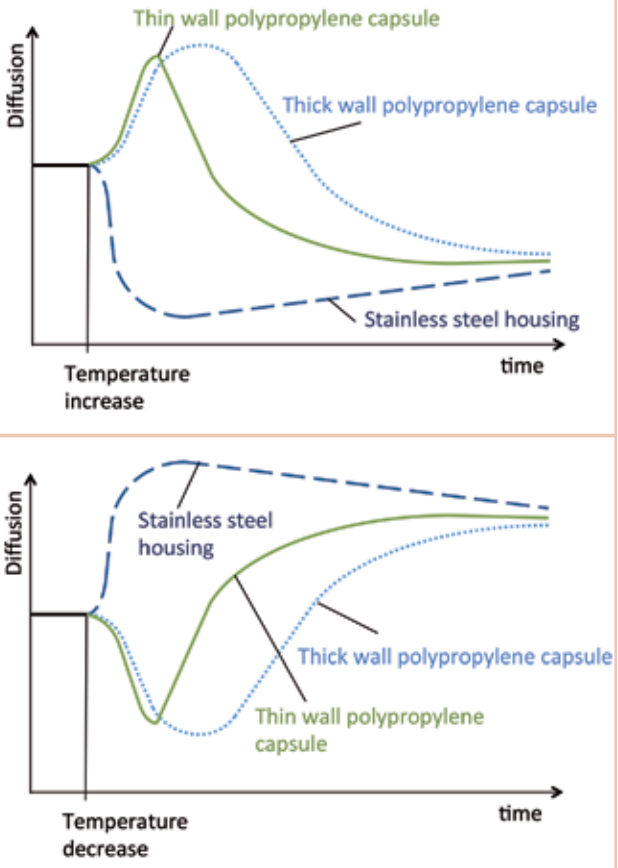


Figure 8: Measured diffusion value versus time and outer wall temperature

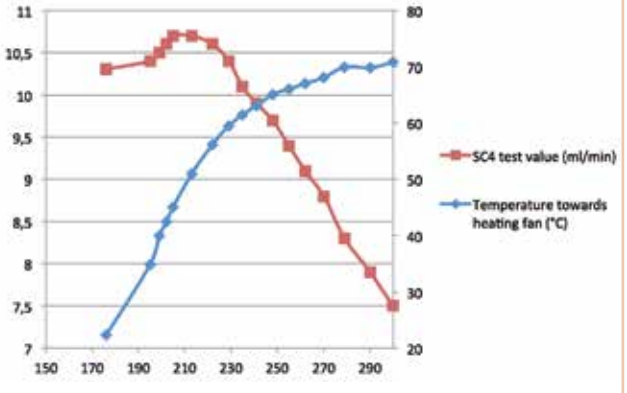


Figure 9: Uneven temperature gradients

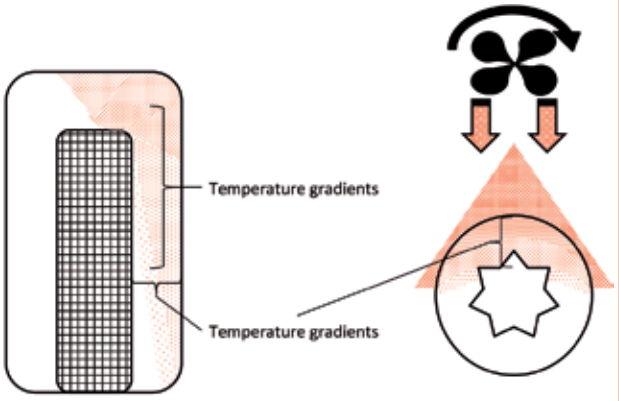
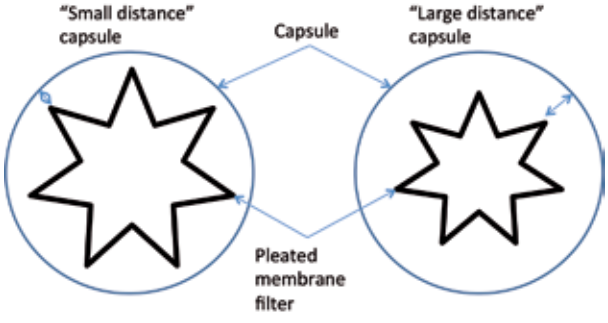


Figure 10: Gas net volume



A robust risk assessment of thermal impact (such as FMEA) on FIT and CCIT that quantifies the effects, defines preventive actions, and improves detectability will help mitigate the risk. It will also increase awareness for both operators and quality assurance.

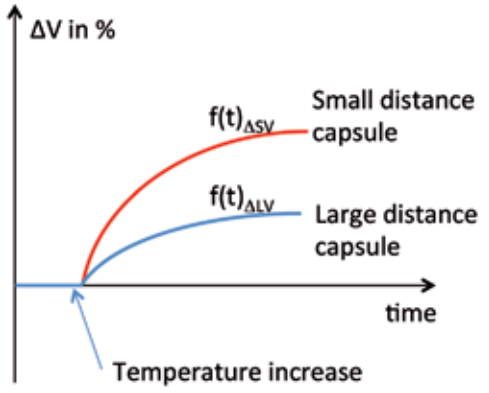
The trials discussed in this article clearly indicate that a risk assessment based solely on the ideal gas law is not adequate. Saying that a temperature decrease of the environment is not quality-critical because it could only increase the diffusion value is wrong. Thermal expansion or contraction of polymer samples (e.g., single-use filter capsules and bags) will counterbalance the prediction of the ideal gas law. Temperature gradients inside the sample will also make predictions difficult regardless of sample material.

The thermal counterbalancing effects of polymer samples apply differently for different materials; in addition, heat-transfer delay between the environment and the test gas is directly affected by wall thickness. Not taking all these parameters into account will lead to false assumptions.

Working under stable thermal conditions, and monitoring and recording temperatures at the point of use help reduce the risk for false passed and false failed test results. Temperature data could be included in the batch report. Stable environmental conditions could be defined as:

- □ Environmental temperature changes below or equal to ±1°C per 5 minutes
- □ No draft (no direct HVAC airflow)

Figure 11: Time-dependent function for volume change



- □ No direct sunlight
- □ No nearby heat sources such as autoclaves, heat-jacketed bioreactors, or warm piping

The operator must also avoid touching or moving the tubing and/or the sample being tested. Filter wetting should only be done with a liquid at ambient temperature ±1°C, unless validated.

Knowing the specific behavior of the sample when exposed to monitored temperature changes would make it possible to use software algorithms in the integrity testing device to either predict its impact on the test result or adjust the measured value to eliminate the risk for false passed and false failed results. ‹›

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About the author

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A VARIABLE SAMPLING AND ACCEPTANCE POLYGON APPROACH FOR CONTENT UNIFORMITY

Thomas Stepinac and Muhanned Saeed

We propose a method for demonstrating content uniformity in the context of variables sampling and relate this to the acceptance criteria and probability of passing the USP CU test. We demonstrate that a variable sampling plan with 99.4% coverage between 83.5% and 116.5% of label content is approximatively equivalent to (and even stricter than) the 95% probability of passing the USP test.

The views expressed in this paper are professional opinions of the authors and may not necessarily represent the position of Novartis.

To ensure the consistency of dosage units, individual batch units are controlled to achieve drug substance content within a sufficiently narrow range around the label claim. The most common test for content uniformity (CU) of dosage units is described in United States Pharmacopeia (USP) general chapter <905>.[1] The USP requirements and CU acceptance values for oral solid dosage (OSD) forms (e.g., tablets and capsules) are well known and summarized in Table A, where:

AV is the acceptance value
$\bar{x}$ is the mean of the samples (as percent of the label claim)
s is the standard deviation of the samples
k is the acceptability constant
If n = 10, then k = 2.4 (Stage 1)
If n = 30, then k = 2.0 (Stage 2)

The reference value *M*
= 98.5 if $\bar{x} < 98.5$
= 101.5 if $\bar{x} > 101.5$
= $\bar{x}$ if $98.5 < \bar{x} < 101.5$

This paper proposes a method for demonstrating CU using acceptance sampling plans and relates it to acceptance criteria and the probability of passing the USP CU test.

A variable sampling plan ensures that at least a specified proportion of a population is within a specified range with a given confidence. Variable sampling plans can be used to set acceptance criteria and support process validation or batch release. This ensures that at least a certain proportion of tablets in a batch have an assay value that falls between defined limits with a given confidence.

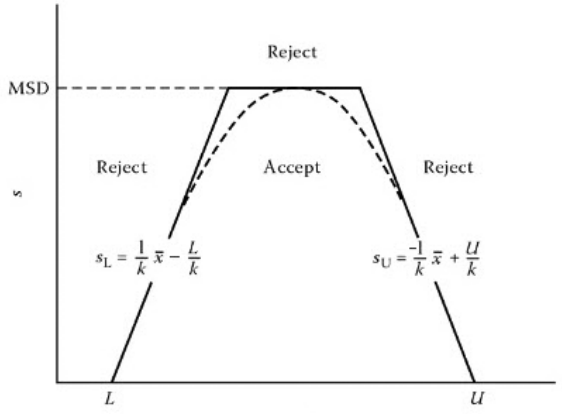
The shape of the acceptance region as a function of the mean and standard deviation of a sample can be approximated by a polygon, as shown in Figure 1. For more details, refer to Schilling.[2]

The acceptance polygon equation consists of two separate one-sided tolerance intervals with an upper limit on the maximum standard deviation (MSD):

$\bar{x} - ks > L$
$\bar{x} + ks < U$
$s < MSD$

Where:
$\bar{x}$ = sample mean
s = standard deviation
k = one-sided tolerance factor; the k value is a function of the confidence level desired, proposed coverage, and number of samples
U = upper specification limit
L = lower specification limit
MSD = (U – L) * F, where F is a tabulated value

Figure 1: Acceptance region for a variable sampling plan



Source: Acceptance Sampling in Quality Control, Second Edition, by Schilling, Edward G.; Neubauer, Dean V. Reproduced with permission of Taylor and Francis via Copyright Clearance Center.

Table A: USP <905> requirements		
Stage	Number tested	Pass if:
S1	n = 10	$AV = \lvert \bar{X} - M \rvert + ks < 15$
S2	n = 30	$AV = \lvert \bar{X} - M \rvert + ks < 15$

The lot or batch shall be considered acceptable if the applicable k and F criteria are met.

For double-sided specifications:

1. Both $(U - \bar{x})/s$ and $(\bar{x} - L)/s$ must be ≥ k to meet the k criterion
2. $s/(U - L)$ must be ≤ F to meet the F criterion

$\bar{x}$ = sample mean
s = sample standard deviation,
U = upper specification limit
L = lower specification limit

Criterion 2 can also be expressed as $s \leq s_{max}$, where $s_{max} = (U - L) * F$ is the MSD. The k and F values are shown in Tables H and I for 90% or 95% confidence and 99% coverage. For any confidence and coverage values, tables can be generated as follows:
k is the critical distance and can be calculated from the noncentral t-distribution:
$k = t^{-1}(1 - \alpha, n - 1, \phi) / \sqrt{n}$

Where:
1– α = confidence level
n = sample size
$\phi = \sqrt{n} * z_p$ = non-centrality factor (p = coverage)

F can be calculated as:

1. Find the upper tail normal area p** corresponding to $z_p^* = k$
2. Find z_p^{**} corresponding to a normal upper tail area of p**/2
3. $F = 1 / (2\ z_p^{**})$

Example (in R) for n = 30 with 95% confidence and 99% coverage (from Table I):
k = qt (0.95, 29, 12.74193) / sqrt (30) = 3.063901
p** = 1 – pnorm (3.063901) = 0.001092356
z_p^{**} = qnorm (0.001092356 / 2, lower.tail = F) = 3.265592
F = 1 / (2* 3.265592) = 0.1531116

For details see Schilling and Natrella.[2–3]

EXAMPLES

The following section shows two examples to illustrate the method. The first represents simple sampling; the second shows stratified sampling with repeated measurements per location.

Single sample

We want to demonstrate with 95% confidence that 99% of a batch assay is between 85 and 115. (We will show later that this corresponds to > 97% probability of passing the USP test with 95% confidence.)

One sample was taken at 15 locations during the process (Tables B and C). We can therefore state with 95% confidence that 99% of the batch is between 85 and 115, and that acceptance criteria for validation have been met.

Multiple samples

We want to demonstrate with 95% confidence that 99% of a batch is between 85 and 115.

Duplicate samples (j = 2) were taken from 15 locations (i = 15) for a total of 30 samples (Table D). First the within, between, and overall standard deviations were estimated by variance component analysis. This can be done easily with statistical software such as Minitab (Table E):

The associated degrees of freedom are:

- Between location: i – 1 = 14
- Within location: i (j – 1) = 15

Total was calculated using Satterthwaite approximation:

$$df_{tot} = \frac{(\sigma_T^2)^2}{\frac{(\frac{\sigma_R^2 + J^*\sigma_L^2}{J})^2}{(I-1)} + \frac{(\sigma_R^2(1-\frac{1}{J}))^2}{I(J-1)}}$$

$$df_{tot} = \frac{(10.223)^2}{\frac{(\frac{5.72 + 2^*4.503}{2})^2}{(15-1)} + \frac{(5.72(1-\frac{1}{2}))^2}{15(2-1)}} = 23.66 \approx 24$$

The calculation of the acceptance test is shown in Table F. Therefore, we can state with 95% confidence that 99% of the batch is between 85 and 115 and that the acceptance criteria for validation are met. This corresponds to > 97% probability of passing the USP <905> with 95% confidence.

ACCEPTANCE REGIONS AND OC CURVES

The purpose of validation is to provide a high degree of assurance that a process will consistently produce a product that meets its specifications and quality characteristics. For the USP <905> CU test, one approach is the "Bergum method"[4] (named after its inventor), which is the basis of ASTM Standard E2810.[5]

Our proposed alternative to this standard, based on the concepts of acceptance sampling, is easier to use and can be applied to any number of tested samples. The concept of acceptance sampling is easy to understand and easy to justify as it is standard in quality control.

Tolerance interval methodology can be used to set acceptance criteria for validation or release[2] and relates to variable acceptance sampling plans. When using acceptance sampling by variables, the acceptance region can be approximated by a polygon;[8] this is the so-called "k method" for double-sided specification limits.[2] In this article we will link the probability of passing the USP test to the statistical confidence level and coverage of a variable sampling plan.

We will demonstrate that a variable sampling plan with 99.4% coverage between 83.5 and 116.5 is approximatively equivalent to (and even stricter than) the 95% probability of passing the USP test.

Constructing the acceptance region

USP requirements and CU acceptance criteria for OSD forms are given in Table A. For the first Stage, 10 samples are taken and an acceptance value is calculated that must be smaller than 15. If this acceptance criterion is met,

Figure 2: USP Stages 1 + 2 acceptance region

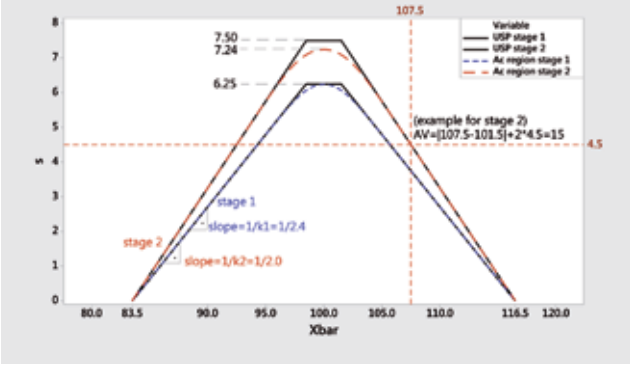


Figure 3: Acceptance region plot and OC curves

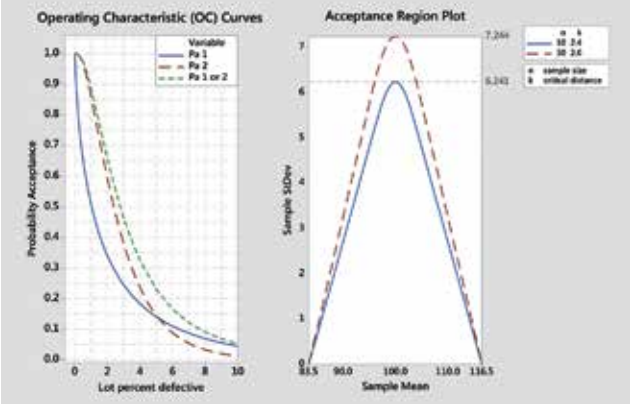


Figure 4: Rescaled acceptance region

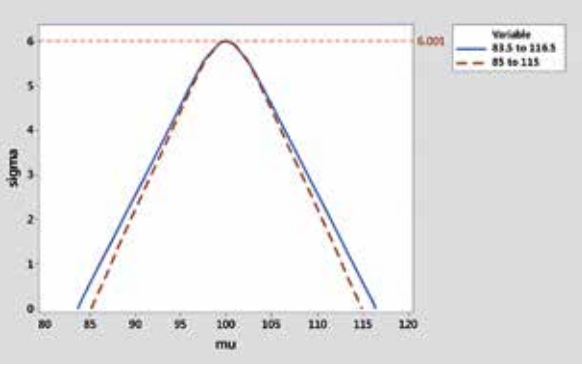


Figure 5: OC curves for multiple numbers of samples

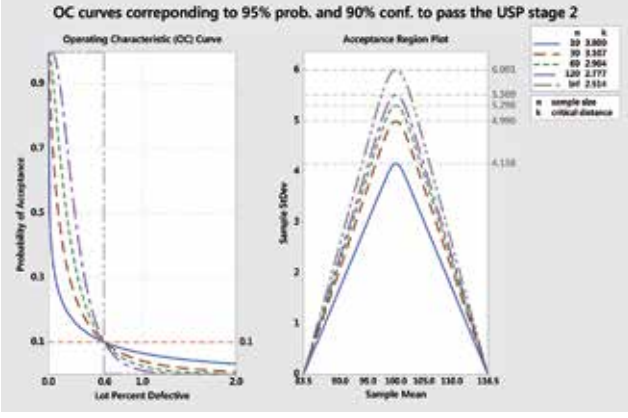
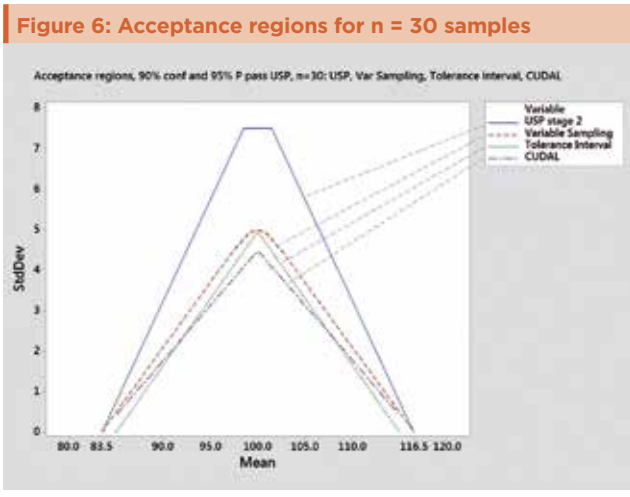


Figure 6: Acceptance regions for n = 30 samples



the test is passed. If this acceptance criterion is not met, another 20 samples are taken and an acceptance value on the total of 30 samples is calculated. If this acceptance criterion is met the test is passed. The probability of passing the test is the combined probability of passing Stage 1 or Stage 2.

The geometric region where the USP CU test acceptance criteria are fulfilled can be represented as a function of the measured mean $\bar{x}$ and standard deviations (Figure 2). Each point on the acceptance curve corresponds to an acceptance value (AV) of 15. Any point on or below the acceptance curve would pass the test (AV ≤ 15) and each point above would fail it. This acceptance region resembles the acceptance polygon of a variable sampling plan from Figure 1. Note that the standard deviation converges to zero when the mean is 83.5 or 116.5. This is why we will take 83.5 to 116.5 as our limits.

Stage 1 can be approximated with a variable sampling plan with n = 10 samples, critical distance k = 2.4, and limits between 83.5 and 116.5. Stage 2 can be approximated with a variable sampling plan with n = 30 samples, critical distance k = 2.0, and limits between 83.5 and 116.5. This is a conservative approximation, as the acceptance region is always smaller and within the USP acceptance region. (Stage 1 and Stage 2 of the USP are shown in Figure 2 as black polygons.)

All points on the polygon have an acceptance value of 15, all points inside have an acceptance value < 15, and all points above have an acceptance value > 15. Figure 2 shows an acceptance value of 15. This geometric region can be approximated by a double-variable sampling plan with Stage 1 having n = 10 samples and critical distance k = 2.4 for limits between 83.5 and 116.5, and Stage 2 having n = 30 samples and critical distance k = 2.4 for limits between 83.5 and 116.5.

Each variable sampling plan (for n = 10 and n = 30) has an operation characteristic (OC) curve. This shows how the probability of acceptance for a lot, which is based on the sampling plan utilized and changes with the percent defective of a lot (quality). The OC curves for Stage 1 (approximated), Stage 2, and combined Stages 1 + 2 are shown in Figure 3.

Table B: Single sample method

Location	Sample
1	98.1
2	98.6
3	101.8
4	94.2
5	94.5
6	96.5
7	97.4
8	92.4
9	96.9
10	98.2
11	94
12	96.7
13	96.1
14	99.7
15	102.6

Table C: Single sample results

Name	Variable or Formula	Value
Number of samples	n	15
Sample average	$\bar{X}$	97.18
Sample standard deviation	s	2.828
Lower specification limits	L	85
Upper specification limits	U	115
k value (from Table I)	k	3.52
F value (from Table I)	F	0.1351
Maximum standard deviation	smax or MSD = (U – L) * F	(115-85) * 0.1351 = 4.053
Lower quality index	$Q_L = (\bar{X} - L) / s$	(97.18-85) / 2.828 = 4.307
Upper quality index	$Q_U = (U - \bar{X}) / s$	(115-97.18) / 2.828 = 6.301
Lower limit acceptance criterion	$Q_L > k$	4.307 > 3.52 (pass)
Upper limit acceptance criterion	$Q_U > k$	6.301 > 3.52 (pass)
s_{max} acceptance criterion	$s < s_{max}$	2.828 < 4.053 (pass)

Table D: Multiple samples method

Location	Sample 1	Sample 2
1	100.1	103.0
2	98.9	101.66
3	99.6	97.9
4	101.8	100.8
5	102.4	104.6
6	98.7	101.1
7	99.2	99.5
8	99.5	96.5
9	99.3	97.3
10	99.8	104.6
11	102.8	108.6
12	106.8	103.5
13	102	102.1
14	96.2	100.5
15	109.1	102.6

The Stage 2 OC (red) is stricter than the combined Stages 1+2 OC (green). Furthermore, the green curve can only be calculated numerically. It is therefore an acceptable approximation to consider only the Stage 2 of the USP CU test. This corresponds to a critical k = 2 distance and 30 samples.

The probability of passing only Stage 2 of the USP CU test will always be smaller than the probability of passing the combined Stages 1 + 2 test, as seen when comparing the red to the green curve in Figure 3.

Characterizing the USP CU test based on the probability of passing Stage 2 only, therefore, is a conservative but valid approximation. Furthermore, the combined Stages 1 + 2 can only be computed numerically while the red OC has an analytical solution and can be described by the noncentral t distribution.

$P_{(pass\ stage\ 2)}$ = 1 – pt (2 * sqrt (30), 29, qnorm (1 – LotFractionDefective) * sqrt (30))

Example: For 0.6% tablets outside the 83.5 to 116.5 interval, the probability to pass the USP Stage 2 is:

1 – pt (2 * sqrt (30), 29, qnorm (1 – 0.006) * sqrt (30)) = 0.9493999 ≈ 0.95

This establishes a correspondence between the probability of passing the Stage 2 USP CU test (95%) and the proportion of samples inside the 83.5–116.5 interval (99.403%). The 95% probability of passing combined Stages 1 + 2, computed numerically, is 99.34. The probability of passing Stage 2 or the combined Stages 1 + 2 is fairly close in the upper domain of the OC curve. The probability of passing the USP versus the coverage between 83.5 to 116.5 is given in Table G.

Table E: Variance component analysis

Source	Variance components	% total	SD
Location	4.503	44.05	2.122
Error	5.720	55.95	2.392
Total	10.223		3.197

Figure 4 shows rescaled acceptance regions for 95% probability passing the USP with 83.5 to 116.5 limits and 85 to 115 limits (100% confidence for infinite number of samples). The acceptance region is smaller with the narrower border, especially when the mean is close to the border.

Since the real mean and standard deviation are unknown but estimated from a finite number of samples, we need to add a confidence level (typically 90 or 95% in cases of process validation).

Figure 5 shows OC curves corresponding to 95% probability and 90% confidence to pass the USP Stage 2 for various numbers of samples. We can clearly see that this corresponds to a variable sampling plan with a rejectable quality level (β = 10%) at 0.6% lot percent defectives. In other words, a batch with 0.6% points outside the 83.5 to 116.5 interval (or 99.4% inside) has a 90% chance of being rejected (or 10% chance of being accepted).

The critical distance k and MSD for varying numbers of samples and 99.4% coverage between 83.5 and 116.5 (corresponding to > 95% of prob-

Table F: Acceptance test calculation

Name	Formula	Value
Number of samples	$n \approx df_{tot}$	24.0
Sample average	$\bar{X}$	101.35
Sample standard deviation	s	3.197
Lower specification limits	L	85.0
Upper specification limits	U	115.0
k value (from Table I)	k	3.181
F value (from Table I)	F	0.1481
Maximum standard deviation	s_{max} or MSD = (U – L) * F	(115 – 85) * 0.1481 = 4.443
Lower quality index	$Q_L = (\bar{X} - L) / s$	(101.35 – 85) / 3.197 = 5.514
Upper quality index	$Q_U = (U - \bar{X}) / s$	(115 – 101.35) / 3.197 = 4.270
Lower limit acceptance criterion Upper limit acceptance criterion s_{max} acceptance criterion	$Q_L > k$ $Q_U > k$ $s < s_{max}$	5.514 > 3.181 (pass) 4.270 > 3.181 (pass) 3.197 < 4.443 (pass)

ability of passing the USP) are given in Tables J and K for 90% and 95% confidence.

These acceptance criteria provide an alternative to the ASTM approach by simply employing variables sampling plans.

MATCHING THE ACCEPTANCE REGION

Some practitioners might argue that the range from 83.5 to 116.5 used by current USP is too large. In the following example, we rescaled the acceptance criteria to 85–115 by matching the acceptance region at the MSD. We previously shown that 99.403% coverage between 83.5 and 116.5 corresponds to more than 95% probability to pass the USP test when the number of samples is infinite. This corresponds to a critical distance k = 2.514 and MSD = 6.001. When we are on target with a mean at 100 and a standard deviation of 6.001, the proportion inside the 85–115 interval is 98.76%, which would be the new coverage. The corresponding k value, the left tailed quantile of normal distribution corresponding to 98.76% coverage, is 2.243. Table L gives the coverage between 85 and 115 for various probabilities of passing the USP.

Note that the rescaled acceptance region is always more conservative than the original one between 83.5 and 116.5, especially when the mean is close to the limit. Figure 4 shows the acceptance regions for 83.5–116.5 and 85–115 for an MSD of 6.001.

Table L shows a few interesting test properties:

- 96% coverage between 85% to 115% and 50% confidence corresponds approximately to 50% probability to pass the USP test with 50% confidence. This could be a minimal requirement for releasing batches and could be used, for instance, in PAT application when more than 30 samples are taken.
- 99% coverage between 85% to 115% corresponds approximately to 97% probability to pass the USP test. The confidence is typically chosen at 90% or 95%, since round numbers that are easy to justify and acceptance tables with 99% percent coverage are readily available.

DISCUSSION

Variable sampling vs. ASTM E2810

Bergum[4] published a method for constructing acceptance limits that relate directly to the probability of passing the USP test. These acceptance limits are defined to provide, with a confidence level (1 – α), a stated probability (P) of passing the USP test. This approach was incorporated in the ASTM Standard E2810.[5]

Table G: Probability of passing USP Stages 1, 2, and 1+2 vs. coverage between 83.5 to 116.5

Probability passing USP test	Stage 1 (n = 10) exact			Stage 2 (n = 30) exact			Stages 1 + 2 (n = 30) numeric		
	Cov % (83.5–116.5)	k	MDS	Cov % (83.5–116.5)	k	MDS	Cov % (83.5–116.5)	k	MDS
99	99.995	3.898	4.061	99.69	2.741	5.571	99.67	2.716	5.616
98	99.989	3.705	4.256	99.60	2.65	5.736	99.56	2.617	5.798
97	99.983	3.583	4.388	99.52	2.592	5.846	99.48	2.559	5.911
96	99.976	3.492	4.492	99.46	2.549	5.931	99.4	2.515	6
95	99.969	3.419	4.58	99.40	2.514	6.001	99.34	2.479	6.074
90	99.923	3.168	4.904	99.17	2.394	6.254	99.07	2.355	6.341
85	99.866	3.001	5.146	98.97	2.314	6.435	98.84	2.271	6.536
80	99.795	2.87	5.353	98.78	2.25	6.585	98.62	2.204	6.698
75	99.709	2.758	5.542	98.60	2.196	6.718	98.41	2.147	6.843
70	99.607	2.658	5.721	98.41	2.147	6.842	98.19	2.095	6.98
65	99.487	2.567	5.896	98.22	2.102	6.96	97.97	2.047	7.111
60	99.344	2.48	6.07	98.03	2.06	7.075	97.73	2.001	7.241
55	99.175	2.397	6.246	97.83	2.019	7.19	97.48	1.957	7.371
50	98.973	2.316	6.429	97.61	1.979	7.306	97.21	1.913	7.504

Table H: 90% confidence that 99% of population is between limits

Acceptance criteria: $\bar{X}$ + ks <U; $\bar{X}$ – ks > L; s_{max} = F * (U – L)

n	k	F	n	k	F	n	k	F	n	k	F
10	3.532	0.1347	40	2.793	0.1661	70	2.662	0.1731	100	2.601	0.1767
11	3.443	0.1379	41	2.786	0.1665	71	2.66	0.1733	101	2.599	0.1767
12	3.371	0.1406	42	2.78	0.1668	72	2.657	0.1734	102	2.598	0.1768
13	3.309	0.1429	43	2.773	0.1671	73	2.654	0.1736	103	2.596	0.1769
14	3.257	0.145	44	2.767	0.1675	74	2.652	0.1737	104	2.595	0.177
15	3.212	0.1468	45	2.761	0.1678	75	2.649	0.1739	105	2.594	0.1771
16	3.172	0.1485	46	2.756	0.1681	76	2.647	0.174	106	2.592	0.1772
17	3.137	0.1499	47	2.75	0.1684	77	2.644	0.1742	107	2.591	0.1772
18	3.105	0.1513	48	2.745	0.1686	78	2.642	0.1743	108	2.589	0.1773
19	3.077	0.1525	49	2.74	0.1689	79	2.64	0.1744	109	2.588	0.1774
20	3.052	0.1537	50	2.735	0.1692	80	2.638	0.1745	110	2.587	0.1775
21	3.028	0.1547	51	2.73	0.1694	81	2.635	0.1747	111	2.585	0.1776
22	3.007	0.1557	52	2.726	0.1697	82	2.633	0.1748	112	2.584	0.1776
23	2.987	0.1566	53	2.721	0.1699	83	2.631	0.1749	113	2.583	0.1777
24	2.969	0.1574	54	2.717	0.1701	84	2.629	0.175	114	2.582	0.1778
25	2.952	0.1582	55	2.713	0.1704	85	2.627	0.1751	115	2.58	0.1779
26	2.937	0.159	56	2.709	0.1706	86	2.625	0.1753	116	2.579	0.1779
27	2.922	0.1597	57	2.705	0.1708	87	2.623	0.1754	117	2.578	0.178
28	2.909	0.1603	58	2.701	0.171	88	2.621	0.1755	118	2.577	0.1781
29	2.896	0.1609	59	2.697	0.1712	89	2.619	0.1756	119	2.576	0.1781
30	2.884	0.1615	60	2.694	0.1714	90	2.618	0.1757	120	2.574	0.1782
31	2.872	0.1621	61	2.69	0.1716	91	2.616	0.1758	150	2.546	0.1799
32	2.862	0.1626	62	2.687	0.1718	92	2.614	0.1759	200	2.514	0.1818
33	2.852	0.1631	63	2.683	0.172	93	2.612	0.176	300	2.478	0.1841
34	2.842	0.1636	64	2.68	0.1722	94	2.611	0.1761	400	2.456	0.1855
35	2.833	0.1641	65	2.677	0.1723	95	2.609	0.1762	500	2.442	0.1864
36	2.824	0.1645	66	2.674	0.1725	96	2.607	0.1763	1,000	2.407	0.1887
37	2.816	0.1649	67	2.671	0.1727	97	2.606	0.1764	2,000	2.383	0.1903
38	2.808	0.1653	68	2.668	0.1728	98	2.604	0.1765	3,000	2.372	0.191
39	2.8	0.1657	69	2.665	0.173	99	2.602	0.1766	Inf	2.326	0.1941

Table I: 95% confidence that 99% of population is between limits

Acceptance criteria: $\bar{X}$ + ks < U; $\bar{X}$ – ks > L; s_{max} = F * (U – L)

n	k	F	n	k	F	n	k	F	n	k	F
10	3.981	0.1207	40	2.941	0.1588	70	2.765	0.1675	100	2.684	0.1719
11	3.852	0.1244	41	2.932	0.1592	71	2.762	0.1677	101	2.682	0.1721
12	3.747	0.1276	42	2.923	0.1596	72	2.758	0.1679	102	2.68	0.1722
13	3.659	0.1304	43	2.914	0.16	73	2.755	0.1681	103	2.678	0.1723
14	3.585	0.1329	44	2.906	0.1604	74	2.751	0.1683	104	2.676	0.1724
15	3.52	0.1351	45	2.898	0.1608	75	2.748	0.1685	105	2.674	0.1725
16	3.464	0.1371	46	2.89	0.1612	76	2.745	0.1686	106	2.672	0.1726
17	3.414	0.1389	47	2.883	0.1616	77	2.742	0.1688	107	2.671	0.1727
18	3.37	0.1406	48	2.876	0.1619	78	2.739	0.169	108	2.669	0.1728
19	3.331	0.1421	49	2.869	0.1623	79	2.736	0.1691	109	2.667	0.1729
20	3.295	0.1435	50	2.862	0.1626	80	2.733	0.1693	110	2.665	0.173
21	3.263	0.1447	51	2.856	0.1629	81	2.73	0.1694	111	2.663	0.1731
22	3.233	0.1459	52	2.85	0.1632	82	2.727	0.1696	112	2.662	0.1732
23	3.206	0.147	53	2.844	0.1635	83	2.724	0.1697	113	2.66	0.1733
24	3.181	0.1481	54	2.838	0.1638	84	2.721	0.1699	114	2.658	0.1734
25	3.158	0.149	55	2.833	0.1641	85	2.719	0.17	115	2.657	0.1735
26	3.136	0.15	56	2.827	0.1644	86	2.716	0.1702	116	2.655	0.1735
27	3.116	0.1508	57	2.822	0.1646	87	2.714	0.1703	117	2.654	0.1736
28	3.098	0.1516	58	2.817	0.1649	88	2.711	0.1705	118	2.652	0.1737
29	3.08	0.1524	59	2.812	0.1651	89	2.709	0.1706	119	2.651	0.1738
30	3.064	0.1531	60	2.807	0.1654	90	2.706	0.1707	120	2.649	0.1739
31	3.048	0.1538	61	2.802	0.1656	91	2.704	0.1709	150	2.611	0.176
32	3.034	0.1545	62	2.798	0.1659	92	2.701	0.171	200	2.57	0.1785
33	3.02	0.1551	63	2.793	0.1661	93	2.699	0.1711	300	2.523	0.1813
34	3.007	0.1557	64	2.789	0.1663	94	2.697	0.1712	400	2.495	0.183
35	2.995	0.1562	65	2.785	0.1665	95	2.695	0.1714	500	2.476	0.1842
36	2.983	0.1568	66	2.781	0.1667	96	2.692	0.1715	1,000	2.43	0.1871
37	2.972	0.1573	67	2.777	0.1669	97	2.69	0.1716	2,000	2.399	0.1892
38	2.961	0.1578	68	2.773	0.1672	98	2.688	0.1717	3,000	2.385	0.1901
39	2.951	0.1583	69	2.769	0.1674	99	2.686	0.1718	Inf	2.326	0.1941

While our variable sampling plan and the ASTM approach have similarities and fulfill the same purpose, the variable sampling plan has several advantages, in our view:

- An acceptance polygon is easy to calculate and is defined by just two numbers: the critical distance k and the MSD. There is no need for computer-generated acceptance tables as with the ASTM method. Acceptance criteria can easily be derived for any sample size.
- Our generalized approach relates the probability of passing the CU directly to the distribution of the batch and the USP. This is less abstract than the ASTM and allows a better understanding of the process.

Variable sampling vs. tolerance intervals

Tolerance intervals, another alternative to the ASTM E2810, have recently been discussed in the literature.[7] Bergum[6] proposed a double-sided tolerance interval method and a coverage of 98.58% between 85% and 115% corresponding to 95% probability of passing the USP. When rescaling our results for 95% probability of passing the USP Stage 2 or the combined Stages 1 + 2 to an interval between 85% and 115%, we found coverages of 98.76% and 98.64%, respectively—fairly close to Bergum´s value of 98.58%. The value of 98.76% was derived analytically, while the values of 98.64% or 98.58% (combined Stages 1 + 2) are based on numeric simulations.

Bergum[6] showed that the shape of the OC curve is very strongly dependent on the position of the mean, while in our work it is not. This is because Bergum's OC curve calculations are based on an 85%–115% range, while the USP test was conceived with an 83.5%–116.5% limit (Figure 2). Bergum also used the USP acceptance regions (black polygon in Figure 2), while we used the more conservative acceptance region of a variable sampling plan that best matches the USP.

In Figure 6, we compared different acceptance regions corresponding to 95% probability and 90% confidence to pass the USP for n = 30 samples. We compared the content uniformity and dissolution acceptance limit (CUDAL)/ASTM acceptance region, a variable sampling plan with critical

Table J: 90% confidence and 99.403% coverage between 83.5-116.5 (corresponding to 95% probability of passing USP <905> with 90% confidence.
Acceptance criteria: $\bar{X}$ + ks < 116.5; $\bar{X}$ – ks > 83.5; s < MSD

n	k	MSD	n	k	MSD	n	k	F	n	k	MSD
10	3.8	4.158	40	3.01	5.133	70	2.871	5.351	100	2.805	5.46
11	3.705	4.255	41	3.003	5.144	71	2.868	5.356	101	2.804	5.463
12	3.627	4.339	42	2.996	5.154	72	2.865	5.361	102	2.802	5.466
13	3.562	4.412	43	2.989	5.165	73	2.862	5.365	103	2.801	5.468
14	3.506	4.476	44	2.982	5.175	74	2.86	5.37	104	2.799	5.471
15	3.457	4.533	45	2.976	5.184	75	2.857	5.374	105	2.798	5.474
16	3.415	4.584	46	2.97	5.194	76	2.854	5.378	106	2.796	5.476
17	3.377	4.631	47	2.964	5.203	77	2.852	5.383	107	2.795	5.479
18	3.343	4.673	48	2.959	5.211	78	2.849	5.387	108	2.793	5.481
19	3.313	4.711	49	2.953	5.22	79	2.847	5.391	109	2.792	5.484
20	3.286	4.746	50	2.948	5.228	80	2.845	5.395	110	2.79	5.486
21	3.261	4.779	51	2.943	5.236	81	2.842	5.398	111	2.789	5.488
22	3.238	4.809	52	2.938	5.244	82	2.84	5.402	112	2.788	5.491
23	3.217	4.837	53	2.933	5.251	83	2.838	5.406	113	2.786	5.493
24	3.198	4.863	54	2.929	5.258	84	2.836	5.41	114	2.785	5.495
25	3.18	4.888	55	2.924	5.265	85	2.833	5.413	115	2.784	5.498
26	3.163	4.911	56	2.92	5.272	86	2.831	5.417	116	2.782	5.5
27	3.148	4.933	57	2.916	5.279	87	2.829	5.42	117	2.781	5.502
28	3.133	4.953	58	2.912	5.285	88	2.827	5.424	118	2.78	5.504
29	3.12	4.972	59	2.908	5.292	89	2.825	5.427	119	2.779	5.506
30	3.107	4.991	60	2.904	5.298	90	2.823	5.43	120	2.777	5.508
31	3.095	5.008	61	2.9	5.304	91	2.821	5.433	150	2.747	5.561
32	3.083	5.025	62	2.897	5.31	92	2.819	5.437	200	2.713	5.621
33	3.072	5.04	63	2.893	5.315	93	2.818	5.44	300	2.675	5.691
34	3.062	5.055	64	2.89	5.321	94	2.816	5.443	400	2.652	5.733
35	3.052	5.07	65	2.886	5.326	95	2.814	5.446	500	2.637	5.762
36	3.043	5.083	66	2.883	5.331	96	2.812	5.449	1,000	2.599	5.832
37	3.034	5.096	67	2.88	5.337	97	2.81	5.452	2,000	2.574	5.882
38	3.026	5.109	68	2.877	5.342	98	2.809	5.455	3,000	2.563	5.904
39	3.018	5.121	69	2.874	5.347	99	2.807	5.457	Inf	2.514	6.001

Table K: 95% confidence and 99.403% coverage between 83.5-116.5 (corresponding to 95% probability of passing USP <905> with 95% confidence.
Acceptance criteria: $\bar{X}$ + ks < 116.5; $\bar{X}$ – ks > 83.5; s < MSD

n	k	MSD	n	k	MSD	n	k	F	n	k	MSD
10	4.28	3.723	40	3.167	4.905	70	2.98	5.178	100	2.894	5.314
11	4.142	3.839	41	3.157	4.919	71	2.976	5.184	101	2.892	5.318
12	4.029	3.939	42	3.148	4.933	72	2.973	5.19	102	2.889	5.321
13	3.935	4.026	43	3.139	4.945	73	2.969	5.195	103	2.887	5.325
14	3.855	4.103	44	3.13	4.958	74	2.965	5.201	104	2.885	5.328
15	3.786	4.172	45	3.121	4.97	75	2.962	5.206	105	2.883	5.331
16	3.726	4.234	46	3.113	4.981	76	2.958	5.212	106	2.881	5.334
17	3.673	4.29	47	3.105	4.992	77	2.955	5.217	107	2.879	5.337
18	3.626	4.341	48	3.098	5.003	78	2.952	5.222	108	2.877	5.341
19	3.583	4.388	49	3.091	5.014	79	2.949	5.227	109	2.876	5.344
20	3.545	4.431	50	3.084	5.024	80	2.945	5.232	110	2.874	5.347
21	3.511	4.47	51	3.077	5.034	81	2.942	5.237	111	2.872	5.35
22	3.479	4.507	52	3.07	5.043	82	2.939	5.242	112	2.87	5.353
23	3.45	4.542	53	3.064	5.053	83	2.936	5.246	113	2.868	5.356
24	3.424	4.574	54	3.058	5.062	84	2.933	5.251	114	2.867	5.358
25	3.399	4.604	55	3.052	5.07	85	2.931	5.255	115	2.865	5.361
26	3.376	4.632	56	3.046	5.079	86	2.928	5.26	116	2.863	5.364
27	3.355	4.659	57	3.04	5.087	87	2.925	5.264	117	2.861	5.367
28	3.335	4.684	58	3.035	5.095	88	2.922	5.268	118	2.86	5.37
29	3.316	4.708	59	3.03	5.103	89	2.92	5.273	119	2.858	5.372
30	3.298	4.73	60	3.025	5.111	90	2.917	5.277	120	2.857	5.375
31	3.282	4.752	61	3.02	5.118	91	2.915	5.281	150	2.816	5.442
32	3.266	4.772	62	3.015	5.126	92	2.912	5.285	200	2.772	5.517
33	3.252	4.791	63	3.01	5.133	93	2.91	5.289	300	2.723	5.604
34	3.238	4.81	64	3.006	5.14	94	2.907	5.292	400	2.693	5.658
35	3.224	4.827	65	3.001	5.146	95	2.905	5.296	500	2.673	5.695
36	3.212	4.844	66	2.997	5.153	96	2.903	5.3	1,000	2.624	5.785
37	3.2	4.861	67	2.992	5.159	97	2.9	5.304	2,000	2.591	5.848
38	3.189	4.876	68	2.988	5.166	98	2.898	5.307	3,000	2.577	5.877
39	3.178	4.891	69	2.984	5.172	99	2.896	5.311	Inf	2.514	6.001

distance k = 3.107 corresponding to 99.4 coverage between 83.5 and 116.5, and a double-sided tolerance interval corresponding to 98.58% coverage between 85 and 115. For comparison, the acceptance region corresponding to USP Stage 2 is also given.[6]

Differences in shape between these acceptance regions are apparent. The acceptance region calculated by CUDAL/ASTM E2810 is the narrowest, arising from the very conservative way the confidence limits are calculated using Lindgren´s simultaneous confidence region.[4] This acceptance region has a triangular shape and converges to zero at 83.5 and 116.5, like the USP test. Bergum's tolerance interval approach and our variable sampling approach nearly match at the s_{max}. The tolerance interval approach is more restrictive, however, with a triangular acceptance region, while the variable sampling plan acceptance region is elliptical (can be approximated by a trapezoidal polygon) and larger.

CONCLUSION

We derived a relationship between the probability of passing the USP and a variable sampling plan ensuring with a certain confidence that a certain proportion of values are between certain limits. The limits of the USP CU are between 83.5 and 116.5%, but narrower limits like 85% to 115% (or others) are also possible.

To assess the capability of intrabatch CU within process validation, different confidence and coverage values and interval ranges (corresponding to various probabilities of passing the USP test) are possible. We suggest taking typically 90% or 95% confidence and 99.4% coverage between 83.5% and 116.5%. This most closely matches 95% probability of passing the USP CU. A more conservative value would be 99% of tablets between 85 and 115. This corresponds to > 97% probability to pass the USP.

We recommend taking 30 samples, with 15 being a minimum. The smaller the sample size, the higher the risk to fail validation as the size of the acceptance region shrinks with a decreasing number of samples.

Table L: Matching the acceptance region at S_{max}

Probability of passing USP Stage 2	S_{max}	k = 1/slope 83.5–116.5	Coverage % 83.5–116.5	k = 1/slope 85–115	Coverage % 85–115
99	5.571	2.741	99.69	2.453	99.29
98	5.736	2.65	99.60	2.369	99.11
97	5.846	2.592	99.52	2.316	98.97
96	5.931	2.549	99.46	2.276	98.86
95	6.001	2.514	99.40	2.244	98.76
90	6.254	2.394	99.17	2.133	98.35
85	6.435	2.314	98.97	2.059	98.02
80	6.585	2.25	98.78	2	97.73
75	6.718	2.196	98.60	1.95	97.44
70	6.842	2.147	98.41	1.906	97.16
65	6.96	2.102	98.22	1.864	96.89
60	7.075	2.06	98.03	1.825	96.6
55	7.19	2.019	97.83	1.787	96.3
50	7.306	1.979	97.61	1.75	95.99

Another advantage of this method is that it is also easily applicable when there are several samples per location.

This paper provides a clear methodology to assess intrabatch capability based on total observed variability. Further controls on location means stratified sampling can also be pursued to protect against undesirable within-batch trends that cannot be controlled by capability assessment alone. ‹›

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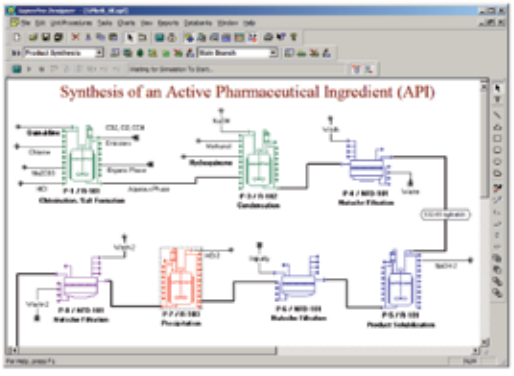

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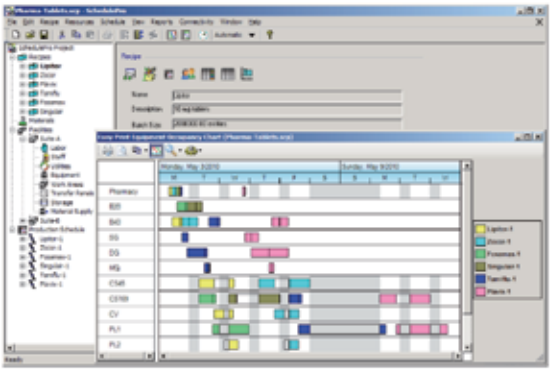

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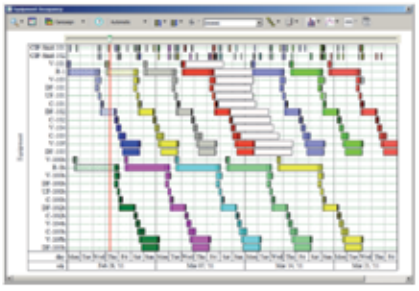

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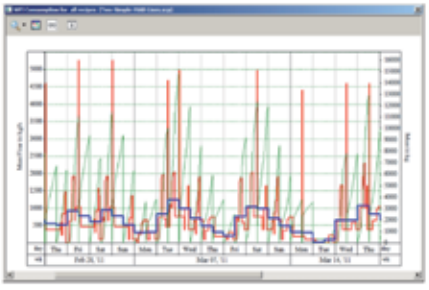

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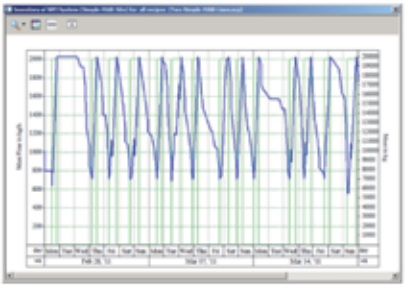

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EPIGENETICS IN DISEASES OF AGING

A vibrant avenue of research and drug development has opened up with the discovery that epigenetic changes affect gene expression, alter cellular development, and can lead to disease. Epigenetics are chemical modifications that affect gene expression, such as cytosine methylation of DNA, and acetylation and methylation of the histone proteins that package DNA. These processes are important to the development of cell types and, while epigenetic modifications do not alter the cell's underlying nucleotide sequence, the changes can persist for generations.

According to Jean-Pierre Issa, MD, an expert in the field, most diseases of the elderly probably have an epigenetic component. Issa studies myelodysplastic syndrome (MDS), a group of blood diseases that predominantly affect people over 65 in which bone marrow can become almost completely filled with cancerous cells. The cause has not been determined, but exposure to agents that damage DNA—radiation, benzene, long-term exposure to pesticides, and some chemotherapies—are known risk factors.

There are four FDA-approved epigenetic therapies. One class inhibits enzymes that modify histones and includes romidepsin and vorinostat, which are used in the treatment of cutaneous T-cell lymphoma. The other class interferes with the function of DNA methyltransferases (DNMT) and includes decitabine, a hypomethylation tumor therapy approved in 2006 for the treatment of MDS, and azacitidine, a treatment for MDS and other blood cancers.

Transparency Market Research pegs the market value of epigenetic drugs and diagnostic technologies at $5.7 billion by 2018.[1] Among companies keen on moving into epigenetic therapies, Merck will invest as much as $515 million on the development and commercialization of these drugs.[2]

Issa, director of the Fels Institute for Cancer Research and Molecular Biology at Temple University in Philadelphia, outlines the challenges for the development of these novel drugs: "There is no one magic bullet," he said. "Some epigenetic drugs have broad activity, affecting a thousand or ten thousand genes, while others have a narrow effect on only a hundred. Each drug may not work in the same disease or in the same way as another one."

Designing clinical trials to test these agents is also a challenge since they don't work the same way as chemotherapy, which uses toxins to kill as many cancerous cells as possible, and the effects of epigenetic drugs may take a long time to show up.

Cell type and function rely on epigenetics, and changing modifications on DNA or histones can alter cellular identity. While most of the genes affected by DNMT inhibitors are abnormally methylated—and those are the ones you want to target—off-target effects are a concern. While normal cells usually return to their previous epigenetic pattern after they've been exposed to epigenetic drugs, there is evidence from animal models that changing epigenetic modifications can lead to new cancers.

These off-target effects might also have benefits, however. "Epigenetic drugs can sensitize patients to immunotherapy or chemotherapy," Issa said. One thought is that the drugs trigger an inflammatory response by activating endogenous retroviruses that are normally kept inactive by DNA methylation. "Activation of these genes may be one of the ways these drugs work to complement cancer therapies. While this is promising, it might not be a universal property of all epigenetic drugs, which means we have to find out which drugs sensitize cells to a particular therapy. We also have to watch for autoimmunity, which is one of the concerns with chronic hypomethylation."

There are likely more drugs in use that have epigenetic properties than the four approved by the FDA. At least one traditional Chinese medicine might work because it's an epigenetic drug. "Arsenic trioxide was discovered serendipitously centuries ago and works well in some forms of leukemia," Issa said. It is currently available as the FDA-approved Trisenox, manufactured by Teva. "It's possible that we've been using epigenetic therapies for hundreds of years without knowing it."

Issa's group has found that cardiac glycosides—sodium-potassium pump inhibitors—have prominent epigenetic activity, and valproic acid, an anti-seizure medication that has been used in children for decades, has weak histone deacetylase inhibitor activity that may be responsible for its efficacy.

As people age, accumulated epigenetic changes accompany the onset of cancers, Alzheimer's disease, and respiratory conditions. Issa's team is particularly interested in type 2 diabetes, another age-related disorder. AstraZeneca and MRC Technology are collaborating to find epigenetic candidates for chronic obstructive pulmonary disease and asthma,[3] while Oryzon has five drug candidates in clinical trials, including ORY-2001, a potent and highly selective dual LSD1-MAOB inhibitor for the treatment of Alzheimer's disease, Huntington's chorea, multiple sclerosis, and some forms of cancer.[4–5]

"There's likely some degree of epigenetic deregulation in all aging diseases," Issa said. "There are still many challenges ahead of us, but epigenetic therapies are a rich and promising area of drug development." ‹›

—Scott Fotheringham, PhD

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