PHARMACEUTICAL ENGINEERING®

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Joseph Famulare
Compliance Challenges for a Global Industry

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EDITOR'S VOICE

COMPLIANCE AND SUSTAINABILITY: CONFLICT OR HARMONY?

When we discussed assembling this month's special report on sustainability, the idea of pairing it with an issue on compliance challenges was not an obvious choice. Despite those initial misgivings, the reality is that these two topics are a superb pairing; the drive for both sustainability and harmonization of regulations illustrate the evolution of our industry from a mindset of unquestioning compliance to thoughtful stewardship of public trust.

Personally, the impediment I most often encounter when exploring issues of sustainability (say by optimizing cleanroom performance, challenging air change rates and velocities) is cultural and perceived regulatory inertia—that unquestioning compliance mindset.

Now I'm no fan of the term "sustainability"; it's hard to muster any enthusiasm for staying in one place. Rather, let's talk about increasing efficiency, eliminating waste and maturing our processes. Increasing efficiency is the natural function of engineers. Our job is to apply scientific understanding to real world problems, building solutions that are both cost-effective and of real benefit. "Lean" and "green" should be synonyms, not antonyms, and they should fit seamlessly with our mandate to assure the safety, purity, and quality of our products.

Assurance of quality flows naturally from a deep understanding of process and product. The better we understand what does and does not affect a product, the better we can control its quality. This insistence on rigor and challenging the status quo leads to an appreciation that there is no single design for all facilities. Contamination controls that are appropriate for one product may be inappropriate (or worse, ineffective) for another. With new breakthrough therapies, technologies, and processes developing seemingly every day, this understanding is more important than ever.

With cell and gene therapies utilizing viral vectors to transform the essential code of our DNA, continuous processing transforming the layout of our facilities, and closed single-use technologies transforming the very definition of what we call a pharmaceutical facility, this may be one of the most challenging and exciting periods in our history. It's also the reason I am optimistic for ISPE's opportunity to help bring about material change.

Seeking ways to refine and focus our efforts on the real drivers of product quality is perfectly natural for an organization of pharmaceutical engineers, scientists, and regulators who have dedicated their careers to the discovery and production of safe treatments to enhance and extend lives.

Some 15 years ago, in "Pharmaceutical cGMPs for the 21st Century" the FDA charged us to "... encourage implementation of risk-based approaches that focus both industry and agency attention on critical areas ... based on state-of-the-art pharmaceutical science."

Now, a decade and a half later, we find ourselves in the middle of the transformation, our community wrestling with the very core of this mission: to understand the underlying issues that influence quality and address them consistently across the globe.

We do indeed live in interesting times, with change coming at us at an ever-increasing rate. But with change comes opportunity, and the opportunity to make safe products with lower environmental impact and cost has never been more promising. ‹›

—Norm Goldschmidt, Sr. Principal and President of Genesis Engineers and Guest Editor

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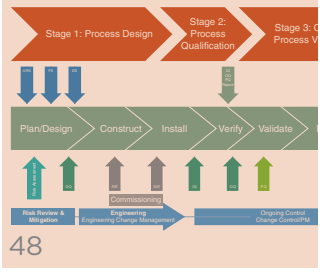

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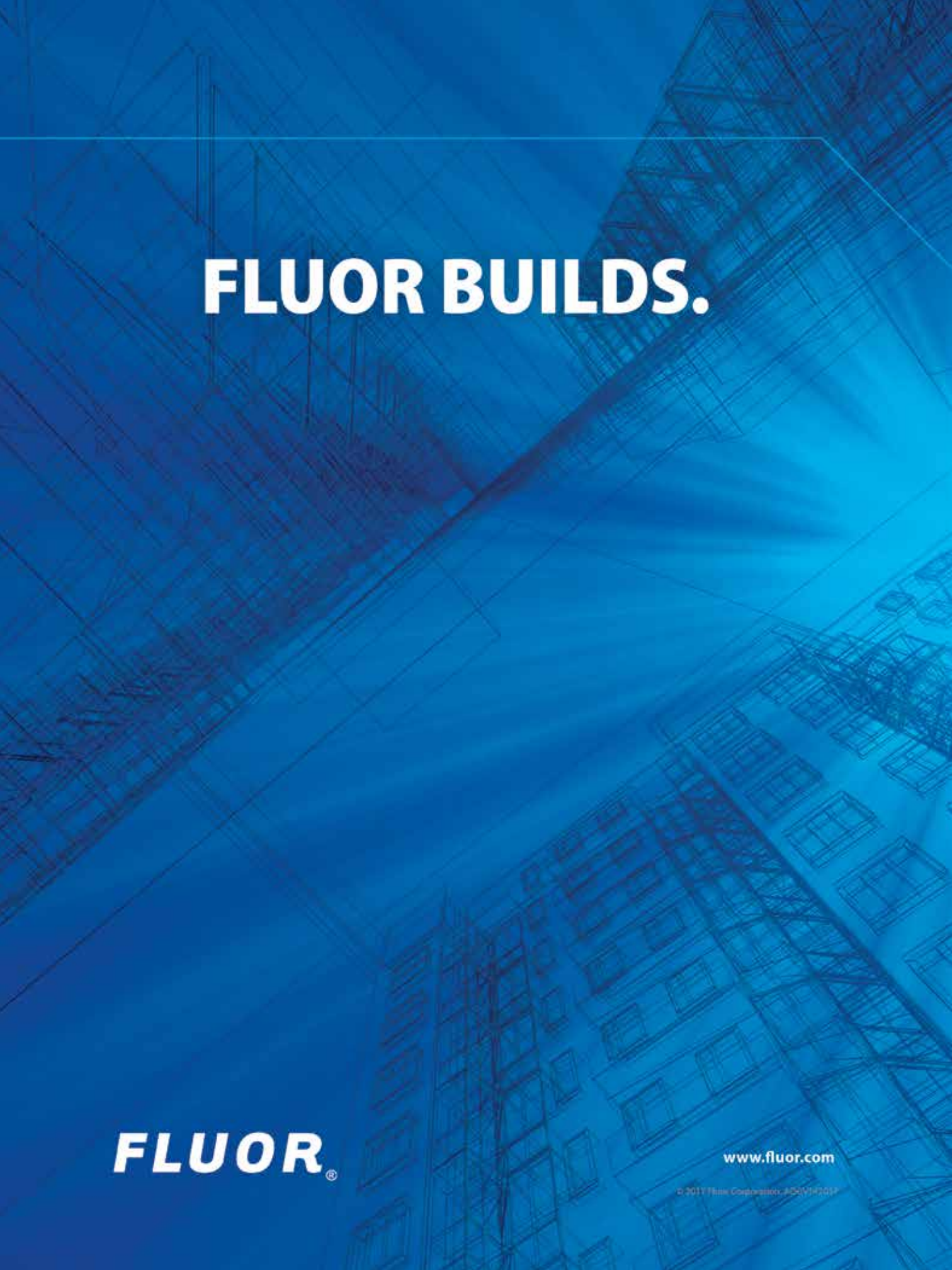
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PARTNERSHIPS: A POTENTIAL GAME CHANGER

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

The *Pharmaceutical Engineering* November-December 2016 editorial, "Collaboration Key in the Quest for Quality," written by editor in chief Anna Maria di Giorgio, said it well: Collaboration is a strength, and "ISPE members are its ambassadors." Therein lies our opportunity—to move the needle, or to be (as some might say) disruptively innovative in our industry.

"Disruptive innovation" is often associated with the use of technology in decisions and events that transform our businesses. But I believe the term also applies to the opportunity to develop partnerships that could have a similar game-changing effect on industry and our efforts to meet patient expectations. Here's an example from my experience in the investigational medicinal product (IMP) arena that makes my point.

Let's start with the use of interactive response technology, or IRT. In the IMP world, this technology has the capability to manage several areas of clinical trial conduct: good manufacturing practice and good clinical practice. Examples include distribution, random assignment and dispensing to patients, expiry date management, drug accountability, recalls, and others. Here's the interesting point: The banking industry has used this form of technology for at least the past 15 years in ATM machines and credit card transactions. It has also been used (or at least attempted) to manage expiry date transactions for investigational medicinal products for equally as long. It has not been accepted in the global regulatory arena, however, and even today cannot be used to manage clinical trial processes outside the United States.

Why is this the case? Well, it's not for lack of trying. I participated in a presentation to several non-US regulatory agencies in an effort to gain approval for global use of this technology. In my experience, even though the regulators quickly understood the technology and its many benefits (quality and compliance) they were interested but not supportive. They were not supportive for one significant reason: the lack of industry standards on the use and development of IRT technology.

If we think about it, this makes sense. How can we expect regulators to endorse a "process" that could conceivably have hundreds of variations with no global standards or definitions? It would be an inspector's nightmare and difficult for them to effect remediation.

If we as an industry don't strive for standardization and alignment, we will experience similar challenges as we look to implement additional technologies such as electronic labels, dispensing verification, and others on the horizon.

So how can we implement new and innovative ways to conduct our business when we have no standards and our efforts are not globally aligned? One likely way is through the development of partnerships with like-minded societies and organizations, which could drive the appropriate level of standardization and use of these innovative technologies!

Regulatory agencies like the Pharmaceutical Inspection Co-operation Scheme (PIC/S) provide examples of what can be done. The welcome message on the PIC/S website reads:

> *The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a non-binding, informal co-operative arrangement between Regulatory Authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. It is open to any Authority having a comparable GMP inspection system. PIC/S presently comprises 49 participating authorities coming from all over the world (Europe, Africa, America, Asia and Australasia).*
>
> *PIC/S aims at harmonising inspection procedures worldwide by developing common standards in the field of GMP and by providing training opportunities to inspectors. PIC/S' mission is* ***to lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products****.* [emphasis in original]

One only needs to visit the PIC/S website to see some of the significant accomplishments they have made as a result of this partnership. There is clearly an opportunity for professional organizations like ISPE to partner with each other and, in a way, drive disruptive innovation and facilitate more efficient implementation of innovative technologies. Working collectively in the interest of our industry would be a game-changer. Industry, as well as our patients, would benefit tremendously.

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1 Australasia Affiliate
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2 Ireland Affiliate
HVAC in BioPharma Event & Seminar
Cork, Ireland

3 Boston Area Chapter
Annual Ski Trip
Waterville Valley, New Hampshire

6 Singapore Affiliate
Designing a Risk-Based Cleaning Program
Singapore

7–8 Aseptic Conference
Reston, VA

8 DACH Affiliate
CoP GAMP D/A/Ch Forum mit Vortragen
Ettlingen, Germany

France Affiliate
Atelier GAMP Francophone: Archivage
Paris, France

13 Turkey Affiliate
QbD & PAT Workshop
Istanbul, Turkey

14 CaSA Chapter
24th Annual Life Sciences Technology Conference
Raleigh, North Carolina

15 New Jersey Chapter
Professional Development Day
Piscataway, New Jersey

16 Boston Area
Continuous Manufacturing Biopharmaceuticals
Cambridge, Massachusetts

Brazil Affiliate
Training: Validation of Electronic Spreadsheets
São Paulo, Brazil

16–17 Technology Transfer (T19)
ISPE Training Institute
Tampa, Florida

23 Benelux Affiliate
Fourth Annual Seminar
Leiden, Netherlands

France Affiliate
Atelier Reflexion GMP EU Draft Annexe 1
Paris, France

Nordic Affiliate
Multipurpose Facility Biotech & Containment
Sodertalje, Sweden

UK Affiliate
3M Innovation Centre
Bracknell, England

27–28 Process Validation in Biotech Manufacturing (T32)
ISPE Training Institute
Tampa, Florida

27–29 Basic GAMP 5, Annex 11/Part 11 (T45)–*Updated*
Manchester, England

28 San Francisco/Bay Area Chapter
26th Annual Vendor Night
San Francisco, California

29 Brazil Affiliate
Training: Concepts & Applications Data Integrity
São Paulo, Brazil

30 Italy Affiliate
Industry 4.0 E Operational Excellence
Bologna, Italy

APRIL

3–4 OSD (T10)–*Updated*
ISPE Training Institute
Tampa, Florida

3–6 ISPE Europe Annual Conference
Barcelona, Spain

5–6 Q7A GMPs for API (T30)–*Updated*
ISPE Training Institute
Tampa, Florida

6 Chesapeake Bay Area
Mid-Atlantic Life Sciences Showcase
Rockville, Maryland

6-7 Cleaning Validation Principles (T17)
ISPE Training Institute
Tampa, Florida

10 Nordic Affiliate
PAT CoP Spring Meeting
Copenhagen, Denmark

10–11 Brazil Affiliate
Training: Quality by Design
São Paulo, Brazil

13 Boston Area Chapter
Educational Program
Boston, Massachusetts

San Francisco/Bay Area Chapter
Program
San Francisco

17–18 Brazil Affiliate
Training: Compressed Air Systems
São Paulo, Brazil

18 Belgium GAMP COP
Benelux Data Integrity Workshop
Oss, Netherlands

19 New Jersey Chapter
Student Poster Competition & Industry Event
New Brunswick, New Jersey

21 San Diego Chapter
Spring Golf Tournament
San Diego, California

21–22 India Affiliate
Annual Conference
Sterile Manufacturing Technology
Mumbai, India

24–25 Overview Biotechnology Manufacturing Processes (T24)–*Updated*
ISPE Training Institute
Tampa, Florida

24–26 Brazil Affiliate
Training: GAMP 5
São Paulo, Brazil

25 UK Affiliate
GAMP UK Forum
Nottinghamshire, England

25–26 Conference on Quality Culture and Quality Metrics
Bethesda, Maryland

25–27 Poland Affiliate
Data Integrity, Agile, Mobile Solutions
Warsaw, Poland

26–28 Basic GAMP® 5 Annex 11/ Part 11 (T45)–Updated
ISPE Training Institute
Tampa, Florida

27 Ireland Affiliate
ASTM-E2500 & Gala Dinner
Dublin, Ireland

MAY

2 Nordic Affiliate
Critical Utilities CoP Network Meeting
Stockholm, Sweden

6 Nordic Affiliate
Critical Utilities CoP Network Meeting
Copenhagen, Denmark

8–9 ISPE Workshops on Operationalizing Serialization
Philadelphia, Pennsylvania

Operational Excellence (T56)–*New*
Institute of Technology Management
University of St Gallen
St. Gallen, Switzerland

Water Generation (T04)–*Updated*
Biotechnology Manufacturing Facility Design (T31)*
San Diego, California

Cleaning Validation Principles (T17)
Overview Biotechnology Manufacturing Processes (T24)–*Updated*
Copenhagen, Denmark

8–10 GAMP Data Integrity (T50)–*Updated*
San Diego, California

GAMP Data Integrity (T50)–*Updated*
HVAC (T14)–Updated
Copenhagen, Denmark

9 –10 Indonesia Affiliate
Annual Conference
Jakarta, Indonesia

9–11	Poland Affiliate Forum QC Lodz, Poland
	HVAC (T14)–*Updated* **San Diego, California**
	Process Validation (T46) **Copenhagen, Denmark**
10–11	**Sterile Manufacturing Facility (T12)** **Water Storage and Qualification (T23)–New** **San Diego, California**
	OSD (T10)–*Updated* **Facility Project Management (T26)*** **Copenhagen, Denmark**
11	San Francisco/Bay Area Chapter Commuter Conference San Francisco, California
16	Brazil Affiliate Biotech Workshop São Paulo, Brazil
16–17	**C&Q for New & Renovated Facilities (T55)–New** **National Institute for Bioprocessing Research and Training** **Dublin, Ireland**
17	Belgium Affiliate Annual Meeting/Networking Event Brussels, Belgium
17–18	Brazil Affiliate Training: Life Sciences Project Management São Paulo, Brazil
	Poland Affiliate YP & SME Process Control & MES Systems Lodz, Poland
18	Greater Los Angeles Chapter 24th Annual Vendor Night Exhibit Show Los Angeles, California
	Nordic Affiliate Annex 15, Continuous Manufacturing Copenhagen, Denmark
18–19	Japan Affiliate Annual Meeting Toyama, Japan
	Clean-in-Place Fundamentals (T03) **Commissioning & Qualification (T40)** **ISPE Training Institute** **Tampa, Florida**
22	Carolina–South Atlantic Chapter Golf Tournament Cary, South Carolina
25	Ireland Affiliate Operational Excellence Limerick, Ireland
30–31	Brazil Affiliate Training: Regulatory Requirements Calibration São Paulo, Brazil

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PERSEVERANCE AND GRIT: EFFORT COUNTS TWICE

Brody Stara
International Young Professionals Committee Chair, Member since 2008

Now that we're all finding smart mentors and career coaches (see the YP State of Mind article in the January-February issue of *Pharmaceutical Engineering*), I want to reflect on an important skill: perseverance.

Engineers and scientists by nature look for methodical ways to solve problems, so for us some level of perseverance is a must. In her book Grit: *The Power of Passion and Perseverance*, psychologist Angela Duckworth says that perseverance, or "grit," as she calls it, is a trait that may count more than we realize.

Intelligence alone, she argues, isn't enough to get you to the highest levels of success. You need to put in effort over time and persevere through the setbacks. In fact, effort was so important in her calculation that she counted it twice:

Talent × Effort = Skill
Skill × Effort = Achievement

Put these equations into the workplace and you realize that "effort" is what gets you noticed by colleagues, managers, and recruiters. They don't judge you on your IQ score, they judge you on your effort and passion for the work you do.

Duckworth compares grit and perseverance to the 10,000-hour rule, widely believed to be "the amount of time one must invest in practice in order to reach meaningful success in any field."[2] At 40 hours per week, that translates to about 5 years. Take a second to think about that number, and compare it to your long-range plan and career goals. You're going to need a lot of effort and grit to get there.

Being "gritty" in your day-to-day actions can mean a lot of things. The first example that comes to mind is powering through setbacks. When a project goes awry or an experiment fails, you don't give up or spend time complaining. You persevere and work around it. You ask for help, collaborate with your team, and find a new way to succeed. In fact, you aren't afraid to make the mistake in the first place. You take risks because you know that if you fail, you'll keep trying.

As a Young Professional designing a temperature control loop for a bioreactor, you find the heat load needed to keep your cells happy. When the system finally gets installed, however, you find that the vessel must be brought to temperature significantly faster than you calculated. If you're a gritty person in this situation, you don't point fingers; you jump into the new problem and quickly determine how to get the system up to operational needs. Simply being smart won't fix the problem. You need to work for it.

"EFFORT" IS WHAT GETS YOU NOTICED BY COLLEAGUES, MANAGERS, AND RECRUITERS

Another great example is stepping up to lead when there are known challenges ahead. This happens all the time in ISPE student chapters. Leadership is constantly turning over and new, gritty leaders need to step up and develop their skills to lead, knowing that it won't be easy. Perhaps the past chair didn't save any documents or your industry mentor moved away. The easy thing is to stand by and wait until you graduate, but stepping up to organize the student body and create meaningful events builds your leadership skills and your grittiness.

It shouldn't surprise you that these are characteristics every employer wants to hear about. Stories of perseverance through tough times show hiring managers that your past performance is a good indicator of future success for you and for the company. An article in *Digitalist Magazine* supported this theory, indicating that "grittier" employees are easier to onboard as they engage more with the manager and staff to get up to speed. They take a more active role in their own professional development, and "when an employee is dedicated to improving their existing skills and advancing within your organization, you know you have someone on your team who can offer real value."[3]

Armed with this knowledge, we Young Professionals need drive and stamina to put in the effort required to achieve our goals. We need to remind ourselves that to achieve our 5-year plans, our 10-year plans, and our ultimate career goals, we'll need to jump-start our grittiness every time we start to settle into that comfortable routine. ‹›

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COMPLIANCE CHALLENGES FOR A GLOBAL INDUSTRY

Amid the great opportunities that flow from extending their networks of facilities around the globe, pharmaceutical manufacturers are facing compliance challenges in emerging markets—especially culturally distinct ideas about safety, risk, and quality. Take, for example, the use of bamboo scaffolding in construction, which is common in parts of Asia, most notably Hong Kong. While safety issues, sourcing material difficulties, and labor shortages have led to a decline in the practice, it continues to be used to erect buildings as tall as skyscrapers.

"Workers will climb up twenty stories on bamboo scaffolding with no netting on the outside of it," said Maurice Parlane, director at New Wayz Consulting in Auckland, New Zealand, which supports pharmaceutical companies' compliance, quality, and operational needs. "Their norm of safety and acceptance of risk are different from Western notions."

Joseph Famulare

These differences can affect pharmaceutical manufacturing and are some of the significant compliance challenges facing global companies today, along with the ongoing need to address drug shortages and secure storage and sharing of data.

Joseph Famulare, Vice President of Global Compliance and External Collaboration at Genentech and immediate Past Chair of ISPE's Board of Directors, sees compliance as an evolving process. "It's living, takes work, and needs maintenance," he said.

GMP and GDP, he noted, both require attention to data integrity and regulatory compliance with the manufacturing license. Achieving these things and modernizing processes and facilities while managing post-approval changes needs carefully planned strategies to ensure compliance. Improving processes for efficiency also influences supply, improves business sustainability, and helps prevent drug shortages. "Health care is heading toward new paradigms such as personalized medicine, and that is a positive development for the patient," Famulare continued. "The industry is adapting new technologies for some new treatments on the horizon where the patient is now part of the supply chain."

ISPE members are taking a page from the book written years ago by sectors like auto manufacturing and telecommunications, which sought not only to rely on guidance from regulators but to improve quality based on connections forged directly with customers.

"The food industry, automotive industry, and personal electronics are well connected to their customers," said Parlane. "There are companies in these sectors with high quality standards and an appetite for improving their quality based on the desires of the market, rather than because a regulator told them to. Pharma is catching up in this regard, changing how it sees things."

WHAT PRICE QUALITY?

Pharmaceutical manufacturing requires a global approach to compliance as companies look for competitive advantages in regions such as Asia, not only for lower labor costs, but because China and India are emerging markets with huge populations of potential customers. A global company instituting a quality system must often adjust its approach, depending on the location of the facility. Regulatory authorities seeking to harmonize standards also face challenges with regional disparities in the perception of risk.

"When you export Western GMP to a place like Asia, it depends on people and their culture," said Parlane, who is also a Director on the ISPE Australasia Affiliate Board and ISPE's Member of the Year in 2016. "You can't assume that everyone shares the same view of what GMP is."

Manufacturers in emerging markets sometimes make versions of a drug for two distinct populations: an external market beyond their borders for which they must comply with international regulations, and an internal market that may be willing to tolerate reduced quality in exchange for lower-priced products. This dichotomy creates a dilemma for drug makers, regulators, and governments.

"Governments in these countries need to look after their own populations," said Parlane. "Keeping in mind the health care pillars of affordability and accessibility, there is also a move to lift the level of quality."

He believes that tiers of quality—and pricing—might evolve, perhaps resulting in a double standard in terms of compliance. "You can make a ten-cent tablet, for which the quality standards and cost of manufacture is lower, or you can make a dollar tablet for export. Of course, within these markets there are also consumers who are demanding higher quality, which drives production toward the dollar tablet."

Complicating matters is the difference between mature markets—Singapore, Japan, parts of China—and places like Bangladesh or North Africa. Parlane cites Vietnam as an example where drug makers might want to raise quality, but if this makes the drug unaffordable it defeats the purpose. "The government might say they're happy with a 60-cent drug," he said. "From a Western perspective we might question the quality of a cheaper alternative, but they might be willing to make this risk-benefit analysis."

Also contributing to this discrepancy is the nature of the industry in China, where many drugs are legacy products or generics, the manufacture of which, according to Parlane, lags behind the science and innovative developments in the rest of the industry.

And, while Singapore is a biologics production hub, Parlane thinks much of Asia will take a while to catch up. He believes that efforts in emerging Asian economies should be directed at things like infant vaccine programs, as they are in places like Bangladesh, India, and Vietnam, where biologics and vaccines are produced for the local market. "In Africa it will be even more challenging to get that industry to where it can supply large numbers of people at the right price," Parlane said. "I have confidence that this will get figured out. There are very smart people and a thirst for knowledge throughout these regions."

Cultural sensitivity

Parlane suggests that while ISPE is a technical organization, steeped in operations and an understanding of what makes a quality system good, there are sensitivities about addressing cultural issues. "We have this paradigm that a factory's a factory, and GMP is GMP. But the people runnin g the factory have a different tolerance level for things and they make tolerance and risk decisions in a different context. It can't be only about knowledge transfer. You can't change culture in a hurry.

Paul Gustafson

"We need to respect and understand and not force a system onto others. If you want a particular way of working to fit, you have to adjust it to the environment. In a cynical way, we think 'Here's the QC system,' and we assume it will be implemented the way it is in Europe. We're forgetting that one of the big enablers is the people, and the people are different."

HARMONIZING REGULATIONS

One way that regulators and manufacturers are bridging the gap between regional differences in approaches to quality and compliance is to harmonize regulations and inspections globally. "Harmonization and convergence efforts are extremely important to global manufacturers in terms of having standards that meet all the various requirements," said Famulare.

"When an area takes on learning the fundamentals of quality, GMP, quality mindset, and disposition, it will take a lot of time," he continued. "There have been difficulties in terms of data integrity and accurate reporting, leading to a trend in FDA [US Food and Drug Administration] warning letters. Programs have to be put in place to meet these global standards. The International Conference on Harmonisation (ICH), for example, is issuing guidelines for technical standards and finding ways for health authorities from additional countries to become observers or full participants of the organization. Industry also has to be an important part of that discussion, because they have the technology and responsibility and manufacturers to drive both the discussion and the culture."

HARMONIZING INSPECTION PROCEDURES

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a non-binding cooperative arrangement of regulatory authorities focused on GMP of medicines.

"PIC/S aims to harmonize inspection procedures worldwide by developing common standards and by providing training opportunities to inspectors," said Paul Gustafson, Chair for the PIC/S subcommittee on harmonization of GM(D)P. "By facilitating co-operation and networking between competent authorities and regional and international organizations, it increases mutual confidence."

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PIC/S members share a comparable GMP inspection system; members include the US FDA, the UK Medicines and Healthcare Products Regulatory Agency, and 47 other regulators. Some countries have more than one participating authority in PIC/S.

"PIC/S has always taken great pride in featuring itself as a purely technical organization in the field of regulatory GMP," explained Gustafson. "A firm belief of PIC/S is to not become politically involved, such as might occur if membership was country based."

Gustafson points out a number of ways that a PIC/S member raises the GMP standards within its country and helps manufacturers build an internal quality culture. "Internationally harmonized guidance such as the PIC/S GMP Guide [equivalent to the EU GMP Guide] provide a solid foundation for compliance requirements."

The participating authority also contributes to the enhancement of global and regional quality culture through participation in PIC/S meetings and training, both of which offer forums for exchanging ideas and experience with inspectors around the globe. "This helps build a culture of quality in the inspection community with common understandings," Gustafson continued. "Regulatory authorities can then be in better positions to influence the building of a quality culture in the companies through internationally harmonized regulatory oversight."

"Even though PIC/S isn't a legally binding organization, it has been influential in organizing to harmonize inspection approaches and reaching into a variety of large and small countries," said Famulare. He believes that PIC/S can promote government-to-government reliance or even mutual recognition. "The sharing of inspection reports under mutual reliance might eliminate duplicate inspections at the same plant or serve, when fully implemented, to accept inspections in each other's territories. Inspectorates would then be free to redirect resources to other areas."

As Gustafson sees it, membership diversity is one of PIC/S strengths. "It allows for positive influences to be considered from all of its members," he said. "Each member has opportunities to make distinct impacts in bringing about continuous improvement in how PIC/S develops and promotes harmonized GMP standards and guidance documents, trains GMP inspectors, assesses GMP inspectorates, and facilitates co-operation and networking for regulators.

"The framework and governance under which PIC/S operates allows each participating authority the opportunity to contribute and collaborate on distinct elements that reflects upon values important to their organization and fit with their pharmaceutical industry," he added.

The challenges faced by PIC/S, including capacity building and harmonization of GMP inspections among different regulatory authorities, are similar to those faced by industry in the implementation of global pharmaceutical quality systems.

"PIC/S and its members overcome many of these challenges through an effective governance structure that is based on consensus and mutual trust," Gustafson said. "Admission of new members that have been qualified, and older members, which have been reassessed for compliance, reduces harmonization challenges across regions and cultures.

"As the pharmaceutical industry becomes increasingly globalized, no single authority can manage alone the risks related to pharmaceutical products and active pharmaceutical ingredients," he continued. "A harmonized approach between authorities on aspects such as regulations and training is critical to face globalization."

DATA TAMPERING, LOSS, OR THEFT CAN LEAD TO COMPLIANCE PROBLEMS

With his expertise in Asia, Parlane has seen a change in the relationship between regulators and industry. "There is more open dialogue at conferences and meetings, and regulators are becoming more engaged in event planning and the documents that ISPE prepares," he said. "There is still some official distance maintained, particularly in the United States and European Union, but I think that forums such as ICH and IFPAC [International Foundation Process Analytical Chemistry], and increasingly ISPE and similar organizations, where regulators and industry alike are present, are encouraging more open discussion. I think this is healthy."

MITIGATION OF DRUG SHORTAGES

Drug shortages continue to be a problem, especially for sterile injectables, which account for the great majority of shortages.[1] While the US FDA Safety and Innovation Act of 2012 seems to have resulted in a reduction of new shortages, there were still 120 in the first three quarters of 2016.[2] At least one-quarter of shortages are due to manufacturing problems or regulatory issues, though the number is likely much higher.

"PIC/S holds the view that noncompliance with GMP continues to contribute to the drug shortages experienced globally," Gustafson pointed out. He said that PIC/S promotes work in this area following workshops held last year among its members and partner organizations such as the European Medicines Agency (EMA) and the World Health Organization. "With a view of mitigating drug shortages, PIC/S intends to update content in its Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File[3] in collaboration with an EMA drafting group that includes PIC/S representation."

ISPE and the PEW Charitable Trusts recently surveyed executives from 10 pharmaceutical companies to identify the causes of drug shortages and provide recommendations.[4] Their report identified the burden of meeting regulatory challenges as one of the factors preventing companies from investing in expanded capacity or updated equipment, especially for legacy products that are 10–20 years old and continue to be an essential medicine. These challenges include the time and cost of submitting an Abbreviated New Drug Application.

"This could be due to older processes or equipment that hasn't been kept up to date due to a lack of investment because many older products, for example, have not warranted that investment for a variety of reasons as noted in the Pew report," said Famulare. "Also the expectation of having to update all the licenses in every country that the product is approved in is one complicator in the process. Streamlining those efforts will be important to industry and health authorities."

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Mayurice Parlane

CYBERSECURITY AND COMPLIANCE

Ever-increasing amounts of data are being shared across networks of facilities, with external partners, between patients and companies, and across regions with different regulatory regimes and cultures. Fully connected factories can lead to a reduction of errors, which enhances compliance.

"Advances in network connectivity to leverage data sharing and analytics provide opportunities to significantly transform drug quality and regulatory compliance to the benefit of patients who depend on these pharmaceuticals," said Gustafson. "This increased information flow from manufacturing and testing equipment that can be collected and processed is expected to facilitate improved consistency in production, optimize equipment maintenance schedules, and provide more control and oversight to reduce human error. There may be significant financial return on such investments for manufacturers, and it is believed patients will also benefit from improved drug quality and fewer shortages."

The rapidly growing Internet of Things further expands this connectivity to include machines, robotics, and devices that are internal to a company as well as medical devices that patients use. Connectivity across a factory and between facilities around the world mean that data is accessible to anyone unless rigorously protected. Protecting intellectual property such as proprietary drug formulas, process information, R&D data, and patient confidentiality is paramount.

"The pharmaceutical industry is not on its own when it comes to protecting data," said Parlane. "There's more of a threat out there. When we share the info we're collecting on patients and on clinical trials around the globe, there are more risks."

Data breaches, which cost the health care industry upwards of $5.6 billion each year,[5] can lead to regulatory penalties, litigation, and loss of customer confidence. To make things worse, pharmaceutical companies are the main targets of UK cybercrime,[6] and experts believe that the proliferation of ransomware attacks on enterprise seen in 2016 is a trend that will continue.[7]

Equally important to preventing theft is maintaining data integrity. Data tampering, loss, or theft can lead to compliance problems.

"I have confidence that ISPE is keeping pace with the technology," said Famulare. "You want to protect data not only from criminal intent or malfeasance, but from the obfuscation of a result, either intentionally or by mistake. It's important to have a culture where, if a result is not within the meaning you want, you're able to protect that data from being manipulated."

"If you ignore the high-profile examples of companies that aren't doing this well—and there are companies like this in the US and Europe as well China and India—everyone's in the same boat in terms of data integrity and security," said Parlane. "You have to be a lot more cautious about data than we have been. When people are involved, there will be mistakes. The amount of data we produce is one of the problems because, even if error rates are low, the amount of data means that errors do happen. For example, a batch document for a small molecule might have 1,000 data points."

As in health care, prevention trumps the cure in terms of time, resources, and money. Security requires a multilayer approach. Indeed, adherence to regulatory compliance can enhance security of the production process.[8]

"Just as we need to password-protect our personal data, the same fundamentals are in play in the industry," said Famulare. "Once a data point is created, it needs to be handled so it's secure and not subject to alteration."

Gustafson pointed out that data integrity is important regardless of the storage approach. "Manufacturers may wish to consider the recently published PIC/S draft guidance document 'Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments.'[9] This document, although written for use by inspectorates, can help manufacturers establish the necessary frameworks to ensure the integrity of their data, regardless of where and how it is stored. This framework starts with the inclusion of data governance systems and good risk management approaches being built into their pharmaceutical quality system."

When it comes to the ways that manufacturers are paying attention to quality and compliance, Parlane likes what he is seeing. "In the past ten years the focus in the industry has changed from looking inward on quality to an outward focus on the impact on patients," he said. "Manufacturers know more about their patients now, which is a good thing, and when we encounter a manufacturing problem, it's not just a manufacturing problem. It affects lives." ‹›

—Scott Fotheringham, PhD, and James Hale

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REGULATORY CHANGES AFFECTING THE SUPPLY CHAIN

The global nature of the supply chain has meant that pharmaceutical manufacturers have to adhere to a hodgepodge of regulations in the diverse regions in which they operate. Efforts to harmonize standards and inspection procedures between countries continue, most notably with ICH. All this is aimed at protecting consumers from products that are illegitimate, substandard, counterfeit, or unapproved, as well as maintaining the integrity of the supply chain. Here are some of the ongoing changes affecting supply chain compliance.

DSCSA In the United States, the 2013 Drug Supply Chain Security Act created an electronic system to identify and trace drugs down to the level of the individual package. Provisions related to this act continue to be rolled out by the US Food and Drug Administration, including product identification, lot-level product tracing, the establishment of systems for the verification and handling of suspect or illegitimate product, and confirmation that trading partners are licensed.[1]

FMD The 2011 Falsified Medicines Directive of the European Union (EU) has mandated implementation of a track-and-trace system using identification codes on individual packages-a 2D barcode—as well as antitampering devices on products by February 2019. It requires serialization at the point of manufacture and verification at point of sale by dispensers. Risk-based verifications at the wholesaler level will occur for products at greater risk of falsification, which is different than the tracking of packages at every transaction that will be required in the United States.[2]

In the United Kingdom, the Secretary of State for Health said he believes the nation will not be part of the European Medicines Agency (EMA) or the EU's drug regulatory framework post-Brexit.[3] As the UK Medicines and Healthcare Products Regulatory Agency makes significant contributions to EMA research, however, it is likely that the two authorities will continue to work together closely.

SNCM In 2016 a revised version of Brazil's National Drug Control System legislation set a timeline to bring drug product traceability to the country. While the process is moving more slowly than officials anticipated, the aim is to mandate a national track-and-trace system in the next few years.[4]

—Scott Fotheringham, PhD

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"The degree to which quality is embedded in an organization's culture can mean the difference between success and failure."

—François Sallans, Johnson & Johnson

Register at ISPE.org/2017-Quality-Culture-Quality-Metrics-Conference

ISPE 2016 EUROPE GAMP®/ DATA INTEGRITY REGIONAL CONFERENCE

There is still a lot of uncertainty on how to effectively structure a corporate data integrity program. It starts with the definition of the scope and often it ends with parallel work between departments who are owners of different systems along the value chain.

Global regulatory authorities have growing concerns about the reliability of records and data on which product quality and patient safety decisions are based. This is demonstrated by numerous regulator citations and the publication of data integrity guidance from the UK Medicines and Healthcare Products Regulatory Agency (MHRA), World Health Organisation (WHO), US Food and Drug Administration, and Pharmaceutical Inspection Co-Operation Scheme.

The prominence of data integrity as an industry challenge was also clearly illustrated by ISPE's sold-out Data Integrity Conference held in Copenhagen from 4–5 October 2016. Speakers included industry representatives, suppliers, and consultants, bringing perspectives that ranged from technologies to consumers. The conference was also supported by David Churchward (MHRA) and Ian Thrussell (WHO), who provided insight into regulatory concerns and expectations.

The conference addressed the three dimensions of data integrity—culture, processes, and technology—and the 150 delegates in attendance participated in highly interactive sessions that featured challenging and interesting discussions.

HIGHLIGHTS

David Churchwood, Expert GMP Inspector, MHRA posed a question: Why is data integrity still an issue, given that the requirements have existed in their most basic form since 1989?

He identified three major reasons: impact of quality for the patient, breadth of scope, and outdated control measures. Unreliable data can lead to "precision guesswork" and wrong conclusions that can damage corporate reputations. The fear of failure can often cause wrong behavior, and the complexity of proposed remediation leads to aspiration instead of action.

Noting that "perfection is a barrier to progress," he said that the right quality risk management approach, balanced with other GMP priorities can play an important role. Management understanding that "it can happen here" and communication of realistic expectations helps create an open reporting culture and teaches personnel the importance of reliable data and its effect on patients and the organization.

Churchward encouraged attendees to avoid data integrity "blind spots such as non-laboratory data, failure to control paper records, data manipulation outside of a controlled environment, and the challenge of supervising international supply chains. The benefits of good data governance, he concluded, lead to better decision-making and protect corporate reputations.

Valeria Frigerio Regazzoni, Deputy Vice-President Quality Auditing and Compliance, Merck Serono, discussed the main action areas in a corporate data integrity program, which include regulated electronic records and signatures, data backup, access control, and traceability. She presented a very interesting "GAPs solutions portfolio" and finally reviewed Excel sheets and other stand-alone systems management.

Per Westerberg, Head of Corporate Quality Systems and Projects, Xellia Pharmaceuticals presented a roll-out project plan for a corporate-wide data integrity implementation program. His main findings when analyzing the readiness of an organization were access control as the "top gap," back-up and archiving, understanding data review, and audit trail review for both technical and business audits. Overall data integrity, he added, must be understood as a part of a quality culture.

Brian Duncan, Vice President of Engagement Operations, QXP Quality Executive Partners,

OVERALL DATA INTEGRITY MUST BE UNDERSTOOD AS A PART OF A QUALITY CULTURE

focused on factors that lead to breaches. Using the needle in the haystack analogy, he noted that "absence of evidence is not evidence of absence." He discussed the forensic investigation approach to data integrity breaches, which on areas in which potential data integrity breaches would be most likely be found, and explained the role of witness interviews. Elements for a strong data integrity culture are:

- Data integrity included in employee handbook
- Clearly defined, anonymous program for reporting issues
- Data integrity findings reported to a quality council
- Risk assessment conducted for every system to evaluate security, access controls, audit trail, and backup
- Clear remediation plans for systems with missing controls
- Interim controls established
- Third-party service providers know site policies and the limitations of their roles

Monica J. Cahilly, President, Green Mountains Quality Assurance LLC defined data life cycle management as a planned approach to assessing and managing risks to data in a manner commensurate with its potential effect on patient safety and product quality. It determines how data is captured, processed, reviewed, analyzed and reported, transferred, stored and retrieved, monitored, and retired.

The European Medicines Agency says that data life cycle refers to how data is generated, processed, reported, checked, used for decision-making, stored, and finally discarded at the end of the retention period. Data governance according to MHRA includes the "sum total of arrangements to ensure that data, irrespective of the format in which is generated, is recorded, processed, retained and used to ensure a complete, consistent and accurate record throughout the data lifecycle."

From a management perspective, organizations should move toward a culture that views data as a competitive asset rather than a necessary evil, and define clear goals for data quality improvement.

Peter Falcon, Associate Director, Global QA, IT Quality, Compliance and Projects, Ferring Pharmaceuticals reviewed challenges encountered during a data integrity remediation program. While many assume that this is a set of new regulations, there is nothing fundamentally new. Furthermore, there is a real need to ensure that data is classified correctly and that data defined as critical is appropriately controlled (e.g., identify critical process parameters and critical quality attributes), validate analytical methods with upper and lower limits, and retain raw data files from HPLC with the metadata for analysis.

Christian Woelbeling, Senior Director Global Accounts, WERUM IT Solutions, explored the operations business. His main message was "transformation in the design and execution of the manufacturing control strategy has to follow a data integrity by design approach." Without data integrity, data flow can support neither a business process flow nor a manufacturing process flow. The ALCOA data quality requirement is essential. Risk-reducing strategies should be considered a management responsibility, as indicated in ICH Q10. He gave examples for data integrity in manufacturing execution systems (see Figure).

OUTLOOK

This event was a collaboration between the ISPE Nordic Affiliate and ISPE corporate organization, a very successful alliance certain to be repeated in the future.

Due to the great success of this event, ISPE plans to include much of the GAMP conference content at the ISPE 2017 Europe Annual Conference in Barcelona, 3–5 April 2017, and launch a new ISPE GAMP Records and Data Integrity Guide at the conference as well. ‹›

— Thomas Zimmer, ISPE Vice President European Operations

EAST TO EAST: JAPAN AFFILIATE ON THE ROAD IN THE UNITED STATES

Akihiro Matsuki, Mitsubishi Chemical Engineering Corporation

Michael J. Lucey, JGC Corporation

First and foremost, the authors wish to express their sincere gratitude to the several persons in the US, former or present seniors in the ISPE global organization, and of course the host plants themselves, without whom the 2016 plant tour could not have been materialized. We are deeply grateful for the consideration extended to the Japan Affiliate.

Twenty-one professionals from the ISPE Japan Affiliate participated in its 13–16 September 2016 plant tour in the eastern United States, including Executive Director Akihiro Matsuki and Adjunct Director Michael J. Lucey, who had led the Organizing Committee made up of Affiliate board members. As in previous years, the mission was well balanced, with seven members from pharmaceutical companies, 10 from engineering/construction companies and four from equipment manufacturers.

MEDIMMUNE

Tour members visited MedImmune's large-scale cell culture plant in Frederick, Maryland. The facility was impressive for flexibility of reactor layout and effective use of the multistory building. In addition, utmost consideration has been given to the prevention of operational error, including the adoption of training programs and highly reliable software for the manufacture of different kinds of products. For enhanced productivity, a three-shift basis is applied.

BIOGEN

The Research Triangle Park, North Carolina, flexible volume manufacturing facility visited on this tour was established in 1995 and is a large-scale

bio-production facility staffed with 1,100 employees and equipped with culture tanks having a total capacity of 90,000 liters. The facility is a hybrid combination of existing fixed facilities and single-use facilities. Biogen's investment planning for equipment and facilities suggests a company having the momentum to grow in the future.

MERCK

Merck's vaccine production facility in Durham, North Carolina, was the next visit. Merck implemented a plan to increase vaccine production capacity over a three-phase period (construction: 2004–2012) to double production. The following constructional features were noted:

- Modular execution: Efficient construction realized by the assembling of prefabricated modular units
- One-team: Construction period shortened through highly cooperative work by 50 equipment manufacturers and 46 subcontractors
- Six Sigma approach to commissioning, qualification, and validation: The Lean Six Sigma approach applied to CQV to cope with the challenges of large-scale facility construction and a very tight schedule

Tour members were permitted ample time to view the facilities. Through this, members recognized the merits of modular design, which included not only a shortened construction period but also easily cleanable flat walls.

BRISTOL-MYERS SQUIBB

BMS is a global biopharmaceutical company that is further transforming itself into a specialty company. Members were shown the R&D facility in Hopewell, New Jersey, as well as Building No. 17. In the R&D facility, the biomanufacturing line was viewed, as well as an investigational drug manufacturing process. Diverse areas of the campus were shown, including an animal facility. Office space and R&D facilities at Hopewell are being further expanded, and the site area is clean and well maintained. Tour members were again impressed by the funding ability of BMS as a global business enterprise in securing its future position in the industry.

Plant tour itinerary

Tuesday, September 13	Departed Tokyo for Washington, DC
	Afternoon: MedImmune, Frederick, MD
Wednesday, September 14	Afternoon - Biogen, Research Triangle Park, NC
Thursday, September 15	Morning: Merck, Research Triangle Park, NC
Friday, September 16	Morning: BMS, Hopewell, NJ
Saturday, September 17	Afternoon: ISPE Annual Meeting registration
September 18–21	ISPE 2016 Annual Meeting, Atlanta, GA
Thursday, September 22	Departed Atlanta for Tokyo

MedImmune large-scale cell culture plant, Frederick, Maryland

Biogen flexible volume manufacturing facility, Research Triangle Park, North Carolina


Merck vaccine production facility, Durham, North Carolina

POST TOUR

At the Affiliate's Winter Meeting in December 2016, registrants were given an overview of the US plant tour through a highly visual poster display. To promote networking among Affiliate members, a reunion for participants from all U.S. plant tours is held every year. The joint reunion for participants in the 2008–2016 plant tours was held in Tokyo in February 2017.

2017 ISPE TRAINING

EUROPE

Effective and Efficient Deployment of Operational Excellence—Striving for World-Class Performance in Pharmaceutical Operations (T56)

8–9 May

Institute of Technology Management (ITEM-HSG), University of St Gallen, Switzerland

Do you know how to measure operational excellence and identify solutions to address manufacturing and compliance issues? 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, providing the pharmaceutical industry with a knowledge base from which to promote the use of best practices.

Effective and Efficient Deployment of Operational Excellence—Striving for World Class Performance in Pharmaceutical Operations is designed to provide participants with a deep understanding of how to measure operational excellence, including insights on relevant qualitative enablers as well as meaningful quantitative performance indicators. Using the well-established architecture of the St. Gallen OPEX benchmarking, the course leverages this industry-tested benchmarking approach to identify appropriate solutions for specific problems to address issues in manufacturing and compliance.

A GAMP® Approach to Data Integrity, Electronic Records and Signatures, and Operation of GxP Computerized Systems (T50)

8–10 May

Copenhagen, Denmark

Can your data integrity process stand up to regulatory scrutiny? Data integrity is currently one of the highest cited areas in regulatory observations and a topic of great interest for both industry and regulatory agencies that are reevaluating industry guidance and their enforcement strategies. *A GAMP Approach to Data Integrity, Electronic Records and Signatures, and Operation of GxP Computerized Systems* will cover data integrity, electronic records and signatures, and the compliant operation of GxP computerized systems to provide the tools and techniques to implement proper data controls to ensure the integrity and validity of the information throughout the data lifecycle.

HVAC (T14)

8–10 May

Copenhagen, Denmark

Are you able to resolve common HVAC issues for bio, bulk, laboratory, packaging, OSD, sterile, and warehousing operations? The *HVAC* course will include risk-focused discussions about change-rate frequency, facility classification, cross-contamination, system or individual component qualifying, common issues and problems in the operation of a facility, and maintaining readiness for cGMP inspection. Topics include control system alarm management, common system construction deficiencies, cGMP documentation, how to maintain an "inspection-ready" state, frequency of testing and balancing, airflow visualization, and air change-rate reduction. The course is a thorough review of global cGMP regulations, their common interpretations, and how they can apply to your facility.

C&Q for New and Renovated Facilities: Guidance and Improvements for Successful Delivery (T55)

16–17 May

National Institute for Bioprocessing Research and Training (NIBRT)

Dublin, Ireland

Can your C&Q program meet GxP regulations and comply with other relevant local and international governing codes, laws, and regulations? The successful delivery of manufacturing facilities (including small, large, new, expansion, or renovation projects), regulated by various authorities, poses significant challenges to manufacturers, engineering professionals, and equipment suppliers. This *C&Q for New and Renovated Facilities: Guidance and Improvements for Successful Delivery* course is designed to improve the way in which the industry delivers regulated manufacturing capacity: improving the ability to meet documented process requirements, controlling risks within the manufacturing process, producing high-quality products, and consistently operating to meet product and process requirements.

An Overview of Biopharmaceutical Manufacturing Processes (T24)

8–9 May

Copenhagen, Denmark

Can you effectively evaluate and compare various process alternatives for manufacturing biotech products? *An Overview of Biopharmaceutical Manufacturing Processes* covers the principles and unique challenges of biotech manufacturing processes. Topics include: identifying important operating parameters for each unit operation and how they impact process performance, parameters for process validation, critical factors for developing a viable commercial manufacturing process, process/facility relationships, options for single use technologies, cell culture and fermentation, harvest and recovery, viral removal and inactivation, tangential flow filtration, centrifugation, size exclusion, and adsorptive chromatography. Additional content will review current regulatory guidance affecting process development and execution, compare various process aspects of upstream and downstream operation, technology transfer, and trends and future biomanufacturing developments.

Cleaning Validation (T17)

8–9 May

Copenhagen, Denmark

Can you establish, manage, and maintain a scientifically sound cleaning validation program? With the US FDA's risk-based regulatory initiatives focusing new attention on the risks of cross-contamination, understanding lifecycle management techniques for an effective cleaning validation program is paramount. *Cleaning Validation* topics include: risk-based approach to cleaning development and verification; risk analysis, control, review and communication; procedures and evaluation tools including FMEA/FEMCA; master planning; PAT; periodic assessment and monitoring; selection of analytical and sampling methods; determination of residues to be targeted and appropriate limits in various pharmaceutical and biotechnology processes; and establishment of scientific rationales acceptable to regulatory inspectors. For mature cleaning validation programs, concepts such as understanding process control, capability, learning to effectively self-audit a cleaning validation program, and documentation will be essential takeaways.

Facility Project Management in the Regulated Pharmaceutical Environment (T26)*

10–11 May

Copenhagen, Denmark

Do you have the tools for successful project delivery? The interactive Facility Project Man-

agement in the Regulated Pharmaceutical Environment course provides more than the usual project basics. It develops the concept of project lifecycle from initiation through delivery of business benefits, along with tools to manage all project resources. It is specifically targeted to the needs of facility projects within the regulated pharmaceutical industry and demonstrates the value inherent in the use of "good practice" project management. Trends in regulatory compliance; environmental, health, and safety legislation; project delivery methodologies; and product speed-to-market expectations all affect how pharmaceutical facility projects are managed. Each course module introduces key project management concepts and tools as well as methodologies that specifically support successful project delivery.

OSD: Operations, Quality, Equipment, and Technology (T10)

10–11 May

Copenhagen, Denmark

Do you understand the latest issues associated with oral solid dosage forms? The newly updated *OSD: Operations, Quality, Equipment, and Technology* course examines current technology and provides scenario-based exercises for system troubleshooting and investigational events for process deviations, discusses quality management and GMP inspection preparation, and provides guidance on advanced asset lifecycle management strategy. A process and production video simulation for unit ops, including mixing, blending, drying, sizing, tableting, encapsulating, and coating gives participants a visual demonstration of current manufacturing and engineering practices. The simulation will present vivid real-time experiences to identify and analyze the problem, identify the root cause, and present solutions.

Practical Implementation of Process Validation Lifecycle Approach (T46)

9–11 May

Copenhagen, Denmark

Do you need a practical understanding of PV principles and expectations in the US and EU? This three-day course, *Practical Implementation of Process Valid ation Lifecycle Approach* includes a blend of presentation of concepts and details, followed by related practice application scenarios and exercises that will define the requirements for preparation, planning, and execution of validation/process validation and show how to maintain a state of control. It explores the three stages of the validation product lifecycle, including process design, equipment and utility qualification, establishing and implementing process performance qualification (US) or process validation (Europe) requirements, and putting an ongoing/continued process verification program in place.

UNITED STATES

Applying the Biopharmaceutical Manufacturing Facilities Baseline® Guide Principles (T31)*

8–9 May

San Diego, California

Do you know the regulatory requirements for new or for renovating biopharmaceutical facilities? Using case studies and exercises our course

in facility design provides an overview of the concepts utilized in the development and renovation of sound designs for facilities that manufacture biopharmaceutical products.

Applying the Biopharmaceutical Manufacturing Facilities Baseline® Guide Principles includes a review of facility design and regulatory issues important in the United States and Europe that involve industry trends and changing regulatory policy. Participants will discuss current case studies on a wide array of facility topics and complete class exercises that involve developing facility scope of work and deliverables to meet corporate economic goals and regulatory requirements.

A GAMP® Approach to Data Integrity, Electronic Records and Signatures, and Operation of GxP Computerized Systems (T50)

8–10 May

San Diego, California

Can your data integrity process stand up to regulatory scrutiny? Data integrity is currently one of the highest cited areas in regulatory observations and a topic of great interest for both industry and regulatory agencies that are re-evaluating industry guidance and their enforcement strategies. *A GAMP Approach to Data Integrity, Electronic Records and Signatures, and Operation of GxP Computerized Systems* course will cover data integrity, electronic records and signatures, and the compliant operation of GxP computerized systems to provide the tools and techniques to implement proper data controls to ensure the integrity and validity of the information throughout the data lifecycle.

Pharmaceutical Water Generation (T04)

8–9 May

San Diego, California

Are you able to differentiate regulatory requirements from regulatory myths for water treatment, storage, and distribution? Using the USP, EP, JP Monograph, USFDA "Guide to Inspections of High Purity Water Systems," current FDA views, and cGMP requirements, the *Pharmaceutical Water Generation* course will provide a sound regulatory framework to understand common water system myths. A variety of practical system designs will be evaluated for compliance, as well as their advantages and disadvantages. Particular attention will be paid to microbial control, laboratory water, key design philosophies, systems and component sanitization procedures, operation, testing and maintenance of equipment, and systems for water generation. Attendees will examine methods for proper water quality selection as well as study compendial and noncompendial water, fundamentals of basic water chemistry, and information on common unit operations (deionization, reverse osmosis and distillation). Pretreatment systems, detailed guidance for selection of construction materials, and operation issues related to pharmaceutical water generation systems will also be discussed.

HVAC (T14)

9–11 May

San Diego, California

Are you able to resolve common HVAC issues for bio, bulk, laboratory, packaging, OSD, sterile, and warehousing operations? The *HVAC* course will include risk-focused discussions about change rate frequency, facility classification, cross contamination, system or individual component qualifying, common issues and problems in the operation of a facility, and maintaining readiness for cGMP inspection. Topics include control system alarm management, common system construction deficiencies, cGMP documentation, how to maintain an "inspection-ready" state, frequency of testing and balancing, airflow visualization, and air change-rate reduction. The course is a thorough review of global cGMP regulations and their common interpretations and how they can apply to your facility.

Storage, Delivery and Qualification of Pharmaceutical Waters (T23)

10–11 May

San Diego, California

The *Storage, Delivery and Qualification of Pharmaceutical Waters* course provides the essential concepts and principles of specification, design, C&Q of equipment, and systems used to store and distribute water in pharmaceutical manufacturing. Additional topics include understanding the importance of microbiological control, analyzing the principles behind water system testing and qualification, the impact of water quality requirements (compendial and noncompendial), basic requirements for water distribution system component installation and overall system construction, integrating and streamlining commissioning and validation activities, and identifying alternative system designs and their advantages and disadvantages.

Sterile Product Manufacturing Facilities: Applying the ISPE Baseline® Guide and FDA Guidance Principles to Design and Operation (T12)

10–11 May

San Diego, California

Do you know the key requirements and GMPs for sterile manufacturing facilities? Through lectures and group exercises the *Sterile Product Manufacturing Facilities: Applying the ISPE Baseline® Guide and FDA Guidance Principles to Design and Operation* course reviews regulatory philosophy, aseptic process and equipment considerations, aseptic clean room design and operation, differential pressure requirements, airlocks; basic utility system monitoring, US and European HVAC considerations, C&Q issues, and a brief introduction to barrier isolation technology. An exercise in the layout of an aseptic filling facility will be used to demonstrate how to use process flow diagrams and an accommodation schedule to thoroughly define facility requirements before advancing to the floor plan layout stage. Additional topics include the use of RABS and isolator systems, and methods for contamination control.

Clean in Place Fundamentals (T03)

18–19 May

ISPE Training Institute

Tampa, Florida

Do you have the tools to design, build, and implement a cleaning process and identify cleaning solutions to complex cleaning processes? *The Clean in Place Fundamentals* (T03) 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 with 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. A dynamic hands-on workshop

will allow participants to work in groups to design, build, and implement a cleaning process for a pharmaceutical application. Participants will apply knowledge gained from the course to identify cleaning solutions to complex cleaning processes.

Science and Risk-based Commissioning and Qualification—Applying the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification (T40)

18–19 May

ISPE Training Institute

Tampa, Florida

Is your equipment and facility "fit for use" as defined by current global regulatory authorities? Guidance on the transition of an organization's approach to C&Q to one that incorporates a science- and risk-based approach is the basis for our *Science and Risk-based Commissioning and Qualification—Applying the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification* (T40) course. A detailed review of the principles and activities that constitute an efficient and acceptable approach to demonstrating facility and equipment fitness, improving the ability to meet documented process requirements, controlling risks within the manufacturing process, producing high-quality products and consistent operation to meet product user requirements will be explored. Additional emphasis will be placed on a review of ICH documents Q8 (R2), Q9, and Q10 and ASTM E2500.

Turning QbD into a Practical Reality (T43)

1–2 June

ISPE Training Institute

Tampa, Florida

Do you know how to use QbD to reduce costs, improve manufacturing and meet regulatory expectations? *Turning QbD into a Practical Reality* interactive uses group exercises to provide examples of how products and processes can be developed, using QbD with special emphasis on the considerations for implementing these processes in manufacturing. Topics include: understanding the principles of a science-and-risk-based approach; product and process understanding and patient requirements; using tools and techniques provided to understand QRM; implications of relevant ICH, EMA, ASTM E2500, and USFDA Guidelines; QRM tools (FMEA, risk ranking); applying FMEA to control strategy selection; relationship between PQS and GMP and how they link to control strategy; considerations when implementing a control strategy derived from enhanced QbD approaches; and opportunities for continual improvement arising from application of statistical techniques.

A Risk-Based Approach to GxP Process Control Systems: Applying the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (2nd Edition) (T21)

8–9 June

ISPE Training Institute

Tampa, Florida

Are your process control systems fit for use? Using a lifecycle approach for the development and management of process control systems, *A Risk-Based Approach to GxP Process Control Systems: Applying the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (2nd Edition)* course demonstrates how the principles and concepts of GAMP® 5 may be practically applied. The course covers both regulated company and supplier quality management systems and the full system lifecycle from concept to retirement. You will learn how appropriate QRM and specification and verification activities should be an integral part of the normal system lifecycle and how to leverage supplier documentation and activities to avoid unnecessary duplication, cost, and waste.

Basic Principles of Computerized Systems Compliance using GAMP® 5, Including Revised Annex 11 and Part 11 Update (T45)

12–14 June

Lilly MQ Learning Center

Indianapolis, Indiana

Are you leveraging a risk-based approach when validating your GxP computerized systems? The *Basic Principles of Computerized Systems Compliance using GAMP® 5*, Including Revised Annex 11 and Part 11 Update course explores tried, tested, and internationally recognized methods and provides a pragmatic and effective framework for achieving computerized systems that are fit for intended use and meet current regulatory requirements. ‹›

* *ISPE has been reviewed and approved as a provider of project management training by the Project Management Institute (PMI®)*

NEW GUIDANCE DOCUMENT AVAILABLE

ISPE GAMP® Good Practice Guide: Global Information Systems Control and Compliance (Second Edition)

The ***ISPE GAMP® Good Practice Guide: Global Information Systems Control and Compliance (Second Edition)*** covers major issues related to multisite computerized systems, and provides guidance on effective and efficient control, and compliance of globally deployed IT systems throughout their life cycle.

In particular, this guide aims to assist in the following aspects of widely used, regulated, global information systems:

- Development
- Management
- Validation
- Implementation
- Maintenance

This revised guide is intended to be used in conjunction with *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* and other ISPE GAMP® guidance documents. It reflects changes in typical system architecture since the First Edition, and also covers Software as a Service (SaaS) and other cloud solutions.

Thank you to all guide contributors:

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MEET YOUNG PROFESSIONAL TAKENORI SUMI

Takenori Sumi

Takenori Sumi (second from left) at a Japan Affiliate YP working group meeting

There's an adage that says "the first step in getting anywhere is knowing where you want to go." That certainly seems to hold true for Japanese Young Professional Takenori Sumi, who not only has mapped out the things he must learn to advance his career, but also has a clear idea of where the pharmaceutical industry itself is headed.

Born in 1989 in the Fukuoka Prefecture on Japan's main island of Kyushu, Sumi is a young man with a love of Japanese dishes like tonkotsu ramen, motsunabe hot pot, and mentaiko, as well as a fondness for watching James Bond movies while drinking Scotch. He graduated from the Keio University Faculty of Science and Technology in 2011, and completed his master's course at the Keio Graduate School of Fundamental Science and Technology. He majored in the organic synthesis of natural products and the electrosynthesis of organic chemistry, with specific research on the study of synthetic macrolide compounds and electrochemical reaction mechanisms via boron-doped diamond electrodes.

AN ONGOING EDUCATION

As with most people, Sumi's education has continued on the job. Following graduation, he joined the Japanese specialty pharmaceutical firm Asahi Kasei Pharma Corporation, which has a global presence and focuses on the development of new drugs in selected therapeutic fields.

"I was assigned to the Nagoya pharmaceutical plant, our formulation plant, as a pharmaceutical engineer," says Sumi. "I was assigned to the Pharmaceutical Technology Department and engaged in establishing the manufacturing process, involving qualification and verification of oral dosage and injection."

Still very new in his career, Sumi already sees some areas where he would like to grow. "I have a great interest in the study of optimizing drug formulation," he says. "Since joining the company, I have consistently been involved in pharmaceutical manufacturing. Therefore, I understand the manufacturing processes for both oral dosage and injection. On the other hand, I have no experience with designing drug formulation as the upstream development process of manufacturing. I believe that acquiring knowledge of drug formulation is helpful for establishing a robust manufacturing process.

"In addition, I need overseas experience for my career as a pharmaceutical engineer. Since I have no experience with going abroad in a business situation, I am sure that such experience will lead to my own growth."

INVOLVEMENT WITH ISPE

Sumi views ISPE as a catalyst for personal growth. "As far as foreign experience goes, I feel that ISPE offers many fascinating opportunities to communicate with overseas companies and regulatory authorities," he says. "While I have only been involved in the events held by the Japan Affiliate thus far, I would like to attend international ISPE events in the future."

Sumi's first contact with ISPE was at the Japan Affiliate's eighth Young Professionals seminar in September 2014. The seminar was on the basics of oral solid dosage, and Sumi had been assigned to OSD jobs for the first time. "I remembered that there was a good-feeling atmosphere to ask questions and communicate with each other," he says. "Since then, I have attended the YP seminar many times. At the 2016 Japan Affiliate Annual Meeting in April, the YP workshop was held and I had a great opportunity to make a presentation at the twelfth YP seminar as a representative of all attendees."

Sumi says he appreciates ISPE's place in the pharmaceutical industry and how it provides access to beneficial technological information as well as opens communication channels between

Takenori Sumi (third from left) and ISPE Board Chair Mike Arnold (right) at the 2016 Japan Affiliate Meeting

industry and regulatory authorities. "ISPE's Baseline Guides are widely accepted in the pharmaceutical industry," he says. "We [members] can expand our knowledge and build a wide human network through ISPE. And the Japan Affiliate offers new technological information at the YP seminars at a reasonable and affordable price."

THE ROAD AHEAD

As he looks ahead to the next decade in the pharmaceutical industry, Sumi predicts that more efficient manufacturing will be a dominant theme. "Therefore, the role of the pharmaceutical engineer will be increasingly important," he says. "As an example, continuous manufacturing process has received a lot of attention in recent years. To develop the continuous manufacturing process, it is important that the pharmaceutical industry and regulatory authorities move forward though cooperation. I believe ISPE can activate communication and enable the sharing of opinions and ideas.

"I strongly believe that pharmaceutical engineers can contribute to the development of the pharmaceutical industry by speaking actively through ISPE events. And I feel it important that the YPs of the world have more relationships with each other. By involving YPs with each other, new and unique technology can be created; this leads to the further development of the pharmaceutical industry. ISPE will be the trigger to promote communications between YPs and I will be happy to help achieve the transnational communications with YPs in the years ahead," he concludes. ‹›

—Mike McGrath

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—Amy R. Loerch

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MEET YOUR BOARD


Timothy Howard


James Breen


Frances Zipp


Joseph Famulare

Pharmaceutical Engineering consulted ISPE's new Board of Directors Executives to discuss making a difference, member concerns, objectives for 2017, and their visions for the future.

In this issue, we talk to:

Timothy Howard, Vice Chair: Vice President of Strategy and Development, Commissioning Agents, Inc.; ISPE member since 1993

James Breen, Treasurer: Vice President Lead, Biologics Expansion, Janssen Pharmaceuticals; ISPE member since 2000

Frances Zipp, Secretary: President & CEO, Lachman Consultant Services, Inc.; ISPE member since 2013

Joseph Famulare, Past Chair: Vice President, Global Quality Compliance and External Collaboration, Genentech/Roche, Pharma Technical Operations; ISPE member since 2001

1. IN YOUR ROLE AS BOARD EXECUTIVE, HOW DO YOU DEFINE "MAKING A DIFFERENCE"?

Tim Howard: The first thing that comes to mind when I hear "making a difference" is the patient, or the end-user of the products. Whether it be initiatives to drive down drug shortages, collaborating on facilities of the future, or training the next generation of technical professionals, ISPE has recurring opportunities to make a huge difference to those who need and use the products of our industry. Our strategic plan identifies the areas where we are best suited to make such a difference. Executing this strategy is how the board can make a difference.

Jim Breen: Ensure that the thoughts, desires, and needs of all ISPE members globally and across all facets of the industry are heard, that their views are used as input into ISPE strategy, and that our programs help members prepare for the future.

Fran Zipp: ISPE has been a source of education and guidance for many pharmaceutical professionals since its inception. I strongly believe the role of every Board member is to be personally committed to this by assuring our knowledge reflects technology leading edge and compliance best practices with global awareness in all we do.

Joe Famulare: "Making a difference" means being able to ensure we can efficiently deliver medicines to patients, and we keep that in front of us while we delve into the many areas of expertise and technology we bring to our membership as part of our goal to deliver high-quality medicines.

2. WHAT IS THE ONE OBJECTIVE YOU BELIEVE YOU MUST ACHIEVE IN 2017?

Tim Howard: I fully support the initiative championed by our Chair, Mike Arnold, which is to drive greater engagement and involvement with ISPE's Young Professionals. Success with this objective will reap benefits in the short term as well as in the decades to come.

Jim Breen: I feel we need to progress this industry in the Facility of the Future area so we can deliver quality products at the right time at the right price to our customers around the world. We have added a Facility of the Future category in the ISPE Facility of the Year Awards, and we ran a very successful Facility of the Future event in October 2017 with a great response globally.

Fran Zipp: My personal objective is to support ISPE's overall goals. Another critical objective from my perspective is to support transparent and timely communication to our entire community and then turn the dialog into action.

Joe Famulare: In achieving one that is important, it is valuing the diversity of our membership from our active programs with Young Professionals, Woman in Pharma, and recognizing the diverse talents we have in all parts of the world, making up ISPE's strength at present and for the future.

3. HOW DO YOU STAY IN TOUCH WITH MEMBER CONCERNS AND SUCCESSES?

Tim Howard: The best way to connect is through the Chapters and Affiliates, which is where most members experience or interact with ISPE as an organization. My goal over the next two years is to attend as many Chapter and Affiliate events as I am able, which will allow me to connect with members.

Jim Breen: By attending our ISPE International events, local Chapter programs, and talking with industry thought leaders. I try to track the pulse of what is important in the industry and the concerns of our members globally. In my job, I interact with many service providers (engineers, builders, consultants, etc.), equipment suppliers, industry organizations, and academic institutions, so I use all these inputs to ensure that what ISPE provides to our members is relevant, timely, and of the best quality.

Fran Zipp: I engage as both a participant and a leader in several educational sessions and find the open discussions most helpful to take a pulse on key concerns and achievements. I also rely on

industry contacts, fellow Board members, and ISPE staff to share perspectives—especially from groups such as Young Professionals.

Joe Famulare: Our meetings conferences and training events are the best way. The opportunity to interact and network cannot be underestimated and is the best way to get really frank feedback. We also have electronic forums such as our CoPs and electronic media that are of value to members.

4. HOW DO YOU SEE ISPE GROWING OVER THE NEXT THREE YEARS?

Tim Howard: I don't see growth in terms of member numbers or a geographic footprint. I see it as broader access to and collaboration with ISPE's core body of knowledge. I expect ISPE will continue to improve and evolve with respect to how members can access our body of knowledge and collaborate with industry professionals.

Jim Breen: I see ISPE helping its members prepare for future changes within the industry. Examples include more focus on Young Professionals, members in emerging markets, new training programs, Women in Pharma, Facility of the Future, etc. ISPE is also reaching out to new partners in industry, government agencies, and academia in an effort to develop the best programs for our members. We are much leaner and more flexible, which allows us to react to the changes in the industry.

Fran Zipp: ISPE is continuing to evolve to meet the needs of the changing workforce. Under ISPE and Board of Directors leadership, we are focusing on Young Professionals and Women in Pharma as well as breakthrough technologies and the needs of the global community. We are building on our history of strong technical capabilities to help educate and harmonize across our broad network.

Joe Famulare: ISPE will grow in the diversity of membership, need for new efficient technologies, and the need to make medicines accessible to patients worldwide. I encourage all members to look at our strategic plan, as we are guided by it as a Board of Directors. ‹›

CFDI INVITES ISPE EXPERT TO PARTICIPATE IN TRAINING PROGRAM FOR NATIONAL GMP INSPECTORS

Training new recruits is something the Center for Food and Drug Inspection (CFDI) takes seriously. The Chinese agency has steadily increased its international inspection coverage over the last five years, and the number of National GMP Inspectors has rapidly risen to 649. The agency recently invited Charles Tong, PhD, Executive Council Member of ISPE China's Board, to lead a one-day training session on process development and validation as part of an eight-day training event. More than 40 new National GMP Inspectors attended the session held in December 2016 at the Ritan Hotel's conference center in Beijing.

"Training participants found the session helped them understand important principles and learn practical applications related to process validation in a lifecycle approach," said Dr Tong.

The training session was one-day in-class training program that uses material adapted from the ISPE "Practical Implementation of Process Validation Lifecycle Approach" training course. The program, conducted in English, consists of a lecture and presentation followed by a question-and-answer session.

"This program strengthens the collaboration between ISPE and CFDI, and furthers ISPE's goal of sharing knowledge on topics important to the industry and the regulatory agencies," said ISPE CEO and President John E. Bournas. ‹›

CAREER PIVOT: FOUR STEPS FOR A SUCCESSFUL TRANSITION

Hi David, I am trying to make a career change. I want to move into a different area of engineering, and I am not having any luck. How can I be more effective?

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

Transitioning to a new functional area can be difficult; it requires a different approach than pursuing opportunities in the same space.

GATHER DATA

First, gather data so you can assess the change you want to make; it's critical that you understand the job function you want to pursue. Job descriptions are a good source of information, but you will likely need to dig deeper. Use LinkedIn to research the background of people currently in a role that you want to pursue. Examine their job histories, education, and training—how do they compare to yours?

Informational interviews are also important. There often is no better source for understanding job requirements than top performers who are currently doing the job. Asking about their career paths, how they obtained their positions, and what they learned along the way can provide a great deal of insight. A personal connection might also be able to help with a resume review or even a recommendation.

Attending ISPE conferences or other networking opportunities can also help focus on the area you are pursuing. These events are often excellent sources for information about the kind of work performed, new technology, and best practices.

LOOK INWARD

Once you've gathered your data, you will need to look inward and complete a thorough gap analysis. Ask yourself several questions

- What projects, training, and technology would be directly applicable in my new function?
- How critical is this knowledge to the core function of the role I am pursuing?
- What have I *not* been exposed to?
- Am I being realistic? Do I have the knowledge and experience to be successful?
- How would I close these gaps? Do I need to take a course? Should I consider job shadowing or taking on a project to gain knowledge or experience?

There are many tools on the internet that can help you with this exercise. Whichever one you choose, however, make sure it helps you understand what you would bring to the role on Day One, what support you would need to transition, and what gaps you can reasonably close by your own means.

Before applying, there are several other ideas to consider.

HERE OR THERE?

It is usually easier to pivot into a new department within the company you are already working for. You likely already know about its systems and procedures, which will make training in other areas easier. You also probably have internal connections that can provide help and advice. Your track record and demonstrated learning agility is also known.

Sometimes an internal move is not possible—the firm may be too small or the desired function does not exist. In this case, you will need to find a way to obtain the necessary knowledge and relationships with another company.

While organizations often look to external candidates that offer a different background and fresh way of thinking, hiring managers know that they take on potential risk when they hire someone without direct experience. You will need to utilize the information from your assessment, your knowledge of the company, and any connections you've made to help frame the argument that you would be a great fit with minimal risk of failure and high potential for long-term success.

If this bar is too hard to clear, you may want to consider a lateral move to an organization that would allow you to move internally once you have gained knowledge and a track record. You will need to use your data-gathering method to assess the potential for such an internal pivot.

FOCUS YOUR RESUME

Focus on where you want to go in relation to where you have been. Review the job description you are considering and go through an exercise of turning each job duty and requirement into a question. Your answer should indicate the training or experience you have to prove you meet the requirements. Where you lack direct experience, think about what you have done that is similar and transferable. Don't forget to add real outcomes (cost savings, improved safety, reduced errors, etc.) to enhance the value of what you choose to highlight.

This should help translate your experience so that the hiring manager can better understand your qualifications. It can also tell you what to eliminate from you resume. I can't overstate the importance of customizing your resume in this way. I have heard countless comments from hiring managers wondering why a candidate applied for a certain job with a resume so focused on irrelevant skills and experiences that he or she appeared to be seeking a completely different kind of role. ‹›

Thank you once again for your questions. I hope you will find this guidance helpful. If you are curious about other topics, please email me at david.g.smith@biogen.com, and I will likely answer in a future column.

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THE GROWING INFLUENCE OF PIC/S IN ASIA PACIFIC

Bob Tribe, ISPE Asia Pacific Regulatory Affairs Advisor and former Chair of PIC/S, Canberra, Australia

The Asia Pacific region, which comprises 24 culturally diverse countries, contains 60% of the world's population and is the fastest growing region in the world today.

This article describes the growing influence of Pharmaceutical Inspection Co-operation Scheme (PIC/S) in the Asia Pacific region. Of the 24 countries in the Asia Pacific region, 19 are being influenced in some way by PIC/S in their regulation of medicine manufacturers

PIC/S was established in 1995 as an extension of the Pharmaceutical Inspection Convention (PIC), which had been created in 1970 and entered into force in 1971.[1]

PIC/S celebrated its 40th anniversary with an international symposium involving regulatory authorities and industry representatives in Geneva, Switzerland, in May 2011. During the symposium, Dr Margaret Hamburg, the Commissioner of the US Food and Drug Administration (FDA) at that time, delivered a keynote address that summarized succinctly the role and importance of PIC/S as a global leader in helping to ensure the quality of medicines.[2] She said:

No one country is capable of inspecting the world on its own. The US FDA considers PIC/S to be a global leader in helping to ensure the quality of drugs. For the US FDA, PIC/S represents the best way to avoid duplication of efforts and to allocate resources based on risk. All Regulatory Authorities should co-operate more closely and share information on GMP inspections.

But what is PIC/S? PIC/S is an informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing Practice (GMP) for medicinal products for human and veterinary use. As membership of PIC/S is not legally binding, it enables information such as GMP inspection reports to be exchanged with ease between member authorities. The above statement by Dr Hamburg clearly encapsulates PIC/S's information-exchange role.

Membership of PIC/S is open to any regulatory authority that has a system of GMP inspection controls in place that is equivalent to the procedures and requirements of current PIC/S member authorities. Currently, there are 49 regulatory authorities from around the world that are members of PIC/S. (Refer to Table 1 below.) The Thailand Food & Drug Administration (Thai FDA) was the most recent regulatory authority to become a member of PIC/S in August 2016.

An essential prerequisite to becoming a member of PIC/S is that the applicant authority must have in place a fully functional Quality Management System covering the systems and procedures of the Inspectorate, including GMP inspection procedures, manufacturer licensing procedures, document control procedures, complaint and recall handling procedures, a program for the training of inspectors, Code of Ethics for inspectors, etc.

PIC/S aims to harmonize GMP inspection procedures by developing common standards in the field of GMP and providing training opportunities for GMP inspectors. It also aims to facilitate cooperation and networking between competent authorities, thus increasing mutual confidence and trust.

This is reflected in the PIC/S mission statement, which is:

To lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products.

The philosophy of PIC/S is based on cooperation, communication, and trust. As information sharing within PIC/S is voluntary, it is up to the receiver of the information to decide how to use it. For example, a member authority can use the outcome of an inspection conducted by another member authority to avoid duplicating an inspection.

GROWING INFLUENCE OF PIC/S IN ASIA PACIFIC

Of the 24 countries in the Asia Pacific region, 19 are being influenced in some way by PIC/S in their regulation of medicine manufacturers. This is summarized in Table 2 below.

It is worth noting that of the nine regulatory authorities that became members of PIC/S over the past 4 years, seven of these authorities were from the Asia Pacific region. Furthermore, there are at least six regulatory authorities, including China and India, that are showing an interest in joining PIC/S. This highlights the strong interest in PIC/S being shown by regulatory authorities in Asia Pacific.

Although the regulatory authorities of Cambodia, Laos, and Myanmar have not yet shown an interest in joining PIC/S, they have committed to using a "PIC/S-equivalent GMP inspection framework" under the Association of Southeast Asian Nations (ASEAN) Sectoral

Table 1: 49 PIC/S Member Authorities (as at 1 August 2016)

Regulatory authorities of:

Argentina	France (hum)	Latvia	Slovenia
Australia	France (vet)	Liechtenstein	South Africa
Austria	Germany	Lithuania	Spain
Belgium	Greece	Malaysia	Sweden
Canada	Hong Kong	Malta	Switzerland
Chinese Taipei	Hungary	Netherlands	Thailand
Croatia	Iceland	New Zealand	Ukraine
Cyprus	Indonesia	Norway	UK (hum)
Czech Rep. (hum)	Ireland	Poland	UK (vet)
Czech Rep. (vet)	Israel	Portugal	USA
Denmark	Italy	Romania	
Estonia	Japan	Singapore	
Finland	Korea Rep.	Slovak Rep.	

Mutual Recognition Arrangement (MRA) on GMP,[3] including the adoption of the principles of the PIC/S GMP requirements.

Although only four of the 10 ASEAN member countries are currently members of PIC/S, regular cooperation between PIC/S and the ASEAN Consultative Committee takes place whenever PIC/S training seminars are held in the ASEAN region. The purpose of these meetings is to discuss how PIC/S can support those ASEAN inspectorates seeking to join PIC/S as well as support the training of inspectors from the ASEAN region.

In recognition of the growing importance of the Asia Pacific region, PIC/S has over the past 9 years arranged for its annual training seminars for GMP inspectors to be held in three different locations in the Asia Pacific region. Furthermore, the PIC/S training seminar in 2017 will be held in Taipei. (Refer to Table 3 below.)

Incidentally, the 2016 PIC/S training seminar was held in Manchester, UK, on the topic of "Inspectorates of the Future." [4]

Although PIC/S training seminars are open only to GMP inspectors (from PIC/S member authorities and authorities interested in joining PIC/S), ISPE usually arranges for an appropriate representative to give an "industry perspective" presentation related to the seminar topic.

The current Vice Chairman of PIC/S is Meow Hoe Boon of the Health Sciences Authority (HSA) in Singapore. He will become the Chairman of PIC/S in 2018 for a period of 2 years. (The current Chairman of PIC/S is Paul Hargreaves of MHRA, UK.) Boon is currently the Chairman of a PIC/S project to establish the PIC/S Inspectorates' Academy (PIA), which is an online training platform for PIC/S GMP inspectors.[5] ISPE is in regular communication with Boon about contributing ISPE e-learning training materials to the PIA.

Upcoming challenges for PIC/S will include the handling of membership applications from the regulatory authorities of China and India, which are expected to be submitted in the future. These two regulatory authorities will be difficult to assess in comparison to most other applicant authorities, mainly because of their use of decentralized inspection offices covering vast areas of China and India.

From the time the formal application is lodged, it usually takes between 3 and 4 years for an applicant authority to become a member of PIC/S. Applications that exceed the 6-year timeline set by PIC/S are rejected. This has happened to at least three applicant authorities to date, but each of these authorities was invited to re-apply—which it did. An applicant authority can request a "stop clock" of up to 12 months in situations such as the adoption of new legislation or a major reorganization by an authority.

The first stage of the assessment process involves a desktop review of the systems and procedures of the Inspectorate against a checklist of 78 key indicators to determine whether the Inspectorate's Quality System and related procedures are equivalent to PIC/S requirements. This desktop review is undertaken by a rapporteur and co-rapporteur appointed by the PIC/S Committee, with this stage usually taking 1 or 2 years to complete.[6]

The next stage of the assessment process is an onsite visit by a PIC/S assessment team of five or six experienced PIC/S inspectors to confirm that the Quality System of the Inspectorate is acceptable and determine whether GMP inspections are equivalent to PIC/S inspection standards. The latter involves observing several typical GMP inspections to see how inspections are performed and how manufacturers, particularly manufacturers with GMP problems, are handled.

While the length of a PIC/S assessment visit is usually 1 week, more than a week may be needed for China and India to observe a good cross section of regional inspection offices, including their operations, procedures and inspection standards. The PIC/S assessment team will usually include one or two persons who speak the language of the country in which the assessment is being undertaken.

During the assessment period, various changes and improvements are usually recommended by PIC/S. If necessary, follow-up visits are undertaken to verify the suitability of corrective actions.

Table 2: Asia Pacific Regulatory Authorities

Regulatory authorities of:

Current PIC/S Members (at 1 August 2016)		Interested in joining PIC/S	Using the PIC/S GMP Guide
Australia	*From January 1993*	P.R. China	Cambodia
Singapore	*From January 2000*	India	Laos
Malaysia	*From January 2002*	Bhutan	Myanmar
Indonesia	*From July 2012*	Brunei	
New Zealand	*From January 2013*	Vietnam	
Chinese Taipei	*From January 2013*	Philippines	
Japan	*From July 2014*		
South Korea	*From July 2014*		
Hong Kong	*From January 2016*		
Thailand	*From August 2016*		

Table 3: PIC/S Training Seminars in Asia Pacific since 2007

Singapore	2007	Inspection of the Manufacture of Solid Dosage Forms
Kuala Lumpur, Malaysia	2010	GMP Inspection of Manufacturers of Traditional/Herbal Medicinal Products
Nusa Dua, Indonesia	2015	Biopharmaceuticals (Biotechnology & Biologicals): How to Inspect
Taipei, Chinese Taipei	2017	Quality Control Laboratories; How to Inspect

SUMMARY

Of the 24 countries in the Asia Pacific region, 19 are being influenced in some way by PIC/S in their regulation of medicine manufacturers. The regulatory authorities of 10 of these countries are already members of PIC/S, while at least another six countries are showing interest in becoming members of PIC/S, including the regulatory authorities of China and India.

The assessments of China and India for PIC/S membership will be a challenge for PIC/S mainly because of the use of decentralized inspection offices covering vast areas of these countries. ❮❯

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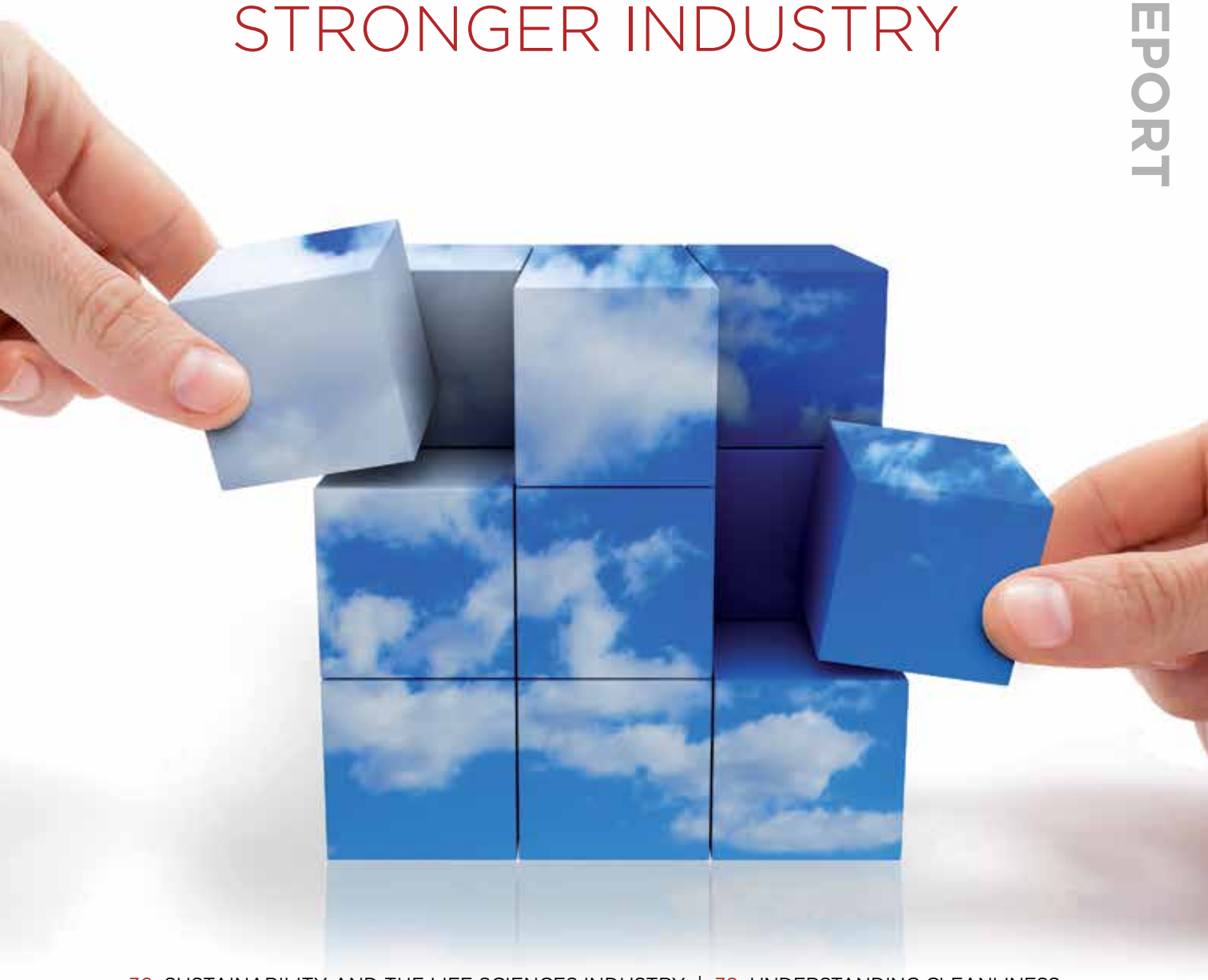

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SUSTAINABILITY AND THE LIFE SCIENCES INDUSTRY

Rob Bowen

Sustainability, also referred to as sustainable development, has, in the pharmaceutical industry, been, in the main, in the background, especially when it comes to facilities and engineering. In the few cases where dedicated individuals or companies have recognized the long-term benefits of being early adopters, it has been questioned as to its relevance. An element of this is the belief that sustainability is a fad word with short-term political relevance, or that it is just about sensible energy management at a time of high energy prices.

Well, that may seem so, but many see a wider definition and believe that adopting a sustainable policy, whether there is or is not a belief in climate change, makes for strategic relevance providing sound ethical and economic base case for operation.

Ahead of ISPE's production of a handbook on the topic, the key pharmaceutical global players (based on Forbes's 2016 top ten "2016 Global 2000: The World's Largest Drug and Biotech Companies") have produced sustainability policies that are embedded in their company policy set.

In this short article, we touch on the history and breadth of sustainability, why ISPE produced its Sustainability Handbook, give some insight into the basis the writing team adopted, the topics covered, and why it is both an important document and an essential topic.

WHY AN ISPE SUSTAINABILITY HANDBOOK?

ISPE's involvement in sustainability began in 2008, when Paul Malinowski of Becton Dickinson (USA) and Nigel Lenegan of Energy and Carbon (UK) established the Sustainability Community of Practice (CoP), which has since merged with the HVAC CoP to form the HVAC and Sustainable Facilities CoP. This was followed in 2009 by the first annual Facility of the Year Award for Sustainability.

During 2013 the CoP, realizing that there was no other pharmaceutical industry–focused guidance on the topic, put forward a proposal for a Good Practice Guide, supported by a *Pharmaceutical Engineering* article later that year.[1] The 14-member contributing team, led by this author and Nick Haycocks of Amgen, ably guided by the ISPE in-house publications and editing team, developed a two-part document. On review, it was agreed that it was more of a handbook than a guide.

To produce a globally relevant handbook, the team opted to adopt the United Nations (UN) take on sustainability. The UN, following reports such as 1972's "The Limits to Growth," reacting to perceived global changes in temperature and weather patterns, as well as recognizing a reduction in finite resources and imbalancing increases in population, set up the World Commission on Environment and Development in 1983. This commission, chaired by Dr Gro Harlem Brundtland—widely referred to as the Brundtland Commission—produced the highly influential report "Our Common Future" in 1987. This provided what is now considered the primary definition of sustainability: "development that meets the needs of the present without compromising the ability of future generations to meet their own needs." This definition was adopted for the handbook.

Since 1987 the UN has held yearly conferences on sustainability and climate change. The key conference initiating action was held in Kyoto in 2002, leading to the adoption of the Kyoto Protocol, setting global targets based on a 1990 baseline for the accepting countries and an expectation of improvements in many areas. The last significant conference was held in Paris, France, from 30 November to 12 December 2015, and produced the Paris Agreement, which outlined Kyoto follow-on targets aimed at global carbon neutrality by the end of this century. The primary target of the agreement is to limit the increase in global average temperature to 1.5°C above preindustrial levels with, post peak, more significant reductions based on the best available science.

This latter objective will make demands of all industrial operations. It was also, unlike Kyoto, entered into by both the United States and China. Participants agreed to meet every five years to set more ambitious targets, as required by science, and to report through use of a robust transparent and accountable reporting system very similar to our global pharmaceutical regulatory systems. These targets are significant and place a heavy onus on global political systems to ensure implementation.

To this end, our industry, as one focused on the health of the patient, has a particular ethical interest in sustainability and implementation in all its forms.

WHAT DOES THE HANDBOOK COVER?

The handbook is split into two sections, the first on principles and policy and the second on design and engineering applications.

In the first instance, we address the principles, some history, and contextual background, along with legislation, regulation, and the "how-to" of setting a sustainability policy. The team opted to help make the path toward a sustainable future operation understood through provision of direction and examples and, through the appendix, by providing useful links. The section ends with some thoughts on future trends with a focus on waste—or rather, a challenge to the need for waste.

The application section of the guide is broken down into discipline-based

guidance and focused sections on energy and waste. These include topic areas covering carbon footprinting, green chemistry, facility sustainable design principles, HVAC design concepts, voltage optimization, clean utility optimization, and waste management. Each topic area was chosen to aid both understanding of lines of research and practical integration of sustainable practices into project working.

HOW DO WE ENGAGE?

The expectation is for engagement at all levels of operation, particularly through the inclusion of sustainable development based objectives into the programs of all projects. At pre-project and concept-design levels this may be achieved through the application of sustainability by design as an adjunct to key quality parameters, as a key element of quality by design, and made a part of project and operational metrics from the beginning.

At board level, this may be supported through a reaffirmation of an ethical clinical stance paralleled by a commitment to sustainable objectives and investment through adoption and reportage on sustainability. This can be achieved through the setting a sustainability policy that includes sustainability-based long-term goals when master planning, carrying out life cycle assessment studies of both sites and projects, and implementing individual environmental design assessments to ensure that preset targets are both understood and met.

From procurement of materials to choice of supply chain methodology, the encompassment of sustainable systems neither has to be costly nor time consuming, and the results have shown to be both ethically satisfying and economically beneficial through setting sound achievable long-term sustainability based goals.

The *ISPE Handbook: Sustainability* aims to act as an aid, source and Guidance Document in achieving these objectives. ‹›

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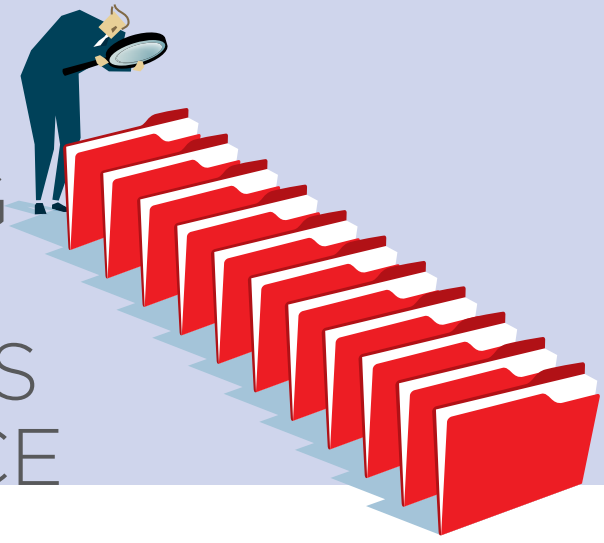
About the author

Rob Bowen is Director of Facilities Integration, an architect-led pharmaceutical consultancy specializing in master planning, concept design, and design development. He has spent over 35 years as a practicing architect, more than 25 of which have involved specializing in the design of complex specialist facilities. He is a past research fellow of the University of Warwick on an oral solid dose continuous processing study culminating in a design for a factory of the future. The overall study won the UK IChemE Outstanding and Project awards for 2012 for GSK, GEA, Siemens, Sagentia, and Warwick, Surrey, and Newcastle Universities. Rob is a past Director on the UK Affiliate Board, a Guidance Document Committee member, and a member of ISPE's HVAC/Sustainable Facilities Community of Practice. He led the ISPE *Sustainability Handbook* team with Nick Haycocks and was a chapter lead on the 2013 ISPE *Biopharmaceutical Facility Guide*. He has been an ISPE Member since 2001.



UNDERSTANDING CLEANLINESS CLASSIFICATIONS FOR LIFE SCIENCE FACILITIES

Norman Goldschmidt and Gordon Farquharson

In recent years we have observed misunderstanding and confusion over correlation between the 2004 US Food and Drug Administration (FDA) environmental cleanliness requirements for sterile product manufacture[1] and those of the European Medicines Agency EudraLex Volume 4, Annex 1.[2]

This misunderstanding, which began before the demise of Federal Standard 209, has been exacerbated by the introduction of the ISO cleanliness classification system standards in 1999 (14644-1:1999) and most recently in the 2015 revisions (14644-1:2015). The situation has since become more critical because the Annex 1 requirements in are replicated virtually verbatim in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and World Health Organization (WHO) good manufacturing practice requirements, which are used by regulators around the world. Such broad adoption of virtually identical regulatory guidance based on the European Union (EU) system has also aggravated the situation.

The strong similarities between the systems are likely to have led to the common misapplication of designations and incorrect correlation between classification systems. In addition, subtle differences in the requirements can cause even greater confusion:

- Both EU and PIC/S require "in-operation" and "at-rest" classifications.
- Both EU and PIC/S specify a "cleanup" or "recovery" time and qualification thereof.
- The FDA standard classifies and monitors airborne particles at a single size threshold of ≥ 0.5 µm; EU and PIC/S use two size thresholds: ≥ 0.5 and 5.0 µm.
- EU and PIC/S airborne ≥ 5.0 µm particle concentration limits for grade A cleanliness do not align with ISO 5 class limits.
- Designation and qualification of a class below ISO 8 in operation (Grade C) as ISO 8 at rest (Grade D) vs. ISO 9 in operation or "controlled, not classified" (CNC).

Before beginning a discussion of differences within modern classification systems, it is perhaps advisable to review space classification before harmonization efforts led to the current systems.

ISPE HAS ATTEMPTED TO BRIDGE THESE SOMEWHAT CONFUSING DIFFERENCES WITH A SINGLE COMPOSITE CLEANLINESS GRADING SYSTEM INTENDED TO SATISFY INTERNATIONAL REGULATORY BODIES AND MAKE GOOD SCIENTIFIC SENSE

FS 209

The classification of space by airborne particulate concentration began with Federal Standard 209 in 1963 and is the source for the classifications still used by the US Pharmacopeia and FDA (Table A):

Other countries established standards that further complicated the terms and nomenclature affecting the design and cleanliness classification of global cleanroom facilities (Table B).

As you can see, our current issue of aligning two standards is small by comparison to the historical alignment of diverse global standards. What's more, the current underlying harmonized standard for space classification serves to align regulations to a great degree. To fully understand the similarities and differences between regulatory requirements, we must understand the harmonized space classification system on which they are based.

Table A: FS 209: Space classification by particle concentration per cubic foot

	Particle size, µm				
Class	0.1	0.2	0.3	0.5	5.0
1	35	7.5	3	1	–
10	350	75	30	10	–
100	–	750	300	100	–
1,000	–	–	–	1,000	7
10,000	–	–	–	10,000	70
100,000	–	–	–	100,000	700

ISO 14644-1:1999 (superseded): This standard defined classes of cleanliness by airborne particle count concentration following a decimal system. The classes are illustrated in Table C for a series of size ranges. The relationship between ISO class number, particle number concentration, and reference particle size is defined in the standard by the formula $Cn = 10^N \times (0.1/D)^{2.08}$, where Cn is the particle count, N is the ISO class, and D is the particle mean diameter in millimeters.

ISO 14644-1:2015: This standard replaces ISO 14644-1:1999, but serves the same purpose as the prior standard (Table D), with some notable changes:

- There is no class limit particle count specified for ≥ 5 µm particles at ISO 5 due to the uncertainty of counting these large particles at low concentration.
- Monitoring ≥ 5 µm particles at low concentration must be done in concert with another particle size; the "macro particle" descriptor M should be added to communicate the uncertainty of the reading.
- The decimal classification system must be adjusted to 0.5 class increments (e.g. ISO 4, ISO 4.5, ISO 5)

Although this common standard now harmonizes space classifications in regulations across the world, differences in interpretation can result in some ambiguity.

US FDA APPLICATION OF ISO CLASSIFICATIONS

The 2004 FDA Guidance for Industry cited at the beginning of this article provides some clarification of the FDA use of ISO grades. At all grade levels the FDA assumes a particle size of ≥ 0.5 µm and that classification and monitoring occur with the room in operation. The guidance also assigns unique definitions to some classifications:

ISO 5: A space that has been classified to meet ISO 14644-1 requirements (3,520 particles/cubic meter) for airborne 0.5 µm particulate in the in-operation state. These spaces are constructed with a "flushing" or "sweeping" generally unidirectional airflow that protects critical areas, with a suggested velocity of 0.45 meters per second ±20%, or as justified and qualified via airflow visualization.

ISO 9: A space that has been classified to meet ISO 14644-1:1999 requirements (35,200,000 particles per cubic meter) for airborne 0.5 µm particulate in the in-operation state. This classification does not actually appear in FDA guidance but is found in some FDA-regulated facilities.

Terms and Definitions

Ambient environment: Environmental conditions where no HVAC systems are present.

Uncontrolled (UC): Areas where HVAC systems may be present, but no claim is made or qualified for the specific control of particulate, temperature, or humidity. These areas are sometimes referred to as "general" or "comfort-controlled" areas within pharmaceutical facilities such as office and technical space. May also be designated "not controlled (NC)."

Classified space: Areas in which HVAC systems are designed to reduce airborne contaminants below a specified level as defined in ISO 14644-1 (tested per ISO14644-2,3) and both temperature and RH are controlled more tightly than in the ambient environment. These areas must be performance verified/qualified. They may be tested to meet ISO requirements for airborne 0.5µm particulate and viable organisms in the "in-operation" state to meet US FDA requirements, or they may be tested to meet ISO requirements for airborne 0.5 and 5.0 µm particulate as well as viable organisms in both the "in-operation" state as well as the "at-rest" states to meet EMA and PIC/S requirements. Where EMA and PIC/S requirements are to be satisfied, the transition between the two states should take place in 15–20 minutes. This can be verified via the "recovery test" as specified in ISO 14644-3.

Recovery: A test defined in ISO 14644-3 that challenges room environmental performance by measuring the time required for contamination to reduce by 1 to 2 log after particle generation in the space ceases.

ZLG Aide Memoire 07121104 Grade E: A classified space that satisfies the airborne viable microorganisms requirement of < 250 CFUs per cubic meter.

ZLG Aide Memoire 07121104 Grade F: A classified space that satisfies the airborne viable microorganisms requirement of < 500 CFUs per cubic meter.

Table B: Historical comparison of classification systems

Particles per cubic meter ≥ 0.5 µm	US FS-209E, 1992	US FS-209E equivalent per cubic foot	EU EudraLex Vol.4 Annex 1, 1997	France AFNOR, 1989	Germany VDI 2083, 1990	Britain BS 5295, 1989	Japan JISB 9920, 1989	ISO 14644-1 and CEN 243
1								
3.5					0		2	2
10	M1							
35.3	M1.5	1			1		3	3
100	M2							
353	M2.5	10			2		4	4
1,000	M3							
3,530	M3.5	**100**	B: at rest A: at all times	4,000	3	E or F	5	**5**
10,000	M4							
35,300	M4.5	1,000			4	G or H	6	6
100,000	M5							
353,000	M5.5	**10,000**	C: at rest B: dynamic	400,000	5	J	7	**7**
1,000,000	M6							
3,530,000	M6.5	**100,000**	D: at rest C: dynamic	4,000,000	6	K	8	**8**
10,000,000	M7							

Table C: ISO 14644-1:1999 air quality classes

Particles per cubic meter (cubic foot), by size

ISO Class	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm
1	10	2	0	0	0	0
2	100	24	10	4 (0.1)	0	
3	1,000	237	102	35 (1)	8	
4	10,000	2,370	1,020	352 (10)	83	
5	100,000	23,700	10,200	3,520 (100)	832	29
6	1,000,000	237,000	102,000	35,200 (1,000)	8,320	293
7				352,000 (10,000)	83,200	2,930
8				3,520,000 (100,000)	832,000	29,300
9				35,200,000 (1,000,000)	8,320,000	293,000

1 cubic meter = 35.2 cubic feet

When referring to US FDA guidance only the 0.5 µm particle size (highlighted) is measured

Table D: ISO 14644-1:2015 classification of air cleanliness by particle concentration

Maximum allowable concentrations

Particles per cubic meter for particles equal to and greater than the sizes shown [a]

ISO Class	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm
1	10 [b]	[d]	[d]	[d]	[d]	[e]
2	100	24 [b]	10 [b]	[d]	[d]	[e]
3	1,000	237	102	35 [b]	[d]	[e]
4	10,000	2,370	1,020	352	83 [b]	[e]
5	100,000	23,700	10,200	3,520	832	[d–f]
6	1,000,000	237,000	102,000	35,200	8,320	293
7	[c]	[c]	[c]	352,000	83,200	2,930
8	[c]	[c]	[c]	3,520,000	832,000	29,300
9	[c]	[c]	[c]	35,200,000	8,320,000	293,000

a. All concentrations in the table are cumulative, e.g., for ISO Class 5, the 10,200 particles shown at 0.3 µm include all particles equal to and greater than this size.

b. These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

c. Concentration limits are not applicable in this region of the table due to very high particle concentration.

d. Sampling and statistical limitations for particle in low concentrations make classification inappropriate.

e. Sample collection limitations for both particles in low concentrations sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

f. In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size (see C.7).

g. This class is only applicable for the in-operation state.

EU, PIC/S, AND WHO

EudraLex Volume 4, Annex 1 requirements for sterile products stipulate in-operation and at-rest airborne particle count limits at both ≥ 0.5 and 5.0 µm particle sizes. It further directs that spaces recover from the in-operation to the at-rest state after a 15–20-minute cleanup period. Some other unique definitions are:

Grade A: A classified space that satisfies European Medicines Agency (EMA) and PIC/S requirements to meet:

- ISO 5 measured via airborne ≥ 0.5 µm particulate
- ISO 4.8* measured via airborne ≥5.0 µm particulate in the in-operation and at-rest states
- Airborne viable microorganisms < 1 colony forming unit (CFU) per cubic meter

These spaces are normally unidirectional flow with a suggested air velocity of 0.36–0.54 meters per second. These spaces surround product only and must be absent of people.

Grade D: A classified space that satisfies EMA and PIC/S requirements to meet ISO 8 measured via:

- Airborne 0.5 and 5.0 µm particulate in the at-rest state only
- Airborne viable microorganisms < 200 CFUs per cubic meter.

Aside from these differences in particle size and operational state, there is a good deal of alignment between the classification systems for the US, EU, PIC/S, and WHO. We summarize these similarities and differences in Table E.

The table's colored areas show areas of alignment between regulations, while the yellow areas show the differences between the US and other classification systems. Although US, EU, PIC/S, and WHO systems have four identified classes, they do not map directly, as each has one class the others do not.

ISPE has attempted to bridge these somewhat confusing differences with a single composite cleanliness grading system intended to satisfy international regulatory bodies and make good scientific sense.

To meet these objectives, the ISPE HVAC Community of Practice suggested that the ISPE grading system, originally proposed in the second edition of *Sterile Products Manufacturing* Baseline™ Guide, be modified as shown in the 2013 Baseline Guide Volume 6: *Biopharmaceutical Facilities* (Table F and Table G).

REVISED ISPE GRADES

The ISPE Sterile Guide team has suggested a further refinement, replacing the ISPE grades with a US/EU designation as follows:

* The use of ISO 4.8 in lieu of ISO 5 for 5.0 µm particles in Grade A appears to be the result of aligning this limit on the lowest number possible, working ISO 14644 sample size calculations backward using a 1 cubic meter sample size.

THIS UNIFIED SYSTEM CAN HELP ELIMINATE COMMON MISUNDERSTANDINGS ABOUT CLASSIFICATION ALIGNMENT AND CLARIFY THE INTENT OF ENVIRONMENTAL CONTROL WITHIN FACILITIES

Grade 8 (ISO 8/Grade C): A classified space that satisfies FDA requirements for:

- ISO 8 measured via airborne 0.5 µm particulate in the in-operation state
- EMA and PIC/S requirements to meet ISO 8 measured via airborne 0.5 and 5.0 µm particulate in the in-operation state
- ISO 7 measured via airborne 0.5 and 5.0 µm particulate in the at-rest state, with a 15–20-minute transition between states
- Airborne viable microorganisms < 100 CFUs per cubic meter

Grade 7 (ISO 7/Grade B): A classified space that satisfies FDA requirements for:

- ISO 7 measured via airborne 0.5 µm particulate in the in-operation state
- EMA and PIC/S requirements to meet ISO 7 measured via airborne 0.5 and 5.0 µm particulate in the in-operation state
- ISO 5 measured via airborne 0.5 and 5.0 µm particulate in the at-rest state, with a 15–20-minute transition between states
- Airborne viable microorganisms < 10 CFUs per cubic meter

Grade 5 (ISO 5/Grade A): A classified space that satisfies FDA requirements for:

- ISO 5 measured via airborne 0.5 µm particulate in the in-operation state
- EMA and PIC/S requirements to meet ISO 5 measured via airborne 0.5 µm particulate
- ISO 4.8 measured via airborne 5.0 µm particulate in the in-operation and at-rest states
- Airborne viable microorganisms < 1 CFU per cubic meter. These spaces are normally unidirectional flow with an air velocity of 0.20–0.45 meters per second.

Controlled not classified with local monitoring (CNC+/Grade D): Areas where HVAC systems are designed to reduce airborne contaminants below the level of the ambient environment and in which both temperature and relative humidity (RH) are controlled more tightly than in the ambient environment. Claims for environmental control in these areas are related to both system design and system performance; installation qualification and operational qualification are common.

These areas are typically qualified to meet ISO 8 requirements at rest only, and to control temperature and humidity within a specified band. They are monitored for viable particulate during operation to provide background information for investigations and to assure adequate layers of closure. These areas are generally aligned with PIC/S designation Grade D and airborne viable microorganisms < 200 CFUs per cubic meter.

Controlled not classified (CNC): Areas where HVAC systems are specifically designed to reduce airborne contaminants below the level of the ambient environment and both temperature and RH are controlled more tightly than in the ambient environment. Claims for environmental control in these areas are related to the design of the system; installation qualification is common. No claim is made or qualified for the specific control of particulate. Typical systems will have heating, cooling, and filtration meeting minimum efficiency reporting values of 13 or better. These areas are sometimes referred to as "pharmaceutical" or "clean" areas within pharmaceutical facilities.

Temperature controlled: Areas where HVAC systems are specifically designed to control both temperature and (where applicable) RH more tightly than in the ambient environment. Temperature and RH are usually qualified in these areas and temperature mapping is expected. This is designation is typically found in warehouse spaces, cold rooms, and logistics. Some companies apply the CNC designation for these areas.

This unified system of classification, whether by stating the grade and ISO number or by referencing both the ISO class and the EU grade can help eliminate common misunderstandings about classification alignment and clarify the intent of environmental control within facilities.

In closing, the authors offer terms and definitions in the sidebar on page 37 to clarify any remaining confusion regarding common classification and environmental control terminology. ❮❯

Table E: Comparison of regulatory requirements

FDA		In-operation (particles per cubic meter)	Active air action	EU, WHO, PIC/S	In-operation (particles per cubic meter)		At-rest (particles per cubic meter)		Active air action
ISO	**USP**	**0.5 µm**	**Limits**	**Grade**	**0.5 µm**	**0.5 µm**	**0.5 µm**	**5.0 µm**	**Limits**
ISO 5	100	3,520	1	A	3,520	20	3,520	20	< 1
ISO 6	1,000	35,200	7	N/A					
ISO 7	10,000	352,000	10	B	352,000	2,900	3,520	29	10
ISO 8	100,000	3,520,000	100	C	3,520,000	29,000	352,000	2,900	100
N/A	N/A	N/A	N/A	D	N/A	N/A	3,520,000	29,000	200

Table F: ISPE cleanliness grading system: Environmental control requirements in regulations

ISO Class	USP particles per cubic foot	US FDA in-operation limit, particles per cubic meter	EU and PIC/S grade	EU and PIC/S				ZLG "aide-memoire" 07121104	Active air action limits, colony-forming units per cubic meter
				In-operation limit, particles per cubic meter		At rest limit, particles per cubic meter			
	≥ 0.5 µm	≥ 0.5 µm		≥ 0.5 µm	≥ 5.0 µm	≥ 0.5 µm	≥ 5.0 µm		
ISO 5	100	3,520	A	3,520	20	3,520	20	N/D	< 1
ISO 6	1,000	35,200	N/D	35,200	290	3,520	29	N/D	7
ISO 7	10,000	352,000	B	352,000	2,900	3,520	29	N/D	10
ISO 8	100,000	3,520,000	C	3,520,000	29,000	352,000	2,900	N/D	100
ISO 9	1,000,000	35,200,000	N/D	N/A	N/A	N/A	N/A	N/D	N/D
N/A	N/A	N/A	D	N/A	N/A	3,520,000	29,000	N/D	200
N/D	N/A	N/A	N/D	N/A	N/A	N/A	N/A	E	250
N/D	N/A	N/A	N/D	N/A	N/A	N/A	N/A	F	500
CNC*	N/A	N/A	N/D	N/A	N/A	N/A	N/A	N/D	N/A
U/C*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/D	N/A

* Not ISO classes; these are common designations without a standard definition

Table G: ISPE cleanliness grades†

ISPE grade	In-operation limit, particles per cubic meter		At-rest limit, particles per cubic meter		Active air action limits, colony-forming units per cubic meter
	≥0.5 µm	≥ 5.0 µm	particles per cubic meter	≥5.0 µm	
Grade 5	3,520	20	3,520	20	<1
Grade 6	35,200	290	3,520	29	7
Grade 7	352,000	2900	3,520	29	10
Grade 8	3,520,000	29,000	352,000	2900	100
CNC+*	N/A	N/A	3,520,000	29,000	200
CNC*	N/A	N/A	N/A	N/A	N/A
UC*	N/A	N/A	N/A	N/A	N/A

† 2013 Biopharmaceutical Facilities Baseline Guide

* Not ISO classes; these are common designations without a standard definition

Notes on Tables F and G

- N/D = not designated
- Values may be averages; EU and PIC/S require measurement of particles up to and including 0.5 µm and 5 µm, the US standard requires 0.5 µm, hence the table incorporates both to ensure compliance with the most stringent requirement.
- Samples from Grade 5 areas should normally show no viable organisms.
- Recovery from the in-operation to the at-rest state should be verified to occur within 15–20 minutes for ISPE grades 6, 7, and 8. The recovery test as defined in ISO 14644-3:2005 and IEST RP003 may be carried out to verify a one or two log reduction test. Recovery testing may also be performed for informational purposes.
- At-rest figures are given to support recovery and "static" room classification testing. Maintenance of these levels during idle (not in use) periods is not intended.

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About the authors

Norman Goldschmidt is Sr. Principal and President of Genesis Engineers, a full service A&E and EPCMV firm. He has over 30 years of experience in planning, engineering and construction in the life sciences, including 20 years as Executive Director of Global Engineering at Bristol-Myers Squibb. Norman is a recognized expert in the design and operation of internationally compliant pharmaceutical facilities, with particular emphasis on control of critical environments. He holds four patents for innovations in HVAC and pharmaceutical processing, is an ISO delegate/expert/author, adjunct professor at the New Jersey Institute of Technology, contributing author on numerous ISPE Baseline Guides, and is an instructor for ISPE, ASHRAE, NSF and several regulatory agencies. An ISPE member since 1996, Norman studied mechanical engineering at the University of Buffalo and engineering management at the State University of New York.

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WHY IS 90 FPM CONSIDERED THE STANDARD FOR CLEANROOM AIRFLOW?

David Brande, Dan Milholland, and Nick Haycocks

In 1961, while working at Sandia Laboratory in New Mexico, Willis Whitfield and his colleagues developed the world's first cleanroom and clean benches. These developments were instrumental for the electronics, aerospace, and later, pharmaceutical industries, where particulate contamination had to be minimized or eliminated.

"Willis Whitfield, Claude Marsh and Gordon King discovered that the air emerging from newly developed HEPA filters did so at a uniform and predictable speed, and that the flow could carry away particles in its path," says David Brande, lead consultant with Cleanroom Project Management, Inc. "That phenomenon became known as 'laminar flow,'" but that term is a widely adopted misnomer."

Rectifying that error by using the technically correct term "unidirectional" flow is important, but so is investigating how and why unidirectional airflow velocity in cleanrooms became carved in stone at 90 feet per minute (fpm).

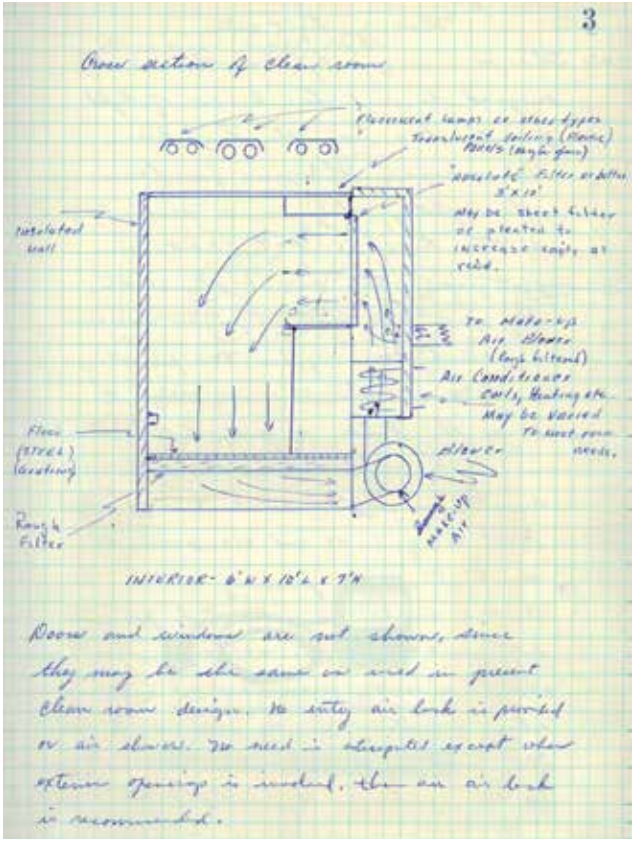
This velocity was adequate to meet the basic criteria of controlling the particle concentration; in addition, parameters such as settling rates, personnel comfort, and noise were acceptable. If true science had been applied, however, the performance would have been tested and documented over a very wide range of velocities (25–250 fpm, for example). The approach" used in the early 1960s confirmed that 90 fpm worked, but it was never deemed optimal.

THE SCIENCE

According to Claude Marsh, who worked with Whitfield, 90 fpm was established among the empirical calculations that created the first cleanrooms. "The window between 70 fpm and 100 fpm was established by the inertia of the airflow mass at 70 fpm being marginal as compared to normal personnel movements within the directional flow and the objectionable airflow at 100 fpm," recalls Marsh. "Energy efficiency was not a consideration."

Many suggest that the science for the 90 fpm standard may have employed Stokes's Law and Cunningham correction factor to determine the settling rate of 5 micrometer (µm) particles in a horizontal-flow cleanroom airstream. Laboratory notes and presentations over the years suggest that with an airflow of 90 fpm, particles would remain airborne above the work surfaces farthest from the filter bank and settle less than 2 feet over a distance of 20 feet in a horizontal-flow cleanroom.

The movement of people in the cleanroom was another factor. Airflow patterns recovered quickly from the turbulence created by personnel walking at a normal rate. Also, the 90 fpm airflow velocity was not perceptible when a cleanroom worker walked toward the filter bank. Thus cleanroom personnel did not feel like they were working in a wind tunnel.



Willis Whitfield's notebook page showing "Cross section of clean room"

"Probably the most significant factor in Dr. Whitfield's concept of [unidirectional] airflow was that it was a completely different idea about contamination control," recalls Marsh. "Why try to 'control' contamination? Why not just eliminate it?"

According to Marsh, early attempts to measure airborne contamination in unidirectional flow rooms and cabinets yielded near-zero particle counts, even when measured biologically in petri dishes in their working environments. "Eventual improvements in particle detection and counting instrumentation continue to challenge this," he notes.

WHY TRY TO "CONTROL" CONTAMINATION? WHY NOT JUST ELIMINATE IT?

THE LEGENDS

Those who worked in the industry in the early 1960s have their own theories.

"Gordon King told me that 90 fpm was selected as the velocity that would carry a certain size particle out of that soffit and onto the floor before it could fall onto the work surface," says George Cadwell, retired vice president of Flanders Filters (and current consultant to the company). "Gordon couldn't remember the size of the particle, but my good friend Vijayakumar calculated the size for me and it was somewhere upwards of 200 [µm], which makes me think that if there is any credence to Gordon's story, the 90 fpm was designed to carry the particle out from the filter bank before it settled into the airstream."

Cadwell also recalls that Whitfield told Bill Whyte that the reason for 90 fpm was that the fan he had made too much noise if it was run at higher volumes, but that 90 fpm was needed to wash away all the particles that were generated when several people were in the room.

Not everyone is convinced that 90 fpm is the only efficient speed for unidirectional flow. "Faster moving air is not necessarily better," says Brande. "It may seem counterintuitive, but lowering airspeed can provide better protection for a critical area. Increasing airspeed may even be counterproductive by increasing turbulence and a reverse air flow around obstructions."

FS 209

In December 1963, 90 fpm was codified when Sandia Laboratory produced Federal Standard 209 "Clean Room and Work Station Requirements, Controlled Environment," which stated in a nonmandatory appendix, that clean rooms should maintain an airflow velocity of 90 fpm (within ±20 fpm).

The FS 209 committee was handpicked by Gordon King, who was in charge of unifying the different military requirements of the US Air Force, Navy, and Army to get a common specification for cleanrooms used for building warheads and guidance systems—systems with over a thousand moving parts.

According to Brande, 90 fpm became the standard for the pharmaceutical industry because the FDA used FS 209 as a reference.

The 90 fpm guidance remained in force through FS 209's many revisions (see timeline), in part because of the agency's concern about air movement at the point of fill vs. the airflow rate measured at the filter above the aseptic operation. Questions about its universal utility were raised periodically, however.

At the Controlled Environment Testing Association's twentieth annual meeting in 2012, for example, comments on "Response to the FDA's Concept Paper: Sterile Drug Products Produced by Aseptic Processing" suggested that 90 fpm was "known to be a fallacy" within the cleanroom industry for over 25 years. Changing the standard, however, never seemed to get any serious industry or regulatory backing.

Willis Whitfield steps out of a mobile cleanroom, which could be transported to remote sites. Sandia National Laboratories

THE LUMS EXPERIENCE

Dan Milholland of Dan Milholland and Associates recalls that the 1994 LUMS (Lilly, Upjohn, and Merck) project that investigated the use of an isolator for aseptic filling found that a unidirectional airflow at significantly less than 90 fpm was efficient in dealing with particle contamination.

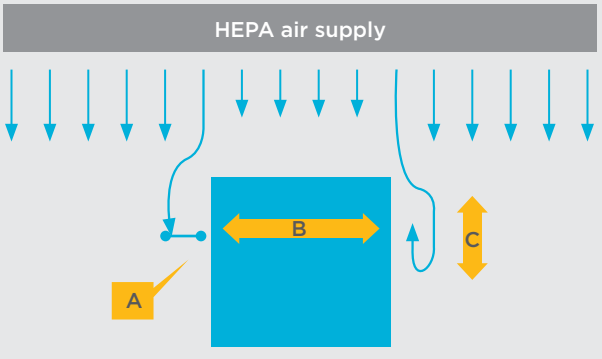
Figure: Airflow over a box

The distance the airflow diverts away from the vertical side of the box can be reduced by:

1) Decreasing the airflow volume/velocity directly above the box (obstruction)

2) Decreasing the width of the box B

The distance of the reverse airflow C is reduced as distance A is reduced. Airflow patterns can be improved by including zones of nonuniformity, i.e., < 70 fpm



Note: *Dimension A decreases as the airflow volume directly above the box is decreased and/or by decreasing the width of the box B. The reverse flow C decreases as dimension A decreases.*

THE ELECTRONICS INDUSTRY HAS FOUND THAT GREATER CLEANLINESS CAN BE ACHIEVED AT LOWER AIR VELOCITIES DUE TO REDUCED TURBULENCE AROUND OBJECTS IN THE FLOW PATH

LUMS participants, says Milholland, built a prototype production isolator system for vial filling and did aseptic media fills in which there was no human contact with the product; glove ports enabled workers to reach into a sterile environment.

"The FDA liked the idea, it was good technology," says Milholland. "We were working great at 40 fpm, and there was no contamination at the lower velocities in the first aseptic filling isolator."

In the end, however, the technology was rejected by one of the participating companies because the unidirectional flow did not meet the FDA's 90 fpm expectation. "Some in industry did not want to rock the boat," recalls Milholland. "They wanted the first production isolators to conform to the 90 fpm guidance rather than have the unidirectional airflow move at a slower speed." Current installations have also found improved flow with lower velocities—particularly where vertical airflow hits a filling machine top plate. Lower velocities can produce less turbulence, with a smoother transition to the flow into the air returns.

TIMELINE: REFERENCES TO 90 FPM

- 1963: FS 209 debuted at only nine pages, which included the scope, references, definitions, and actual standard. Appendix A stated that the provisions specified were "not mandatory." Section 40.2 set the airflow velocity preference at 90 fpm ±20 fpm.
- 1966: FS 209A retained 90 fpm in the nonmandatory appendices, but added that "individual circumstances may dictate other values."
- 1973: FS 290B, Sec. 40.2 changed the variable unit from 20 fpm to 20% above or below 90 fpm, and stated that in "certain applications where user requirements permit, airflow velocity … may be reduced below the 90 fpm level."
- June 1987: FDA aseptic guidelines stated that 90 fpm (±20%) was the desired velocity for aseptic operations and that "… higher velocities may be needed where operations generate high levels of particulates or where equipment configuration disrupts laminar [*sic*] flow."
- October 1987: Just three months later FS 209C dropped all references to cleanroom airflow velocities.
- 2001: The last revision, FS 209 E (1992), was replaced with ISO 14644.
- 2004: A footnote in FDA's revised Aseptic Guidelines stated "A velocity from 90 feet per minute is generally established, with a range of plus or minus 20 percent around the set point."

ISOLATORS USED FOR SEMICONDUCTORS

Interestingly, "the electronics industry has found that greater cleanliness can be achieved at lower air velocities due to reduced turbulence around objects in the flow path," explains Milholland. "The typical microelectronics room is designed to operate at 55 to 70 fpm."

He notes that modern semiconductors are built in isolators and never exposed to air. These mini environments operate with 25% to 33% filter coverage with a filter face velocity of 65 fpm, or the equivalent of approximately 20 fpm with raised floors, rather than sidewall returns.

Semiconductor isolators operate two orders of magnitude cleaner than the FDA requirements for pharmaceutical aseptic operations. Milholland recently measured particle concentration in the duct upstream of the ULPA filters at 175 particles 0.1 µm and larger per cubic foot of air. This meets ISO Class 3 at 0.1 µm before the ULPA filters.

"That's pretty clean!" he says. ‹›

About the authors

David Brande is Lead Consultant for Cleanroom Project Management, Inc. During his 28 years in the cleanroom industry, he served as director of controlled environment testing for PSCBiotech, Inc., and as founder and president of Contamination Control Technologies, Inc. David earned a BS from North Carolina State University in 1977, and has been certified as an Accredited BioSafety Cabinet Field Certifier, Cleanroom Performance Testing Supervisor, and Qualified HEPA/ULPA Filter Tester. He also served as Chairman of ISO/Technical Committee 209 from 2006–2012. David has been an active member of ISPE since 1999, serving as Past President of the Carolina South Atlantic Chapter and a member of the HVAC CoP Steering Committee.

Dan Milholland has extensive experience in filter testing and cleanroom contamination control in the semiconductor, aerospace, and pharmaceutical industries. He completed both his undergraduate and graduate studies at North Carolina State University, where he was awarded a master's degree in biochemistry. Milholland founded Biocon in1980, and was part the Contamination Control/Cleanroom Group at SEMATECH from 1987 to 1988 in Austin, Texas, a joint effort between the US government and industry to regain world leadership in microelectronics. He was a member of the IEST Working Group 100 for the revision of Federal Standard 209D, and served as US Expert Council for ISO 14644. An ISPE Member since 1991, he is also on the NEBB Cleanroom Committee to certify cleanroom certifiers.

Nick Haycocks, C.Eng. FI Mech.E, is a Chartered Mechanical Engineer with over 20 years' experience in the pharmaceutical industry. Nick has worked for GSK, Schering Plough, and Amgen in their technical organizations, as well as on-site supporting projects in various locations including China and Singapore. He is Co Chair of ISPE's Guidance Documents Executive Committee, Chair of the HVAC and Sustainability CoP, and has contributed to the HVAC, Process Gas, and Good Engineering Practice Good Practice Guides. Nick currently works in Amgen's Quality Department as part of a small team implementing a risk-based approach for facility and equipment qualification. He has been an ISPE Member since 2002.

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CLEANING VALIDATION CONSIDERATIONS FOR AUTOMATED WASHING SYSTEMS

Paul Lopolito, Olivier Van Houtte, and Marcel Dion

What is cleaning validation and where does it fall in the life cycle validation scheme? How can an automated washing system be validated? This article provides insights that may help answer these questions.

The life cycle approach is a good way to standardize manufacturing and cleaning processes. The 2011 FDA guidance document entitled "Process Validation: General Principles and Practices," which "aligns process validation activities with a product lifecycle concept," segments process validation into three stages: process design, process qualification, and continued process verification.[1]

For automated washing systems, Stage 1, process design, comprises the user requirement specifications (URS)—items that should be considered when acquiring the system and the outside parameters that affect its proper use. Stage 2, process qualification, covers the validation strategy, including washer load configuration, cycle operation, acceptance criteria, analytical and sampling methods, and other items. Stage 3, continued process verification, consists of preventive maintenance activities, periodic reviews, and continued monitoring of the cleaning process that can help maintain a state of control when producing drugs at a commercial scale.

LIFE CYCLE APPROACH

Cleaning is a critical process meant to prevent contamination from active ingredients, excipients (or nonactives), cleaning agent residue, microbial residue, or other contaminants from one process to the next.

The traditional approach to cleaning validation paid little attention to the design of the cleaning parameters. Instead, more emphasis was placed on cleaning validation activities.[2] This usually meant at least three cleaning trials and testing of extreme conditions (such as the lowest possible detergent concentration), wash and rinse cycle temperatures, and times for the various steps of the cleaning process. When this approach is applied to validation, the analyst often observes some out-of-specification (OOS) results that may require additional testing and justifications. Once the test runs are acceptable and the report written and approved, however, the company then considers the automated washer and cleaning cycle validated. Change or optimization is a huge hurdle.

In contrast, the life cycle approach places more emphasis on understanding the cleaning process, equipment design, and continued monitoring of the operation to ensure quality results. This approach, presented in the abovementioned FDA guidance, incorporates recommendations from International Conference on Harmonisation (ICH)* guidance documents covering pharmaceutical development and quality by design (Q8), quality risk management (Q9), and pharmaceutical quality systems (Q10).[3–5]

The life cycle approach guiding principles are:

- Quality must be built into the process
- Quality is not guaranteed by in-process or final process testing
- To ensure consistent quality, manufacturing processes must be defined, and continued monitoring applied

Because the life cycle approach can be applied to cleaning validation of automated washer systems, this article covers equipment design requirements of the automated washer cycle all the way through continued verification of the equipment and cleaning cycle.

Three stages

The life cycle approach is divided into three stages:[1]

Stage 1: process design—The commercial manufacturing process is defined, based on knowledge gained through development and scale-up activities. This ensures that variables within the process are identified and critical variable limits are defined.

Stage 2: process qualification—The process design is evaluated to determine if it is capable of reproducible commercial manufacturing. This verifies that the process, as designed, produces the expected results.

Stage 3: continued process verification—Critical variables are monitored to ensure that the process remains in a state of control during routine production.

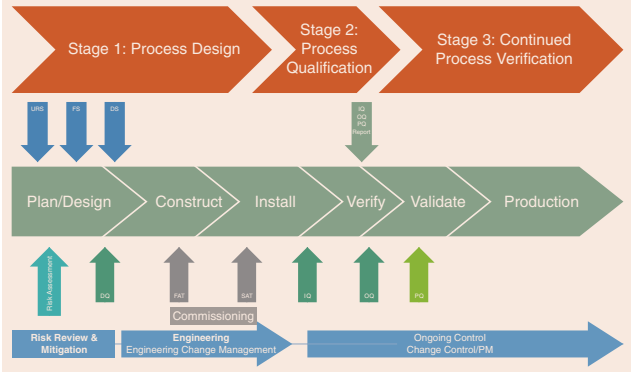
The life cycle approach emphasizes the design and monitoring stages of the process. This includes understanding critical cleaning parameters

* *Full title: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*

(CCPs) and noncritical cleaning parameters, and defining critical quality attributes (CQAs) for cleaning. Increased emphasis on continued monitoring ensures that the process is running in a state of control. Process analytical technology, which relies on continuous monitoring to record and process data in a timely manner, can also be used to satisfy Stage 3 continued process verification requirements.[6]

The flow chart shown in Figure 1 depicts the life cycle approach as it relates to traditional markers in sourcing an automated washer and using it for cleaning parts within a validated cleaning process. The initial focus in Stage 1 is on various specifications, key process attributes, and acceptance criteria, while using a risk-based approach to avoid over- or under-designing the process.

Figure 1: Life cycle approach[7]



STAGE 1: PROCESS DESIGN

This stage requires a validation strategy. A cleaning validation master plan should already be in place and include items such as cycle development, selection of cleaning agents, analytical and sampling methods, calculating acceptance criteria, handling and storage procedures for cleaned components, and cleaning equipment validation.

If this is a new equipment installation—often the case with automated washer cleaning validation—then the equipment URS, functional specifications (FS), and design specifications (DS) are also important. This information will be critical to successful commissioning and validation.

Validation strategy

The validation strategy for automated washers should start by collecting information on the parts to be cleaned, including materials of construction, type of product contact soil, and condition of the soil on the surface. This information, shown in Table A, is critical for a risk-based approach in developing a grouping strategy, designing the cleaning cycle, and defining the parts loading configuration.

To develop loading configurations, the best option is a custom-designed rack that provides a specific place for each item. A second would be to have a range of sizes for items that can be placed at specific locations, such as a 200-, 400-, 600-, 800-, or 1000-milliliter beaker that can be placed on a single spindle for cleaning. Yet another option would be to use baskets in which the description, quantity, and orientation of the items would be defined per basket, and the location or placement of the basket would be defined on a parts washer rack. During this design stage, it's important to group or bracket items by comparing largest and smallest sizes, for example, to test worst-case load configurations.

A single process soil may be cleaned, as would be the case with filling equipment, or several soils can be washed in a single cycle. In either case, the cleaning cycle must remove residues to acceptable health-based limits. Both the sampling technique and analytical methodology should demonstrate that these limits are met.

CLEANING IS A CRITICAL PROCESS MEANT TO PREVENT CONTAMINATION

Cleaning cycle development

The goal of cycle development is to adjust the critical cleaning parameters to meet acceptance criteria using the shortest and most energy-efficient cleaning cycle.

Cycles in a parts washer generally consist of:[8]

- Prewash
- Wash
- Rinse
- Final rinse
- Drying
- Additional wash and rinse steps (optional)
- Additional steps such as sanitization or lubrication (depending on the parts to be cleaned)

Cycle development may be performed at the manufacturing site or during the commissioning steps after installation. Waiting too long could create major schedule delays and difficulty modifying equipment after fabrication.

The best time for cycle development is during the preparation of the parts washer URS, using laboratory (coupon) studies, as shown in Figure 2. For these studies the process residue is coated on a coupon of material similar to the parts, conditioned as it would be during processing, and then cleaned in a manner similar to the parts washer.

Laboratory testing is a great tool for defining cleaning cycle CCPs such as cleaning agent, concentration, temperature, wash time, water quality, water prewash temperature, and dirty hold time.[9] The goal should be to define the normal operating parameters (often called the area of control) to meet cleanliness criteria, define the area of success, and develop your area of knowledge. What condition, for example, would result in a failure? This

Figure 2: Coupon studies

understanding of the design space is outlined in ICH Q8[3] and should be part of the cleaning cycle development work.

To assist in cycle development, process and cleaner evaluation services are also available pre- and post-installation through cleaning agent suppliers. This type of laboratory testing can also help define a worst-case soil that can be used during validation activities, which can save time during the validation stage.[10–12]

Analytical and sampling methods

As defined by the US Code of Federal Regulations, Title 21, Part 211, Subpart I, Section 211.165, "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented."[13]

ICH Q2B guidance—a harmonized approach to the requirements for analytical method validation—provides additional information.[14] ICH Q2B guidance was not developed specifically for analytical methods used in cleaning validation; the required elements of linearity, precision, range, robustness, accuracy, ruggedness, specificity, limit of quantitation, and limit of detection, however, are commonly applied to analytical method validations for cleaning validation (Table B).[2]

Analytical methods can fall into two categories:

Specific methods (preferred) identify the number of targeted species found in the presence of expected interferences. These methods can be ultra-performance liquid chromatography, ion chromatography, and atomic absorption.

Nonspecific methods, which can be total organic carbon (TOC), conductivity, and titration, take into account residue from all contributing factors. Visual inspection should be included for each item removed from the parts washer, and the procedure should classify a course of action for observed scratches, etching, dents, dings, and the like. These items may not be cleaning-related visual failures, but could be due to handling or wear.

The most common sampling methods are surface swabbing and rinse sampling. A less common procedure is direct surface sampling with an instrument such as a handheld Fourier transfer infrared spectroscopy or near-infrared spectroscopy.

For swab sampling, most companies use a single-swab method. In this approach, the surface is first sampled in overlapping strokes, then the swab is flipped over and used in overlapping strokes at a 90-degree angle to the first set (Figure 3). In the two-swab method, an area is sampled with a wet swab as noted above, then sampled by a second dry swab utilizing the same method. In both methods, water or another diluent is added to a vial with the swab or swabs. The analyte is extracted (or desorbed) from the swabs for analysis. Swab templates can be used for training, but not for actual part sampling, due to possible cross-contamination from the template to the swab.

In rinse sampling, small bottles, beakers, and other items are placed in a sterile plastic stomacher bag. Rinse water is added, the bag is sealed, and the contents mixed by shaking. A final rinse water sample or in-line measurement for conductivity and possibly TOC is used; the items must also be visually clean.

Whether using swab or rinse sampling methods, it is important to establish residue-recovery studies. The final rinse water specification and visually clean criteria should be confirmed with some level of surface sampling through swab, rinse, or direct methods.

Acceptance criteria

The cleaning validation master plan should help determine which residue to test for, and justify the limits established for surfaces or final rinse water samples. It is common to use purified water specifications for pH, conductivity, TOC, and microbial limits, along with a carryover estimate calculation based on residue toxicity. Residue limits are commonly calculated for drug active, cleaning agent, and bioburden, but may also include endotoxins, degradation products, excipients, or even the presence of color and fragrances. It's helpful to include photographs or diagrams of the items to sample, and provide a rationale for selecting them. Such examples may be difficult-to-clean parts or those with the most complicated design.

In addition to setting limits on residue, it is often common to set acceptance criteria for the level of residual water left behind after the drying step. No droplets or residual water should remain on or in the items because this can lead to microbial growth.

If the cycle includes a sanitization/disinfection step, thermal strips or biological indicators can be used during the design phase to establish a log reduction. Chemicals, such as blends of hydrogen peroxide and peracetic acid (such as SporKlenz RTU disinfectant at a 1:50 dilution for 5 minutes), or hot water are effective sanitizers. Common time and temperature used for hot water pasteurization is 30 minutes at 63°C, 15 seconds for 72°C, and one second for 83°C.[15]

Figure 3: Swabbing method

Figure 4: Semipermeable cover

Figure 5: Riboflavin coverage testing

THE LIFE CYCLE APPROACH EMPHASIZES THE DESIGN AND MONITORING STAGES OF THE PROCESS

Handling and storage procedures

Activities in Stage 1 should also define handling and storage procedures for cleaned items. These should be removed dry and covered during storage to prevent surface particle collection and microbial contamination. Semipermeable wraps or covers are an excellent way to protect clean items (Figure 4).

An acceptable storage time or clean hold time is generally based on handling and storage practices using visual inspection, with bioburden monitoring after a defined storage time. (Bioburden testing is also performed on dirty items to establish the bioburden load and types of microbes commonly seen.) Some companies skip the bioburden testing after the cleaning/sanitization cycle but keep the bioburden testing after the clean hold storage time to confirm the bioburden reduction of the cleaning cycle, and to verify that the handling and storage is sufficient.

User requirement specifications

In situations where an automated washing system is used, the URS plays a major role in the validation process. This information allows suppliers to provide equipment that will be optimized for the specific application. Incorrect or incomplete URS are likely to cause problems down the line, so it is very important to get them right from the start. A URS document details all information the supplier needs to provide the best equipment for the stated purpose. Description of the application, items to be cleaned, washer chamber size, project schedule, and timeline are some URS fundamentals. Table C lists most common items found in a URS document for an automated cleaning system.

Factory acceptance test

After the washer has been manufactured according to the URS, it is a good practice to execute a factory acceptance test (FAT). This highly recommended practice may help minimize overall qualification time, since some portions can potentially be reused for on-site qualification. Once the unit is installed, some tests may not need to be executed again (depending on risk assessment).

The FAT should allow enough time to review the design, manufacturing, and qualification documentation, and verify that all desired features, options, and accessories are present and meet the user's expectations. Typically, all alarms, inputs, and outputs are tested. In most cases, operational tests are also conducted to ensure compliance with functional specifications. In addition, the user may perform a simultaneous audit of the supplier's quality system.

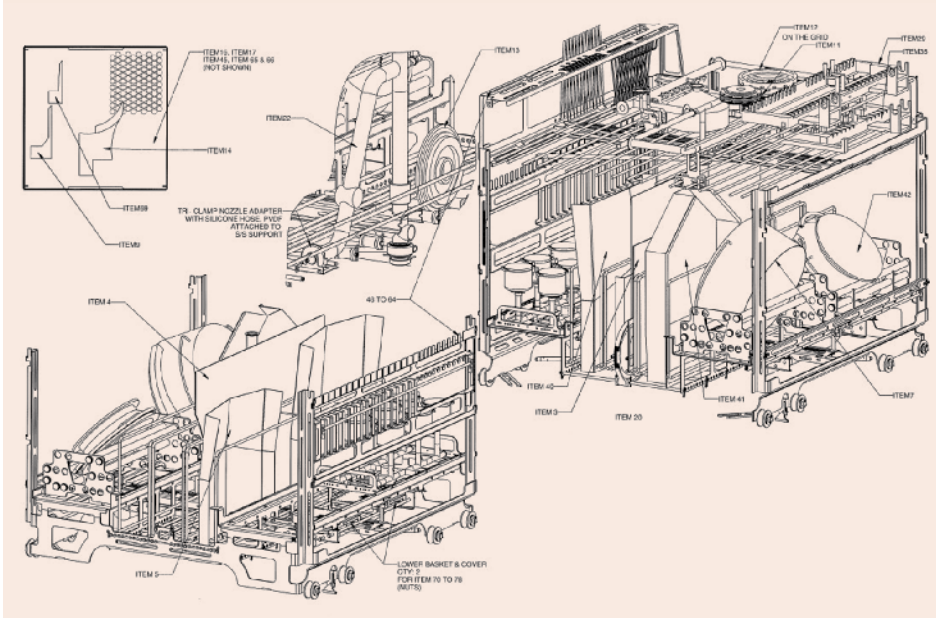
Coverage testing, another important portion of the FAT, should be performed with the parts that will be used on-site. Coverage is often considered the most critical cleaning parameter, since a lack of coverage means that the cleaning solution does not reach all internal or external load items surfaces. Coverage testing is even more important when difficult-to-clean items such as tubing, hoses, or complicated parts are processed. Capturing potential coverage issues during the FAT will prevent the risk of rework and delays at the user's site.

In a typical coverage test, the inside surface of load items are sprayed with riboflavin, then positioned on loading racks according to the predefined specifications.[17] The washer chamber, loading racks, and load items are then also sprayed with riboflavin (Figure 5), and the solution is allowed to dry for a few hours at ambient temperature.

A short rinse-only cycle should then be run. Once the rinse cycle is completed, the load items should be removed quickly from the wash chamber and inspected in a dark area using an ultraviolet light. Since riboflavin is water-soluble, this will identify areas where it is still present, which indicates that water did not reach that area. (Many equipment suppliers also offer to perform actual cleaning tests with user-provided parts, soils, and cleaning agents.)

To ensure consistent cleaning results are achieved, the washing system manufacturer can develop a loading specification document (Figure 6) that shows the respective locations of the parts on the loading accessories. It is critical that operators replicate this pattern when loading the washer with actual dirty parts, because a surface that is not in contact with water (and cleaning solution) will never be clean.

Figure 6: Example of a customized loading rack



STAGE 2: PROCESS QUALIFICATION

Stage 2, qualification of the automated parts washer and cleaning validation could be approached as a readiness check. Before starting the process, the following should be confirmed:

- □ Cleaning documentation including protocols and operating procedures have been approved
- □ Personnel have been trained on the documentation and procedures
- □ Utility supply systems have been qualified
- □ Analytical methods and sampling procedures have been validated
- □ Suppliers of cleaning agents have been approved
- □ Automated washer equipment is fully functional

Qualification

Stage 2 typically includes installation qualification (IQ) and operation qualification (OQ) to determine that the automated washer:

- □ Has been installed as specified and the utilities are sufficient to maintain operation
- □ Is operating as specified

These procedures may include a repeat of the riboflavin coverage testing, a successful run of a complete cleaning wash cycle, verification that all alarms are functioning properly, and confirmation that sensors/probes are calibrated and functioning as designed.

The next step is to execute the performance qualification (PQ) of the washer. Sampling should be performed on the soiled parts to establish a baseline, and on the cleaned items to demonstrate that the final rinse water acceptance criteria corresponds to the cleanliness of the parts washed.

Cleaning validation

As noted above, the traditional cleaning validation (PQ) approach of evaluating three runs may not be applicable. Instead, the number of runs may depend on the testing performed during the Stage 1 design and risk assessment. Evaluating worst-case critical parameters is also not applicable because critical parameters identified during the design stage were identified and monitored or controlled. The goal of the PQ is to demonstrate that the normal operating cleaning cycle using the automated parts washer successfully removes the residue(s) of interest to predetermined acceptable limits.

The PQ process should be thoroughly documented and approved. Any deviations, changes, or OOS events should be recorded and a risk assessment performed to assess impact to the PQ activities.

STAGE 3: CONTINUED PROCESS VERIFICATION

The main purpose of the third life cycle stage is to provide continued assurance that the cleaning procedure is performing as expected, and that it

Table A: Parts information table

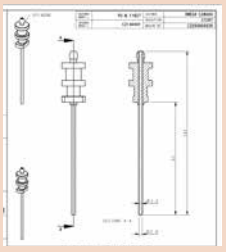
Description	Quantity	Height, mm	Outer diameter (OD)	Weight, kg	Critical information	Drawing or picture number	Notes
Filling needle	8	110	15	NA	Process soil: low concentration protein		Photo 28
Filling pump	8	174,5 for pump 150 for plunger	Pump OD 70,6 Plunger inner dia. 18	NA	Process soil: Low concentration protein, material: external is 316L SS, pump internal is porcelaine, can separate wash		Photo 29
Glass bottle	1	300	180	NA	Process soil: low concentration protein		Photo 30

Table B: Recommended criteria for analytical method validation

Characteristic	Recommended criteria
Precision	Precision should be assessed using at least nine determinations (3 concentrations with 3 replicates each) covering the specified range and reported as Relative Standard Deviation (RSD).
Limit of quantitation (LOQ)	The LOQ can be estimated by measuring the baseline noise multiplied by 10. This value must be less than the cleaning validation acceptance limit.
Limit of detection (LOD)	The LOD can be estimated by measuring the baseline noise multiplied by 3. This value must be less than the cleaning validation acceptance limit.
Accuracy	Accuracy should be assessed using at least nine determinations (3 concentrations with 3 replicates each) covering the specified range and reported as percent recovery. The percent recovery should be close to 100%.
Specificity	Specificity may be demonstrated by comparing the test results of samples containing analyte plus other expected components versus samples of analyte only.
Linearity	Linearity should be established with a minimum of five concentrations and three replicates each. The coefficient of determination (R2) of the linear regression should be not less than 0.99.

Table C: User requirement specifications

Project scope

- □ Application description
- □ Items to be cleaned
- □ Washer chamber volume
- □ Project schedule

Loading accessories (racks)

- □ Storage for unused accessories
- □ Design requirements
- □ Documentation expectations

Standards and guidelines

- □ 21 CFR Part 11 for electronic records
- □ Bio-processing equipment (ASME BPE 2012) [16]
- □ GAMP (good automated manufacturing practices)
- □ Local electrical and piping codes
- □ Others?

Available utilities

- □ Water (type, pressure, temperature, flow)
- □ Electricity (voltage, amperage)
- □ Steam (type, pressure, flow)
- □ Condensate return to boiler
- □ Compressed air (type, pressure, flow)
- □ Exhaust (flow, temperature)
- □ Cleaning agents (acid, alkaline, neutral pH, booster, etc.)
  - Ability to add more than one cleaning agent simultaneously

Washer location environment

- □ Recessed or freestanding installation
- □ Single or double door for barrier wall pass-through operation
- □ Available space in the room (include room layout if available)
- □ Available ceiling height
- □ Requirements for drain (pH neutralization, effluent cool down)
- □ Location of chemical containers
- □ Maximum noise level allowed (dBA)

Design requirements

Electrical
Instrumentation (preferred vendors, accuracy)
Tagging for instrumentation
Labeling

Mechanical
- □ Slopes
- □ Surface finish
- □ Materials
- □ Preferred door system (sliding, drop down, hinged, manual, automatic)

Control system
- □ Preferred supplier
- □ Human machine interface (HMI)
- □ Load side, unload side
- □ Interface with user's supervisory control and data acquisition (SCADA)
- □ Interface with uninterruptible power supply (UPS)
- □ Security requirements (passwords, access levels, audit trail, alarms)

Process monitoring
- □ Pressure
- □ Conductivity
- □ Total organic carbon (TOC)

Process records
- □ Printer
- □ Download to external computer
- □ Stored locally

Documentation requirements

Paper or Electronic
Language

Design documentation
- □ Functional specifications
- □ Control system (hardware and software design and test specifications)
- □ As-built equipment drawings
- □ Traceability matrix

Manufacturing documentation
- □ Welding
- □ Material certificates
- □ Polishing, surface finish
- □ Cleaning and passivation
- □ Quality plan

Manuals
- □ Installation
- □ Operation
- □ Maintenance

Qualification
- □ FAT protocol
- □ Site acceptance Test (SAT) protocols
- □ Installation/operation/process qualification protocols

remains in a state of control for the life of the product(s) being manufactured. In this stage, the facility is manufacturing product and the cleaning procedure and automated washer are operating within the normal range.

Stage 3 typically includes regular reviews of the cleaning performance, cleaning procedures, training program, change controls, deviations, corrective and preventive actions, and preventive maintenance activities.

Preventive maintenance

The initial preventive maintenance program of the automated washer and parts should be based on the manufacturer's recommendations, and adjusted as the equipment ages or real-time performance metrics support indicate. Laboratory testing can also be used to investigate items such as compatibility between gasket and tubing materials.

Table D: Effect of cleaning process changes

Changes to	May affect
Detergent	Cleanability of the soils
Cleaning parameters	Cleanability of the soils
Analytical method	Surface coverage, equipment drainability, change over time
Personnel	Training and level of experience
Dirty hold time	Cleanability of soils, level of bioburden
Cleaning hold time	Extraneous matter, bioburden

Stage 3 includes trend analyses of the measured CPPs and CQAs (e.g., online conductivity and TOC of the final rinse water) as well as drying temperature/time and ramp rates, which can increase cycle times.[18–19] Data trending helps supports corrective actions prior to deviations or OOS results, which can compromise the quality of products manufactured.

The life cycle approach, which emphasizes understanding and effective continuous verification of the cleaning process, should be open to change control to improve its efficiency and drive down production costs while maintaining high quality standards. Table D lists changes to the cleaning process and possible results of the of the change.[2]

CONCLUSION

The cleaning life cycle approach (design, qualification, and continued verification) focuses on design and monitoring of the cleaning process as well as a better understanding of the design process (critical parameters and URS of the automated parts washer). This promotes continuous improvements and real-time science-based responses to OOS results and change management. Industry tools are the backbone to the life cycle approach and these elements can be incorporated into cleaning validation when using automated parts washers. ‹›

WHETHER USING SWAB OR RINSE SAMPLING METHODS, IT IS IMPORTANT TO ESTABLISH RESIDUE-RECOVERY STUDIES

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EU CLINICAL TRIALS REGULATION: THE APPLICATION PROCESS

Juliette Kirk

One of the major changes introduced by the European Union (EU) regulation 536/2014 is an application procedure that will require sponsors to apply for authorization to conduct an interventional/low-intervention clinical trial (CT) via a new EU portal.[3] The regulation's effective date is dependent on the availability of the portal and its associated database, which are now in development and subject to user acceptance testing by EMA stakeholders. According to the most recent European Medicines Agency (EMA) confirmation,[1] the regulation will be applicable by no later than October 2018.

While this is a major change, it is also seen by many as a key benefit. The regulation introduces a single approach for the application and maintenance of a CT authorization, and applies to both single or multiple member state trials. This procedure not only combines the content of what can be currently referred to as the "regulatory" and "ethics" applications, but also combines the scientific, technical, and ethical review necessary to receive approval to conduct a CT in the EU. In addition, the regulation defines procedural timelines, harmonizes document requirements, and aims to reduce the administrative burden of applications.[2]

Note: *This article does not cover notifications of milestones or unexpected events that are required by the new regulation.*

INITIAL APPLICATION

Content

The application content and assessment are divided into two parts: Part I contains scientific and medicinal product documentation; Part II contains the national and patient-level documentation (see Table A).

There is provision for cross-referencing to existing applications, which will further reduce the current administrative burden of EU CT applications.

Process and timelines

For many sponsors, the application process may require internal administration to support sponsor registration and role allocation where required by the CT arrangements (e.g., allocating work to contract resource organizations, affiliates, or personnel). User training will be essential; it is expected that the EMA will offer system training.

We will learn more as development of the portal and database progress, but we do know that there will be provision for both compiling an application within a workspace facility and for uploading an application that has been compiled outside of the system.

The application is submitted via the portal to all concerned member states (CMSs) in which the sponsor intends to conduct the CT (Figure 1). At the time of application, the sponsor proposes a reporting member state (RMS), who will be confirmed by day 6 following submission. The sponsor's RMS proposal may not always be accommodated, and in these cases the member state that has either self-nominated or been selected will instead be the RMS.

Validation

Following submission, there is a validation period to assess whether the application is complete and whether the application is in scope of the regulation. During this period the member states may request additional information from the sponsor. Member state requests for information during validation should be sent within 10 days of the submission. A 15-day extension can be allocated if needed to resolve issues; this provides an additional 10 days for the sponsor to respond/update the application and 5 days for member state confirmation, based on the information provided. The validation date is the date the RMS notifies the sponsor of the end of validation, or the natural end of the 10 or 10 + 15 days, whichever comes first.

The regulation requires strict adherence to the maximum timelines for each phase of the application procedure and has provisions to ensure that delays from any party do not hold up the process. If the RMS does not provide validation feedback within the defined time frame, for example, this will lead to the automatic (tacit) withdrawal of the application in all CMSs. The portal will determine when the milestones such as the

Table A: New CT application summary

Part I	Part II
Application form	Informed consent form and subject information leaflet
Cover letter (including sponsor's justification for the classification as a low-intervention CT, if necessary	Compensation arrangements
Investigator's brochure	Suitability of investigators and facilities
Good manufacturing practice documentation	Proof of insurance or indemnification
Investigational medicinal product dossier/ Auxiliary medicinal product dossier	Data protection rules
Scientific advice	Proof of fee payment
EU Paediatric Investigation Plan decision	***Note:*** *Precise content will be determined by each member state*
Example of investigational and auxiliary medicinal product labeling	

THE EU CT REGULATION INTRODUCES A NEW PROCEDURE, NEW TIMELINES, AND REVISED APPLICATION CONTENT. ALTHOUGH IT MAY INCREASE OR DECREASE THE OVERALL TIMELINES IN SOME MEMBER STATES, IT WILL BRING WITH IT INCREASED PREDICTABILITY FOR CT START-UP IN THE EU.

validation date have been met. Table B provides a summary of the CT application procedural timelines.

Assessment

The RMS assesses Part I of the application in accordance with the aspects described within Article 6 (1b)2 of the regulation, and authors an assessment report that includes determination that the conduct of the CT is either:

- Acceptable
- Acceptable subject to specific conditions
- Not acceptable

For a multistate CT application, the 45-day assessment process includes:

- RMS releases draft assessment report to CMSs
- CMSs coordinated review of the draft report
- RMS sends final assessment report, including CMS considerations and how they have been addressed

If further information is required, the RMS will issue a request for information to the sponsor via the portal. If this occurs, the 45-day assessment period will be extended by 31 days to incorporate the sponsor response (via the portal) and RMS/CMS assessment of the new information. The 31-day period includes 12 days for the sponsor to respond. If the sponsor exceeds this time frame, the application will be considered as lapsed (or a tacit withdrawal). This forces sponsors to adhere to the deadline or face having to resubmit.

The reporting date is the date the final assessment report is sent via the portal to the sponsor and CMSs. It will occur within 45 days of the validation date unless there are requests for information and/or the CT is for an advanced therapeutic medicinal product (ATMP) or biologic. The assessment period for CTs concerning ATMPs or biologics may be extended by up to 50 days to allow consultation with experts.

ASSESSMENT OF PART II

Part II will be assessed individually by each MS and in accordance with Article 7(1)(3). The assessment will be performed by an ethics committee and in accordance with the national law of the MS within the overall timelines defined by the regulation. Each CMS will submit an assessment report listing their conclusions to the sponsor (via the portal) within 45 days of the validation date. Within the 45-day period MSs can request further information from the sponsor regarding aspects covered by Article 7(1). In addition, as per the Part I provisions, the 45-day period can be extended by 31 days to allow the sponsor to respond to MS requests and the requesting MS(s) to assess the information.

Outcome

The sponsor can choose to submit only Part I for assessment, and then submit Part II within two years of the Part I reporting date. If the sponsor does not submit Part II within two years, the Part I application in that MS will lapse.

A sponsor may withdraw an application at any time until the reporting date, but can only withdraw the full application rather than in chosen MSs.

Parts I and II will be assessed in parallel unless the application contains only Part I. If Part II is submitted at a later date following Part I approval, then the MSs cannot request information concerning Part I.

Each MS will notify the sponsor of its single decision covering both Part I and Part II via the portal within 5 days of the Part I assessment reporting date, or within 5 days from the last day of its Part II assessment, whichever is later. This is the notification date. If a CMS does not provide a decision within this time frame then the Part I assessment report conclusion will be considered as the CMS decision on the application—i.e., a tacit approval.

If the RMS Part I assessment concludes that the CT is not acceptable, it shall be deemed to be the conclusion of all CMSs. If the RMS Part I assessment by the RMS concludes that the CT is acceptable or acceptable

Table B: CT application procedural timelines

	Validation	Assessment	Outcome	Total duration
	Submission date to validation date	Validation date to reporting date	Reporting date to notification date	Submission date to notification date
Initial application	10–25 days	45–76 (+50 days for ATMPs or biologics)	5 days	60–106 days (+50 days)
Addition of a CMS	—Not Applicable—			52–83 days
Substantial modification	6–21 days	38–69 days	5 days	49–95 days

Some member states may work to shorter timelines for single state applications; UK and Belgium have suggested this would be the case for applications they receive for Phase I CTs.
If the clinical trial is authorized, then the notification date = authorization date.

with conditions, it shall be deemed to be the conclusion of all CMSs.

A CMS can disagree with these conclusions, but only on the grounds of set criteria, including:

- Participation in the CT would lead to a subject receiving an inferior treatment than the normal clinical practice in their MS
- Considerations regarding subject safety, data reliability, and robustness
- Violation of MS rules on use of cell therapy
- Disagreement with RMS conclusion based on safety and data reliability, and robustness considerations as raised during the assessment procedure
- Aspects addressed in Part II of the assessment report are not complied with
- An ethics committee has issued a negative opinion, which in accordance with the law of the CMS is valid for that entire MS

In cases where the CMS disagrees with the RMS conclusions and does not grant approval, that CMS shall provide for an appeal procedure. It has yet to be seen how MSs will interpret and apply these grounds for not accepting RMS conclusions.

Adding a new MS

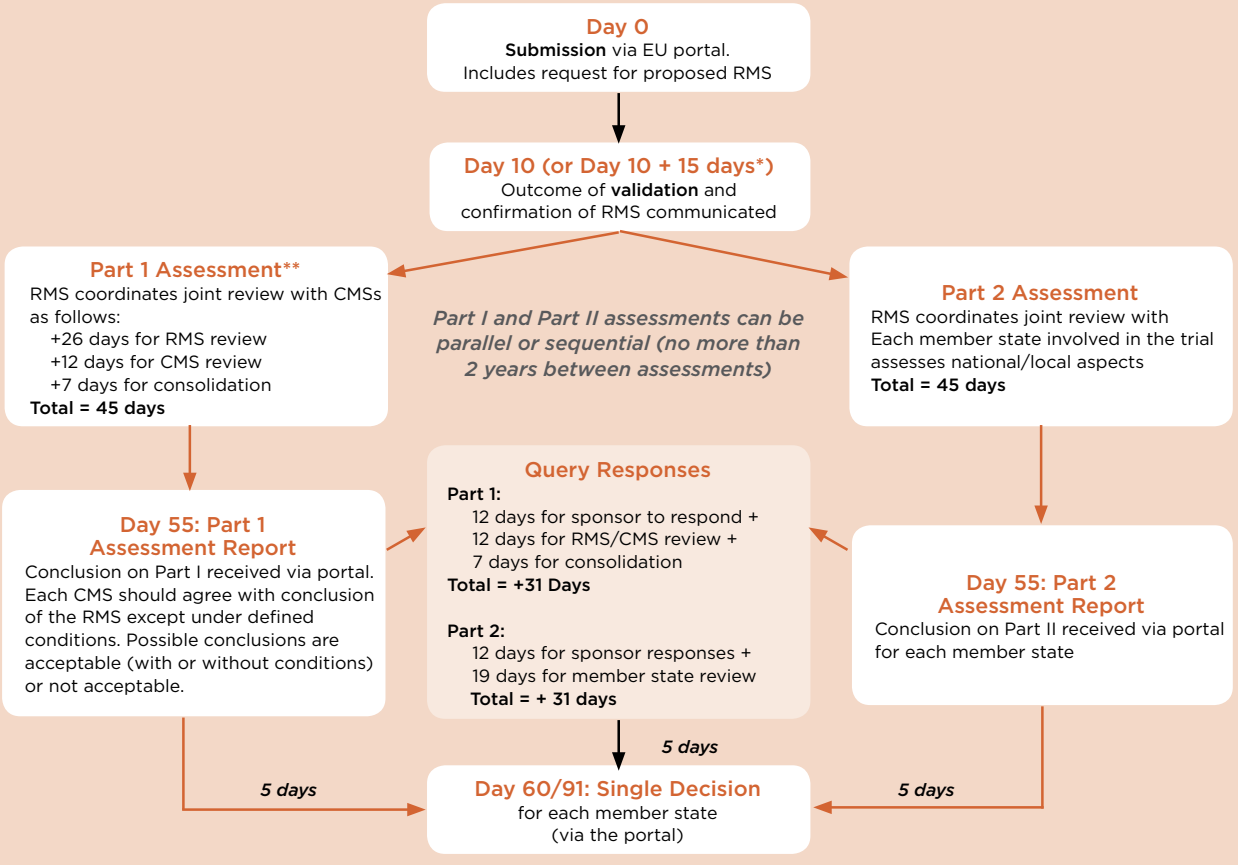
Following the notification date for an initial or substantial modification application, a sponsor can apply to modify a CT application to add an additional MS. Sponsors must wait for approval of the initial CT application and any subsequent substantial modification application before applying to add an additional MS. For such applications, the RMS will remain the same, and the new CMS will assess the application to the same criteria (as if the MS were part of the initial application); the same timelines of 31 days for requests for information apply. Any requests for information will be submitted to the sponsor via the portal and will also be sent to the RMS and existing CMSs. The additional MS must confirm the single decision for their country within 52 to 83 days of the submission.

Post-authorization changes

Just as in the CT directive, only substantial changes (which the regulation calls "modifications") require approval prior to implementation. The criteria for a substantial modification described within the regulation are similar to those of the CT Directive.

Essentially, changes that are likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of

Figure 1: Application process



* + 15 days for addressing validation comments :10 Days for Sponsor to respond + 5 days for RMS decision

** Overall assessment can be increased by RMS for a further 50 days in the case of advanced therapy products and biologics (for purpose of consulting with experts)

the data generated in the CT are considered "substantial." Substantial modification can be for Part I, Part II, or both. In terms of the application, the initial application approach applies: The RMS is the same, it includes a validation step, 31 days can be added to the timeline to accommodate requests for information, and a 5-day period follows the reporting date for CMSs to confirm their single decision The RMS will validate the application within 6 days of the submission and the reporting date will be 38 days (or 69 days if there are questions) from the validation date. If a modification affects both Part I and Part II, the assessment of each will be run in parallel in accordance with the timelines for a substantial modification.

An application cannot be submitted if another is ongoing. Tracked-changes versions of the modified documents may be required for the application.

IN SUMMARY

The EU CT regulation introduces a new procedure, new timelines, and revised application content. Although it may increase or decrease the overall timelines in some MSs, it will bring with it increased predictability for CT start-up in the EU.

Significant changes are afoot for the MS competent authorities, ethics committees, and sponsors.

- At the MS level, ethics committees and competent authorities will need to agree how to work together to achieve the review outcome within the required timelines.
- At the EU level, MSs will need to agree how to work together to achieve what is required to complete the application review.
- Industry CT sponsors will need to prepare themselves to confirm country selections without negatively affecting planned study start-ups (i.e., avoiding multiple applications to add MSs), respond to application review queries within short timelines, and manage changes so they can be submitted when needed rather than waiting for an ongoing application to complete. ‹›

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EU CLINICAL TRIAL REGULATION: ANNEX VI PERIOD OF USE LABELING REQUIREMENTS

Charles Gentile and Martin Waldherr

Guidance from ISPE's Investigational Medicinal Products Community of Practice

Introduced on 16 April 2014, the European Union clinical trial regulation No. 536/20141–2 is expected to be implemented by October 2018.[1–2] One of its most significant changes is found in Annex VI, which covers the labeling requirements for authorized and unauthorized investigational medicinal products (IMPs) and auxiliary medicinal products used in EU clinical trials.

In general, the new requirements are more restrictive than those of the still-applicable Volume 4, Annex 13 guidelines on good manufacturing practice.[3] One of the most important changes—and the focus of this article—is that the regulation will no longer permit the period of use to be omitted from the immediate packaging under defined circumstances (immediate and outer packaging provided together and/or small immediate packaging).

In addition to industry concerns for patient safety and study validity,[4–5] this change will create serious technical challenges for pharmaceutical companies when it comes to IMP packaging—particularly retest date extension labeling operations. When an IMP's retest date is extended based on new stability data, all patient kits containing this IMP must be given an additional label showing the new retest date as well as a unique identifier (e.g., study number). In this article we describe this process as "retest date extensions."

The main concern is that the retest date must be printed on the immediate packaging label; as a result, patient kits will have to be opened during retest date extension labeling. This change has the following major negative implications:

- **Efficacy and quality:** IMP storage conditions (e.g., cold storage, protection from light) may be compromised if the outer container is opened for retest extension labeling.
- **Risk of error/tamper evidence:** Retest date extensions on the inner container in blinded trials create a severe risk of error, since blinded treatments cannot be differentiated. Tamper-evidence seals would also need to be broken for extensions on the inner container. As a result, patients would either receive medication with broken tamper seals or the outer packaging would have to be replaced completely to reestablish an unbroken tamper seal.
- **Legibility:** Space on immediate containers is often very limited. Adding retest date labels may alter the legibility of the original label as well as other important information mandated by Annex VI.
- **Waste and environmental impact:** Small immediate containers like ampoules or injection devices (e.g., prefilled syringes) may not provide enough space for retest date extension labels. In these cases, clinical trial materials might have to be discarded rather than extended, increasing waste and environmental impact.
- **Supply continuity:** Additional labeling of the immediate container will increase retest date extension processing time and might generate the necessity for additional transportation (e.g., to avoid impact to storage conditions during labeling operations). This could delay clinical trial execution or even extend the trial duration and thus affect market authorization application timelines.
- **Cost:** In addition to increasing material overage (and waste), retest labeling of the immediate container will also directly increase costs associated with labeling operations. All depots and sites within the clinical supply chain will have to be paid for the additional effort of labeling the immediate container during extension operations.

For a more detailed description of these concerns and an example of the advocacy efforts in this space, please refer to the EFPIA position paper.[4]

Another potential concern is a restriction on the use of interactive response technologies (IRTs). The extent to which these technologies can be used for supply management in clinical trials will be severely limited. Omitting the retest date from labels managed by an IRT will no longer be allowed under the new regulation. The industry considers this a retrograde and innovation-inhibiting step that will limit the flexibility of managing a clinical trial.

The current understanding is the regulation would not be amended prior to implementation, but there is some hope that Annex VI could be influenced post-EU implementation.

In the following bullet points, we want to discuss some potential options on how to deal with the new requirements in Annex VI around labeling and also make readers aware of some potential pitfalls when adjusting their clinical supply chains.

- For packaging of solid dosage forms, it is possible to avoid printing and extension of the period of use on the immediate and outer container by avoiding multiple levels of packaging. This can be achieved by using (for example) high-density polyethylene bottles or blister cards. In both cases, no second level of packaging is

THIS CHANGE WILL CREATE SERIOUS TECHNICAL CHALLENGES FOR PHARMACEUTICAL COMPANIES WHEN IT COMES TO IMP PACKAGING—PARTICULARLY RETEST DATE EXTENSION LABELING OPERATION

needed, thus making extension operations a lot safer, regardless of the location of the medication within the supply chain (depots, sites, etc.).

- Consider avoiding tamper-evidence seals on multilevel patient kits, as they would have to be broken to allow retest date extensions on the immediate container. This means that either patients would receive kits with broken seals or the outer packaging would have to be resealed or even replaced completely. As tamper-evidence seals are an important indicator for patient kit integrity, the risks and benefits of such a decision should be considered carefully.
- Very small vials and ampoules have a limited area in which to place retest date extension labels. Flag labels could provide the additional space needed; this technology is already well established.
- Retest date extensions can become risky in blinded trials. Every immediate container at every site or depot in the trial will have to be removed from its outer packaging, creating a high risk of errors (mix-up of study medication). One possibility to mitigate this risk would be to add a unique identifier on all immediate and outer packaging. This could be the blinded container number, a randomization number, an RFID tag, or a 3D matrix on both the inner and outer packaging. This would help limit the possibility of mix-ups when applying the retest date extension label.

SOLUTIONS

To avoid the abovementioned issues, we also want to discuss some potential options for dealing with the new Annex VI labeling requirements. Several are being discussed in the pharmaceutical industry:

- Limit the size of packaging campaigns and hold stock levels in the supply chain to a level that will avoid the need for retest date extensions. Alternatively, packaging campaigns could be separated between EU (with retest date on the immediate container) and non-EU (without retest date on the immediate container) supplies. Because both of these options would require more packaging campaigns and very good stock monitoring, study costs would undoubtedly increase.
- In some cases, packaging design could be adjusted to simplify the retest date relabeling operations for immediate containers (e.g., pack one vial per kit instead of four). This would also add complexity and increase workload on stock level management.
- Print the period of use on the immediate and outer container during initial packaging, but limit extensions to the outer packaging. This would need to be stated clearly on the immediate packaging label as well as in the study protocol. There is currently no guidance to indicate whether such an approach would be accepted by EU authorities.
- Labeling of secondary packaging and patient kits only occurs after a request for medication is received from a clinical site. This "just-in-time labeling" would very likely be done at regional packaging sites to avoid long transportation lead times, and would require a harmonized quality control system and trained staff at the regional/local packaging sites and/or regional/local depots.
- Electronic replacement labels might, in the future, eliminate the need for physical retest date extensions. While there have been some promising developments in the field and industry working groups are exploring this new technology, eLabels have not yet gained regulatory approval. Because current regulations state that the retest date must appear on each label in manner that avoids any ambiguity, it is not clear if eLabels will be accepted by EU authorities.

In summary, several modifications to current practice can be considered in preparation for the implementation of Annex VI of the EU clinical trial regulation. The strategies suggested here will need to be discussed and agreed by organizations wanting to conduct or support clinical trials in the EU. ‹›

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COMPUTERS AND DATA INTEGRITY IN DRUG MANUFACTURING: US AND EU REGULATIONS 1978–2016

Yoel Bergman

US regulations on computers in drug manufacture first appeared in 1978, followed by the EU in 1992. Understanding the different motives for regulations, modifications, and approaches could help better comprehend current US and EU regulations, especially those on data integrity.

Computers and software are used for a wide variety of purposes in the drug manufacturing industry, and are generally classified for either automation control or data handling. After their wide use in the industry began in the late 1970s and early 1980s, regulations on their design, operation, and data handling were needed to minimize risk to product quality and patient safety—the main goals of the current good manufacturing practices (GMP). These GMP, with other relevant regulations and documented policies, are the first to be followed by the industry.

US computer regulations were first introduced in the updated 1978 GMP (US Code of Federal Regulations [CFR] 21, Part 211) focusing on data accuracy. Following questions from the industry in the early 1980s, more regulations were added to cover lifecycle issues.

The initial EU computer regulations, introduced as Annex 11 of the EU GMP in 1992,[23] did address several parts of the lifecycle, but too concisely, leading professional bodies to write supplemental guides. By 2011, Annex 11 computer regulations generally concerned either the operational phase or the project phase.

One aim of regulations in the project phase was to promote computerized audit trails and access controls that would help meet data-integrity and other GMP requirements in the operational phase. Another was to ensure built-in quality and proven performance by requiring supervision and testing of computer planning, development, coding, and construction, ending with the industry acceptance tests. Here, regulations first appearing in the 1980s prompted the industry to acquaint itself with design, coding, and release phases.

Computer validation, the rigorous test method recommended to prove regulatory compliance with specifications and consistent intended performance began to be implemented by the industry with supplements from suppliers. Lopez has recently pointed out that between 1990 and the mid-2000s computer validations were the focal point in site audits.[1] Consensus standards have helped the industry plan and perform validations. For detailed guidance on computer validation, the GAMP® 4 Guide (*Validation for Automated Systems*) was recommended by an FDA 2003 guidance[18] and GAMP® 5 (*A Risk-Based Approach to Compliant GxP Computerized Systems*) in 2015 by an MHRA guidance.[21] As the importance of computer validation became apparent, detailed requirements to enhance data integrity were added to the 2015 MHRA guidance and the 2016 FDA draft guidance.[22]

US COMPUTER REGULATIONS WERE FIRST INTRODUCED IN THE UPDATED 1978 GMP

Necessary data integrity attributes were identified by the acronym ALCOA: attributable, legible, contemporaneous, original (or a true copy), and accurate. Computer validations under these guidelines verify data integrity workflows that ensure ALCOA, as correct data recordings verified by audit trails, and proper calculations by manufacturing execution system (MES). Since systems that produce electronic data (MESs, enterprise resource planning, laboratory information management systems) interface differently the features to ensure ALCOA validations will differ.

In the operational phase, regulations are aimed largely at data integrity, although this term was little used at the beginning and its scope was limited at first. The 1978 GMP, for example, required measures for data accuracy that nowadays are part of ALCOA. The 1997 CFR Title 21, Part 11, added additional design and procedural requirements to safeguard, among other things, the integrity of electronic records (ERs) which included different forms of digital information, including electronic data. (Part 11 was not strictly part of the GMP but applied to the industry.)

The requirements became stricter over time. As an example, the 1992 Annex 11 recommended the use of computerized audit trails; Part 11 in 1997 made them compulsory and specified what is to be recorded. The updated 2011 Annex 11 added the need for periodic review of audit trail information to its previous recommendation. The 2015 MHRA and the 2016 FDA draft guidance cover audit trails, periodic reviews, and who should perform them.

By 1978 the regulations above were applied to common operations on different computers. In the 1980s, the FDA began to issue policies on specialized computer operations. In one example, the GMP required significant stages during manual production to be recorded on a batch

record by the operator, checked by a supervisor, with both required to record their names. In a computerized process, fewer checks were required.

By 2016, the United States and European Union covered similar aspects and closed the differences on issues such as data and records (to be discussed in the sections below). These advances and growing similarities were facilitated by guidelines published by international organizations and authorities such as ISPE/GAMP, APV, ICH, and others. A detailed review of their contributions, however, would require a separate article. Suffice to say that their essential concepts eventually found their way into the regulations.

One notable difference between 1978 and 2016 was the EU emphasis, beginning 1992, on protecting electronic data. In the United States this was a more complicated story, with the 1978 GMP focusing (as did the later EU Annex) on electronic data. Little was said about electronic records that come out of the processes or labs tests. This changed in 1997 with the introduction of Part 11, where process and other records became the basic entities to be protected.

US regulations have also tried, much more than those in the EU, to justify new regulations on existing ones made in the days of manual operation and hardcopies. In addition, all EU computer regulations can be found in a single source and further explained by consensus standards. US regulations and policies post 1978 are covered by US CFR Title 21, Parts 11 and 211, and five policy guides. Various FDA guidelines, although not strictly regulations, have provided more detailed requirements and perspectives.

CHRONOLOGY

The following paragraphs examine the main evolutions in computer regulations in chronological order. Key changes described in the introduction are underscored:

1963—First US GMP issued: On 14 February 1963, the FDA issued the first GMP[2] (CFR 21, Part 133, changed in 1975 to the current Parts 210 and 211).[3] There was no mention of computers, electronics, or automated equipment, only equipment in general. The final rule on the GMP in the June 20 1963 Federal Register did allow the use of automatic, mechanical, or electronic equipment, possibly following a proposal by the industry, or rethinking by the FDA.[4] The permission to use electronic equipment in the 1960s was relevant to local electronic controllers, since very few digital computers were in use. By the 1970s, digital computers were integrated for on-line control. In the early 1980s, computer systems became inexpensive and powerful enough to be used extensively.[5–6]

1978—First regulations on computers in US GMP: In 1976, the FDA proposed including computer regulations in its planned major update of the GMP.[7] A public discourse ensued. In 1978, the updated GMP was issued, including newly required checks on input and output data in daily operations and backing electronic master batch records that were entered.[8] When the GMP was published in the Federal Register, the FDA commissioner remarked that ERs were allowed, as were those created during batch operations. This took place even before clear permission to use ERs; specific instructions were not given until Part 11 in 1997.

1983—FDA Guide to Inspection of Computerized Systems in Drug Processing: This guide, known as "the Blue Book," was published to educate FDA staff and inspectors on technology and regulations and to answer industry questions that arose in the early 1980s. It presented requirements for industry not found in the 1978 GMP, such as computer validation reports, the need to understand the structure and content of application source code, controlling in-house software development through procedures, periodic backups, monitoring of computer operations and alarms, system recovery checks, and maintenance. The guide's detailed technical explanations on computers are still helpful today.[9]

1982 to 1987—Five FDA official compliance policy guides: The CPGs put Blue Book issues, including those on the project phase, into a more official framework. Other issues included industry and vendor responsibilities over the fitness of the software, industry controls over the source code, the need for validating the performance of the batch computer program, and equating the application/code to a master batch record for the purpose of applying existing GMP controls to the software.[10] Lopez remarked that the FDA attention to computers was not very significant until 1988.[11] Computers seem to have become important in 1988 following the maturation of a comprehensive policy based on the CPGs.

1987—FDA Guideline on General Principles of Process Validation: This guideline concerned process validation, first required in 1978. The first step, installation qualification, was intended to provide evidence on proper equipment design, construction, and operations, including the capability to control the process.[12] Since control involves software, it touched areas

under computer validations as well, creating a potential for duplicate tests. In addition, the term "installation qualification" (and later "operation qualification") was adopted by some in computer validation as the first stage in computer on-site validation, replacing software terms such as integration, functional and performance tests.

1991—Good Automated Manufacturing Practice (GAMP®) Forum: A UK forum of industry members and officials was formed in response to various FDA findings of noncompliance by local drug manufacturers during audits in 1991.[13]

1992—New EU GMP Annex 11, Computerised Systems: This document focused on securing electronic data in daily operations while covering in brief the whole computer lifecycle. Development records, validation reports, secure access controls, and an audit trail on operators' activities were required. Some measures soon appeared in the US Part 11. The Annex did not provide enough guidance on how to perform validations or what to require from the suppliers, and was soon considered by some as too concise.

1996—APV Guideline Computerized Systems: Published by the German-based International Association for Pharmaceutical Technology (APV) forum and intended to supplement Annex 11, this guidance was based on the software development, quality, and project standards ISO 9001/ISO-9000-3. It added development requirements from the software world to regulations that grew out of immediate manufacturing concerns, which are the central issues in the EU and US GMP. The guideline was appended to the 1996 GAMP guide.[14]

1995–1996—First and second editions of the *GAMP Supplier Guide*: The guides introduced specific supplier and industry responsibilities on testing and documenting activities such as planning, design, and implementation. These were applied to all system parts, including software, hardware, peripherals, equipment, and electricity.[14] The detailed activities in each major phase were described, and document templates were appended for user requirements specification, software design specification, etc. The guide introduced a risk-based approach to determine the extent of validations, according to the type of software being purchased or developed. More commercially proven software with no options for users to change the program, were required for less validations. Like the APV guideline, the GAMP guide was based on general software quality standards ISO 9001/ISO-9000-3 and British/Swedish TickIT, providing important and missing guidance on how to plan and test computers for pharmaceutical use.

1997—US CFR Title 21, Part 11, Electronic Records; Electronic Signatures: Since records are primary evidence for compliance, the industry met with the FDA in 1991 to determine on how to accommodate ERs under the GMP. The GMP requires protected storage of various on-site records, such as batch, production, laboratory, distribution, and complaints. Each record type is required to present specific types of data. It was therefore a primary technical and procedural concern when going electronic. Soon the scope was expanded to apply to the other regulated sectors, such as medical devices.

After the issuance in 1997, the industry had to comply with both the more detailed Part 11 as well as with the existing GMP in Parts 210 and 211.[15] While Part 11 was restricted only to those systems that handle electronic records, Part 211 applied to data in general. Thus, computers that control or measure and yield simple printouts, for example, were still required to comply with the GMP electronic data requirements.

ERs in Part 11 were defined as any combination of digital information in various forms—text, graphics, data, audio, or pictorial. As Part 11 aimed to protect ERs, it included requirements for controlled user access, computer validations, protected storage of ERs, and computerized audit trails on operator creations, changes, and deletions (similar to the 1992 Annex 11). New measures were the concepts of closed and open systems and regulations on electronic signatures not found in EU regulations.[16]

Despite consultation with the industry, Part 11 soon turned out to be controversial. The industry did not clearly understand that Part 11 applied to ERs that replaced specific and official paper records. The status of hybrid systems—those with ERs printed and signed at the end of the process—was also unclear. Cross-the-board requirements for validation of any system that complies with Part 11 and the need to implement computerized audit trails turned out to be burdensome, and believed by some to be unnecessary.

Richman suggested in 2005 that the industry was not generally prepared for Part 11 due to an underestimation of the needed changes and costs, clouded by great efforts at the time to implement process validations. Yet since 1997, Part 11 has been a high-profile center of attention and a catalyst of a significant, but grudgingly accepted, culture change in the industry's approach to software and computerized systems.[17]

2002—FDA General Principles of Software Validation; Final Guidance for Industry and FDA Staff: This document provided detailed guidance on software project management, development, and documentation, including validation methods. The scope, methodology, documents, and their contents were similar to those in the APV and GAMP, guiding the industry on issues as software development and validations.

2003—FDA Guidance for Industry: Part 11, Electronic Records Electronic Signatures—Scope and Application: By 2003, the FDA recognized that Part 11 (a) no longer fits the agency's stated direction with respect to risk-based assessments of compliance, (b) some broad interpretations of the rule could serve to restrict the use of electronic technology, which was not what FDA intended, (c) compliance costs had increased to a level unforeseen by the architects of the policy, due to broad interpretations, and (d) it discouraged innovation and technological improvement without benefitting public health. As a result, the FDA decided to exercise "enforcement discretion," which enabled the agency to highlight and enforce egregious violations, but take a risk-based approach in less meaningful cases.

The 2003 guide was an outcome of the updated policy. It provided a more precise and narrower definition of ERs subject to Part 11. For those systems that did comply with Part 11, less enforcement would be applied on validation requirement, audit trails, record retention, record copying, and systems that were operational before the effective date of Part 11 (also known as legacy systems). The industry was given the authority to decide what systems to validate and the extent of validations. The decision to apply computerized audit trails was also relegated to the industry. In both cases, a risk-based approach to quality was recommended for making the decisions. For further guidance on computer validations, the agency recommended the GAMP 4 guide or FDA "General Principles of Software Validation."[18]

2003—PIC/s Good Practices for Computerised Systems in Regulated "GxP" Environments: This guide was intended to supplement EU Annex 11 as the APV, especially after the publication of US Part 11. It covered all the phases and aspects of the lifecycle including development, systems daily operations, and the use of electronic records and signatures.[19]

2011—Annex 11 Update: As stated on its first page, the Annex was updated for the first time since 1992 due to the increasing complexity of computerized systems.[20] It seemed to have attempted to close gaps with Part 11 and the various guides published to supplement it. More controls on suppliers, development, and (electronic) data were introduced and reference was made, albeit briefly, to ERs and ESs. The annex recommended a risk-assessment process for determining the extent of validations and when data integrity controls shall be applied as audit trails.

Like the 2003 FDA version, the updated Annex 11 seems to have been intended to prevent overspending. Like the 1992 version, it remained focused on electronic data and not records. Data was considered electronic information entered into and coming out of the computer, to be stored and retrieved. This implied that data includes all types of digital information, including electronic records, which were viewed as a special set of data, as for batch release. In Part 11, this was the other way around as electronic data was a component in the ER. One novelty of the 2011 update was the expectation that computer design and operation can minimize risk to data integrity, in addition to minimizing risk for the two main GMP goals, product quality and patient safety.

2015—MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015: While its focus is on computers, the guidance was intended to list the UK Medicines and Healthcare Products Regulatory Agency's expectations on data integrity, whether the data is recorded by hand or by computerized means (although the focus is on computers). It develops the computer and integrity requirements of the 2011 Annex 11 in greater detail, including definitions of electronic data (raw data, manipulated data, and metadata), with records as a special data type. Specific data governance measures were introduced to ensure the integrity of data on computers and or paper. One example is new recording and review requirements for audit trails.

Validations play an important part in the guidance, and industry is required to supplement supplier validations by validating the systems with electronic data for their intended use. As intended use includes compliance with the integrity governance requirements, validation becomes a major tool to demonstrate integrity compliance. The guidance recommends, as does the 2003 FDA guidance, the GAMP Guide for executing the validations. This indicates again, the importance of consensus guidelines in the field of validation mentioned in the paragraphs above.[21]

2016—FDA Data Integrity and Compliance with CGMP -Draft Guidance: The guide follows increasing FDA observations on current GMP violations involving data integrity during site inspections. It stresses that commonly found requirements on electronic data and records integrity can be inferred from the GMP in Part 211. Examples include backing up original data or complying with record-keeping practices that prevent data from being lost or obscured,

CONSENSUS STANDARDS HAVE HELPED THE INDUSTRY PLAN AND PERFORM VALIDATIONS

a requirement that can be met with a computerized audit trail. Not all can be traced to the GMP, and the guidance refers readers to Part 11 to comply with electronic signatures and record-keeping requirements. The guidance can thus be viewed as one single main and updated document for complying with GMP integrity requirements, as in the MHRA. The guidance emphasizes that any data needed to satisfy a CGMP requirement becomes a CGMP electronic record, thereby helping to minimize or eliminate the differences between electronic data and records. Audit trail reviews, as in the MHRA, are required and industry validations for intended use are deemed necessary.[22]

SUMMARY AND CONCLUSIONS

This essay examined EU and US regulations on computers in the industry from their beginning in 1978 through 2016. Regulations were added during that period to the entire computer lifecycle, as regulators became aware of important issues that provided assurance on data integrity and computer performance. This was aided by professional bodies working through international cooperation. The current 2015 MHRA and 2016 FDA draft guidance on data integrity provide updated and more stringent requirements. Overall, EU and US regulations from 1992 onward have become similar; despite the bumpy road in forming the regulations and compliance, they have catalyzed needed changes in this highly regulated industry. ‹›

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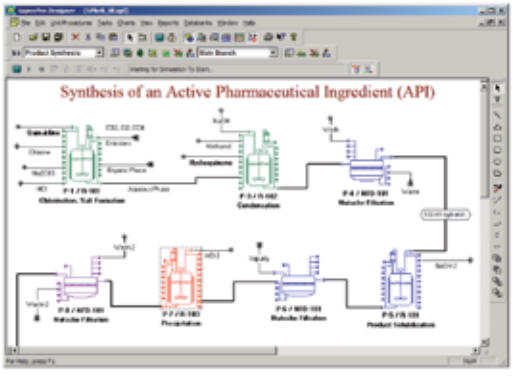

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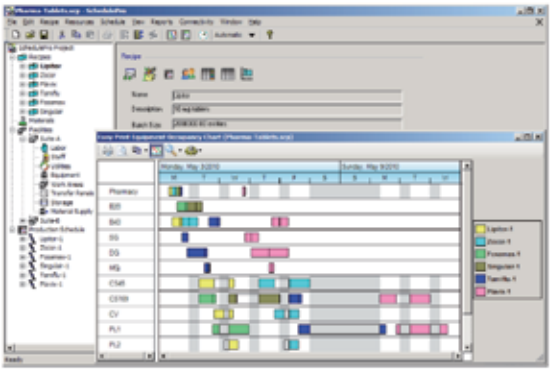

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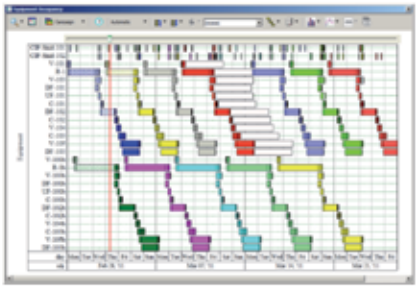

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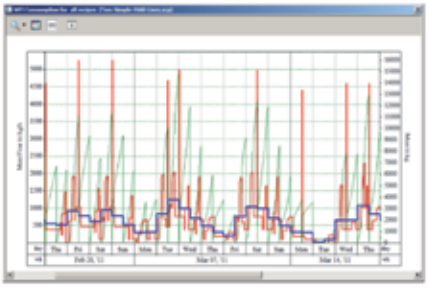

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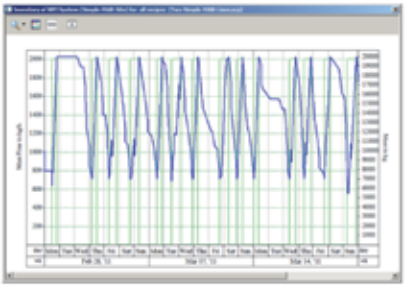

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ACHIEVING AND MAINTAINING GAMP® 5 COMPLIANCE: A RISK-BASED APPROACH TO SOFTWARE DEVELOPMENT AND VERIFICATION

Diana Bagnini, Barbara De Franceschi, and Margherita Forciniti

Given the growing level of automation, validation of computerized systems must be an integral part of projects to guarantee the quality of products and process controls.

This article focuses on the software verifications of two machine models. A multidisciplinary group performed a software risk assessment and control to identify the level of the risk for each software module and to carry out a series of activities and tests. This process increased software quality and improved maintenance.

The reference standards and methods used to validate the systems are those set by GAMP® 5, which follows a risk-based approach.[1]

INTRODUCTION

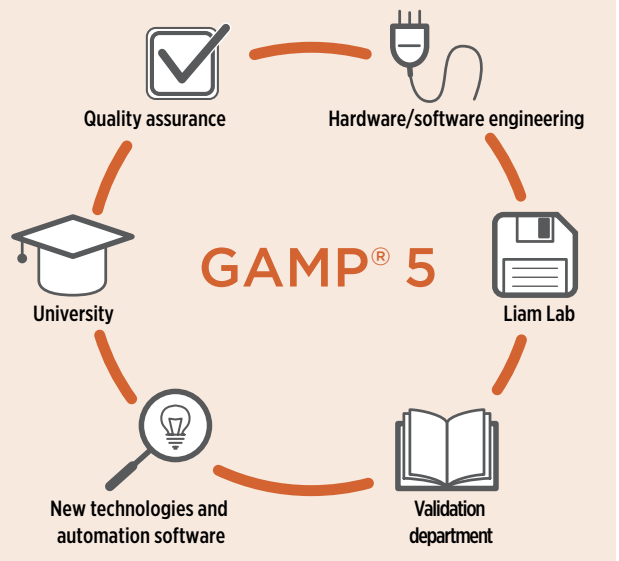
Automatic machine suppliers must always be conscious of the regulatory requirements placed upon their customers to ensure that all critical equipment is capable of being implemented to meet validation requirements and ensure patient safety, product quality, and data integrity. GAMP® (Good Automated Manufacturing Practices) guidelines are designed to interpret validation requirements and apply them to all aspects linked either directly or indirectly to pharmaceutical product quality.

GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems introduces the concept of risk management for automated and computerized systems, focusing validation and control only where necessary, and identifying the functions and processes that pose the most risk for the pharmaceutical product.[1]

Given growing levels of automation, the functions and processes previously managed by mechanical devices are now carried out with the aid of software, giving increasing importance to these components. As an automatic machine supplier operating in the pharmaceutical sector, our aim is to guarantee the quality of products and process control, even where a computerized system takes the place of a manual operation. In the development of our latest machine models, therefore, we have paid particular attention to software design, using GAMP 5 principles and framework.

The multiphase risk-assessment and control project described in this article involved the collaboration of various professional figures, including members of the quality assurance department, software engineers, validation and risk assessment experts, as well as coworkers from research laboratories and the University of Bologna (Figure 1).

Figure 1



GIVEN THE GROWING LEVEL OF AUTOMATION, VALIDATION OF COMPUTERIZED SYSTEMS MUST BE AN INTEGRAL PART OF PROJECTS TO GUARANTEE THE QUALITY OF PRODUCTS AND PROCESS CONTROLS

FOLLOWING THE RISK ASSESSMENT, RESOURCES FOCUSED ON THE MOST AT-RISK MODULES AND FUNCTIONS, AND CORRECTIVE ACTIONS WERE DIRECTED SOLELY WHERE NECESSARY

CASE STUDY

The project focused on the software of two machine models: the first is an automatic rotary tablet press for producing single-layer tablets that allows all production volumes to be processed. The second is a laboratory system for granulation and/or core coating processes. To ensure that the software used in these machines can be classified as Category 3 (nonconfigured), we had to carry out a series of activities, as follows:

1. Study

Before conducting the risk assessment, it was necessary to understand the context of application and make an in-depth study the software architecture of the two machine models under consideration.

Software architectures are made up of two macro systems: machine control and user interface. Both were designed and implemented in-house.

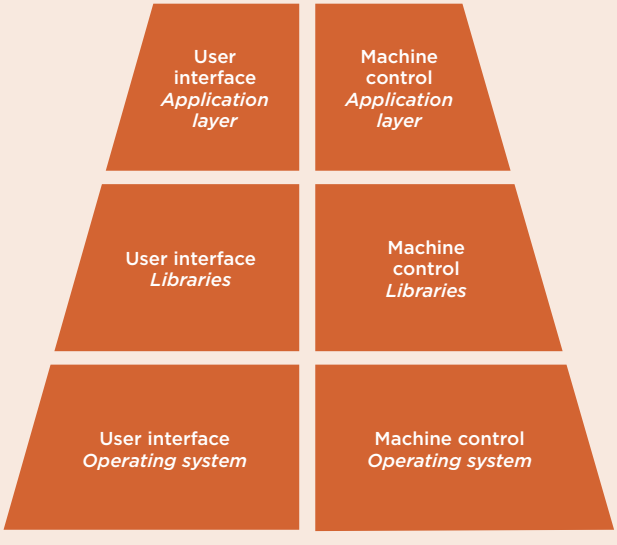
The machine control software processes all machine movements, phases, data, and functions. It can be installed on a PC or on a programmable logic controller.

The user interface, on the other hand, is the means of communication between the machine and the operator. It manages data flow to and from the machine control and displays information on the monitor; it also collects data and statistics regarding product quality. It is installed on a PC.

Figure 2 shows a schematic representation of the two macro systems. Both consist of three software layers: operating system (present only if the machine control is installed on a PC), libraries, and application. The libraries implement the functions shared by all machine models. The application layer is specific to the machine model; through the libraries, it implements the main functions for which machine control and user interface are responsible.

The risk assessment covered the libraries and application layer only; no further action was envisaged for the operating system, as it was accepted by virtue of its successful widespread use.

Figure 2



2. Method

The method used for the risk assessment and risk control is the failure mode effect and criticality analysis (FMECA), one of the standard methodologies put forward by ICH Q9.[2] Based on the steps provided by the FMECA, the critical issues of a process or product are analyzed as follows:

- **Risk identification/risk analysis:** Various failure modes (hazards) are assessed, as are the severity of their effects on the system, their probability of occurrence, and whether or not controls are in place to detect the failure modes.
- **Quality risk evaluation:** Quantitative values are assigned to the severity, occurrence, and detection ratings to calculate the risk priority of each failure mode.
- **Risk control:** Depending on the risk priority number generated, activities and corrective actions are established to make the risk level acceptable.

Since the object of the risk assessment and control application in this project is the software, the hazards considered do not concern broken or damaged components, but software behavior (bugs) unforeseen or not assessed by the designer.

The goal of this phase was to define objective evaluation scales and avoid the arbitrary attribution of values. From this phase onward, collaboration with various professional figures was essential: software designers who had the required expertise on the software in the machine models, validation experts who understood the documentation required by the customer, coworkers from research laboratories and the University of Bologna who were armed with the very latest software-design methodologies, and representatives from the quality assurance department, due to their expertise in the risk assessment methodology.

Given the different characteristics of the machine control and user interface, it was necessary to define the evaluation scales and assign values to the three parameters:

- **Severity:** The impact of the hazards on patient health and/or data corruption, with particular focus on data consistency and integrity.
- **Probability:** A preliminary study on the probability of software bugs found two determining factors—maturity and complexity. The more mature the software, the lower the probability of bugs, as the software has been widely used over time by numerous users. Complexity depends on factors such as the programming language and the

foundations on which it is based. Complexity scales present in the literature were studied and then adapted to the automation context. In the machine control study, for example, only cyclomatic complexity was considered; the user interface required several additional indicators specific to the programming language (object-oriented programming), such as coupling between object class and depth of inheritance.

- **Detection:** This parameter required examination of each instrument capable of providing evidence of a hazard or its underlying cause, from both developer and end user perspectives (e.g., error trace or error message visible on user interface).

The scale for each parameter listed above has three levels: high, medium, and low.

3. Execution

Software modules that implement various functionalities were analyzed individually. All possible hazards were listed for each one, along with the effects they could have on the product, the integrity of the data, and the patient's health. The main hazards encountered for machine control affected patient health; user interface risks relating to data integrity and consistency were more common.

Based on the assessment scales, values of severity, occurrence, and detection were given for each hazard-effect pair and the risk priority was calculated, as suggested by the tables in chapter 5.4 of GAMP 5. Depending on the risk priority that emerged for each pair, identified actions were taken.

Table A shows an example of the analysis carried out on three different modules with resulting different risk priorities. For simplicity, a single hazard is shown for each module.

4. Actions

Depending on the risk priority levels detected, activities were identified for each module. For low risk priority modules, no additional action was taken other than the tests normally performed during internal testing on the machine (e.g., checking report generation, verifying production charts). Modules with a medium risk priority were evaluated on a case-by-case basis, with corrective actions such as code review or targeted tests performed as needed. For high risk priority modules, activities were aimed at lowering the risk priority. An assessment was made whether to carry out dedicated tests or to intervene directly on the software, for example to lower the probability of a hazard occurring or increase detection by adding specific controls.

For the dedicated tests, the goal was to reproduce the system status by simulating the hazard presumed in the risk assessment, checking the response, and correcting any errors found in the software. All tests were fully documented and the results obtained were noted.

If a particularly large module was found to be high risk and require a very long series of activities, it was separated during the analysis phase into its underlying functions to isolate those that were most critical and focus activities solely on them.

Choosing the granularity (module or function) with which software was

Table A: Sample analysis of three modules

Module	Lamps handler (machine control)	Lubrication pump handler (machine control)	Recipe OCX handler (user interface)
Function	Signaling column management	Pumping lubrication oil activation	Writing values in the recipe archives that are then exported to the audit trails
Hazard	Wrong configuration of color-machine status couplings	Wrong lubrication pump deactivation	Incorrect recipe values recording
Potential effect	Signaling column's color not consistent with machine status	Overabundance of oil in the machine	Wrong recipe values in the audit trails
Severity	Low: impact only on visualization	High: possible product contamination	High: incorrect values
Probability	Low: very mature function with low complexity	Low: very mature function with low complexity	Low: very mature function
Detection	Medium: visual feedback	Medium: visual feedback	Low: detectable only with a targeted verification of audit trails data
Risk priority	Low	Medium	High
Actions	Functional tests already on the machine	Test: turn off the pump and make sure it does not pump oil	Test: enter recipe data and check that the values in the archives and audit trails are consistent with those entered

separated did not follow a fixed rule; the developer in the analysis team decided based on context and type of software.

5. Maintenance

The inherent nature of software is that it undergoes continual evolution for the purposes of improvement, to accommodate mechanical and electrical modifications, or adapt to new machine functions. This means that risk assessment and control must also evolve and be updated at the same pace as the software itself. Therefore, for every software version issued after the first one analyzed, it is necessary to update the risk assessment and control table also, reviewing modules that have been modified or added and those that the modifications or additions affect.

This produces a risk assessment and control table for each software version.

CONCLUSIONS

The project described here had a variety of benefits.

Resources were optimized: Following the risk assessment, resources focused on the most at-risk modules and functions, and corrective actions were directed solely where necessary. Of all the modules analyzed, approximately 20% were high risk—almost entirely application-layer modules developed from scratch for new machine models. Approximately 30% were medium risk. Eighty percent of these were application-layer modules. The remaining 20% were library modules shared by all machines. Consequently, the greatest efforts were focused on approximately 50% of the software, instead of the software in its entirety.

Another benefit was an improvement in software quality. Following the risk assessment, corrective actions included software changes to eliminate errors, add further controls (thus increasing hazard detection), or simplify software functionality.

In addition, the analysis team was directed to evaluate not only software functionality hazards, but those of product quality and data integrity and consistency as well. Finally, the risk priority resulting from the assessment is objective, thanks to the method of constructing the evaluation scales of the severity, probability, and detection parameters.

Given that risk assessment and control tables are always aligned to software revisions, they are also key document tools. If software changes need to be implemented, even by a different designer than the one who wrote the original software, it will be possible to implement them more quickly and accurately. ‹›

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Margherita Forciniti received an MSc in electronic engineering from the University of Calabria in 2008. She has worked in customer quality control for Elica S.p.A., as a quality control engineer for the American Navy, and as a software quality test engineer in the Vega launcher project developed by the Italian and European space agencies. Since 2012 she has worked in the quality assurance department of IMA (Industria Macchine Automatiche) S.p.A., customer quality branch, where she is involved with the computer system validation projects of the Pharmaceutical Business Unit. She has been an ISPE Member since 2012.

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Many chemotherapy drugs are harsh tools that are anything but precise, with side effects on off-target tissue that can make life miserable for the patient. They are like an herbicide that kills every plant it touches when what we want is a hoe that removes a weed without damaging the crop around it.

What if we could aim these toxins directly where they are needed and nowhere else, poisoning tumor cells specifically?

Ensuring precise, localized delivery to minimize side effects and boost efficiency is a major goal of experimental research to develop novel drug delivery systems. One promising new technology for the treatment of autoimmune disorders such as multiple sclerosis involves injecting hydrophilic carbon clusters combined with polyethylene glycol (PEG-HCC) just under a patient's skin.[1] These nanoparticles form a temporary tattoo that fades away over a week as they are taken up selectively by T cells, which in patients with MS are believed to have lost the ability to distinguish between host and foreign invaders. PEG-HCC inhibits the T cells by scavenging reactive oxygen molecules that T cells use to fight pathogens.

Other inventive ways of introducing medications include bypassing the protective layer of skin via absorption through hair follicles,[2] gradual release of antibiotics from a thin biodegradable coating added to synthetic joints prior to joint-replacement therapy,[3] and cutting-edge biologics that use gene-editing techniques such as CRISPR to target non-germline tissue, such as lungs affected by cystic fibrosis.

GETTING MEDICATION INTO OUR BODIES AND SENDING IT WHERE IT IS NEEDED HAS ALWAYS BEEN A CHALLENGE

These innovations are still in the experimental stage, but for some cancers we are already seeing targeted delivery using antibody drug conjugates (ADC). ADCs harness the binding specificity of monoclonal antibodies to deliver, directly to cancerous tissue, a toxic payload to which they're attached via a linker.

Only two ADCs are currently on the market, but many more are in the pipeline. Brentuximab vedotin (Adcetris) won accelerated approval from the FDA in 2011 for the treatment of refractory Hodgkin lymphoma and anaplastic large cell lymphoma. Trastuzumab emtansine (Kadcyla) was approved by the FDA in 2013 for HER2-positive metastatic breast cancer that has proved unresponsive to other treatments.

We are also seeing introductory forays into a new field of treatment, bacterial therapeutics, that uses microbes to convey drugs. Researchers at the California Institute of Technology in Pasadena have created genetically engineered bacteria that respond to subtle temperature shifts—the kind that could be administered to a tumor using ultrasound— to turn on the expression of a gene and release medicine directly to the tumor.[4]

Another exciting proof-of-concept experiment brings science fiction to drug delivery in cancer treatment. Researchers at Polytechnique Montréal—who originally hoped to design a nanorobot to deliver drugs to tumors—have demonstrated that a bacterium carrying chemo drugs can be coaxed to transport its payloads directly to the actively growing part of tumors in mice.[5]

Researchers used a magnetic field to direct *Magnetotactic cocci*, which has an internal compass made of iron, toward colorectal tumors. The strain has the additional beneficial characteristic of gravitating toward oxygen-poor environments, meaning it homes in on tumor cells. The chemo drugs were encapsulated in liposomes modified to adhere to bacteria. More than half the injected bacteria made it to the tumor, where the liposomes were released and taken up by the tumor cells. The bacteria are heat-sensitive and die after 30 minutes in the mouse. Much work has yet to be done and the immune reaction in humans is unknown, but findings like this are promising.

Precise delivery—using a hoe to weed the garden—should leave patients better off, allowing maximum dosages and fewer side effects. ‹›

—Scott Fotheringham, PhD

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