The Official Magazine of ISPE

PHARMACEUTICAL ENGINEERING®

March-April 2016 | Volume 36, Number 2

Compliance matters

ISPE-Pew Joint Drug Shortages Project

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Quest for the Magic Bullet

Special Report: DATA INTEGRITY

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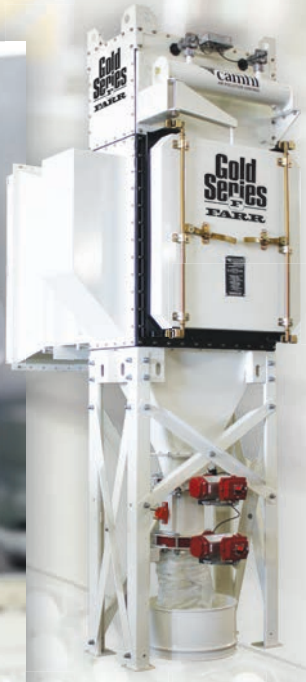

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What do we have if we don't have integrity?

Anna Maria di Giorgio, Editor in chief

No, this isn't an existential question or a rhetorical one at that. It's THE question facing regulatory agencies, the industry, and our members. Because data integrity touches the lives of our key stakeholders: patients, both current and potential.

Data integrity is the cornerstone upon which we build trust with patients. Patients need to trust that the drugs they take have been manufactured according to strict regulation and oversight, and are of the best quality. They need to trust that the quality of drugs they put into their bodies to treat ailments and diseases, has passed the test; that all pharmaceutical companies, regardless of geography, have complied with regulations, and embraced a culture of compliance, ethics and quality. Integrity.

It seems a simple ask. Yet the response is complex.

In upcoming issues, we will explore the interrelationships between compliance, culture, quality, and integrity, their impact on the industry, and on the lives of patients. We'll also look at the role human error and, even, belief systems play across the manufacturing process.

In this issue, we begin with the basics. Thomas Cosgrove talks about the OMQ's role in enforcing compliance, while conceding that "one can find various degrees of CGMP violations at just about every drug manufacturing facility, if you're looking hard enough." Joe Famulare argues that combining the capability, quality, and technology of the manufacturing process with quality systems results in true compliance. Michael Rutherford and Peter Boogaard define data integrity principles and present perspectives on how you can implement and manage a corporate data integrity program. And authors Thomas Haag and Charlie Wakeham look at the role human error plays in data integrity.

As an association that represents professionals in the pharmaceutical manufacturing industry, we have as much difficulty accepting that the quality of drugs patients take may be compromised as we do the existence of drug shortages. We want to tackle this issue with our members, industry leaders, and regulatory agencies, so that we may contribute pragmatic solutions, and training, where needed. ■

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(Design department)

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Pharmaceutical Engineering is a magazine that inspires engineers and regulators across all ranks, around the world, with provocative and useful articles that come from trustworthy and reliable sources.

From technical articles that provide how-to advice that is current and immediately applicable on the job, to thought-provoking features on current issues, *Pharmaceutical Engineering* offers readers a global picture of the profession and the industry.

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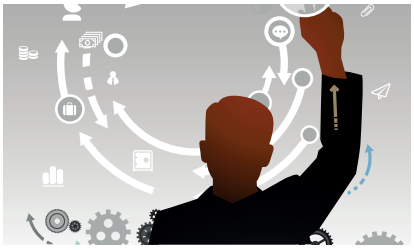
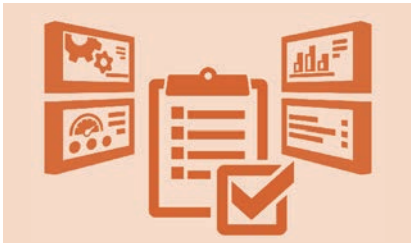
Special Report: Data Integrity
39-67



Technical Articles



Back Page

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Please address editorial correspondence to:

The editor, Anna Maria di Giorgio
amdigiorgio@ispe.org

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April 2016

4–5 A GAMP® Approach to Data Integrity (T50)
Manchester, UK

5–7 DACH Affiliate
Vortrage und Stand aud den Lounges
Stüttgart, Germany

7 Nordic Affiliate CoP
Biotech Network Meeting
Stockholm, Sweden

San Diego Chapter
QbD and Compliance Session
Carlsbad, California

8 Delaware Valley Chapter
Volunteer Day

10–11 China Spring Conference
Shanghai, China

11–12 China Spring Conference
Shanghai, China

11–14 ISPE Training Event
Biopharmaceutical Manufacturing; Facility Project Management*; GAMP® 5; OSD; Water Generation and Storage
Manhattan Beach, California

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

13 Italy Affiliate
Drug Supply Chain: "Thinking the Future"
Bologna, Italy

Carolina–South Atlantic Chapter
Educational Event
Decatur, Georgia

14 Carolina–South Atlantic Chapter
Education & Therapeutic Thursday
Raleigh–Durham, North Carolina

14-15 Japan Affiliate
Annual Meeting

15 San Diego Chapter
Spring Golf Tournament
Carlsbad, California

20 Nordic Affiliate
Critical Utilities Conference
Copenhagen, Denmark

UK Affiliate
GAMP UK Forum
Gatwick, England

Greater LA Chapter
Cleaning Part 2
Los Angeles, California

20–21 2016 ISPE Continuous Manufacturing Conference
Baltimore, Maryland

21 Italy Affiliate
Assemblea Annuale dei Soci
Milan, Italy

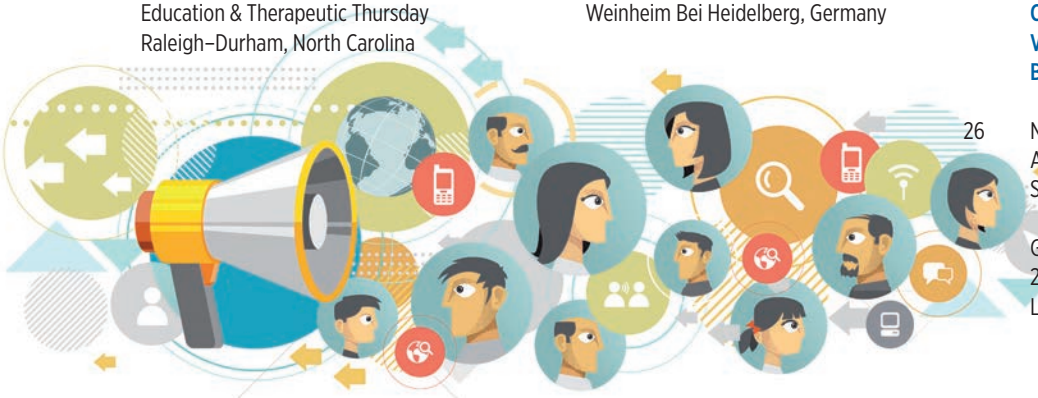
Midwest Chapter
YP Thirsty Thursday
Kansas City, Missouri

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

22–23 India Affiliate
Annual Conference
Mumbai, India

26 Benelux GAMP CoP
Mobile Applications in Life Science Industry
Veghel, Netherlands

28 DACH Affiliate
Animals in Human Medicine
Weinheim Bei Heidelberg, Germany



May 2016

2 Delaware Valley Chapter
23rd Annual Golf Classic
Huntingdon Valley, Pennsylvania

9–10 GAMP® Approach to Data Integrity (T50)
ISPE Training Institute
Tampa, Florida

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

10–11 DACH Affiliate
Pharma 2025 Containment
Heidelberg, Germany

12–13 Managing the Risk of Cross Contamination (Risk-MaPP) (T41)
ISPE Training Institute
Tampa, Florida

16 Carolina–South Atlantic Chapter
Golf Tournament
Cary, North Carolina

16–17 Science and Risk-Based C&Q (T40)
ISPE Training Institute
Tampa, Florida

17 San Diego Chapter
Padres vs. Giants Baseball Game
San Diego, California

19 Midwest Chapter
TechEd Day
St. Louis, Missouri

23–24 Turning QbD into a Practical Reality (T43)
ISPE Training Institute
Tampa, Florida

23–25 ISPE Training Event
Biopharmaceutical Manufacturing; Cleaning; C&Q; GAMP® 5; Process Validation
Brussels, Belgium

26 Nordic Affiliate
Annex 15 Updates & Continuous Process
Stockholm, Sweden

Greater LA Chapter
23rd Annual Vendor Night Exhibit Show
Los Angeles, California

June 2016

6–7 **Sterile Product Manufacturing Facilities (T12)**
ISPE Training Institute
Tampa, Florida

6 –8 **ISPE/FDA/PQRI Quality Manufacturing Conference**
Bethesda, Maryland

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

13–14 **Process Validation in Biotechnology Manufacturing (T32)**
ISPE Training Institute
Tampa, Florida

15 UK Affiliate
Latest Developments to Guidelines & Regulations
Birmingham, England

Greater LA Chapter
Joint Meeting with Lean Construction Institute
Thousand Oaks, California

16 France Affiliate
Atelier Eau PPI
Paris, France

France Affiliate
Annual General Meeting
Paris, France

20–21 **Q7A: Implementing Good Manufacturing Practices (T30)**
ISPE Training Institute
Tampa, Florida

23 Carolina–South Atlantic Chapter
Education & Therapeutic Thursday
Tampa, Florida

Midwest Chapter
YP Thirsty Thursday
Kansas City, Missouri

San Diego Chapter
Brewery Tour and DNA Presentation
San Diego, California

27–28 **Auditing for the Pharmaceutical Industry (G07)**
ISPE Training Institute
Tampa, Florida

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Compliance

As director of FDA's Office of Manufacturing Quality (OMQ), Thomas Cosgrove oversees a team of about 80 professionals whose key responsibility is enforcement. While this always has been in FDA's purview, he says "it's wonderful to be able to play a central role in helping to move the ball forward."

Cosgrove says the ultimate goal is to ensure the availability of safe and quality medicines. "There are many direct interactions with companies to help make that reality, and usually public warnings or enforcement actions are not needed." But when action is needed to advance public health, moving the ball forward definitely is one of Cosgrove's skills. Since he took on OMQ's directorship, his team has issued 22 warning letters and 32 import alerts. With the rate of foreign violative inspections on the rise — on average 20% each year — the new OMQ will strive to meet some aggressive goals. By the end of 2016, Cosgrove would like to take actions in half the time it does now; he intends to improve even further in 2017.

The office also helps increase transparency about drug quality for consumers and patients.

Prior to a reorganization in 2014 (see sidebar), the Office of Manufacturing and Product Quality (OMPQ) handled enforcement matters among other things. Its mission was broad: CGMP enforcement, regulatory standard-setting through guidances and regulations, CGMP surveillance, and review of all foreign inspection reports. Cosgrove was director of that office as well.

"For me, CGMP enforcement was always the most interesting part of the OMPQ portfolio," he says, "And now we get to do it full time."

Constituting a cadre of compliance officers had its challenges. The new OMQ encourages its compliance officers to think strategically about enforcement actions. Compliance officers feel equally comfortable pulling the available regulatory levers when needed, like import alerts or injunctions, or passing on a case when warranted. "These objective decision-making skills are now practiced daily, "he says, "and that was sometimes hard to do under OMPQ, when the office also had a review function and heavy involvement in non-violative inspections and facility reviews."

Cosgrove points out that he does not want most inspections to turn into enforcement actions, although he concedes one can find various degrees of CGMP violations at just about every drug manufacturing facility if looking hard enough. "We now screen out non-violative cases, and we can focus solely on the true, OAI cases that present risks to patients and require agency action."

A shift in focus, not priorities

Patient risk

OMQ prioritizes cases that put patient health in peril and takes swift action to protect them. "The cases that we work involve the most significant risks to patients posed by poor drug quality," says Cosgrove.

He goes on to cite several examples: sterility failures that increase the risk a drug may be contaminated when it reaches the American market and manufacturing deficiencies that result in sub-potent or super-potent drugs. OMQ believes strong enforcement against troubled firms helps deter others who might think about cutting corners when it comes to drug quality.

"It's gratifying to play such a direct role in public health," says Cosgrove. "When we decide to issue an import alert, the drugs we are keeping out of the U.S. market pose a real risk to patients."

Transparency

Cosgrove believes the office also has an important role to play in increasing transparency to consumers and patients about drug quality.

"While it is frequently talked about in the context of metrics, promoting transparency is also very relevant to enforcement actions," he explains. All warning letters are publicly posted so they convey FDA's regulatory standards and expectations to industry as a whole. They also communicate important information to consumers and patients. When OMQ sends a warning letter to a firm, it serves as notice of the violations it must promptly correct. When controls essential to making safe drugs are not in place at a facility, FDA warning letters shine a bright light on what's going on.

Recently, an inspection revealed a firm had been fabricating environmental monitoring data. "That's something I'm certain patients would want to know," says Cosgrove.

No tolerance for compromised data

The majority of FDA drug inspections find that firms are complying with federal manufacturing quality standards; violations if any are relatively minor and easily corrected. "We see potentially serious violations (OAI) in about 15% of inspections," explains Cosgrove, "and within that subset, we're seeing lots of fundamental problems with quality systems and quality oversight.

"Probably the most significant problem we see on a daily basis is the failure to rigorously investigate out-of-spec and out-of-trend results; this is such a fundamental part of CGMP. Mistakes happen, and when they do, it's critical to figure out why so they don't happen again. We see too many firms that don't really do the hard work of conducting a root cause analysis to find the source of the problems. We also see investigations that are undertaken outside of the quality system, which is contrary to our regulations, and which often are not, coincidentally, insufficient."

There also are failures relating to the quality of data. "I've said before that quality data is the underpinning of all of the CGMPs," says Cosgrove, "and I continue to believe that. Regulators can't be everywhere, and we depend on true and accurate information about manufacturing operations, and about clinical trials as well, for that matter. When a firm puts its thumb on the scale by altering or masking the data, it undermines the scientific basis for ensuring safety and efficacy.

"We continue to see too many instances of deletion and fabrication of critical quality data, such as HPLC (high performance liquid chromatography) data. Sometimes these practices are directed by managers, and sometimes, it's the result of employees being in impossible situations and they feel like they can't take the time to do the job right. So, they cut corners. In either case, the risks to patients can be serious."

From an enforcement perspective, says Cosgrove, OMQ does not focus on isolated occurrences of data failures, or cases of occasional sloppiness. It looks for systemic practices where important information is deliberately deleted, fabricated, or shielded from review by FDA. (*See PE's special report on data integrity, beginning on p.39*)

"I am surprised to see data integrity violations are still a problem. The good news is that many firms are making commitments to improve, so I think we're trending in the right direction. On the other hand, there are some firms out there that don't appear to have gotten the message at all."

Looking ahead

OMQ's streamlined focus means it will have more capacity to issue "for cause" inspections. "For instance, we've been hearing from confidential informants the last few years, particularly from overseas," says Cosgrove, "from companies, big and small. I want to do more inspections based on those tips. I also want to more quickly and rigorously follow up following bad inspections, to ensure remediation is proceeding apace."

OMQ will also be looking more closely at contract manufacturing. "We have a draft guidance on contract manufacturing that's gotten a good bit of attention from industry. We're really interested in looking at how sponsors are overseeing quality in outsourced manufacturing operations. It's the responsibility of both sponsors and contract manufacturers to ensure quality; that responsibility can't be outsourced. I could see conducting some inspections specifically to take a look at whether certain sponsors are living up to their quality obligations."

Voluntary disclosure can be the difference between a happy outcome and an FDA enforcement action. Yet often, firms try to deal with issues on their own, and then still get tripped up during the next inspection. "We'll put you through the paces," says Cosgrove, "but the result will be a quicker resolution of the problems and a meaningful reduction in regulatory risk."

Cosgrove's one overriding message to ISPE members who work in a firm that discovers quality problems: "Pick up the phone and call the Agency." ■

From OMPQ to OMQ

The Office of Manufacturing Quality, OMQ, is the successor to the Office of Manufacturing and Product Quality, OMPQ, and was created as part of the FDA's Center for Drug Evaluation and Research (CDER) restructuring that also created CDER's Office of Pharmaceutical Quality (OPQ). Many of OMPQ's program areas were shifted to OPQ: pre-approval facility review is now with OPQ's Office of Facility Review (OPF), surveillance inspections are managed by OPQ's Office of Surveillance, and policy work dealing with substantive quality standards is now led by a policy shop within OPQ.

OMQ is a new office in CDER Compliance that's strictly focused on enforcement of current good manufacturing practices (CGMPs). It handles CGMP-related Warning Letters, Import Alerts, Injunctions and Consent Decrees for CDER. It also works closely with FDA's Office of Criminal Investigations. It focuses on cases that involve significant violations of CGMP regulatory standards, which might require agency enforcement action.

Of note is the merger of international and domestic staff to better accommodate the way the pharmaceutical industry has changed: most major pharmaceutical firms have an international presence. "It really doesn't make sense to have one group of people working on "domestic" and another set working on "international' cases for the same firm," says Cosgrove.

"With the staff now combined, we can have a compliance officer handle the entire case inventory for a particular firm, which lets him or her take a more global, comprehensive perspective. We can also have a compliance officer specialize in product categories no matter where the drugs might be made." ■

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Also in this section

NPR Discusses Drug Shortages with ISPE Board Chair

ISPE Board Chairman Joseph Famulare, Vice President, Global Quality Compliance and External Collaboration Genentech/Roche, Pharma Technical Operations, joined NPR guest host Maria Hinojosa on *The Diane Rehm Show* on Monday, February 1, 2016.

Three other experts – Dr. Sheri Fink of the *New York Times*, Dr. Yoram Unguru from the Children's Hospital at Sinai and Johns Hopkins University, both in Baltimore, Maryland, and Capt. Valerie Jensen of the US Food and Drug Administration (FDA) – joined Dr. Famulare for a roundtable discussion about drug shortages.

The discussion opened with Dr. Fink, whose 29 January 2016 article in the *New York Times* called drug shortages "the new normal in American medicine."[1] Fink noted that the American Society of Health-System Pharmacists currently rates the supply of more than 150 drugs as inadequate; chemotherapy and related cancer-fighting agents are especially limited. These shortages have led to rationing, she said, and often force physicians to make difficult choices in caring for their patients.

Dr. Unguru added, "These drugs include chemotherapeutics, antibiotics, [and] critical care drugs so you're going to be impacted no matter who you are." Many of them have no substitutes, he added.

"Joseph Famulare, you are the chairman of the International Society for Pharmaceutical Engineering," said Hinojosa. "[W]hat do you say is causing these drug shortages?"

Famulare explained that "manufacturing and quality problems" were a factor in many shortages, adding that ISPE's drug shortages initiative is bringing various segments of industry together to help address the problem.

"To really [focus] attention on this, we have partnered with the Pew Research Institute to put together a study on all those business factors, supply chain issues, etcetera, and to publish that this year to further dig into what may be causing even more holistically this multifactorial problem."

From l: Maria Hinojosa, Dr. Yoram Unguru, Joseph Famulare and Capt. Valerie Jensen

Patient perspective

Much of the panel's conversation focused on how the shortages affected patients.

Hinojosa asked Capt. Jensen "[W]hy can't the federal government just tell the drug companies that they have to manufacture an adequate supply of a life-saving drug that's already on the market? Why can't the federal government do that? I'm imagining a patient saying, why can't the federal government protect me?"

Jensen said that until the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law in 2012, the agency wasn't able to monitor potential shortages until it was too late. "So now, with this new law … companies are coming to us early on and we can work with them and we can take the steps that we can take … to help companies make more supply and meet needs," she explained.

Dr. Unguru said that "due to the work by Capt. Jensen and industry and others" the number of drug shortages had dropped from its previous year high of 185.

Famulare said that a multifaceted approach from quality, business continuity, building capability is required to prevent shortages. We have to go from reacting to them to preventing shortages." Part of that effort, he said, involved recognition, communication, and cooperation between industry and the FDA.

Ethical dilemmas

Several audience members called to add their perspectives to the discussion. One, a bladder cancer patient, talked about problems getting a reliable supply of the biologic BCG. "[Y]ou start to think, number one, I'm not getting the drug, my cancer's gonna get worse. Number two, what about the other people that are coming into the office that are getting their treatment delayed? … The ethical dilemma put upon the patient by this problem is unbelievable," she told the panel.

"Industry is very empathetic to the needs of patients," said Famulare. "[A]ll production planning and [scheduling] is really based on delivering quality supply to patients.

"[J]ust stockpiling alone is only one facet of it," he added, stating that supply chain issues are equally important. That means "obtaining ingredients, reliable supplies, understanding what are your critical and sole-source drugs, [and] where possible, go to dual sourcing. …In terms of the purchasing and supply, if there's a known shortage, as Val Jensen said, we work with FDA."

The discussion concluded as it began, with an observation from Dr. Fink: "I think one of the important things is that this has been largely hidden from the general public, from all of us who could be affected by it. So go out there, learn more about it, and if this is a priority for us as a nation, we've managed to surmount other large problems that have complex causes. It's not a reason to give up. It's a reason to focus harder on it." ■

Listen to the show or read the transcript at: https://thedianerehmshow.org/shows/2016-02-01/shortages-of-childrens-cancer-drugs-and-how-to-allocate-them

References

1. Fink, Sheri. "Drug Shortages Forcing Hard Decisions on Rationing Treatments." *New York Times*, 29 January 2016. www.nytimes.com/2016/01/29/us/drug-shortages-forcing-hard-decisions-on-rationing-treatments.html?partner=rss&emc=rss&_r=1

ISPE and Pew Launch Joint Project

Research will explore factors that contribute to shortages of sterile injectable products

Drug shortages have been a serious concern in recent years, and significant attention has been given to determining both their causes and solutions. While past studies have focused on the impact that less-than-robust quality systems have on shortages, ISPE recognizes that the issue also encompasses elements related to manufacturing and the supply chain, as well as market economics. To that end, ISPE and the Pew Charitable Trusts have launched a joint research project to explore the relationship between these forces and their ability to influence and contribute to drug shortages of sterile injectable products.*

The ISPE and Pew Charitable Trust collaboration builds on work completed by ISPE's Drug Shortages Initiative to help identify the contributing factors behind drug shortages and the solutions needed to address them. ISPE's efforts focused on the technical, scientific, manufacturing, quality and compliance issues that could affect a company's ability to produce and maintain a steady and stable supply of products at risk for shortages. ISPE's innovative *Drug Shortages Prevention Plan* was published in 2014, followed by the *Drug Shortage Assessment and Prevention Tool* in 2015.

The ISPE–Pew collaboration is working to go one step further by identifying the connections between external market considerations and internal organizational decisions that can influence how much attention companies give to their business continuity plans, supply chain network design and management, as well as how the competitive landscape for certain drugs (prone to shortages) has evolved over time.

ISPE and Pew have secured the services of PricewaterhouseCoopers (PwC), a global management consulting firm, to help design the study and conduct the research.

"We are very excited about this important research project," says Dr. Theodora Kourti, ISPE's Senior Vice President for Global Regulatory Affairs. "It provides an opportunity for companies to give their account on the issues surrounding shortages and solutions to mitigate them, it builds on ISPE's work, and brings us another step closer to the goal of preventing drug shortages."

Methodology

The project will be divided into two information-gathering phases: guided interviews and an anonymous questionnaire. Confidential in-depth interviews will use a case study approach to better understand both issues and possible solutions to mitigate shortages. In addition, participating companies will be asked to complete a questionnaire that will be used to validate and confirm findings generated by the interviews.

This is a neutral and fact-driven opportunity for companies to share the realities of the aseptic manufacturing market with policy stakeholders and regulators in a positive and proactive way.

PwC will ensure strict confidentiality controls to maintain the anonymity of participating companies. No identifying information will be shared with ISPE or Pew, nor will any identifying information appear in the ultimate report. The final report will only use de-identified data and will not name participating companies.

A report on this research will be released in the third quarter of 2016, and will contain findings and potential business and policy insights for regulators, policymakers and the pharmaceutical industry. ■

For more information, please contact Dr. Theodora Kourti, ISPE's Senior Vice President for Global Regulatory Affairs: tkourti@ispe.org.

* *Scope: branded and generic sterile injectable products and intravenous formulations, including vaccines but excluding plasma products.*

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ISPE Announces FOYA 2016 Category Winners

On 1 February 2016, ISPE named six category winners and three honorable mentions as recipients of its twelfth annual Facility of the Year Awards (FOYA). The awards recognize innovation and creativity in pharmaceutical and biotechnology design, construction and operation.

Both winners and honorable mentions will be celebrated at the FOYA Banquet on 7 June 2016 at the ISPE-FDA-PQRI Quality Manufacturing Conference in Bethesda, Maryland.

The overall winner will be announced at the ISPE Annual Meeting, 18–21 September 2016, in Atlanta, Georgia.

FOYA 2016 Category Winners

Baxter BioPharma Solutions

Operational Excellence

Baxter's parenteral manufacturing plant in Halle, Germany, demonstrates operational excellence principals and innovative manufacturing concepts. The facility combines state-of-the-art isolator technology, combined with high flexibility for rapid changeover and broad flexibility to manufacture a wide variety of liquid formulations.

Ethicon, LLC

Sustainability

Sustainability efforts at Ethicon's San Lorenzo, Puerto Rico, facility reduced energy consumption by 4.4 million kilowatt hours (26%) and reduced water consumption by 1.25 million gallons (9%), while increasing production volume by 11%, compared to 2010 consumption levels. Genentech (a member of the Roche Group)

Genentech, a Member of the Roche Group

Process Innovation

Genentech, a member of the Roche Group, has been honored for its large-scale cell culture biologics drug substance plant 2 (CCP2). Located in Vacaville, California, this facility revamped an existing CCP2 facility to support new process technology, which resulted in a $50 million capital savings.

Janssen Vaccines AG

Project Execution

In response to the 2014 Ebola outbreak in West Africa, Janssen accelerated its fast track refurbishment for Ebola vaccine production at its facility in Bern, Switzerland. Through parallel activities in process development and facility design and construction, the facility was completed for engineering runs by September 2015.

Pfizer, Inc.

Equipment Innovation

Pfizer's portable, continuous, miniature and modular (PCMM) prototype unit for oral solid dosage forms transforms raw materials into uncoated tablets in minutes. The equipment fits into a portable facility called a POD that can be shipped to any location. The PCMM model increases project speed, enhances product quality, and reduces project cost.

Takara Bio, Inc.

Facility Integration

To improve operational and cost efficiencies, Takara's Center for Gene and Cell Processing (CGCP) in Shiga, Japan, housed cell products, viral vectors and recombinant proteins within the same facility. To eliminate risk of cross contamination, Takara incorporated facility and operational containment measures, including a restricted access barrier systems sterilization process using dry-type vaporized hydrogen peroxide, segregated air conditioning systems, and full-height partitions to close contamination pathways.

Honorable Mentions

Greater Pharma Co., Ltd.

Greater Pharma's Bangkok, Thailand, facility is the first of its kind to apply Western standards to design a pharmaceutical facility for tablets, capsules, sachets and liquids for the Southeast Asian market.

University of Strathclyde

The Centre for Continuous Manufacturing and Crystallisation at the University of Strathclyde in Glasgow, Scotland, is a collaboration between industry, academia and government that represents the future of pharmaceutical manufacturing and supply chain R&D framework.

West Pharmaceutical Services, Inc.

West Pharmaceuticals' facility expansion in Kinston, North Carolina, is recognized for its industry-leading efforts to align primary components manufacturing process with current industry trends and standards.

FOYA 2016

Facility of the Year Awards

Congratulations!

FOYA 2016 Category Winners

- Baxter BioPharma Solutions
- Ethicon, LLC
- Genentech, a Member of the Roche Group
- Janssen Vaccines AG
- Pfizer, Inc.
- Takara Bio, Inc.

Honorable Mentions

- Greater Pharma Co., Ltd.
- University of Strathclyde
- West Pharmaceutical Services, Inc.

ISPE 2015 FOYA Overall Winner

Photo: Yossi May, Washington Talent

ISPE's 2015 FOYA Overall Winner was AstraZeneca China. From left: Peter Marshall, Tom Stanway, Denton He, Kwame Agyei-Owusu, Alan Osborne, Martin Teo, Mark Sullivan and Andy Skibo, ISPE Board of Directors Past Chair.

Boston and Beyond — Japan Affiliate Revisits the United States

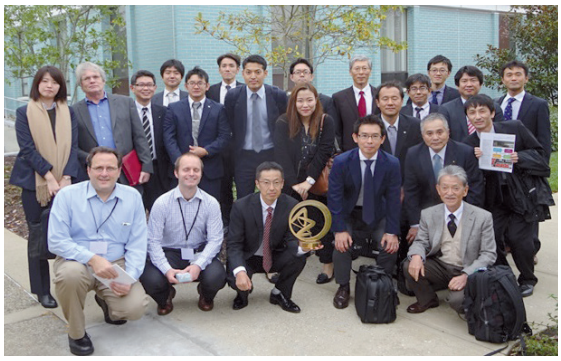
Akihiro Matsuki and Michael J. Lucey

This report must begin by giving praise where due. It means expressing the sincere appreciation of the ISPE Japan Affiliate to the five host plants in the US, to the Boston Chapter for facilitating and hosting, and to certain individuals for their highest level of support to help meet the Affiliate's goals. Those persons know who they are!

The ISPE Japan Affiliate held its annual pharmaceutical plant tour in the United States from November 4-6, 2015, in conjunction with the 2015 ISPE Annual Meeting in Philadelphia, Pennsylvania. Twenty professionals from across Japan participated in the tour as well as the meeting, including Japan Affiliate Executive Director Akihiro Matsuki and Adjunct Director Michael J. Lucey, who had led the organizing committee which was made up of Affiliate board members. The mission was well balanced, with eight tour members from pharmaceutical companies, nine from engineering/construction companies, and three from equipment manufacturers.

Shire

Members visited Shire's biopharmaceuticals development and manufacturing facility in Lexington, Massachusetts. The plant, a large-scale biopharmaceuticals facility, started operation in 2010 and later adopted a single-use system. It operates seven days a week on three shifts, manufacturing three clinical products and two commercial products. In addition to emphasizing flexible production, detailed consideration is also given to quality control and facility cleanliness. To prevent dust accumulation, for example, locker tops and other surfaces are angled, not flat. Tour members were also shown the production area, where specially developed mechanical parts were introduced. All members were impressed by Shire's high-level capabilities in process development.



AstraZeneca: Manufacturing and distribution

AstraZeneca: R&D facility

Boston Chapter reception

Biogen

Biogen's Cambridge, Massachusetts, site has 2,100 employees, including 333 manufacturing staff, 87 engineers, and 142 quality staff. Major products are Avonex and Plegridy for the treatment of recurrent multiple sclerosis, and Elocate for hemophilia A. Members visited Building 2, where they were shown the bulk production facility, a large facility with five culture process lines in three rooms on the first floor and three refining process lines in three rooms on the second floor. Raw materials and process feed were transported between buildings located across the road using pressurized containers. Members were shown the production area and given quality explanations on process from a position very close to the equipment. This allowed them to appreciate Biogen's high-level technology for production systems and design concept for production facilities.

AstraZeneca: R&D

After driving from Boston through wonderful scenery, team members saw AstraZeneca's beautiful Gatehouse Park BioHub appear in an expanse of land surrounded by woods. Employing over 700 researchers work for eight companies, this research facility realizes open

Japan Affiliate plant tour itinerary

Date	Activity
Tuesday, November 3	Departed Tokyo, Japan, for Boston, MA
Wednesday, November 4	Morning – Shire: Lexington, MA Afternoon – Biogen: Cambridge, MA Evening – Boston Chapter reception
Thursday, November 5	Morning – AstraZeneca: Waltham, MA Afternoon – Pfizer: Groton, CT
Friday, November 6	Afternoon – AstraZeneca: Newark, DE
Saturday, November 7	Morning – New York sightseeing Afternoon – Arrived in Philadelphia, PA
Sunday, November 8 – Wednesday, November 11	ISPE Annual Meeting
Thursday, November 12	Departed Philadelphia, PA, for Tokyo, Japan

innovation through facility sharing and information exchange. Various considerations in facility design encourage researchers' work, such as desk layout that promotes good communication, with security measures taken where necessary. While the BioHub was a repeat visit for some of the organizers, the AstraZeneca R&D facilities continue to greatly impress.

Pfizer

Pfizer's central R&D facility in Groton, Connecticut, which sits on 160 acres (approx. 0.65 hectares), has a site area of 2.8 million square feet (260,128 square meters) and employs approximately 4,000 people. Here tour members visited a prototype continuous-production module. Targets are accelerated development, cost reduction and meeting market changes, while key requirements are homogeneity, high quality and supply reliability. Hosts were at the final stage of facility qualification, but still provided detailed explanations. Members entered the machine room and were given detailed explanations ranging from system configuration to system development considerations. The Q&A session enabled members to learn about continuous production.

AstraZeneca: manufacturing and distribution

AstraZeneca's Newark, Delaware, facility is one of the company's American manufacturing and distribution bases. With approximately 300 employees, the facility houses primary and secondary packing functions, as well as formulation. The company's ongoing Newark Facility Transformation Project is constructing a new formulation building and improving existing facilities for various efficiencies without interrupting the manufacturing process. Mission members were given on-site explanations of these improvements, present or planned. Good internal communications and full discussions with the FDA are a critical factor, and the company's stringent approach to safety and quality is posted on facility walls.

Home again

Later, at the Japan Affiliate's Winter Seminar held in December, an outline of the tour was shown as a poster display. Moreover, to widen its members' networks, the Affiliate holds a reunion every year for all US tour participants. In February 2016 a joint reunion was held for participants of tours during the eight years from 2008 to 2015. These events have proven successful and a source of pleasure for all. ■

Strength in Numbers

Henrik Goldschmidt refers 57 new members in two years

Henrik Goldschmidt

When Henrik Goldschmidt was a student at the Technical University of Denmark during the 1980s, he intended to work in the oil business – a natural choice for a chemical engineering student who lived close to the North Sea oilfields.

His career took a different turn, however, and he joined the pharmaceutical industry instead. He's now a senior GMP specialist for the Rambøll's Group's Pharma and Biotech Consultancy. While the company's main focus is engineering consultant work in fields like planning and urban design, environment and health, and energy, it supports a small but growing pharmaceutical department – the second largest in Denmark. Goldschmidt says that when he joined the company three years ago the group numbered only 30 people. It's now 100, and is expected to hit 200 in 2020. He works with the production team, whose focus is cleanroom and production technology.

Goldschmidt became an ISPE member in 2000, when he attended the newly launched Nordic Affiliate's first conference. He's now the affiliate's Vice Chair, head of the membership committee, and board liaison for the cleaning validation community of practice, which he also founded.

Member benefits

He says joining ISPE was a natural fit for him, because he had a lot of questions. "I wanted to know the right way to do things, and what different terms meant. I wanted to know 'How clean is clean?'" he says. He found answers in the organization's conferences and publications, which establish standards for process and procedure, and define common industry vocabulary.

In addition to his role as Nordic Affiliate Vice Chair, Goldschmidt chairs ISPE's Membership Development Committee, whose primary roles are to evaluate membership benefits and recommend programs to enhance the value of membership for all Members worldwide. The group meets by phone every two months. "We talk about how we can promote ISPE more, and engage members more. We ask 'What works for you?' and 'What works for us?'"

Now that he's in what he calls the "late autumn" of his career, Goldschmidt has another ambition: He takes particular interest in helping young professionals when they seek his advice. He's eager to share what he's learned, both as an ISPE member and in his work at Rambøll.

Network

For Goldschmidt, the biggest benefit of ISPE membership is its network. "That's the highest value for me," he says. "It's always there when I have a problem." He also likes the online discussion forums and lower costs for conferences and guidance documents.

His enthusiasm for ISPE membership appears to be contagious: In the past two years he's referred more new members than anyone in the organization. In 2014 he brought in 18 referrals, and to date has referred an additional 49 new members. Because ISPE's "refer a friend" program provides a free month of membership for each successful referral, Goldschmidt has earned free membership for 2015 and 2016.

But free membership isn't his motivation. "It's personally rewarding to enlist new members," he says. "You can engage them in the community," he adds, and increase the benefits of sharing knowledge. His goal, he says, is to build both Nordic Affiliate and the greater ISPE network.

In his 16 years with ISPE, Goldschmidt has done numerous presentations, many on purified water, water for injection, and steam systems. As part of the Nordic Affiliate Board of Directors, he's one of the driving forces in that group's activities. He's currently gearing up for the Nordic Affiliate Cleaning Validation Conference on 20 April, followed by the Cleaning Validation/EU GMP Annex 15 Conference on 26 May. ■

Meet Your New 2015-2016 Executive: Part 2

We announced ISPE's 2015–2016 ISPE Board of Directors in the December issue of *Pharmaceutical Engineering*. In the January/February issue of Pharmaceutical Engineering, we asked the newly elected chair and vice chair to provide some insight their new roles as well as their plans for the year ahead.

This issue, we get to hear from Board Treasurer Tim Howard and Board Secretary Jim Breen.

2015-2016 officers

Chair
Joseph Famulare, Vice President, Global Quality Compliance and External Collaboration at Genentech/Roche, Pharma Technical Operations

Vice Chair
Michael A. Arnold, RPh, Business Process Owner for Investigational Products and Senior Director of Strategic Partnerships, Global Clinical Supply Chain, Pfizer

Treasurer
Timothy P. Howard, CPIP, PE, Vice President of Global Operations, Commissioning Agents, Inc.

Secretary
James Breen, Jr, PE, Vice President, Worldwide Engineering and Technical Operations, Johnson & Johnson

Photo: Yossi May, Washington Talent

Timothy Howard, Treasurer

1. How do you see your new role on the Board?

I see myself working closely with the CFO, the Financial Audit Committee and Executive Committee to provide oversight and support of ISPE's finances. Specifically, this will mean regularly reviewing ISPE finances, which include assessing performance to annual budget; identifying opportunities to mitigate risks or improve performance against annual budget; and reviewing ISPE investments and confirming alignment with the investment strategy.

2. What are the top 3 items on your list of things to do in 2016?

These are my top 3:
1. Identify opportunities to enhance current revenue streams
2. Continued improvement with our conferences
3. Achieve or beat budgeted top line revenue and operating income goals

3. What role will you play in the execution of ISPE's strategic plan for the next 3 years?

Our entire board is invested in execution of the strategic plan, although we each have areas of focus to make sure that all aspects of the plan are represented with board support. My areas of focus are with training, programs and continuing education conferences. As such I work very closely with our Vice-President of Programs, Susan Krys, and her team.

4. What do you believe is the most difficult part of your role?

Like many of our hard-working volunteers and staff, I have a great passion for ISPE and its mission. With this passion come many ideas for initiatives and activities that would serve our membership and further the mission of ISPE. It is impractical to act on all of these good ideas and initiatives. We have limited resources and must apply them in a manner that is best aligned with the strategic plan and annual business plan. Having to say "no" or "not now" to some good ideas presented by very passionate volunteers is very difficult.

5. What can ISPE members expect from you?

They can expect a passionate and engaged leader committed to ISPE's mission.

Photo: Yossi May, Washington Talent

James Breen, Secretary

1. How do you see your new role on the Board?

I see my role as serving the membership of ISPE to ensure the pharmaceutical industry can meet patient needs globally. And also, to ensure ISPE is in a better position three years from now, when I complete my board assignment.

2. What are the top 3 items on your list of things to do in 2016?

These are my priorities for the year:
1. Progress the factory of the future concept for pharmaceuticals to deliver medical solutions at competitive prices, with the highest quality when and where patients need it.
2. Expand the amount of collaboration between the affiliates and ISPE on a global basis.
3. Focus on attracting younger professionals to ISPE membership and retaining them, as they truly are the future of our organization and the pharmaceutical industry.

3. What role will you play in the execution of ISPE's strategic plan for the next 3 years?

I would like to see us make ISPE a truly global organization, serving the needs of all its members with appropriate local solutions; that is at

the top of my list. Additionally, I would like to see us prepare ISPE members for the changes coming to the industry and ensure ISPE provides appropriate training and education to allow its members to flourish in any new environment. Finally, I would like to drive increased collaboration between owners, service providers and regulatory authorities; without this collaboration we can not optimize solutions for the industry.

4. What do you believe is the most difficult part of your role?

Prioritizing our ISPE objectives for maximum value, with limited resources, will be the most difficult, I believe.

5. What can ISPE members expect from you?

Members can expect from me, transparency and openness; a global solutions mindset; and a desire to advance ISPE and industry to drive better solutions for patients, which is the ultimate goal.ill be made with their best interests in mind. ■

Photo: Yossi May, Washington Talent

2015 – 2016 Board of Directors

Appointments

Vice President, Marketing Communications and Membership

Photo: Neal Nachman, ISPE

With more than 15 years' experience in global medical and scientific associations, **Wendy Sturley** is ISPE's new Vice President for Marketing Communications and Membership.

In her most recent position with the Endocrine Society, Wendy led a team that increased professional membership by more than 20%, with notable growth in developing countries, using targeted content marketing strategies and social media channels to grow acquisition and increase retention among both members and readers. She also created marketing and messaging strategies for the society's publications, products, and professional development programs to individual physicians and scientists, as well as partner organizations and industry supporters. During her tenure with this organization, she led the launch of a new website, new online store, and led the marketing strategy for the Society's four publications.

Prior to the Endocrine Society, Wendy was the director of membership and marketing at the Society for Neuroscience. There she and her team provided member services for more than 42,000 members, and enjoyed a 3–4% growth in membership each year. In addition, chapter numbers grew by more than 20% under her supervision, and the number of international chapters increased by more than 40%.

Wendy also has experience directing international marketing and branding efforts for the American Association for the Advancement of Science (AAAS), including Science magazine's 25,000+ international members and subscribers. She expanded the international presence of AAAS and Science in Asia, working with Japanese and Chinese agents to create websites and other content in local languages, which led to increased memberships and article submissions from this area. Wendy also spearheaded the launch of Science's digital edition while based in Cambridge, England, leading to several thousand new subscribers in both the Americas and abroad.

Director of Continuing Education

Photo: Neal Nachman, ISPE

John Donaldson, ISPE's new Director of Continuing Education, has over 20 years' experience in training, meeting planning, and national/international association and education program/project management, including serving as a department director for three associations. At the Teachers of English to Speakers of Other Languages International Association, John led a staff team for nine years as the director of education programs for a global profession of 13,000 educators and administrators, resulting in systemic growth of diverse in-person and online programs, meetings and services, including being a core part of the cross-functional senior management team for annual conference with over 6,000 attendees. His education program experience includes managing every aspect of successful international conferences in locations such as China, Brazil, Qatar, Spain and Argentina, to name a few. John was a key part of the association's strategic planning and program implementation process.

Throughout his career, John has held many speaking engagements both in the US and internationally including keynote speaker for IMEX Association Day in Frankfurt, Germany, and plenary session speaker for the World Congress of Association Executives in Manila.

John has traveled and worked in 41 countries. He speaks Japanese, and also taught English full time for six years at a vocational school in Tokyo. ■

Guidance Documents

New releases

Sustainability Handbook

The *Sustainability Handbook* was written to provide information at the front end of projects to help the project team understand sustainability criteria, with examples where considered useful. It is based on the premise that there is a viable path to achieving sustainability that corresponds to all precepts of the life sciences industry. Sustainability is an especially important ethical consideration for the health care industry, which has a focus on maintaining and improving the health of patients. For more information or to order, visit http://www.ispe.org/ispe-handbooks/sustainability.

Discussion paper

"Determining the Number of Process Performance Qualification Batches Using Statistical Tools – Supplement to 'Topic 1 – Stage 2 Process Validation'" is presented as supplement to the original discussion paper issued in August 2012: "Topic 1 – Stage 2 Process Validation: Determining and Justifying the Number of Process Performance Qualification Batches (Version 2)." This original paper proposed answers to the questions:

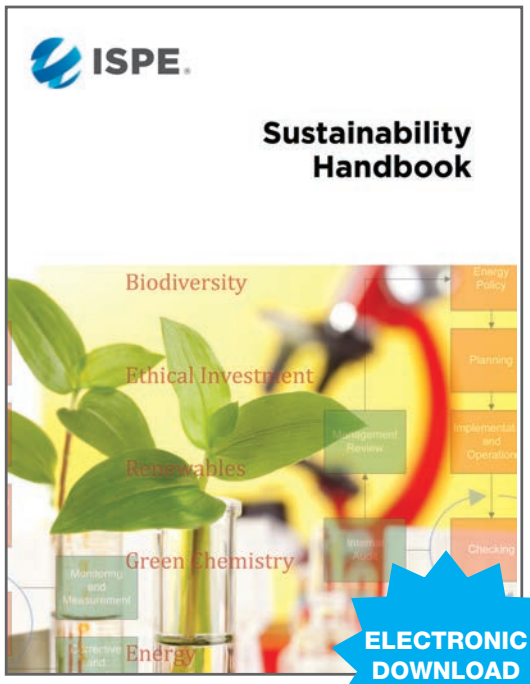
- How many process performance qualification batches (PV Stage 2) are needed to demonstrate a high degree of assurance in the manufacturing process?
- Is the control strategy is sufficiently robust to support commercial release of the product?

The new supplemental paper presents four statistical tools that may be applied to determine the number of PPQ batches, discuss the statistical approaches along with their limitations and assumptions, and also present simulated examples.

The team is interested in learning about other approaches that could be used, and would like to hear about lessons from use of the proposed approaches described in the original discussion paper, with additional examples. The new paper may be modified or expanded sometime in the future to reflect additional input. To download this paper and provide feedback, visit http://www.ispe.org/publications/discussion-papers. ■

Our Newest Release Now Available

ISPE Sustainability Handbook



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

Key objectives of this guide are to:

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

Three Goals for YP Development

There's a lot you can't control at work: changing management strategies, new regulatory requirements, new people on the team, and business unit restructuring, among others. But the great thing, when starting your journey as young professional, is proving to yourself what you are really capable of. These changes can become challenges that help you grow.

Based on my experience, I have identified three goals that can help you focus on your development as a young professional:

1. Personal fulfilment
2. Professional career
3. Be the best you can be

Personal fulfilment

You invest a lot of time and energy in your job, so how do you meet personal goals at work — especially when you face challenges?

Start by asking yourself these very personal questions:

- What is my passion?
- What am I really good at?
- What gets me up every morning?
- What do I like best about my work?
- What do like most about my peers?
- How am I transforming my work into something I love?
- How do I get motivated?
- How do I envision my future?

When reconciling personal fulfillment and professional career, be honest with yourself. If your answers no longer correlate with your work, it might be time to move to a new challenge. Look left and right in your organization, use the network ISPE provides and try out new responsibilities. These will help you grow, achieve happiness, and find a job you love.

My personal goal in life is to be happy and be fulfilled. When I think of happiness, I visualize having fun and laughing with family and friends. My passion is to deliver the best quality medicines possible for the people who need them the most.

What does happiness mean to you? What's your passion?

Professional career

Just as I ask myself questions about personal fulfillment, I have written some career questions in a notebook that I review from time to time:

- Am I open to change and am I able to adapt?
- From which of my peers can I learn the most?
- Is there someone in the company who could be my mentor?
- Who is my role model in the company?
- Do I want to discover new drugs?
- Do I want to find new technological solutions?
- Can I support senior managers with my young perspective?
- How can I help the bioprocess go faster?
- Do I feel comfortable with leadership?
- Do I strive to ensure excellent quality medicines?
- How well do I connect R&D and the market?
- Do I like setting up strategies?
- Is project management my strength?
- How do I increase accessibility of medicines in emerging economies?

To develop your professional career to its fullest potential, a good mindset and attitude is to constantly be learning something new. You can do this through networking with peers and experts in our industry, participating in extra webinars outside of your company, and working within ISPE on Communities of Practice and industry initiatives. These are great opportunities that you do not want to miss.

I've just started my sixth year as a professional in the pharmaceutical industry. In my career, I decided to merge my interest in technology with my interest in biotech medicines as I neared the end of my bioprocess engineering studies. I found my way to Sartorius, an international pharmaceutical and laboratory equipment supplier. Because I'd spent time at a biotech startup working in quality, operations and sales, I started as a sales engineer in Integrated Solutions, the company's end-to-end process engineering solutions group, then went on to technical marketing. Here I had the opportunity to work cross-functionally and was able to interact with senior management

> Dreams are extremely important. You can't do it unless you imagine it.
> — George Lucas

Be the best you can be

No matter where you're working — in quality, operations and technology, engineering or supply chain — don't limit yourself to your comfort zone. If you are in process engineering at an innovator or a contract manufacturing organization working in upstream, for example, be bold and expand your knowledge to downstream, and learn about the consequences your optimizations may have.

As young professionals we set our goals high. We want to outperform the expectations of experienced professionals at work — and realize our own goals as well. I believe that the road to personal fulfillment, career development, and continuous improvement starts with honest self-assessment. ■

Author's note: What has your experience been? Which steps did you use to achieve your goals? Please connect with me (linkedin.com/in/robertlandertinger/en) and share your thoughts. I learn just as much from you as you do from me.

Robert W. Landertinger Forero is Chair of the ISPE Young Professionals Committee and a core team member of the Drug Shortages Initiative team. Fluent in 5 languages (German, Portuguese, Spanish, French and English) Robert is an invited speaker in countries like Mexico, Ireland, China, the USA, and Germany. He has written for or been covered by *Pharmaceutical Engineering, BioPharma-Reporter*, and other publications.

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Meet Young Professional Maša Ivanković

Over the course of a career, many of us experience defining moments – times when decisions we make influence the path of our lives from that moment forward. Canadian Young Professional Co-Chair Maša Ivanković had just such a moment … and ISPE played a role.

Born in Belgrade, Serbia, Ivanković moved to Canada with her family when she was six years old. They settled in Montréal, a bilingual city in the province of Québec that gave her the opportunity to study in both English and French. She completed her bachelor of science at McGill University in 2006, then earned a second bachelor's degree in chemical engineering at École Polytechnique de Montréal in 2010.

Maša Ivanković

It was during her time at École Polytechnique that she had her first encounter with ISPE: She saw a poster advertising an upcoming event. "I saw it was for the International Society for Pharmaceutical Engineering and I thought that was interesting, so I went," says Ivanković. "It was a plant tour with an educational event afterwards, and I really liked it because there was something for students where you could meet people with similar interests, but it had a very professional side to it too."

During her studies, she also did a summer internship in the validation department at contract drug manufacturer Delpharm Lille in France. While she enjoyed her first hands-on experience in the pharmaceutical industry, she was still unsure what she would do after graduation. "When you graduate, you have to apply for several kinds of jobs, and I applied for some jobs in the pharmaceutical industry. I got my first job because I already had some pharma experience due to my internship," she says. "It's a very positive industry because we make drugs that can help everybody."

We are trying to build a concept, a plan and a calendar to get more young professionals involved in ISPE.

In 2010, Ivanković was offered a position as a pharmaceutical validation specialist at Draxis Pharma (now Jubilant HollisterStier) in Montréal's West Island area. She stayed there until 2012, when she accepted a validation specialist position at Montréal's SNC-Lavalin, an engineering and construction company that serves a wide range of industries, including pharmaceuticals. "I accepted the position at SNC-Lavalin because they provided me with the opportunity to travel," says Ivanković. "Throughout my travels, I was given the opportunity to work in the United States for about a year and when I came back seeking greater responsibilities, they gave me the opportunity to manage two projects in the agri-food industry. And now here I am, in business development, with more and more responsibilities and working with different departments and clients."

Growing involvement with ISPE

Ivanković – who speaks English, French, Serbian and basic German – has maintained her involvement with ISPE since that initial event. From 2008 until 2010, she served as student section secretary for the ISPE Canada Affiliate and, since 2013, has served as a member of its Board of Directors. Earlier this year she also took on the role as Co-Chair of the affiliate's Young Professionals Committee. Her Co-Chair is Entela Brahimi, of Sage Engineering Services in Toronto.

"This is brand new in Canada," she says, speaking of the Young Professionals Committee. "Under the umbrella of the ISPE Canada Affiliate and with the help of other YP committees that are more developed, we are trying to build a concept, a plan, and a calendar to get more young professionals involved in ISPE. This committee will be built together with all our members and future members. We are trying to create a community of young professionals in the Montréal and Toronto areas. Of course, if somebody from another city wants to join and come to an event, they will be more than welcome."

Ivanković says that the Canada Affiliate's main committee will play an active role in coaching the YP Committee in their quest to build their group. "We'll develop a calendar of different kinds of events. We'll have educational events that are targeted toward a younger audience, such as career or curriculum building events, and other events that ISPE Canada's more senior members would also be interested in attending. We'll have merged events with the main affiliate, such as technical events that look at new regulations in the pharma industry, or new technologies, or even older technologies that have been revisited. It could be anything that is technical and that will appeal to both

They were very good examples of how to lead your professional life, yet not to let it take over the rest of your life.

the younger professional and the more senior audience. We're also looking to have purely social events. For example, the affiliate recently held a ski night. The goal is simply to get together and get to know each other on a more personal level."

The importance of mentorship

Looking back at her young career, Ivanković notes the roles others have played in helping her shape her professional life. "During my internships, there were two women, one of whom was in the pharmaceutical industry and the other was not, and I really liked the way they were doing things," she says. "They were extremely efficient and were able to do a huge amount of work in a very calm way while still maintaining a very balanced personal and professional life."

She remains in touch with both women even though her internships were in 2007 and 2009. "They were very good examples of how to lead your professional life, yet not to let it take over the rest of your life."

Today, in her position at SNC-Lavalin, Ivanković sees Business Development VP Richard Fecteau as a strong leader. "Richard is driven and knows where he's going ... and I'm trying to follow him. And there is another gentleman here in our office, Mr. André Saidah, Director of the Process Engineering Group, who has a lot experience in project management. Anytime I have a question, I go and see him and he always takes the time to answer no matter how busy he is. They are both great examples for me."

She has also seized the opportunity to give back as well by giving talks at her old school. "The École Polytechnique hold seminars where former students talk about their current work and their current life to give students an idea of what they can do with their degree. I went there and I described my job and I answered some very basic questions – from what time do I get up to what time I leave work. But then at the end there was one girl who came to me and she said she went into engineering because she thought she'd like it, but her parents didn't think it would be a good fit for her. She wanted to talk to see how I felt about it. So we went for coffee and we talked and she asked a lot of questions. We're still in touch and I'm trying to encourage her to do internships. I'm just trying to give back what other people gave to me," she says. ■

Mike McGrath

ISPE Pacific Northwest Chapter

Focused on value for members

It's an ongoing debate for many Affiliates, Chapters and Groups around the world: Is it better to hold many events in various venues to give all members a chance to attend, or to hold fewer events that are perhaps more significant? For ISPE's Pacific Northwest Chapter, the answer is clear: less is definitely more.

To broaden its outreach and help recruit new members, the Chapter is establishing partnerships with other not-for-profit organizations in the region.

Emily Stump

The Pacific Northwest Chapter, which currently serves just under 200 members, covers the Northwestern states of Washington and Oregon, in addition to serving members from Vancouver, British Columbia, in Canada. The majority of the Chapter's activities are held in and around Seattle, the largest city in the Pacific Northwest region and a hub for pharmaceutical and biomedical firms as well as academic and research institutions. According to Pacific Northwest Chapter President Emily Stump, however, the Chapter intends to reach out more to its Oregon and British Columbia members in 2016.

"We're trying to branch out and hold at least one activity per year in Oregon," says Stump. "Each year, our Board of Directors has a strategic planning session, and this year we identified the membership as a top priority. As part of our plans for this year, we're focusing on membership retention and growth as well as demonstrating value to the members."

Stump, who is the Director of Operations, Pacific Northwest, at Commissioning Agents Inc., first joined ISPE when she was studying microbiology at Colorado State University (CSU) in 2006. She attended a Lunch & Learn about ISPE and her interest was piqued. She soon formed the student chapter of ISPE at CSU as part of the Rocky Mountain Chapter. "When I graduated from CSU in 2007, I continued to work with the student chapter as the Industry Liaison to the Student Chapter and I eventually joined the Board of Directors for the Rocky Mountain Chapter. I was on the Board there until 2011 when I moved to Oregon," she says.

Once in Oregon, Stump sought out the Pacific Northwest Chapter, joined the Board of Directors and continued to progress through the ranks until she was elected President in August 2015.

"We have a new Board as of August 2015 ... and we have a really good team dynamic" she says. "Everyone is very active and engaged and excited about our new path for 2016."

A focus on membership value

In looking back at 2015, Stump says that the Chapter now realizes that its members are best served by fewer events. "The lesson learned is that less is more. . . . [W]e found that fewer more meaningful, more exciting events are better for membership than trying to do a bunch of smaller events that don't have a strong turnout."

"Our events tend to be mostly social networking events," she says. "We incorporate vendor shows and vendor exhibits at a few of those events to try to give some visibility to the vendors and provide them opportunities to network

Pacific Northwest Chapter Contacts

Title	Name	Company
Director	Nathan Coy	Commissioning Agents, Inc.,
	Travis Foley	CMC Biologics, Inc.
	Todd Gill	GLY Construction
	Robert Munday	CMC Biologics, Inc.
President	Emily Stump	Commissioning Agents, Inc.
Vice President	Robert Vizenor	SABArchitects
Treasurer	Caryn Twombly	CMC Biologics, Inc.
Secretary	Erik Bedell	GLY Construction Inc.
Past President	Robert Mackey	Harris Group, Inc.
Chapter Manager	Melissa Schwab	Association Management, Inc.

as well. We [also] found that our membership really enjoys doing facility tours. We have a lot of members who are involved in engineering, design, fabrication, the specification of facility equipment, utilities and the infrastructure that goes along with that. So many of our members are interested in doing tours of facilities that are in the conception stage, have been newly renovated, or are undergoing expansions. So those events tend to be very successful; and they have an educational component to them as well beside the networking piece."

One of the Chapter's more successful events in 2015 was held at the Allen Institute in Seattle. "Paul Allen [cofounder of Microsoft] is a famous name around the Pacific Northwest, and he invests heavily in biomedical research and in the biomedical industry," says Stump. "The institute focuses on all kinds of biomedical research, and our member companies work with the institute and the academic institutions." The Chapter also sprinkles a few "traditional" events, such as annual golf tournaments and holiday parties, into its calendar.

For 2016, with membership retention as a primary objective, the Chapter's Board Members have committed to a series of events that gives Members opportunities to network and exchange knowledge with potential clients, collaborators, mentors or like-minded professionals. "We've decided that we will be doing a Lunch & Learn roadshow at different companies within Oregon and Washington," explains Stump. "Board members have volunteered to put this roadshow together and then volunteered to go out to our member companies and potential member companies, and to recruit members to do presentations. That's going to be our primary mechanism for recruiting this year."

Partnering with nonprofits

In a challenge shared with many ISPE Chapters and Affiliates around the globe, the Pacific Northwest Chapter is challenged by its volunteer-led structure. Because the volunteers have day jobs, it can be difficult for organizers to juggle everyone's priorities. "But the more volunteers we have, the easier it is to share the workload, to follow up on action items and get to the point where we're doing the things we say we're going to do. I think it's always a challenge to get engaged and active volunteers and it's something that we're always trying to improve upon," says Stump.

To broaden its outreach and help recruit new members, the Chapter is taking a unique approach: establishing partnerships with other not-for-profit organizations in the region. "We're working to partner with Life Science Washington, the Oregon Bioscience Association and the Building Commissioning Association," says Stump. "We're working on trying to partner with them on some events this year."

When making a recruitment pitch to young professionals or others considering membership in the Chapter, Stump relies on her personal journey with ISPE. "I see value in the organization," she says. "From my perspective, the ISPE has given me the opportunity to develop professionally in areas that I may not have had in my day job. It has given me professional development in project management and leadership, how to run meetings, how to hold people accountable for following up on action items and how to deal with conflict resolution."

"I also tell people about the educational benefits of the ISPE, like all of the baseline guides that I frequently reference in my day-to-day work. Similarly, going to ISPE trainings — I have been a trainer and have participated in training development for ISPE, so I know how much work and effort goes into developing those courses and how much information can be learned. So I encourage people to take advantage of those training opportunities. And then finally, the networking opportunities: You never know when the next person you're going to meet may open an opportunity for you. My current job and many of my current customers have come about through my interactions with ISPE. So, there's a lot to be gained from having that social network," she concludes. ■

Mike McGrath

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Millennials: Searching for Meaning … and Willing to Move On

The 2016 Deloitte Millennial Survey: Winning over the next generation of leaders

The generation branded as "millennials" — those born after 1982, who reached adulthood at the turn of the century — is characterized in many ways, and usually not in a positive light. Often cited in wildly general terms as entitled and narcissistic, millennials are now moving into senior management ranks around the world, causing those who track business trends to take a serious look at what they want from a career.

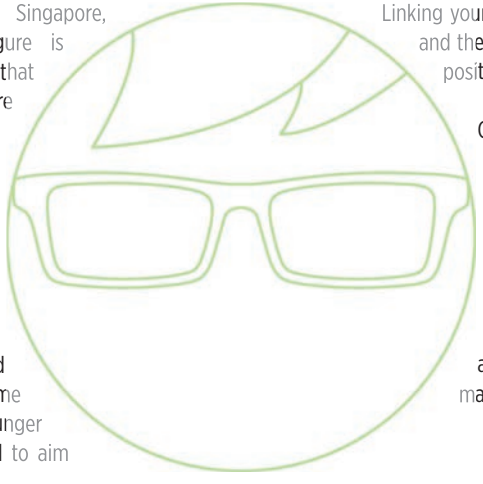
In its fifth global report on millennials, Deloitte Touche Tohmatsu Limited surveyed 7,700 well-educated and employed millennials at large companies (100 or more employees) in 29 countries. The company found a generation expecting jobs that fulfill their aspirations of leadership in organizations that look beyond mere profits. And if they don't find satisfaction, they are more than willing to jump ship.

One-quarter of those surveyed said they planned to leave their current employer within a year, and 44% reported they'd be gone within two. Of the millennials employed full time in the US, almost two-thirds said they would be working for a different employer by 2020. Possibly of most concern to employers is that 12% of those who say they are willing to leave are department or division heads within their organizations, and 7% hold senior management or board positions. For organizations that invest heavily in recruiting and training skilled managers, this is disconcerting.

What makes those in their mid-30s so willing to leave well-paid jobs for greener pastures?

A huge factor is receiving the proper training, direction and encouragement for leadership roles. Sixty-three percent of those surveyed said their "leadership skills (are) not being fully developed." In some countries, including Brazil, Singapore, Malaysia and Thailand, that figure is over 70%. The survey concluded that "millennials believe businesses are not doing enough to bridge the gap to ensure a new generation of business leaders is created."

Perhaps not surprisingly, those who demonstrate the most loyalty to their employers are likely to agree that their organization provides a lot of support and training to those who want to assume leadership roles, and that younger employees are actively encouraged to aim for leadership roles.



The values expressed and demonstrated by organizations also motivate employee loyalty. Eighty-two percent of those who intend to stay with their current employers for the next five years believe that the organization reflects their personal values. Among those values deemed significant by millennials are:

- Employee satisfaction/loyalty/fair treatment: 26%
- Ethics/trust/integrity/honesty: 25%
- Customer care/focus: 19%
- Quality/reliability: 13%

Good products and innovation were rated at a distant 7% and 6%, respectively — a notable finding for pharmaceutical manufacturers.

Above all, millennials don't express much interest in corporate profits. Eighty-seven percent said that "the success of a business should be measured in terms of more than just financial performance." Only in Germany and South Korea do more than 20% of millennial employees believe that business should be measured by financial success.

While millennials believe that corporations should focus on values over profits, they are, nevertheless, attracted to jobs that pay well. The survey concludes: "Pay and financial benefits drive millennials' choice of organization more than anything else." That conclusion is a constant across all 29 markets surveyed.

When salary and other financial benefits are removed from the equation, young professionals give high marks to work/life balance. Almost 17% stated that — salary aside — a good work/life balance tops the list when they consider a new position. Thirteen percent look for opportunities to progress into leadership roles and 11% look for alternative arrangements like remote work and flexible hours.

For organizations that want to retain worker loyalty and build a committed cadre of thirty-something employees, the survey recommends a number of prescriptive approaches, including:

- Identify, understand and align with millennials' values
- Satisfy millennials' expectations of employers
- Support millennials' ambitions and professional development

Linking younger employees with mentors is also strongly encouraged, and the survey notes that 94% of millennials with a mentor report positive results.

Overall, millennials most likely to remain loyal to their employers are those who feel they have chosen and are in control of their career paths, and are not locked into employment models designed by management without employee input.

The study concludes that "rather than hastening their exits, empowering millennials might help retain them." And while it appears that their sense of entitlement may be real, the survey makes it clear that these entitlements come in many flavors. ■

James Hale

Illustration: The 2016 Deloitte Millennial Survey

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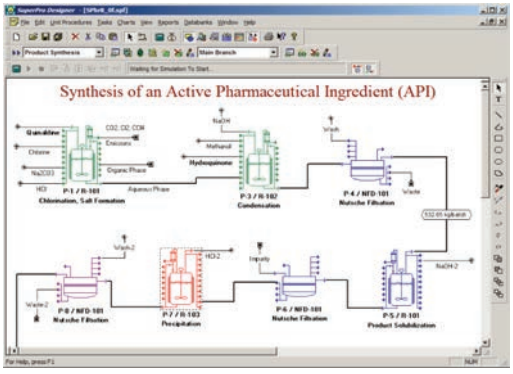

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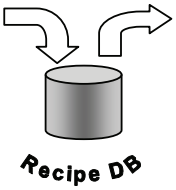

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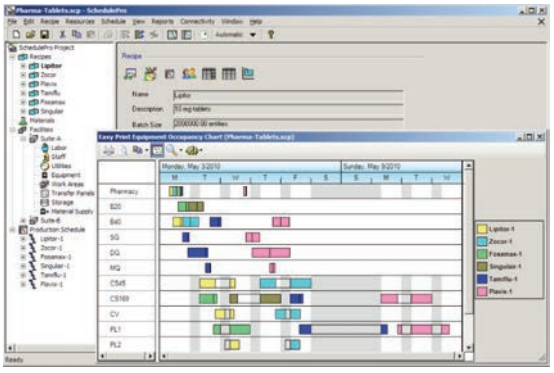
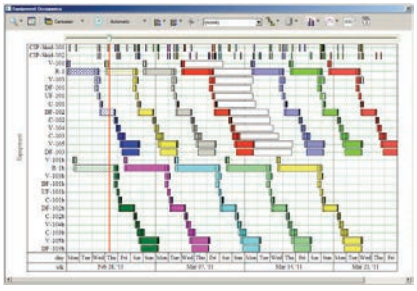
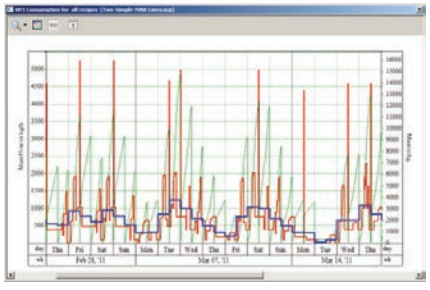


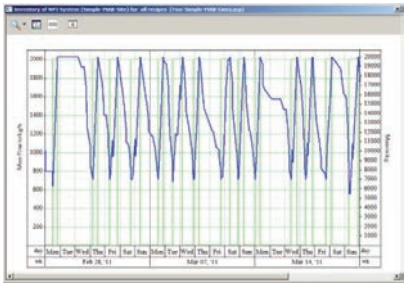
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling



Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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Quality and Compliance

ISPE Chair on Getting Things Right

A decade ago, the FDA published *A Vision for 21st Century Manufacturing*. The document was a call to action designed to move the pharmaceutical industry from mere compliance to true quality.

While much progress has been made in the intervening years, its goal — to improve the quality of drugs, processes and manufacturing facilities — remains a multifaceted challenge.

As Joe Famulare explains, "You have to combine and embrace the technology, quality and capability of the manufacturing process with quality systems to successfully achieve compliance, what others in past have called true compliance."

He should know.

A foot in each camp

Famulare, now ISPE Board Chair and Vice President, Global Quality Compliance and External Collaboration for Genentech/Roche's Pharma Technical Operations, was also a member of the FDA committee that wrote *A Vision for 21st Century Manufacturing*. The document, he says, was intended to make clear to industry that simply meeting minimum regulatory standards could never result in a robust process. The agency dared the industry to do more and better, to increase quality, and modernize manufacturing which at the same time would improve efficiency.

"Clearly, the profession has made strides since then," he reflects, "although I would like to see greater modernization of manufacturing and more focused attention on both inspections and review to achieve global regulatory harmonization. We're not yet where we need to be."

The industry, he says, produces materials for global markets in single factories, and requires manufacturers to navigate a maze of GMP and approval requirements; this makes true compliance both difficult and complex.

"In terms of how well industry is doing on a compliance basis, the FDA's quality metrics program has taken us to the cusp of learning how to measure that," he says. One area in particular has shown improvement: identifying shortages attributed to manufacturing and quality issues. "We have worked hard to shrink that part of the circle," states Famulare, "but on the prevention side, there's more that we need to do."

Shortages prevention

Famulare says ISPE is also working hard to help its members tackle drug shortages prevention, citing two examples: the **Drug Shortages Survey** and the **Quality Metrics Initiative**.

If you just try to achieve compliance for compliance's sake … you're not getting it right.

Photos: Yossi May, Washington Talent

"The drug shortages initiative started with a survey in 2013, and we acted on the results to create the *Drug Shortages Prevention Plan* in 2014. We adopted a data- and fact-driven approach to move forward. And if you look at quality metrics, we did the same thing: We used data to drive through some of the discussion and concerns, and sometimes angst, in that area."

Famulare believes that only an organization like ISPE, "with its full multidisciplinary, scientific, regulatory, engineering, manufacturing, and development background" can really engage regulatory agencies around the world in fact-based conversations on the subject.

"ISPE's continual focus on data integrity and quality culture, and how to measure them, is an area of strength for the organization, a reflection of its membership and the one of the basic tenets of our strategic plan."

Biotechnology

Famulare doesn't distinguish between the traditional chemically derived drugs and those produced by biotechnology, other than to note that biotechnology as we know it today only came into being in the 1970s. He sees both industries at a similar point of departure today.

"Both are [on the] cusp of being able to respond to the needs of patients by looking at technology in a friendly manner — as an enabler even — in bringing forward what needs to be done."

A more patient-centric approach to drug manufacturing means that the blockbuster model of mass-produced drugs for specific diseases are now being overshadoweded with personalized medicines for smaller patient populations. Because these tend to be high-potency drugs, it means special containment, and therefore, smaller processing lines.

Looking at biotechnology and its emerging dominance in pipelines, will require more factories and greater capacity and or more throughput, says Famulare . It also presents opportunities for better, tighter efficiencies and, he adds, growth.

An organization like ISPE, with technology experts among its members, has an opportunity to lead and bring industry forward. All our members, the seasoned and the young, need to embrace science, technology and engineering in manufacturing."

In with the new

Famulare believes that young professionals in particular will play a significant role in introducing new ideas and new ways of looking at industry challenges. "How we automate, how we manufacture, how we create records, how they become transparent across supply chains — young professionals have an opportunity to bring their education and diverse backgrounds and apply them to ISPE's initiatives.

Famulare says that whatever problem the industry is trying to solve — shortages, continuous manufacturing, the realities of emerging markets, or diverse regulatory requirements — it can only gain from new ways of looking at it all.

"And that is the only way we can begin truly to get things right." ■

Anna Maria di Giorgio

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Biopharma Dominates Smartest Companies List

Gilead, Amgen and Bristol-Myers Squibb (BMS) were among the 13 life sciences companies to make it onto the prestigious *MIT Technology Review* of "50 Smartest Companies 2015." To earn a place on the list, the editors explained, "[A] company must have truly innovative technology and a business model that is both practical and ambitious, with the result that it has set the agenda in its field over the past 12 months."

Pharma and biotech had a much more impressive showing in 2015 than in previous years, mostly for pioneering technologies that can tackle challenging illnesses. With approval of 11 new blockbuster drugs last year, it's no wonder the editors chose three pharmaceutical manufacturers for their list.

Gilead Sciences, ranked number 15, was tapped for introducing drugs that cure up to 99% of hepatitis C cases. Sales of the company's breakthrough therapeutics Sovaldi and Harvoni totaled $19.1 billion in 2015. The drug maker also hopes to launch a combination therapy of Sovaldi and velpatsvir later this year.

Gilead might well repeat on next year's list, as it has two potential billion-dollar HIV combination drug therapies coming onto the market this year; these will add to its arsenal, which already includes the blockbuster Truvada, a nucleoside analog reverse transcriptase inhibitor used to treat HIV-1 infection.

Amgen (19) was noted for the gene database of its subsidiary deCODE genetics. Headquartered in Reykjavik, deCODE has sequenced the genomes of 10,000 Icelanders – information that could be used to identify those at risk for diseases as well as to develop new drugs.

"deCODE, as a unique and powerful human genetics organization, is a renowned center for the study of factors that influence human health, including important new therapeutic mechanisms that we can train our drug discovery sights on," said Alexander "Sasha" Kamb, Senior Vice President, Discovery Research, at Amgen.

The database can provide accurate information about the genomes of the entire Icelandic population, since most of citizens of the country are closely related. Thorny medical ethics questions notwithstanding, the information offers great potential for personalized, precisely targeted medicine. For example, Icelanders – whether or not they participated in the database project – could be notified if it were suspected that they carried the BRCA2 gene mutation, which greatly increases the risk of breast and ovarian cancers.

Pharma and biotech had a much more impressive showing in 2015 than in previous years, mostly for pioneering technologies that can tackle challenging illnesses.

BMS (26) was tagged for Opdivo, its PD-1 checkpoint inhibitor for skin and lung cancer, which sold $475 million in Q4 last year and holds 84% of the immuno-oncology market. The drug recently received an expanded approval as part of its combination immunotherapy with Yervoy for advanced melanoma.

Biotechnology companies were also well represented on this year's list. Among them was Intrexon (44), noted for its synthetic biology technology and biopharmaceuticals. The company had the prescience to acquire Oxitek last year and, with it, a genetically modified mosquito that is being used to combat the Zika virus.

Juno Therapeutics (8) is a biotech company developing personalized cellular immunotherapies to treat cancer: A patient's T cells are genetically transformed with sequences that result in the high-affinity recognition of antigens that are unique to that patient's cancer cells.

OvaScience (11) uses the discovery of egg precursor cells for treatments that can improve a woman's egg health, thus increasing her chances of successful IVF. The first baby whose parents used this stem cell technology was born last April in Canada.

Alnylam Pharmaceuticals (30) uses RNA interference to develop new drug treatments for rare or unmet diseases. Its lead drug, patisiran, aimed at treating ATTR amyloidosis, is currently in a Phase III study.

Bluebird Bio (34) uses gene therapy such as genome-editing technologies to treat and, hopefully, cure diseases such as sickle cell anemia and cancer.

Rounding out the list of life sciences companies are: Illumina (3), for its DNA-reading machines used in hospitals and cancer clinics; Counsyl (5), a private startup that develops cheap DNA tests for prenatal screening and cancer-risk analysis; AliveCor (14), which has a heart monitor that connects to the iPhone; Enlitic (39), with technology used to spot tumors in scans; and DNAnexus (45), for its technology that helps drug companies store and analyze genetic data. ■

Scott Fotheringham, PhD

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Special Report

DATA INTEGRITY

March-April 2016

Here, Large, and Not Going Away.

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Here, Large, and Not Going Away

Data integrity is a fundamental element of a pharmaceutical quality system and has a direct impact on product-related decisions and traceability. Accountabilities for ensuring data integrity run throughout an organization, from product development, through manufacture and testing, to product distribution and safety monitoring.

Defined by the Medicines and Healthcare Products Regulatory Agency (MHRA) as "the extent to which all data are complete, consistent and accurate throughout the data lifecycle," data integrity is increasingly the focus of regulatory agencies around the world. Companies must now ensure they are appropriately addressing data integrity and data governance, and organizational/procedural and technical controls must also be considered as part of an overarching data-governance system. In addition, the effort and resources committed to data integrity must be commensurate with the role it plays in assuring product quality.

Why is data integrity so important? Karen Takahashi, a senior policy advisor at US Food and Drug Administration (FDA), summed it up in three key points during her presentation at the ISPE/FDA/PQRI Quality Manufacturing Conference, June 1-3, 2015, in Washington, DC:

First, regulatory agencies, as well as industry, rely on accurate information to ensure drug quality. If the information associated with a drug product is not accurate or reliable, there is no way a company can ensure the safety and efficacy of their product for the patient.

Second, data integrity problems break trust between industry and regulatory agencies. The regulatory agencies are not and cannot be responsible for ensuring the quality of our products. They are not our quality organization. If they find compliance gaps, regaining trust can be a very costly and time-consuming task.

Third, regulatory agencies rely largely on trusting the firm to do the right thing when the regulatory agencies are not watching. Regulatory agencies have limited resources and they cannot be present at every site which produces drug products. As stated earlier, they are not our quality organizations; it is our responsibility to act as an ethical company and ensure patient safety.

Data integrity is a global regulatory and compliance expectation, as seen by the increased data integrity rigor by the FDA and guidance by the MHRA and the WHO. Global regulatory agencies are becoming more aligned around these expectations. What can data integrity problems mean for your firm? They can result in recalls of products, regulatory citation, import alerts, injunctions, seizures, application integrity policy invocations/legal action, and most concerning, patient harm. It is as much a compliance issue as it is a financial issue.

Key implementation considerations for a corporate data integrity program include development of a high-level strategy, identifying and gaining executive sponsorship, focusing on management accountability, implementing tools for knowledge sharing, and developing and providing the appropriate levels of training. It is imperative that your data integrity program addresses behavioral factors and drives a strategy that focuses on prevention, detection and response. And be prepared to implement a plan for continuous improvement. This is an issue that's here to stay.

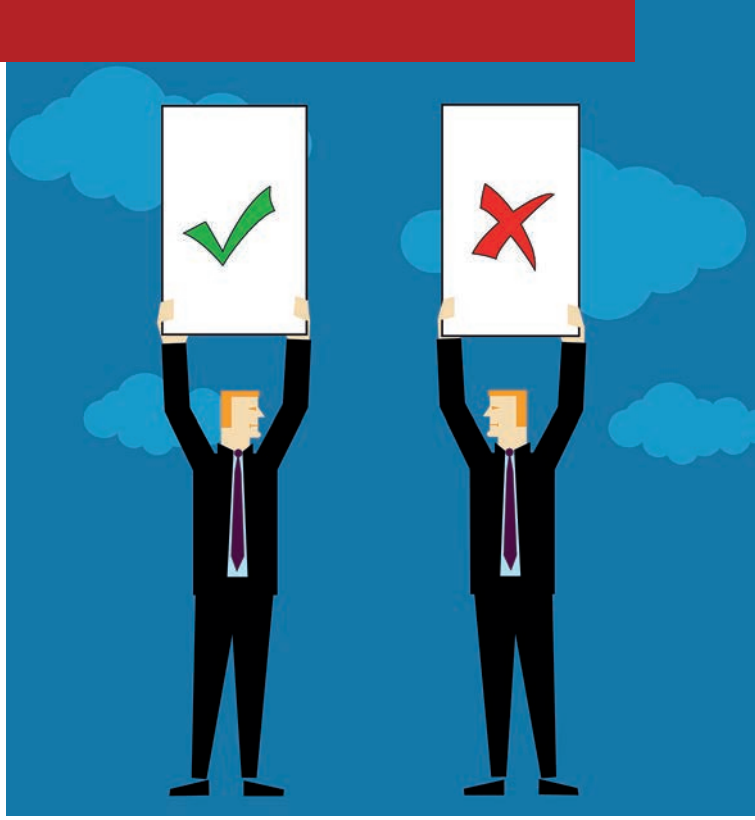
Christopher Reid

In this section

According to the FDA, source data should be "ALCOA": attributable, legible, contemporaneous, original and accurate

ALCOA+

Desired state		
A	Attributable	Who performed an action and when? If a record is changed, who did it and why? Link to the source data
B	Legible	Data must be recorded permanently in a durable medium and be readable
C	Contemporaneous	The data should be recorded at the time the work is performed, and date-and-time stamps should follow in order
O	Original	Is the information the original record or a certified true copy?
A	Accurate	No errors or editing performed without documented amendments
+	Complete	All data including repeat or reanalysis performed on the sample
+	Consistent	Consistent application of data time stamps in the expected sequence
+	Enduring	Recorded on controlled worksheets, laboratory notebooks, or electronic media
+	Available	Available/accessible for review/audit for the lifetime of the record



Throwing People into the Works

Human error can disrupt even the best-planned and -implemented IT system. Leadership and organizational culture can have a positive effect on data integrity.

Software applications follow logical processes and thus generally produce a repeatable outcome from a given sequence of steps – although there are occasional exceptions to this where a fault condition arises at inconsistent intervals. A process of validation can be used to give a high degree of assurance that the application, when properly controlled and used, will consistently return the same result.

Throwing people into the works – people by nature being unpredictable and prone to variability in techniques and judgment – can disrupt even the best-planned and implemented information technology (IT) system.

In P. G. Wodehouse's 1934 novel *Right Ho, Jeeves*, the phrase "He should have had sense enough to see that he was throwing a spanner into the works" is used to describe a character who is deliberately causing disruption and disorder.

The monitoring of human-error rates can be a powerful indicator of a company's error culture.

A perfect example of this can be found in an April 2015 US Food and Drug Administration (FDA) Warning Letter:[1]

> *[T]he analyst at your firm altered the file name in the spectrophotometer containing the sample identification information for (b)(4) API lot # (b)(4), tested on April 2, 2014, to support the release of two previously manufactured lots, # (b)(4) and (b)(4). . . . This practice is unacceptable and raises serious concerns regarding the integrity and reliability of the laboratory analyses conducted by your firm.*

This statement clearly indicates an analyst deliberately falsified a result in a computerized system. (It should be recognized, however, that while some GxP data changes may not be the result of intentional falsification, they also lead to data-integrity issues.)

The importance of leadership

Management responsibilities

ISO 9001:2015[2] clearly identifies one of the key roles of management: ensuring the availability of resources. This is reaffirmed in many, if not all, GxP regulations around the world.

Applying this requirement to data integrity, management must:

- Provide sufficient competent people to complete the assigned tasks: Overworked people may feel pressured to maximize yield or productivity at the expense of data integrity.
- Provide sound, reliable equipment and instrumentation for production and quality personnel to achieve the expected throughput: Outdated equipment may neither provide the technological controls for data integrity nor produce accurate data. Frequent equipment downtime can increase pressure on the staff to seek alternative ways keep up with their workload.
- Maintain the facilities and operating environment in a fit state for their intended purposes: Lack of physical security and poor IT infrastructure can themselves jeopardize data integrity by allowing unauthorized access to a server room, for example, or by losing data from a local hard drive.

These responsibilities are in addition to providing leadership in all matters of data integrity and compliance, as effective executive leadership is a critical component in maintaining a high level of data integrity. A corporation must emphasize the importance of data integrity to the organization through word and action, including embedding the quality requirements within the business process.

Executive leadership must encourage right behaviors by prioritizing data integrity when setting objectives, performance targets and incentives.

Leadership should drive a strategy that focuses on prevention, detection and response. The priority of effort for prevention should be greater than the priority of effort for detection; effort for detection should be greater than effort for response. This translates into:

- Select, install and configure systems that are capable of providing the technical controls essential to protecting data integrity, such as unique accounts, granular privileges and audit trails. (A more comprehensive discussion on technical controls and data integrity by design can be found in "An Ounce of Prevention.")
- Ensure that effective review processes are in place to detect any data-integrity issues throughout the operational life. (Detailed information on results review, audit-trail review, periodic review, data audits, etc., is covered in "Big Brother Is Watching.")
- On detection, ensure that the preventive actions implemented reduce or eliminate data-integrity risks by technical or design controls (preferred) and by influencing human behavior. (This is discussed in "Doing the Right Thing.")

Leadership must first accept that there have always been – and always will be – data-integrity issues on some level. Investigating and understanding the existing data-integrity issues within an organization is a strong foundation from which to begin the process of reducing such issues.

The MHRA Data Integrity Definitions and Guidance states the objective as being to "design and operate a system which provides an acceptable state of control based on the data integrity risk, and which is fully documented with supporting rationale."[3] Once a system with inherent controls has been put in place, detection is the next essential safeguard against the daily threats to data integrity. The reporting process for data-integrity problems must be understood from the top level all the way down to the line operators, and it must come with immunity from management censorship or retribution.

Metrics

Poorly chosen metrics can undermine integrity by encouraging the wrong behaviors and potentially providing the "pressure" element envisaged by Donald Cressey in his hypothesis on fraud[4] and pictorially represented in the "Fraud Triangle" (see Figure 1).

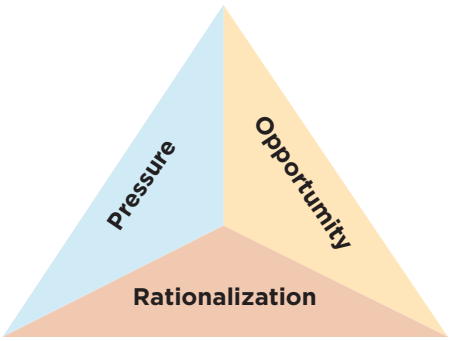


Figure 1 The fraud triangle

When such pressures are combined with the opportunity for data falsification presented by poor technical controls, it can be just a small step further for an employee to rationalize that altering the data is a minor misdemeanor and may even save the company money in the long term. At this point, the employee now has the motive (pressure) and ability (opportunity) to commit fraud and has even convinced himself or herself that it in the company's best interest to do so (rationalization) – when, in reality, fraud can only be detrimental to both the company and the employee.

As an example of pressure resulting from metrics, some companies may determine and monitor the throughput of the laboratory performing quality-control analyses. If the lab's performance is measured through the number of samples analyzed during a time period, then there is no pressure on the analysts relating to the pass or fail status of the samples analyzed. This prevents any temptation to "encourage" samples to pass but could give rise to poor-quality sample and column preparation as the analysts have no incentive to care about the result.

Redefining the metric as the number of passing samples in a time period, however, may provide substantial motivation for the analysts to make samples pass by whatever means they can in order to return a high efficiency, especially if there is potential for a pay rise or promotion linked to this.

A carefully chosen metric may involve the number of samples analyzed in a time period, but it would also need to factor in any incorrect test results as detected by second-person review or even repeat testing as part of an investigation.

Falsification for profit is discussed in more detail in "Doing the Right Thing," as is the use of positive metrics linked to rewards.

Cultural considerations

Cultural considerations can refer to a corporate culture (that is, the paradigm within which an organization operates) or a geographic culture (the moral and behavioral norm within a particular country or region).

Corporate culture

Corporate culture can vary widely, from a family-owned private company to a publicly traded corporation with an independent board of directors that comprises leading industry figures and subject-matter experts.

From a regulatory perspective, there is no difference: The expectation for data integrity and product quality remains the same. The publicly traded corporation may, however, by its very nature lend itself to significantly more transparency than the family-owned private company:

- The corporation may be subject to Sarbanes–Oxley or other financial audits that could identify any corporate culture of adverse data practices.
- There are no family loyalties and potentially fewer conflicts of interest involved in the corporation if an employee reports a data-integrity concern outside of his direct reporting structure.
- The corporate directors should consider the impact of any company activity on their individual industry reputations.

It should be noted, however, that a larger corporate business may suffer from:

- A level of inertia that must be overcome, especially when it is required to update the quality system and the way of working to mitigate (perceived or real) gaps in the quality system
- A lack of crossover knowledge, such as having more resources dedicated solely to "quality functions," but such specialism may restrict an understanding of laboratory processes

  Small start-up companies, common in the fields of biotechnology, sensing, and software development, have their own unique challenges:
- Little or no segregation of duties – all personnel have multiple roles
- Minimal independence and impartiality of departments
- A reliance on improvisation and innovation to work around problems
- An immature, and possibly incomplete, quality management system
- Potentially less focus on specific industries (particularly in a software start-up)

A company looking to succeed and grow should be amenable to input and suggestions from its customers, including ways to strengthen its data-integrity approaches.

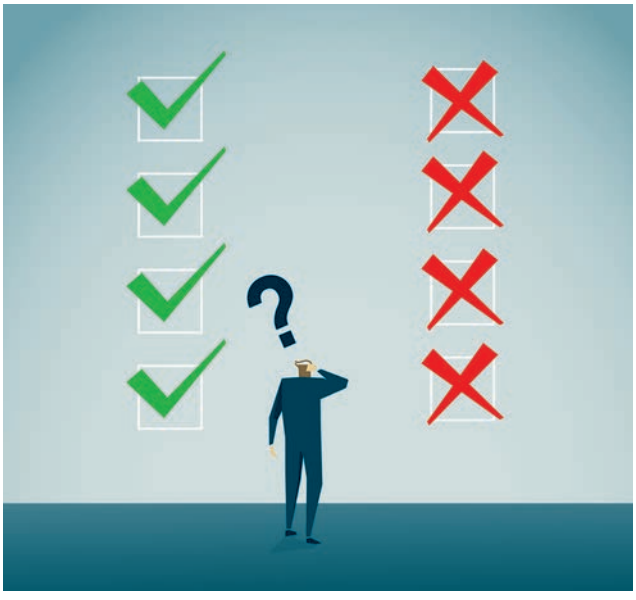
Geographic culture

Even in today's global society, geographic culture has a significant impact on site operations. There are many published works on geographic culture available; some of the cultural classifications in this section were taken from *The Culture Map*, by Erin Meyer.[5]

Cultures based on an egalitarian style with consensus decision making – as found, for example, in Scandinavian countries – may have a natural advantage in promoting data integrity. Openness and a willingness to discuss difficult situations can support an environment where failing results are seen as a group problem to be resolved with clearly documented corrective actions that mitigate the manufacturing or other root cause.

Similarly, people from cultures that tend toward direct negative feedback, such as in the Netherlands, will likely feel comfortable escalating an issue through the management structure.

In a more hierarchical society, especially one that intuitively uses indirect negative feedback, as might be found in highly traditional cultures like Japan or China, reporting an out-of-specification result could be seen as either a personal failing on the part of the analyst or even an implied criticism of the manufacturing department. Such cultures will have to invest significant effort to consciously overcome traditional thinking in order to achieve the openness around data integrity that is needed for compliance.



Effective executive leadership is a critical component in maintaining a high level of data integrity

Human error

"Doing the Right Thing" focuses on intentionally fraudulent actions that undermine the integrity of data; it is, however, important to recognize that such actions are thankfully in the minority and that data is more often affected by genuine human error.

Minimizing human error

In his three-part article "Optimizing Human Performance," Gerry McAuley sees human error as indicative of failures in the systems and processes within the organization.[6–8] When transparent, open investigations are conducted to determine the true root cause – which may be a combination of failures across a number of individuals and processes – and followed up with effective solutions, the incidence of human error can be reduced.

McAuley proposes moving from the current and pervasive mindset that human errors should be dealt with by "reprimanding, retraining, adding extra lines to SOPs, and thinking people just need to read them" to a paradigm based on openness and a real understanding of people and behaviors and ultimately to a corporate culture where "individuals who try to hide, ignore, or respond inappropriately to perceived human errors are not able to exist in the business."

The monitoring of human-error rates can be a powerful indicator of the company's error culture, with a consistently high incidence of error changing little over time showing that mistakes are accepted as inevitable with no effort made to improve working practices.

Effective mechanisms to reduce human-error rates include (most effective first):

Use people less: Increased use of direct interfaces between systems in place of human manual transcription should mean less human error.

Use people only for their strengths: Humans are very effective at monitoring multiple systems simultaneously, whereas it would require a highly complex automated system to achieve the same monitoring function. The data in Table A, however, shows that humans are naturally poor at manual data entry, so this should be avoided by implementing the direct interfacing of equipment and automated transfer of data.

Limit opportunities for human error: Use drop-down lists in place of free text entry, for example, so that searching for a particular product name will not fail due to a spelling error.

Human error rates

Professor Raymond Panko at the University of Hawaii has been collating data on human-error rates and has uploaded key figures to his website; a small selection of that data has been reproduced here. It should be noted that even a second-person review will not necessarily catch 100% of the errors present and so the actual error rate may be higher than quoted here (see Table A).

Interestingly, more recent data from Potter[9] seems to suggest that entering data in a more critical system – in-flight management, for example – does not lower error rates, as one might be expect given the perceived importance of the situation; it can actually give a worse error rate than situations without such pressure. Alternatively, the increased error rate could be attributed to less accurate keyboard input from users accustomed to word processing and spell-checking to correct errors compared to the necessity for high accuracy among professional typists using manual typewriters in the earlier studies (although spell-checking itself can create errors when it "corrects" a word erroneously and thus changes the meaning of the statement).

Table A Selected error rates in data entry

Scenario	Error Rate*	Researcher, Date
Expert typist	1%	Grudin, 1983
Student performing calculator tasks	1–2%	Melchers and Harrington, 1982
Entries in an aircraft flight management system, per keystroke; higher if heavy workload	10%	Potter, 1995

* Detected by second-person review

Table B Selected error rates in spreadsheet development

Summary	Error Rate*	Auditor, Date
50 spreadsheets audited; 0.9% of formula cells contained errors that would give an incorrect result	86%	Powell, Baker and Lawson, 2007
7 spreadsheets audited	86%	Butler, 2000
22 spreadsheets audited, only looking for major errors	91%	KPMG, 1998

* Percent of spreadsheets with detectable errors

A regulator does not distinguish between human error and data falsifications when assessing the impact of a data-integrity failure.

It should also be noted that Potter's study found that the error rate increased with a heavy workload, which reinforces the message in the section on Management Responsibility: It is essential to have sufficient staff to manage the workload and preserve data integrity.

Panko has further researched error rates in spreadsheet programming. In his article "What We Know About Spreadsheet Errors,"[10] he leverages experiences from financial spreadsheet audits by lead auditing companies to compile an error rate for spreadsheet development (see Table B).

While it may not be feasible for companies to audit all of their data entry in such a formal and controlled fashion using an outside company, careful tracking and trending of the findings from properly conducted root cause investigations should be able to provide some measurable metric around the incidence of human error within the company. This metric can then be monitored to measure the efficacy of data-integrity activities as part of the company's ongoing commitment to quality.

When discussing the incidence of genuine human error, it's important to note that a regulator does not distinguish between human error and data falsifications when assessing the impact of a data-integrity failure.

This is clearly evident in a January 2015 FDA Warning Letter:

> *In correspondence with the Agency, you indicate that no malicious data integrity patterns and practices were found. Also, you state that no intentional activity to disguise, misrepresent, or replace failing data with passing data was identified and no evidence of file deletion or manipulation was found. Your response and comments focus primarily on the issue of intent and do not adequately address the seriousness of the CGMP violations found during the inspection.*[11]

This statement shows that the FDA does not make allowances for how the data-integrity issues occur; it only cares that the issues have occurred and may impact product quality and patient safety.

Conclusion

Corporate leadership, corporate culture, and geographic culture all have a significant impact on the integrity of data. Strong corporate leadership should provide the paradigm to improve data integrity. Furthermore, implementing an effective framework of administrative safeguards and technical controls – examined in "An Ounce of Prevention" – should minimize genuine human error and ultimately reduce opportunities for deliberate falsification. ■

Charlie Wakeham and Thomas Haag

Implementing a Corporate Data Integrity Program

This article provides a condensed version of a presentation the author made at the ISPE Europe Annual Conference, 7-9 March 2016, in Frankfurt, Germany. Both the article and presentation are compiled from materials developed by the ISPE GAMP® Data Integrity Special Interest Group. Both also borrow from "Considerations for a Corporate Data Integrity Program," a recently published ISPE GAMP Community of Practice concept paper that shares implementation considerations based on the experiences of several companies, including successes and challenges. Although the specifics of each company's data-integrity program are different, the considerations described provide direction for creating a successful corporate data-integrity program.

A well-defined strategy is the cornerstone of any data-integrity program.

A well-defined strategy is the cornerstone of any data-integrity program.
To design and implement a successful program you must have a keen understanding of your current state of affairs and business process knowledge; you must also make sure that those processes support your data-integrity requirements.

The assessment activities outlined below can serve as a basis for defining and establishing your strategy. The high-level plan presented here will define the approach, timeline, resource requirements, and rationale required to execute your data-integrity program. It may also provide a means to track progress for senior management reports, as well as a documented rationale and plan to outline your program and actions during audits and inspections. Finally, it outlines a method that can help align multisite activities and provide a holistic approach to compliance.

At a minimum, a well-defined strategy demonstrates your commitment to managing data-integrity issues within your company and creates a corporate governance oversight process.

Identifying and establishing executive sponsorship is crucial to getting support for your data-integrity program. The sponsor is responsible for the program's overall success, and will be required to set direction, define priorities, provide resources and break down organizational barriers. The sponsor will also help executives be aware of the four key benefits that a data-integrity program can deliver: financial, risk reduction, regulatory, and legal product liability.

What are the critical success factors?

Management accountability

While a successful data-integrity program requires cross-functional oversight and participation, management accountability at all levels of the corporation – from the CEO to operations floor supervision – plays a key role in ensuring data integrity. Managers should "walk the talk" and personify integrity in response to a failure. They should foster an environment in which employees are encouraged to identify and report data-integrity issues on the shop floor. They should never incentivize data falsification and should always discourage the "wanting-to-please" mentality that can lead to data corruption.

Accountable managers also provide the appropriate resources to ensure data integrity – including people, capable instruments and systems, along with sound and understandable business processes. They acknowledge that data-integrity issues will occur, and that human error contributes greatly to data integrity issues. And they drive a strategy that focuses on prevention, detection and response.

Knowledge sharing and training

As you roll out your data-integrity program, sharing and addressing a number of questions will help build a good data-integrity foundation across your organization. These include, but are not limited to:

- What does data integrity mean and how does it apply to my day-to-day business activities?
- What role do equipment qualification and computerized system validation play in data integrity?
- How does data integrity relate to 21 CFR Part 11 and EU GMP Annex 11?
- What are our roles and responsibilities? What are those of the regulatory agencies?
- When does data integrity start and when does it end?

It's important to make information readily available to all levels of the organization. Employees from the executive suite to the shop floor should have appropriate levels of knowledge and accountability about data-integrity requirements and expectations.

Establishing a data-integrity knowledge repository or knowledge base is a great way to provide historical and current information. Consulting subject matter experts both within and outside of your organization early in the process is crucial to establishing an appropriate knowledge foundation.

Data integrity should be inherent to your processes, so that it can provide a foundation for more focused training. Data handlers should be trained to understand that they are data-integrity stewards. They should understand the business processes and the data they generate. They are responsible for identifying and escalating concerns regardless of the effect on delivery, quotas, or timelines. Those in quality and compliance roles should have advanced training to ensure that data-integrity requirements are implemented within systems and processes, and that they support the business processes and business owners.

Are your controls in place?

Quality management system

Data integrity and data governance are an integral part of your quality system. It's appropriate to start with organizational and procedural controls, therefore, when designing a data-integrity program.

Does your quality management system (QMS) adequately address the regulatory requirements associated with data-integrity? An assessment will identify any procedural controls that might be lacking. Do adequate processes exist within the QMS to prevent, detect, report, and address data-integrity failures? Are the ALCOA+ requirements clearly addressed within the QMS? Are there adequately defined processes to generate and review data? And are there proper controls for the entire data life cycle? If you have a good and well-defined corporate QMS aligned with current GxPs, most of

Data integrity and data governance are an integral part of your quality system.

these items should be addressed and traceable to the appropriate regulation applicable to your business processes.

Organizational gaps are more likely to be identified as sites and local business areas define and execute their local procedures, however, a more detailed gap assessment may be required to truly understand the state of data-integrity controls in place at this level.

Corporate quality culture

This leads to another control you should assess and understand: corporate and quality culture.

Just as behaviors can promote appropriate actions and foster an environment that champions integrity, the opposite is equally true: Cost-saving measures may encourage password sharing due to limited user license purchases; poorly conducted investigations may blame human error or find no assignable cause. Changing a standard operating procedure (SOP) may be proposed as a preventive action, but all too often it can be ignored and not truly address the root issue.

Poorly chosen metrics can also undermine data integrity. Metrics that encourage pressure, opportunity, and rationalization can support fraudulent practice and may encourage data-integrity issues. Emphasizing speed rather than accuracy and quality, for example, can force employees to cut corners and focus on the wrong things.

Technology

As with organizational controls, you must also assess technical controls, which include your equipment and computer systems. Are these properly qualified and/or validated to ensure data integrity? All too often, systems are not qualified, designed, or configured to ensure data integrity. System access and security should be properly defined and audit trails properly utilized to review, detect, report, and address data integrity issues.

Compliance

Understanding how organizational and technical controls are executed and applied in your business processes is critical. An audit or self-assessment process should monitor compliance with your QMS and the regulatory requirements of your business. A quick measure of data-integrity compliance can be taken with a review of the self-assessment, internal audits, and third-party reports and observations associated with these activities. What types of data integrity issues exist? Are there repeat findings related to data-integrity issues? Are there systemic issues and do they stem from a corporate or quality culture issue?

Of course it is only possible to review this data if these self-assessment and audit processes are designed and able to identify data-integrity risks and gaps. They should utilize forensic audit techniques and focus on data-integrity compliance issues. This will be critical to the long-term monitoring and overall effectiveness of your program; it will also help ensure you are identifying and addressing data-integrity issues before regulatory inspections find them.

If you are fortunate enough to have received an inspection visit from a regulatory agency that has implemented forensic data-integrity inspection techniques, you will be able to use the results of that visit as yet another indication of your acceptable state of control of data-integrity risks. Otherwise, a review of regulatory observations from other companies can

Worth the effort?

This question is often asked as companies determine how to address data integrity within their organizations. The MHRA GMP Data Integrity Definition and Guidance for Industry March 2015 provides some interesting perspectives related to this question.

It states that "Data Integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality." It goes on to say that "The data governance system should be integral to the pharmaceutical quality system … " So there is clearly an expectation that companies address data integrity and data governance in their pharma quality system because it is fundamental to ensuring product quality.

Does this mean that companies must implement elaborate and highly resourced programs to address data integrity? The MHRA guidance further states that "The effort and resources assigned to data governance should be commensurate with the risk to product quality and should be balanced with other quality assurance resource demands." So the effort and resources should be aligned with the risk and with other quality demands.

It also states that "As such, manufacturers and analytical laboratories are not expected to implement a forensic approach to data checking on a routine basis, but instead design and operate a system which provides an acceptable state of control based on data integrity risk, and which is fully documented with supporting rationale." The emphasis is on designing and implementing a system to provide an acceptable state of control based on data integrity risk.

The MHRA guidance also says that "consideration should be given to the organizational (e.g., procedural) and technical (e.g., computer system access) controls applied to different areas of the quality system" and the "effort and resources … be commensurate with its criticality in terms of impact to product quality attributes."

provide insight into current trends and concerns. Data-integrity observations issued for one site are potential indicators of issues in other sites. You should determine if similar issues exist within your sites and develop action plans to close any gaps. There is no faster way to lose the trust of a regulatory agency than to have the same issues identified at multiple sites within your organization, as it highlights not only the possibility of a systemic issue, but corporate and quality culture issues as well.

Define your metrics

Defining and establishing appropriate data-integrity program metrics are necessary for two reasons: First, it ensures a positive return on investment. Senior management that invests time, money, and resources into a program expects a return on that investment, otherwise why invest in the first place? Second, metrics also measure the success of the program and demonstrate progress against goals.

In early stages of the program, reporting of data-integrity issues will increase with increased awareness and improved detection, which may skew the metrics. It is important to manage this "bad news" and continue to foster an environment of open reporting. A program-reporting process will also bolster success. Your plan should define the reporting expectations to senior management, area business leadership, the program team, and those on the shop floor. It is an opportunity to share metrics and progress to date, as well show progress against the plan. It also identifies and communicates issues and provides a mechanism to agree on next steps.

Audit your processes

Audit processes also are critical to the success of the program. Multiple types of audits should be conducted, including, but not limited to:

- Initial gap assessment or audit of nonconformance
- Periodic audit of long-term data archives
- Supplier qualification
- Closeout gap assessment or full audit following program completion
- Ongoing internal quality audits of established data integrity controls to ensure continuing effectiveness and compliance

These will provide critical information to set a baseline and measure success, as well as highlight possible gaps, corrections, and additions to your project scope. For initial and closeout assessments, consider using an independent auditor. (This does not necessarily mean an outside expert, but someone independent of the internal core team.)

Conduct review processes

A final key to successful implementation of a data-integrity program is defining and implementing a robust review process, including result reviews and periodic reviews.

Result review: Results review is defined as the review of individual results or sets of results conducted prior to making an accept/reject decision about product or data quality. It should compare results against specifications, limits, and acceptance criteria. It should also evaluate the completeness and correctness of metadata. The review process makes room for judgment about the accuracy and integrity of any manually entered values; it also reviews information associated with any decisions or actions taken.

The reviewer shoudl assess and understand the effect that any manual adjustments or alterations of the data or metadata might have on the results or product decision, and should also be aware of any changes to method versions used in creation of the result. The reviewer should also assess the results' conformity to sound scientific practice and documented procedures. Increased review rigor should be applied for manual adjustments and/or results that barely meet specifications.

Three Key Factors to Consider

I am frequently asked "How much effort is required to implement a corporate data integrity program?"

MHRA GMP Data Integrity Definition and Guidance for Industry March 2015 makes it clear:

> *The degree of effort and resources applied to the organizational and technical control of data lifecycle elements should be commensurate with its criticality in terms of impact to product quality attributes.*

My typical answer is, "It depends," because three factors should be considered to develop your initial data-integrity strategy and define your corporate program:

First: What were the outcomes of the gap assessments and audits of your organizational controls (i.e., your QMS and procedures)? If significant gaps exist, then a greater effort will be required to address the integrity risks. This may also result in the creation of site and/or local procedures to implement the new controls and processes.

Second: What were the outcomes of the gap assessment and audits of the technical controls associated with equipment and computer systems? This could result in updates, reconfiguration, or even replacement of a number of systems, all of which must be qualified and/or validated. Depending on the extent of the changes to these systems, the amount of effort and resources required will vary by projects and/or system.

Third: Are there gaps associated with business processes and their execution? These are typically identified by conducting a detailed business process review and gap assessment with the people responsible. Changing business processes is not always easy, especially when they have been in place for a significant period of time. Mitigating gaps may require changes in procedure and the organization's quality and business culture. Training may be required to support the changes. As always, management accountability and support is critical and will have a direct influence on successful implementation, especially when dealing with multiple sites.

Understanding how organizational and technical controls are executed and applied in your business processes is critical.

The result review should not overlook the audit trail review,[1] which provides the most effective means of assessing data integrity. Unfortunately, in some cases the audit trail is not easily accessible or permanently associated with the result, making the review difficult to complete and data-integrity issues difficult to detect.

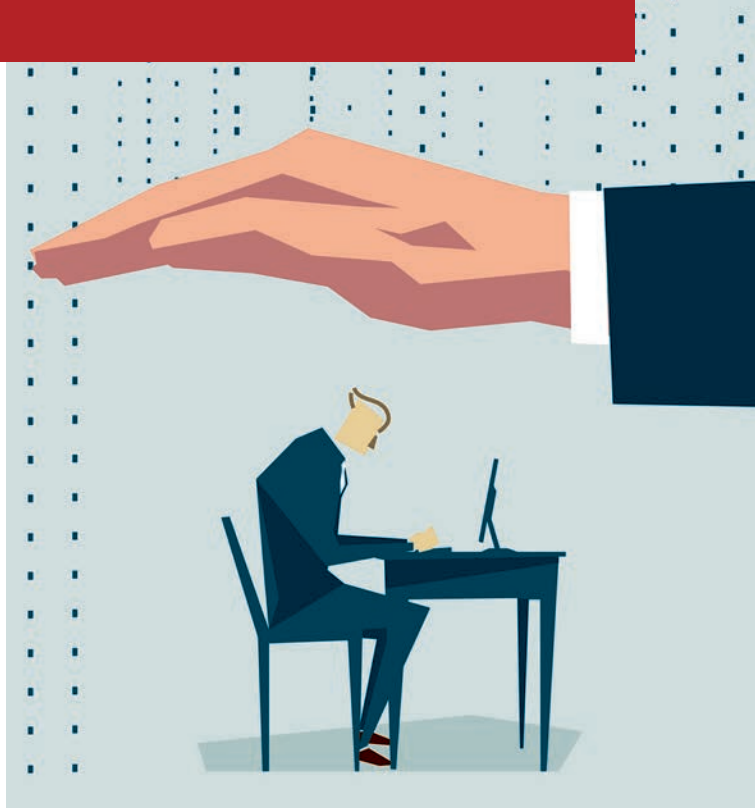
Appropriate and accessible audit trails can prevent and detect data-integrity issues, but reviewing the audit trail and metadata associated with the volume of results generated in today's business processes can present logical and resource challenges. Technology controls implemented within many systems, however, have provided a means to review by exception.

This applies risk-based methodology to data review based on alerts highlighting a subset of results that require additional detailed review; these may be results and data that are within but close to the specification limit, have been manually manipulated (i.e., integration), or have been reprocessed. These types of systems also require validation to verify and document the alert functionality.

Periodic reviews: Computer systems require periodic reviews to ensure they continue to operate in a matter consistent with their intended use and remain in a validated state consistent with that use. GAMP® 5 is a great resource that outlines the concepts of periodic review. From a data-integrity perspective, periodic review should include evaluation of any changes to system configuration that could affect data integrity. It should also focus on any data deletions, including what was deleted, why, and by whom. In addition, the review should target system administration activities and user accounts, especially accounts disabled following unsuccessful login attempts.

Other periodic review activities include SOP review to ensure that appropriate data integrity controls are addressed, system validation records are current and reflect the intended use of the system, required SOP records are maintained, change control process is functioning properly, and system performance is not affected negatively by the intended use of the system. ■

Michael Rutherford



An Ounce of Prevention

The administrative and technical controls needed to mitigate risks to data integrity prove Ben Franklin's maxim that "an ounce of prevention is worth a pound of cure."

Computerized systems' functionality is based on a combination of hardware, software, processes, personnel and environment. When such systems are used for the collection, storage, sharing, use and archiving of regulated data, the following guiding principles will apply:

- Data should be collected, stored, shared and used only for legitimate business purposes.
- Data should be collected, stored, shared and used in a secure manner.
- Any data that is to be shared externally must be transferred by secure means.
- Active, responsible data stewards should be assigned to all critical data.
- Users should only have access to the data needed to do their jobs and should be granted access levels commensurate with the requirements of their jobs.
- Data, as well as any associated metadata that provides content and meaning to the data, must be retained for the relevant retention period.

- Any change to critical original data must be recorded in an audit trail. This should capture who made the change, the old and new values, the date and time of the change and the reason for the change.
- All data users should be appropriately trained on requirements related to data collection, storage, sharing, integrity and use.
- When the same information is available from multiple systems, the authoritative source of the information should be documented in the quality system and some effective mechanism put in place to ensure that the other systems are updated and remain consistent with the authoritative source.
- Specific definitions for and the purpose of data collected in electronic systems must be clear to users.
- Consistency checks should be implemented within and between records.
- Quality oversight of data processes is essential.
- All computer systems used for data collection, storage, sharing, use, and archiving must be validated for their intended use.

Administrative safeguards

Administrative safeguards consist of administrative controls – generally documented in policies and procedures – to manage the selection, development, implementation and maintenance of security measures to protect GxP data, and to manage the conduct of the workforce in relation to the protection of that data. Appropriate controls must be established for all phases of the data life cycle, from initial creation through processing (including any modification, deletion, transformation, or migration), use, retention, archiving and retrieval.

Policies and procedures

Pharmaceutical companies typically have numerous policies and procedures that impact data integrity in some way, including, but not limited to, the following examples:

- Good documentation practices
- Data life cycle approach
- Computerized systems validation
- Risk management
- Security management, including access management
- System administration
- Change control, especially manual direct database updates by information technology (IT)
- Incident response and management
- Backup and restore, including monitoring for backup errors
- Disaster recovery and business-continuity planning
- Archiving and record retention
  - Retrieval and readability checks on archived data and metadata, including audit trails
  - Archived data security and data-integrity controls
- Review processes, including audit-trail review (see "Big Brother Is Watching")

Security management process and access management

Many of the system-specific administrative security controls addressed here have an indirect but significant impact on data integrity. While overall responsibility for the controls lies with the business (as the data owners), the actual implementation of some controls may rely on IT or technical organizations.

Appropriate controls must be established for all phases of the data life cycle

Wherever possible, logical security controls for a computer system should be based on technical rather than procedural controls. Security and access controls include, but are not limited to:

- Securing communication of user credentials, such as:
  - Ensuring that you are talking with the correct person before sharing verbal information
  - Verifying the user's identity in person
  - Using one communication channel for the password and a different one for the username
  - Limiting the amount of time that the initial password is valid
- Ensuring appropriate approval(s) for access
- Identifying unique users to ensure nonrepudiation of changes and/or electronic signatures
- Accessing roster review for user accounts
- Removing access or privileges in a timely manner when they are no longer needed
  - Note: An automated method based on job moves provides a much higher degree of assurance than procedural or manual control
- Enacting good password practices such as using pass phrases that are at least eight characters long and include letters, numbers, and special characters; prohibiting password sharing
- Modifying all default passwords (especially for system-administrator accounts)
- Password expiration interval
- Creating challenge questions for reauthentication, such as password resets
- Establishing an appropriate automatic logoff interval (inactivity timeout) within the application
- Ensuring that appropriate role-based security is established
- Segregating business-related duties. For example: System-administrator access data deletion and/or system configuration changes should not be assigned to individuals with a direct interest in the data (anyone who generates, reviews or approves data). Where this is unavoidable due to personnel limitations, mitigating controls should be implemented, such as dual user accounts with different privileges
- Segregating IT-related duties: ensure that the same individual cannot request, grant and approve access for themselves, for example
- Following the least-privilege rule to ensure that each users has only enough privileges to allow him or her to fulfill his or her job function
- Limiting the number of IT system administrators to the minimum possible, taking into account the size and nature of the organization
- Monitoring of turning on/off system audit trails
- Limiting access to other system configuration parameters that could affect data integrity, such as user account modification and number of failed access attempts before lockout
- Configuring security notifications from the application to a designated authority
- Reviewing access logs
- Accessing roster review for nonuser accounts, such as administrator accounts

- Implementing time synchronization and time-clock security controls
- Assuring that vendor-provided software is maintained at a release that is supported by the vendor. This ensures that the latest security patches and service packs can be applied as soon as reasonably possible to close known security risks.

Contracts and other arrangements

From contract manufacturing or laboratory services to outsourcing IT or using "as a service" options such as SaaS, PaaS or IaaS (software, platform, or infrastructure as a service), these service providers have a potential impact on data integrity that must be evaluated, controlled, and mitigated. From the providers' willingness to be audited through the completion of audits or assessments prior to supplier selection, and throughout the ongoing service engagement, data integrity should be an area of absolute focus. Both IT controls and business processes must be reviewed to ensure that appropriate controls are in place to guarantee data integrity. Establishing clear requirements related to data security and integrity in the contract and/or quality agreement provides a baseline for ongoing monitoring to ensure that expectations will be met. Record-retention periods and access requirements (including system availability) must be clearly defined and achieved.

Documentation and data management

The process used to store and manage documentation and data and the repository in which the data resides can have a significant impact on data integrity. Documents or other types of data files stored and managed in a regulated electronic document management system or other validated electronic-record computer system that leverages a relational database can be controlled on a much higher level than documents or other types of data files managed in a file share on a server using a manual process. This is explicitly supported in the MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015,[1] which states:

> *There is an inherently greater data-integrity risk with flat files (e.g., when compared to data contained within a relational database), in that these are easier to manipulate and delete as a single file. [Emphases in the original]*

Paper-based records

It should be noted that while paper-based records have been used for much longer than electronic records, they share many of the same concerns, such as how to ensure the record remains:

- Legible: Considerations around fading ink and the well-known issues with thermal printouts
- Available: How to protect the record during long-term archiving: Will the paper degrade? Is it threatened by moisture or pest species?
- Retrievable: How to quickly locate one record among the many thousands retained; advantages and disadvantages of onsite vs. offsite storage

Paper records, of course, have an additional issue in that they lack the independent audit trail that can accompany an electronic record; this means that it is not possible to identify record backdating, repeat testing of the sample, or whether all results have been retained.

For certain records, there is clear regulatory guidance that the electronic record must be retained, as the paper record is not sufficient. The US Food and Drug Administration (FDA), for example, makes a very clear statement about chromatographic data:

> *For High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) systems (and other computerized systems involving user inputs, outputs, audit trials, etc.), the predicate rules, such as 21 CFR 211.68 and 21 CFR 211.180(d), require the electronic records themselves to be retained and maintained in accordance with those regulations. . . . [T]he printed chromatograms used in drug manufacturing and testing do not satisfy the predicate rule requirements in 21 CFR Part 211. . . . [T]he electronic record must be maintained and readily available for review by, for example, QC/QA personnel or the FDA investigator.*[2]

Technical controls

Technical controls should be introduced to mitigate the risks associated with human actions in the design of the original system. However, because technical controls are designed, tested, and implemented by humans, it is important to recognize that the controls may themselves have design flaws.

Computerized systems are often generalized as IT systems or software solutions. In fact, a computerized system is not limited to software but should be considered as a business process supported by the use of IT solutions. The key here is that business process comes before the technical solution – never the other way around.

Business process comes before the technical solution – never the other way around

Data integrity by design

The integrity of regulated data should be safeguarded in three spaces: during collection and processing, when transferring between systems and in storage.[3] Evaluating the risks to data integrity at each stage of the data flow in a business process can identify opportunities to improve data integrity by intelligent system design; transcription errors, for example can be eliminated from a workflow by directly interfacing the source and target systems such that the data is transferred electronically using a validated process. Transmission security across an open network can be strengthened by using integrity controls such as a checksum and encryption processes. Highly critical data editing or deletion functions can be additionally secured and justified using transactional safeguards such as password authentication at the time of execution, and the recording of an explanation for the action via free text or (preferably) preconfigured reason. A user interface that highlights potential data-integrity issues, such as manually integrated results or repeat samples, assists by focusing review efforts on the results with the highest risk.

Technical controls have an important advantage over human controls. The repeatable and reliable behavior of any validated IT system (whether it is a distributed clinical database or a manufacturing executing system) can be designed, tested, operated, and maintained in such a way that data integrity is ensured and well documented. However, it is also true that even the best systems – in terms of implementation, efficiency, and quality – could not ensure data integrity without qualified data stewards. Data

Introducing humans to a validated IT system creates a more complex and unpredictable interaction

stewards are the guardians of data integrity; their role is to speak up when something is amiss, and they should not fear the repercussions typically associated with slowing down the process to achieve better quality. The repetitive and sometimes heavy lifting of data should be left to validated IT systems, allowing data stewards to concentrate on more valuable and creative endeavors, such as monitoring data across multiple systems and identifying any patterns in the data or process. They are only human, after all.

Physical safeguards

Physical security begins with restricting site access to authorized visitors only.

IT architecture can be selected to improve data integrity by eliminating hard drives within the laboratory with all of the risks inherent in physical access to the storage media. A system based on a client/server architecture provides the ability to isolate the physical data location (the server) in a dedicated, climate-controlled environment (server room) with additional physical security ensuring that only a very select subset of authorized personnel are able to access the server room. Controlling which terminals (clients) can be used for specific functionality can reduce the likelihood of inappropriate system usage. In a distributed system, for example, it may be reasonable to have client terminals throughout the whole site, but those in the warehouse could be prevented from initiating a packaging run on the production line.

Finally, careful consideration should be given to the storage media used for backup and long-term archival storage as the data on it must remain accessible, secure, and protected for an extended period. This may require a process for transferring the archived data to new media due to "shelf-life" limits, a newer system and/or a change of technology.

Computerized system validation

Introducing humans to a validated IT system creates a more complex and unpredictable interaction which, when refined and documented, becomes process. The marriage of the trained human user armed with an efficient process to a validated IT system produces the computerized system. The life cycle for a computerized system is a continuum from the initial idea for the system to its final decommissioning; it must address the potential need for the data to live on after system decommissioning to satisfy record-retention requirements.

Computerized system validation (CSV) is a process that is applied to provide verifiable objective evidence that a system meets predetermined specifications, governed by clearly documented procedures and used only by individuals with appropriate expertise and training. System access should be limited to only those personnel with a legitimate business reason for accessing the system, and granular levels of privileges should be further used to limit personnel access to specific functionality or data within the system, according to their job roles. CSV ensures that a system comprising people, process, procedures, hardware, software, operating system and networks is fit for its intended purpose.

Ensuring data integrity in a GxP system is extended, but not guaranteed, by CSV. It may be necessary to accommodate vendor solutions that have data-integrity gaps in the technical controls; these must be mitigated as part of the validation process. CSV only ensures that a system is fit for its intended purpose; it cannot absolutely prevent data-entry error or intentional misuse of the system.

Computerized systems that handle GxP-relevant data must be validated to ensure that health authority requirements for good (manufacturing, laboratory or other) practices are met, noting that the Code of Federal Regulations Title 21, Part 11,[4] PIC/S GMP Guide[6] and/or the EudraLex Annex 11[5] (along with equivalent regulations for other countries) provide specific requirements around the use of regulated electronic data, records, and signatures.

Conclusion

An effective and well-maintained framework of administrative safeguards and technical controls can "remove temptation" when it comes to falsifying data. The controls can eliminate obvious opportunities for misdeeds and encourage correct use of the system. It is acknowledged, however, that intelligent, skilled people may well be capable of circumventing even sophisticated controls. "Big Brother Is Watching" examines the review processes designed to monitor for evidence of wrongdoing and discusses training approaches to reinforce awareness of data integrity in a GxP environment. ■

Charlie Wakeham and Thomas Haag

How Good Is Your Data?

New methods can increase data integrity in the lab

Chances are the integrity of your data is at risk.

Surprised? Data-intensive science is becoming far more mainstream in daily laboratory operations, and the laboratory has also become a strategic source of scientific evidence to support daily manufacturing and research operations in almost all pharmaceutical operations. Yet in 2013 the US Food and Drug Administration (FDA) reported that laboratory processes and deficiencies associated with laboratory controls are among its top three regulatory observations. The same report also cited a 50 percent increase in warning letters related to aspects of data integrity.

Data integrity is the assurance that data records are accurate, complete, intact and maintained within their original context, including their relationship to other data records. Ensuring data integrity means protecting original data from accidental or intentional modification, falsification, malicious intent (fraud) or even deletion (data loss).

Data integrity is not a new phenomenon; its basic principles have been described in several ISPE Good Automated Manufacturing Practice (GAMP®)

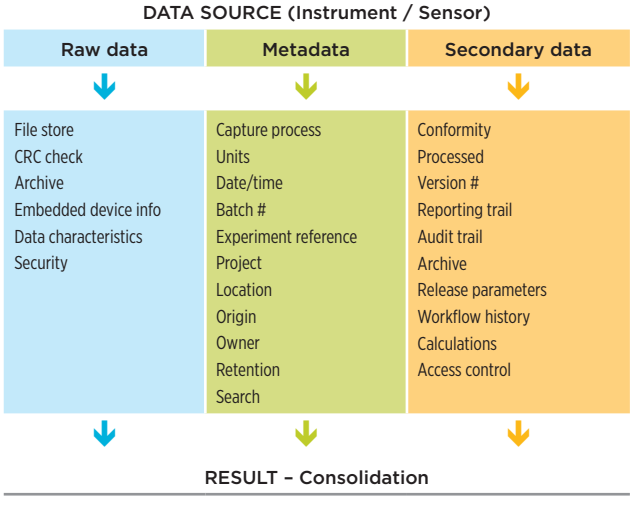
guidelines.[1] This article summarizes some recent regulatory findings and highlights how organizations can reduce data-integrity inconsistencies.

Changing the emphasis

In a data-integrity-focused audit, emphasis shifts from information based solely on technical and scientific contexts to evidence proving that the final analytical results are not false. As regulators increase their focus on data integrity and reliability, auditors are conducting examinations with multiple regulations and standards in mind, including pharmaceutical quality/manufacturing standards,[2] good laboratory practices, GAMP, good clinical practices and application integrity policy in addition to FDA-recognized standards.

According to the FDA, source data should be "attributable, legible, contemporaneous, original and accurate" (ALCOA), and must meet regulatory requirements for record keeping. "ALCOA+" refers to additional terms included by the European Medicines Agency's concept paper on electronic data[3] in clinical trials ("Desired state" table, page 42). It is highly recommended that this concept be used.

Figure 1 Informatics data journey



Informatics data journey

When samples are analyzed, several types of scientific data are created in the laboratory. They can be categorized in three different classes (Figure 1):

Raw data: Created in real time, this is all data on which quality decisions are based.[4] Raw data files can be unstructured, and are often based on a proprietary, vendor-defined format.

Metadata: This "data about the data" is used for cataloging, describing and tagging data resources. Metadata adds basic information, knowledge and meaning, and helps organize electronic resources, provide digital identification, and supports resource archiving and preservation.

Secondary or processed data: This is raw data transformed by scientific methodologies such as spectroscopy, chromatography, etc. To maintain data integrity, altering methods to reprocess will require a secured audit trail functionality, data, and access security.

Data integrity is the assurance that data records are accurate, complete, intact and maintained within their original context

QbD decreases variability

Corrective and preventive action (CAPA) is one of the four elements that support a proactive continuous improvement process within the product life cycle approach. Today's CAPA systems are good, but they focus on a traditional reactive approach. The ICH Q10 guideline[5] recommends a much more proactive approach to make biopharmaceutical manufacturing simple, sustainable, and more robust. Modern laboratory informatics platforms such as a laboratory information management system (LIMS), electronic lab notebook or laboratory execution system will significantly improve the use of previous knowledge created in laboratories. Scale-up information, clinical research, translational medicines and failed reactions during discovery may well contribute to a better understanding of the drug substance than we have anticipated.

Self-documenting processes

Automating metadata capture is very effective for maintaining data integrity and has been adopted by many industries. Scientific laboratories, however, lag behind. More than 75 percent of laboratory experiments or analysis starts with some kind of manual process, such as weighing. The majority of results are still written down on a piece of paper or are retyped into a computer or tablet. Self-documenting processes capture metadata automatically without human interaction, eliminating transcription errors and avoiding the need to retype data.

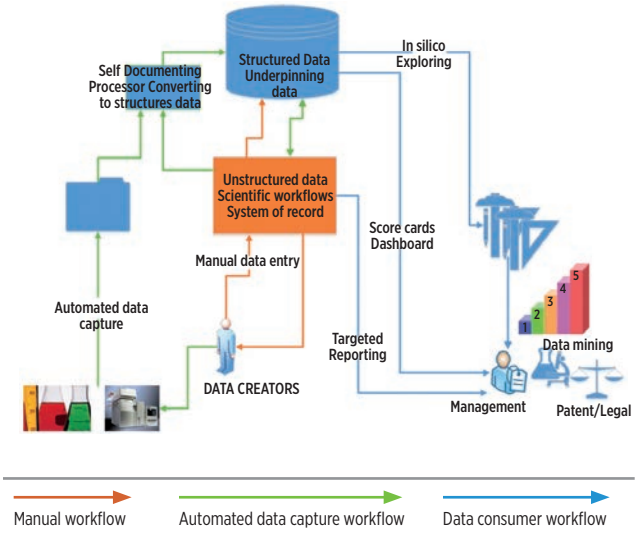
Single point of truth

To avoid data-integrity challenges, it is crucial to have a master copy of the data – a single source of data used across multiple systems, applications and/or processes. To achieve a single point of "truth" and significantly reduce data integrity challenges in the laboratory, we need to understand the key differences between spreadsheets and databases.

Red flags
Alteration of raw, original data and records
Multiple analyses of assay with the same sample **without adequate justification**
Manipulation of a **poorly defined** analytical procedure and associated data analysis in order to obtain passing results
Backdating stability test results to meet the required commitments
Creating acceptable test results **without performing** the test
Using test results from previous batches to **substitute testing** for another batch

Source: FDA

Figure 2 Embed data consumers' compliance requirements – adopt life cycle mindset



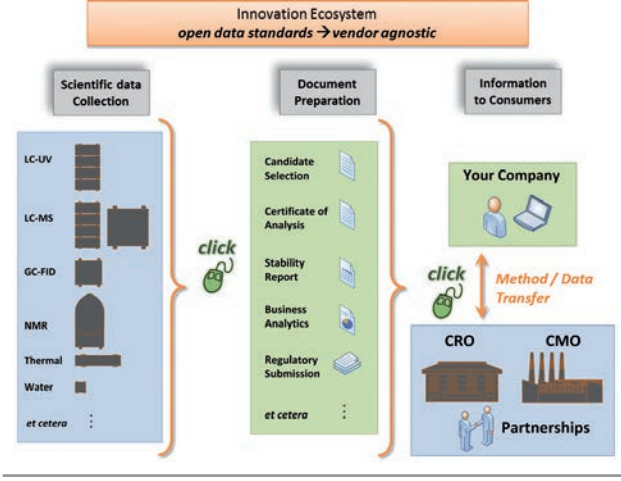
Best practices
Define a **single** point of truth for (meta)data
Reduce, automate, and **simplify** workflow complexities
Stop spreadsheet madness
Implement **self-documenting** processes at the source
Utilize **best-practice** analysis protocols
Adopt and use data **industry standard**s and processes
Embed data consumers (compliance) requirements
Avoid custom software extensions

The perception that a spreadsheet can act as a database is wrong. The primary function of a spreadsheet is to manipulate, calculate and visualize data, whereas the primary function of a database is to store and retrieve data in a structured manner. A spreadsheet has serious drawbacks when used for data storage: It cannot enforce relationships, there are no multi-user capabilities and it offers no data validation or protection against data corruption.

Workflow complexities

Simplifying scientific processes would significantly reduce challenges in data integrity. Although our industry is trying to harmonize scientific processes, other regulated industries are ahead in this field., There are, however, signals that our industry is recognizing the need. For example, balance and titrator suppliers have increased the value of their instruments

Figure 3 Benefits of open data standards



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Simplifying scientific processes would significantly reduce challenges in data integrity

by implementing approved and validated methods and industry best-practice workflows in their firmware. Almost all major suppliers allow methods to be implemented directly into balances and other wet chemistry instruments.

Integrating LIMS processes with enterprise workflows can also significantly reduce the probability of data-integrity issues. Process harmonization will initially increase the validation burden, but the effort will pay off in the long-term, significantly reducing the amount of potential data-integrity failure points and boosting efficiency for laboratory staff and management.

The final example is mapping the entire laboratory workflow and related operations, from sample receipt to release of results, which can consolidate operational workflow. The net effect may significantly reduce validation effort and decrease data integrity risks.

One serious concern is the lack of data standards in the scientific community. Without standards, data integrity will remain challenging and auditing and verifying is an expensive exercise. ■

Peter Boogaard

Big Brother Is Watching

Corporate training can be considered a "human" control for preventing data-integrity problems. Reinforce "right behavior" with ongoing training and monitor effectiveness with review processes.

The foundation for a high level of data integrity is knowing and understanding what data integrity is, the importance it has for a company and the personal role each employee has in protecting it.

Companies should also recognize regulatory authorities' increasing awareness and expectations for data integrity. While this is not new, the focus on and approach to managing and inspecting it are changing. As technologies, electronic systems and business models modernize, the industry must understand how to manage data in a changing environment.

Data-integrity training

Data-integrity problems can affect a company's reputation and profitability. To avoid the problems associated with data-integrity breaches, a "speak up/quality first" culture must be endorsed by company management, as we discussed in "Throwing People into the Works," and data-integrity training should be implemented from senior executives down to the line-operator level.

At the line-operator level, data integrity should be inherent in the process and not compromised to meet delivery timelines. Key data handlers should be formally trained to understand their roles in maintaining the integrity of the data they handle: They are data stewards, responsible for highlighting and escalating any concerns about data and quality regardless of the effect on production quota or deadlines. Training should not only ensure a common understanding of data, data integrity, falsification and data life cycles, but should also emphasize electronic good documentation practices, also referred to as good data management.

Foundational data-integrity training is only part of the bigger data-integrity picture, however. An additional, deeper understanding of technical expectations and requirements, inspection and auditing techniques and process governance are required to establish holistic data integrity for those with data steward or quality assurance (QA) responsibilities.

It is a regulatory expectation that companies understand their data life cycles and how data flows through their processes and systems. Personnel in roles that own these processes and systems (such as business-process and system owners) must understand their responsibilities in maintaining data integrity. These could include:

- Understanding how and where the data is used and its effect on product quality and patient safety
- Knowing what other review processes and data stewards are involved in each data flow, particularly those downstream of the system
- In-depth knowledge of system functionality with the most potential impact on data integrity and how to detect such activity

Personnel in QA and compliance roles must also have an advanced understanding of data-integrity requirements to ensure that these requirements are implemented within the systems and processes, and to support the business-process and system owners.

A corporation's data-integrity training program should be both general and specific. It should target the correct audiences and consider the specific scale of the corporation. In a large pharmaceutical company, high-level training for all employees might be at a foundational level, but the content and focus may be quite different for different functions. (The consequences of a data-integrity issue will be very different for a line operator compared to the operations director, for example.) This training approach might be ineffective for small and/or startup companies, however. In those cases it might be more effective to roll out both foundational and detailed training simultaneously.

Training on the general principles of data integrity could be complemented by more detailed, contextual training appropriate for data stewards who play a direct role in data handling. The specific training provided for such persons (including quality and compliance personnel) must extend beyond

People might cause data-integrity problems, but they are also superior to machines when it comes to detecting them

the general requirements and definitions of data integrity. This role-based training should focus on critical thinking and auditing techniques and could include specific-use cases related to the roles. Data-integrity training for laboratory auditors and process owners, for example, might include a comprehensive review of US Food and Drug Administration (FDA) warning letters that describe data-integrity observations in laboratory settings and practical exercises around examining audit trails.

Review processes

People might cause data-integrity problems, but they are also superior to machines when it comes to detecting integrity issues. Software applications can generate an audit trail, but only a human can decide "Was that integration parameter change a scientifically valid one?" For this reason, review processes remain in the human domain. Review processes can be discrete or continuous, one-off or repeated, and scheduled or unscheduled. In the sections below, different types of review processes and their timing are discussed.

Result review

Result review is defined here as a review of individual results, or sets of results, that is done prior to making the accept/reject decision about the product or data quality. To make that decision effectively, it is essential that the result review:

- Compares the result against specifications/limits
- Evaluates the completeness and correctness of the metadata supporting the result
- Determines the accuracy and integrity of any manually entered values
- Reviews any decisions or actions taken
- Understands any manual adjustment or alteration of the data or metadata
- Investigates any changes to the method versions used in the creation of the result
- Assesses conformity to sound scientific practice and documented procedures

Where there is a data audit trail that is easily accessible and permanently associated with the result, a review is likely to be the most effective route to assessing the integrity of the data.

The MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015[1] states that:

> *Audit trail review should be part of the routine data review/approval process, usually performed by the operational area which has generated the data (e.g., laboratory).*

A data audit trail review should be conducted by someone who really understands the business process supported by the system and therefore understands the impact of the actions recorded in the data audit trail.

Result review should involve increased rigor of focus for results that involve manual adjustment and/or "just passing" results; an application offering the ability to highlight such results automatically provides an additional level of efficiency and assurance and may allow for the review-by-exception approach to data review.

Review by exception

Review by exception applies a risk-based approach to data review. In an environment where hundreds or even thousands of results are generated daily, if an equal amount of time is devoted to reviewing each result, by simple mathematics that amount of time will be very small. For just 100 samples, even spending as little as 2 minutes per result means more than 3 hours' review time daily from each reviewer on those 100 samples – and more than one level of review may be required. Realistically, it is just not possible to review each result and its history effectively in 2 minutes.

Where the process or application permits, review by exception creates alerts to highlight a subset of results requiring additional effort, such as those:

- Within but close to the limit of the specification
- That have been manually integrated
- Where manually entered critical data have been changed
- That have been reprocessed

A detailed result review (as discussed above) is then conducted on this subset of results to understand what has been changed and why in order to decide whether to approve or reject the results. The remainder of the results, where the result is well within specification and no changes or adjustments have been made, can then be approved with a minimal level of review. A company wishing to operate review by exception has the responsibility to determine and document what that minimal level of review is, and to justify it during a regulatory inspection. Some level of validation will be required to document and verify the alert functionality.

Audit trail review

There was much debate within the industry in 2011 when the revised EudraLex Volume 4, Annex 11[2] stated that "audit trails must be regularly reviewed." In reality, audit trail reviews were a regulatory expectation as far back as FDA Warning Letter 06-ATL-09 in 2006,[3] which stated:

> *Although the audit function is discussed in your procedures [for a chromatography data system], there is no specific requirement regarding any review of the audit trails, and your records failed to include documentation that a second person had conducted such a review. In fact, our investigator was told that no such audit had ever been performed. However, a second person must review these audit trails, particularly given the lack of controls for preventing data manipulation. Such an audit may well have detected the data manipulation which was occurring at your facility.*

This has been further reinforced more recently in warning letters 10-NWJ-03 in 2010[4] ("your firm's review of laboratory data does not include a review of an audit trail or revision history to determine if unapproved changes have been made") and 320-12-08 in 2012[5] ("your SOP does not have provisions for any audit trail reviews to ensure that deletions and/or modifications do not occur").

Audit trail review offers a means to detect data-integrity issues but also functions as a deterrent. This is reflected in the National Institute of Standards and Technology Special Publication 800-12: "Introduction to Computer Security":

> *Audit trails are a technical mechanism that help managers maintain individual accountability. By advising users that they are personally accountable for their actions, which are tracked by an audit trail that logs user activities, managers can help promote proper user behavior. Users are less likely to attempt to circumvent security policy if they know that their actions will be recorded in an audit log.*[6]

The last article in this series, "Doing the Right Thing" (p. 60), discusses other behavioral controls that can be combined with the audit trail review to discourage inappropriate activities.

Audit trail mechanisms in clinical and pharmacovigilance systems are the norm in both configurable and nonconfigurable software. Here, audit trails may be regarded as forensic tools to aid investigation when the integrity of a record is questioned; until then, it may be sufficient just to review the audit trail configuration to verify that:

- It is turned on and has not been turned off since the last review
- It is configured to capture the required metadata
- Ability to change the audit trail configuration (including system clock) is subject to the proper segregation of duties

Reviews of system audit trails and logbooks are a more pressing concern in laboratory environments and manufacturing sites, however, where the sophistication of the interfacing systems can limit the ease of transmission between them. Suggestions of what to look for within the system audit trail (as distinct from the data audit trail) are discussed in "Doing the Right Thing."

Audit trail review offers a means to detect data-integrity issues but also functions as a deterrent

Periodic review

During the system's periodic review, the following could be evaluated within the audit trail as part of monitoring human behavior and the effectiveness of the technical controls:

- Changes to system configuration that could impact data integrity controls
- Data deletion: What was deleted and why? If data was deleted as part of an archiving process, verify that the archived data is still accessible
- Account disabling due to successive failed logons: Look for repeat offenders and any timing patterns

Such a review process may only be practical in a system where the audit trail can be filtered. The practicalities and benefits of audit trail reviews are examined in the 2015 article by Perez et al., "A Risk-Based Approach to Audit Trails,"[7] and will not be duplicated in this discussion.

Personnel records and system-administrator logs can be reviewed for ongoing assurance of data integrity by:

- Checking the active user account list to ensure that only current personnel retain access to the system
- Confirming via training records that all active personnel are adequately trained to operate the system
- Ensuring that system/database backups are happening on the defined schedule, the integrity of the backup is verified and trial restoration of the system occurs periodically in a documented manner

Other periodic activities involve the review of standard operating procedures (SOPs), system records, SOP records, change control and system performance. These are essential for ongoing compliance, but they are out of the scope of this article. Periodic review and SOPs are covered in practical detail in the GAMP® Good Practice Guide *A Risk-Based Approach to Operation of GxP Computerized Systems*.[8]

Periodic review should be performed at a defined interval based on the GxP criticality of the system. Review frequency may be increased where issues have been found in system operation or in previous periodic reviews; similarly, a consistent lack of issues may provide justification to formally document and apply a decreased review frequency.

Data audit

A range of data audit activities can be undertaken as part of the scheduled periodic review process, unscheduled as part of an investigation or even in preparation for a regulatory inspection or customer audit.

One effective exercise could be to conduct a mock inspection of a specific data-handling process, where the entire data flow would be explained as if it were being presented to a regulatory official. This will highlight any

confusion about where the data resides and how it passes from one system to another; it may identify areas of weakness in the system(s).

Another exercise could be to pick a single result and trace it back to the raw data, including any laboratory notebook entries. Verify the data integrity and audit trail at each step and demonstrate that all raw data, paper or electronic, is readily retrievable, fully supports the final result and is consistent with any summary data filed with the regulatory agencies as part of an application for approval.

Repeating the exercise in the opposite direction – to verify that all data has been processed and reported and to confirm that there is no orphan data that could indicate trial injections or other malpractices – is equally important.

Further proactive data audit activities could be based on the regulators' own guidance; the FDA Compliance Program Guidance Manual on preapproval inspections,[9] for example, suggests that inspectors should:

- Review data on finished product stability, dissolution, content uniformity and active pharmaceutical ingredient impurity
- Determine if data was not submitted to the application that should have been
- Look for invalidated out-of-specification results and assess whether it was correct to invalidate them
- Seek out inconsistencies in manufacturing documentation, such as identification of actual equipment used

Review process documentation

Within regulated industries, simply completing an action is not sufficient; there must be some documented evidence of when it was completed and by whom. The MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015 requires that:

> *There should be evidence available to confirm that review of the relevant audit trails have taken place. When designing a system for review of audit trails, this may be limited to those with GMP relevance (e.g., relating to data creation, processing, modification, and deletion).*[1]

Reviewing audit trail entries associated with results (i.e., data audit trail) may be governed by a Review of GxP Data SOP and documented by some statement along the lines of "By approving this report I certify that I have reviewed the data, metadata, manually entered values and the audit trail records associated with this data, in accordance with Review SOP XXX." This statement could be included in the signature process for the electronic record and be visible on the printed and displayed report.

The MHRA guidance goes on to state:

> *QA should also review a sample of relevant audit trails, raw data, and metadata as part of self-inspection to ensure ongoing compliance with the data governance policy/procedures.*[1]

Data-integrity problems can affect a company's reputation and profitability

Such a review may occur during the periodic review or be triggered as part of an investigation into a data integrity noncompliance. The issue around reviewing system audit trails – those that capture all logon/logoff activities, system-configuration changes, etc. – is really about scale, and there are implications to be considered for a sampling-based approach to audit trail review (especially where filtering is not available to focus on GxP critical entries. With known system implementations of up to 2,000 users in a global organization, the quantity of entries in an audit trail can dwarf any human effort to review them. Again, this is dealt with more fully in Perez et al.; the point here is whatever the approach – filtered, sampled, or reviewed only as part of an investigation – the approach, the justification for the approach and the completed review process should be formally documented in a manner likely to be acceptable to a regulator.

Conclusion

Happily, the Big Brother state detailed with horrifying clarity in George Orwell's book *1984* did not come to pass. For ensuring data integrity, however, some of the book's concepts of retraining and monitoring are essential, although thankfully at a less drastic level. There is clear regulatory evidence that ongoing monitoring of technical controls via review processes is required to demonstrate that data integrity has been evaluated, achieved and protected. ■

Charlie Wakeham and Thomas Haag

Doing the Right Thing

Tools and techniques encourage positive responses

Good behaviors can promote and encourage integrity within a company, but negative behaviors and measurements can damage integrity. One example of a damaging behavior is a company attempting to save costs by not buying enough user licenses for an application, thus forcing user-account sharing. As a result, system activity cannot be reliably and independently attributed to a single individual.

Poorly conducted investigations often blame the human factor or find no assignable cause. A change to standard operating procedures (SOPs) may be proposed as a preventive action. In reality, human behavioral controls such as SOPs can easily be ignored, and the process may be adversely affected, giving rise to data integrity issues. These behavioral fails can only be detected later, after the harm has occurred. This preventive action will therefore likely fail to guard against similar issues in the future.

Outside of the pharmaceutical industry, falsification and fraud occurred in respected financial institutions such as JP Morgan (2003) and Credit Suisse Group (2007–2008). The article "Compliance Alone Won't Make Your Company Safe"[1] discusses the premise that good people can still behave inappropriately and that creating a "policeman culture" of enforcing rules and procedures may discourage generally honest employees from admitting that they wandered away from the straight and narrow or inadvertently made a mistake.

Personnel involved in pharmaceutical manufacture, development, testing, etc., typically have a strong scientific or engineering background: "If it can be calculated, measured, or analyzed, then it is tangible and will be accepted." In this fact-based environment, the complex interaction of soft skills needed to direct people's behavior and responses is easily overlooked to the detriment

Any person making critical product-quality decisions must be free from commercial, marketing or financial pressure that could influence his or her decision

of data integrity. A properly applied combination of leadership direction, motivation, metrics and independent controls can be used to direct and reward the right behaviors, fostering data integrity.

Behaviors

Improvisation

In "Throwing People into the Works," improvisation was mentioned briefly in the context of small or startup companies, but improvisation is a mindset that can be widespread in any company or country where insufficient or inappropriate resources are a way of life.

Improvisation is the ability to work around a lack of people or absent or damaged equipment, and even a lack of training, to "get the job done somehow." The downside to a culture of improvisation is that SOPs or other controls will not be followed, and the integrity of any data produced by such means is therefore highly suspect. This reinforces yet again the importance of management provision for sufficient and suitable resources.

The scientific and engineering mindset of people in skilled professions can also create a culture in which any rule or impediment will be seen as a challenge to be gotten around: "Ah, but in that case I could ... " and this is more difficult to mitigate. "Big Brother Is Watching" emphasized the importance of training to reinforce the "right behavior" as one defense against this puzzle-solving mentality, but the "six sources of influence" discussed later in this article may prove more effective overall compared to training alone.

Impartiality

Any person making critical product-quality decisions must be free from commercial, marketing or financial pressure that could influence his or her decision.

For example, a quality control (QC) lab supervisor who reports to the operations department may be at risk of undue pressure to pass batches even if he or she has valid concerns about the test results. Good practice would recommend reporting through the independent quality assurance department.

Falsification for profit

Greed has been the motivator in a number of high-profile company fraud cases in recent years. Corporate-scale data-integrity fraud has included such extremes as performing bioequivalence testing on the branded product but presenting the results as those for the generic version; more common and widespread fraudulent activities may include:

- Unofficial testing to see if the sample will pass before running the "official" sample for the batch record. Some examples are US FDA warning letters 320-14-08,[2] 320-14-01,[3] 320-14-005,[4] and UK MHRA Non-Conformance Report 8913/378537-0004 NCR.[5]
- Concealing, destroying, or overwriting raw data and samples. Some examples are US FDA warning letters 320-14-08,[2] 320-15-07,[11] 320-14-11,[6] and Italian Medicines Agency Non-Conformance Report IT/GMP/NCR/INT/1-2014.[7]
- Renaming or misrepresenting results from a passing batch in support of other batches: US FDA Warning Letter 320-15-09[8] and the Trade and Industry Inspection Agency of State of Lower Saxony – Oldenburg, Germany, DE-MI-04 2011029 are examples.
- Manually manipulating chromatography integrations to alter the result: US FDA Warning Letter 320-15-04[9] is an example

The extent of falsification achievable by an individual depends on a combination of their motivation and their seniority within the organization, counteracted by the efficacy of administrative and technical controls to prevent such falsification (see Table A).

The extent and impact of falsification is greatly magnified if collusion is involved. A senior QC manager has the power to direct his or her staff to collude for falsification, resulting in systemic fraud within the laboratory, whereas an individual analyst can only try to persuade a coworker to try to falsify data and inherently runs the risk of being reported to management for inappropriate behavior. Geographic and corporate cultures may also influence the ease with which collusion may occur; strongly hierarchical cultures may be more susceptible to collusion instigated at a senior level as these cultures inherently discourage any disagreement with authority figures. (Cultural considerations are discussed in more detail in the first article in this series.)

Understanding effective risk controls

In formal risk methodology,[12] there are the following risk treatment options:

Avoid: Stop the activity or do it in a different way that eliminates the risk

Reduce (also termed "mitigate"): Adopt measures to reduce the likelihood of occurrence or reduce the severity of harm or increase the probability of detection

Retain: Accept a low level of residual risk

Transfer: Transfer the risk creating activity (more practical for physical risk than data-integrity risk)

Table A: Potential for falsification as a function of motivation and seniority

Motivation	Lab technician	Operations director
Greed	Data integrity issues may now have become quite sophisticated within the lab domain: ■ Variety of saved test methods used for a range of known scenarios to effect the desired result ■ Pool of "good projects" from which data is copied in place of new testing Falsification may be routinely happening to maximize lab or technician throughput in exchange for financial incentives or career advancement.	Data integrity issues may constitute systemic, corporate fraud, where: ■ All raw materials are used and all finished goods are released, irrespective of quality ■ The company benefits from significant savings on staff and equipment achieved through reduced quality and development testing In this scenario, the finished goods may be highly unsafe and ineffective, but all focus is on operating profits and bonuses.
Fear	Data integrity issues here are likely to be on an individual sample or test level, and may take the form of: ■ Test method or parameters altered to influence the result ■ Test samples destroyed ■ Test samples substituted to ensure a passing result Falsification is occurring when samples fail, because the management culture does not promote honesty and cares only about passing results.	Data integrity issues may be focused around production yield, such as: ■ Pressuring the quality department to release borderline product ■ Understating rejected batches or having them mixed with passing batches during rework Falsification is aimed at hiding poor performance from the shareholders, and is endemic throughout the production environment.

Seniority

Within the pharmaceutical industry, it is common to immediately try to control the probability of occurrence as the risk treatment, most often by implementing people-based controls. As discussed throughout this series, however, people are the wild card in data integrity – the major source of variation – so it seems illogical to rely on them to be the controls.

Effective risk controls:

- Do not rely solely on people's actions
- Are built-in
- Are easy to comply with
- Are well communicated and understood
- Are supported and enforced by management
- Have backups/contingencies
- Make errors/failures clearly visible
- Fail over to a safety condition

Controls that rely on people to consistently perform an action the right way out of many possible ways are ineffective. Simply writing an instruction into an SOP may have little or no long-term effect on the probability that someone will do something the wrong way. Single training events may affect the probability of correct performance in the short term after the training, but will have minimal influence in the long term as people move within the organization and old habits reassert themselves.

Six sources of influence

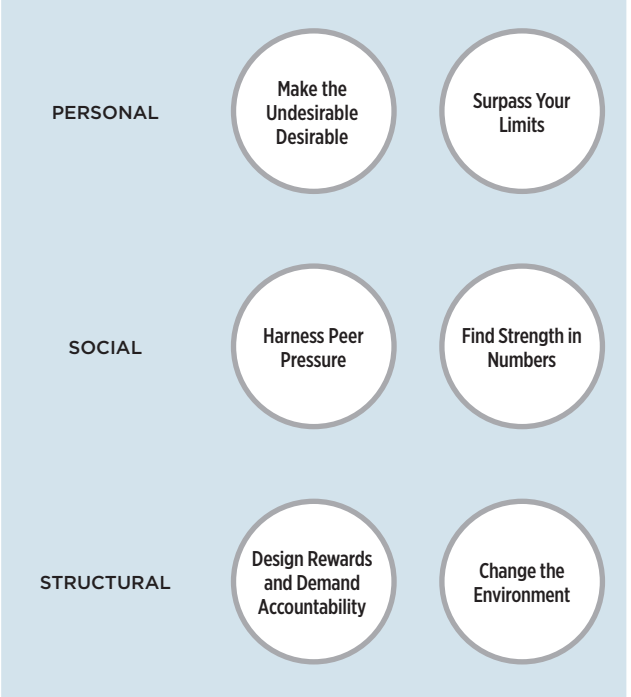
In *Influencer*,[10] Joseph Grenny and his colleagues propose a model for influencing behavior and attitudes. In the example below, this model has been applied to data integrity in a hypothetical QC laboratory (see Figure 1).

Make the undesirable desirable

This first step is about helping employees find the personal motivation to care about data integrity. Analysts testing many samples daily and under pressure to deliver throughput may easily lose sight of what the sample means: It's not a tick in a box or a statistic; it's vital information about whether a lifesaving medication will work.

Connecting the behavior to an outcome has a powerful impact. If possible, find out whose neighbor, child or parent relies on that medication and (with permission) use that person (our "real-life patient") to make it personal for all the lab staff. Spin the story. Add a picture and some background about the real-life patient: What are his or her hobbies? Does he or she have kids? Pets? Now, finding a failing sample is not a blot on the analyst's day; it's an important victory keeping this real person safe and healthy so he or she can continue sailing/studying environmental science at college/playing with his or her grandchildren.

Figure 1: Grenny's six sources of influence



The extent and impact of falsification is greatly magnified if collusion is involved

This type of motivation allows the analyst to find intrinsic satisfaction in the right behavior; his or her diligence during testing has safeguarded the health of a patient who is personally connected to him or her.

Surpass your limits

It's easy to fall into having "just enough" knowledge to get by in a job. In this model, analysts are encouraged to spend time each day – as little as 10 minutes can have an effect – honing their chromatographic and application knowledge. Analysts can improve their understanding of integration, consider ways to improve sample preparation, or begin defining custom field calculations that could be used to eliminate calculation errors and the need to copy data into a spreadsheet for analysis.

It is essential that the lab manager provide strong support for this kind of self-improvement by helping analysts set short-term goals to measure the improvement and providing praise for the achievement.

Harness peer pressure

Here, the social aspects begin to affect behavior. Within the lab, there is likely to be one or more analysts or scientists to whom the others turn for advice and assistance. This person is the opinion leader, and he or she is vital to the success of the data-integrity initiative.

A message about data integrity, written by senior management, distributed throughout the company and read aloud by the lab manager is just a string of words falling on uninterested ears.

A respected colleague (the opinion leader) who really appreciates why data integrity is important and will set the example in the lab makes data integrity part of the lab environment. Once data integrity is embraced as the way to work, then peer pressure will keep everyone focused on integrity.

Every work area has the undiscussable. This is the "elephant in the room" – the topic that nobody is brave enough to raise. An example may be a dosage of a particular product that is always close to the impurity limit because it's made on an older and somewhat outdated manufacturing line. Whatever the topic, bring it into the open. Discuss it at the daily standup or weekly meeting. Acknowledge the problem, and share the experiences (and the frustration) of borderline sample results. Reinforce the need to scrupulously follow the sample preparation SOP, keep to the current method version, and never, ever just "tweak" the integration to turn that "just failed" into "close enough to pass." Making the problem open and shared takes away the temptation to nudge the sample into passing.

Strength in numbers

Research studies have proven repeatedly that groups perform significantly better than individuals. In the new culture of openness within the lab, it

is now time to make data integrity a collective rather than individual responsibility. Analysts should be encouraged to work together to identify potential risks to data integrity and propose mitigations to those risks.

Teams of two or more can be formed to conduct data-integrity reviews (such as data audits, as discussed in "Big Brother Is Watching") periodically as an internal audit or on the first batch of a new product line. After all, who knows better where the data-integrity "holes" may hide than an analyst?

Increasing knowledge and confidence around data integrity will, in turn, lead to continual improvement in the overall integrity of the laboratory data.

Design rewards and demand accountability

It is important to note that the reward step happens late in the influencing process and not as the prime motivator as so many corporate leaders believe.

The dangers of inappropriately selected metrics were discussed briefly at the beginning of this series. The aim is to reward the right behavior rather than rewarding results. (Remember the samples analyzed per time period and all the inherent pitfalls associated with that metric?) Rewards should be small and symbolic rather than substantial enough to fuel a greed motivation.

Our team of analysts conducting the data audits who find a recurring flaw in the sample receipt register could get rewarded with, for example, an extended break to enjoy a round of specialty coffees bought by the company. Remember: Praise and recognition from their peers and their manager can mean just as much as the reward itself.

Good behaviors can promote and encourage integrity within a company, but negative behaviors and measurements can damage integrity

Change the environment

Earlier in this article, we looked at effective controls and found those to be controls that were built in and easy to follow. This influence model makes the same point: If the system is set up to make it easy to do the right thing, then people will do the right thing.

Creating approved methods for instrument control, data processing, and reporting all combine to make tasks quick and simple for the analyst – while ensuring that he or she is doing them correctly. Creating custom field calculations to eliminate calculation errors and getting sample weights read into the system electronically to eliminate transcription errors significantly strengthen data integrity by not only reducing the probability of error but also removing the simplest means for an analyst to falsify the sample weight or the concentration of active ingredient.

Using a combination of software applications, hardware interfaces and workflow design, it is possible to create an environment that, by its very nature, drives data integrity.

Conclusion

Over the course of this series, we have looked at leadership and culture; physical, administrative, and technical controls; training and monitoring; and now behaviors and positive influences. In recognizing the complexity of the problem of protecting data integrity, we have come to understand that there cannot be a single one-size-fits-all solution. Integrity is threatened by both human error and human greed, but greed will be more damaging to data integrity and will affect a greater number of records. We saw that the US FDA does not make allowances for how the data-integrity issues occur – whether by genuine error or deliberate falsification; it only cares that the issues have occurred and may impact product quality and patient safety. We looked at the audit findings from regulators around the world, inspecting to their own national regulations, and saw that they are focusing on and identifying the same data-integrity concerns, such as unofficial testing and failure to keep raw data.

This harmonization of inspection approach among regulators provides the common goal for all regulated companies, but ultimately it is the people factor within those companies that determines whether the goal is attained; all too often, data integrity is not consistently achieved and maintained. It will take a combination of making falsification so utterly unacceptable as to be unthinkable and increasing the probability of detection to the extent that it's simply not even worth it to restore confidence in data integrity across our industry. ■

Charlie Wakeham and Thomas Haag

A Special Interest Group (SIG) for Data Integrity

Launched in January 2014, the sponsor of the Data Integrity GAMP SIG, Mike Rutherford, had signed up some 50 members before the announcement at ISPE's 2013 Annual Meeting. The group now boasts more than 100 members, a sign, says Mike, of the topic's importance in the pharmaceutical manufacturing industry. "The group is working with Board member Chris Reid to make the SIG and ISPE-centric activity that reaches beyond GAMP."

In 2014, the SIG set four overarching objectives:

1. Understand existing and future regulatory expectations, guidance and enforcement strategies.
2. Identify and propose appropriate data integrity control strategies for critical data and key quality attributes throughout the life cycle that also address data management from the operational through to the record retention phase.
3. Provide tools to align requirements with a product's life cycle.
4. Provide a pragmatic and tangible framework for managing data integrity risks across the industry.

In the two years since its formation the SIG has generated presentations on how to identify and mitigate data integrity risk; identified which global GxP regulations and guidances are linked to data integrity; and developed a prototype tool with hundreds of these references which, while available only to GAMP SIG members today, may be rolled out to the broader membership in the future.

Goals for 2016 are three-fold:

1. Develop a GAMP guide on electronic records and data integrity that will include current thinking on governance. A session will take place at the 2016 Annual Meeting in Atlanta, this September, with the guide targeted for publication by Q1 2017.
2. Develop a GPG on how to apply the GAMP guide, as well as one that focuses on pragmatic solutions.
3. Create content for ISPE conferences, such as the Europe Annual Conference just held in Frankfurt, Germany, the 2016 Annual Meeting, and the upcoming GAMP regional conference in Copenhagen. They are also supporting the development of a Data Integrity Workshop at the ISPE/FDA GMP Conference in June of this year.

As a topic that is the focus of regulatory agencies around the world, data integrity "is something you absolutely need to be thinking," says Mike. ISPE is devoting much effort to it and solutions will continue to evolve for this business problem.

"What's important for members to understand is they needn't panic." ■

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About the authors

Peter Boogaard is founder of Industrial Lab Automation. His company provides services to address harmonization, integration, and consolidation of business to help clients enable cross-functional collaboration among research, development, quality assurance, and manufacturing corporations. Peter has extensive experience in laboratory management. He has published papers in international magazines and contributes to several industry advisory boards, is an active member of ISPE, and organizes the annual Paperless Lab Academy congress (www.paperlesslabacademy.com). A Dutch citizen, Peter studied analytical chemistry in Delft, Netherlands.

Thomas Haag has been working at Novartis for more than 13 years in the areas of Clinical Data Management, Systems Validation, and Quality Assurance. He is an experienced project manager, business analyst, and quality assurance engineer with a focus on computerized systems validation and data integrity. Haag, a trained artist, started his career in commercial industrial product development and eventually moved into information technology, application training, and software project management. He lives at the New Jersey Shore with his family and his golden retriever, Alice. He enjoys snowboarding, gardening, and good conversation.

Christopher Reid is CEO of Integrity Solutions Limited, a provider of quality and compliance solutions to regulated companies globally with locations in the UK, Tokyo, and North Carolina. His responsibilities include all aspects of business management, financial management, resourcing, and product/service development. Chris currently works with leading global organisations developing and implementing quality and compliance solutions including defining and implementing strategic quality initiatives, implementing corporate quality policies and standards, skills development, and system validation. Chris is a member of ISPE's International Board of Directors, European Forum, European Leadership Team, Co-Chair of the Knowledge Network Council, and member of the Global and European GAMP® Steering Committees. He has contributed to the development of GAMP 5 and a variety of GAMP® Good Practice Guides. Chris holds a BSc (Hons) in Computing Science from Staffordshire University.

Michael Rutherford is a Consultant – Business Systems Support – Laboratory and Quality Systems, Medicines Development Unit, at Eli Lilly and Company. Mike is a recognized global technical expert in ER/ES, data integrity, computer systems validation and quality, laboratory automation, and laboratory informatics. For the last five years he has been responsible for the technical, administrative, and operational leadership for multiple laboratory and quality related computerized systems, as well as information protection projects across the Lilly MDU. Mike has been involved with ISPE and GAMP leadership since 2003 and currently serves as the Global Chair of the GAMP COP, the past Chair of the GAMP Americas COP, and the sponsor of numerous GAMP Special Interest Groups, including those on data integrity and the cloud. He was the recipient of the 2014 ISPE Max Seales Yonker Member of the Year Award

Charlie Wakeham has more than 15 years' industry experience developing and validating computerized systems for regulated production and laboratory environments. An active GAMP® member for more than a decade, she has contributed to several Good Practice Guides and many ISPE conferences. She is a Regional CSV Consultant at Waters Corporation, where she works directly with customers in the Asia–Pacific region to provide efficient and practical assistance with the validation of the company's laboratory Informatics computerized systems.

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Enhancement of Solubility and Stability of Itraconazole by Formation of Solid Crystal Suspensions Using Hot Melt Extrusion

Jaywant Pawar, Vinod S. Gokarna, Vineeta D. Deshpande and Purnima D. Amin

This article presents research that was the winning entry in the student poster competition at the ISPE 2015 Europe Annual Conference, 4–7 May 2015 in Frankfurt, Germany.

Hot melt extrusion (HME) is a fusion processing technique applied to produce immediate,[1–2] controlled[3] and sustained[4–5] release dosage forms using wide ranges of polymers. The number of HME-based patents has been growing in the past decades as the technique is being widely explored for several poorly soluble drugs.

HME technology offers numerous advantages, like fewer processing steps, reduced process time, continuous operation and green process. HME has been established as a robust means of producing amorphous solid dispersions with improved dissolution rate. Nevertheless, HME has also been used for formulation of cocrystals resulting into enhanced solubility.[6–7]

The present research work focuses on formulation of intimate eutectic mixture of a highly water-soluble crystalline carrier with a crystalline drug resulting in a stable formulation with considerably fast dissolution rate as compared to that of the plain drug. The resulting formulation in known as "solid crystal suspension" (SCS). SCS is made up of highly water-soluble crystalline carrier with a crystalline drug. The approach is different from the traditional solid dispersion made by HME.[8] Out of several crystalline carrier matrices available, we explore xylitol based on its unique crystallization behavior.[9] Itraconazole (ITRA), a biopharmaceutics classification system (BCS) class II drug, has been used as a model drug for the present approach.

Objective

The objective of this study was to enhance the solubility and stability of ITRA by producing ITRA-xylitol SCS using hot melt extrusion.

Materials

Itraconazole and xylitol

Experimental design

The SCS was prepared using hot melt extrusion via a corotating twin screw. Accurately weighed ITRA/xylitol in a 1:5 and 1:9 ratio was premixed in a glass mortar and pestle for 2 minutes. The ITRA/xylitol powder blend was manually fed into the extruder maintained at a temperature of 95–96°C (melting point of xylitol) and screw speed of 150–160 rpm and extruded through a 1-mm diameter die.[10] The brittle extrudates formed by xylitol crystallization were placed in a glass mortar and pestle and further passed through 60-mesh sieve to yield a final powder (i.e., SCS), which was further analyzed.

The SCS was evaluated for saturation solubility, and was also evaluated using dissolution studies, contact angle study, differential scanning calorimeter (DSC), hot stage microscopy (HSM), x-ray diffraction (XRD), and Fourier transform infrared spectroscopy.

Results and discussion

Phase solubility study was performed according to the method described by Higuchi and Connors.[11] The solubility study in water and 0.1N HCl showed increase in drug solubility of SCS to 104.35 µg/ml compared to 4.81µg/ml of pure ITRA in 0.1N HCl, which can be attributed to improved wettability of the formulation.

ITRA SCS 10% and 50% by HME showed 4.4 and 4.2 y-fold increase in dissolution rate compared to pure ITRA (Figure 1). The increase in drug release can be attributed to short-range intermolecular interactions in the SCS of ITRA with xylitol giving improved dissolution rate.

Contact angle is a measure of noncovalent forces between ultrapure water and surface of films, wetting behavior of powder samples. ITRA showed highest contact angle value of 87 degrees, indicating extreme hydrophobicity (see Table A).

Figure 1: Dissolution profile of ITRA SCS

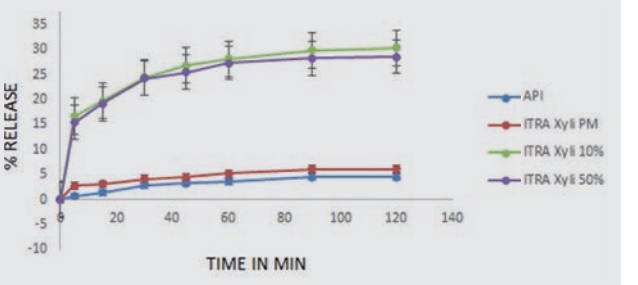


Table A Contact angle values

Substance	Contact angles, degrees 3 SD
ITRA	87 ± 0.36
Xylitol	20 ± 0.87
ITRA-xylitol 10% SCS	*28 ± 0.61*
ITRA-xylitol 50% SCS	35 ± 0.44

Figure 2: FTIR spectra

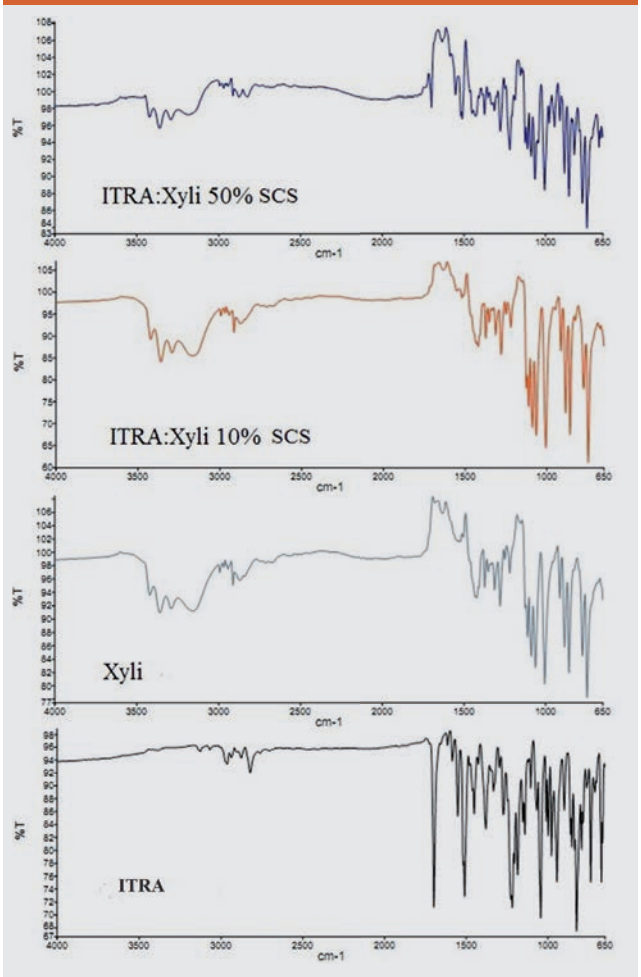


Figure 3: XRD diffractogram

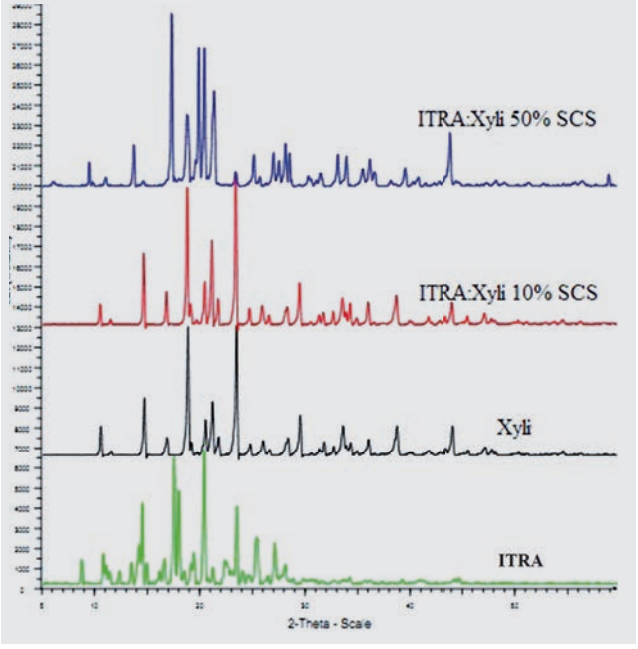
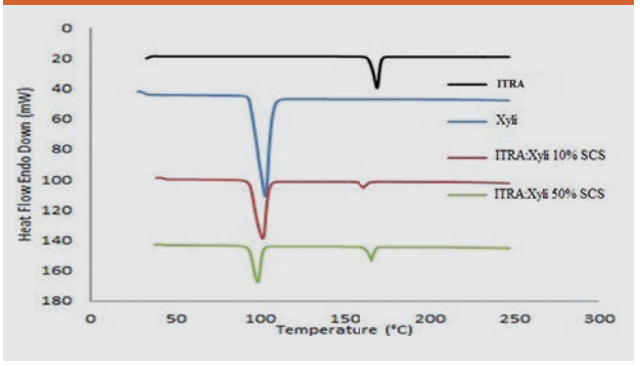


Figure 4: DSC thermogram



Infrared spectroscopy has been widely used to investigate drug–polymer interactions in cocrystal systems. The carbonyl group favorably forms H bonding and intermolecular interactions. For SCS (Figure 2), the –OH stretching bands were found to be broadened and the intensity of the bands decreased to minimal, indicating interaction between the H+ donor groups of ITRA and the H+ recipient group of xylitol.

The XRD of ITRA consists of sharp signals at two theta values (8.73, 10.75. 12.28, 14.46, 17.96, 20.36 23.47, 25.44 and 28.07), indicating its crystalline nature (Figure 3). All signals in the diffraction pattern of the extrudate are found to be consistent with the diffraction pattern of xylitol and ITRA (see Figure 3). This indicates that both the ITRA and xylitol are present in crystalline form in the final extrudate.

The DSC thermogram of pure ITRA showed a single sharp melting endothermic peak at 159.12° C. Xylitol exhibited a single sharp melting endotherm at 105.68° C as shown in Figure 4. The DSC endotherm of SCS provide additional information showing the two components in the formulation exist as a separate crystalline phases. The DSC peaks of 10% and 50% SCS were found to show a small and reduced melting peak for ITRA.

Xylitol was found to be a better crystalline carrier for ITRA resulting in formation of SCS.

HSM studies were conducted to visually determine the thermal transitions and the extent of drug melting within the xylitol at different stages of heating. The ITRA and xylitol shows complete melting at 177° C and 97.4° C in HSM. In case of ITRA 50% SCS HSM, study was found to show complete melting at 170° C temperature (see Figure 5).

Conclusion

The formulation of SCS by HME technology significantly increased the solubility of ITRA. Use of xylitol as a small –molecular-weight matrix-forming carrier showed a fast drug release for poorly water-soluble ITRA. This technique/process provided an alternative approach for enhancing solubility of poorly water-soluble drugs using xylitol as a primary matrix carrier. The obtained extrudates could be further formulated into different dosage forms such as tablets and capsules. ■

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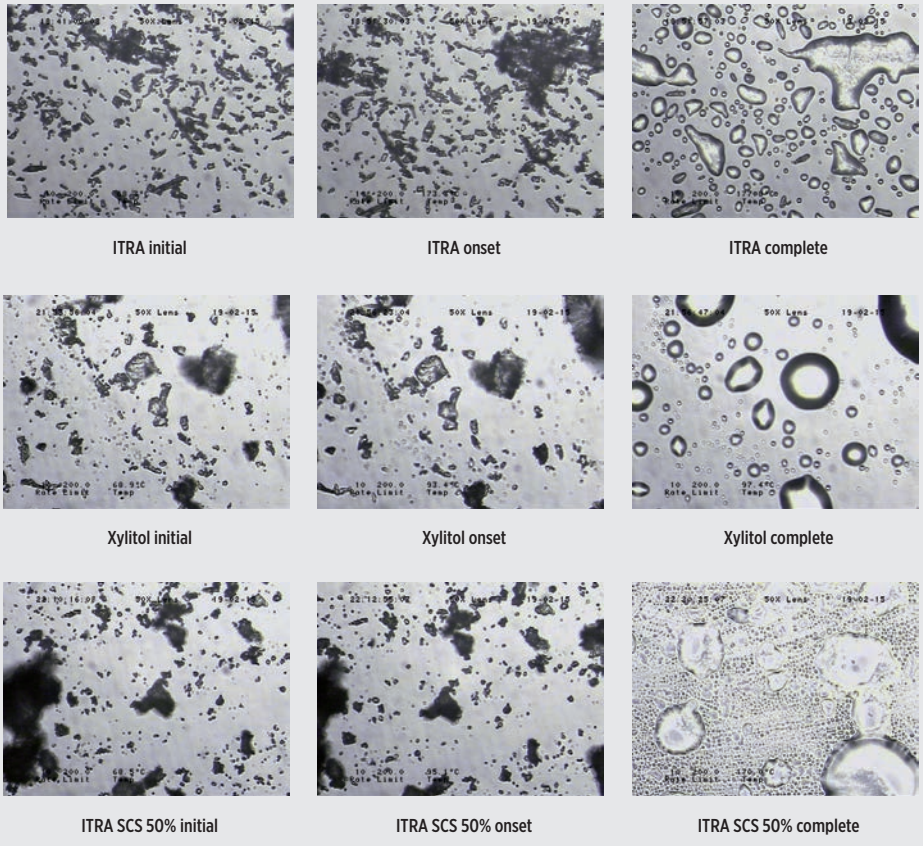
Figure 5: HSM images of ITRA, xylitol and 50% SCS



ITRA initial | ITRA onset | ITRA complete

Xylitol initial | Xylitol onset | Xylitol complete

ITRA SCS 50% initial | ITRA SCS 50% onset | ITRA SCS 50% complete

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About the authors

Jaywant N. Pawar earned his M Pharm degree at Pune University and graduated with first class in the year 2012. Currently he is pursuing his PhD degree at Institute of Chemical Technology, Mumbai, India. His research interests include crystal engineering of pharmaceutical APIs, fabrication and modification of pharmaceutical excipients and their use in drug-delivery systems, amino acids in drug delivery systems, novel drug delivery systems using hot melt extrusion and spray-drying technologies with prime aim of enhancing the solubility as well as bioavailability of poorly water soluble drugs. He is an active member of the American Association of Pharmaceutical Scientists and ISPE. He can be contacted by email at jaywantpawar.ict@gmail.com.

Vinod Gokarnais a doctoral candidate in the department of physics at Institute of Chemical Technology, Mumbai, India. His thesis research is mainly on study of polymer clay nanocomposites. His research areas are structure property relationships of polymer composites and nanocomposites, crystallization kinetics of polymer nanocomposites and hot-melt extrusion of pharmaceutical drugs and targeted drug delivery system. He received his MSc degree from the University of Mumbai. He can be contacted by email py07vs.gokarna@pg.ictmumbai.edu.

Vineeta Dinesh Deshpande, PhD, is an Associate Professor and Head Department of Physics at the Institute of Chemical Technology, in Mumbai, India. She received her undergraduate degree from Shivaji University, Kolhapur, and MPhil and PhD degrees in Physics from Delhi University. She works on structure property relationships of polymer composites and nanocomposites, crystallization kinetics of polymer/polymer composites, bioenhancement of nanodrugs by melt extrusion, solar thermal applications and color assessment of the samples. She can be contacted by email at vd.deshpande@ictmumbai.edu.in.

Prof Purnima D. Amin is a professor and scientist in the department of pharmaceutical sciences and technology at the Institute of Chemical Technology, Matunga, Mumbai, India. She has more than 27 years of experience in teaching in the pharmaceutics and drug-delivery technology fields. Some of her research interests are hot-melt extrusion in drug delivery, development of innovative industrially viable excipients, exploring novel techniques in solubility enhancement of poorly soluble BCS class II drugs, developing industrially scalable formulations based on crystal engineering and nanotechnology, cosmeceuticals and nutraceuticals are. She can be contacted by email purnima.amin@yahoo.co.in.

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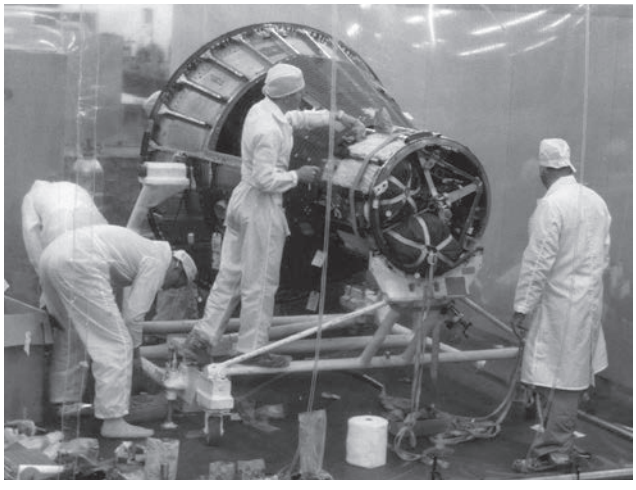
The History of Cleanroom Garments

Jan Eudy

NASA Scientists work on the NASA Curiosity rover. Photo: NASA Goddard Space Flight Center



1960s: Technicians in clean room garments work on Project Mercury spacecraft production at McDonnell Aircraft. Photo: NASA

Clean manufacturing was developed during World War II to improve the quality and reliability of war machinery.

Human sources—equipment, production materials, product and people—are the chief contributors to contamination and compromised integrity in cleanrooms and controlled environments. To control this contamination, equipment is manufactured with components and surfaces that are compatible with the classification of cleanroom in which they are used. Production materials and product may be contained or encapsulated within equipment or packaging. But the number-one control method for preventing human-sourced contamination is the correct selection, donning, wearing and doffing of cleanroom garments designed to encapsulate viable and non-viable particles shed by cleanroom operators.

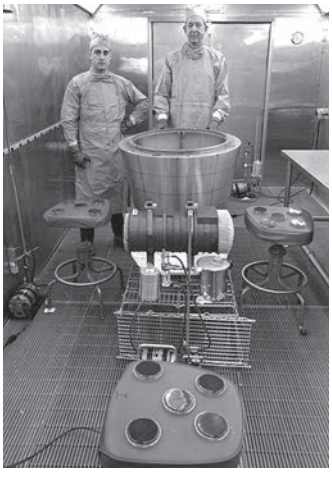
Just as equipment has evolved to be cleanroom compatible, cleanroom garment systems have also evolved to be cleanroom compatible and more comfortable to wear.

Prior to the Willis Whitfield ultra-clean room at Sandia Corporation in the 1960s, clean manufacturing was developed during World War II to improve the quality and reliability of war machinery such as guns, tanks, aircraft and ships. Concurrently, emerging research in biological and chemical warfare by the chemical and pharmaceutical industries also indicated the need for increased contamination control. Employees of these industries began to wear 100% cotton shirts, pants and lab coats on the job to help minimize contamination. At the same time, the importance of contamination control in hospitals was also being realized; soon hospital employees began to wear the same types of cotton clothing.

Editor's note: This article uses terminology appropriate to the era under discussion: "clean room" before 1980, "cleanroom" afterward, except for titles of books and articles.

1960s

This was an exciting decade that saw the development 0f the first clean rooms, filtration and the concept of "laminar flow" (which is actually unidirectional airflow). Laminar flow and the commercial availability of high-efficiency particle air (HEPA) filters significantly reduced the number of particles in the first clean rooms. Particles were still being generated by the clean room operators, however.



1965: A NASA employee and a Sandia National Laboratories employee inspect the sterilization of an interplanetary lander in a Sandia clean room. Photo: Sandia National Laboratories

In March 1967, the Garment and Laundry Committee of the American Association for Contamination Control (A2C2) published "Clean Room Garments and Laundry – A State of the Art Report." The committee consisted of Sy Weisinger as Chairman, with Leon Hertzson, Carl Robinson, Irving Rosen and Thomas Williamson as members. This document states that Federal Standard 209 required that clothing worn in clean rooms be "lint-free."

Additionally, the document states the US Air Force Technical Order No. 00-25-203 required that the garments worn in clean rooms be constructed of a "synthetic fabric with limited linting properties." The document recommended using filament Dacron polyester yarn in the fabric of choice. The two primary fabric weaves were taffeta and herringbone. Generally, taffeta weaves were used for frocks or smocks, surgical style caps and shoe covers, whereas herringbone weaves were used for coveralls. The same Air Force technical order stated:

> *Coveralls and smocks should have no pockets, no pleats, no dust collecting ridges and no raw edges. All seams should be double needled and sewn with 100% Dacron continuous filament thread. Both coverall and smock should have adjustable neck bands and cuffs to allow for tight closure.*

Human sources are the chief contributors to contamination and compromised integrity in cleanrooms and controlled environments.

The A2C2 document recommended that all garments worn in a clean room should be processed in a suitable, environmentally controlled laundry. The document specified water washing and dry cleaning parameters for the garments, as well as packaging specifications. Steam, ethylene oxide (ETO) or dry heat sterilization were recommended for garments worn in pharmaceutical manufacturing.

In 1968, the American Society for Testing and Materials published ASTM F-51, "Standard Test Method for Sizing and Counting Particulate Contaminant In and On Clean Room Garments." It was reapproved in June 1989 and again in 2007, with minor editorial changes. This test method counts particles greater than five micrometers (µm) and fibers microscopically. Clean room industries specified that garments worn in their clean rooms must meet Class A particle cleanliness, which is fewer than 999 particles larger than five µm, and ten fibers per 0.1 square meters of fabric.

In May 1969 the A2C2 Garments and Laundry Committee expanded its original 1967 work to clarify fabric and construction recommendations for clean room garments. Because most clean room garment users had partnered with commercial precision laundries that specialized in laundering the garments, the revised report detailed the requirements for water washing or dry cleaning and packaging. The report also emphasized that "No item of clean room apparel should be issued as received from the manufacturer. It must be laundered first to remove all loose threads and other contaminants possible to adhering to the surface."

1970s

Nonwoven fabrics were developed and disposable garments for clean room use were developed using DuPont's Tyvek, a durable, chemical- and liquid-resistant flash-spun bonded polyolefin formed into an air-impermeable sheet. Because it could also be sterilized, disposable Tyvek garments were worn in pharmaceutical clean rooms.

Calf-high boots were developed because coveralls sometimes did not reach to the shoe covers, allowing particles from inside the coveralls to shed onto the floor. Hoods were developed for clean room operators with long hair, beards and/or moustaches. Kanebo, EV-Guard and Selguard, the first polyester clean room fabrics with carbon yarns to dissipate static electricity, were developed for the semiconductor, microelectronics and aerospace industries.

Workers assemble and test fiber optic systems.
Photo: Steve Jurvetson / Wikimedia Commons / CC- BY-2.0

New drives for notebooks roll off Seagate factory lines
Photo: Robert Scoble / Wikimedia Commons / CC- BY-2.0

AlcatelGowning room with contamination control procedures at Alcatel, London.
Photo: Sam907 / Wikimedia Commons

1980s

In the 1980s, industry leaders and Institution of Environmental Science (IES) members agreed that "cleanroom" should be one word, noting the uniqueness of the filtered, pressurized controlled environments being built throughout the world.

1986: Employee at Sandia National Laboratories is uniformed for work in a cleanroom.
Photo: Sandia National Laboratories

By 1987, the A2C2 Garments and Laundry Committee had been incorporated into the IES. In that same year the committee wrote the tentative recommended practice IES-RP-CC-003-87-T: "Garments Required in Clean Rooms and Controlled Environmental Areas." This document was published in October 1989 as IES-RP-CC-003-89, "Garments Required in Cleanrooms and Controlled Environmental Areas." This recommended practice included the ASTM F-51 test, as well as the Helmke tumble test, particle containment test and extractables test for cleanroom garments. This recommended practice became the basis for the manufacture, cleaning and testing of cleanroom garments. Its 2011 revision, IEST-RP-CC003.4: "Garment Considerations for Cleanrooms and Other Controlled Environments" is still used today.

In the 1980s, W.L. Gore and Associates, Inc., developed Gore-Tex, a laminate that bonds a polytetrafluoroethylene membrane with a pore size of 0.2 µm to a layer of woven polyester and carbon (ESD) yarns. This fabric was used primarily in the semiconductor and microelectronics industries from the 1980s and until the late 1990s.

Medical device and pharmaceutical companies used cleanroom garments constructed of high-density taffeta without any ESD yarns. But garments constructed of this fabric caused tribo-charging, which created static electricity and static discharges. The semiconductor and microelectronics industries used polyester fabric woven with carbon yarns in a grid pattern to better control tribo-charging. As static discharges became more of a problem in the pharmaceutical and medical device industries, they also changed to high-density ESD stripe fabrics.

1990s

During the 1990s, high-density ESD stripe and grid taffeta weave fabrics (C-3 and Maxima ESD) were developed by Burlington Industries. Precision Fabrics Group (PFG) developed high-density ESD stripe and grid taffeta weave fabrics suffused with a durable antimicrobial and Teflon shielding (Integrity 2000 and Integrity 1800). These fabrics had a smaller pore size, durable polyester-carbon ESD yarn and lightweight taffeta weave. Garments manufactured using these new fabrics could also be sterilized by gamma radiation.

1989: Technicians are dressed to work in a unidirectional-flow cleanroom for processing semiconductor wafers. Photo: Sandia National Laboratories

In previous decades, ETO or autoclave steam sterilization had been used to sterilize cleanroom garments. But Tyvek disposable garments sterilized using ETO required a 24 hour out-gassing cycle before delivery to the customer. It became apparent that synthetic cleanroom garments should not be ETO sterilized. Garments sterilized using autoclave steam sterilization immediately became wrinkled and shrank 10–15%. The PFG Integrity 1700 ESD fabric with a twill weave is more common in Europe and the Teijin Seirin ESD fabrics with a twill weave are more common in Asia.

During this decade, 100% polyester nonlinting undergarments or tech suits replaced the 100%-cotton linting scrubs worn under coveralls, hoods and boots in ISO Class 3, 4 and 5 cleanrooms.

DuPont developed its flame-resistant meta-aramid Nomex filament yarns to be used in the fabric and construction of flame-resistant cleanroom garments. Burlington Industries and Stern & Stern began to manufacture flame-resistant cleanroom fabrics using the Nomex filament yarn.

2000s

In 2003, the Institute of Environmental Sciences and Technology published IEST-RP-CC003.3, "Garment Considerations for Cleanrooms and Other Controlled Environments," which revised and standardized the manufacture, cleaning and testing of cleanroom garments for the twenty-first century. Fabrics noted included high-density ESD reusable fabrics and additional nonwoven fabrics for disposable cleanroom garments, as well as other polyester-based materials used in the manufacture of cleanroom garments such as sewing thread, zippers and boot straps.

The document noted that because the use of silicone in the manufacture of cleanroom garments may cause airborne molecular contamination, its use was not recommended. A round-robin testing program using the same 10 cleanroom garments was performed by three laboratories and three cleanroom laundries using the revised Helmke tumble apparatus and procedure to determine limits for garment cleanliness at both 0.5 µm and 0.3 µm. The precision laundering and packaging of cleanroom garments was detailed and standardized. Quality management systems were recommended. By 2000, the major cleanroom garment laundries were ISO 9001 registered.

Technicians and scientists in cleanroom garments check out one of the Webb telescope's first two flight mirrors in the clean room at NASA's Goddard Space Flight Center in Greenbelt, Md. Photo: NASA Goddard Space Flight Center

Students in the clean room facility at NMDC in University of Alabama in Huntsville, doing a wet etching experiment that involves level 4 toxic material Photo: Yorudun / Wikimedia Commons / CC BY-SA 3.0

2010–present

The McIlvaine Marketing Research Company estimates that over 14 million people worked in cleanrooms throughout the world in 2015. That number can only increase: With continuous innovations in nanotechnology; three-dimensional printing; novel biologicals, pharmaceuticals and medical devices; the development of smaller, more powerful computers in the semiconductor and microelectronics industries; as well as ongoing work in the food industries, industry will continue to need cleanroom operators and cleanroom garments.

Scientists wear cleanroom suits at the at the Netherlands Organisation for Applied Scientific Research Van Leeuwenhoek Laboratory in Delft. Photo: ESO / TNO / Fred Kamphues / Wikimedia Commons / CC BY 3.0

As I researched information for this article, I was amazed at the detail of recommendations for cleanroom

Over 14 million people worked in cleanrooms throughout the world in 2015

garments in 1969 and the actual practices of cleanroom garment end users, manufacturers and laundries since the 1980s. Thanks to developments like those chronicled here, when current cleanroom garments are donned, worn and doffed correctly, there is reduced human-sourced contamination and increased control of the cleanroom environment. ■

About the author

Jan Eudy is a cleanroom and contamination control consultant with more than 25 years of experience. She is a Fellow and President-Emeritus of the Institute of Environmental Sciences and Technology. She can be reached at janeeudy@gmail.com.

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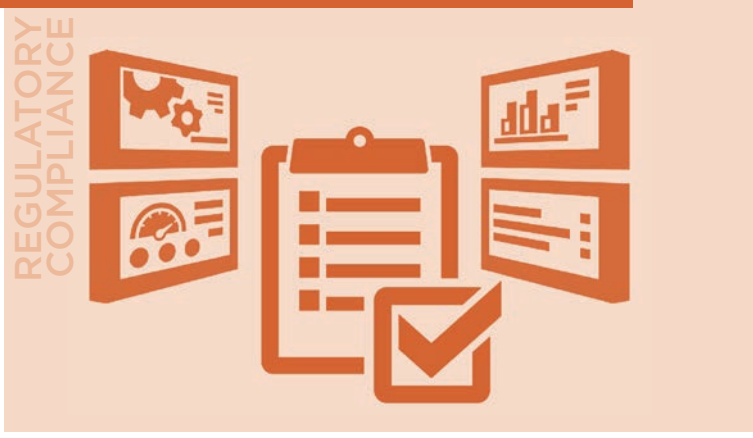
Photo: Sandia National Laboratories

Typical cleanroom head garment
Photo: RudolfSimon - Own work, CC BY-SA 3.0, via Wikimedia Commons



Association of QbD Tools with Biopharmaceutical Classification Systems

Mehtap Saydam

There appears to be rapidly growing interest in quality by design (QbD), one of the most indispensable concepts in the pharmaceutical industry. QbD ensures the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines for the determination of the process and product design spaces.

QbD was first outlined by Joseph Juran, most notably in his book *Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services*, which emphasized that product quality should considered from the earliest stages of development. Juran also stressed that quality cannot be tested in the product, but should be planned or designed in to the product.[1] Fundamental to this approach is a deeper understanding of the relationships between the product critical quality attributes (CQAs), critical material attributes (CMAs) and critical process parameters (CPPs) and their impact on quality target product profiles (QTPPs) based on sound science and quality risk management.[2]

Biopharmaceutics were defined by Wagner as the study of the relationship between the physical and chemical properties of the drug and its dosage forms and the biological effects observed following administration of the drug in its various dosage forms.[3] Pharmacokinetics is defined as the study of rate processes involved in absorption, distribution, metabolism and excretion. To obtain the required action, the bioequivalent/bioavailable formulation can be obtained using the principles of biopharmaceutics and pharmacokinetic equations.[4] QbD facilitates the establishment of relationships based on scientific risk analyses, mathematical prediction tools like *in vitro/in vivo* correlation (IVIVC) and design spaces that ensure biopharmaceutical performance.

QbD-based biowaiver

Drug products are considered to be therapeutic equivalents only if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[22] *In vivo* bioequivalence assessment of solid oral dosage forms is a commonly accepted surrogate for judging therapeutic equivalence of pharmaceutically equivalent drug products, which obviates the need for additional clinical evaluation. To reduce the time and cost of development studies and to eliminate ethical concerns, especially when the drug is cytotoxic, regulatory acceptance of in vitro testing as a reliable surrogate for an *in vivo* bioequivalence study is commonly referred to as "biowaiver." While biowaiver means reduction in the number of *in vivo* bioequivalence studies, it also focuses on prevention and building quality into products – one of the main aims of QbD. Biowaiver decisions can depend on scale-up and post-approval change (SUPAC) guidelines, IVIVC, biopharmaceutical classification systems (BCS) and QbD design space. Historical development of the biowaiver concept and its relation to QbD is summarized in Figure 1.

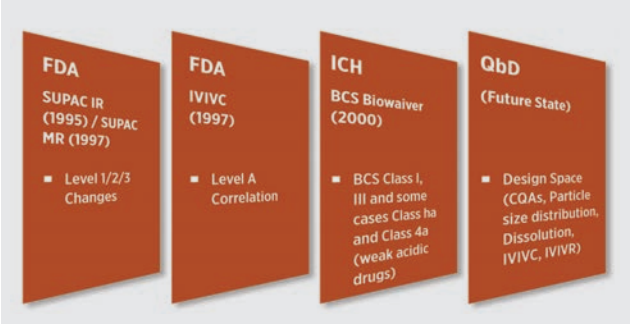
BCS

A QTPP is a prospective summary of the quality characteristics of a drug product that will ideally be achieved, taking into account safety and efficacy of the drug product.[2] In this manner, while important efficacy-related QTPPs are biopharmaceutical and pharmacokinetic properties (i.e., permeability) of active pharmaceutical ingredients (APIs), quality-related QTPP can be dissolution of API from drug product.[5]

Root causes for poor bioavailability in a BCS framework are low aqueous solubility and poor API permeability. Drug dissolution is a prerequisite for drug absorption and clinical response for almost all drugs given orally. For this purpose a very useful BCS was developed by Amidon in 1995.[7] The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability with the *in vitro* dissolution characteristics of the drug product.

A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0–6.8.[6] The ability of a molecule to cross biological membranes (permeability) is a very important biopharmaceutic parameter that governs the absorption, distribution, metabolism and excretion of a drug.[4] A drug substance is considered highly permeable when intestinal absorption is determined to be 85% or higher. An immediate-release (IR) drug product is characterized as a rapid-dissolution product when not less than 85% of the labeled amount of the drug substance dissolves within 30 minutes using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 mL or less of each of the following media:

Figure 1 Development of biowaiver concept



- Acidic media, such as 0.1 N HCl or USP simulated gastric fluid without enzymes
- A pH 4.5 buffer
- A pH 6.8 buffer or USP simulated intestinal fluid without enzymes

BCS validity and applicability have been the subject of scale-up and post-approval changes for IR (SUPAC-IR) products guidance, a dissolution guidance, and US Food and Drug Administration (FDA) guidance on waiver of *in vivo* bioequivalence studies for BCS Class I drugs in rapid-dissolution IR solid oral dosage forms.[6–7] It is not always necessary or appropriate to conduct a clinical pharmacokinetics study to understand differences in *in vitro* release due to variation of material quantities, material attributes or process parameters. Other tools such as dissolution in biologically relevant dissolution media, in silico modeling, *in vivo* studies in animal models, *ex vivo* studies, etc., could be used to link *in vitro* dissolution performance to *in vivo* performance. Rapid and complete dissolution across the physiological pH range, for instance, is likely to be sufficient assurance of good *in vivo* availability for many compounds, even if not formally BCS Class I.[8]

As shown in Table A, while dissolution is sufficient for predicting bioavailability for BCS Class I drugs in general for BCS Class II, III and IV drugs, more detailed studies and prediction methods should be performed to predict bioavailability. Similarly, permeability is an intrinsic attribute and can be managed via risk assessment or design space designation at the very early phases. In some cases, however, some excipients (e.g., sodium lauryl sulphate) or manufacturing conditions (e.g., polymorphic transformation as a result of high temperature and/or pressure) can affect API permeability.[9]

Risk assessment in BCS

Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk-management process. It consists of identifying hazards and analyzing and evaluating risks associated with exposure to those hazards, as described in ICH Q9.[10]

Risk assessment shouldn't be thought of as a single step, but should be included in each step of the QbD implementation pathway. Identifying overall risks on bioavailability for oral dosage forms (see Figure 2) is the first step in the quality risk-management process. In this context, biopharmaceutical properties of drug product should be assessed based on sound science and risk-assessment methodologies.

Translated to QbD, this implies that CQA acceptance criteria, CPP ranges or CMA changes should produce *in vivo* performance within acceptance criteria for bioequivalence. Integration of biopharmaceutics and QbD has recently come to the fore with FDA's Biopharmaceutics Risk Assessment Road Map (BioRAM) program. Major aims of the program are to provide a strategy to support and accelerate drug development, link drug product and clinical outcomes effectively, identify critical knowledge, set QTPP-driven specifications and provide a path for application of the QbD paradigm.[11]

In this manner BCS can be considered a biopharmaceutical risk-management tool for a successful QbD implementation. Low-solubility drugs have higher bioinequivalence risk than high-solubility drugs. Low-permeability drugs are more sensitive to the differences between *in vivo* and *in vitro* "sink" conditions and the effect of excipients is higher than high-permeable drugs. Products with slow or extended dissolution profiles pose a higher risk as well.

In addition, drugs with low bioavailability will show higher variability, which poses a higher biopharmaceutical risk.[11] It is also possible to perform qualitative risk analysis and apply quantitative tools like failure mode and effects analysis (FMEA) to evaluate biopharmaceutical properties. Kubbinga. et al., have described an FMEA risk analysis on bioinequivalence risk with evaluating dissolution, absorption, bioaccessibility and API transit time.[12]

Table A shows a risk assessment of APIs dependent on BCS classification. Narrow-therapeutic-index drugs are excluded from the biowaiver option, because both factors lead to an unacceptably high risk.[12]

The aim of biowaiver guidance is to reduce the risk of bioinequivalence to an acceptable level. By using FMEA risk analyses, the authors showed how clarification of regulatory classifications and definitions could facilitate applications for a biowaiver while still controlling the risk of bioinequivalence based on scientific data.[12]

Design space

Design space is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters demonstrated to provide assurance of quality.

Working within the design space is not considered a change.[2] Design space can be developed by a first-principles approach, statistical design of experiment (DoE) or a combination of these.

In a BCS framework, design spaces that ensure biopharmaceutical performance can be created with mathematical models, i.e., solubility predictions, *in vitro* permeability models, IVIVC, release kinetics and dissolution prediction models.[9] Variation in dissolution rate may not lead to a change in bioavailability, as other physiological absorption processes may dominate (e.g., gastric emptying and intestinal-wall permeation). This means that *in vitro* dissolution could vary within a certain range without any influence on pharmacokinetics.

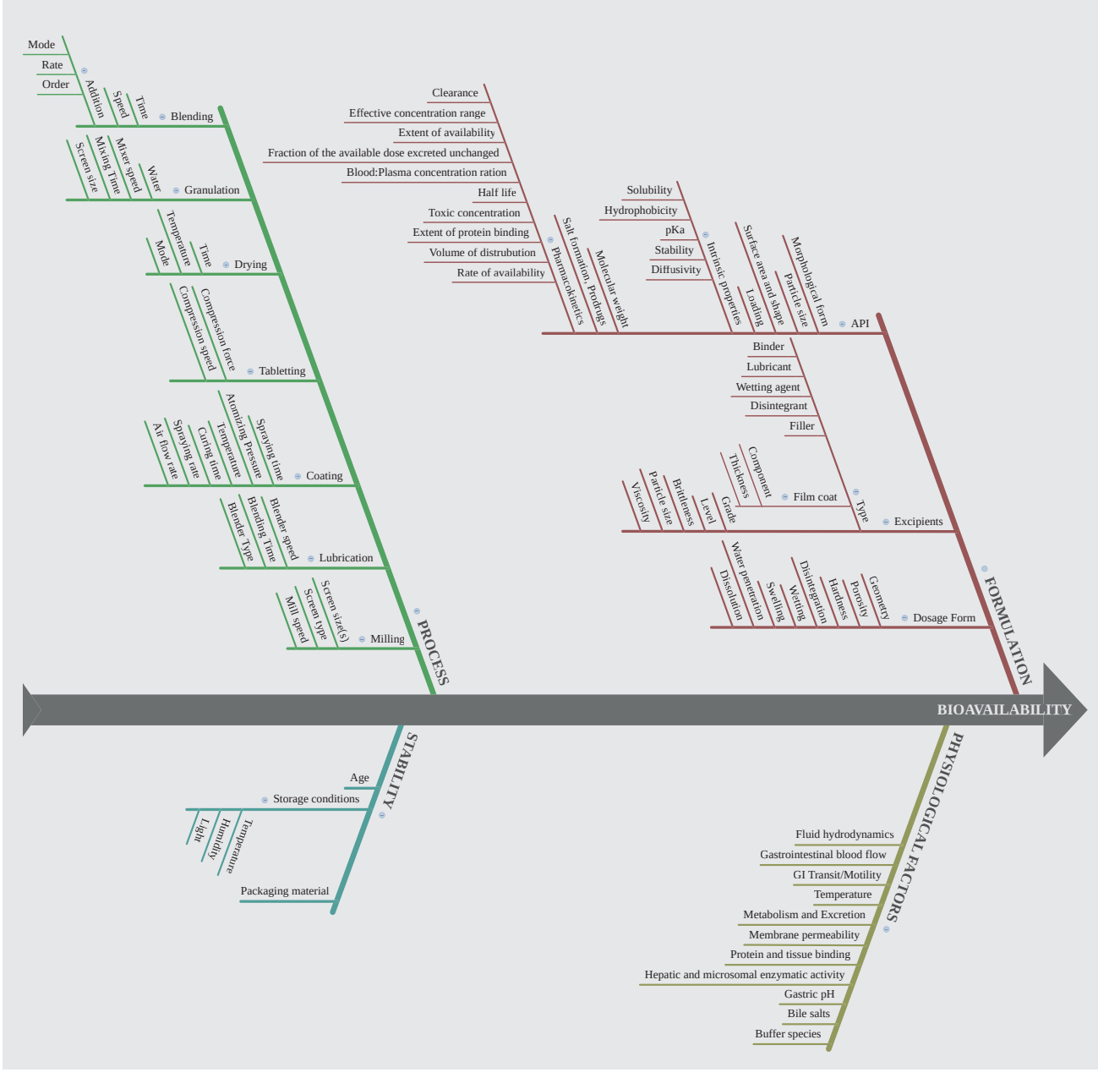
This is often the case not only for highly soluble drugs (Class I and III), but also for well-formulated, moderately soluble Class II and IV drugs when the rate of (*in vivo*) dissolution is much faster than the rate of absorption. Thus for any product there are three options:

1. An IVIVC, where changes in *in vitro* dissolution are correlated to changes in bioavailability, which allows dissolution to be used as surrogate for clinical performance
2. An IVIV relationship (IVIVR) in which no effect on bioavailability would be observed across a range of in vitro dissolution rates (safe space)
3. A mixed safe space/IVIVC result in which bioavailability is only affected for some of the clinically tested in vitro variants[8]

While it is certainly desirable to continue to evaluate and refine algorithms and improve mechanistic approaches relative to IVIVC, it is worth mentioning that each mechanistic element is currently subject to sufficient variability.

A quantitative and mechanistic absorption model can be accurately and easily related to pharmacokinetic models and used to evaluate plasma-concentration profiles. These models are classified into three categories based on their dependence on the spatial and temporal variables:

Figure 2 Bioavailability risks for oral dosage forms



- Quasi-equilibrium models, including the pH partition hypothesis and the absorption potential concept, are independent of the spatial and temporal variables: These models generally provide a basic guideline for understanding drug-absorption trends.
- Steady-state models, including the film model and the mass balance approaches: Steady-state models can be employed to estimate the fraction of dose absorbed.
- Dynamic models, including dispersion, mixing tank and compartmental absorption and transit models, are dependent on the temporal variable: Dynamic models can be used to predict the fraction of dose absorbed and to evaluate plasma concentration profiles.[13]

In this context, a number of pharmacokinetic modeling platforms are available like Gastro Plus, Stella, PK-Sim and Simcyp.

A clinical design space has been developed in the study of Dickinson, et al. They proposed clinically relevant dissolution acceptance criteria based on a series of *in vivo* and *in vitro* studies and supporting pharmaceutics studies using a QbD approach. For a BCS Class II compound, clinical design space has been described as a mixed design space/Level A IVIVC result, in which clinical pharmacokinetics is only affected for a few of the variants tested clinically. This would allow a dissolution specification to be set that allowed Cmax and AUC to be controlled to 10%.[14]

In vitro dissolution testing is a QTPP characteristic that is important for drug product quality. Bioequivalence guidelines and BCS provide a platform for regulatory applications of in vitro dissolution as a marker for consistency in clinical outcomes. *In vitro* dissolution testing, together with BCS consid-

Table A FMEA risk assessment tool for biowaiver and the role of BCS

BCS	Incidence probability[a]	Detection probability[b]	Severity[c]	Justification
Class I High solubility High permeability	**Low**	**Low**	**Low**	Bioavailability can be predicted with dissolution. Transporter and first-pass effect of APIs should be considered.
Class II Low solubility High permeability	**Medium**	**Low**	**Low**	Solubility is rate-limiting step for bioavailability. Bioavailability can be predicted with dissolution only with special biorelevant methods.
Class III High solubility Low permeability	**High**	**Low**	**Low**	Permeability is rate-limiting step for bioavailability. High sensitivity to transporters, food effect, and excipients. *In vivo* absorption simulation studies should be performed to gauge bioavailability.
Class IV Low solubility Low permeability	**High**	**High**	**Low**	Both solubility and permeability are rate-limiting steps for bioavailability. Products with slow or extended dissolution profiles pose a higher risk. *In vivo* absorption simulation studies should be performed to gauge bioavailability.

a) Incidence is low if *in vivo* bioavailability can be modified with dissolution
b) Detection is low if dissolution is sufficient for *in vivo* prediction
c) Severity is low if API is not narrow therapeutic index drug

erations, could provide a key link between manufacturing/product design variables and clinical safety/efficacy in QbD.

Efficient implementation of QbD requires a biorelevant and discriminative dissolution test during product development. In this manner Eaton, et al., have performed a screening fractional factorial DoE study to optimize dissolution test conditions. One of the goals of this study was to identify apparatus variables that require more stringent acceptance criteria to achieve this type of specificity. The ultimate goal is to determine acceptance criteria that will ensure accuracy and precision without unnecessarily tightening limits.[15]

ISPE's Guidance Document *Product Quality Lifecycle Implementation® (PQLI®) from Concept to Continual Improvement, Part 2: Product Realization Using QbD* offers an example on QbD implementation of small molecules.[8]

In this document, "PaQLInol," a poorly soluble Class II API, is selected as model drug. Since dissolution characteristics are important for bioavailability, dissolution is evaluated as a bioavailability-related CQA, and *in silico* modeling of the effect of drug substance particle size for Class II compounds is presented. Additionally, the proposed design space comprises a series of acceptance criteria for input material attributes, such as particle size distribution of API, surface area of lubricant, lubrication time and crushing force of uncoated tablets along with the DoE algorithm used to predict and control dissolution. By doing so, dissolution as an end product test becomes redundant.[8]

Another illustrative example was published in 2009: "Sakura Bloom Tablets P2 Mock." Dissolution of a BCS Class I API as a CQA was evaluated as a high-risk attribute in FMEA risk assessment.[17] Effects of API particle size, lubricant amount, and lubrication time and tableting pressure on dissolution were clarified using a multidimensional DoE analysis. Therefore CMAs were controlled as an input variable in the design space. Because drug-substance particle size, lubricant amount, lubrication time and compression pressures are monitored for control, the dissolution test is omitted from specifications of drug product.[16]

Process analytical technology

Implementing QbD reduces product variability and defects, thereby enhancing product and process understanding, process development and manufacturing efficiencies with a science-based control strategy. Adequate process controls in pharmaceutical manufacture are also required to meet current FDA recommendations, such as process analytical technology (PAT). On the other hand, while DoE, risk assessment and PAT may be used in the QbD process when appropriate, they are not check-box requirements.

Satisfactory tablet manufacture can be complex with interacting CMAs and CPPs such as API particle size distribution, content uniformity, lubrication time, lubricant amount, lubricant surface area and tablet hardness. Larger particle sizes have the potential to decrease dissolution. Higher lubricant surface area can lead to a decrease in dissolution. Similarly, longer lubrication times can cause problems on content uniformity and decrease dissolution.

While dissolution is one of the most important bioperformance indicators of an oral systemic drug product, current methodologies for testing dissolution can vary between different release profiles. Even an immediate-release oral dosage form, when considered with chromatographic studies, is one of the most time-consuming processes for batch release. Thanks to PAT, dissolution testing can be performed with rapid in-line measurement techniques or can be replaced by other surrogate testing with appropriate chemometric correlations.[14, 17] PAT opportunities in evaluating the biopharmaceutical properties of a drug product can include (but are not limited to) to X-ray analysis for API crystallinity determination, spatial filter velocimetry for API particle size, near-infrared (NIR) spectroscopy for quantitative moisture and content uniformity measurements[18] and terahertz pulse imaging to determine coating thickness.[19]

Part 2 of ISPE's *PQLI® from Concept to Continual Improvement* Guidance Document states that API particle size can be controlled by focused-beam reflectance measurement directly in dissolution algorithm.[8] Freitas, et al., reported a comparison between dissolution profiles obtained using a dissolution apparatus (conventional method) and NIR diffuse reflectance spectra. Results indicated that the NIR diffuse reflectance spectroscopy method is an alternative nondestructive tool for measuring drug dissolution in tablets.[20] Similarly Mattes, et.al., developed an NIR method that provides

fast and accurate. Dissolution profiles of intact tablets. The data showed promising results that could reduce laboratory workload in dissolution testing: 31 tablets could be analyzed in fewer than 10 minutes.[21]

Conclusion

In the pharmaceutical industry, implementing QbD is becoming significantly more important. Statistical prediction models, PAT and risk-assessment methodologies are main tools on the implementation pathway of QbD. For successful high-quality, clinically safe and efficient drug development, it is important to link biopharmaceutical properties to drug performance using risk management. Biopharmaceutics and pharmacokinetics are indispensable in accomplishing the goals of drug development, i.e., producing safe and efficacious drugs with reduced development time and cost. *In vitro* dissolution testing, together with BCS considerations, could provide a key link between manufacturing/product design variables and clinical safety/efficacy in QbD. Current dissolution methods are based on providing an acceptable risk level as proven by long-term experience rather than modeling the *in vivo* situation. More *in vivo*–relevant *in vitro* test methods would allow more flexible approaches than described above, further reducing the need for additional *in vivo* studies. In addition, the use of algorithms that model the absorption process in a more mechanistic manner than simple IVIVC approaches would aid the establishment of drug specific definitions of "design space" and to minimize bioavailability risks. ■

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About the author

Mehtap Saydam holds a master's degree in pharmaceutical technology. She is presently working as a Project Executive for Drogsan Pharmaceuticals in Ankara, Turkey, specializing in research and development of generic dosage forms, focusing on bioequivalence study designs, statistical formulation development, quality by design, process analytical technology, design of experiments, statistical process control and computer simulations. She has numerous patents and presentations on QbD both in Turkey and internationally. She is a member of ECA and ISPE.

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- Facilities, Systems and Equipment Workshop (T48), 10 – 11 Nov.
- GAMP® 5 Process Control (T21), 14 – 15 Nov.

DECEMBER

ISPE Training Institute, Tampa, FL

- Basic GAMP® 5, Annex 11 / Part 11 (T45), 5 – 7 Dec
- Cleaning Validation (T17), 12 – 13 Dec.
- OSD (T10), 8 – 9 Dec.
- Sterile (T12), 15 – 16 Dec.

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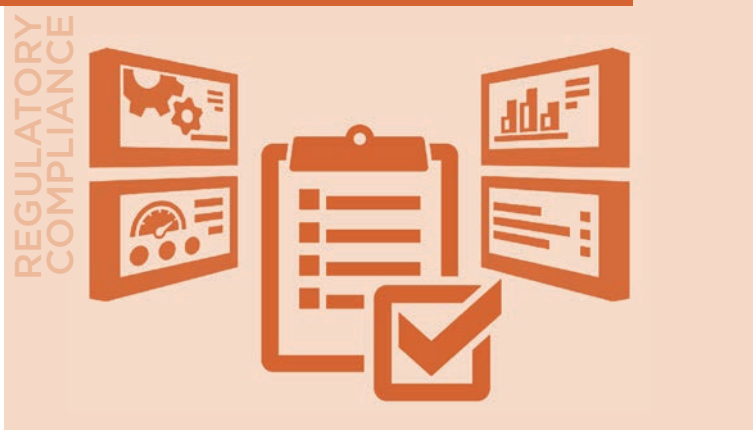


Quality Risk Management for Legacy Products in CMOs

Quality metrics, process performance, risk assessments and continued process verification

Humberto Vega and Ricardo Rivera

The pharmaceutical industry can be divided in two key groups:

- Innovators: companies that develop and may manufacture new drug substances or new drug products
- Generic manufacturers: companies that manufacture generic versions of drug substances or drug products that have/are going off patent

Contract manufacturing organizations (CMOs) operate under the same regulatory expectations as innovators and generic manufacturers, and provide manufacturing capabilities such as formulation, filling or packaging for both groups. They are considered an extension of the company contracting them for the manufacture of drug products.

The discovery, development, and manufacture of drug products is a lengthy, complex and costly process.[1] Generic companies use technical and clinical knowledge from the innovator to develop and market generic versions of drugs. This approach is less costly because there is no need to do expensive R&D with its inherent risks of clinical and toxicological work. By design, this allows the company to get product to market at a lower cost compared to innovator drug.[2] The generic version of a drug will be manufactured based on the knowledge (e.g., intellectual property) and conditions (e.g., process parameters and quality attributes) engineered by the generic company, resulting in a product that is comparable to the brand product in term of strength, quality, efficacy, and performance for the intended use.

Pharmaceutical companies must have robust quality systems in place to ensure drug products meet required quality standards and are manufactured to meet health authority requirements. This applies to innovators, generic manufacturers and CMOs that produce new and/or legacy products. Quality systems should satisfy the following elements:

Regulatory expectations: It is important to keep in mind that CMOs are seen by regulatory groups—including the US Food and Drug Administration (FDA), European Medicines Agency and Medicines and Healthcare Products Regulatory Agency—as an extension of the company that contracts with them. For this reason, quality agreements are developed to define expectations and responsibilities (equipment and utilities qualifications, deviations, change control, product testing, product specifications, etc.) to ensure that the CMO fulfills regulatory expectations. Meanwhile, the CMO's quality program defines the strategy necessary to comply with regulatory expectations.

Process understanding and risk management: Multiple factors are linked to risk management. Among them are:

- *Knowledge management:* The transfer of process and analytical details is needed for the successful manufacture of the drug substance or drug product. This information is usually in the form of technical reports and comprehensive documentation such as process development reports, analytical method reports, manufacturing process description, control strategy, risk assessments, justification of process parameters, and quality attributes.
- *Quality metrics:* These are used to assess the CMO's compliance level while manufacturing the drug substance or drug product. Parameters for routine evaluation are mutually agreed as part of the contract.
- *Process performance:* The level of control and effectiveness of the manufacturing process is monitored by means of statistical tools such as control charts and performance indicators, including process performance (Ppk) and process capability (Cpk). These help identify potential quality issues before an actual failure is experienced.
- *Risk management (assessments, control, communication, review):* A systematic evaluation of the manufacturing process, equipment, utilities, and materials provides the opportunity to identify potential areas for improvement as well as areas that must be monitored to prevent process or product quality failures.
- *Continued process verification (CPV):* Stage 3 under FDA's guidance on process validation, this step requires routine monitoring of the manufacturing process to identify any trend affecting product quality attributes. Monitoring under CPV includes deviations, complaints, process changes, and the use of statistical tools such as control charts. CPV helps detect potential product quality issues based on historical evaluation of product related quality attributes and process parameters.

Discussion

Risk management of legacy products may represent a challenge, since some documentation associated with development and technology transfer may not fully satisfy today's expectations. For example, initial validation documents for legacy products may not provide details about criticality of process parameters, quality attributes or control strategy, or may not consider all potential risks that may affect product quality. However, the experience developed during routine manufacturing throughout the years will provide the manufacturing facility with technical knowledge at full scale that is not feasible at laboratory- or pilot-scale levels.

The CMO quality system and the sponsor granting the contract should be aligned on previously identified elements such as knowledge management, quality metrics, process performance, risk management and CPV. The following section provides aspects that may be considered guidance on

legacy products, regulatory expectations, practices from the industry, role of the aspects and application of the elements at the CMO while mitigating and remediating existing documentation.

Knowledge management

Regulatory expectation

The knowledge gained during the development of a legacy product and its manufacturing process may not be captured in a comprehensive documentation package as discussed in ICH Q8[3] and ICH Q9.[4] However, this should not prevent the manufacturer from compiling the necessary information and creating comprehensive documentation that demonstrates in-depth understanding of the product and manufacturing process.

Practices from industry

Key players from the industry realize the criticality of knowledge management as process improvements and troubleshooting are facilitated by collection and evaluation of product and process data.

Lipa et al.[12] provide an example of the steps taken at Merck & Co. In general, approximately 20% of knowledge is captured in existing documentation (explicit knowledge), while about 80% is considered tacit and needs to be compiled and properly documented. Hubert[5] summarized the key progress on this topic in three steps:

1. *Demystify:* Use a systematic approach to enable growth and flow, and create value based on knowledge management.
2. *Describe and debunk:* Develop an organization in which knowledge is leveraged, optimize products and manufacturing processes, and identify and implement innovative approaches that will bring better financial performance
3. *Develop:* Use knowledge to create teachable moments beyond routine training or searching for an expert.

Quality metrics, process performance, risk assessments and CPV

Neway[6] summarizes the relevance of knowledge management as the accumulation, accessibility and dissemination of institutional knowledge in every teachable moment. To achieve its full potential, data must be presented in the proper context to enable effective actions. Neway also highlights the elements from ICH Q8,[3] Q10[7] and Q11[8] as they relate to the collection and use of data and knowledge management (see Table A). Some information that can be available is:

- Quality metrics: complaints, investigations, product release
- Process performance: critical quality attributes, process parameters, in-process controls (IPCs)
- Risk assessments: root cause evaluations, failure mode and effects analysis (FMEA)
- CPV reports compiling process performance information

CMOs

Information exchange with the CMO is critical, as the manufacturing operation generates a significant amount of information. In the case of legacy products, both explicit and tacit knowledge need to be captured as part of the routine manufacture. If the original developmental work does not satisfy current expectations, a remediation exercise may be considered (e.g., generate the required documentation). An alternative is to consolidate all required information associated with the product and process in a single secure file. This serves as a supplement to the annual product review (APR) and existing process validation documentation package. It also includes quality metric data, critical quality attribute (CQA) capability analysis, critical process parameter (CPP)-CQA links, in-process testing and control strategy and risk assessments. These documents are maintained at the CMO and copies retained by the sponsor.

Quality metrics

Regulatory expectations

While companies often apply metrics and regulatory agencies like to see such metrics applied; no specific requirements are currently in place. Multiple quality metrics are used across the industry to monitor the effectiveness of the manufacturing process and quality system. As described in ICH Q10,[7] the goal is develop and use effective monitoring and control systems for process performance and product quality. Those metrics include, but are not limited to: complaints, deviations, rejected product, reworked/reprocessed product, recalls, process performance indexes and regulatory inspections.

Industry practices

Standard industry metrics known as key performance indicators (KPIs) assess the need for improvements and facilitate troubleshooting of potential product quality and manufacturing process issues. KPIs used to monitor product quality and process performance include: number of manufactured lots, number of released lots, number of rejected lots, on-time delivery, release cycle time, deviation rate (deviations/lot), and overdue complaints.

Quality metrics and quality agreement

As previously mentioned, quality metrics are intended to monitor process performance and product quality. The quality agreement with the CMO should either define those metrics or define the setup for metrics to be used in a routine basis.

CMOs

As previously discussed, metrics may be consolidated in a single file where key information associated with the product and process is compiled. This information serves as a supplement to the APR and existing process validation reports. These documents are maintained at the CMO, with copies retained by the sponsor.

Process performance

Regulatory expectations

Quality risk management is used to identify gaps in process knowledge. Once such gaps are remediated via experiments or using previous knowledge, a control strategy for the manufacturing process is defined. As described in ICH Q10,[7] the control strategy facilitates timely feedback and appropriate corrective and preventive actions (CAPAs) while monitoring the manufacturing process. Parameters and quality attributes identified in the control strategy include, but are not limited to, those related to drug substance, drug product materials and components, facility and equipment operating conditions, IPCs, finished product specifications and associated methods.

In the case of legacy products, a quality risk tool such as FMEA may be used to assess the existing control strategy. Proper tools must be defined (e.g., statistical process control) to confirm the effectiveness of the current control strategy. In the case of legacy products, the link between CPPs and

CQAs may be not fully understood, and further work may be required. Evaluations by CPPs and CQAs may supplement existing process validation documentation. IPC templates and examples of the control strategy and link between CPPs and CQAs are shown in Table B and Table C.

Industry practices

The industry has implemented different approaches to capture the information discussed above. The main consideration is a clear explanation and justification of the relationship between process parameters, quality attributes, and IPCs.

Performance indexes

Performance indexes are used to assess the capability of the process, usually by considering various attributes such as assay, pH, fill volumes, particulate matter. Depending on the amount of data available, two potential indexes are Cpk and Ppk (see Table D and Table E).[11]

Information on Ppk or Cpk can be consolidated as part of the risk assessment and used as supplements to the legacy product validation documents. Table F shows a sample template summarizing the process performance evaluation of a drug product.

This type of evaluation leads to defining control limits, which are used to monitor the manufacturing process. This data is typically presented in the graphical form of a control chart. The sample control chart in Figure 1 shows one data point slightly above the upper control limit; that data point may or may not be investigated depending on how the organization defines the requirements for investigations. If the Ppk is greater than 1.33, for example, the organization may not proceed with a major investigation, given the overall capability, performance indexes, and the location of the data point with respect to the specification value (CL is 118.55 mg, upper specification is 150.0 mg, reported value is 119.0). When Ppk is between 1.0 and 1.33, however, the location of the data point related to the specification should be considered before ruling out the need for further investigation (CL is 118.55 mg, upper specification is 125.0 mg, reported value is 124.0).

Figure 1 Example of a control chart Xbar with no trend

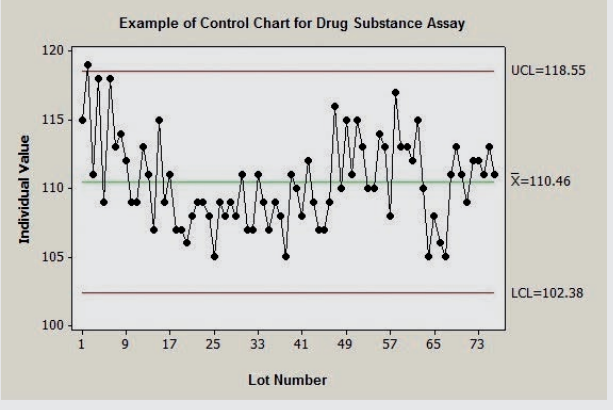
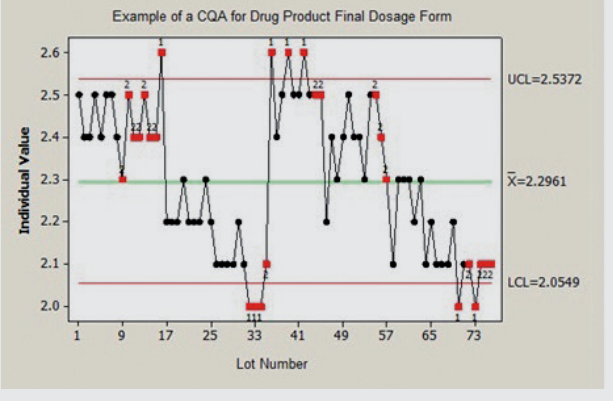


Figure 2 Example of a control chart Xbar with trends



In general, if a process presents no values outside control limits, then the current process performance can be considered similar to historical process performance when the control limits were calculated. In cases where process performance shows an improvement (indicated by increased Ppk or Cpk), such change may be further evaluated to enhance process knowledge.

The main goal of using control charts is to detect any potential drift or shift in process performance. Figure 2 shows an example of a process in which trends triggered further investigation to identify the root cause. In this example, no data is outside the specifications for the process (1.8% to 3.0%). There are two instances, however, when reported test results start running from 2.5 down to 2.1 (toward lower specification of 1.8). This affects the process capability. In this case, an investigation is initiated to identify the root cause via process or analytical testing.

CMOs

Historical data at the CMO is used to estimate process performance and capability indexes. Control limits are calculated and implemented for use as part of routine release testing. A release data review is conducted as part of both the CPV and APR programs. The CMO provides the information to the sponsor contracting them for the manufacture of the legacy drug products.

Risk management

Regulatory expectation

Regulatory groups expect quality risk assessments to be part of the development and implementation of manufacturing processes. The goal of any risk assessment is to identify potential weak and critical points (steps with identified hazard) in a process to either correct and improve such step(s) or implement monitoring controls that prevent the quality of the product from being jeopardized.[4, 8–10]

Table A Knowledge management elements

ICH	Knowledge management elements
Q8 & Q11	"It should be recognized that the *level of knowledge gained, and not the volume of data*, provides the basis for science-based submissions and their regulatory evaluation." [Emphasis added by the author]
Q10	"Sources of knowledge include, *but are not limited to*, prior knowledge [...], pharmaceutical development studies, technology transfer activities, process validation studies over the product lifecycle, manufacturing experience, continual improvement and change management activities." [Emphasis added by the author]

[Emphases added by the author]

Table B Example of template to capture IPC and control strategy

Step	Equipment	Purpose	Parameters	Processing parameter	In-process test	Controls	In-process control?	Cpk/Ppk for IPC	Effectiveness
Compounding – 1	Tank and mixer	Monitoring	Mixing speed	Speed: 47.5 Hz (XXXX) and 55 HzHz (YYYY, ZZZZ)	None	Automation	No		Not applicable
	Temperature probe	Monitoring	Temperature	Temperature: 15–30° C	None	Automation	No		Not applicable
	Scale	Quantity of API required for formulation	Amount of API	Per formulation	Density	Weight	Yes	5.00	Effective
	Scale	Quantity of WFI required for formulation	Amount of WFI	Per formulation	Concentration	Weight	Yes	3.00	Effective
	Timer/clock	Monitoring	Hold time	NMT 49 hrs 17 min	None	Batch record	No		Not applicable
Sterile filtration	Timer/clock	Monitoring	Filtration time	NMT 72 hrs	None	Batch record	No		Not applicable
	Gauge	Monitoring	Pressure	NMT 40 psi	None	Batch record	No		Not applicable
	Integrity tester IT4	Sterility assurance	Integrity of device	Bubble point: NLT 50 psi	Bubble point	Batch record	Yes	No filter integrity failures reported to date	Effective
Filling	Filling machine: FMA on line W, FM B on line Z	Speed of filling operation	Fill rate	Speed: 50–100% fill speed	None	Batch record	No		Not applicable
	Machine: Continuous Climet	Monitoring	Environmental monitoring	Viable/nonviable air particles and surface	Sampling	Batch record	No		Not applicable
	Timer/clock	Monitoring	Bulk hold time	NMT 48 hrs	None	Batch record	No		Not applicable
	Scale	Monitoring	Fill volume	Per formulation	Fill weight	Batch record	Yes	No failures reported	Effective
	Microbial test	Monitoring	Prefiltration volume	NMT 10 CFU/100 mL	Bioburden	CFU/mL	Yes	No failures reported	Effective
Packaging	Gauge	Monitoring	Temperature	Temperature: 15–30° C	None	Batch record	No		Not applicable
	Automation	Monitoring	Product-specific materials	Per formulation	None	Batch record	No		Not applicable
Storage	Gauge	Monitoring	Temperature	Temperature: 15–30° C	None	Batch record	No		Not applicable
	Automation	Monitoring	Expiration date	24 months	None	Batch record	No		Not applicable

Industry practices

The industry has implemented different approaches to capture the information required for risk assessments. The main consideration is a clear understanding of the manufacturing process, including process parameters, IPCs, and quality attributes. The risk assessment format depends on the scope and goal of the assessment, such as: quantitative using risk priority number or qualitative using a hedonic scale ranging from low to high. Table G presents a risk assessment that uses a quantitative scale.

Risk management

Risk management involves assessment, control, communication, and review of the risks identified in the manufacturing process. As mentioned previously, it helps identify weak or critical points within the manufacturing process that require either remediation or close monitoring to ensure no impact to product quality. Once a risk assessment is completed, the impact of remediation or mitigation activities is monitored following the recommendations identified as part of the assessment.

In those cases where the manufacturing process is modified as part of continuous improvement initiatives, the risk assessment should be re-executed as part of the planning phase to assess future effects of the proposed change on the manufacturing process.

CMOs

Risk management involves both the CMO and the sponsor. Process improvements may be initiated by either group and are implemented by the CMO to ensure proper management of the risks (mitigation or elimination). Risk assessments may consider different tools, such as FMEA.

CPV

Regulatory expectation

CPV is the final stage under FDA's 2011 guidance following ICH Q10.[13] The goal of CPV is to monitor the manufacturing process on a routine basis using statistical tools for deviations, changes, and/or complaints to detect and react to potential drifts or shifts on process performance before those changes may affect product quality.

Industry practices

Routine monitoring of quality metrics, CQAs and CPPs is conducted to assess any potential change (drift or shift) on process performance. Validated Excel spreadsheets and other tools have been developed or are available in the market to help CMOs compile and analyze process data.

In addition, periodic evaluation of process data under CPV is consolidated and reported as part of the APR at the end of the review period. CPV data is used to demonstrate the validated state of the process.

Table C Example of template to capture link between CPP and CQAs

Step	Parameters	Unit	Range	Set point	Affected CQA/ compliance attribute	Rationale for link to CQA
Compounding – 1	Mixing speed	Hz	40–50 Hz (XXX-A) or 50–60 Hz (XXX-B, XXX-C, XXX-D)	47.5 Hz and 55 Hz, respectively	Density, composition	Uniformity of solution
	Temperature	°C	Ambient	N/A	Density, composition	N/A
	Amount of API	Kilograms	N/A	Nominal value, gets adjusted based on CofA activity	Density, composition	Defines final concentration
	Amount WFI	Kilograms	N/A	Final QS weight 30 mg 109.2 kg	Density, composition	Defines final concentration
	Hold time	Hours, minutes	Bulk hold time limit is 50 hrs Formulation time limit is 50 hours	N/A	Composition	Prefiltration bioburden
Sterile filtration	Filtration time	Hours, minutes	72 hours	N/A	Sterility	Validated time
	Pressure	psi	NMT 40 psig	N/A	Sterility	Validated pressure
	Device integrity	psi	NLT 50 psig at 23° C	N/A	Sterility	Sterility assurance
Filling	Fill rate	Unit per minute	50–100% speed	N/A	Fill volume, particulate matter, assay, impurities, assay	Amount of liquid added to container
	Environmental monitoring	Viable/nonviable particles	Not listed in MBR; all EM limits are in SOP ABC-1	Not listed in MBR; all EM limits are in SOP ABC-1	Sterility, endotoxin	Sterility assurance
	Bulk hold time	Hours, minutes	Bulk hold time limit is 50 hours Formulation time limit is 50 hours	NA	Assay, impurities, endotoxin, pH, osmolality	Product degradation
	Fill volume	Grams	30 mg 0.32 to 0.40 ml	30 mg 0.36 ml	Fill volume, particulate matter, impurities, sterility, endotoxin	Dose in syringe
	Prefiltration bioburden	Concentration/CFU/mL	NMT 10 CFU / 100mL	NA	Fill volume, particulate matter, impurities, sterility, endotoxin	Endotoxin and degradation
Packaging	Temperature	°C	15–30 °C	NA	Assay, impurities	Product stability
	Product-specific materials	Identification	Product specific information	Product specific information	Labeling	Integrity of product
Storage	Temperature	°C	15–30 °C	NA	Assay, impurities	Product stability
	Expiration date	MM-YYYY	24 months	NA	Assay, impurities	Product stability

Table D Cpk – Capability index

Index	Description
$\hat{C}_p = \frac{USL - LSL}{6\hat{\sigma}}$	Estimates what the process is capable of producing if the process mean were to be centered between the specification limits. Assumes process output is approximately normally distributed.
$\hat{C}_{pk} = \min\left[\frac{USL - \hat{\mu}}{3\hat{\sigma}}, \frac{\hat{\mu} - LSL}{3\hat{\sigma}}\right]$	Estimates what the process is capable of producing, considering that the process mean may not be centered between the specification limits. Assumes process output is approximately normally distributed. In those cases of a parameter with upper and lower specifications, the Cpk is the smaller of the two Cpk values estimated using the specifications. In those cases of parameters with only one specification, the Cpk value is estimated using the only specification available.

Where: USL = Upper specification limit
LSL = Lower specification limit
μ = process mean without potential special causes such as outliers, trends, or shifts in the data
σ = process standard deviation without potential special causes such as outliers, trends, or shifts in the data

Table E Ppk – Process performance index

Index	Description
$\hat{P}_p = \frac{USL - LSL}{6 \times \hat{\sigma}}$	Estimates the performance of the process if the process mean were to be centered between the specification limits. Assumes process output is approximately normally distributed.
$\hat{P}_{pk} = \min\left[\frac{USL - \hat{\mu}}{3 \times \hat{\sigma}}, \frac{\hat{\mu} - LSL}{3 \times \hat{\sigma}}\right]$	Estimates the performance of the process, considering that the process mean may not be centered between the specification limits. Assumes process output is approximately normally distributed. In those cases of a parameter with upper and lower specifications, the Ppk is the smaller of the two Ppk values estimated using the specifications. In those cases of parameters with only one specification, the Ppk value is estimated using the only specification available.

Where: USL = Upper specification limit
LSL = Lower specification limit
μ = process mean with ovvega -erall variation including potential special causes such as outliers, trends,
or shifts in the data
σ = process standard deviation without potential special causes such as outliers, trends, or shifts in the data

Table F Example of template to capture process performance data

Critical quality attribute	Specifications			Statistical summary					Risk criteria: Cpk or Ppk	Risk ranking*
	Units	Lower	Upper	Mean	Standard deviation	Lower control limit	Upper control limit	Cpk or Ppk		
Assay A	%	90.0	110.0	99.9	2.2	93.2	106.6	1.47	≥ 1.33 low ≥ 1.00 medium < 1.00 high	L
Assay B	%	20.0	35.0	24.9	1.0	21.8	27.9	1.61	≥ 1.33 low ≥ 1.00 medium < 1.00 high	L
Ratio of A/B	N/A	3.3	5.3	4.0	0.2	3.5	4.5	1.49	≥ 1.33 low ≥ 1.00 medium < 1.00 high	L
pH	pH	6.2	7.7	6.6	0.1	6.4	6.9	2.16	≥ 1.33 low ≥ 1.00 medium < 1.00 high	L
Particulate matter > 10 µm	Part/syr		6,000.0	101.4	84.1		353.7	23.38	≥ 1.33 low ≥ 1.00 medium < 1.00 high	L
Fill volume: minimum amount	mg	0.3		0.396	0.007	0.4		4.89	≥ 1.33 low ≥ 1.00 medium < 1.00 high	L

*T*otal number of batches manufacture in the review period: 28

* Risk ranking key

L = Satisfactory process capability demonstrated M = Process capability can be improved H = Process capability must be improved

CPV

CPV highlights potential quality issues and associated CAPAs identified during periodic evaluations. CPV data is used to demonstrate the validated state of the process.

CMOs

The CMO implements CPV according to internal policies and procedures. The CMO provides the sponsor with summary reports as part of routine communication involving the manufacture of the drug products.

Conclusion

This article provides an overview of the key elements surrounding quality risk management while working with a CMO to support the manufacture of legacy products. Risk management of legacy products may represent a challenge because some documentation associated with development and technology transfer may not fully satisfy current expectations. The experience developed during routine manufacturing throughout the years provides the manufacturing facility with full-scale technical knowledge that is not feasible at laboratory- or pilot-scale levels. Multiple elements and examples in this document provide information on how to capture data associated with those elements to supplement existing validation documents for legacy products at the CMO: knowledge management, quality metrics, process performance, risk management assessments, and CPV. Once the risk assessment is completed, remediation activities may be defined to further improve product quality by means of continuous improvement of the manufacturing process. ■

The views and opinions expressed in this publication are those of the authors and do not necessarily reflect the official policy or position of Sandoz, Novartis or any of its officers.

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Table G Example of the risk assessment template

Factors	Parameters	Current settings/ specifications	Failure modes	Affected CQA/ compliance attribute	Probability*	Probability Rationale	Severity (S) †	Rationale S	Detectability ‡	Detectability Rationale	RPN §	Risk Level **	Risk mitigation/ control strategy/ CAPAs
API	Assay	Specifications	Vendor variability	Composition (assay)	1	In coming testing	4	Direct impact on quality	1	Procedures and controls	4	L	
	Related compounds	Specifications	Vendor variability	Impurities	1	In coming testing	4	Direct impact on quality	1		4	L	
	Identification	Specifications	Vendor variability	Composition	1	In coming testing	4	Direct impact on quality	1		4	L	
WFI	WFI	Specifications	Contamination	Impurities, endotoxin	1	Routine monitoring	4	Direct impact on quality	1		4	L	
Compounding	Mixing speed	50Hz	Incomplete mixing	Density, composition	1	Monitored	3	Direct impact on quality	2		6	L	
	Temperature	25 °C	Incorrect temperature	Density, composition	1	Monitored	3	Direct impact on quality	1		3	L	
	Amount API	API per formulation	Incorrect amounts API	Density, composition	1	Monitored	4	Direct impact on quality	1		4	L	
	Amount WFI	WFI per formulation	Incorrect amounts WFI	Density, composition	1	Monitored	4	Direct impact on quality	1		4	L	
	Hold time	48 hours	Incorrect time	Composition	1	Monitored	2	Direct impact on quality	1		2	L	
Sterile filtration	Filtration time	72 hours	Exceed time	Sterility	1	Monitored	1	Validated time is 72 hours vs. routine filtration time	1		1	L	
	Pressure	40 psig	Incorrect setting	Sterility	1	Monitored	3	Direct impact on quality	1		3	L	
	Device integrity	Bubble point: 50 psi	Broken membrane or device	Sterility	1	Monitored	4	Direct impact on quality	1		4	L	
Filling	Fill rate	180 units/min	Incorrect setting	Fill volume, particulate matter, assay, impurities, assay	1	Monitored	1	Impact on capacity	1		1	L	
	Env. monitoring	Viable/particle counts	Breach env.	Sterility, endotoxin	2	Monitored	4	Direct impact on quality	1		8	M	Procedures and alarms in place in case of excursions
	Hold time	48 hours	Exceed time	Assay, impurities, endotoxin, pH, osmolality	2	Monitored	2	Validated conditions	1		4	L	
	Syringe/vial	Spec. per CoA	Wrong component	Fill volume, particulate matter, impurities, sterility, endotoxin	1	In coming testing, monitored	4	Direct impact on quality	1		4	L	
	Stoppers	Spec. per CoA	Wrong component	Fill volume, particulate matter, impurities, sterility, endotoxin	1	In coming testing, monitored	4	Direct impact on quality	1		4	L	
	Alum Crimp (on vials)	Spec. per CoA	Wrong component	Sterility	1	In coming testing, monitored	3	Direct impact on quality	1		3	L	
Packaging	Temperature	25 °C	Extended exposure to high temperature	Assay, impurities	1	Monitored	3	Direct impact on quality	1		3	L	
	Prod. specific materials	Spec. per CoA	Wrong component	Labeling	1	Monitored	4	Direct impact on quality	1		4	L	
Storage	Temperature	25 °C	Incorrect temperature	Assay, impurities	1	Monitored	3	Direct impact on quality	1		3	L	
	Expiration Date	24 months	Exceed date	Assay, impurities	1	Monitored	4	Direct impact on quality	1		4	L	

Key : * Probability 1 = Lo 2 = Medium 3 = High 4 = Very high
† Severity 1 = No impact 2 = Negligible 3 = Impact to CQA 4 = Critical impact to CQA
‡ Detectability 1 = High 2 = Medium 3 = Low
§ RPN Risk priority number
** Risk level L = Low M = Medium

About the authors

Dr. Humberto Vega is Associate Director of SANDOZ,Inc., External Supply Operations – Manufacturing Science & Technology, based in Princeton, New Jersey. He has been in the pharmaceutical and food industries for over 27 years in multiple roles including Research Assistant, Process and Manufacturing Head of sterile and non-sterile pharmaceutical operations, Sr. Scientist and Associate Director of Validation Sterile, Vaccine and Biologics, and Technology Head-Vaccine Manufacture. He holds BS and MS degrees in chemical engineering from the University of Puerto Rico and a PhD in engineering science from Washington State University. He holds professional memberships in the Parenteral Drug Association, the Institute of Food Technologists, and ISPE.

Ricardo Rivera is Director of SANDOZ, Inc., External Supply Operations – Manufacturing Science & Technology, based in Princeton New Jersey. He has been in the pharmaceutical industry for almost 20 years in multiple roles including Global Head of Manufacturing Science & Technology – External Manufacturing, Global Technical Services Manager, Technology Transfer Lead and Manufacturing Supervisor. He holds a BS degree in chemical engineering from the University of Puerto Rico.

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Quest for the Magic Bullet

In ancient Greece, doctors such as Hippocrates and Galen considered cancer – which Hippocrates named – incurable. Since then, the dominant metaphor we've used to describe our relationship to this formidable foe has been martial: we wage war on cancer, patients battle the disease and we encourage ourselves that cancer can be beaten. An obscene, two-word, online meme, often posted when a well-known person succumbs to the disease, expresses the kind of direct, personal aggression we expect in combat.

Recent advances in drug development reflect this by alluding to the concept of a magic bullet. The term was coined in the early 1900s by Paul Ehrlich, a German hematologist and immunologist, who sought the means to deliver a deadly payload specifically to cancer cells. Having used methylene blue as a therapeutic agent against the malaria pathogen, he imagined the possibility of precise delivery of such a toxin – or magic bullet – by virtue of its being coupled to a compound that targeted the disease-causing organism. What was needed was a toxin, a delivery system and a way to link the two. The concept was extended to cancer therapy but it would take a century to arrive.

These days we might allow ourselves to believe that *Cancer Can Be Beaten* is not just a hopeful slogan; it might actually be true.

The first chemotherapy treatments were aimed at one of the chief characteristics of cancerous cells; they have escaped from the normal inhibitors that prevent the division of mature cells. The compounds that were chosen damaged DNA or prevented cellular division by other means. Among these were alkylating agents, such as nitrogen mustards, which bind covalently to DNA, RNA and proteins, rendering them inactive; antimetabolites, such as methotrexate, which interfere with cellular metabolism, often targeting DNA synthesis; and anti-microtubule agents that interfere with cell division by disrupting normal microtubule assembly or disassembly, thus truncating mitosis. The damage either prevented DNA replication and division outright or instigated cell cycle arrest and programmed cell death. The problem with these treatments has always been (to continue the martial imagery) collateral damage from friendly fire; cancer cells are not the only cells in our bodies that divide – hair follicles and the healthy lining of the gut are among tissues that also succumb to chemotherapy.

Recent exciting developments in oncology that stimulate or manipulate the immune system to treat cancer have resulted in protocols that tend to have fewer side effects, can be used longer and can be combined with other chemotherapies or treatments without adding to side effects. Among the promising immunotherapies are checkpoint inhibitors, which work by blocking molecules that inhibit immune response or activating stimulatory molecules. The FDA has approved seven such therapies for melanoma in the past five years, including the monoclonal antibody checkpoint inhibitors Yervoy (ipilimumab), which targets CTLA-4, and the two anti-PD-1 agents Keytruda (pembrolizumab) and Opdivo (nivolumab).[1, 2, 3, 6]

Other promising immuno-oncology treatments include adoptive T cell therapy (CAR-T) – in which a patient's T cells are removed, genetically modified to recognize antigens that are unique to that patient's cancer cells and reintroduced into the patient[4] – monoclonal antibodies, therapeutic vaccines, oncolytic viruses and cytokines.

But perhaps the targeted treatment most like Ehrlich's magic bullet are antibody drug conjugates (ADCs). ADCs have three components: an antibody, a pharmaceutically toxic payload, which is usually a microtubule inhibitor, and a chemical linker.[5] While many ADCs are in development, one area they are currently being used is in breast cancer, where treatment usually requires surgery followed by chemotherapy, radiation therapy, hormone therapy or targeted therapy.[6] Targeted therapies for cancers that overexpress the HER_2 receptor include trastuzumab (Herceptin), pertuzumab (Perjeta), lapatinib (Tykerb) and ado-trastuzumab emtansine (Kadcyla).[6]

We have basic science advances in molecular biology, immunology and cell biology to thank for this current spate of breakthrough biologics. These days, among the pink ribbons, PSAs and people willing to be vocal about their colonoscopies, we might allow ourselves to believe that *Cancer Can Be Beaten* is not just a hopeful slogan; it might actually be true. ■

Scott Fotheringham, PhD and James Hale

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