The Official Magazine of ISPE

PHARMACEUTICAL ENGINEERING®

July-August 2016 | Volume 36, Number 4

Novartis CEO Joseph Jimenez Reimagining Medicine

Progress on Drug Shortages

Alan Levy, 2015 ISPE Member of the Year

The Real Cost of Poor Data Integrity

Special Report: SUPPLY CHAIN MANUFACTURING

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The forest and the trees

Anna Maria di Giorgio, Editor in chief

Our industry exists to provide patients around the world with quality medicine. The effectiveness with which we accomplish this task, how we ensure patients are well served by the medicines we make, and the manner and timeliness in which we make them available, are part of our daily focus. And pharmaceutical engineers shoulder a fair portion of that equation.

It struck me during the recent ISPE/FDA/PQLI Quality Manufacturing conference that we spend a lot of time compartmentalizing processes so that we can have a stronger grasp of the whole system. ISPE members know there has been a concerted effort to break down the causes of global drug shortages. We started the ball rolling with our survey, in 2012, and identified the component parts of a prevention plan. Since then, there has been much conversation within the industry, among regulatory agencies, and throughout ISPE, about the subject. Five years since that first survey, drug shortages have declined. While we may not know the complete "why" of that decline, we know colleagues have been steadfast in addressing the many aspects of drug shortages that require attention, like agile quality systems, effective communicating with regulatory authorities, and a robust quality culture.

The Quality Metrics Wave 2 report shed light on industry's strengths and gaps, with quality culture rising to the top. One of the report's key findings is that quality culture has a bearing on quality outcomes, both internal and external.

Analysis of the parts, looking at the trees, tells one part of the story. But then we have to step back and look at the whole, the forest. And when we do that, when we add a holistic approach to problem solving, we have a more complete, better-informed view.

During this year's FOYA banquet, ISPE recognized two companies who, by virtue of the accomplishments for which they won a FOYA category award, are well positioned to avoid shortage situations or mitigate their impact on patients: Baxter Biopharma Solutions and Janssen Vaccines AG. Through their accomplishments, and because their view of the problem was broad, they have strengthened their abilities to mitigate drug shortages and minimize their impact on patients.

Fortunately, for the industry we serve and for us, ISPE members are skilled at both segmented and holistic analyses, and particularly talented at sharing their findings for the betterment of all. ■

Continued on page 6

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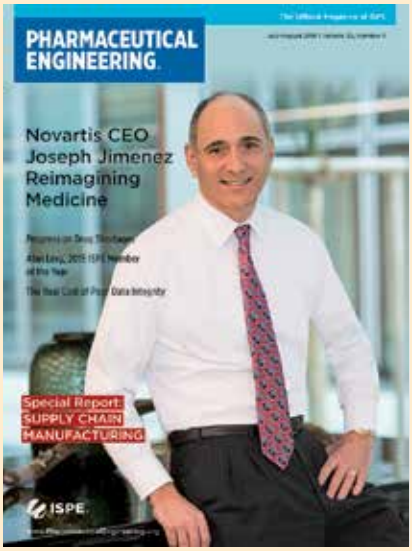

Cover photo: Novartis

Editorial Policy

Pharmaceutical Engineering inspires engineers and regulators around the world with engaging and useful articles. From technical articles that provide practical how-to advice to thought-provoking features on current issues, *Pharmaceutical Engineering* offers readers a global picture of the profession and the industry. Opinions expressed herein do not necessarily reflect the views of ISPE.

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Special Report: Supply Chain Manufacturing

65-80

Technical Articles

Back Page

"Patient Perceptions of IMPs," which appeared in the May/June 2016 Issue, should have included the following:

1. CCBR Clinical Research is also a site management company for the China study.

CCBR
CLINICAL RESEARCH

2. Contributor Paula McSkimming's biography should have read:

Paula McSkimming is currently a Trainee Biostatistician at the Robertson Centre for Biostatistics, University of Glasgow (RCB).

Paula graduated the University of Glasgow in 2012 with a BSc Honours Degree in Statistics. During her time as an undergraduate, Paula successfully completed a 10 week summer internship at Barclays Investment Bank and was offered a placement on their Global Operations Graduate Programme commencing September 2012. Following completion of the 18 month programme which included a 6 week placement in India to provide colleague training in a new processing system and achieving her Investment Operations Certificate, Paula moved to Global Technology within Barclays Plc in March 2014 focusing on projects for the Wealth & Investment Management business unit as a business analyst.

In May 2015, Paula seized the opportunity to utilise her degree and joined RCB where she has been developing her statistical analysis skills as first statistician in a number of observational studies and phase 3 clinical trials including studies that involve data linkage and has been gaining experience of phase 2 clinical trials as 2nd statistician. Paula is a user of SAS and occasionally R.

ISPE

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July 2016

7 UK Affiliate
National Biologics Manufacturing Centre
Darlington, UK

11–13 Basic GAMP® 5, Annex 11 and Part 11 (T45)
ISPE Training Institute
Tampa, Florida

14 San Diego Chapter
Full Day USP Purified Water Systems
San Diego, California

18–20 HVAC (T14)
ISPE Training Institute
Tampa, Florida

20 Greater Los Angeles Chapter
Control Systems: Trends & Legacy
Los Angeles, California

Pacific Northwest Chapter
Annual Golf Tournament
Redmond, Washington

21 Boston Area Chapter
Red Sox Social
Boston, Massachusetts

San Francisco/Bay Area Chapter
Fun Day
Napa, California

25–26 Cleaning Validation (T17)
ISPE Training Institute
Tampa, Florida

August 2016

8 Boston Area Chapter
14th Annual Summer Golf Tournament
New Durham, New Hampshire

8–9 OSD (T10)
ISPE Training Institute
Tampa, Florida

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

12 San Diego Chapter
Golf Tournament
Encinitas, California

17 Greater Los Angeles Chapter
Meeting
Los Angeles, California

19 Rocky Mountain Chapter
Golf Tournament
Erie, Colorado

22–24 Process Validation (T46)
ISPE Training Institute
Tampa, Florida

23 San Francisco/Bay Area Chapter
Cider Fermentation & Tasting
San Francisco, California

24–27 Singapore Affiliate
Conference and Exhibition 2016
Suntec City, Singapore

25 Midwest Chapter
Golf Tournament
Kansas City, Missouri

Singapore Affiliate
Student Poster Competition 2016
Singapore

September 2016

2 Singapore Affiliate
YP Go-Karting Challenge
Singapore

7 UK Affiliate
Quality Risk Management Evening
Event Speke, Liverpool, UK

8 Boston Area Chapter
YP Boston Harbor Boat Cruise
Boston, Massachusetts

Nordic Affiliate
Multipurpose Facilities
Stockholm, Sweden

San Diego Chapter
Tour of Poseidon Water Desalination Plant
Carlsbad, California

San Diego Chapter
Ballast Point Brewery & DNA Presentation
San Diego, California

12–13 Practical Application of GAMP® 5 (T11)
ISPE Training Institute
Tampa, Florida

12–14 Basic GAMP® 5, Including Revised Annex 11 and Part 11 (T45)
San Diego, California

13 Chesapeake Bay Area Chapter
Golf Tournament
Ijamsville, Maryland

15 Boston Area Chapter
Education Program: "Accidental Project Manager"

15–16 Biopharmaceutical Manufacturing Processes (T24)
ISPE Training Institute
Tampa, Florida

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

18–21 **2016 ISPE Annual Meeting & Expo**
Atlanta, Georgia

22 Belgium Affiliate
Technical Meeting: Containment
Isnes, Belgium

22–23 **Biopharmaceutical Manufacturing Facilities (T31)**
Clean in Place (T03)
Cross Contamination: Applying the Risk-MaPP Baseline® Guide (T41)
Technology Transfer (T19)
Atlanta, Georgia

26–28 **A GAMP® 5 Approach to Data Integrity (T50)**
A Risk-Based Approach to GxP Process Control Systems: GAMP® 5 (T21)
HVAC (T14)
QRM (T42)
Risk-Based Verification of Facilities, Systems and Equipment Workshop (T48)
Technology Transfer (T19)
Barcelona, Spain

29 Belgium Affiliate
SIG Automation Meeting
Braine-l'Alleud, Belgium

29–30 **Science and Risk-based C&Q (T40)**
ISPE Training Institute
Tampa, Florida

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Industry's Trusted Source of Knowledge

Photo: Novartis

Reimagining Medicine

Joseph Jimenez, CEO, Novartis

Those of us who have been working in the pharmaceutical industry for many years know that today's healthcare landscape is changing dramatically, and at a pace quicker than we've ever seen before.

Achievements realized over the last 50 years have led us to a milestone moment in health care. Our growing understanding of genomics, advances in medical science, and emerging technologies have put us on the cusp of a new wave of innovation. Today, the industry is identifying treatments for diseases that were once thought incurable, and more innovations are on the horizon. In 2015, a record 51 drugs were approved by the U.S. FDA, the most since 1950.[1] Almost 40% of these approvals were for biologic drugs, up from 22% in 2013. As our understanding of genomics and the way that disease manifests in the body has continued to develop, we can expect to see even further breakthroughs in the coming years.

At the same time, we are facing new challenges as the global population grows in size, age, and illness. The world's population is expected to increase by 1 billion by 2025, adding more than 500 million additional individuals over age 50.[2] According to the WHO, within the next 5 years the number of people over 65 will outnumber children under the age of 5 for the first time in history. As the population ages, chronic diseases such as diabetes, heart disease and cancer are becoming more prevalent. Globally, chronic disease deaths are forecasted to grow to over 70 percent by 2025.[3] In the U.S. alone, over 117 million people, or nearly half of the adult population, have at least one chronic disease.[4]

These environmental factors are putting a considerable strain on health systems around the world. This is because today's health systems were designed years ago and are not equipped to meet these challenges. The result is payer consolidation, more competition, and the emergence of disruptive technologies. We're also seeing increasing pricing pressure and a fundamental shift in how payers evaluate new medicines.

So, what does that mean for the pharmaceutical innovation community? For companies to be successful in this environment, we must adapt to the changing world around us. This means we need to reimagine medicine. To do this, we have to reimagine traditional processes and ways of working, including:

1. R&D, so that we can bring genuinely breakthrough treatments to market
2. Operations, so that we can scale up to meet the growing demand of the future
3. How we demonstrate the value our medicines provide to patients as the environment shifts to one that is increasingly focused on outcomes as an indicator for reimbursement
4. And finally, how our industry conducts business to ensure we never lose sight of who we're working to help: patients

At Novartis, this is what we are aiming to do. Our mission is to discover new ways to improve and extend people's lives. We are pursuing this mission with the vision to be a trusted leader in changing the practice of medicine. This is underpinned by a strong commitment to science-based innovation, allowing us to deliver breakthrough treatments to as many people as possible. As we look to the future, we are working to reimagine medicine in a number of ways.

The first is R&D, so that we can discover and develop innovative treatments that address unmet medical needs.

Innovation is the core of our industry, and we will continue to invest heavily in research and development. In 2015, we invested USD $9 billion in global R&D across our divisions. Our research strategy is focused on understanding how diseases manifest at the genomic level. Today we have more than 200 clinical development projects underway.

Oncology is a key area for Novartis, and one I'm personally passionate about. We have a strong history of innovating for cancer patients. Our drug Gleevec® turned CML from an almost certain death sentence to a chronic illness managed with our medication. Today, our strategy in oncology concentrates on developing targeted therapies and immuno-oncology, both of which are underpinned by a detailed understanding of the genetics of disease. We're prioritizing our efforts in five disease areas—hematology, breast cancer, lung cancer, melanoma, and renal cell carcinomas—where we feel we can have the most impact.

Immuno-oncology is a particularly exciting area, which uses the patient's own immune system to attack cancer. We are leveraging new technologies such as CRISPR (clustered regularly interspaced short palindromic repeats) for the discovery and development of medicines. This technology could potentially allow us treat genetic conditions by easily and precisely deleting, repairing or replacing mutated genes that cause disease.

Our CTL019 treatment that we're developing in collaboration with the University of Pennsylvania, is the first investigational therapy to establish proof of concept for this approach. In a recent study of CTL019 in children and young adults with relapsed or refractory acute lymphoblastic leukemia (r/r ALL), 55 out of 59 patients, or 93% experienced complete remissions. The FDA has granted CTL019 Breakthrough Therapy status. This status is one of the many firsts that have been accomplished for the industry with this new science, and we are committed to continuing to explore this promising area for patients.

Second, we must scale up our operations so that we can meet the growing demand of the future. As the global population ages, we expect demand for our products to rise considerably.

That means we need to begin tackling this challenge now to ensure we can successfully handle the significant increase in manufacturing capacity we expect will be needed over the next several years.

One way we're advancing towards this is by taking steps to increase cross-divisional collaboration across geographies and improving the way we work together internally. We want to combine all of our resources to ensure we have the capacity to support a growing portfolio. Earlier this year, we announced we would centralize our manufacturing operations across divisions within a single technical operations unit. We expect that this will of course help us streamline costs, but it should also help us improve quality. By centralizing our operations, we expect to be better positioned to develop next-generation technologies and share best practices.

In 2015, the US FDA approved a record 51 drugs, the most since 1950. Almost 40% of these approvals were for biologic drugs, up from 22% in 2013.

A great example is our biologics portfolio, which we expect to be an important growth driver for the company. In the next decade, we expect demand for biologics to increase significantly, up to eight times from today. This includes both innovative products, as well as generic versions of biologic medicines, or biosimilars. These products are difficult to make and require special skills and expertise, as well as specific infrastructure. We need to be ready to meet that demand. We are building our capacity for our manufacturing platforms so that we are able to quickly scale up and deliver for patients. We are creating best-in-class capabilities that will enable us to have a smaller manufacturing footprint with increased capacity. For instance, the growing demand for our drug Cosentyx® has prompted us to focus our efforts across the entire chain to ensure that we can meet this in the near term.

We're also leveraging new technologies such as continuous manufacturing to speed up the traditional method of producing and packaging drugs. Historically, it can take up to 12 months to manufacture a drug, but continuous manufacturing can produce the same product in just hours, from start to finish, and at a much lower cost. Companies can save an estimated 30 percent or more in operating costs by reducing product-quality failures,

cutting waste, and shortening production timelines. Since 2007, we have been working with the Massachusetts Institute of Technology to develop the joint Novartis–MIT Center for Continuous Manufacturing, investing $65 million. This is one of MIT's largest industrial research collaborations ever. Together we have already developed the first prototype process that produces drug tablets from raw chemical ingredients in a continuous end-to-end process. In fact, we have already started to implement this technology at one of our manufacturing facilities in Switzerland. We expect this technology will enable us to produce medicines for significantly less cost and with faster lead times, all while helping deliver better quality.

As we work to innovate how we manufacture our drugs, we expect that a key piece of this will be our ability to attract the best talent in the world, with deep functional expertise and leadership capabilities. We want to build the strongest team in the industry, and we aspire to be an employer of choice.

The third piece is how we demonstrate the value our medicines provide.

The aging population is putting enormous pressure on national health care budgets, and we expect this trend to only continue as new innovations reach the market. As budgets continue to shrink, governments and other payers are increasingly linking spend on drugs to demonstrated real world outcomes. These outcomes help payers assess the level of value our products deliver compared to other treatments and inform reimbursement decisions.

As an industry, we need to develop long-term and sustainable solutions. We need to demonstrate the value of our medicines bring to patients, payers and society, and collaborate more than in the past.

For the past several years, we at Novartis have been moving away from the industry's traditional business model of simply selling pills, toward delivering positive patient outcomes. We're developing a number of innovative pricing models, including risk-sharing models, integrated care programs to help improve the overall health of a patient, and social ventures to help expand access in the developing world.

In the U.S., we've developed pay-for-outcomes agreements with health insurance companies including Aetna and Cigna. If our products don't work as we expect them to, we'll reduce the price to payers. Take our heart failure drug Entresto®, for example. If the hospitalization of patients on Entresto exceeds a prespecified threshold, Novartis will reduce its price to payers. This is attractive to payers because heart failure is a growing public health concern that costs the world economy over $100 billion annually. On our drug Entresto, patients are 21% less likely to be hospitalized. Entresto also reduces mortality by 20% compared to those given the current gold-standard treatment. We've reached similar agreements linked to clinical outcomes for our cancer drug Tasigna® and Gilenya® for multiple sclerosis.

Outcomes-based contracting models are a promising way to support access while demonstrating the real-world benefits of innovative medicines. By collaborating with payers on solutions-oriented approaches to reimbursement, we believe we are doing our part to shift the paradigm of pricing in our health care system.

Another way we're doing this is by creating integrated care programs, which offer broader, more holistic solutions "beyond the pill" that can improve overall health, such as physical rehabilitation and medical counseling. For instance, with our multiple sclerosis treatment Gilenya, we're considering the entire patient experience and offering additional support, such as interactive, patient-friendly web-based tools and educational online platforms. Another example is our work in Brazil for the last decade through our program called Vale Mais Saúde, which supports patients and physicians in overcoming adherence challenges. This program provides educational materials to patients, as well as tools such as a virtual help line and medication reminders through text messages. We also offer significant discounts on a large portfolio of products to improve access. Four million patients have taken advantage of this program across 40 products.

We must scale up our operations so that we can meet the growing demands of the future

We realize that we cannot neglect those patients in low- to middle-income countries, so we have established social ventures that expand access to health care by helping bolster infrastructure, strengthen distribution channels, and build local capabilities. In India an estimated 65% of the population does not have access to health care, especially in rural areas. Novartis created *Arogya Parivar* ("healthy family" in Hindi) to expand access to care in these areas. Through the program, Novartis recruits and trains locals to become health educators who inform communities about healthy behaviors. Local teams work with doctors to organize health camps in remote villages to provide access to screening, diagnosis, and treatment.

In addition, we recently launched Novartis Access, a new program that provides a portfolio of 15 on- and off-patent medicines that address key noncommunicable diseases such as cardiovascular conditions, diabetes, respiratory illnesses and breast cancer to low-and middle-income countries. The program launched in Kenya and Ethiopia in 2015, and we expect to introduce the program to five additional countries in 2016.

The final piece is how our industry conducts business. Lack of trust is still a major issue for our industry, and one that we must work together to overcome. I personally spend a lot of time talking with physicians about the topic of trust. Many have told me that they have become disillusioned with some companies about the pricing of medicines. These physicians—among other stakeholders—expect us to help make the world a better place. We share that expectation. We invest in high risk activity to discover new medicines, and most of the time we are not successful. When we are, we must earn a return for this cycle of investment and discovery to continue.

Society has also raised its expectations of our industry. At Novartis, we are making changes to ensure we lead with integrity and demonstrate the highest standards of ethical business conduct. One example is how Novartis is approaching medical education, including congress attendance. From January 2017, the company will offer doctors support to attend medical

conferences based on their active participation in the event. Novartis will also sponsor physicians to speak on its behalf in clearly defined instances, for example, when a new product becomes available, a new indication is added to an existing product, or significant new clinical data are released. On these occasions, doctors are best equipped to brief their peers on how a drug can be used safely and effectively—a crucial step in ensuring that the right patients can benefit from advances in treatment. At the same time, Novartis is investing more than ever before in developing and adopting innovative digital communication tools that will provide a growing number of doctors around the world with important information about the safety and efficacy of its products. Finally, Novartis is also working to incentivize associates—including our field force—based on the values and behaviors we want to encourage. This is a cultural journey for our company. We have to make sure that our associates, no matter the situation they're facing, will act with integrity and do the right thing.

Another way we can change the way our industry conducts business is by strengthening our collective focus on patients, ensuring we do everything we can to improve their lives. At Novartis, we want all of our employees to share this patient-focused mindset through meaningful engagement with our mission. That is why we launched Long Live Life a few years ago, an internal program to rally our people around our mission, and celebrate the fact that a normal life is extraordinary. Because when someone is sick, all they want to do is get back to normal. We asked associates to share photos, stories, and ideas to engage with our mission and explain what it means to them. Long Live Life has since become nothing short of a movement led by our people. It has become a collective expression of what we stand for and believe in. As a result, engagement with our mission has increased at all levels throughout the company, which I believe translates into better business performance and ultimately better medicines for people who need them.

Conclusion

As we look to the future, it's clear that today's health care environment demands that we reimagine how we operate at every junction, from the lab bench, to the manufacturing floor, and to the way we sell our drugs. We must work to build trust in our industry, while reminding ourselves of how important our work is and the impact it has on society. As we reimagine medicine, let us work together to build a stronger industry that will deliver the best medicines and cutting-edge innovation. ■

References

1 Source: *Forbes*, "2015 New Drug Approvals Hit 66-Year High," 2016
2 Source: United Nations, "World Population to Increase by One Billion by 2025," 2013
3 Source: World Health Organization, "The Global Burden of Disease: Updated Projections," 2015
4 Source: Centers for Disease Control and Prevention, "Chronic Disease Overview," 2015

FOYA 2017

Facility of the Year Awards

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Also in this section

General Session On Drug Shortages Reveals Progress

First drop since 2012

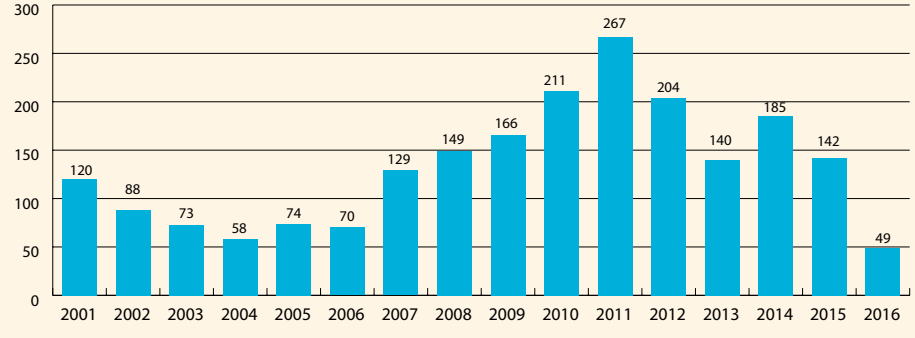
Drug shortages were the topic of the General Session on Day 1 of the ISPE/FDA/PQRI Quality Manufacturing Conference. Speakers during the general session Clinical Implications of Drug Shortages, ranging from private practice to industry, and regulatory agencies, took to the podium to share stories, exchange information, and highlight the progress that has been made. ISPE Chair Joseph Famulare, VP, Global Compliance and External Collaboration, Pharma Technical Quality, Genentech/Roche, US, was the session's moderator.

"This is the first time in five years we have seen a drop in drug shortages"

Famulare began by thanking the ISPE Drug Shortages Task Team under the leadership of François Sallans, CQO at J&J, in moving the drug shortages initiative since ISPE launched the survey on the root causes of shortages (2013) and the associated contribution to FDA's Strategic Plan for Preventing and Mitigating Drug Shortages presented to Congress the same year. He went on to highlight the ongoing and constructive collaboration with both FDA and EMA; the ISPE Drug Shortages Prevention Plan (2014); the ISPE Drug Shortage Assessment and Prevention Tool (2015); the Drug Shortages Introductory Webinar (2016) and the preparatory work done for more extensive drug shortages training; and the drug shortages prevention recognition now included in the FOYA program.

Looking ahead Famulare described ISPE's ongoing drug shortages activities, including participation in exploratory work streams being established by EMA.

NEW NATIONAL DRUG SHORTAGE BY YEAR, JANUARY 2001 – MARCH 31, 2016



Courtesy Erin Fox, Director, University of Utah Drug Information Service

"The solutions to drug shortages is the elimination of drug shortages," stated Dr. Unguru. The slide shows that drug shortages have dropped at a steady pace since 2012, yet more remains to be done to eradicate the problem.

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

Later that afternoon, both François Sallans and Fran Zipp, President and CEO of Lachman Consulting, as well as an ISPE Board member, delivered an update on the ISPE Drug Shortage Assessment and Prevention Tool. Dave Doleski, Acting Deputy Director of the USFDA Office of Pharmaceutical Quality, who introduced the afternoon's session, noted similarities between the ISPE Drug Shortages Assessment and Prevention Tool and material that FDA is developing for the New Inspection Protocol. He encouraged those in the room to download and use the tool, saying that anyone using the (ISPE) tool "may be in a better place when FDA goes to the New Inspection Protocol."

Sallans reminded the audience that ISPE's tool is one that takes theory, and makes it practical. "It is intended to drive interdisciplinary conversations within organizations," he stated. He stressed, too, the need for ongoing communication with Regulatory Agencies, rather than only once a crisis hits.

Dr. Yoram Unguru, MD, MS, MA, Division of Pediatric Hematology/Oncology, Herman & Walter Samuelson Children's-Sinai, Berman Institute-John's Hopkins, US, was Monday's General Session keynote speaker. He delivered an energetic and passionate call to arms, "When Drugs are Short, but the Ethical Challenges are Long: The Absurdity of Having to Choose which Children Receive Scarce Life-saving Chemotherapy."

Readers may recall Dr. Unguru was one of the invited guests on *The Diane Rehm Show*, which aired on NPR on 1 February 2016, and on which ISPE Chair Joe Famulare was also an invited guest.

Dr. Unguru's overriding message is that solving the drug shortage problem will require multilevel stakeholder engagement, yet stakeholders may not share the same set of priorities. He provided background about chemotherapy shortages and the unique ethical issues they raise for clinicians and institutions. He discussed efforts within the childhood cancer community to address the shortages. Delegates will have the opportunity to reflect on their respective organization's responsibility and approach to the drug shortage problem.

Dr. Unguru delivered two surprising news items: that "this is the first time in five years we have seen a drop in drug shortages," with Q1 2016 registering only 49 shortages, and yet, "80% of leukemia drugs are in short supply." Most surprising of all was his reveal that there are more drug shortages in the US than anywhere else in the world. "We own this problem," he said, and "the solution (to drug shortages) is to prevent them." He characterized drug shortages as a "national emergency/natural disaster/national disgrace."

Dr. Unguru stated that drug shortages directly impact patients' lives, especially children with cancer, and that they are particularly vulnerable to drug shortages. "Drug shortages result in increased medication errors, delayed administration of life-saving therapy, inferior outcomes, and patient deaths," he said. "They prevent clinicians from providing a reasonable standard of care and hinder critical clinical research essential to guarantee ongoing advances and improving outcomes."

The core of his presentation focused on the ethical dilemma inherent in administering drugs to children with cancer during a shortage situation. He advocated for clinicians and policymakers to make thoughtful and reasoned prioritization decisions; and for health care authorities "to provide a transparent and defensible framework to assist providers and administrators forced to make difficult, and at times tragic, rationing and prioritization decisions for children with cancer." ■

Anna Maria di Giorgio

Get Published in *Pharmaceutical Engineering* Magazine!

If you would like to publish in *Pharmaceutical Engineering* in 2017, the deadlines and guidelines for publication are ready for viewing at www.pharmaceuticalengineering.org/pharmaceutical-engineering-magazine/editorial-calendar2

The 31 August deadline for content for the **January–February issue** of *Pharmaceutical Engineering* is fast approaching. This kick-off issue for the year will put a spotlight on leaders and innovators across all ranks of the pharmaceutical and biopharmaceutical industry. Know someone who is working on robotics; Someone who is making inroads in sustainable manufacturing; Or someone who has taken CAR-T technology to new levels? Let us know about it! If you have suggestions for profiles you believe your peers would like to read about, please contact me at amdigiorgio@ispe.org.

And on the scientific side of things, we would like to see articles on topics like C&Q and process validation in the **January–February issue** of *Pharmaceutical Engineering*.

Remember, the deadline for scientific article submission is 31 August, so upload your submissions as soon as you can!

Anna Maria di Giorgio

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Nicole Pierson
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China Annual Spring Conference

Ying Qi and Jackie Liu

The 2016 ISPE China Annual Spring Conference, held 10–11 April in Shanghai, China, under the theme "Innovation, Transformation, Globalization: New Paradigms for Pharmaceutical Technology, Quality, and Compliance in China," was a great success. As one attendee put it: "This conference succeeded in covering hot topics with valuable content that showed ISPE's strong technical backbone and leading role in the industry."

Theodora Kourti, Senior Vice President, Global Regulatory Affairs, ISPE, gave the opening address. Michael Arnold, Senior Director, Strategic Partnerships, Global Clinical Supply Chain, Pfizer; David Churchward, Expert GMDP Inspector, UK Medicines and Healthcare Products Regulatory Agency (MHRA); and Christine Moore, Global Head and Executive Director, CMC Policy, Merck; gave keynote speeches on regulation and inspection convergence, quality metrics, data integrity, and the challenges and opportunities associated with the advancement of pharmaceutical manufacturing.

Some 650 participants, from manufacturers, service providers, vendors, and regulatory associations such as the US Food and Drug Administration, the Medicines and MHRA, and the China Food and Drug Administration, actively engaged in five tracks:

- Regulatory, quality, and compliance
- Manufacturing and engineering
- Chemical drug product and manufacturing process
- Biological drug product development
- Manufacturing and clinical supplies

Participation from local companies hit a record ratio of 42%. Attendees enjoyed sharing knowledge with regulators and delegates from flagship enterprises, and exploring better quality and compliance with current regulatory changes. New ideas such as data integrity and continuous manufacturing, under the concept of the "Plant of the Future Manufacturing," are hot topics that continue in WeChat group discussions.

Prior to the conference, a workshop for regulators and industry leaders on 9 April attracted about 50 participants for an intensive discussion on compliance, quality, and data integrity, and advanced manufacturing, including continuous manufacturing, drug development, and product quality improvement. The workshop explored how new technologies can be adapted to regulatory reform while innovation is encouraged to advance drug development.

The conference ended with a tour of the Boehringer Ingelheim, Roche, Fudan-Zhangjiang, and Tofflon facilities. ■

David Churchward keynote address


Data integrity session panel discussion


Question-and-answer session


Dr. Theodora Kourti and Charles Tong at the reception

Michael Arnold keynote address

"This conference succeeded in covering hot topics with valuable content that showed ISPE's strong technical backbone and leading role in the industry."

Dr. Christine Moore, Merck, at the preconference workshop

Ms. Chen Huiping from CFDI of CFDA

Mr. Chen Shifei from Zhejiang FDA

Roche facility tour

Conference speakers and ISPE volunteers

CaSA Chapter Hosts Events for Students and YPs

Résumé and Interview Skills Workshop

Marisol Patino, Chair, Student Affairs
ISPE Carolina–South Atlantic Chapter

Jennifer Hatley www.jlhphotography.com

Technology conference bridge-building exercise

This spring, students from the Carolina–South Atlantic (CaSA) Chapter had the opportunity to attend a Résumé and Interview Skills workshop at North Carolina State University's Biomanufacturing Training and Education Center campus. Panelists comprised 10 professionals with varying roles within the STEM disciplines. All had experience in hiring and recruiting, project management, manufacturing, engineering, career coaching, and R&D. Companies represented included the US Environmental Protection Agency, the DP Group, Mangan, Inc., Catalent Pharma Solutions, Kelly Services, Fujifilm Diosynth Biotechnologies, Hazen and Sawyer Engineering, Seqirus, and Merck.

The workshop kicked off with an open question-and-answer forum. Students were able to ask the panelists about résumés or interviewing. Typical questions covered interview attire, résumé formatting, and dealing with difficult interview questions. Students in the midst of

Participants learned the importance of managing their weaknesses and using their strengths as a springboard for long-term career development.

career changes expressed interest in relating skills from other industries as they sought out new roles. Panel members did an excellent job of guiding students and giving them tips on how to set themselves apart from "the stack of résumés."

In the next segment, each professional worked with two to three students. Students came prepared with their printed resumes, and each got a chance to have a professional review his or her resume and provide one-on-one feedback. Students were also able to compare their feedback and ideas. The industry professionals benefited from the opportunity to meet ambitious and talented students from local universities.

One thing students often underestimate is the willingness of seasoned professionals to share their experiences. Students need not only the resources to excel, but also the encouragement to explore new positions. Making the transition from student to professional can seem uncertain and, at times, even frightening. CaSA aims to connect students and professionals to ease the transition. After all, the real world is a little less scary when you see a familiar face!

Technology Conference

Lindsey Daniel, PE, and Ashley Harp, PE

CRB's Lindsey Daniel, PE, and Ashley Harp, PE, conducted a presentation at the 2016 CaSA Technology Conference for Students and Young Professionals to help attendees identify their strengths and manage their weaknesses.

Participants learned the importance of managing their weaknesses and using their strengths as a springboard for long-term career development. The group discussed how organizations have evolved over the past 10–15 years to focus on developing an individual's strengths and building teams that allow members to use their strengths in their given roles. Organizations that have taken this approach are creating high-functioning teams and outperforming their peers.

CRB sponsorship enabled attendees to take the Clifton StrengthsFinder test. The online assessment comprises 177 questions and has an allotted time of 20 seconds per question to ensure first-instinct responses. Results are based on over 30 years of research and more than 100,000 talent-based interviews. The test measures the individual's talent and highlights the greatest potential for building personal strengths.

After the main presentation, students divided into groups for two breakout sessions. In the first session they worked through discussion questions that led them to assign each member a role on a bridge-building design team based on their strengths. During the second breakout session, the students were given materials to design, budget for, procure materials, build, and sell their bridge. The goal was to work in the identified roles based on their strengths to succeed as a team.

The sessions wrapped up with a group discussion on how to identify others' strengths and use them in a team setting, what strengths are important for roles within the industry, and feedback on the presentation and group activities. The overall feedback was extremely positive as the students enjoyed engaging in the team breakout sessions and felt more aware of their strengths and how they fit into their teams. ■

Resumé and interview skills workshop panel session

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Highlights from the 2016 ISPE/FDA/PQRI Quality Manufacturing Conference

The fourth ISPE/FDA/PQRI Quality Manufacturing Conference, held 6–8 June 2016, provided an avenue for regulators and industry to collaborate on innovations in pharmaceutical manufacturing, and an opportunity to network in a stimulating learning environment. More than 300 attendees had front-row access to some of the pharmaceutical industry's most influential quality manufacturing speakers and regulators. Sessions were packed with attendees as they heard from speakers on four engaging tracks: Manufacturing and Operational Excellence, Transformation of Quality Oversight, Frontiers in Manufacturing Science and Quality, and Quality Metrics. Twenty-two vendors filled the exhibit hall.

A full house listens to the first keynote address.

Data Integrity Workshop

ISPE's first Data Integrity Workshop was held Sunday, 5 June, in conjunction with the Quality Manufacturing Conference. Presentations by regulators and industry leaders gave participants an opportunity to learn about current thinking on the topic of data integrity and compliance with cGMP.

- Fran Zipp, President and CEO of Lachman Consultant Services, and member of ISPE's Board of Directors, asked "Why are we talking about data integrity?" as she opened the half-day event. "It's a basic principle to assure the quality of our health care products. If you're not talking about data integrity, you should be. If don't have a data integrity plan, you probably have a problem and don't know it."
- Sarah Barkow, Team Lead and Consumer Safety Officer at FDA and co-leader of the FDA's new draft guidance discussed data integrity's fundamental role in CMGP. "Without it" she said, "anything can be obscured."
- Sion Wyn, Director of Conformity, Ltd., discussed the importance of data governance, which he defined as behavioral controls (people), procedural controls (process), technical controls (technology).
- Mark Newton, Associate Senior Consultant, QA, Global Laboratory Informatics for Eli Lily and Company, talked about human factors in data integrity.
- Lorrie Vulolo-Schuessler, Manager, Computer Systems Quality Assurance, GlaxoSmithKline, tackled data integrity issues in the laboratory. "In this industry," she said, "we have to get this right. I tell people to work as if your 401(k) depends on it—because it does."
- Barry Rothman, Director of Lachman Consultant Services, discussed data integrity in manufacturing operations and management accountability. "Without management support and buy-in," he explained, "all bets are off. Management accountability starts with effective leadership."
- Mike Rutherford, GAMP Global Chair and Consultant, Business Systems Support, Medicines Development Unit, Eli Lilly and Company, called data integrity a key element of any quality management system. "It's one thing to put the controls in," he noted, "but if you don't execute them properly, you're not better off."
- James Davidson, Vice President, Lachman Consultant Services, closed the session with a presentation on detection, assessment, and prevention of data integrity issues and potential instances of fraud.

An attendee asks a question.

Data Integrity Workshop: Sion Wyn, Director, Conformity Ltd., discusses the importance of data governance.

Data Integrity Workshop: Sarah Barkow, Team Lead and Consumer Safety Officer, FDA, discusses data integrity's fundamental role in cMGP.

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Interactive breakout sessions also allowed attendees to discuss how to identify, mitigate, and remediate potential causes of breaches in data integrity.

Critical takeaways were that companies must be proactive in searching for data integrity issues. If something is discovered, they must investigate, assess, and be transparent. The bottom line: Data integrity ensures patient safety.

Day 1

Dr. Dara Corrigan, FDA's Associate Commissioner for Global Regulatory Policy in the Office of Global Regulatory Operations and Policy, delivered the first of two keynote addresses at the opening session on Sunday, 6 June.

Dr. Corrigan spoke about the FDA Mutual Alliance Initiative, a collaboration with the European Union to ensure that the public has access to quality pharmaceuticals. "Globalization has informed the work we do," she said. "It's changed the way we operate and the way we look at challenges."

"FDA must engage their global partners," she concluded. "There is a need for change and need for action. This year that change is going to happen."

Lynne Krummen, Vice President and Head, Pharma Technical Development, Genentech Inc., delivered the second keynote of the day: "Biotechnology: Past, Present, and Future."

Breakthrough timeline will shrink development timeline, Krummen said, sometimes in half. "But to move toward the future with innovation we need partnership between industry and regulators," she added. "Roche supports efforts for regional and global harmonization."

Dr. Theodora Kourti, ISPE Senior Vice President, Global Regulatory Affairs, addresses the audience.

"Our purpose," she said, "is doing now what patients need next."

Manufacturing and Operational Excellence

Conrad Mutschler, Vice President, Global Supply Chain Strategy, Perrigo Company plc, opened first Manufacturing and Operational Excellence education session on 6 June. In the first of three presentations, Mutschler discussed "Building and Sustaining a Culture of Continuous Improvement."

A continuous improve culture presents challenges and opportunities, he said. But while the concept of continuous improvement may be different in other industries, continuous improvement is what we do in the pharmaceutical industry. "It's why there's a 'c' in cGMP. And cGDP, cGLP, and cGXP," Mutschler explained.

Lynne Krummen (right), Vice President and Head, Pharma Technical Development, Genentech Inc., and Dr. Dara Corrigan, FDA's Associate Commissioner for Global Regulatory Policy in the Office of Global Regulatory Operations and Policy, share a smile with an audience member during the first keynote session.

François Sallans (right), Vice President Quality and Compliance, Chief Quality Officer, Johnson & Johnson, asks a question.

Richard Friedman, Deputy Director, Science and Regulatory Policy, Office of Manufacturing Quality, CDER, FDA, followed with "The Importance of Quality Assurance throughout the Lifecycle." "What is a state of control?" he asked. "It starts with process robustness." This drives sound life cycle decision making, vigilantly monitors processes and product through management oversight."

Brian Severson, Water Systems Engineer for Sage Products, finished the session with "The Effects of Critical Utilities on Product Quality." Severson used an example from industry in which a company had a microbial issue, but couldn't determine its source. After some investigation, they discovered that a faulty water tank vent filter pulled in microbes as the water cooled. "Simple things can end up being huge problems," he said.

Transformation of Quality Oversight

Ingrid Markovic, Special Advisor to the Associate Director for Review Management, Office of the Center Director, CBER, FDA, presented "Knowledge Management over the Product Life cycle" as part of the Transformation of Quality Oversight track on Sunday.

Knowledge management maximizes the use of acquired, analyzed, stored, and disseminated information, as part of an effective change management system. Sources include prior knowledge, published information, development studies, process validation studies, manufacturing experience, deviations, inspection actions, APRs, and PQRs. "Look at the big picture," Markovic said. "Collected information should not be viewed in isolation."

Knowledge management, together with quality risk management, helps establish and maintain the state of control while promoting innovation and continuous improvement. Companies should consider all pertinent sources of knowledge acquired throughout the life cycle in an integrated fashion. Knowledge management should be linked to a change management process, and knowledge should be shared and communicated early within and outside of the firm.

Day 2

Dr. Michael Kopcha, Director, Office of Pharmaceutical Quality, CDER, FDA, delivered the keynote address on the second day of the conference, 7 June 2016,. Dr. Kopcha presented an overview and update on FDA's Office of Pharmaceutical Quality.

Dr. Michael Kopcha, Director, Office of Pharmaceutical Quality, CDER, FDA, delivers the second keynote address.

For 2016, OPQ is focused on four priorities: a more rigorous and comprehensive approach to drug quality surveillance and inspection, team-based quality assessments that integrate quality review with inspection results informed decision-making on facility acceptability and application approvability, formal risk-based regulatory approaches that effectively define the scope and extent of quality assessments, and a collaborative approach with manufacturers that encourages innovation and the adoption of new technologies.

"Our common goal is drug product quality," Kopcha said. "There needs to be a conversation, and it needs to go both ways. It has to be a dialogue, a discussion. Let us communicate, collaborate, and work together to deliver a high quality product that meets the patient's needs—a true partnership."

Alonza Cruse, Pharmaceutical Quality Program Director, FDA/ORA, Office of Operations, fields questions from the floor.

FDA/CDER/OC

Thomas Cosgrove, Acting Director, Office of Compliance, CDER, FDA, presented "Update from the Office of Compliance" at the first Transformation of Quality Oversight session.

"Everything we do in data integrity is in pursuit of Dr. Woodcock's twenty-first-century manufacturing vision, which is as applicable today as it has always been," he said. "This means there should be an appropriate balance between industry and regulators: Regulators should not detract from industry's ability to self-correct and produce quality drugs. But we're ready to step in when needed."

3D Printing

"Frontiers in Manufacturing Science and Quality: Cutting-Edge Developments and Futuristic Products" was the third Emerging Technologies session on Day 2. Moderator Sau (Larry) Lee opened the session by noting that "Emerging technology should receive as much attention as continuous manufacturing."

Adam Procopio, Senior Principal Scientist, Merck & Co., Inc., discussed "Enabling Adaptive Drug Products via Additive Manufacturing," the first presentation in the session.

Three-dimensional printing, also known as additive manufacturing, is a small but quickly growing part of the pharmaceutical industry. "3D printing is a revolution," said Procopio. "Once I saw 3D printers in action," he continued, "I saw the light about what they could do for drug production in the future."

"Additive manufacturing is poised to bring about a revolution in the way drug products are designed, manufactured, and distributed to end users," he concluded.

Facility of the Year Awards Banquet

Martin Teo, Project Director, AstraZeneca China and winner of the 2015 Overall FOYA Award, was the banquet keynote speaker.

ISPE and industry leaders recognized the 2016 Facility of the Year Award (FOYA) category winners for their innovation and creativity in pharmaceutical and biotechnology facility

Genentech group

Rich Kennedy, Director, Pharma Partner Business Development, Baxter BioPharma Solutions

Joel Delgado Hernández, Facilities Management Site Manager, Ethicon, LLC

Chris Schreil, Senior Principal Engineer/ Project Advisor, Genentech, a Member of the Roche Group

Peter-Jost Spies, Lead Engineering & Maintenance, Janssen Vaccines AG

Pfizer Inc. group

J&J Companies: Left: Janssen Vaccines AG. Fourth from left: Jim Breen, VP Worldwide Engineering–Technical Operations, Johnson & Johnson, and FOYA Judges Chair . Second and third from right: Ethicon. Far right: François Sallans.

Takara Bio Inc. group

FOYA Ceremony Highlights Drug Shortages Prevention Efforts

Janssen Vaccines AG and Baxter Biopharma Solutions recognized at FOYA awards ceremony

ISPE honored nine exemplary projects from around the globe at the 2016 Facility of the Year Awards (FOYA) reception and banquet. The ceremony was part of the 2016 ISPE/FDA/PQRI Quality Manufacturing Conference, held June 6–8, 2016, in North Bethesda, Maryland.

During this year's banquet, ISPE recognized two companies who, by virtue of the accomplishments for which they won a FOYA category award, are well positioned to avoid shortage situations or mitigate their impact on patients.

Baxter Biopharma Solutions, category winner for Operational Excellence, expanded capacity to service the CMO market of parenteral oncology, thereby accommodating the need for lifesaving unit dose products. Janssen Vaccines AG, category winner for Project Execution, responded to the 2014 Ebola outbreak in West Africa by accelerating the development of its candidate Ebola vaccine, resulting in a launch capacity of up to 5 million doses annually.

"Both are truly visionary projects," said Bournas, "and very much in line with our commitment to the manufacture of quality medicines for patients. We thank each of winners for working to ensure that quality medicines reach the people who need it, when they need it, anywhere in the world."

Daniel O. Blackwood, Director, Advanced Technologies Prototyping & Implementation, Pfizer Inc.

Junichi Mineo, Managing Director, Takara Bio Inc.

Mr. Sanchai Pilenkaew, Assistant Managing Director, Greater Pharma Manufacturing Co. Ltd.

John Mulgrew, Project Manager, University of Strathclyde, CMAC

Ed Hill, Sr. Program Manager, West Pharmaceutical Services, Inc.

design, construction, and operation at the FOYA reception banquet on Tuesday, 7 June.

Dave DiProspero, Associate Director of Pharmaceutical Process Technology, CRB, ISPE FOYA Committee Chair, and the evening's host, welcomed 125 guests and winners from around the globe at the opening reception and dinner to celebrate and highlight the best of the best in 2016—the exemplary projects that epitomized the spirit of FOYA.

ISPE President and CEO John Bournas took the stage to thank the honorees. He also recognized Category Winners Baxter BioPharma Solutions and Janssen Vaccines AG for their exceptional leadership in Drug Shortages Prevention. (*For more information see "FOYA Ceremony Highlights Drug Shortages Prevention Efforts" page 27.*)

James Breen, Vice President, Engineering & Technical Operations, Johnson & Johnson, and Chair of the judging committee, thanked his fellow judges and introduced a new category award for 2017: Facility of the Future. This award will recognize the application and/or implementation of innovative design concepts, new technologies, and unique solutions that exemplify the next generation of agile, flexible, efficient, and effective new and existing Life sciences facilities.

Martin Teo, AstraZeneca China, winner of the 2015 Overall Award and the evening's keynote speaker, shared his experience in becoming a FOYA winner and the importance of the win not only for the company but his country as well. ■

Amy R. Loerch
All photos by Rick Brady Photography, Riva, Maryland

FOYA 2016 Category Winners and Honorable Mentions

Category	Project	Winner
Category winner: Operational Excellence Special Recognition: Prevention of Drug Shortages	Solutions Oncology Manufacturing Expansion	Baxter BioPharma Solutions
Category winner: Sustainability	San Lorenzo Conservation Strategy	Ethicon, LLC
Category winner: Process Innovation	CCP2 Manufacturing Facility and Return to Service	Genentech, a Member of the Roche Group
Category winner: Project Execution Special Recognition: Prevention of Drug Shortages	Fast Track Refurbishment for Ebola Vaccine Production	Janssen Vaccines AG
Category winner: Equipment Innovation	The Portable, Continuous, Miniature, and Modular Collaboration	Pfizer Inc.
Category winner: Facility Integration	Center for Gene and Cell Processing Construction Project	Takara Bio Inc.
Honorable Mention	Greater Pharma Manufacturing New Facility	Greater Pharma Manufacturing Co. Ltd.
	Technology & Innovation Centre	University of Strathclyde, CMAC
	Kinston, North Carolina, Ready-to-Sterilize (RS) Expansion	West Pharmaceutical Services, Inc.

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ISPE Releases Wave 2 Quality Metrics Report

On Wednesday, June 8, 2016, at the ISPE/FDA/PQRI Quality Manufacturing Conference in North Bethesda, Maryland, members of the ISPE Quality Metrics Core Team debuted ISPE's much-anticipated Quality Metrics Wave 2 Report.

Panelists included Peggy Speight, Executive Director, Bristol-Myers Squibb; Steve Greer, Quality Assurance External Engagement, Procter & Gamble; Paul Rutten, Partner, McKinsey & Company; Vanya Telpis, Director of Knowledge, McKinsey & Company; and Mairead Goetz, Head of Compliance, Novartis Pharmaceuticals Corporation.

Wave 1 was released in spring 2015. Like Wave 1, Wave 2 was conducted in partnership with McKinsey and Company, who conducted confidential data collection and analysis. ISPE received only aggregated data; individual sites could not be identified.

A key goal of Wave 2 was to evaluate proposals given in an FDA Federal Register Notice (FRN) and "Request for Quality Metrics" Draft Guidance. The design of Wave 2 included the following objectives:

- Test the proposed FDA metrics
- Help develop appropriate definitions
- Understand data-collection challenges
- Evaluate the logistics and effort of gathering data at a product-application level

Metrics and Analysis

The Wave 2 Pilot Program met its objectives and confirmed findings from Wave 1.

The Wave 2 Report detailed the list of metrics evaluated as external quality outcomes, internal quality outcomes, and culture indicators (Figure 1). Three of the four metrics proposed by the FDA in Draft Guidance were evaluated:

- Lot Acceptance Rate
- Product Quality Complaint Rate
- Invalidated Out-of-Specification (OOS) rate

Enrolment

With the completion of Wave 2, the total number of participants in the survey increased from 44 sites and 18 companies in Wave 1 to 83 sites from 28 companies in Waves 1 and 2 combined. The total number of companies in Wave 2 was 21.

Sample sizes increased across all technologies over Wave 1, giving good representation. While the sample is dominated by originator companies/sites and those with revenues greater than $1 billion, the proportion of smaller companies increased from about 10% to about 17% (Figure 2).

Key Findings

In discussing the results from the Wave 2 Report, Mairead Goetz said that one finding was "the realization of how compelling this body of work really is." Citing "the 'wow factor' of what ISPE has sponsored," she thanked the organization "for the vision that created this work."

Vanya Telpis noted that the report identified more and stronger relationships between indicators and outcomes compared to Wave 1, confirming Wave 1 insights and adding others. Despite these connections, however, the sample is still insufficient to evaluate trending.

Paul Rutten explained that the culture survey questions scored participants in five categories: capabilities, governance, leadership, mindset, and integrity. At industry average level, he said, the highest scores were seen in capabilities and integrity, the lowest scores in governance and leadership. In culture, we saw highest variability in metrics, dialogue, and Gemba. "That's where we as an industry have opportunities for improvement," he said.

The report, Rutten continued, found industry-wide strengths in training, patient focus, personal responsibility for quality, open escalation of quality issues, and motivation to ensure quality. Industry-wide gaps were revealed in metrics visualization and understanding, management presence on shop floor, and daily dialogue.

Some findings were disappointing. Mairead Goetz explained that Wave 2 Report did not produce data that could relate metrics evaluated to drug shortages. In addition, although she had initially thought it might be possible, the sample was insufficient to evaluate trending.

Wave 2 data, however, did indicate the following:

- FDA metrics as proposed were not found to have relationships with quality outcomes or directly with cultural indicators.

Mairead Goetz, Head of Compliance, Novartis Pharmaceuticals Corporation

Background and Objectives

Following issue of the "ISPE Quality Metrics Initiative: Wave 1 Report" it was broadly agreed that there is a continuing appetite in the pharmaceutical manufacturing industry for information about quality metrics to support continual improvement. ISPE therefore initiated a Wave 2 Pilot, which commenced in July 2015. In addition to collecting metrics and estimating the burden of proposals given in the FDA draft Guidance, initial objectives were:

- Expand the data set across segments, geographies, and time to further the learnings from Wave 1 and evaluate trending patterns.
- Continue to develop measures, tools, and dialogue related to quality culture and process capability to facilitate ongoing industry development and self-assessment.
- Enable continued objective and data-driven dialogue with FDA and other health authorities.

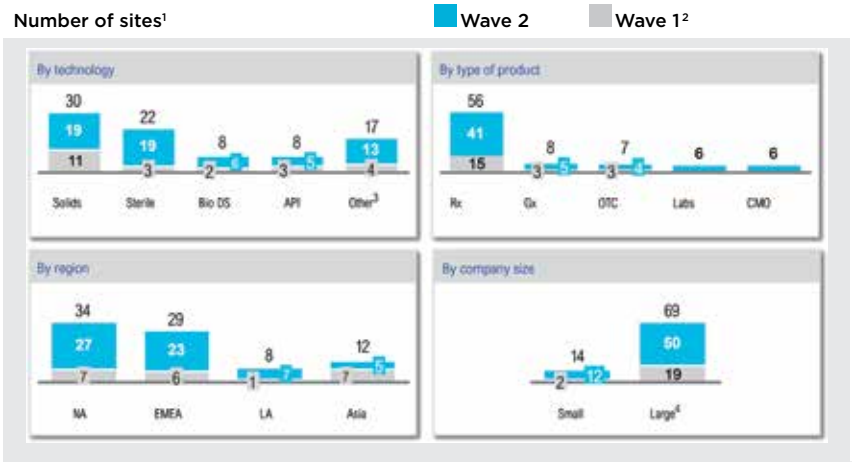
- Alternative metric calculations proposed by ISPE showed better relationships. All three FDA draft guidance metrics with ISPE recommended definitions evaluated in Wave 2, for example, have a relationship with a culture indicator.
- FDA draft guidance metrics definitions should be adjusted.
- Lots pending disposition data point has limited usefulness, and has high burden.
- FDA proposed optional metrics have limited utility, and were inconsistently applied.

Figure 1: Detailed metrics

External Quality Outcomes	Internal Quality Outcomes	Culture Indicators
■ Total Complaints Rate – Per million packs, incl. lack of efficacy – Per million packs, excl. lack of efficacy – Per '000 attempted lots released, incl. lack of efficacy [1] – Per '000 attempted lots released, excl. lack of efficacy [2] ■ Critical Complaints Rate – Per million packs – Per '000 attempted lots released ■ Total Recall Events per year [1]	■ Lot Acceptance Rate (%) – Per finally dispositioned lots – Per attempted lots [2] ■ Invalidated OOS Rate – Per '000 lots tested – Per '000 tests performed – Per total OOS per tests performed [2] ■ Right First Time Rate (%) per released lots attempted ■ Deviations Rate – Per '000 finally dispositioned lots – Per '000 attempted lots ■ Recurring Deviations Rate (%) ■ Lots pending disposition more than 30 days (%) per lots attempted [2]	■ Culture survey scores (% top boxes) – Total score – Leadership score – Integrity score – Mindset score – Governance score – Capabilities score ■ CAPAs with Preventive Actions (%) ■ Planned Maintenance Rate (%) ■ Employee Turnover Rate (%) ■ Human Error Deviations (%) ■ Deviations with No Assigned Root Cause (%) ■ CAPA Requiring Retraining (%) [2]

[1] Recalls are normalized on annual basis for sites that have submitted periods different from 12 months
[2] FRN metrics, tested at site and product level

Figure 2: Enrolment details, Waves 1 and 2



[1] If a site has more than one technology we count the number of separate templates they will fill, usually one per technology
[2] Sites that participated in both Wave 1 and Wave 2 are reported under Wave 2 only
[3] e.g., soft gels, transdermal
[4] Over $1 billion in annual revenue

Steve Greer, Quality Assurance External Engagement, Procter & Gamble

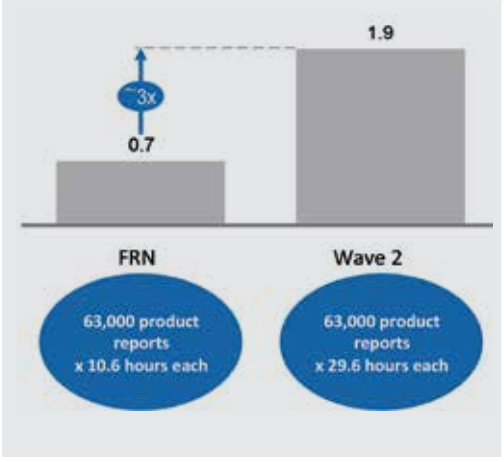
Left to right—Paul Rutten, Partner, McKinsey & Company; Vanya Telpis, Director of Knowledge, McKinsey & Company; and Mairead Goetz, Head of Compliance, Novartis Pharmaceuticals Corporation

Five Consistent Metrics

One of the most important findings from the report is that data from five metrics was consistent in both Waves 1 and 2:

- Total Complaints Rate including lack of effect (per million packs)
- Critical Complaints Rate (per million packs)
- Lot Acceptance Rate (per lots finally dispositioned, %)
- Deviations Rate (per thousand lots finally dispositioned)
- Recurring Deviations Rate (%)

Figure 3: Annual industry effort for three FRN metrics



Effort Assessment and Industry Burden

Paul Rutten noted that effort for the FDA's three FRN metrics was evaluated at 29.6 hours annually for one product report—almost three times higher than the 10.6 hours projected in the FRN. "Most of this—about two-thirds—is data collection," he said, "but there's some manual work, too, reviewing the material and drawing conclusions. The actual effort is likely to be even higher."

This translates into 1.9 million hours for the 63,000 products in industry—1.3 million hours for data collection and 0.6 million for guidance and review, the equivalent of 1,080 full-time employees (Figure 3).

Some companies and sites, such as those with complex supply chains, will experience higher burden, Rutten added. OTC sites needed 60% more time to collect data than did originator or generics sites.

The effort spent on general guidance varied significantly. Guidance and coordination effort was highest for companies outside the United States and Europe, and in companies with complex supply chains (10 or more sites). Guidance effort per one period of reporting per product ranged from an average of 9.1 hours to a maximum of 69.5 hours.

The bottom line, Rutten said, is that Wave 2 overall effort estimate for data collection is at least three times higher than the FRN estimate.

Vanya Telpis, Director of Knowledge, McKinsey & Company (left), and Mairead Goetz, Head of Compliance, Novartis Pharmaceuticals Corporation

IT Systems

The report indicated that most companies leveraged existing IT systems to source some or most of the data points. ERP and Trackwise systems were used by 75% to 95% of sites. Despite the widespread use of computerized systems, however, a third to half of participants still had a significant amount of manual processing.

Outliers and Statistical Analysis

Vanya Telpis noted that "This is a very difficult question. We don't know enough about the sites, and even the sites themselves can't always explain outliers. Since we don't know what we don't know, we excluded outliers beyond two standard deviations.

"We cared very much about statistical significance—the *p* value," she continued. "Most are less than 1%, which is pretty strong. We don't need more explanation than that."

Correlations were based on samples excluding consistent set of outliers, Telpis explained, but noted that this is something that the industry might explore further: Which ones are "true" outliers related to unique circumstances, or and which represent larger legitimate subpopulations?

"We used common sense," she said. "We tried to find reasoning behind these relationships. If we couldn't, we didn't include them."

"I must stress strongly," she concluded, "that correlations found and given in the report do not indicate causation. There are hidden influences of variables and factors not studied, and the sample is not the full population."

Quality Culture

Wave 2 confirmed the importance of quality culture, with some further relationships identified. Almost every culture indicator evaluated (five out of six—all but human error deviations) has a relationship to either an internal or external quality outcome. "Culture affects everything we do," said Vanya Telpis.

Draft Guidance Response

Mairead Goetz noted that preliminary findings from Wave 2 were used to develop ISPE's response to the FDA Draft Guidance and FRN. The final analysis confirmed that ISPE supports FDA's effort to implement a quality metrics program, and recommends a small, phased, targeted approach using three of the FDA proposed metrics to minimize the burden. "Think big, start small," Goetz said, "but start!"

Next Steps

The core team's next objectives, said Goetz, are to disseminate the Wave 2 Report to global regulators, continue engagement in cross-industry dialogue, and progress the ISPE quality culture program.

She encouraged attendees to download the Wave 2 Report and take the Quality Metrics Initiative webinar to learn more about the initiative. Both are available on the ISPE website (www.ispe.org).

The next quality metrics update will be presented at the at the 2016 ISPE Annual Meeting during the Quality Metrics Session on Wednesday, 21 September, in Atlanta, Georgia, US. ■

Amy R. Loerch

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The 25th Anniversary of GAMP®

Balancing quality, safety, and compliance with technical innovation and progress, the GAMP Community of Practice is celebrating 25 years of innovative good practice in 2016!

GAMP 5 launch: Copenhagen, April 2008

Siôn Wyn

In 2016, the GAMP Community of Practice (CoP) celebrates 25 years of helping the pharmaceutical and associated life science industries achieve compliant and validated computerized systems. Since its formation in 1991, it has developed into a fully international and collaborative effort.

What Is GAMP?

ISPE CoPs are groups of like-minded professionals who engage in networking and sharing good practices, often building a community-specific body of knowledge. The GAMP CoP works with other ISPE CoPs in support of the organization's strategic objectives. The GAMP CoP also works to form relationships, coordinated through ISPE, with like-minded industry associations to create or support globally harmonized standards or guidance.

GAMP's objectives have progressed from a focus on compliance to include encouragement and support for innovation and technical progress that benefits both the patient and the public. The scope of GAMP has also moved from a primary emphasis on pharmaceutical manufacturing to embrace the whole life cycle for various GxP-regulated areas, including medical devices and blood products.

The integrity and accuracy of records and data are essential throughout the product life cycle, from research and development to preclinical studies, clinical trials, production, and quality control to marketing; this is also reflected in the objectives and activities of GAMP.

In summary, the GAMP CoP's mission, as defined by the GAMP Global Steering Committee, is:

Collaborating with regulators and industry experts, GAMP promotes the innovative use of automation and computer technology by applying a science- and risk-based approach that safeguards patient safety, product quality, and data integrity throughout the product life cycle.

The Birth of GAMP

The organization that we know as GAMP was initiated in 1991 by David Selby (Glaxo), the founding Chair, Clive Tayler (Wellcome), and a small team of other experts in the United Kingdom who realized that the pharmaceutical industry needed to consider and meet evolving regulatory agency expectations for computerized system compliance and validation. This was primarily in response to a number of pivotal US Food and Drug Administration (FDA) inspections in the late 1980s and early 1990s.

During this period, the FDA and other regulators were taking an increasing interest in the role of computerized systems in regulated processes and had concluded that the reliability and integrity of these systems played an important role in product quality and patient safety. In response to this increased scrutiny, it became clear that an industry reaction was required, including guidance on expectations and good practice.

The first document, the *GAMP Supplier Guide,* produced by a subteam led by Tony Margetts (ICI Pharmaceuticals), was released to the membership on 1 March 1994 and officially published a year later. As expectations and industry good practices continued to evolve, so did the guide, with the launch of *GAMP 2* in Amsterdam in late 1996 and a two-volume *GAMP 3* in 1998. By this time, GAMP was a truly international effort with increasing involvement from contributors from around the world.

GAMP 5 describes a life cycle approach to the management of computerized systems

These initial GAMP guides were focused primarily on good manufacturing practice (GMP) systems until the scope was broadened to all GxP systems in late 2001 with the release of *GAMP 4*. This version quickly established itself as the definitive source of industry good practice for computerized system compliance and validation. Between 2001 and 2008, a number of ISPE GAMP Good Practice Guides (GPGs) applied, expanded, and clarified the principles of GAMP good practice to a wide variety of computerized systems and regulatory areas. The topics covered by these GPGs included calibration, process control systems, laboratory systems, infrastructure, global information systems, and manufacturing execution systems (Figure 1).

GAMP founders (from left): Tony Margetts, Guy Wingate, and David Selby

GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems, the current version of the main GAMP guidance, was published in 2008. It was created in response to the changing regulatory and industry environment, which placed greater emphasis on science- and risk-based management approaches, product and process understanding, and the application of quality by design concepts.

GAMP 5 provides a cost-effective framework of good practice to ensure that GxP-regulated computerized systems are fit for their intended use and compliant with applicable regulations.

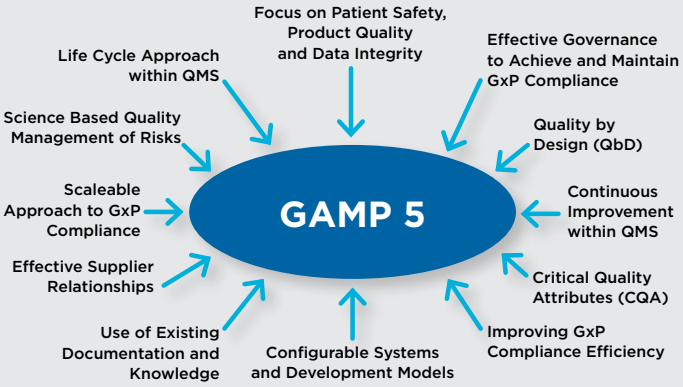
The framework aims to safeguard patient safety, product quality, and data integrity while also delivering business benefit (Figure 2).

GAMP 5 describes a life cycle approach to the management of computerized systems—defining and performing activities in a systematic way from conception, understanding the requirements to development, release, and operational use to system retirement.

The *GAMP 5* life cycle (Figure 3) includes a general specification, design, and verification process aligned with the ASTM E2500-07: "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment."

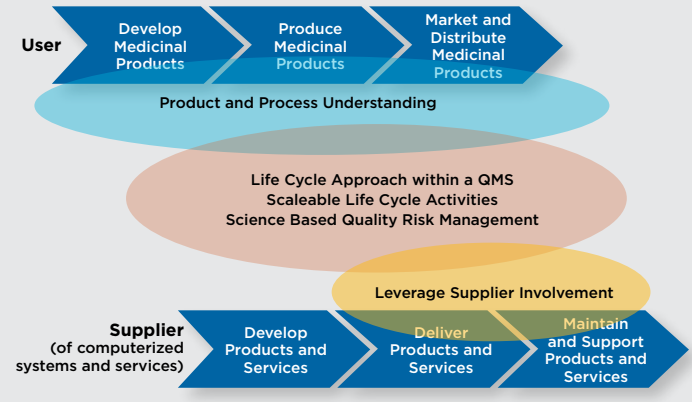
Associated with, and supporting, the main *GAMP 5* Guide is a series of GPGs (Figure 4). These documents provide practical guidance on the implementation of GAMP for different applications. All are intended to be used in conjunction with the main GAMP Guide.

Figure 1: Drivers for GAMP 5



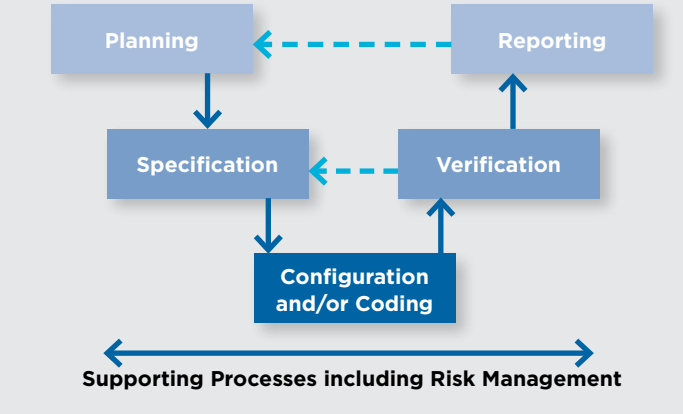
Source: International Society for Pharmaceutical Engineering. *GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems.* © Copyright ISPE 2008. All rights reserved. www.ISPE.org.

Figure 2: GAMP 5 key concepts



Source: International Society for Pharmaceutical Engineering. *GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems.* © Copyright ISPE 2008. All rights reserved. www.ISPE.org.

Figure 3: GAMP 5 specification and verification approach



Source: International Society for Pharmaceutical Engineering. *GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems.* © Copyright ISPE 2008. All rights reserved. www.ISPE.org.

Since its formation in 1991, GAMP has developed into a fully international and collaborative effort

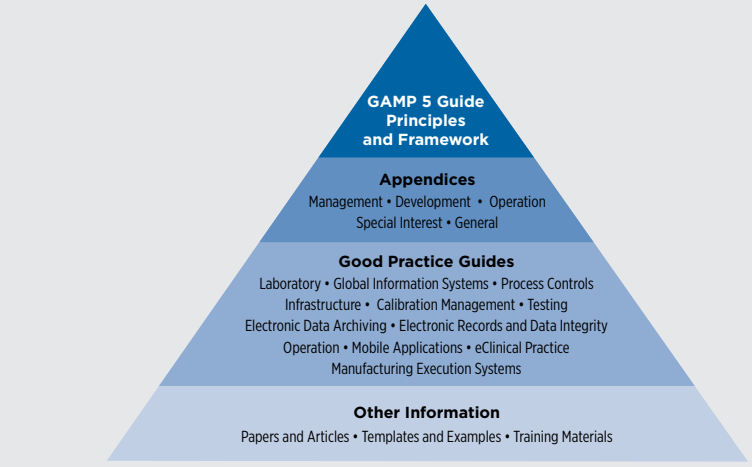
The Present and Future of GAMP

The GAMP community is as busy as ever, working to achieve quality, safety and compliance while encouraging technical innovation and progress.

Timely revisions of the GAMP Good Practice Guides *Global Information Systems Control and Compliance and IT Infrastructure Control* and *Compliance* are to publish by end of year.

Current GAMP activities also include the development of a very significant new GAMP Guide: *Electronic Records and Data Integrity*, supported by the GAMP Data Integrity Special Interest Group (SIG). This will provide practical and pragmatic guidance on meeting current regulatory expectations for the management of electronic records and data, including the need for integrity, security, and availability. It describes how a risk-management approach may be used to ensure the compliance of regulated electronic records and signatures, and managing risks to integrity of underlying data, through the application of appropriate and commensurate controls.

Figure 4: GAMP documentation structure



Source: International Society for Pharmaceutical Engineering. *GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems*. © Copyright ISPE 2008. All rights reserved. www.ISPE.org.

In other developments:

- The R&D and Clinical SIG has published several concept papers and is working on a major Good eClinical Practice Guide on the validation of computerized systems in good clinical practice.
- The Cloud SIG has published articles and concept papers addressing the pressing issue of how to exploit cloud technology while maintaining an acceptable level of quality, control, and compliance.
- Other SIGs are working on articles, papers, and potential future guides. Regional and local GAMP CoP groups, working closely with ISPE Chapters and Affiliates, develop and run many conferences, forums, and workshops.

Keep an eye out for information on these and other activities in Pharmaceutical Engineering and on the ISPE website.

Celebratory Events

To recognize this significant achievement, celebrations will take place at the following ISPE events:

- ISPE Annual Meeting, Atlanta, Georgia, USA (Monday 19 September)
- GAMP Europe Regional Conference, Copenhagen, Denmark (Tuesday 4 October)
- GAMP CoP UK Forum and ISPE UK Affiliate Annual Conference, Leeds, UK (Thursday 10 November)

Watch for further details on the ISPE website and in ISPE conference information. Please join us in celebrating 25 years of GAMP! ■

GAMP CoP: Past and present

2016 ISPE Conferences

- **ISPE Annual Meeting & Expo**
  18 – 21 September
  Atlanta, GA

- **ISPE GAMP Data Integrity Europe Conference**
  4 – 5 October
  Copenhagen, Denmark

- **ISPE Europe Conference on Biotechnology**
  24 – 25 October
  Frankfurt, Germany

- **ISPE Process Validation Conference**
  24 – 26 October
  Bethesda, MD

- **ISPE Process Validation Statistics Conference**
  25 – 27 October
  Bethesda, MD

- **Pharma EXPO 2016**
  6 – 9 November
  Chicago, IL

- **ISPE Facilities of the Future Conference**
  14 – 15 November
  Bethesda, MD

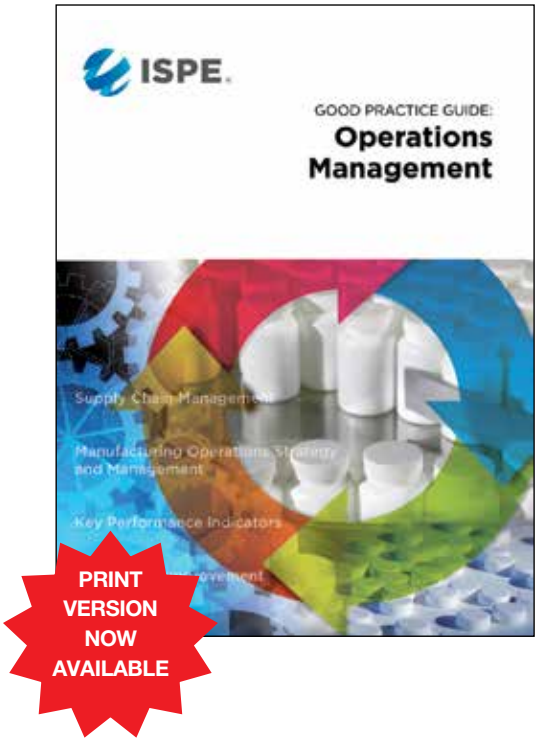
- **ISPE Biopharmaceutical Manufacturing Conference**
  5 – 7 December
  San Francisco, CA

www.ISPE.org/Events

ISPE

NEW Release

ISPE Good Practice Guide: Operations Management



The ISPE Good Practice Guide: Operations Management aims to provide the pharmaceutical industry with a knowledge basis to promote the use of best practices and operational excellence within pharmaceutical operations management.

For the purposes of this Guide, operations are defined as the transformative process within a series of activities, along a value chain extending from supplier to customer. Operations Management designs, operates, and improves supply chain systems for getting work done.

This Guide addresses all operations along the supply chain from the selection of raw materials through to the distribution of final product.

Topics considered by this Guide include:

- Supply Chain Strategy and Management
- Manufacturing Operations Strategy and Management
- Key Performance Indicators
- Continual Improvement and Innovation
- Methods and Tools for Continual Improvement

This guide is intended to be read in conjunction with other ISPE guidance, ICH guidelines, and industry recognized standards.

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www.ISPE.org/Guidance-Documents

ISPE Guidance Documents Coming Soon

ISPE Management of Engineering Standards Good Practice Guide

This Good Practice Guide is intended to provide guidance on how to establish and maintain an engineering standards program. It covers the entire life cycle of an engineering standard, from chartering to retirement. In addition, it includes a description of the governance process for the engineering standards program. Although it is intended for an engineering standards program, the principles would apply to other document programs. The application of the recommendations in this Guide are scalable, based upon the size of the organization, number, and type of documents to be managed.

ISPE GAMP® Cloud SIG Concept Papers

The GAMP Cloud Special Interest Group has created three companion Concept Papers covering the topics of software as a service (SaaS) and platforms as a service (PaaS):

- "SaaS in a Regulated Environment—The Impact of Multi-Tenancy and Subcontracting" is focused on the SaaS cloud model description, various business models used by the SaaS providers and security and privacy concerns related to those models.
- "Using SaaS in a Regulated Environment—A Life Cycle Approach to Risk Management" looks into the life cycle of the relationship between regulated company and SaaS provider and delves deeper into the issues a delivery team can face in their exploration of moving a business supporting system to a SaaS provider.
- "Evolution of the Cloud: A Risk-Based Perspective on Leveraging PaaS within a Regulated Life Sciences Company" is intended to help to explain how PaaS compares to other cloud solutions (specifically infrastructure as a service, or IaaS), as well as discussing risks and associated pragmatic controls that regulated companies should consider when leveraging PaaS within their organization. ■

Meet Alan Levy: 2015 ISPE Member of the Year

Alan S. Levy

For someone who did not originally plan to work in the pharmaceutical industry, Alan Levy, ISPE's 2015 Member of the Year, has had a remarkable career. "Pharmaceuticals weren't my original intent," he told *Pharmaceutical Engineering*. "Growing up in Hannibal, Missouri, with a chemist for a father, I knew early on I wanted to be a chemical engineer, but I expected it would be process engineering in some heavy industrial setting."

With a Chapter of over 1,000 members, we needed ways to enhance our service offerings

Alan actually did process engineering as a co-op for BASF during college at the University of Missouri–Rolla (now Missouri University of Science and Technology), where he graduated in 2000 with a BS degree in chemical engineering. After college, he and his wife moved to Philadelphia when he landed a production engineering position for Johnson-Matthey, making catalytic converters for the automotive industry. "We ran the production lines; it was labor-intensive and messy," Levy recalled, "and I learned that I didn't really enjoy production work." To further his career, he took a design engineering position with Javan & Walter (now Javan Engineering) in their industrial group. "The first day on the job, they did not have an industrial project for me, so they asked me to help with pressure relief devices for Merck. I've been in pharmaceuticals ever since!"

Shortly afterward he had the opportunity to work with several groups at Merck's West Point, Pennsylvania, site in roles ranging from maintenance and operations to reliability engineering to a site-wide HVAC retro-validation initiative. "I loved my years working with Merck, but to keep growing my career, I decided to go back to the office and pursue project management for engineering and design," he said. As a project manager for Javan, Levy took on increasingly complicated projects, developing a solid reputation in facility and utility renovation designs, engineering studies, and qualification for the pharmaceutical industry. He was Javan's youngest employee of the year in 2008, and earned a master's certificate in applied project management from Villanova University in 2009.

One of his most complicated projects was designing a replacement steam-distribution system for a pharmaceutical site whose existing buried pipes were rapidly corroding. "There was a mile of pipe in both directions—literally," he said. Levy's team was asked to change the buried system into an above-ground, over-roof system. "We had to develop innovative solutions for isolating and controlling multiple feet of thermal expansion, vibration, wind and ice loads, and many other variables that were different for every support on buildings with different styles of roof construction. It was truly challenging," he said. "My structural engineers told me it was more difficult than designing a skyscraper!"

In 2013, Levy received the honor of being named Delaware Valley Young Engineer of the Year by the Engineering Club of Philadelphia, for excellence across professional experience, professional society experience, education, and charitable service. The following year, he joined Mace North America as Senior Program Manager over engineering, design, and sustainability governance; shortly thereafter, taking a role as interim global lead for GlaxoSmithKline's Worldwide Real Estate and Facilities Sustainability group. He is currently the Global Lead of Sustainability for GSK's R&D "Places" Program, which is consolidating and reinvigorating GSK's R&D campuses.

ISPE

Alan joined ISPE's Delaware Valley Chapter in 2004. "My boss thought that going to a Chapter meeting would be a good thing," he recalled. He became increasingly involved in the organization, and joined the membership committee in 2006. Two years later he was named the committee Co-Chair, then became Chair the following year. "I would've stayed on membership longer," he said, "but the incoming president had other ideas."

Levy's next role was as Chair of the Education Committee. "I was asked to integrate our education offerings," he said. "We went from having one very large conference per year to monthly or bimonthly evening classes covering different topics. It was the start of the recession in 2008, and member companies were not supporting large conferences, so we needed to find new ways to bring value to our members and generate revenue for the Chapter. This change allowed us to drop event prices while reaching more people and providing more depth of content. Thankfully it took off, and it's still doing well 7 years later." Levy is particularly grateful to GSK and ISPE Board of Directors Member Tom Hartman for hosting these events. "The monthly classes would not have been possible without their support in providing us a home."

After 3 years as Vice President of the Education Committee, Levy became Secretary, then Executive Vice President, and finally President of the Delaware Valley Chapter in 2014. During his term, the Chapter experienced its most profitable year since 2008, and hosted its largest

Levy took on increasingly complicated projects, developing a solid reputation in facilityand utility renovation designs, engineering studies, and qualification for the pharmaceutical industry

Vendor Expo to that point. While serving as President, Levy also chaired the 2015 ISPE Annual Meeting Social Events Committee.

"I started coming up with ideas once I learned the Annual Meeting would be in Philly," he explained. "I wanted to welcome our colleagues from all over the world, and show them what makes Philadelphia special." This led to three facility tours (AstraZeneca, Morphotek, and Merck–West Point) that included elements of American history, stopping at Longwood Gardens, Valley Forge, and a local craft brewery. He also helped develop the "Taste of Philly" concept for the Annual Meeting Party. "We all thought the party in Las Vegas was going to be impossible to beat, so rather than trying to one-up it, we came up with something completely unique to Philly."

He had some serious help in this massive undertaking. "ISPE has given me a lot of amazing industry colleagues," he said, "and I chose my team for their specific talents and connections. In addition to the never-ending support and dedication from ISPE's staff and leadership, we built a local team to develop logistics and timing, buses, site permissions for each of the tours, tour content, sponsorships, and marketing strategy. He further acknowledged, "None of this would have been possible without the support from Mace. Mace and my managers understood how important this was to me and allowed me the time and freedom to see it through."

As Chapter President, Levy continued to challenge the Chapter's educational paradigm. "Getting us to 4–6 sessions per year with around 50 people per session was great, but with a Chapter of over 1,000 members, we

2015 Board Chair Joseph Famulare (left) and Board Member Thomas Hartman (right) presented Alan Levy (center) with his award at ISPE's 2015 Annual Meeting.

needed to keep looking for ways to enhance our service offerings." To that end, Levy came up with the idea of virtual Communities of Practice (CoPs). "It's built on the notion that ISPE already has thought leaders and subject matter experts across our industry, we just need a way to connect them to everybody. With a virtual system, any member can get whatever they need, whenever they need it, at any level of depth. When you have 50 people in a live session, they all have different levels of experience so you have to align content to the median. A virtual system provides for any level of depth and breadth from 'What is GMP?' to 'How do I calculate NPSH to size a pump?' That's what we're building."

A virtual system provides for any level of depth and breadth

Levy says the Chapter is looking at multiple categories: "Facilities, Biotech, C&Q—things like that." Through the Chapter website, users will go to their CoP and choose from the different conversations they see. "Say I had an interesting experience and I wanted to tell people about it," Levy said. "I go into my CoP and set up a meeting for anyone who wants to hear about it. It's ad hoc, whatever the topic needs to be, whenever you want to have it. The infrastructure has been purchased and we're currently recruiting SMEs to beta-test the system. We just need a few people to dedicate a bit of their free time to help us get it off the ground."

Levy realized the virtual system could be used to reach university students as well. "We are working with Villanova University to develop a professional curriculum for students using our new web tools. Students will log into the class, where they can ask questions and take tests. Because it's virtual it can be taught from anywhere with a good internet connection. We also want to accomplish a different professional curriculum for freshmen, sophomores, juniors, and seniors. Freshmen would learn things like the basics of project management and handling yourself professionally. For sophomores, we'd offer legal, finance, and business—things every engineer needs to know after college, taught by people who do it for a living."

Building Bridges

Levy was honored with the Max Seales Yonker Member of the Year Award at the 2015 ISPE Annual Meeting. The award is bestowed annually on the ISPE Member who has made the most significant contribution to the Society during the past year. ISPE President and CEO John Bournas called Levy "one of ISPE's greatest advocates."

On the day of our conversation, he said he'd been at Drexel University the previous evening. "I talked to their biomedical engineering students, welcoming them into the industry and telling them about different paths to grow and succeed in their careers. But he doesn't limit his outreach to students. At Drexel that same evening, he struck up a conversation with a cognitive design professor who was also talking to the biomedical students. "She was getting into GAMP and compliance for app-based medical devices," he said. As they talked, "it became apparent that ISPE would be useful to her, even though she didn't know we existed. I connected her with the Co-Chair of GAMP and probably recruited a new member in the process."

During his time with the organization, Levy has also built collaborative relationships with other professional societies. "I firmly believe collaboration is a better model for us than competition," he said. Levy started pursuing this philosophy after the recession in 2008 when most employees could only join one organization. "Being industry-centric," he explained, "ISPE has a significant demographic overlap with many discipline-centric groups. Rather than fighting each other for members, we started informal local partnerships with these groups. We do collaborative events, co-promote each other, and attend events at member prices without being members. This creates better programming and encourages mutually higher attendance, which is better for all involved." The Delaware Valley Chapter first allied with the International Society of Automation, and has since started collaborating with the American Society of Mechanical Engineers, American Institute of Chemical Engineers, American Society of Civil Engineers, and the Institute of Electrical and Electronics Engineers.

When asked about the benefit of ISPE membership, Levy says that while he is obviously enthusiastic about the educational and networking opportunities, for him the biggest value is friendship. "It's so great. You get to know so many people who work in the same industry and have similar challenges that you do. You learn from them, they learn from you, and you end up with lifelong friends that you'd never have met without ISPE!" ■

Amy R. Loerch

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Singapore Affiliate: A Leading Force in Southeast Asia

Geoff Brown

Singapore is a unique place. A small island city-state with only 720 square kilometers of land, Singapore has a multicultural population of 5.5 million, mainly of people of Chinese, Malay, Indian, Thai, and European descent. Despite its small size, Singapore is a global commerce, finance and transportation hub. Its pharmaceutical and biotechnology industry is world-class, featuring all of the global industry's top names. In this context, it seems appropriate that the ISPE Singapore Affiliate would mirror the country's multicultural character and have an expatriate American at the helm.

"One of the interesting things about Singapore is that it really is the most multicultural place in the world," says Geoff Brown, President of the Singapore Affiliate. "There's never been a place in the world quite like this. Along with the predominantly Chinese majority, you have Malaysians, Indians, people from all the other countries in the region, plus large expat communities from the Western countries. You can be sitting on a train and you'll have people from 25 different countries all on that one train; it's pretty crazy!"

Brown himself is an expat from the United States. Born in Colorado, he joined the US Navy straight out of high school and served for 7 years as an engineering supervisor, training coordinator, and nuclear ship superintendent. After leaving the navy, Brown took on a consulting role for a pharmaceutical company doing commissioning and qualification. It was then that he joined ISPE.

"I had a lot of engineering and technological know-how, but when you come into the industry, you're assaulted with all these different new terms," says Brown. "I understood the mechanical and electrical and energy principles, but there was new equipment and new things to learn and ISPE's training guides and training events really helped me out when I first started in the pharma industry."

I'm quite happy that as president I can now contribute to the organization that helped me so much when I was starting out

When he moved to Singapore 3 years ago, Brown quickly became involved with the Singapore Affiliate, including participating in the organization of the Affiliate's annual conference. In January 2016, he was elected president. "I'm quite happy that as president I can now contribute to the organization that helped me so much when I was starting out," he says.

Founded in 2000, the Singapore Affiliate is the oldest Affiliate/Chapter in the Southeast Asian region. The Affiliate has always been strong and active, and members continue to benefit from numerous training courses as well as networking and social opportunities. "The ISPE Singapore Affiliate offers a chance to connect with professionals throughout the different pharma, biotech, and life sciences [companies] within Singapore and the region," says Brown. "It gives members a wide training base, from niche topics to broader topics and also provides a lot of interesting social benefits during things like quiz night, soccer events, and other activities."

2016 Annual Conference and Exhibition

The Affiliate's largest and most popular event is its annual conference and exhibition, which will be held August 24–27, 2016 at the Suntec Singapore Convention & Exhibition Centre. "We have an exciting lineup this year, with lots of international and local leaders including the US FDA [Food and Drug Administration], WHO [World Health Organization] and HSA [Health Science Authority—Singapore's local regulatory body], site tours and influential industry experts," says Brown.

Open to all pharma and bio manufacturing professionals, the annual conference, attracted 550 attendees from 12 countries last year. This year's event, the sixteenth annual, features numerous tracks: HVAC; aseptic process and technology; Good Automated Manufacturing Practices (GAMP); critical utilities; regulatory compliance; risk-based approaches to commissioning, qualification, and validation; plant of the future; operational optimization, and chromatography community of practice—as well as the annual student poster competition.

"We want our conference to be an opportunity for members to speak with regulators from around the region and for ISPE to provide training to the regulators," says Brown. "The advantage of that is that it connects our affiliate and the ISPE brand to the regulators, and our training plans reflect what their intentions are. It also

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provides a chance for our members to interact with regulators in a more relaxed setting. I think that's going to benefit our members quite a bit and I think it's going to benefit the regulatory bodies as well."

The annual conference is also the Affiliate's main driver for its other events, since it generates the revenues that allow the Affiliate to offer other social and networking events as well as training courses. It is also a main driver for membership.

Seeking Membership Stability

While membership levels at the Singapore Affiliate are strong at approximately 300, Brown acknowledges that he would like to see more stability in those numbers. "Singapore is interesting because we get large swings between 250 and 400 members," he says. "We had this event called the Gen Y Challenge, an olympiad-type event where we had sporting events and a quiz portion; it is a real fun event for the students. When they would sign up for the event, they would get a student membership, but that would just lapse a year later, so it was a cyclical process. One of our goals this year is to stabilize things."

To help achieve that stability, the Affiliate has recently reintroduced its student executive committee and will continue their work with the major universities:(National University of Singapore and Nanyang Technical University) and polytechnics in the country. They also have a young professionals committee and will be working closely with ISPE global headquarters on some of their young professional initiatives. "We have an event that is like a head start in the pharmaceutical industry and we're using that as a bit of a membership drive. A few senior members like myself and others will give presentations on different roles within the pharmaceutical industry and provide an overview on different topics to initiate the discussion with the students and young professionals on what they could do for internships, work, their career paths, and so on," says Brown.

Ongoing Growth of a Leading Affiliate

ISPE has long recognized Singapore as an important pharmaceutical market. Indeed, ISPE once had an office in the country, but it was closed in 2012 following the global economic downturn. Meanwhile, the Affiliate has played an important role in helping the ISPE grow within the region, with other Affiliates opening in Malaysia, Thailand, Indonesia, Australia, to name a few.

"When the ISPE office closed down, it made our communication with headquarters weaker. One of our initiatives has been to connect stronger with other the countries in the east and to push to form the APAC," says Brown, in referring to the ISPE's Asia Pacific Affiliate Council.

Today, the Singapore Affiliate plays a leading role in APAC, with its former president assuming the role as Chair of the council. "We intend to keep working with our neighbors to provide more training and communicate better throughout the region. I think that will benefit the members quite a bit because there is a lot of travel within Southeast Asia."

Therein, Brown explain, lies the challenge for the Affiliate and ISPE in general. "Singapore is a very mature market, but the surrounding countries are less mature. So the training that the ISPE offers in our country has to be pretty agile because of the difference in skill levels. We have to make sure we can offer the latest in high-tech training, because that's where the Singapore government is putting a lot of funding. We need to make sure the training we offer reflects what the government is offering for their R&D and technology sectors."

The Affiliate is taking additional steps to ensure its members continue to be well served. It has established a Community of Practice (CoP) for its executive committee; this functions as an online forum and file storage for the Affiliate. "This is an exciting update as it serves as a repository and database for our executive committee's collective knowledge," says Brown. "By collecting our communications in one spot, we can learn lessons from different committees and these lessons will be stored for future generations of executive committee members. It will also help new members to get up to speed when they are elected during our annual general meeting." ■

Mike McGrath

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The Real Cost of Poor Data Integrity in Pharmaceutical Manufacturing

James G. Davidson, PhD

James G. Davidson

The reliability and integrity of all data generated for pharmaceutical products across the entire product life cycle are both a fundamental requirements of the pharmaceutical industry regulations around the world, but are also key to the safety and efficacy of all pharmaceutical products. The potential and real impact of good manufacturing practice (GMP) deficiencies that may affect data reliability and confirmed data-integrity breaches on the pharmaceutical industry, in terms of lost sales of impacted products and remediation costs, is well documented.

What is less understood, however, are the costs resulting from regulatory actions, such as Warning Letters (WLs) and import alerts to the industry in terms of product-approval delays and overall industry profitability. The following document provides an overall analysis of the real costs of poor data integrity and presents the case for a proactive approach to the assessment of risks to data reliability and accuracy in the pharmaceutical industry.

The Importance of Data Integrity to the C-Suite

Every business faces risk. Broadly speaking, the primary categories of business risk are market, financial, execution, and regulatory. Successful companies have developed a core competency in managing these risks, turning risk management into a sustainable competitive advantage. For drug manufacturers, recent trends have underscored the importance of managing regulatory risk in order to remain a viable business. More specifically, these trends have raised the profile of data integrity (DI) as a business risk.

Figure 1 summarizes the major trends that have led to the rise in importance of DI in the eyes of the regulatory agencies. It is important to understand that DI scrutiny is applied across the product life cycle, from development to market to product cessation. Most DI (and GMP) enforcement actions to date have focused on products in the market, but it is our assessment that the same scrutiny is now being applied to products in development, and this focus on the entire pharmaceutical product life cycle will only continue to increase.

The Challenges and Costs of Not Doing It Right

To be clear, ensuring that data is generated and maintained in a way that determines its reliability and accuracy is a continuous challenge, and getting DI systems and controls right requires a concentrated, continuous effort to develop and maintain the policies, culture, and discipline required to avoid regulatory issues. The challenges and costs to the pharmaceutical industry of NOT doing it right, however, are far greater. The time, hard costs, opportunity costs, and strategic distraction of fixing a DI regulatory deficiency significantly outweigh the investment of time and energy to create appropriate DI systems and controls. It is our opinion that appropriate DI systems and controls afford a company a sustainable strategic advantage.

The Regulatory Basics

The basics of the new DI regulatory environment can be found in the following four elements:

Who does it apply to?

In today's regulatory environment, GMP compliance and DI are expected from the entire pharmaceutical supply chain. This includes companies responsible for clinical trials, research, manufacturing, testing, and distribution. For the US Food and Drug Administration (FDA), import alerts and other market actions, as well as delaying the review of, or rejecting, New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), are the tools of choice to enforce compliance.

Key focus areas

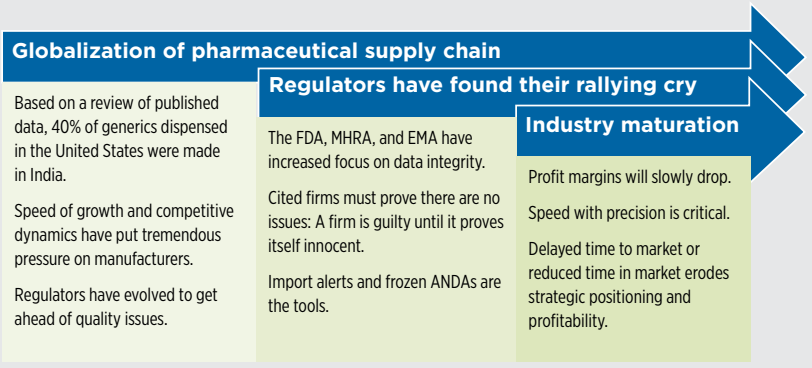
Regulators in the United States, Europe, and the United Kingdom recognize the growth in complexity and scale of the pharmaceutical industry and the contract service providers and global manufacturing partners that support it. Based upon multiple public presentations, regulators are increasing global inspections, as well as the focus of those inspections, to get ahead of product problems that may impact patient safety, product efficacy, and marketplace interruptions. Any laboratory or manufacturing data used to support regulatory approval or commercial product release is a constant focus for regulatory inspection. More specifically, the FDA and the Medicines and Healthcare products Regulatory Agency (MHRA) have both announced that they will continue to focus regulatory review and inspections on the integrity of data of all types.

Guilty until proven innocent

The FDA's stated policy is to not waste resources reviewing applications where there is a question of reliability. If the FDA feels that an applicant's processes, adherence to processes, or compliance history are not pristine, additional evidence in the form of supporting documentation and increased regulatory oversight to ensure compliance and the reliability and accuracy of data are required. Many market actions are now based on "lack of assurance" of GMP, as opposed to the specific finding or direct evidence of product defects.

For drug manufacturers, recent trends have underscored the importance of managing regulatory risk in order to remain a viable business

Figure 1: Key generic drug trends[1]



Aggressive data forensics

Regulatory investigators apply forensic investigative techniques to search for common deficiencies that may directly impact DI, including a lack of:

1. GMP knowledge
2. Understanding of regulatory expectations
3. Management interest in compliance reporting
4. Escalation of internally detected DI problems to management
5. Continuous improvement techniques
6. Mature and knowledgeable QA oversight
7. Strong electronic record controls

Recent Regulatory Environment

The United States FDA provides notice of regulatory deficiencies in a Form 483; when a firm's responses to this notification are not acceptable, the agency issues a WL. A review of publicly available information indicates that in the first 10 months of 2015, the FDA issued 16 WLs, of which 12 were DI specific, up from 10 in 2014 and six in all of 2013.

The FDA is not alone in its heightened focus on data integrity. The UK's MHRA report on inspections in 2013 highlighted an increase in DI issues while announcing the agency's heightened awareness in searching for such issues.[2] Of 630 GMP inspections in 2013, 216 showed major or critical deficiencies. According to the MHRA report, DI issues have been the key reason for the growth of critical deficiencies since 2013.

James G. Davidson and Stephen C.Mahoney, Senior Director, Global Quality & Compliance, Genentech, Inc., chat during a break at the Data Integrity Workshop.

From recently published information in Europe, the European Medicines Agency (EMA) conducted 50% more GMP inspections globally in the first half of 2015 than the same period in 2014. Its inspectors have also revised their approach to inspecting DI, becoming more aggressive and focused on detecting vulnerabilities in this critical area.

Impact of Regulatory Deficiencies on Profitability

With the rapid growth of the market for generic pharmaceuticals, economic and regulatory pressure on pharmaceutical manufacturers is increasing. In this environment, time to market has become even more critical to

shareholder value creation and sustainable profitability than it was before. However, speed without precision leads to compliance issues, particularly DI issues. With the frequency that DI is being cited in regulatory deficiency statements, DI problems are fast becoming the biggest threat to profitability for the pharmaceutical manufacturer, particularly generics. Market removal or delayed market entry could wipe away significant profits. Generic atorvastatin, for example, earned more profits in the first 180 days than in the subsequent 3.5 years.[3] In addition, market removal or delayed market entry significantly impacts project internal rate of return (IRR) along with the company's return on capital employed (ROCE) and cost of capital.

Certainly, regulatory actions will stress profitability, but this only adds to current market-driven pricing pressures expected over the next few years. Margins on products sold to the United States will be squeezed as reduced insurance reimbursement and higher deductibles are passing a larger percentage of drug costs onto the consumer. In addition, generics competition is increasing across most drug categories. To wit: The number of new market entrants grew by 7.7% annually from 2010 to 2015[4] (Figure 2).

Cost of Market Removal

Receiving a WL or other notice of regulatory deficiency will have longstanding financial impacts on a company. These impacts go beyond the profitability of the period in question (the annual loss of revenue and increase in costs); they continue to drag on profits over the long term by reducing a company's strategic options. Impacts such as lost pricing leverage by being late to market, increased costs of capital, a lower market cap, and employee and customer distrust all make it more expensive to do business. The scale of these impacts will vary based on a firm's product and manufacturing facility differentiation, along with access to other markets and access to capital. For example, a global firm with a strong product portfolio will weather the storm far better than a company with few product or facility options. To illustrate the impact of market removal due to regulatory action, case studies from four high-profile generics manufacturers are summarized in Table A. Along with regulatory highlights, the impact of regulatory action on revenues, expense, and opportunity costs are estimated based on publicly available information.

Cost of Delayed Market Entry

Analyses of historical performance data show that the bulk of generic profits are generated in the 6-month first-to-file exclusivity period. The average price point during exclusivity is 73% of the pre-generic high, while the average price point after exclusivity is 43% of the pregeneric high. This erosion grows with the number of market entrants for that drug.

The average number of manufacturers during the period of exclusivity has historically been fewer than two. Post-exclusivity, for drugs with over $100 million in combined annual sales among all manufacturers, there are at least seven manufacturers on average. Where the drug market size is around $40 million annually, there are just under five manufacturers on average.[7] The impact this has on pricing is significant (Figure 3).[8]

To illustrate this in the context of avoiding regulatory delay, consider a hypothetical generic drug product seeking a 180-day exclusivity entering a market where the branded price is $100 per unit. If the generic manufacturer has a $10-per-unit cost of production, the difference between achieving exclusivity and not (using averages) creates a difference of 19% gross margins. The bulk, if not all, of that gross margin goes directly to the bottom line. In an industry that averages just above 12% net margins, this is significant. Since regulatory action is based on the facility, and not the product, that effect could be multiplied across the products being produced at that facility.

When looking at opportunity costs associated with a market delay, these can also be significant. Figure 4 summarizes that analysis.[9]

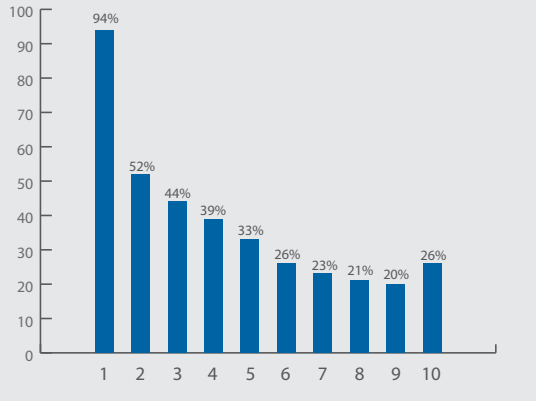
Diminished Strategic Options

Those who are familiar with regulatory action know that revenue and cost impacts are only part of the story. The longer-term impacts on strategy are several. Being forced from the market eliminates product leadership in that category and any price advantage such leadership might carry with it. The operational friction of response leads to inefficient allocation of management and line personnel, forcing decisions about which projects to focus on. The media attention causes embarrassment, which can impact employees, clients, and partners. Those same partners may renegotiate

Figure 2: Factors that affect profit margins

Branded generics	Branded pharmaceuticals leveraging manufacturing, regulatory, and distribution assets to continue production as branded generics.
M&A activity	Market concentration by larger players may increase pricing pressure on non-differentiated smaller players.
Fewer drugs coming off patent	Future off-patent cohorts will be smaller than in recent years, reducing opportunities for higher-margin generics. Drug R&D is generally being reduced or held steady due to investor and revenue pressures.

Figure 3: Generic price per dose by number of manufacturers in market



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- Therapeutic products manufacturer

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Figure 4: Average opportunity cost of ANDA delay

$50,000: The average monthly opportunity cost of an ANDA delay.

This does not take into account expected profits on the drug once it goes to market, as that can vary considerably based on 180-day exclusivity, size of market, and company profitability.

Categories of Impact ↓

- Lower profits
- Disgorgement of profits
- Fines, regulatory burden
- Investor concern
- Lost opportunities
- Delayed time to market
- Partner friction
- Lost pricing leverage
- Increased cost of capital
- Lower IRR
- Reduced market cap
- Reduced M&A

terms to compensate for their increased risk. The reduction in cash to invest in the business, market products, or acquire assets hamstrings strategic-growth efforts. At the same time, the company's cost of capital is likely to increase as equity and debt become more expensive as the company risk profile increases. If a company is already in a poor cash position, equity dilution and uncomfortable loan covenants are possible. Finally, regulatory delays could reduce the attractiveness of the private company as an acquisition or merger candidate or make any terms very unpalatable.

For a generic drug manufacturer, the key levers to maximize time to profit for each product are in drug development, drug approval, and delivery to market. Managing regulatory risk through improved DI directly minimizes time to market by minimizing delays due to import alerts, remediation of compliance issues, and approval delays.

Strategies to Thrive

Of the 1,000+ generic pharmaceutical manufacturers across the globe, it is unclear how many operate in a way that ensures compliance with current and future regulatory agency DI expectations. Our experience tells us that the number is painfully low. Regardless, what does this mean for YOUR organization?

The decision on how to approach regulatory compliance is a strategic one, and varies based on the size and state of your company. It's risk–reward.

Table A: Market removal case studies

Regulatory details	Lost revenue and hard costs[5]	Opportunity and other costs
Major global manufacturer received a WL in early 2012 for a US plant, highlighting GMP and testing issues. This led to reduced output and the eventual closure of the facility for 9 months. The WL was closed out 2 years later. **Total cost: $64 million**	**Revenue:** Facility projections were reduced by **$20 million** for the remainder of FY 2012. Production shifted elsewhere, mitigating lost revenues post-2012. **Costs: $35 million** in remediation.	**Opportunity:** With a historical ROCE of 20%, opportunity cost of reduced profits estimated to be **$9 million**. The impact on delayed ANDAs is unpublished.
Large India-based manufacturer received a WL for a facility in late 2015. A previously FDA-approved innovator drug was rescinded, and generic production was forced to move. Site re-inspection is not likely until Q2 2017. **Total cost: $113–$133 million**	**Revenue:** Projected loss of **$50 million**[6] a year from a drug delay for at least the length of the import alert period (estimated at 18 months). Production at the facility is being shifted elsewhere. **Costs:** The amount of remediation and write-downs is expected in the 2016 annual report. Estimated to be **$25–$45 million**.	**Opportunity:** With a historical ROCE of 21.6% and net margin of 33%, the opportunity cost of reduced profits and increased expenses is estimated to be **$13.5 million**. The impact on delayed NDAs and ANDAs is unpublished.
Global manufacturer received a WL and import ban for two facilities in Jan 2015 and Mar 2015. Currently in remediation. **Total cost: $148–$178 million**	**Revenue:** Exports dropped $48 million from the previous year, after growing 39% over the previous 4 years. EBIT dropped $41 million. **Costs:** The amount of remediation and write-downs is expected in the 2016 annual report. Estimated to be **$40–$70 million**.	**Opportunity:** With a historical ROCE of 20%, the opportunity cost of reduced profits and increased expenses is estimated to be **$26 million**. 41 ANDAs and 38 DMFs are in jeopardy of experiencing delays.
Large India-based manufacturer received an FDA import alert in early 2013, followed by an MHRA recall of multiple products. Received a second facility import alert in late 2013, which was expanded to include all company APIs. All US products were recalled in early 2015. The MHRA closed out in late 2015, with the FDA closeout expected in Q2 2016. **Total cost: $911 million**	**Revenue:** US revenues dropped from 50% to 24% of totals from 2013 to 2015. A total revenue loss of $760 million is expected. **Costs:** Write-off of **$18 million** plus unknown remediation expenses. Further amounts expected in 2016 according to the annual report. Estimated to be over **$100 million**.	**Opportunity:** With a historical ROCE of 18.6%, the opportunity cost of reduced profits and increased expenses is estimated to be **$51 million**. **Other:** 7.2 million units were recalled, a loss of **$2.3 billion** in market cap.

Given the strategic complexities and challenges that generics will increasingly face, however, DI can be a sustainable competitive advantage in balancing speed with precision.

We have found those companies that have accepted that quality is an investment rather than an accounting cost center also realize that DI done right can create a sustainable competitive advantage. Investing in a system of accurate, effective, and sustainable compliance will protect profitability and shareholder equity in the long run, as well as serve to maintain brand goodwill among customers.

This requires a mindset shift away from being a victim of the winds of regulatory demands to proactively seeking the source of quality deficiencies. Many regulatory agency inspection-deficiency letters specifically highlight the lack of preventive actions as a reason for regulatory action.

With this in mind, we offer a few strategic tips to ensure that your company thrives in this regulatory environment and critical time in the pharmaceutical industry:

1. Develop improved R&D capabilities to fight pricing pressures on nondifferentiated offerings.
2. Develop a diversified manufacturing strategy of multiple products in multiple locations.
3. Speed time to market and maximize time in market by investing in the area of greatest focus and consequence during regulatory inspection: DI.

Best practice recommendations:

1. Be proactive and work with experts.
   - Work proactively with an outside specialist (fresh set of eyes!) to educate your firm and leadership on their responsibilities and the need for absolute personal accountability in ensuring the integrity of practices, data, records, and documentation.
2. Staff appropriately for the new challenges and increased expectations.
   - Ensure that your firm has sufficient quality and supervisory personnel with knowledge of DI systems, control, and oversight requirements.
3. Make DI standards clear.
   - Create and enforce company-wide standards for DI, the behaviors required to follow such standards, and provide expert training to effect, sustain, and monitor compliance with these standards for effectiveness.
4. Keep testing and monitoring for compliance.
   - Continuously and rigorously audit actual performance against integrity standards for the systems, procedures, controls, and documentation practices that ensure the reliability of data, records, and their documentation.

Support and Next Steps

To better understand the risks at your firm, it is recommended that knowledgeable and experienced, internal or external, resources be strategically and continuously employed in four primary areas to ensure the integrity of your firm's data.

Audit: Recommended prior to anticipated regulatory agency inspections and as a regular part of the internal efforts to ensure DI. Resources must understand the control and use of data systems and be able to review such systems electronically.

Training: Ensure, through continuous training and employ effectiveness measures that laboratory, production and quality staff can understand and apply, current and evolving DI principles.

Systems enhancement: Enhance procedures and policies as knowledge is gained and new regulatory requirements and expectations are communicated. Address internal and external inspectional observations.

Sustainability and controls: Ensure the adequacy of staffing, conduct internal and external audits, gather and analyze appropriate metrics, and commit to ongoing continuous improvement. ■

References

1. *Wall Street Journal*. Corporate Intelligence Blog. May 14, 2014.
2. UK Medicines and Healthcare Products Regulatory Agency. "GMP Inspection Deficiencies 2013." https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448609/Good_manufacturing_practice_inspection_deficiencies_2013.pdf.
3. Generic company gross margin of ~25% used, calculated against post-exclusivity price of $31 per dose; atorvastatin price per unit averaged $239 during exclusivity. Atorvastatin sales and per unit price from publicly compiled data.
4. IBIS World. "Generic Pharmaceutical Manufacturing in the US: Market Research Report." NAICS 32541b. September 2015.
5. Financial details from company annual reports for the periods in question.
6. In some cases, securities analyst research was reviewed where figures were unavailable. Securities firm names withheld to protect company confidentiality.
7. Olson, Luke M., and Brett W. Wendling. "The Effect of Generic Drug Competition on Generic Drug Prices during the Hatch-Waxman 180-Day Exclusivity." Working Paper no. 317. April 2013. https://www.ftc.gov/sites/default/files/documents/reports/estimating-effect-entry-generic-drug-prices-using-hatch-waxman-exclusivity/wp317.pdf.
8. *Ibid*.
9. Cost of generic-drug development is $1 to $5 million, with the median cost around $3 million. Sources include "Gaining Market Share in the Generic Drug Industry through Acquisitions and Partnerships," Thomson Reuters, 2011. A review of public company records shows a reasonable ROCE in the pharmaceutical industry is 20%.

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About the Author

James Davidson, PhD, is the Vice President of the Science and Technology practice at Lachman Consultants. He is currently responsible for all aspects of Lachman's work in the areas of laboratory compliance, including data integrity, as well as API, dosage form and analytical development and QbD. He held positions of increasing levels of responsibility during his 20 years in the pharmaceutical industry at a major global pharmaceutical company, prior to his career in pharmaceutical consulting. Dr. Davidson has been responsible for all aspects of technical, chemical, analytical, and pharmaceutical development, from early development through commercial development and technology transfer of processes and analytical methods to commercial manufacturing. He holds an AB degree in chemistry from Hope College and a PhD degree in organic chemistry from the Georgia Institute of Technology.

JHL Biotech: From Start-Up to cGMP Manufacturer in Less than Three Years

From its beginnings in late 2012, JHL Biotech set out with a vision of making world-class biopharmaceuticals affordable and accessible to patients. Fast-forward just a few years, and the company is clearly on its way to achieving that lofty goal after having already accomplished the improbable by growing from a start-up to a certified cGMP pharmaceuticals manufacturer within three short years.

Founded in 2012 by Racho Jordanov, Rose Lin, and a team of industry veterans, JHL Biotech (JHL) is an emerging biopharmaceutical company that concentrates on developing biosimilar and new protein drugs and biosimilars that comply with international standards that will allow distribution into all major and emerging markets.

"Our approach has been to invest a proportion of the money that we raised to build infrastructure and retain an amount that allows us to progress at least two of our end products to initial clinical trials," explains Nick Kotlarski, Vice President, Validation & Engineering at JHL. "Our initial goal is to focus effort on manufacturing high quality products; it is to be a wholesale manufacturer and find a retail partner that will deliver them to patients."

"We've since done a design analysis that showed that we should be able to add 1,000-liter reactors within the same footprint," says Kotlarski.

Pilot Project in Taiwan

In early 2013 the company defined its first infrastructure project, locating a technical and administrative center in "Greater China" (i.e., strategically positioned to provide ready access to the Chinese market and global commercial markets) to quickly build their testing and development labs and a GMP pilot plant to manufacture biological products.

The site at Hsinchu was selected due to its established infrastructure in the heart of Taiwan's high-tech manufacturing hub. Equidistant from Taipei and Taoyuan Airport, Hsinchu is positioned on a national highway as well as on a high-speed rail link. The building selected for the facility houses a number of other start-up companies, meaning that there was a compact 2,350-square-meter footprint into which the facility had to be designed to fit.

As a young company with fewer than 15 employees at the time, JHL selected GE Healthcare Life Science as a technology partner. GE provided their FlexFactory equipment, a fully integrated biomanufacturing platform that provides standard single-use bioprocessing equipment, facilitating rapid creation of cGMP manufacturing capacity for biologics such as monoclonal antibodies or vaccines from cell culture through to bulk product formulation. FlexFactory can be tailored to fit either new installations or existing facilities, such as the one JHL had selected; its extensive application of single-use technology was expected give JHL the flexibility to develop a completely new production line within the facility in a short period of time. "GE offered more than just bioprocess equipment," says Kotlarski. "Their service encompassed facility design, start-up services like validation, tech support, training, and optimization of the single-use components as well as the process equipment supply. As a young company, they gave us tall shoulders to stand on."

Purification room with three chromatography systems set up with reusable columns

A Short Timeframe

A mere four months following the foundation of the company, design work on the Hsinchu facility began in collaboration with GE and the construction and engineering firm L&K Engineering.

The collaboration included the site selection stage, which ran in parallel with specification of the FlexFactory equipment and long lead-time utilities. The process control and monitoring system was guided by JHL's process design, operational and regulatory requirements, and the final design of the facility. Configuration documentation and detailed equipment specifications were also developed. In parallel, a detailed commissioning and qualification (C&Q) program and test protocols were defined and developed to align with JHL's qualification program.

Crucially, construction of the process development laboratory space was prioritized in the build; a single-use 50-liter bioreactor was delivered at an earlier stage than the full FlexFactory. This enabled easily scalable process development work to be undertaken prior to the commissioning of the 500-liter bioreactor production lines.

Once the production and functional testing of the FlexFactory was completed by GE, factory acceptance testing (FAT) was carried out at GE's US facility in Marlborough, Massachusetts, in the presence of JHL, to verify the outcome of the functional testing.

One of two pairs of 50- and 500-liter bioreactors with a common HMI

QC laboratory showing bench instruments and HPLCs

With FAT approved by JHL, the entire FlexFactory setup was transported to the site for installation.

In parallel with fabrication and testing of the FlexFactory process equipment, L&K Engineering completed detailed design, construction of the site, and commissioned the utilities, including the field wiring for the FlexFactory process control system. Once delivered, the FlexFactory equipment was positioned; site acceptance tests (SATs) conducted according to the C&Q program were completed within a month, followed by operator training.

The realization of a fully integrated single-use bioprocessing facility required close collaboration between JHL and its key service providers. The complexity of the project necessitated a highly skilled team, able to address and to decide on issues related to process design, equipment specification, automation quality, regulatory, and project management. The combined project team from JHL, GE, and L&K Engineering exemplified this approach; together they were able to deliver the fully functional facility in December 2013, within nine months from contract signature to SAT.

By mid-2014, JHL had obtained the two key licenses needed for a biopharmaceutical facility to operate in Taiwan: an occupancy license gated by approval of the fire protection systems and a pharmaceutical license. The design–build approach enabled a shorter and more efficient application process for the occupancy permit and ultimate award of the pharmaceutical license.

The combined project team from JHL, GE, and L&K Engineering were able to deliver the fully functional facility in December 2013, within nine months from contract signature to SAT.

The JHL team credits the adoption of standard process equipment and control system from a single supplier for streamlining commissioning and qualification. Planning of commissioning and qualification front-loaded testing in the FAT phase and achieved rapid execution of SAT, where testing of only critical functionality was required. The installation and operational qualification followed a similar approach. Consistently using a modular document template format from FAT to operational qualification minimized document review/approval cycles and facilitated fast execution of all testing phases.

In April 2015 JHL completed its first GMP manufacture and lot release of a 500-liter scale batch for a privately held Chinese biotech company of its oncology monoclonal antibody product for use in Phase 1 clinical trials.

Project timeline

March 2013
First inspection of the site by the design team

Contract with GE to design the facility and supply a FlexFactory signed

May 2013
Phase 1 construction of Process Development laboratory completed

June 2013
50-liter single-use bioreactor delivered and started first run in same month

August 2013
Construction of pilot cleanroom area commenced

November 2013
First Shipment of FlexFactory equipment arrived

500L bioreactors (2x XDR500) arrived

December 2013
SAT Completed

July 2014
Factory License granted

Pharmaceutical License granted

December 2014
Installation and Operational Qualification (IOQ) of process train completed

April 2015
Completion of GMP manufacture and lot release of first 500-liter scale batch for a privately held Chinese biotech company of its oncology monoclonal antibody product for use in Phase 1 clinical trials

September 2015
TFDA approval letter issued

FlexFactory harvest system hardware

By the end of 2015, the Hsinchu plant received its approval letter from the Taiwan Food and Drug Administration (TFDA). Despite the novelty and uniqueness of the project for the region, the final facility cost was $1 million below the original budget of $18.7 million. These savings were achieved primarily because of the efficiency in design–build specification and speed of execution while still maintaining quality.

Despite the novelty and uniqueness of the project for the region, the final facility cost $1 million below the original budget of $18.7 million.

Built-In Scalability

While the Hsinchu plant was built as a pilot facility for JHL, they nonetheless designed in some scalability. The facility is designed for doubled capacity with four bioreactors installed when greater throughput is required. The automation and utilities were designed with the extended capacity in mind, so that when the second pair of 500-liter bioreactors are added, they can simply be installed and enabled on the system without any changes to the automation system or utilities.

"We've since done a design analysis that showed that we should be able to add 1,000-liter reactors within the same footprint," says Kotlarski. "The disposable equipment is able to cope with a double in batch size just by changing some tube sizes on some of the chromatography skids and adding a few more of the mixing vessels."

Blueprint for Commercial Production

While the pilot plant project was in progress in Hsinchu, JHL made a commitment to build a commercial site in China, with a planned completion for late in 2016. The FlexFactory platform approach is enabling JHL to develop manufacturing processes in the Taiwan facility and rapidly transfer them to its laboratory in Wuhan, China, which utilizes the same platform and will enable seamless scale-up to 2,000 liters.

50-liter XDR bioreactor supplied in June 2013

"The commercial-scale plant will use the same operations, the same chromatography, and the same pump skids for filtration," says Kotlarski. "We will use the same 50- and 500-liter reactors and can scale up to a 2,000-liter reactor, so this gives us the opportunity to transfer over standard operating procedures for everything except the production bioreactors. We will get about 80% of our standard operating procedures already prepared before our commercial plant is up and running, which will make it a lot quicker for us." ■

Mike McGrath

JHL Biotech

Project:	Single-use biopharmaceutical pilot and clinical manufacturing plant in Hsinchu, Taiwan
Location:	Hsinchu, Taiwan (ROC)
Project Mission:	Establish a biologics API development and clinical manufacturing center capable of commercial launch for niche products.
Site information:	2,351 square meters within an existing six-storey building

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- OSD (T10), 8 – 9 Aug.
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- GAMP® 5 Data Integrity (T50), 26 – 27 Sept.
- GAMP® 5 Process Control (T21), 27 – 28 Sept.
- HVAC (T14), 26 – 28 Sept.
- Technology Transfer (T19), 27 – 28 Sept.
- QRM (T42), 26 – 27 Sept.

San Diego, CA

- Basic GAMP® 5, Annex 11 / Part 11 (T45), 12 - 14 Sept.

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- Application of GAMP® 5 (T11), 12 – 13 Sept.
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- C&Q (T40), 29 – 30 Sept.

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- Cross Contamination (Risk-MaPP) T41, 22 - 23 Sept.
- Technology Transfer (T19), 22 - 23 Sept.
- Clean in Place (T03), 22 - 23 Sept
- Biomanufacturing Facilities (T31), 22 - 23 Sept.

OCTOBER

Boston, MA

- Bio Process Validation (T32), 19 – 20 Oct.
- Cleaning Validation (T17), 17 – 18 Oct.
- GAMP® 5 Data Integrity (T50), 17 – 18 Oct.
- Project Management* (T26), 17 – 18 Oct.
- QRM (T42), 19 – 20 Oct.
- Water Generation, Storage, Delivery and Qualification (T04 and T23), 17 – 20 Oct.

Copenhagen, Denmark

- Basic GAMP® 5, Annex 11 / Part 11 (T45), 31 Oct. – 2 Nov.

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- Auditing (G07), 17 – 18 Nov.
- HVAC (T14), 7 – 9 Nov.
- Facilities, Systems and Equipment Workshop (T48), 10 – 11 Nov.
- GAMP® 5 Process Control (T21), 14 – 15 Nov.
- Q7A (T30), 3 - 4 Nov.

DECEMBER

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- 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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Regulatory Harmonization Depends on Global Industry Connectivity

Roger Nosal

An ISPE Member since 2007, **Roger Nosal** is Vice President and Head of Global Chemistry, Manufacturing and Controls at Pfizer. Roger has contributed to the evolution of Quality by Design and has advocated for global regulatory harmonization through several PhRMA, ICH, ISPE, PQRI, AAPS, IFPAC, ACS, and DIA technical committees. He is currently Chair of the *Pharmaceutical Engineering* Committee and co-chair of ISPE Regulatory Track and DIA Quality Program Committee.

During the last 35 years I have witnessed a gradual transformation in the pharmaceutical industry. Until the 1990s, industry and regulatory authorities were often at odds not only on **what** but **how** the industry should be regulated. The industry did not do itself any favors. Screw-ups, particularly failures to communicate quality issues, eroded trust and prompted increased regulatory scrutiny. Regulations have generally been enacted only after repeated industry failures.

As a result of growing economic and political pressure to reduce costs and improve product quality, efficacy and safety, regulatory authorities led by the US, EU and Japan, in conjunction with industry, issued a call to reform industry's focus on quality. For their part, the industry largely embraced the challenge to transform traditional sequential development, improve attention to quality and largely abandon trial and error manufacturing paradigms.

While technological advancements in discovery and product development created opportunities for product innovation, perhaps the single most progressive factor in promoting innovation has been increased transparency, harmonization and connectivity among companies and regulatory authorities globally. ISPE has provided an effective forum, infrastructure and global reach to foster, cultivate and develop sustainable progress in pharmaceutical innovation.

The adoption of the concept of *Quality by Design* shifted the paradigm for pharmaceutical development from a traditionally retrospective approach for manufacturing optimization to a prospective assessment of process understanding. In 2007, representatives from several companies who had filed regulatory submissions in the FDA Pilot Program realized that the only way to progress these new concepts was to share their respective experiences of what they had learned during the pilot. ISPE provided the forum for stimulating constructive engagement, technical alignment and policy consistency.

In fact, ISPE established the *Product Quality Lifecycle Initiative (PQLI)*, which emerged as a leading industry voice on **how** to implement science and risk-based approaches described in ICH Q8 – 12 guidelines. Subsequently, IPSE hosted multiple meetings, workshops and forums in the US and regionally, under the banner of *PQLI* fostering connectivity of technical and regulatory data, experience and perspectives.

The increased transparency and engagement has highlighted the importance of connectivity in leveraging scientific understanding and robust risk management as the common vernacular for continuous improvement and manufacturing innovation. *PQLI* reinforced the mission of ISPE as an authoritative source for pharmaceutical manufacturing and quality knowledge.

This common vernacular transcends regional borders as well. Connectivity of ISPE Affiliates and the value they bring to understanding and harmonizing the scientific, technical and regulatory landscape of pharmaceutical development and commercialization has enhanced the knowledge and global significance of PQLI. In fact, ISPE meetings in EU, Japan, China and India have been instrumental in connecting regulators with industry and refining the concepts required to effectively innovate pharmaceutical manufacturing. Global connectivity of innovative technology, ideas and approaches among companies and regulatory authorities may be the most enduring legacy of QbD, PQLI and ISPE. ■

Have a point of view you would like to share? Let yourself be heard! Send your submission to amdigiorgio@ispe.org

All of the YPs I have met have similar challenges in common

How to Create a YP Start-Up Network

Before starting your Young Professional start-up network, you should be sure you believe and are passionate about solving challenges that your peers face in their careers and that can be overcome by building a network at ISPE. All of the YPs I have met have similar challenges in common: 1) not knowing peers with the same jobs from other pharmaceutical companies and 2) understanding the technical language of other departments. So to start a YP start-up network there are four focus areas: idea, product, team, and execution.

Idea: Be Mission Oriented

I encounter challenges with a "do-it" attitude and I never lose in any situation in my career. Either I win or I learn something new. This does not mean that you will just go and do things without setting a strategic plan.

When I first started a Young Professionals group within the DACH (Germany, Austria, and Switzerland) Affiliate, I failed. I went to copy and paste the process described from previous "best practices" existing in our Young Professionals Knowledge Platform. But there were several bottlenecks, which led to this initial failure:

- Not having a clear mission statement that intrinsically would make people follow
- Not making others accountable from the first day
- Not having built a diverse and interdisciplinary group

In my second attempt, I went out to the local ISPE DACH conferences and wrote to over 500 people on LinkedIn who wanted to "join a volunteering board" (this is a profile setting). Today we are six founding members, with a very international background from different disciplines in the pharmaceutical industry.

The mission I communicate when talking with new potential Young Professionals is that everything we do is focused on bringing faster and better quality medicines to the people who need them the most.

Product: Build Something Our Peers Love

Your main focus should be building something incredibly simple to use that your peers in the pharmaceutical industry love and need. Additionally, get some young professionals from outside your founding team—a YP testing group—to love what you have to offer, learn their needs extremely well, and get close to their cultural reality.

The Ireland Young Professionals have one of the highest YP attendance rates in Europe at their events. Over the years they have built events that add value to their peers by creating YP-focused events joining industry leaders. Additionally, they provide local events in Cork and Dublin, to go where their peers are and give them the knowledge and network they need.

In DACH we have over 10 pharma hubs, which we are not able to access equally during a start-up phase.

Our focus is to create something simple and provide extremely short knowledge exchanges using VideoCons inviting an experienced professional to teach us, for example, "How to Prepare an Audit." This solution came out of the needs we identified during conversations with YPs.

Team: Build Trust in Your Relationships

When looking for people to join the YP start-up network, try to get a group of people who are diverse culturally, interdisciplinary, and with different personalities.

When talking with potential volunteers you can ask several questions:

- Are they smart?
- Do they get things done?
- Do I want to spend a lot of time around them?
- Are they great communicators?
- Are they courageous?
- Would I feel comfortable reporting to them?
- What have they done?
- How have they solved tough work challenges?
- With whom have they worked?
- What did they specifically do?

The essence of all relationships is building trust with your partners. To be able to say out loud that you trust someone, you will have to share experiences together. We all agree that the richest human experiences are the ones we have face-to-face with other human beings. There are nevertheless ways of working through this in a remote and mobile environment.

Establish a working culture between your team that surrounds all new mobile ways of working. You should also set a plan to have regular face-to-face meetings where you should always have some networking opportunities besides focusing on specific tasks. This is especially possible at local Affiliate/Chapter/Board meetings, where you have the opportunity to build a bridge between different experience levels.

Execution: The Do-It Attitude

You will have to get things done. The YP vision to get faster and better quality medicines to the people who need them the most can be broken down to tiny projects, which can then be executed.

There are two important parts in execution:

1. Focus
   - Say no a lot
   - Set three key goals and repeat them
   - Communicate
   - Maintain momentum and growth
   - Work together face-to-face and physically in person

2. Intensity
   - Implement a relentless operating rhythm
   - Set an obsession with execution quality
   - Be biased toward action
   - Break everything into small projects involving Young Professionals from outside the founding group
   - Do whatever it takes

Your main focus should be building something incredibly simple to use that your peers in the pharmaceutical industry love and need

Bringing It All Together

FFocus everything on your product all the time. People will hear about the great things you are providing, and they will be able to learn something, which is not possible in their work or online courses or on LinkedIn. If challenges arise and you are not able to agree on a topic in your founding group, ask your YP testing group. Don't send them an email—VideoCall them.

Set an operating rhythm by defining when you will offer products (events, networking opportunities, etc.), add smaller updates by sharing small knowledge exchange opportunities through a VideoCon, and review and report on your YP engagement numbers. ■

This article is based on the video lectures from Stanford University about "How to Start a Start-Up" from September 2014 available on YouTube (www.youtube.com/channel/UCxIJaCMEptJjxmmQgGFsnCg/feed) from Sam Altmann from Y Combinator, a start-up accelerator.

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.

Meet Young Professional Tiffany Coleman: An Advocate for Diversity

Diversity. It is something that Tiffany Coleman speaks of as an objective for ISPE and the pharmaceutical industry as a whole. It is also the way she lives her life, from her educational path to her personal hobbies and the way she is building her professional career.

A native of Jackson County, Missouri, Coleman is the Business Development Regional Manager—Midwest Region for Sequence Inc., a full-service consulting firm specializing in providing quality and compliance services to regulated industries such as pharmaceuticals. She is also an active member of ISPE, an avid online gamer, an organic farmer, as well as an advocate in the social justice movement for equality in the United States and around the world for women and members of the LGBT community.

An Unconventional Path

Following three years of service in the US Army, where she enlisted immediately after finishing high school, Coleman jumped right into the job market. "I wasn't thinking of going on to college at the time," says Coleman. "But I met an amazing man named Chiming Huang at the University of Missouri–Kansas City (UMKC). He was my first mentor, and he brought me into his lab to do undergraduate research. At the time I wasn't even in school, so undergraduate research was a bit of a misnomer, because I was really a research assistant. But I did really good work there and he encouraged me to start going to school."

Coleman enrolled at UMKC, graduating in 2011 with a bachelor's degree in liberal arts with an emphasis in chemistry. "My education was really long," she says. "I was uncomfortable with the idea of being a full-time student, so it took me ten and a half years to finish my undergraduate degree studying part-time."

Coleman augmented the typical science and mathematical courses with courses in communications and risk management. "I was trying to simulate the level of scientific inquiries that was had by people like Newton," she says. "Today we have a pretty much cookie-cutter educational track, which I'm sure is very effective for some, but it was different for people who were innovating 100, 200, or 300 years ago. So I decided that I wanted to take a different track, which meant that I took classes that no other chemistry major would have taken. But I think that has allowed me to be successful in my life, because many people who focus only on chemistry don't have the understanding of communications or analytical thinking outside of the technical methods in a lab, which they need to be successful in a constantly changing environment."

> I found that I really love helping patients have a better quality of life and that I felt that the only way to make that happen was for everyone to be compliant, because when we're not compliant, the patients suffer."

As Coleman continued to work at UMKC while taking courses part-time, she was encouraged by one of her professors to consider joining the pharma industry. "I was working in an organic product synthesis lab and he said I was doing really good work, but that I should see how the discovery science I was doing was being applied in the field," she says. "I did that and it was the same science I was doing in the lab, but on a clinical or a commercial scale. The problem solving is what kept me with it, because of the level of complexity of these processes; there so many steps and so many things that you have to get right."

Around that same time, in 2008, Coleman was first introduced to ISPE at a quality conference in Baltimore. Her boss was unable to attend and offered to send Coleman instead. "I went and it was amazing," she says.

Tiffany Coleman

While attending the conference, she met Stephanie Wilkins, who has since become her ISPE mentor. She also met Jennifer Lauria-Clark, who at that time was just starting to put together the society's first Young Professional group. "She pulled me into a focus group of 10 people, and the gentleman who was leading the group spoke about how important it was to have young professionals make a bigger splash in ISPE. That reeled me in, because I felt like they really cared about me."

Since then, Coleman has continued to be very active within the ISPE. She has served as a Committee and Board Member in the ISPE Midwest Chapter, where she is currently the Board Secretary. She and her Chapter have received ISPE International honors and awards for Committee of the Year in 2012 and Most Young Professional Growth in 2014 and 2015. Coleman fully intends to remain active and says would relish the opportunity to serve on the ISPE International Board one day.

A Change of Perspective

As Coleman became more active within ISPE, she was exposed to several new and interesting areas of the pharmaceutical industry, which led her to a number of job changes. "I tried a number of different things because there was so much available for me to learn and do," she says.

"I was working in packaging of investigational products and I enjoyed that, but then I learned about computer system validation so I went and I did that for a while. But then I wanted more, so I moved on to a specific quality supervisor position and while I was doing that, I found that I really love helping patients have a better quality of life and that I felt that the only way to make that happen was for everyone to be compliant, because when we're not compliant, the patients suffer."

Coleman's career growth path can be seen as somewhat unique in two respects; the first being the diverse jobs that she has held and, second, that she once held anti-pharma beliefs. As mentioned earlier, Coleman is an organic farmer and she shared the beliefs of many of her farming colleagues. "I was always against big pharma in general. I thought that big pharma, big oil, and big agriculture don't care about the consumer except as an aggregate because there is money there. But what I found after being in the pharmaceutical industry is that it is not the case at all. In some cases, the vice presidents, presidents, and CEOs of these companies, the only thing they think about day in and day out is the little girl that needs her leukemia medication, or the grandmother who needs to take her blood pressure pill. For me, being in ISPE has helped remove that veil and now, as a consultant, I have worked for many pharmaceutical companies and have seen that almost all of them have that same eye on the patient. It really is about improving the quality of life of people who are suffering, and that is pretty awesome. Since I'm Buddhist, the whole idea of reducing someone suffering is a big deal for me."

The Road Ahead

As she looks ahead to the next stages of her life and career, Coleman, now 34, has a plan. "I really love what I'm doing I am now in the business development department of Sequence," she says. "I have a five-year plan, and a big part of that is to grow my region by 30 people this year. From there, I hope to go from being a regional manager to an international director. I really believe that the future with regard to pharma is producing things in Southeast Asia, because that's where most of the population of the planet lives."

To help make that happen, she has set a personal goal to learn Mandarin so that she can be better prepared to perhaps open an office for her company in China.

On the personal side, she will also continue to advocate for diversity and equality. "It was really a huge deal for me when same-sex marriages were made legal in the United States, because I was able to marry my partner of over six years. For over half my life, I have been actively participating in political activism in regards to equality in the United States and around the world," she says.

"I really think that diversity is important. From the ISPE standpoint, a big part of what I try to do is make sure committees are more inclusive and discuss the fact that we should have women on committees and in positions of, not so much authority, but of expertise. Because in my opinion diversity is what allows us to be successful as a nation, and if we embrace it even more than we have been, it will be even better." ■

Mike McGrath

A Talent Acquisition Perspective

David G. Smith

David G. Smith knows a thing or two about talent acquisition and career development in the pharmaceutical industry. Over the last 17 years, Smith has worked with tens of thousands of job candidates and has been involved in hiring thousands of individuals. Today, as a Senior Recruiting Partner at Biogen, Inc., Smith works out of the company's Raleigh-Durham, North Carolina, facility where he is responsible for talent acquisition for Biogen's manufacturing and quality organizations in the United States.

A chemist by training—he has an undergraduate degree in chemistry with a minor in biology from Stephen F. Austin State University in Texas—Smith worked offshore in the oil and gas industry to get himself through school. Job prospects were not favorable when he completed his studies, however, so he found a job at an analytical laboratory, where he had an interesting conversation with the director of the lab.

"He told me his wife was working for a company that hires scientists and engineers and that she was having a real hard time finding someone that understands the language that scientists and engineers speak," explains Smith. "He wanted me to have a conversation with his wife to see if I might be a good fit for her organization. Next thing you know, I had started my career in talent acquisition."

Much of Smith's career has been on the consulting side. From 1999 through 2012 he was a member of the team at Kelly Services, a third-party organization that provides talent acquisition support for a variety of companies. "For the last 17 years, I have been working in talent acquisition largely for the life science space, ranging from commercial, R&D, quality and general administrative professionals, as well as on the operational side of things with manufacturing and engineering," he says. "I have pretty much dabbled across the entire spectrum of pharma, from interns and new graduates through the VP-plus level, and with companies ranging from two-person startups to some of the largest pharmaceutical companies in the world."

An Appreciation for ISPE

Smith was first introduced to ISPE through a chance encounter in 2004. He had relocated to North Carolina from the Dallas-Fort Worth area and had a conversation with a person in the industry who mentioned an upcoming event. "I went to a planning session as my first introduction to ISPE, and it was a really neat opportunity to hear what the chapter was all about and their plans regarding things they wanted to accomplish for the year," he says. "They provided a great opportunity for me to talk to a few folks that were leading different committees and I latched on to the programming committee because I thought I might be able to help out by identifying speakers, and away we went!"

David G. Smith knows a thing or two about talent acquisition and career development in the pharmaceutical industry

He has been an active member of the ISPE Carolina–South Atlantic (CaSA) Chapter ever since, and has served in a number of different capacities including a variety of Board and Committee positions. "I chaired a Biotechnology Day committee—an event held at the Museum in downtown Raleigh—where we brought industry and kindergarten through grade 12 individuals together to showcase the coolest things that the industry is doing," he says. "It was a really great opportunity, and we averaged well over 6,000 attendees each time we did it."

"I have been involved with the Students and Young Professionals pretty much the entirety of time I have been involved with ISPE," he says. "I had a number of different roles supporting Young Professionals and the Student Committee. We held symposiums on an annual basis for Students and Young Professionals to learn more about how to find a job. I also serve as an industry advisor for the Student chapter at NC [North Carolina] State."

This past March, Smith also arranged an opportunity for Biogen to partner with the Student Chapters across the area on a Biogen Career Night where approximately 240 students registered to learn about Biogen and the various functional areas involved in the company's local manufacturing efforts. "We had more than 30 business leaders who came out to talk to students and help them understand what a 'day in the life' might be in various capacities, to start conversations around the differences between the span of roles in engineering, manufacturing support, or other roles that these students have interest in. It was a really neat opportunity to bring us out to the students and have an open house."

Advice for Students and YPs

As a talent-acquisition professional, Smith is in an ideal position to provide expert advice to Young Professionals and Students alike. He intends to do this in upcoming issues of *Pharmaceutical Engineering* magazine (see Sidebar for more information).

His first piece of advice for any job candidate is straightforward: Know what the company does and what is expected in a particular role. "There are many highly intelligent and talented people who come out of engineering programs and hear about career opportunities and what they should do when they graduate," he says. "But many of them don't fully understand what is really required in those positions. We see people applying for positions that are more senior than what they really have the skill set for; and when it comes down to the interview process, their lack of understanding of what the job entails makes it difficult for them to highlight the knowledge and skills they gained at school that could be directly impactful in the role that they're trying to pursue."

"I think that we, and a number of other companies, are trying to highlight what it is like actually working in a biomanufacturing facility. We provide countless opportunities for Students to be able to either come to our facility—for example the Biogen Career Night earlier this year—as well as a number of other touch points with ISPE and other organizations to allow Young Professionals to get a sense of what they're signing up for," he concludes. ■

Mike McGrath

Send David Your Questions

Do you have questions about job searches in the pharma industry? Not sure about your career path? Send your question to david.g.smith@biogen.com. We'll publish your Q&A in an upcoming issue!

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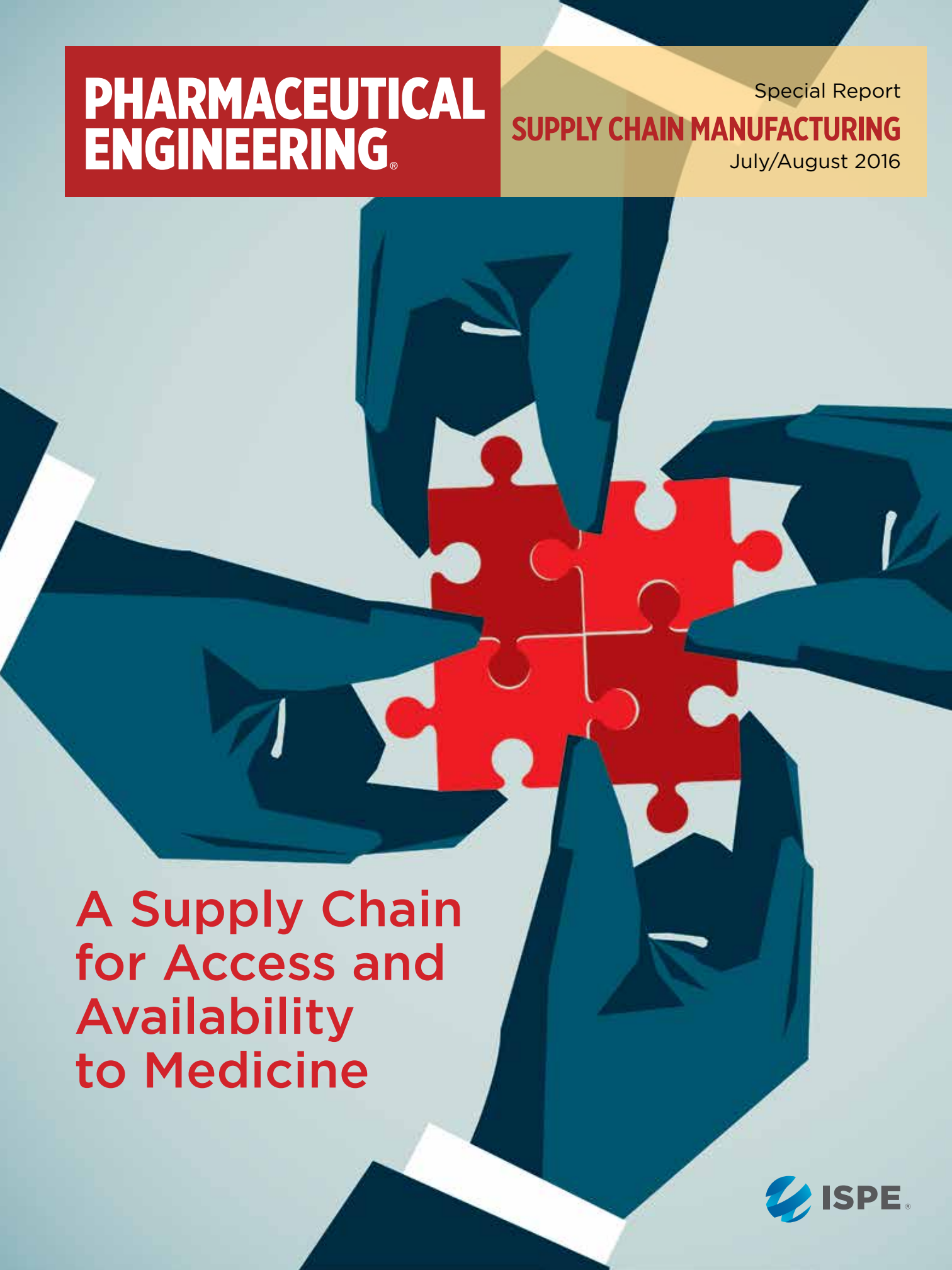
July/August 2016



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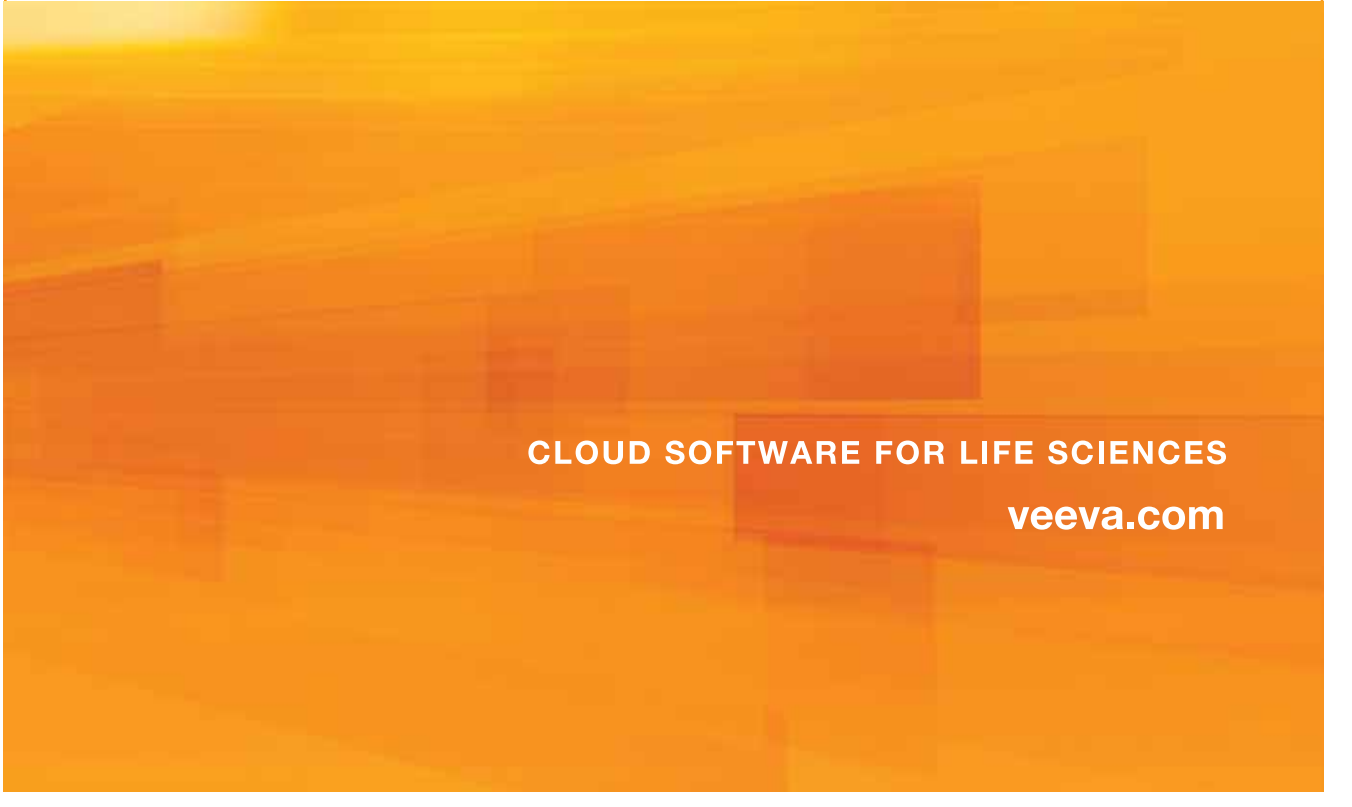

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We Do It to Make Medicine Available Anywhere in the World

This special report is focused on three main topics, which are vitally important to the pharmaceutical industry, and are interrelated:

- The new Operations Management Good Practice Guide
- The importance of data integrity in the industry, and
- The impact of globalization on pharmaceutical supply chains

The **Operations Management Good Practice Guide**, published earlier this year, is intended to provide access to best practices in all aspects of operations in the supply chain, from supply to manufacture, and delivery to customers. The industry faces challenges in adapting to changes on many fronts. The growth of biologics and introduction of continuous manufacturing are two examples.

Biological and chemical-based products now coexist in supply chains, with differences in projected growth patterns for product categories. While there are some similarities in certain supply chain processes, there are also differences that must be managed. Differences in lead times, carrying costs for inventory, additional sterile environments, and cold chains, are some examples of differences that add complexity to mixed environments.

The introduction of continuous manufacturing moving products from the traditional batch manufacturing will also affect the supply chain processes before and after the manufacturing process itself. The entire chain will need to be synchronized.

Change is not new to the industry and the guide is meant to be a toolbox to deal with it. "One size does not fit all" is a key concept; it has been evident in the need to deal with differences among legacy products, seasonal products, and life-saving drugs. The guide focuses on continuous improvement, and innovation tools and techniques, which stress the importance of operational flexibility to deal with change, as well as some statistical techniques to identify appropriate segmentation of the supply chain to manage the differences in a mixed environment.

Data integrity has obvious importance for regulatory requirements, and there is much focus on the developmental phases of the product life cycle. In commercial operations the importance of operational accuracy, particularly for quality requirements, is well known.

Supply chain performance is heavily dependent on data integrity as well for operational management and planning, as well as improvement in design. The value of time must be recognized as a key parameter, for example the timing of real-time plant floor updates can be as important as the accuracy of the data itself.

Transparency is important in working relationships with partners so that data are made available to customer/supplier entities. The technology exists to provide electronic records for quality data, production schedules, batch data, etc. The timing of when the data are made available is an important aspect of partner transparency.

The re-use of process data for all types of modeling should be part of planning the data architecture. Simulation and optimization modeling are heavily data dependent, but are very valuable in improving operations in individual plants and laboratories, as well as interrelated supply chain functions.

Globalization impacts pharmaceutical supply chains in numerous ways. Some aspects that may come immediately to mind are the differences in country and regulatory requirements, or tax and financial differences. The need for a replicative "capability" should also be a concept that should be part of our thinking.

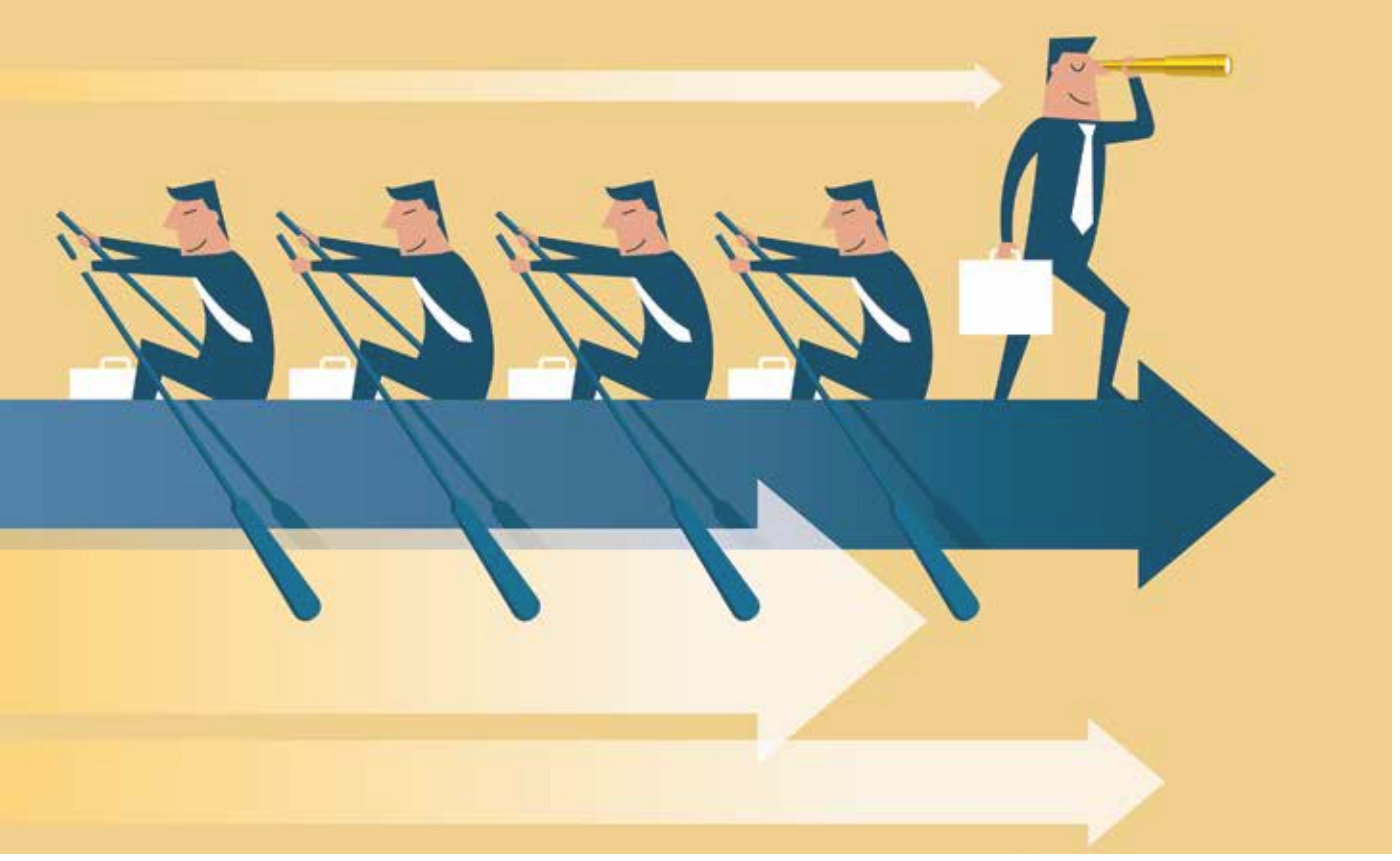
Capability implies that things are done the same way throughout a company worldwide, or across product lines. It also facilitates change, so that the supply chain can be extended to new markets, as needed, or new plants or suppliers can be introduced using a routine process.

At its core the capability is defined by a standard set of supply chain processes for operations, planning, and strategy, which are cross functional, touching most functions in the company. These define how things are done and how they are measured so that the metrics provide the basis for management evaluation and potential improvement.

Planning the global operation with a standardized supply chain capability provides the basis for improvements at the strategic, tactical or detailed level. Strategically, an example may be to plan for redundancy in case of catastrophic events. Tactically, managing contract manufacturing in the same manner as internal facilities may be an example. An example at the detailed operational level could be introducing a label to order process to improve efficiency in country labeling as part of an overall delayed differentiation strategy.

The importance of these three interrelated topics to the management of pharmaceutical supply chain and its impact of global drug availability will continue going forward.

Jim Curry, Owner, Op Stat Group Inc.



Moving the Needle Forward

Operations Management and the Supply Chain

Five years on, the *Operations Management Good Practice Guide* (GPG), the brainchild of Giuseppe Ravizzini and Alain Cruset, has seen the light of day. And at the 2016 ISPE Annual Meeting, attendees will be able to hear the results of a survey that gauges where the pharmaceutical engineering industry stands on operations management best practices.

***Pharmaceutical Engineering* met with team leaders Jim Curry, Marzio Mercuri, and Giuseppe Ravizzini to talk about the GPG and their industry survey.**

"You're only as strong as your weakest link" is a saying familiar to many professionals. And it's one that is often evoked at the start of a project that requires continual teamwork, precision timing, and absolute trust.

Whether you're pulling together a team to manage a manufacturing operation or write a GPG, it's much the same, says Giuseppe Ravizzini, Group Engineering and Maintenance Manager, Recordati Group.

"This guide took years to develop. We were teaching at local ISPE meetings in Europe when we came up with the idea for an operations management guide."

"They saw that there was a need in the industry to provide information on how to manage and improve operations across the supply chain," says Jim Curry, owner, OpStat Group Inc. "They had to establish the Operations Management community of practice before they could even get started."

"As time went by, industry and company changes affected teams and authors who were available to work on the GPG," says Ravizzini, "but we persevered. Many people in the industry—authors from around the globe—have put an enormous amount of effort into this guide."

The 166-page document was released in April 2016, and early indications are that it may be an ISPE "best-seller." "By addressing how specialty, bulk API, and drug-product manufacturing systems are organized and operated throughout the supply chain, this GPG delivers a consistent message," explains Marzio Mercuri, Technical Operations Director, Polpharma Group: "even a state-of-the-art cGMP production plant can embrace continuous improvement."

This GPG delivers a consistent message: even a state-of-the-art cGMP production plant can embrace continuous improvement.

The guide's original objectives were straightforward, says Mercuri:

1. Provide guidance and support to pharmaceutical operations managers, in selecting the most appropriate solutions for the identification and completion of the objectives of their manufacturing operations within the framework of their whole organization, including external stakeholders and regulatory bodies
2. Provide operations management with sound support in understanding how compliance and operational excellence can be achieved at the same time, and in a win- win approach, given the extent of tight regulation in the pharmaceutical industry
3. Define a common language, and provide guidelines for performance measurement and improvement
4. Identify new performance-improvement tools, clarifying what is applicable, and what is not in pharmaceutical operation
5. Provide a reference for pharmaceutical operations.

This ISPE guidance document brings together topics presented in its Baseline® and Good Practice Guides—facility design, validation, regulatory and quality assurance, goods import/export—in a ready-to-use "toolbox." This multidisciplinary document provides a comprehensive review of everything involved in the manufacture and supply of life science products—whether they're pharmaceutical, biotech, or medical devices.

According to Mercuri, it will provide guidance to pharmaceutical operations professionals who need to identify the most appropriate solution for a specific problem. "That's why we call it a toolbox," he says. "Where it doesn't provide an answer, it will help the user frame the questions needed to move a project forward." Ultimately, adds Curry, "it establishes both a framework and a vocabulary to discuss operations management by defining a common language for the industry. It also introduces lean concepts."

Taking the Pulse of the Industry

The guide is also intended as a basis to help both professionals and organizations develop further using a recognized industry standard/practice. And so lean manufacturing will receive particular attention at ISPE's 2016 Annual Meeting in Atlanta, Georgia. Attendees will be able to hear the results

It Takes a Global Village

A task team led by Marzio Mercuri and Giuseppe Ravizzini, and supported by the ISPE Operations Management Community of Practice, produced the *Operations Management Good Practice Guide*.

Core team and chapter leaders | **Chapter writers and team reviewers** | **Contributors**

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To order a copy of the ISPE *Operations Management Good Practice Guide*, please visit www.ISPE.org/ispe-good-practice-guides/operations-management.

of a survey that gauges where the pharmaceutical manufacturing industry stands on best practices.

"We decided to undertake this project to establish a baseline for further study," says Curry. A six-question survey went out to some 2,000 members of the Operations Management community; more than 5% completed it. A team from the Operations Management steering committee will be collating and analyzing results over the summer, and presenting its findings on September 20, as part of the End-to-End Supply Chain Management track. The team, led by Niranjan Kulkarni, who is Chair of the track, includes Rodney Neal and Lori Chelemedos, as well as Curry.

"What we're trying to do is determine where industry stands in relation to some of the best practices we have laid out in the guide," says Ravizzini. Adds Curry, "And from that be able to move the needle. In other words, if most of the industry is not using practices presented in this guide, what do we do?" Curry's best guesstimate is that the industry will land somewhere "in the middle of the road." "On a scale of 0 to 5, probably between 3 and 4," he says. "The pharmaceutical manufacturing industry is somewhat behind other manufacturing industries, such as electronics, because healthy profit margins delayed recognizing the need for improvements related to operations practices and supply chain."

Mercuri agrees. "This means that some companies will be at 5 and others at 1," he says. "Our industry is not an anomaly and operational excellence does not have the same maturity level throughout it," he says, "You cannot replicate the same business management model. We have big pharmaceutical companies, generics, midsized companies, small start-ups, etc. Operations management models and practices have to be adapted."

"There is a difference in terms of scale and factor of industry," says Ravizzini. "The maturity of a supply chain management model depends on the player's position at a given moment." The survey addresses this by asking about company size, age, and type of business (generic or contract manufacturing). The intent is to identify differences in maturity levels according to these responses.

Mercuri believes that a focus on continuous improvement and cost-effectiveness makes generic companies better positioned to achieve operational excellence. In generic companies, says Mercuri, "effectiveness is a matter of life or death." Whereas big pharmaceutical company margins may be as

There's no better justification for expenditure than improved performance.

high as 95 %, generics, when they do well, may hit between 60% and 65 %, and when they don't, they may generate margins between 40 % and 50%, and even lower. "However the R&D challenges facing generic pharmaceutical companies are huge, because in that particular sector, innovation is key: companies face a wall of patents, and speed to market really matters."

Lean Manufacturing Matters

"Pharmaceutical companies must have the flexibility to proactively adapt to changing demands both in the mix and the volumes due to new products and market introductions. To do this effectively all aspects of the supply chain must have sound cross-functional processes and predictive metrics to ensure that capability in all areas is available before it is needed to accommodate change."

— Jim Curry, owner, OpStat Group Inc.

"Pharmaceutical business requires strong ethical standards. We produce products that must comply with rigid regulations, and match demanding quality standards to cure diseases and enhance the lives of patients. We employ people who develop and manufacture drug products with active substances that if not adequately handled and processed could pose serious harm to health. We must operate our industrial facilities, which have both social and environmental impact on adjacent communities, responsibly. More than any other industry we deal with people and their lives. This practice document has the ambition to guide the reader on a journey after which we hope that the professionals in our industry will have more awareness about continuous improvement and operational excellence as a foundation for a truly sustainable business.

— Marzio Mercuri, Technical Operations Director, Polpharma Group

"Lean principles came late to the pharmaceutical sector because there existed a perception that they could not be applied in such a highly regulated environment. Continuous improvement was considered the opposite of rigid GMP rules; yet operations performance and efficiency, along with quality and GMP, should also be considered priorities. They weren't in the past. This Good Practice Guide shows how modern pharmaceutical companies may consider all operations as a single, integrated complex system... and how this system can support the company's business, overall."

— Giuseppe Ravizzini, Group Engineering and Maintenance Manager, Recordati Group

A Holistic Point of View

In addition to basic business drivers of operations strategy, such as speed to market and ROI, factors like regulatory compliance come into play. And in a global environment, they become complicated to manage. There is only one solution, says Mercuri: a holistic approach to management.

Business Factors Driving Operations Strategy

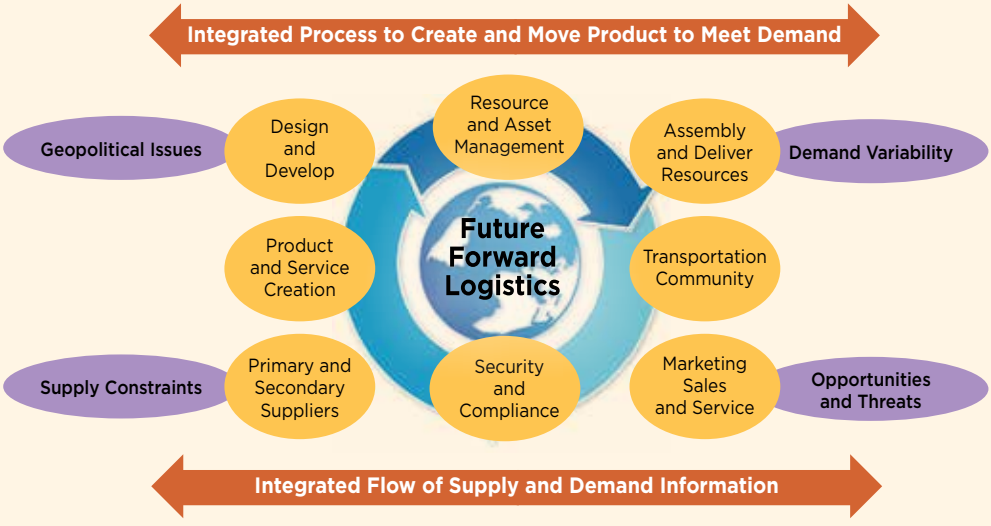
The Fundamentals

Professionals who purchase the *Operations Management GPG* will find that they don't have to reinvent the wheel. It provides answers to questions already asked and answered by their peers. "This will eliminate waste and ultimately make all initiatives leaner," says Curry. "For example, one of the first concepts introduced in the book is the PDCA (plan-do-check-act) cycle. This is a standard process management tool that, if properly used, may add value in an organization at any level." Adopting the concepts outlined in the guide will help readers become more effective and efficient. "There's no better justification for expenditure than improved performance," he adds.

"When young professionals join an operations management team, they often ask 'where do I begin?' or 'What questions should I ask?'," says Mercuri. "While I believe all questions are valid, we counsel young professionals to keep in mind supply-chain fundamentals."

"Supply chain has to do with sourcing, manufacturing, and delivery," adds Ravizzini. "These are the fundamental issues to consider for each step in the process every time a new element is introduced.

Holistic Supply Chain Model—Understanding All Elements Across a Complex Global Landscape



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"You do need standard practices that govern all the detailed processes, down to the country level, and to sourcing, manufacturing, and delivery that tend to be in different places," says Curry. "It is important to design a standardized holistic process."

"When we started work on this guideline, we explained we needed to have an approach to operations that focused on the whole," says Ravizzini. "We didn't want to consider one monolithic subject; rather, we wanted to embrace a complete process from raw materials to finished product. This was the leading idea."

"There is not one only question to ask, there are several; relating to each of the three fundamentals, and the multiple variables inherent in each."

A holistic view implies a need to understand how each part of a process relates to the next step and to the previous one. Because there is a series of cross-functional processes that affect almost each layer of an organization, it is important to adopt what Curry calls "cross-functional thinking."

The team's key message to readers of *Pharmaceutical Engineering*: "Buy the guide, read the guide, and apply its principles," they respond in unison. ■

Anna Maria di Giorgio

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Beyond Compliance:

How Regulators Encourage a Culture of Data Integrity

Complete. Consistent. Accurate.

Manufacturers rely on good data throughout the production cycle to ensure consistency and quality. We tend to trust the information they give us about their products. In fact, it's usually all we have to go on when making decisions. So, when a company like Volkswagen betrays that trust, as it did when it falsified emissions data, the harm goes far deeper than a reduction in share price, auto recalls, reduced sales, and financial penalties. Unreliable data does long-lasting harm to a valuable brand that is difficult to repair.

The stakes are even higher in pharmaceutical manufacturing, where patient health and safety are paramount and rely on data integrity. When we reach for a painkiller – whether brand name or generic – to treat a headache we expect that the ingredients and dosage are listed accurately and that potency does not vary from bottle to bottle.

"Well-publicized events in the pharmaceutical and automotive industries have demonstrated the enormous reputational damage caused by falsification of data," said David Churchward, Expert GMDP Inspector at Medicines & Healthcare Products Regulatory Agency (MHRA).

He's referring to the multiple pharmaceutical firms globally that have received regulatory sanctions recently for, among other citations, falsifying laboratory records.[5, 6, 9, 17] Although these drug companies and Volkswagen chose to evade regulators – and are now paying a heavy price – Churchward promotes collaboration between pharmaceutical companies and the international inspectorate as an effective way to ensure data integrity and product safety and efficacy.

"Regulatory agencies have an important role to play in ensuring data integrity throughout the product lifecycle and supply chain, which extends beyond verification during inspections," he said. "MHRA's view is that greater compliance progress can be made through education compared to inspection alone. Education empowers industry to 'design systems to comply', rather than simply monitoring and reacting to failure."

This is in keeping with recent moves by companies to institute what some are calling a culture of forgiveness that learns from quality problems instead of relying solely on compliance.[16]

Both the MHRA and FDA use the terms "complete, consistent, and accurate" to define data integrity. The FDA draft guidance on data integrity stresses that data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).[1]

The Focus on Data Integrity

Regulators and industry rely on accurate information to ensure the quality of drug products and provide consumers with safe, effective drugs. "Important decisions that are made daily regarding safety, efficacy, and quality of medicines are based on data," said Churchward. "If the data are unreliable, this can have an adverse impact on drug quality and patient safety."[13]

Having accurate, trustworthy data shows regulators that firms are following GMP and can reduce the inspection burden. On the other hand, violations can

result in regulatory action, product recalls, and suspended product approvals, which threaten the profitability of products. This is especially true when there is a delay in entry to market of a new generic since the bulk of profits tend to come during the First-to-File exclusivity period in the initial six months.[12]

Just as importantly, data integrity problems damage the trust between a company and regulators; the inspectorate just doesn't have the resources to monitor every site, all the time. Correcting a breakdown in trust can be expensive and time-consuming for a drug maker.[3]

Despite the increased focus on data integrity by the global inspectorate since 2013,[12] the MHRA is still seeing a high number of deficiencies in this area.[13] While data integrity problems in India and China have been making the news,[4, 7, 8, 10] Churchward offered a balanced assessment of the global situation. "It's important to remember that there's a significant supply from these territories. *Pro rata*, the MHRA has not seen a significant difference in data integrity failures between the UK, US, India, or China." And it's not just Indian and Chinese CMOs that are being slapped with warnings; statements of non-compliance have been issued by European regulators to companies in the US [11, 18] and Europe. [19, 20]

Churchward points out that even with the increased focus on data integrity, the problems have not been solved. In 2015, along with a significant number of FDA warning letters and European Medicines Agency (EMA) statements of non-compliance, the MHRA recorded 339 deficiencies that referenced data integrity.[13]

But it's not just compliance that regulators like Churchward seek. He sees regulators as valuable partners that can help companies instill a culture of data integrity throughout their manufacturing processes to support GMP. According to a report issued by Lachman Consultants, the most important thing firms can do to decrease the risk of running afoul of regulators is to improve data integrity.[12] Viewing regulators as allies as opposed to adversaries can be smart medicine.

One way that companies can benefit comes from regulatory inspection powers, including access to proprietary information, that allow an assessment of manufacturing systems in ways that industry may not as easily achieve on its own.

"We can use the knowledge gained from experience of good and bad practices to reinterpret existing standards, new regulations, or as educational material," Churchward said. "Of particular relevance to data integrity is sharing our observations relating to the influence of organizational behavior, and address myths relating to the type of organization, geographical location, and activities that are impacted. We have found these insights particularly valuable and feel they're important to share with industry."

He asserts that this partnership benefits everyone as it allows key messages to be communicated throughout the production process and supply chain faster and more widely than inspectorate resources would otherwise allow. "This has a positive impact on product quality and builds confidence in data used for decision making and regulatory submissions. This can contribute to a reduced regulatory risk profile and the possibility for companies to enjoy a degree of regulatory relief from risk-based inspection oversight and product lifecycle management flexibility."

Instilling a Culture of Data Integrity

It all has to start with a robust internal culture of data integrity that requires strategy, executive buy-in, management accountability, sharing knowledge, and training.[3] Part of training is encouraging a 'speak up/quality first' culture.[15] Ultimately, manufacturers have to create this culture and adhere to the principles of GMP, but regulators can help.

"It is up to organizations to create a culture that achieves the desired behavior and quality outcomes," Churchward said. "An effective quality culture may be different in its implementation for organizations of different size, complexity, or geography. Regulators can identify signatures of good and bad behavior, then refer to these when engaging with stakeholders."

This leadership has to come from the top of an organization. "Good leadership is the foundation for a culture of data integrity. Senior leaders need to understand the indicators of success, measures that demonstrate protection of the patient and achieving company values.

"An understanding of product, process, and quality system are all required to determine relevant indicators and assess their associated metrics in context. For instance, a low rate of non-conformance reporting may be due to a high degree of process control and capability. Conversely, it may indicate a reluctance to report undesirable information, and the possibility of data manipulation to maintain the appearance of a process under control. Con-


David Churchward

textual assessment of metrics will assist decision making. These factors will differ on a case-by-case basis.

"This is ICH Q10 in action – senior management taking responsibility for implementing and monitoring systems in a way that addresses the interaction of organizational behavior, procedures, and technical measures."

While data integrity requires strong leadership, all levels of the organization need to be empowered. "Senior and middle management need to trust the integrity and expertise of their personnel, which starts at the recruitment stage and continues with training to foster the right behavior and understanding of how their role impacts the patient and organization. Communication of this trust is an important part of empowerment."

This brings us back to Volkswagen and the pharmaceutical manufacturers with data integrity failures. Churchward believes this behavior originates in the internal quality culture. "The incentive to manipulate data can come from two perspectives – fear of reprisal from failing to meet expectations or reward schemes that incentivize output far in excess of what is reasonably achievable."

Churchward promotes collaboration between pharmaceutical companies and the international inspectorate as an effective way to ensure data integrity and product safety and efficacy

Determining whether a non-compliance issue results from human error or deceit is not straightforward. In fact, regulators do not focus on intent when they uncover GMP shortcomings and do not consider it a mitigating factor.[14]

"The primary focus of the regulator is to determine whether there has been a GMP non-compliance such as data integrity failure and assess the potential impact to the product and patient," Churchward said. He pointed out that it is also difficult to make an assessment from the review of non-compliance communications from other regulators as the underlying motivation may not be stated, even if it is known.

"The concept of intent requires careful consideration. A person may record an inaccurate result on a manual record due to a desire to please management or from fear of reprisal for reporting an undesirable result. While this may be a conscious act, the more relevant underlying issue is the organizational culture that drives this behavior, rather than a perceived intention to willfully deceive or falsify for personal gain."

With these caveats in mind, MHRA inspections point to most data integrity non-compliance arising from faults in the data systems. "The majority of the data integrity deficiencies that the MHRA uncovers during inspections relate to bad practice and opportunity for error, without evidence of a willful intent to deceive," Churchward said. "Typically, issues relate to poorly designed systems and training that result in opportunities to amend, delete, or recreate data, and failure of detection mechanisms to identify these activities."

When Churchward finds that system design played a significant role in putative human errors – which is often – he asks three questions. "How did the organization's behavior and messages to staff result in an incentive to manipulate data or believe that this action was acceptable? How did the design of the business process, procedures, and control of equipment lead to an opportunity to influence the generation and reporting of data? Why did the approach to routine data verification fail to detect these failures and address the causes?

"A corporate culture that understands the impact of system design on human behavior is better equipped to apply risk-based control measures that reduce the opportunity for error and increase detection effectiveness."

Given this, he realizes that the MHRA and other regulators have a good opportunity to educate companies. For example, regulators can positively impact cultural norms that might prevent reporting of non-compliance issues in countries that have a culture of conformity or deference to authority. "Being sensitive to geography and culture is important when we assess the maturity of a firm's quality systems, which differ from region to region," Churchward said. "In countries where challenges to hierarchy and the communication of unfavourable information are culturally unacceptable, it might be necessary to place greater stress on oversight and secondary review." One method he suggests for achieving this level of control is to have mechanisms in place for anonymous reporting.

"To be effective in the long term, measures need to be compatible with cultural norms. Regulatory agencies can positively interact with differing cultural norms by assessing effectiveness in the context of the local environment and developing guidance that is compatible with this approach.

MHRA Publishes Draft GxP Data Integrity Guidance

Data integrity is important throughout the pharmaceutical lifecycle. To enable greater stakeholder understanding of data integrity expectations in laboratory studies, clinical trials, manufacture and commercial supply, MHRA published draft GxP data integrity guidance for public consultation in July.

Readers are encouraged to take the opportunity to engage with MHRA in developing this important guidance. The consultation will last for three months, and be launched via web alerts and an inspectorate blog (https://mhrainspectorate.blog.gov.uk/).

Fear of data integrity failure and reputational damage can cause managerial paralysis, leading to an unachievable pursuit of perfection.

"Organizational behavior can be worsened if incorrect assessments are made relating to intent, especially if the company's corrective action is to terminate someone's employment," Churchward said. "This may lead to a culture of fear, preventing further reporting and increasing the incentive to falsify data in the future.

"Fear of data integrity failure and reputational damage can cause managerial paralysis, leading to an unachievable pursuit of perfection. The organization becomes unable to apply quality risk management principles to data governance, and fails to take simple interim measures to reduce risk pending completion of longer term control measures. This also doesn't address the behavioral and procedural environment in which these long-term solutions will operate, further limiting their effectiveness."

Again, responsibility lies with senior management to provide leadership to data governance programs. "By avoiding messages such as 'zero tolerance,' this leadership can remove the fear of reprisal when an employee discovers a problem," he said. "Thus, management can reduce the incentive to falsify or manipulate data by setting realistic expectations that are compatible with the organization's capacity and process capability."

The push for greater accountability for data integrity is global, with regulatory agencies around the world working together to ensure robust standards. Sharing data and best practices, regulators are also working with manufacturers to ensure a healthier industry, one in which data integrity protects consumers as well as industry. Churchward sees this as a win-win for regulators, industry, and the consumers they ultimately serve.

"Good data governance leads to better decisions, which in turns leads to quality improvement, reduction of defects, streamlined prioritization of resources, and consistent supply of product. It also boosts the confidence that firms have with their suppliers, with consumers, and with regulators."

In this era of greater regulatory scrutiny of manufacturing data, it makes sense for pharmaceutical manufacturers to take advantage of the expertise and assistance afforded by regulators. It's one way to ensure safe and effective products while protecting valuable brand reputations. ■

Scott Fotheringham, PhD

References

1. FDA. "Data Integrity and Compliance With cGMP Guidance for Industry: Draft Guidance." April 2016. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf
2. MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/412735/Data_integrity_definitions_and_guidance_v2.pdf
3. Here, Large, and Not Going Away. Christopher Reid. PE, March/April 2016, p. 41
4. FDA Notification. "Notification to Pharmaceutical Companies: Clinical and Bioanalytical Studies Conducted by Semler Research Are Unacceptable." 20 April 2016. http://www.fda.gov/Drugs/DrugSafety/ucm495778.htm
5. FDA warning letter. "Emcure Pharmaceuticals Limited 3/3/16." 3 March 2016. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm489735.htm
6. FDA warning letter. "Megafine Pharma Limited 5/19/16." 19 May 2016. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm503699.htm
7. FDA warning letter. "Tai Heng Industry Co., Ltd. 5/12/16." 12 May 2016. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm501282.htm
8. MHRA. Statement of Non-Compliance with GMP. Issued to Rusan Pharma. India. 4 April 2016. http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do?ctrl=searchGMPNCResultControlList&action=Drilldown&param=34550
9. The Main Pharmaceutical Inspectorate. Statement of Non-Compliance with GMP. China. Issued to Chengdu Okay Pharmaceutical. 19 February 2016. http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do?ctrl=searchGMPNCResultControlList&action=Drilldown&param=33815
10. State Institute for Drug Control. Statement of Non-Compliance with GMP. Issued to Hubei Hongyuan Pharmaceutical. China. 20 January 2016. http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do?ctrl=searchGMPNCResultControlList&action=Drilldown&param=33316
11. EMA Statement of Non-Compliance with GMP. 15 May 2016. http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do;jsessionid=Ug9zhtS8chTLo0KvFQe5h-KzxBkAunScbBwSyz2pIgoQIUzbi2xHU!1188882614?ctrl=searchGMPNCResultControlList&action=Drilldown&param=35188
12. Lachman Consultant Services, Inc. "The Real Cost of Poor Data Integrity in Pharmaceutical Manufacturing." http://www.lachmanconsultants.com/2016/05/white-paper-the-real-cost-of-poor-data-integrity-in-pharmaceutical-manufacturing/
13. Churchward, D. "Regulatory developments in data integrity: trends and strategy for a global supply chain." Japan keynote. Slide 7
14. Wakeham, C. and T. Haag. "Throwing People Into the Works." Pharmaceutical Engineering. March/April 2016. pp. 42-46.
15. Wakeham, C. and T. Haag. "Big Brother Is Watching." Pharmaceutical Engineering. March/April 2016. pp. 56-60.
16. De Cremer, D. and B Lemmich. "Compliance Alone Won't Make Your Company Safe." Harvard Business Review. 18 May 2015. https://hbr.org/2015/05/compliance-alone-wont-make-your-company-safe
17. French National Agency for Medicines and Health Products Safety. Statement of Non-Compliance with GMP. Issued to Medreich. India. 3 December 2014. http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do?ctrl=searchGMPNCResultControlList&action=Drilldown&param=26624
18. MHRA. Statement of Non-Compliance with GMP. Issued to Pharmaceutics International. US. 15 June 2015. http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do?ctrl=searchGMPNCResultControlList&action=Drilldown&param=35704
19. Spanish Agency of Medicines and Medical Devices. Statement of Non-Compliance with GMP. Issued to Farma Mediterranea. Spain. 2 February 2016. http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do?ctrl=searchGMPNCResultControlList&action=Drilldown&param=33564
20. Spanish Agency of Medicines and Medical Devices. Statement of Non-Compliance with GMP. Issued to Desarrollos Farmacéuticos. Spain. 12 January 2016. http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do?ctrl=searchGMPNCResultControlList&action=Drilldown&param=33159

A Risk-Based Approach to Clinical Research: Solving Problems Before They Occur

Patricia Santos-Serrao

Now more than ever, the pharmaceutical industry is focused on risk. Why? Because the cost, duration, and complexity of conducting clinical trials continue to increase. In 2014, the estimated average cost to develop a new drug and get it approved reached $2.6 billion, a more than threefold increase from $802 million in 2001.[1] Clinical research constitutes a significant part of the cost of bringing a pharmaceutical product to market, with studies lasting an average of one to three years, and in some cases even longer. This large investment of time, money, and resources naturally comes with risk. Things like poor trial protocol design and simple human error in executing the protocol pose risks to the integrity of trial data and can extend the length of a trial, leading to possible regulatory, financial, and legal implications.

In clinical research, risk includes any event—particularly procedures followed incorrectly or not at all—that could negatively affect the integrity and quality of trial data, and ultimately the ability to execute a valid, successful clinical trial. Risk mitigation assesses the probability that an event could negatively affect a study. Risk management implements proactive measures to reduce the likelihood that event will ever happen; it also involves developing a plan of action to address a risk incident once it occurs.

To better understand the difference between risk mitigation and risk management, consider a house fire: *Risk mitigation* is like preventing a house fire from starting by never leaving burning candles unsupervised, or setting an automatic timer to turn off the oven in case it is forgotten. *Risk management* is like stopping a fire once it starts—using smoke detectors, fire extinguishers, and sprinklers—in the event the risk mitigation measures fail. Risk mitigation is to risk management as preventive actions are to corrective actions, and quality assurance is to quality control. While very different, the two go hand in hand. Ultimately, a great risk mitigation plan is the best risk-management plan.

Although risk is not new to pharmaceutical product development, methods of mitigating risk that have largely gone unused in clinical research are now receiving noteworthy attention from regulatory bodies.

Risk-Mitigation Methods for Clinical Trials

Given the growing cost of conducting clinical research, forward-thinking sponsors and clinical research organizations (CROs) look to risk mitigation during the research phase to avoid unnecessary delays and additional costs.

In clinical trials, user error is the source of most risk, often due to insufficient training

Clinical quality by design

Quality by design (QbD) is a risk-management approach that has gained significant traction in the pharmaceutical industry in recent years, as evidenced by the initiatives and guidances issued by various regulatory agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Conference on Harmonisation (ICH), to name a few. QbD is also well understood in quality as "corrective and preventive action," or CAPA.

Formally introduced in 2009 under revisions to ICH Q8,[2] QbD was identified two years later by the Clinical Trial Transformation Initiative (CTTI) as a strategy that could increase data integrity and improve the quality of clinical trials. The CTTI began a series of workshops to explore the concept, resulting in the June 2015 release of a toolkit and recommendations for QbD.[3] The EMA also released its draft reflection paper on risk-based quality management in 2011 to facilitate the development of a more systematic risk-based approach to quality management of clinical trials and to promote good clinical practice principles and standards.[4]

Because of the dramatic increase in the number and complexity of clinical trials, it is impossible for regulatory agencies to perform on-site monitoring for each and every one. In lieu of this, regulators look to alternative monitoring approaches to ensure appropriate oversight. In the 2013 Guidance for Industry "Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring,"[5] the FDA signaled an intention to maximize its oversight of clinical trials by promoting effective risk-based monitoring across the industry. Without ever using the term, this document essentially promotes QbD.

In practice, QbD and its design principles provide a more consistent and efficient method for producing high-quality output while minimizing risk throughout the clinical process. As a result, QbD reduces compliance issues by preventing them before they occur, and addresses them more systematically if they do.

Risk-based protocol design

In the context of clinical research, risk mitigation involves carefully analyzing the trial protocol to understand where the likelihood of risk exists, and then modifying the protocol design accordingly to eliminate or reduce the probability of risk incidents.

Every protocol has areas where the likelihood of noncompliance or failure to follow procedures is heightened. Take, for example, a clinical trial in which the investigational product requires refrigeration to maintain the product's quality and effectiveness. If the product is not stored properly, its effectiveness may be compromised. At best, the trial data will show a product as ineffective; at worst, the product may become toxic or harmful to patients. Compared to a product that can be stored at room temperature, the product-storage requirement in this example elevates the risk of invalid trial data, bringing with it the potential to extend the length of the trial as additional patients may need to be enrolled to validate the results. To mitigate risk in such a situation, a number of measures can be taken:

- In the trial protocol, include requirements for periodic monitoring of product storage temperatures by an appointed person.
- Apply highly visible labeling on the investigational product—ideally a brightly colored label with a warning in large font size—to indicate that it must be refrigerated.
- As a second line of defense, introduce product packaging that maintains the desired temperature for extended periods of time in the event that it is improperly stored.
- Design and provide protocol-specific training for site staff that emphasizes investigational product storage requirements to emphasize the importance of this topic.

As with any investment, there is an up-front cost involved with taking these measures, but they can save big in the long run. Given the tremendous average cost of a clinical trial, the cost of risk mitigation is a small price to pay compared to the loss incurred if the trial data show inconsistency across sites and patients due to a compromised investigational product.

Even if risk mitigation measures are taken, however, they do not guarantee that a product will be stored properly 100% of the time. In other words, risk mitigation can only go so far, and this is where a sound risk-management plan comes into play. In the product storage example, risk management would address the following questions:

- What actions should be taken if a product has been stored improperly for an extended period of time?

QbD and its design principles provide a more consistent and efficient method for producing high-quality output while minimizing risk

- What actions should be taken if a patient was administered an improperly stored investigational product?

A risk-management plan requires these questions to be answered before the situation occurs, defines the actions that must be taken if risk mitigation is no longer possible or has failed, and identifies plans to address a risk incident after it has occurred. In the improper product storage example, a risk-management plan may include:

- Quarantining the questionable product
- Assessing exposure to patients who took the product
- Monitoring patients who have been exposed to a compromised product
- Taking action on patient data, such as withdrawing patients from a trial or excluding affected data from the outcome

Risk-management measures can be even more costly than risk mitigation, because addressing a risk incident once it has already occurred is far more expensive than preventive risk-mitigation activities, particularly as the severity of the risk is compounded by multiple related risk incidents.

As with any investment, there is an up-front cost involved with taking these measures, but they can save big in the long run

Risk-based training

It has famously been said that to err is human. In clinical trials, user error is the source of most risk, often due to insufficient training. Each clinical study is unique, and the more unique factors or processes associated with a study, the greater the potential for negative quality events and the higher the level of risk. An important part of any risk mitigation plan is to identify each unique factor in the protocol and highlight them in a protocol training plan.

A great method for mitigating risk via training is designing a protocol-specific training curriculum. This should include detailed questions that focus on the highest-risk areas of the protocol. This is not to say that a protocol should include 50 questions and a pass-or-fail standard, but rather a handful of questions that draw attention to that particular protocol's unique factors, emphasizing areas of concern to ensure that staff have been informed of the requirements.

A learning-management system can be a useful tool in this endeavor. Investing in a highly configurable training system will allow a study management team to create and execute a protocol-specific curriculum quickly and efficiently. It is important that such a system be easy to deploy to external parties, such as a sponsor for a CRO or a clinical study site team.

Conclusions

Global regulatory authorities such as the FDA and EMA encourage organizations to take a risk-based approach to quality management in all areas of business, including clinical research. While there are no regulations that mandate the use of risk-based monitoring or QbD principles in pharmaceutical product development, initiatives and guidances related to QbD highlight its growing importance. As these programs show, risk mitigation and risk management increase efficiencies, reduce cost, and improve quality. So the question is not *why should* pharmaceutical companies implement a risk-based monitoring system, but *why wouldn't* they?

Clearly, now is the time to incorporate thorough risk-mitigation and -management plans that can be used as strategic tools to provide organizations with the foundation of a sound quality approach to clinical trial management. ■

References

1. Tufts University. Tufts Center for the Study of Drug Development. "Cost to Develop and Win Marketing Approval for a New Drug is $2.6 Billion." 18 November 2014. http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: "Pharmaceutical Development: Q8 (R2)." August 2009. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf.
3. Clinical Trials Transformation Initiative. "CTTI Releases New Recommendations and Toolkit to Help Organizations Implement Quality by Design." 15 June 2015. http://www.ctti-clinicaltrials.org/briefing-room/ctti-blog/ctti-releases-new-recommendations-toolkit-help-organizations-implement#.VY1hi3nbK71.
4. European Medicines Agency. "Reflection Paper on Risk Based Quality Management in Clinical Trials." Draft. EMA/INS/GCP/394194/2011. 4 August 2011. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf.
5. US Food and Drug Administration. "Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring." August 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.

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Patricia has worked for several Tier 1 pharmaceutical companies, and has assisted pharmaceutical, biotechnology, and medical device companies worldwide with electronic document management and submission solutions, and compiling electronic common technical documents. She holds a BS degree in business administration from Western Connecticut State University and the University of Phoenix. She is a member of the Regulatory Affairs Professional Society (RAPS) and Drug Information Association, and has a Regulatory Affairs Certification from RAPS and the Regulatory Affairs Certification Board.

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CPPM for Effective Multivariate Risk Modeling for Life Cycle Management

Matej Janovjak, John Cunningham, Adam Fermier, Steve Mehrman, and Roger Holenstein

Regulatory initiatives such as ICH Q8, Q9, Q10, and effective process and product life cycle management (LCM) highlight the need for a science-based causal and mechanistic understanding of all up- and downstream processes to ensure the development and manufacture of a safe and effective product. This requires new levels of process and product knowledge, the ability to master the variability of relevant sources, and understand relationships between the process and product, as well as knowledge of all associated risks and their effect on product quality (Figure 1).

An adequate and universally applicable method is needed, therefore, to integrate available data, knowledge, and expertise and provide:

- Science-based modeling and process behavior simulation and its effect on product quality
- Multivariate quantitative quality risk management (QRM) that considers propagation of associated risks along the process and their effects on product quality risk

The causal process and product mapping (CPPM) approach provides these capabilities and offers a unique combination of scientific data, expertise, and multivariate quantitative risk assessment. The generality of the approach lends itself well to QRM applications at any life cycle stage for any development and manufacturing processes, providing model-based proactive solutions for LCM.

CPPM Methodology Background

A system's behavior is determined primarily by cause-and-effect interactions between its elements.[4] System dynamics (SD) is a methodology[3] first developed by Jay Forrester in 1950s[1] to help model and manage complex processes by mathematically documenting the factors and interactions that influence a system. Using that same approach, we built CPPM models for quality risk management in pharmaceutical manufacturing. This approach leverages some of Forrester's core principles about gathering the complex process and product knowledge required to build an effective model and documenting it in a social/collaborative environment—in this case, a mixture of scientists and engineers who were specific subject matter experts (SME).

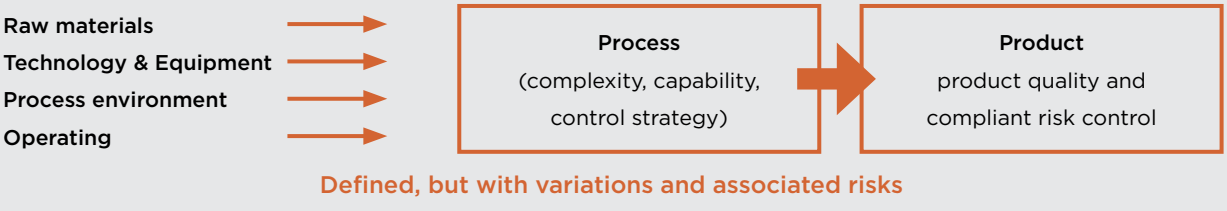
Using SD to document SME knowledge around the portion of the process in which they are experts, then linking these domains can provide a holistic model of the entire process. This can then be used to help the team build a testable model of their knowledge, which can validate their collective understanding. The approach helps overcome:

- Individual differences in perception and knowledge
- Practical limitations in identifying complex interconnections and thinking in causal networks
- Difficulties in processing multivariate individual experiences in a group

SD helps elicit the hidden assumptions that each SME holds by integrating them into more transparent and causal representation. This enhances understanding, consistency, and knowledge of data in addition to its implementation in the model-building process. It's important to note that the strategy should be considered complimentary to traditional integrated data-management strategies.[2] While the actual data around the processes is paramount, it's simply impossible to cover all possible variations—hence the need for the CPPM approach.

In summary, the CPPM methodology enables modelling and simulation of complex process behavior through comprehensive understanding of multivariate relationships, process and product variability, and associated risks. The approach requires a precise definition of the system boundary to be modeled; this will allow systemic process steering on operational, tactical, and strategic levels.[7]

Figure 1: Schematic illustration of process and product focus



The CPPM approach can be accomplished with a variety of software packages. We chose Vensim[5] as it specializes in SD methodology[6] and delivers a graphical interface that makes it easy to visualize the process and interact with the SMEs.

CPPM Models

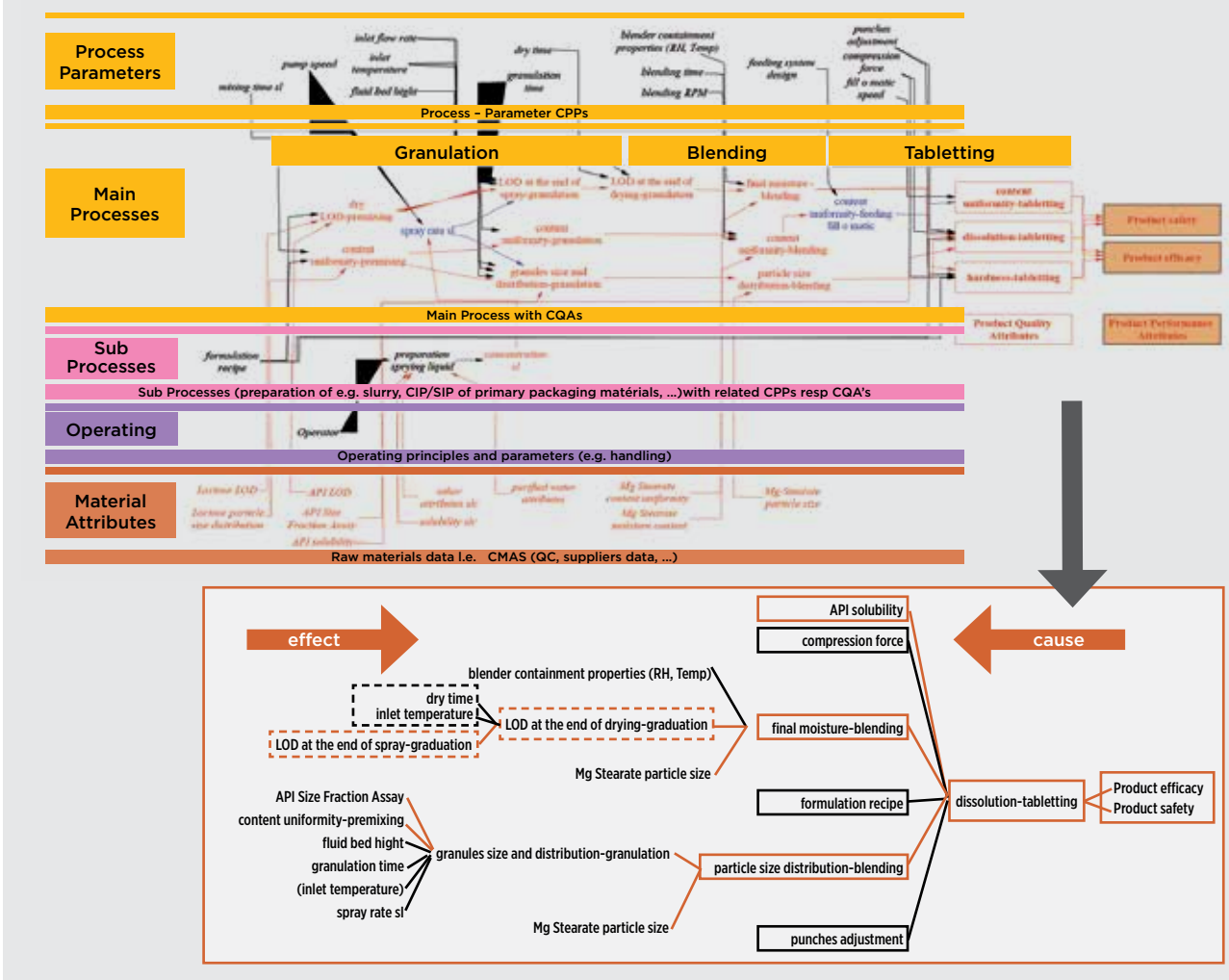
CPPM allows scientific process and product modeling while capturing multivariate cause-and-effect relationships (including interaction feedbacks) between process parameters (PPs), material attributes (MAs), and product quality attributes (QAs). The approach also considers relevant context, conditions, and environment, such as prior knowledge and experience, data, process, and operation. The CPPM model represents complex process pathways and functions, enabling organizations to generate consistent (and common) understanding of cause-and-effect process and product relationships.

Each captured PP, MA, operation activity, and product QA is represented in the CPPM model as an individual variable. All causal relations, sketched as graphical connections, are automatically captured as unambiguous allocated variable relations. A generic template for the approach was adopted to ensure a structured representation and understanding of the process and product.

A practical CPPM application can be demonstrated by a case study on a simplified solid manufacturing process. The qualitative CPPM model-building process begins by capturing all relevant PPs, MAs, and parameters that describe operation and product QAs and their causal relations. For any variable—such as the finished tablet dissolution QA—the automatically generated cause-and-effect tree captures the causal relations of process and product (Figure 2), showing us in an easily understandable way the process pathways at each step and along the entire process.

The finished tablet dissolution cause-and-effect tree, for example, identifies which PPs (e.g., compression force) MAs (e.g., API solubility), and intermediate product attributes (e.g., final moisture–blending) affect its attributes. Deeper tree levels manifest further product and process attributes: Blended material moisture is affected by Loss on Drying (LOD)

Figure 2: CPPM model of simplified solid manufacturing process and cause-and-effect tree with focus on finished tablet dissolution



of dried granules, which are in turn affected by drying process parameters (dry time, inlet temperature) and LOD at the end of the granulation phase. The effect of any PP, MA, and operation parameter on any product QA could be analyzed in similar way.

Cause-and-effect trees could be generated for any model variable, producing appropriate level depth in both directions, offering a deep understanding of causal process and product relationships, and enabling a multivariate cause-and-effect analysis with focus on process performance and product quality. This capability provides a justifiable simplification by modeling the real system while mapping "what is well known," understanding "what is unknown," and exploring "how to get it better known."

The qualitative CPPM model represents a paradigm change of the causal description of the process and product to identify PPs, MAs, and operation parameters that might affect process performance and product quality. From this point of view, qualitative CPPM model leverages and improves individual and collective process understanding, the qualitative CPPM enhances the scientific understanding of data model design and the meaning of gathered data.

The model-based solution approach requires determination of quantitative simulation results, i.e., it calls for approved data and model-building expertise to produce a valid applied model. A quantitative CPPM model is created by quantifying the input parameters and functional process interactions of a qualitative CPPM. The quantification is based on mechanistic process knowledge, experimental/multivariate analysis data, and expert estimation. Consequently, the quantitative CPPM delivers simulations that can analyze the effect of process variations on product quality attributes across an entire process.

In a pharmaceutical development tablet formulation project that included experimental data and process modeling information in the CPPM model, the design of knowledge space for process development was effected in a proactive manner. As a result, CPPM helped provide greater process understanding and reduced the effort and resources needed (i.e., number of development and scale-up batches, costs, time). The ability to perform adaptive parameterization ensured the alignment required for tech transfer (scale-up and site harmonization) as teams worked collaboratively on the model. In addition, the model-based approach provided both knowledge transparency and greater opportunities to "recycle" knowledge so that design decisions were improved.

Any model-based approach requires proof of the validity of the model. Validation of a CPPM model is supported by Vensim techniques and is carried out in following four steps:

1. Structural fit (verification of the cause-and-effects relations based on data and expertise)
   Causal analysis by means of the cause-and-effect trees
2. Behavior correctness (dynamic and logical behavior are verified, based on data and expertise)
   Simulation of dynamic behavior (parameter adjustment, reality check)
3. Plausibility and consistency (proof of completeness and consistency, based on data and expertise)
   Simulation on change, sensitivity simulations
4. Validity for model-based process and product development (precise adjustment of simulation results with experimental values)
   Nonlinear (and other) model adaptations; model optimization (calibration, policy)

The validity of the executed CPPM model assures its compliant application.

A special case of CPPM quantification is provided by using risk assessment data and determining risk propagation along the process. As a result, a risk model could be carried out and applied for multivariate quantitative QRM applicable to any life cycle phase. The design journey of this approach and its practical applications are described in the next section.

CPPM-Based Risk Model for Multivariate Quantitative QRM

Quantitative risk determination requires causal understanding of variation-inducing and hazard-eliciting risk as well as knowledge of the mechanism of risk propagation across the entire process. The scientific content of CPPM cause-and-effect relations and the capabilities of Vensim software raised the idea to build a risk model applicable for a multivariate quantitative quality risk management.

A risk-focused quantification of PPs, MAs, and operation parameters, as well as functional process and product interactions can turn a qualitative CPPM model into a quantitative risk model. This could help determine the multivariate quantitative effect of risks associated with process variations on risks associated with product quality at each process step, and indicate propagation along the process on risks associated with the final product quality attributes.

The Vensim software capabilities open up the possibility of determining sensitivity and ranking the effect of risks associated with variations of PPs, MAs and operating parameters on risk of variations of product QAs.

In addition, the risk model–based QRM approach must comply with ICH Q 9 QRM process.[8] It must also implement failure mode effects analysis (FMEA) and data scoring from risk assessment results. Figure 3 shows how the idea of risk model–based multivariate quantified QRM was compiled and put into practice.

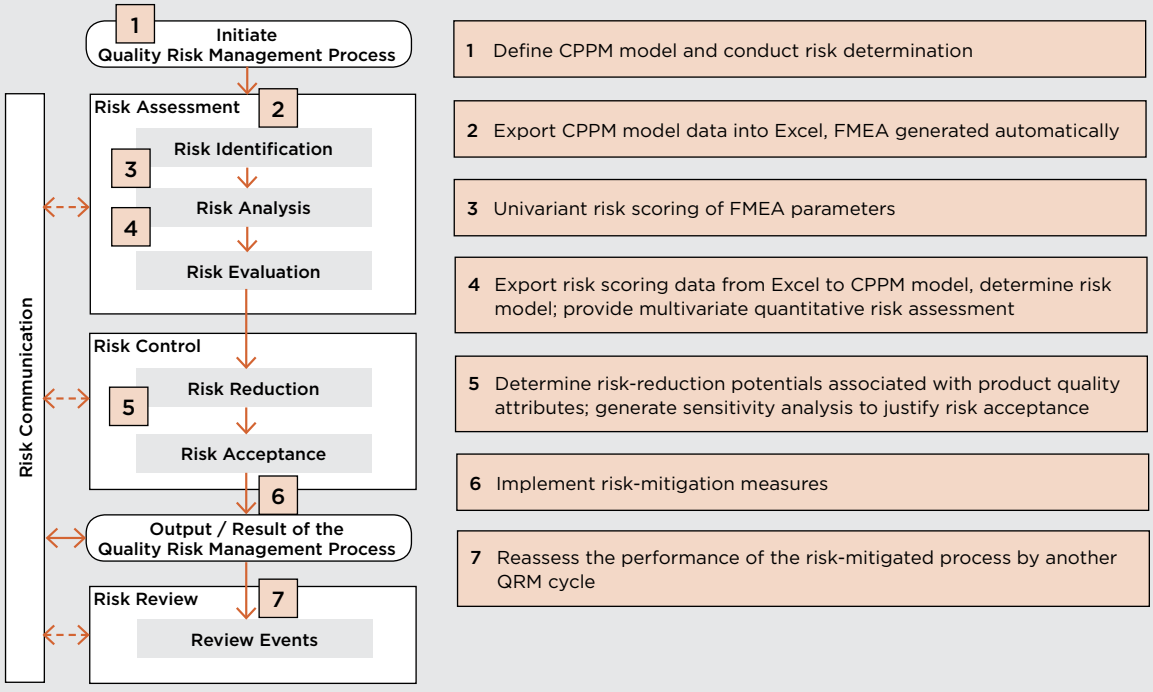
The risk model should be able to manage complexity and the inherently multivariate nature of process and product and associated risk assessment.

Quantifying the risks of process input parameters will apply common risk definitions, with capability to customize them to be compliant with the implemented QRM system. The risk propagation algorithm and simulation technique will follow process interactions characteristics.

Risk potential number

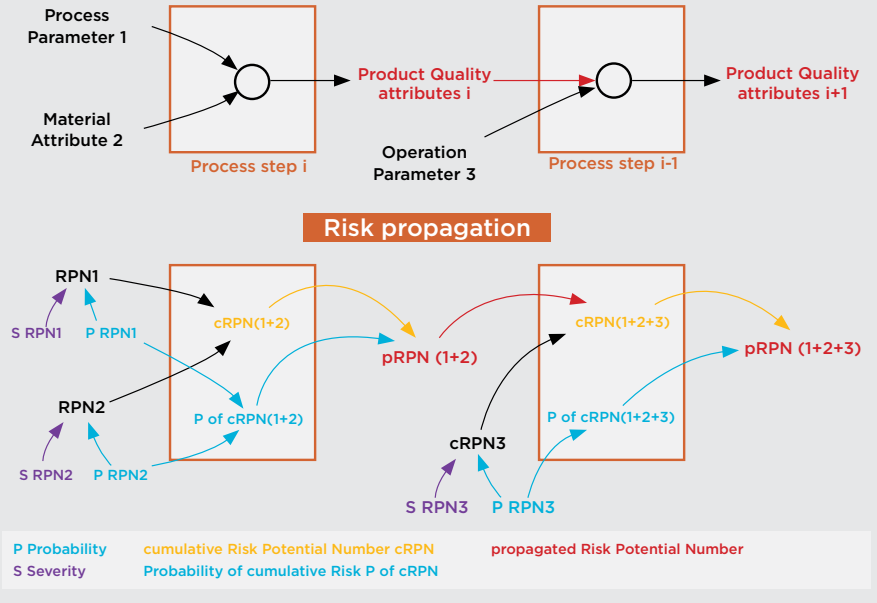
The basic causal effect of any process input parameter at any process step on intermediate product QAs is expressed by its risk potential number

Figure 3: Process flow of the risk model–based multivariate quantified QRM in alignment with QRM process taken from ICH Q9



Source: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. "Quality Risk Management: Q9." Step 4 version, 9 November 2005.

Figure 4: Qualitative CPPM Model and corresponding risk propagation calculation



For simplicity, detectability has been omitted

(RPN) value. Process input parameter variations are expressed by variations of its RPN.

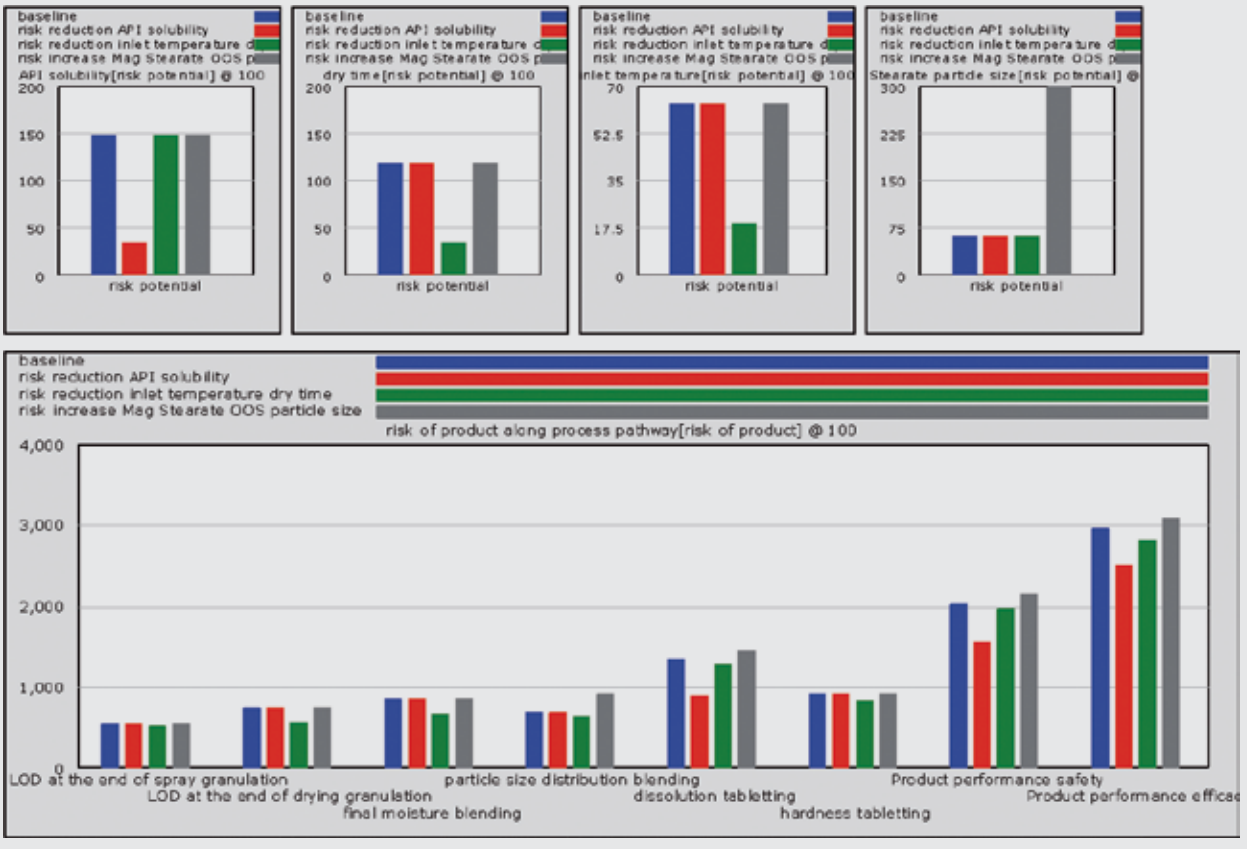
RPN = Severity S × Probability P × Detectability D

Severity S = severity of impact of process input parameter variations on product quality attributes

Probability P = probability of occurrence of process input parameter variations
Detectability D = capability to detect and monitor these variations

All of the above values could be assigned with a customized risk rating matrix, e.g., from one to 10. Implementing the FMEA procedure (i.e., using risk assessment RPN data as a model input parameter) makes the approach universally applicable and easily leverages current QRM toward a multivariate quantitative QRM.

Figure 5: Illustration of effect of risk reduction of Process Parameters on risks of product QAs along process pathway



Calculation of risk propagation

Risk propagation captures multiple input parameter risk effects (PPs, MAs, operation [handling]) on risks associated with product QAs for each process step as well as along the process pathway (Figure 4).

cRPN = cumulative risk potential of propagated risk
cRPN: algorithm is simple or weighted sum of risk potential of considered risks; in principle the algorithm must follow process step characteristics
P of cRPN = probability of propagated risk occurrence
P of cRPN: algorithm applies standard formula from probability theory (values between 0 and 1)

Propagated risk potential (pRPN) = cRPN × P of cRPN

The pRPN is determined for each consecutive step and relevant intermediate product QAs without any limitations on the number or type of risk parameters (i.e., without any constraint on the process complexity). Determination of pRPN sensitivity could be provided under selective consideration of the probabilities population (e.g., Monte Carlo).

The simulation techniques provide a way to determine the impact of any process input parameter variation on the variation of any QAs. Further, the optimization policy (i.e., Monte Carlo and payoff definition) offers the unique ability to determine the impact ranking (criticality) of individual variations of particular (i.e., one-to-many) process input parameters on arbitrarily selected product QAs. This provides highly effective risk mitigation and defines a more effective process control strategy for more robust process design.

Provided that the RPN determination and risk propagation algorithm represent process input parameters and process step behavior accurately, the simulated risk-focused process behavior could approach actual process behavior correctness, plausibility, and consistency. Applying available data in combination with expertise could provide an appropriate verification of the risk model. Executed applications confirmed the correctness and practicality of this approach. Consequently, a multivariate quantitative risk model–based QRM can be applied to determine process control strategy, execution of investigational analysis for troubleshooting and optimization of the process performance.

To unfold the risk model details for multivariate quantitative QRM, we will continue with the solid manufacturing process case study, following the QRM process flow in Figure 3.

1. **Define CPPM model and conduct risk determination** (see "CPPM Models")

2. **Export CPPM model data into Excel, FMEA generated automatically:** Qualitative CPPM data (i.e., model variable with description and information of causal linkages) will be exported automatically into a customized Excel file and allocated into appropriate structured FMEA templates (macros).

3. **Univariant FMEA parameter risk scoring:** The univariate risk scoring of RPN for PPs, MAs, and operation parameters (model input parameter) will be executed following FMEA procedure.

4. **Export risk scoring data from Excel to CPPM model, determine risk model, provide multivariate quantitative risk assessment:** RPN data will be imported automatically back to the CPPM model with unambiguous allocation to the considered model variable. Risk model quantification is finalized by determination of risk-associated functional process interactions and risk propagation. The result is a risk model ready for multivariate quantitative determination of risk propagation along the process pathway. The simulation with primary determined RPN value is captured in Figure 5 as baseline.

   Another important risk assessment is evaluation of the most critical input parameters. For this, the simulation optimization policy determines their impact ranking. This could be executed for multiple inputs on one or more outputs.

   Returning to the finished tablet dissolution product attribute, which was used to illustrate cause-and-effect relations, we first ranked the impact of all PPs, MAs, and operating parameters on dissolution of finished tablet (Table A).

   Risk potential values indicate the primary determined risk RPN score.

   A payoff is a single number that summarizes a simulation (result valuation). In this application it defines relative risk score of impact of parameters on dissolution. The corresponding ranking indicates the priority of risk mitigation. This lets us understand that variation of the API solubility and formulation recipe affects the dissolution of tablets most, followed by compression force on tablet press, and granulation process PPs.

Table A: Impact ranking of PPs, MAs, and operating parameters on finished tablet dissolution

Policy focus: Product Attribute "dissolution-tabletting"		
Sorted Parameter Sensitivities = Ranking of impact		
Parameters are changed by ± 20%, if 0 by ± 0.2	Ranking	Payoff
API solubility[risk potential]=150	1	12120
formulation recipe[risk potential]=63	2	3436
compression force[risk potential]=96	3	1939
binder solubility sl[risk potential]=96	4	1357
inlet temperature[risk potential]=64	5	1164
pump speed[risk potential]=72	6	1018
granulation time[risk potential]=56	7	792
mixing time sl[risk potential]=75	8	758
Lactose particle size distribution[risk potential]=72	9	727
Mag Stearate particle size[risk potential]=64	10	646
fluid bed height[risk potential]=64	11	646
dry time[risk potential]=120	12	485
etc.		

5. **Determine risk-reduction potentials associated with product quality attributes; generate sensitivity analysis to justify risk acceptance:** Achieved risk assessment results could be used to define the risk-mitigation focus and provide adequate simulations of the risk-reduction assessment. Subsequently, the effect of any PP, MA, and operation parameter variations (expressed by their RPNs) on any product QA variations (determined by their pRPNs) could be determined. Figure 5 shows three sample risk control simulations.

   The first focuses on determining risk reduction of product attributes, assuming improved API solubility. The second zooms in on the granulation process. Earlier, we explored the effect of variations in

Figure 6: Impact of variation of O2 sparging on variation of dissolve oxygen DO and of harvest CQAs

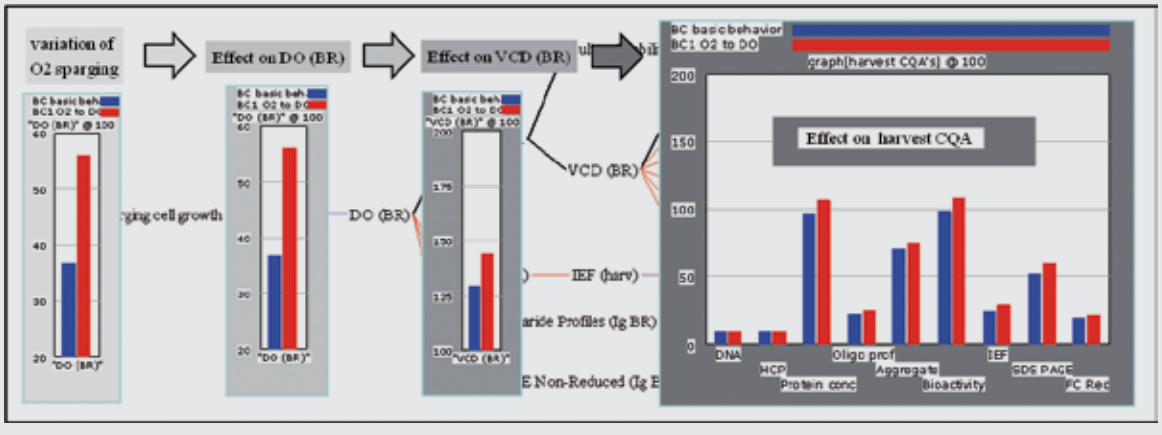
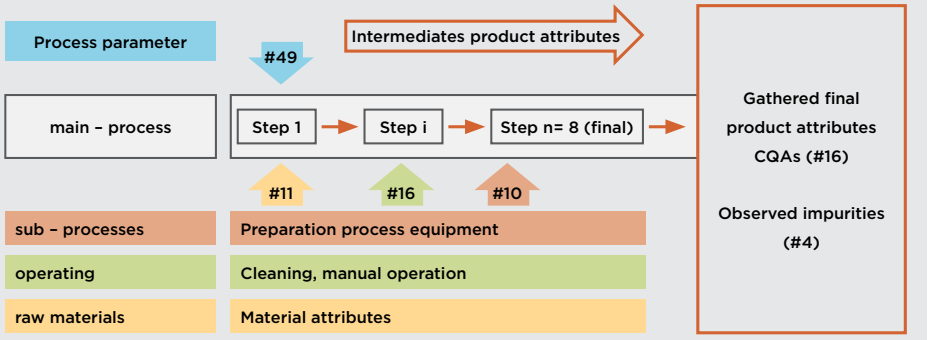


Figure 7: Illustration of structure and complexity of the risk model



dry time and inlet temperature on dried granule LOD on finished tablet dissolution and associated product efficacy. In the third case, risk control focuses on determining risk increase in product QAs as a consequence of out-of-specification deviation of material attribute. As the sequence of product QAs follows the process pathway, the bar graphs illustrate how the risk is propagated and how the risk potential of product QAs change in comparison with the baseline.

The structural fit of the risk model and the plausibility and consistency of the simulation demonstrate the capability to generate a realistic multivariate determination of risk associated with variations within an entire process and to provide unprecedented multivariate understanding of risk-based process behavior and its effect on product quality. Consequently, analyzing simulation results can provide an adequate justification of risk acceptance.

6. **Implement risk-mitigation measures:** The multivariate quantitative understanding of the effect of risk mitigation measures on risk associated with product quality enables to provide an effective and efficient implementation.

7. **Reassess the performance of the risk-mitigated process by another QRM cycle:** Based on results, the risk model could be adapted as needed and prepared for next QRM cycle.

The applied software technique enables the risk model assess any combination of multiple input parameters (PPs, operating and material attributes) and focus on any combination of multiple output parameters (product QAs). Consequently, the risk model tool is applicable for a wide range of situations relevant to multivariate quantitative QRM for LCM.

In similar way, a rash of practical CPPM applications and risk model–based multivariate QRM was executed (Figure 8). The short extract of following two practical applications may indicate the capability of CPPM approach to handle even high process complexity and demonstrate the benefit of risk model–based multivariate quantitative QRM and its implementation for investigational analysis and process development and optimization.

Practical Applications

Example 1: Multivariate criticality analysis of the bioreactor process

The goal of the project was to support the evaluation of the potential causes that may have resulted in an observed shift in certain product quality attributes. For this purpose, the risk model was established and a focused multivariate quantified risk analysis was executed. The process diagnosis (ranking the impact of possible causes), for example, indicated that O2 sparging PP was one of the significant causes. The subsequent simulation showed the effect of O2 sparging variation on dissolved oxygen and intermediate product attributes (e.g., viable cell density), and consequently on harvest critical product attributes (CQAs), measured by variation of risk potential respective of propagated risk (Figure 6).

This risk model–based investigational analysis supported concurrent evaluation and development. The captured complexity includes approximately 11 seed CQAs, 37 PPs, 16 MAs, and 80 process interactions. The responsible SMEs had actively contributed to the risk model design, provided the risk quantification, and verified the quantitative risk model. The efficiency of the model-building and simulation processes, content and suitability of achieved results, and leverage of collective knowledge confirmed the practicality, applicability, and benefit of this approach (Figure 8, number 4).

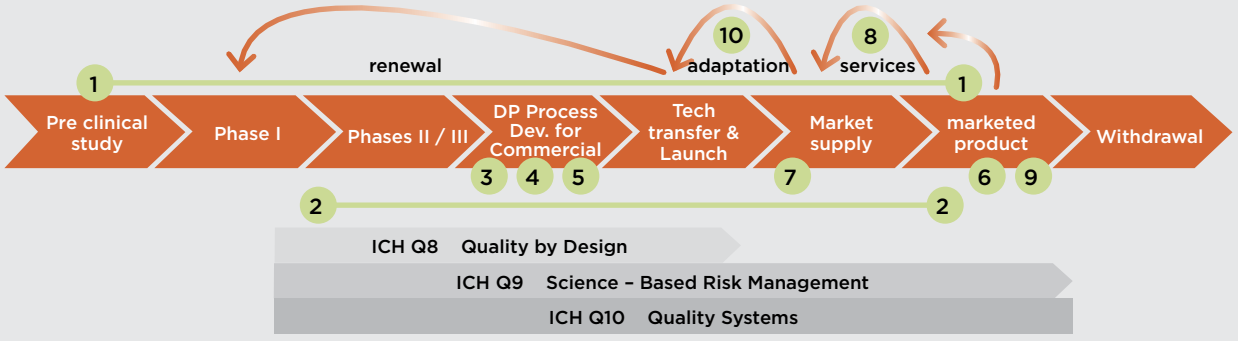
Example 2: Multivariate investigational analysis to improve process robustness

The purpose of the project was to support the investigational analysis of the causes of observed shift in certain product quality attributes and to improve robustness (i.e., reduce impact of variations induced by variation of biological raw material attributes on the considered product attribute) in a manufacturing process with high complexity (variation of MAs, multiple process steps, number of PPs, diverse technologies). At the beginning of the project the SMEs had different perceptions and knowledge about the cause-and-effect interactions of process and product. For this reason—and to support ongoing improvement—the company decided to use CPPM and to apply the multivariate quantitative risk assessment by means of risk model.

As a goal, the risk model should provide an enhanced scientific understanding of cause-and-effect interactions of process and product and include a deep-dive multivariate risk analysis to evaluate the potential causes that may have resulted in observed shift in the product quality attribute being considered. For this purpose, the risk model had been established with special focus on inherent chemical and microbiological processes that affect the considered product quality attribute.

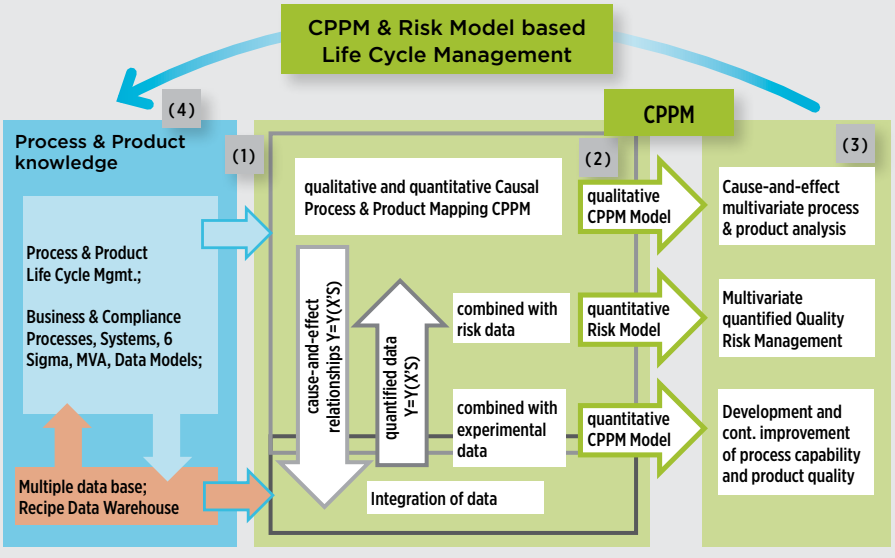
The structure and complexity of the manufacturing process risk model is illustrated in Figure 7. The cause-and-effect relations represented in the

Figure 8: Overview of practical applications of CPPM and Risk model approach with life cycle stage allocation



1 CPPM, System Dynamics methodology & Vensim, the range of applicability
2 CPPM and Risk model based multivariate QRM for LCM
3 Tablets, CPPM mechanistic model based support of FBG process development and site harmonization
4 Biotech, Bioreactor, Example 1 in this article
5 Tablets, CPPM and Risk model based multivariate quantitative process behavior (performance) analysis
6 Capsules, CPPM Model / 6 Sigma optimized QC for yield improvement
7 Sterile Pre-Filled Syringe, Risk Model based process re-design by comparison of 3 different processes
8 Transdermal patch, CPPM / 6 Sigma model criticality analysis and justification of process controllability
9 Sterile liquid, multiple manufacturing process, Example 2 in this article
10 Capsules, CPPM and Risk model based technology harmonization across 3 manufacturing sites

Figure 9: Overview of the CPPM and risk model–based LCM



model captured and calculated approximately 20 interactions per process step. Another interesting aspect was the existence of feedback interactions between the critical product quality attribute CQAs (each process step averaged about seven CQA interactions).

To understand the complexity of the process from an operation and risk mitigation perspective, the ranking (criticality) of individual impact of variations of particular process parameters on arbitrarily determined product QAs was established. Simulation results determined the risk potential of intermediate critical product attribute CQAs at each process step as well as of final product. These results allowed a better understanding of the process behavior, while the sensitivity analysis captured the risk impact of any process parameter variations and their combination on variation of product quality attributes. Consequently, appropriate practical operating measures for each manufacturing process were stipulated in order to support concurrent investigational and process improvement processes. This enhanced the meaning of the simulation results and the alignment of the experiments' conceptual approaches. Comparing results achieved through concurrent experiments with simulation results confirmed the application validity of the risk model.

The contribution of responsible SMEs and operation managers in the risk model building process led to a significant alignment and leverage of process understanding and knowledge, and resulted in sustained process robustness improvement: During the last 2-year period, product attributes were within specifications and no batch was rejected (Figure 8, example 9).

Overview of executed practical applications

These examples demonstrate the flexibility and wide applicability range of CPPM and risk model approaches.

As these practical applications show, the CPPM and risk model generate new levels of process and product knowledge and can provide an enhanced LCM. This includes:

- Identifying critical PPs and critical MAs to justify criticality of each process step
- Defining multivariate establishment of the process with predefined impact on product quality and risk control
- Ranking the impact (criticality) of process parameters variations on product QAs to determine risk mitigation and optimize process control strategy
- Providing proactive analysis and determine process design improvements
- Comparing performance of manufacturing processes at different manufacturing sites
- Determining and understanding the mechanisms of intrinsic (e.g., equipment, process) and extrinsic (e.g., operating) risks and their impact on risk of intermediates and final product QAs

Summary and Conclusions

Figure 9 illustrates CPPM and risk model–based LCM:

1. Expertise and data input from deployed processes and systems
2. Creation of the CPPM and risk models
3. Determination of new expertise and knowledge
4. Feedback and implementation into deployed processes and systems

CPPM applications confirm its capability to handle the complexity of the considered system (processes, procedures, data integration) in a universally applicable way. Simulation capabilities, augmented with sensitivity simulations and solution-focused optimizations support process development, strengthen troubleshooting, and enhance continuous process capability and product quality improvement. The execution practice verifies the trouble-free and flexible implementation of the CPPM approach, with transparent and simple interpretation of the results. The integration of the data, validity of the CPPM model, compatibility of the risk model with state-of-the art and approved QRM procedures and tools, and the capability of applied Vensim software ensure an a priori compliant and high-performing support for LCM.

The results of executed practical applications of the CPPM models and risk model–based multivariate quantitative QRM confirm the unique capability of this novel, innovative, and advanced approach for LCM.

Finally, CPPM implementation increases collaborative process understanding, speeds up knowledge management process, and emphasizes the power of systems thinking for managing process and product complexity. ■

References

1. The field of system dynamics was founded by the pioneering efforts of Jay W. Forrester to apply the engineering principles of feedback and control to social systems. One of the earliest (and still one of the best) references in this field is his book *Industrial Dynamics*, Cambridge, MA: MIT Press, 1961.
2. A. M. Fermier, T. Murphy, P. McKenzie, L. Poulson, and G. Schaefer. "Bringing New Products to Market Faster" Pharmaceutical Engineering online exclusive (July/August 2012).
3. A simpler introduction to system dynamics, along with a number of exercises is *Principles of Systems*, by Jay W. Forrester. Cambridge, Massachusetts: The MIT Press, 1968).
4. Stermann, John D. *Business Dynamics: Systems Thinking and Modeling for a Complex World*. McGraw-Hill Education: 2000.
5. Vensim software is a modeling environment produced by Ventana Systems, Inc., 60 Jacob Gates Road, Harvard MA 01451
6. Ventana Systems UK, Ltd. "Why Use Ventana Models?" http://www.ventanasystems.co.uk/Files/Why%20use%20Ventana%20Models.pdf .
7. Schwaninger, M., and M. Janovjak. "Innovative Models for steering organizations: A Systemic approach within the Pharmaceutical Industry." In *Management Models for the Future*, by Jan Jonker and Jacob Eskildsen, Springer Verlag, 2009.
8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. "Quality Risk Management: Q9." Step 4 version, 9 November 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

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The Color of Drugs

Color matters. The color of the paint on our walls can alter our mood. Color can be used to influence behavior, as in the case of Australia's anti-smoking campaign that plasters "the world's ugliest color"—opaque couché—on all tobacco products.[1] It has even been shown to affect the performance of athletes: Sports teams that wear red are more likely to win.[2]

It turns out that color choice matters for new drugs too. Choosing the right color for pharmaceuticals can provide marketing and safety benefits.

And with an aging population taking multiple drugs daily, the need for distinctive colors has become pressing, according to Jill Morton, CEO of Colorcom and a color specialist who consults with the pharmaceutical industry. "If people are taking 10 medications a day, it's critical that drug makers come up with the right colors to help avoid confusion," she says.

A survey of consumers using over-the-counter meds found that enhancing the esthetic experience by manipulating color enhances compliance and brand loyalty.[3] While Morton admits that this type of study needs to be replicated with larger sample sizes, it provides drug makers with valuable information.

"We have these personal experiences with color," she says. "If you're in an accident with a red car, it can permanently affect how you experience red. On the other hand, there are scientific studies that demonstrate crossover in the brain between the senses that can impact color perception. Neither the science nor personal experience trumps the other when it comes to choosing color. Drug manufacturers need to consider all this data and go with the best bet. There's no magic-bullet color."

Morton helped Tylenol choose the red, silver, and blue of its Extra Strength Rapid Release Gels. To balance the intensity of the red—one of the colors associated with the brand—she suggested a soothing sky-blue band and separated the two with a silver band in the middle to connote high technology. "Sky blue is a color that represents tranquility and peace to everybody around the world," she notes.

There are no regulatory requirements for color other than the US Food and Drug Administration dictum that tablets be distinguishable by color, shape, or markings to reduce medication errors and allow rapid identification in cases of accidental overdose.

"In most cases, drug manufacturers can choose any color they want or no color at all," says Jerry Phillips, President and CEO of the Drug Safety Institute, a subsidiary of the Brand Institute. The company helps with color choice for new meds as part of its medication-error-prevention analysis for new product labels and packaging.

Choosing the right color for pharmaceuticals can provide marketing and safety benefits.

There are a few meds—warfarin, levothyroxine, and estrogen—that use distinctive colors so patients can identify different strengths of the same drug. Other than these exceptions, for which the color coding applies to generics as well, the color of a generic is not dictated by that of the innovator drug.

There are good reasons, however, that a generic should mimic the color of the brand-name product. It can benefit those taking multiple medications, as well as first responders who rely on quick identification. It may even improve adherence. When epileptics switched from one anti-seizure drug to a generic of a different color, a 2013 study found they were far more likely to stop taking the medication.[4] Choosing a similar color allows a generic to piggyback on the branding and goodwill established by the innovator drug, but it can also trigger corporate trade dress protection, a subset of trademark law that protects a product based on its distinctive packaging or appearance.

It did just that for AstraZeneca's purple pill, Nexium. The company won a temporary restraining order last November against Dr. Reddy's Laboratories to discontinue using purple for its generic esomeprazole.[5] Dr. Reddy's has since changed the color of its pills to blue.

When consulting with drug makers, Morton starts by understanding who the intended consumers are, noting their gender, age, and nationality. "Most of my clients don't know what a particular color symbolizes," she says. "But once I know the target demographic, I can spin the color wheel to choose the best multipurpose color."

There is one color that both Morton and Phillips agree should not be on that color wheel: "Do you want a black tablet?" asks Phillips. "Probably not." ■

References

1. Tan, D., "The 'World's Ugliest Color' May Be Able to Discourage Smoking." Design Taxi. 3 June 2016. http://designtaxi.com/news/386508/The-World-s-Ugliest-Color-May-Be-Able-To-Discourage-Smoking/?utm_source=DT_Newsletter&utm_medium=DT_Newsletter&utm_campaign=DT_Newsletter_03062016&utm_term=DT_Newsletter_03062016&utm_content=DT_Newsletter_03062016.
2. Hill, R. A., and R. A. Barton, "Red Enhances Human Performance in Contests." *Nature* 435 (19 May 2005): 293. http://www.cnbc.cmu.edu/~samondjm/papers/HillandBarton2005.pdf.
3. Srivastava, R.K., and Aarti T. More, "Some Aesthetic Considerations for Over the Counter (OTC) Pharmaceutical Products." *International Journal of Biotechnology* 11, no. 3/4 (2010): 267–283.
4. Kesselheim, A.S., et al. "Variations in Pill Appearance of Antiepileptic Drugs and the Risk of Nonadherence." *JAMA Internal Medicine* 173, no. 3 (2013): 202–208. http://archinte.jamanetwork.com/article.aspx?articleid=1487287.
5. United States Court. District of Delaware. *AstraZeneca AB, AstraZeneca LP, and AstraZeneca Pharmaceuticals LP v. Dr. Reddy's Laboratories, Inc.* Restraining order. 6 November 2015. http://freepdfhosting.com/822115c494.pdf.

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