The Official Magazine of ISPE

# PHARMACEUTICAL ENGINEERING®

September-October 2016 | Volume 36, Number 5

## Lou Schmukler of BMS on Creating Supply Chain Excellence

How to Fight a Bully: An Interview with Nicole Pierson

Meet Your 2016-2017 Board of Directors

Quarterly Report: BIOTECHNOLOGY

ISPE®

www.PharmaceuticalEngineering.org

# WHY WE DO IT

# CLEAN AIR MATTERS

We believe breathing clean air is a human right that employees, friends and family members in the workplace all deserve. Contact Camfil APC to learn more.

**camfilapc.com/cleanairmatters**


Farr Gold Series®
Camtain Dust Collector


Quad Pulse Package
Dust Collector

camfil
AIR POLLUTION CONTROL

Dust, Mist and Fume Collectors

www.camfilapc.com • e-mail: filterman@camfil.com • 855-405-2271

# CHANGE IS OPPORTUNITY

Some see change as a problem; we see change as an opportunity. Adapting to the evolving trends and ever-changing regulations in the life sciences industry is what we're known for. We're driven to find the right solution to the most technically challenging problems. And we're satisfied only when we've produced results that make you successful.

crbusa.com


Biological
OSD
Fill/Finish
Vaccines
API's

Animal Health
Blood Fractionation
Oligonucleo/Peptides
Medical Devices
Nutraceuticals

Engineering | Architecture | Construction | Consulting

## A First Time for Everything

My introduction to the world of biopharma occurred in June 2015 as I listened to Andy Skibo, then Chair of ISPE's Board, deliver his "Biologics Supply Chain Risks" keynote address at the ISPE/FDA/PQRI Quality Manufacturing Conference in Washington, DC. He emphasized the potential effect of supply chain risk on biologics, which are projected to account for 80% of the pipeline and 70% of sales revenue by 2020—just three short years away. The unsettling possibilities may have given many in the audience reason for pause.

That presentation is the introduction to our first Quarterly Report on Biotechnology, which offers a variety of viewpoints on what it takes to succeed in biotech and biopharma. Other highlights include the role of sustainability and Ireland's impressive bio footprint. Our cover story features Lou Schmukler, president of Bristol-Myers Squibb's Global Manufacturing and Supply organization, who shares his insight into leadership, supply chain excellence, and achieving superior performance.

This issue has a few other firsts, as well: Our first patient interview tells Nicole Pierson's story of a parent's struggle to keep her son alive and healthy; it also presents a patient's perspective on access to the knowledge required to do that. If you heard her keynote address at ISPE's 2016 Annual Meeting you know that she's a passionate and engaging advocate.

Inside you'll also find two new columns: "Message from the Chair" gives 2016–2017 Board Chair Mike Arnold a forum for discussion; "Career Q&A," penned by Biogen's David Smith, answers questions that are front of mind for our YP members. We also take a look at the ISPE Training Institute as it celebrates its first anniversary. Lastly, we introduce you to your 2016–2017 Board officers, ISPE's new CFO and VP of Administration, and, we hope, to new concepts with the technical articles published this issue.

This issue truly reflects the diversity of thought, experience and knowledge of our members and I hope you enjoy it. ■

*Anna Maria di Giorgio, Editor in chief*



*Continued on page 6*

# INTEGRATED SOLUTIONS


FLUOR®

www.fluor.com

# PHARMACEUTICAL ENGINEERING®

Volume 36, Number 5
Published since 1980


## 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.

*Pharmaceutical Engineering* is published six times a year by ISPE.


**ISPE Headquarters**
7200 Wisconsin Ave., Suite 305
Bethesda, MD 20817 USA
Tel: +1-301-364-9201
Fax: +1-240-204-6024

**ISPE Operations and Training Center**
600 N. Westshore Blvd., Suite 900
Tampa, Florida 33609 USA
Telephone +1-813-960-2105
Fax +1-813-264-2816

ISSN 0273-8139

**US Postmaster**
*Send change of address to:*
Pharmaceutical Engineering Magazine
600 N. Westshore Blvd, Suite 900
Tampa, Florida 33609

*Periodicals postage paid at Tampa, Florida, US, and additional post offices*

**Canada Postmaster**
*Send change of address and undeliverable copies to:*
Pharmaceutical Engineering Magazine
PO Box 122
Niagara Falls, ON L2E 6S8 Canada

*Canada Post mail agreement #40012899*






New Column

### Message from the Chair



### New 2016 Board Executive



## Cover



## Features





## ISPE News



## Profile




## A YP State of Mind



## Career Q&A

*"Fristams are the best pumps going."*

- Plant Maintenance Manager, Midwest Production Facility


# PD Pumps From the Experts You Trust

For decades, Fristam WFI and CIP-return pumps have set the industry standard for clean, reliable, and efficient processing.

Our FKL positive displacement pumps are built with that same traditional Fristam quality and manufactured of 316L stainless steel, for high performance and long-lasting reliability. Fristam FKL PD pumps are designed to safeguard the integrity of your product and keep your critical path up and running.

Like all Fristam pharmaceutical pumps and parts, the FKL is available with comprehensive documentation and comes with the best service and delivery time in the industry.

Contact Fristam, your trusted resource for pharmaceutical pumps, to learn more.

Fristam PUMPS®

*Engineered For Lasting Performance®*

1.877.841.5001 | fristam.com/pharma

## Quarterly Report: BIOTECHNOLOGY

**47-81**






## Technical Articles



## Back Page



ISPE

*Continued from page 2*



**Biotechnology Quarterly Report**
**Guest editors:** Andy Skibo and Britt Perry

**Collaborators**
Scott Fotheringham, PhD, James Hale, Michael McGrath

**Advertising and Sales**
Director of global sales: Neil Boylan, +1 415-827-2222
Manager, Sales operations: Diane Munda, +1-813-739-2275
Sales coordinator: Robin Lane, 1-813-960-2105

**Illustration, p.60,** Philippe Béha

**Stock Photography and Illustration**
iStock

**Art Direction and Graphic Design**
Kaki Design Inc., www.kakidesigngraphique.com

**Letters to the editor**
*Pharmaceutical Engineering* welcomes readers' comments. Letters must include the writer's full name, address, organization, and years of ISPE membership. If published, letters may be edited for length and clarity. Please address editorial correspondence to: The editor, Anna Maria di Giorgio (amdigiorgio@ispe.org).


"Imperfections? I like them in people. OPTIMA equipment I like to be perfect."

**Birgit Breitmoser**
Technical draftswoman
(Machine Engineering)

**A filling line from Optima, puts you on the safe side right from the beginning. Because we build complete lines that feature all the advantages: Perfect machine performance made to order, consistent documentation, an ideal software solution including a central contact who is passionate about looking after your smallest concerns. The one thing we refuse to deliver is imperfection. Because we have understood that only perfection translates into absolute customer satisfaction.**

**PHARMA EXPO Chicago | November 06 - 09 , 2016 | Booth W 731**

# OPTIMA

EXCELLENCE IN PHARMA

**OPTIMA pharma GmbH** | Otto-Hahn-Straße 1 | 74523 Schwaebisch Hall | Germany
Telefon +49 791 9495-0 | info@optima-pharma.com | www.optima-pharma.com

Member of
PACKAGING VALLEY
Germany

## September 2016

2 Singapore Affiliate
YP Go-Karting Challenge
Singapore

6 Nordic Affiliate
CoP Clean Utilities Network Meeting
High Purity Water and Future Technologies
Gentofte, Denmark

7 Nordic Affiliate
CoP Clean Utilities Network Meeting
High Purity Water and Future Technologies
Tuusula, Finland

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

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

Carolina–South Atlantic Chapter
Annual Planning Meeting
Cary, North Carolina

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

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

12 Brazil Affiliate Training
Commissioning and Qualification
São Paulo, Brazil

**12–14 Basic GAMP® 5, Annex 11/Part 11 (T45)**
**San Diego, California**

13 Chesapeake Bay Area Chapter
Golf Tournament
Ijamsville, Maryland

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

Pacific Northwest Chapter
Member Appreciation Night
Seattle, Washington

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

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

20 UK Affiliate
Bombay Sapphire Distillery Tour
Whitchurch, England, UK

22 Belgium Affiliate
Technical Meeting: Containment
Isnes, Belgium

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

26 Brazil Affiliate Training
Cold Chain Day
São Paulo, Brazil

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

27–28 Brazil Affiliate Training
GxP Process Control Systems Validation
São Paulo, Brazil

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

Ireland Affiliate
Driving Growth through Process Development
Saggart, Ireland

29–30 Poland Affiliate
Pharmaceutical Conference

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

## October 2016

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

4–5 Europe Affiliate
GAMP®/Data Integrity Regional Conference
Copenhagen, Denmark

5 Boston Area Chapter
Annual Product Show
Foxboro, Massachusetts

UK Affiliate
Cleanroom Workshop: ISO 14644-1
Milton Keynes, England, UK

6 Brazil Affiliate Training
HVAC
São Paulo, Brazil

New Jersey Chapter
30th Anniversary Celebration
Pittstown, New Jersey

11 GAMP® CoP Benelux
IT Infrastructure Qualification & Control in Life Science Industry
Ordina, Mechelen, Belgium

France Affiliate
Conference IPIL, Produits Steriles
Lyon, France

13 San Diego Chapter
Facility Tour
San Diego, California

17 Brazil Affiliate Training
Good Engineering Practices
São Paulo, Brazil

**17–20 Cleaning Validation (T17)**
**Facility Project Management (T26)**
**GAMP® 5 Data Integrity (T50)**
**Process Validation in Biotechnology Manufacturing (T32)**
**QRM (T42)**
**Water Generation (T04)**
**Water Storage, Delivery and Qualification (T23)**
**Boston, Massachusetts**

19 Boston Area Chapter
Tips and Practices for Innovation
Medford, Massachusetts

20 Greater LA Chapter
Golf Tournament
Los Angeles, California

Midwest Chapter
YP Thirsty Thursday
Kansas City, Missouri

UK Affiliate
Could the Future Be Bright?

24–25 ISPE Europe
Biotechnology Conference: Reinventing Commercial Biomanufacturing
Frankfurt, Germany

24–26 Brazil Affiliate
Annual Conference
São Paulo, Brazil

25–27 Process Validation Statistics Conference
Bethesda, Maryland

27 Boston Area Chapter
Fall Social: Oktoberfest
Boston, Massachusetts

France Affiliate
Atelier GAMP® Francophone

**31 Oct–2 Nov**
**Basic GAMP® 5, Annex 11/Part 11 (T45)**
**Copenhagen, Denmark**

## November 2016

1 Brazil Affiliate Training
Maturity of Validated Systems
São Paulo, Brazil

**3–4 Q7A (T30)**
**ISPE Training Institute**
**Tampa, Florida**

6–9 2016 Pharma Expo
Chicago, Illinois

7 Brazil Affiliate Training
Calibration
São Paulo, Brazil

**7–9 HVAC (T14)**
**ISPE Training Institute**
**Tampa, Florida**

8–9 Brazil Affiliate Training
Risk Management
São Paulo, Brazil

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

10 Boston Area Chapter Education Program

UK Affiliate Annual Conference Leeds, England, UK

**10–11 Verification of Facilities, Systems and Equipment Workshop (T48) ISPE Training Institute Tampa, Florida**

14 Facilities of the Future Conference Bethesda, Maryland

**14–15 GAMP®5 Process Control Systems (T21) ISPE Training Institute Tampa, Florida**

17 Nordic Affiliate Annual Conference Copenhagen, Denmark

**17–18 Auditing for the Pharmaceutical Industry (G07) ISPE Training Institute Tampa, Florida**

22–23 France Affiliate Healthcare Coldays Lyon, France

23 Belgium Affiliate Bio Processing Braine-l'Alleud, Belgium

Brazil Affiliate Training Manufacture São Paulo, Brazil

23–24 Brazil Affiliate Training Project Management São Paulo, Brazil

25 France Affiliate Atelier GAMP® Francophone avec L'AFDIT

28 Brazil Affiliate Training Biotechnology São Paulo, Brazil

28–Dec 2 Singapore Affiliate Effective Pharma Audits & Self-Inspections Singapore

29 Belgium Affiliate Young Professionals Networking Event Huizingen, Belgium

## December 2016

5 Brazil Affiliate Training Suppliers Advisory Council Suppliers Qualification São Paulo, Brazil

5–7 Biopharmaceutical Manufacturing Conference San Francisco, California

Brazil Affiliate Training GAMP® 5 São Paulo, Brazil

**5–7 Basic GAMP® 5, Annex 11/Part 11 (T45) ISPE Training Institute Tampa, Florida**

8 Boston Area Chapter Education Program

France Affiliate Atelier GMP Commentaires Annexe 1 Paris, France

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

12 Brazil Affiliate Training Medical Devices São Paulo, Brazil

**12–13 Cleaning Validation (T17) ISPE Training Institute Tampa, Florida**

**15–16 Sterile Facilities (T12) ISPE Training Institute Tampa, Florida**

# Training

### High-Quality, In-Depth Skill Development

ISPE has been delivering training courses since 1998. We've earned the title of the "Industry's Trusted Source of Knowledge" and are viewed by manufacturing professionals and regulators worldwide as the go-to resource for expert-knowledge.

Our robust body of knowledge is delivered onsite, online, or at our new ISPE Training Institute.

### ISPE Training Institute

Classroom training courses delivered at ISPE's office in Tampa, Florida. Visit http://www.ispe.org/training for more information.

### ISPE eLearning

Convenient access to our global knowledge through online training courses and webinars. Visit www.ispe.org/elearning to learn more.

### ISPE Onsite Training

We can help stretch your training budget by bringing our courses to you. Contact Training@ispe.org to request a quote.

# eLearning

Online courses and webinars help you expand your skills from the comfort of your desk.

- Expanded Online Training
- General Industry Knowledge Courses
- Fundamental Industry Knowledge Courses
- GMP Courses
- Webinars

### Onsite training

Bring customized ISPE training courses to your company.

Topics include:

- Biotechnology
- Cleaning
- C&Q
- Facilities
- GAMP®
- GMPs
- HVAC
- Manufacturing
- Process Validation
- Project Management*
- Quality by Design
- Validation
- Water

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

GAMP® is a set of guidelines for manufacturers and users of automated systems in the pharmaceutical industry and a registered

**Industry's Trusted Source of Knowledge**

# Are technological advancements driving your production into the unknown?

## Success in the new pharma reality relies heavily on succesfully implementation of new manufacturing technology.

When you introduce new products and processes at your production site, it often requires a parallel introduction of new technology and practices. But implementing new technologies such as single-use components and continuous manufacturing equipment can be challenging, just as entering into combination products is unfamiliar territory for most pharmaceutical companies.

With in-depth knowledge of the technogical advancements in pharma, NNE Pharmaplan's experts can help you select the right solution for you. We'll help you to successfully implement new technologies, providing your business with optimal, future-proof solutions.

Learn more at nnepharmaplan.com

**Meet NNE Pharmaplan's experts at booth 21 or catch them during the education sessions.**

nne pharmaplan®
Focused pharma engineering

# Transparency, Diversity, Collaboration, and Strengthening Our Core

*Michael A. Arnold*

Welcome to a new column, from Mike Arnold, Senior Director at Pfizer, and Chair of ISPE's 2016-2017 International Board

**I want to thank each of you** for the tremendous opportunity to be your 2016-2017 International Board Chair. I am truly honored and humbled by your vote of confidence. I also want to thank Joe Famulare, immediate Past Chair, for his leadership and mentorship over the past year. ISPE continues to achieve positive growth in membership and revenue, which is a reflection of the leadership of Joe, the Board of Directors, ISPE staff, and our volunteers.

Looking to the year ahead, I see both opportunities and challenges for ISPE. It is clear to me that our 2016-2019 strategic plan entitled "Embracing the Challenge" remains directionally correct and we will continue to work toward that plan. The challenges we face relate to the complexity and competitiveness of our environment. If we embrace these challenges head on and become progressive in our approach to them, we as a Society will benefit substantially.

I've communicated to our Board of Directors that ISPE membership has entrusted us to lead the organization and represent their professional interests. It is a responsibility that must not be taken lightly. In the coming months, we will likely encounter difficult challenges and business decisions that will test our collective strength. In these situations we will need to be both inclusive in thought and decisive in action.

In the coming year I've identified four primary areas where I will focus. These are:

1. Transparency
2. Business Diversity
3. Collaboration
4. Strengthening Our Core

## Transparency

Ensure the appropriate level of awareness and input on strategies and key business decisions at all levels of the organization.

## Business Diversity

Seek business opportunities through engaging and establishing effective partnerships with academia and other not-for-profit organizations with common industry goals and objectives. Leverage existing ISPE expertise and structure to enhance global effectiveness.

## Collaboration

Leverage our Chapters and Affiliates to more effectively share and promote knowledge and expertise globally. Leverage the skills and insights of our Young Professionals in the development of current and future strategies.

## Strengthening Our Core

Identify opportunities to enhance efficiencies in the development and execution of our conferences, technical documents, and member services.

Through this column and via a communication portal on our website, I will provide you with updates on our progress and timely information on topics that affect us all.

Ultimately, the Board is your voice, and we are here to establish goals that support you. I look forward to working with you, and together we can continue to progress the success and respect of ISPE.

# ISPE Announces Board of Directors Election Results

The results are in and the 2016-2017 International Board of Directors reveals a slate of strategic leaders from myriad pharmaceutical industry sectors. Welcome to one newly elected officer, former Board director Frances (Fran) M. Zipp, and four newly elected directors, Peter S. Carbone, Christine M. V. Moore, PhD, Fatma Taman, and Jöerg Zimmermann. Led by Chair Michael A. Arnold, the 2016-2017 Board members, responsible for the governance and strategic direction of ISPE, will assume their elected positions at the 2016 ISPE Annual Meeting & Expo, 18–21 September in Atlanta, Georgia.

"I am looking forward to collaborating with the incoming International Board of Directors to further the organization, and advance the Society's mission and vision," said John Bournas, ISPE CEO and President. "The new leadership team will not only provide invaluable guidance with regards to our strategic direction and efforts to support the biopharmaceutical manufacturing industry, but will continue the organization's further globalization."

Pharmaceutical industry leaders elected to the 2016–2017 ISPE International Board of Directors are:

## Officers

- Chair: Michael A. Arnold, RPh, Business Process Owner for Investigational Products and Senior Director of Strategic Partnerships for Pfizer's Global Clinical Supply Chain.
- Vice Chair: Timothy P. Howard, CPIP, PE, Vice President of Strategy and Development, Commissioning Agents, Inc.
- Treasurer: James A. Breen Jr, PE, Vice President, Worldwide Engineering and Technical Operations, Johnson & Johnson.
- Secretary: Frances (Fran) M. Zipp, President & CEO, Lachman Consultant Services, Inc.
- Immediate Past Chair: Joseph Famulare, Vice President–Global Quality Compliance and External Collaboration, Genentech/Roche, Pharma Technical Operations. He will continue to serve on the Board in 2016–2017.

## Directors

### Reelected Director

Joanne R. Barrick, RPh, Advisor in Global Validation Support, Eli Lilly and Company, served in 2014–2016 and has been reelected to a second two-year term.

### New Directors

- Peter S. Carbone, Vice President, Global Head External Relations, Group Quality, Novartis

*Michael A. Arnold*

*Timothy P. Howard*

*James A. Breen Jr*

*Fran M. Zipp*

*Joseph Famulare*

> "I am looking forward to collaborating with the incoming International Board of Directors"
>
> —John E. Bournas, ISPE President and CEO

- Christine M. V. Moore, PhD, Global Head and Executive Director, GRACS CMC–Policy, Merck
- Fatma Taman, General Manager, PharmaVision
- Jöerg Zimmermann, Vice President of Vetter Development Services, Vetter Pharma-Fertigung GmbH & Co. KG

### Continuing Directors

- Tony (Antonio) Crincoli, Executive Director and Head of Global Engineering Services, Bristol-Myers Squibb
- Thomas Hartman, Vice President of GMP Operations, Biopharm CMC, GlaxoSmithKline
- Robert "Bob" Matje, PE, CPIP, Vice President of Technical Operations, Qualitest/Endo
- Antonio (Tony) R. Moreira, PhD, Vice Provost for Academic Affairs, University of Maryland, Baltimore County (UMBC)
- Christopher "Chris" Reid, CEO, Integrity Solutions Ltd.

### Outgoing Directors

ISPE gratefully acknowledges the service of these Outgoing Board Members:

- Andy Skibo (Past Chair): Executive Vice President, Operations, MedImmune/AstraZeneca
- Jeff Biskup, President and CEO, CRB
- Jennifer Lauria Clark, Executive Director, Strategic Development, Commissioning Agents, Inc.
- Britt Petty, Director of Manufacturing Operations, Biogen, Inc.

Complete biographical information on all of ISPE's International Board can be found at www.ispe.org/meet-your-new-board. Read more about the Board of Directors and election policies at www.ispe.org/volunteers/governance-structure.pdf. ■

ISPE®

TWO SIGNATURE CONFERENCES. ONE LOCATION.

# ISPE Process Validation Conference

## 24 – 26 October 2016

### Advancing the Validation Lifecycle Approach

**This Year's Process Validation Conference Will Provide Current Thoughts On:**

- *Overcoming Top Challenges in the Application of Statistics in the PV Lifecycle*
- *Practical Implementation of Continuous Process Verification through Advanced Process Controls*
- *Effective Utilization of the Lifecycle Approach to PV by Contract Manufacturers*
- *PV Lifecycle Application for a Direct Compression Continuous Manufacturing Process*
- *Impact of Excipient Variability*
- *Translating DOE Data into Registered Process Ranges*
- *Biologics Lifecycle Validation and the Benefits of a Quality by Design Approach for PV*
- *Packaging for Validation*

**This Year's Process Validation Statistics Conference Will Enhance Your Knowledge In:**

- *Statistics as an Enabler of Regulatory Compliance of Process Validation*
- *Implementation of Statistically Based Routine Release Testing*
- *Using Defect Rate to Determine PPQ & 3A Sampling and Monitoring*
- *Statistical Considerations in PV for Continuous Manufacturing*
- *Statistical Considerations in PV for Packaging*
- *Improved Acceptance Limits for ASTM Standard E2810 Using a Bayesian Approach*

## Featured Speakers

This year's conference features a half-day Combined Regulatory Session for PV and PV Stats attendees on

26 October 08.30 AM – 12.30 PM

*(included in the registration fees when you register for either or both the conferences).*

**Regulatory Speakers include:**

**Ashley Boam**
Acting Director, Office of Policy for Pharmaceutical Quality, FDA/CDER (Invited)

**Lawrence Yu, PhD**
Deputy Director FDA/CDER/OPQ (Invited)

**Karthik Iyer**
Acting Branch Chief, FDA/CDER/OC/OMQ

**Alex Viehmann**
Operations Research Analyst, FDA/CDER/OPQ/OS (Invited)

*Agendas are subject to change without notice. Every precaution is taken to ensure accuracy, but ISPE cannot accept responsibility for information distributed or contained in these programs, or for any other opinion expressed.*

# ISPE Process Validation Statistics Conference

## 25 – 27 October 2016

### Breaking New Ground with Statistics in the Process Validation Lifecycle

**Early Bird Registration**

Register **before 24 September 2016** and save!

*Discounted rates apply for groups of 3 or more.*

Bethesda Marriott | Bethesda, MD

*Lou Schmukler*

# Creating Supply Chain Excellence, Achieving Superior Performance

An Interview with Lou Schmukler, President of Global Manufacturing and Supply at Bristol-Myers Squibb

**The transformation of Bristol-Myers Squibb (BMS) from a large, diversified pharma company to a focused, specialty biopharma company has been widely recognized as a remarkable business success story. The transformation started in 2007 and was guided by the vision to create a company that would represent the best of both pharma and biotech. The company pursued a three-pronged strategy defined by innovation, integration, and improvement. With the patient as the focus, innovation efforts centered on select therapeutic areas targeting serious disease and significant unmet medical need. The company's "String of Pearls" business development strategy largely defined its approach to selective integration. And a comprehensive continuous-improvement program drove efficiency and effectiveness across the entire company. BMS divested businesses, rationalized the portfolio, consolidated the manufacturing footprint, and much more. By practically all measures, the transformation has elevated it to a position of industry leadership, but the company is not complacent. It continues to be bold and evolve with an eye on the future.**

**BMS's Global Manufacturing and Supply (GMS) organization played a key role in the company's transformation. Pharmaceutical Engineering met with GMS President Lou Schmukler, who shared some views on a number of key supply chain topics. Schmukler started on the shop floor more than 35 years ago and has broad experience across various sectors of the industry.**

> Reducing variability is synonymous with improving and attaining high quality.

**PE What is your philosophy with respect to supply chain strategy for the industry?**

LS It depends, and by that I mean that the supply chain strategy should be fully aligned with the business strategy for the enterprise. The best supply chain strategy, and the corresponding required capabilities and performance targets, should be primarily driven by the enterprise's business model and objectives. For example, the optimal supply chain strategy for a specialty-care biopharmaceutical company may be quite different from that for a generics pharmaceutical company. That said, there are certainly key emphasis areas that are universally important.

I like to refer to these universal areas as "non-negotiables expectations" or "table stakes." These should be foundational to any supply chain and the target should be excellence. These areas include such things as product quality, GMP compliance, safety, environmental sustainability, people development, and organizational culture. I believe that no supply chain organization can aspire to world-class status without first having these core elements well established.

Once this strong foundation is in place, the supply chain organization can focus on the next level of strategy, which encompasses making a series of important strategic decisions that will serve, in large part, to define the future strategic framework and operating model for the supply chain. By working closely with R&D and commercial partners, the supply chain organization can make the best strategic choices so that finite resources are best allocated toward those areas that support the overarching company priorities and create a superior competitive advantage. This effort can lead to what's sometimes referred to as a "segmentation" strategy to supply chain management. The approach entails having different operating principles, investment plans, and metrics across the business from both the portfolio and geographical perspectives, based on unique business needs. An example of this is where two different planning models may be utilized, such as make-to-order vs. make-to-stock.

The third level of supply chain strategy builds on the first two. This is where specific priority programs and projects are identified to really maximize the supply chain value proposition for the company and its customers and patients. You could consider these the "game changers" because they unlock tremendous value. These plans usually involve substantial cross-enterprise collaboration and thinking differently about the business. To be a little more specific, for us at BMS Global Manufacturing and Supply, these efforts are mainly associated with the acceleration of bringing new transformational medicines to patients and enhancing the customer-patient focus and experience. An example of this would be a project to re-engineer the new product-launch process such that the time from approval to patient is measured in hours vs. days.

**PE Are there some key elements you have developed or learned through experience?**

LS First, strategy is about choices and tradeoffs. Deciding what you are not going to do is often more important than deciding what you are going to do. I believe this is where some organizations struggle. Without making necessary difficult decisions, prioritization suffers and the resulting dilution effect on focus is not a recipe for success. Said another way, when everything is a priority then nothing really is.

The second point is the importance of having a robust strategic planning process. At BMS Global Manufacturing and Supply we utilize Hoshin Kanri, which is a method for ensuring that the strategic goals of the organization drive progress and action at every level within the organization. It eliminates the waste that can come from inconsistent direction and poor communication, and it strives to get every employee pulling in the same direction at the same time. It achieves this by aligning strategic goals with plans of middle management and the work performed by all employees. Achieving this level of alignment within a large organization is not easy but is absolutely key. Vision and strategy without execution is just hallucination. Hoshin Kanri coupled with strong program management discipline ensures effective execution.

Lastly, the ultimate measure of a good supply chain strategy is if it provides the right roadmap that supports the company objectives both near and long term and drives superior competitive performance. By definition, it is an iterative process always involving the cost-benefit analysis and respective tradeoffs of the various operational components.

*TThe company's new multi-host, multi-product, small-scale single-use biologics facility in Bothell, Washington*

**PE What other supply chain key capabilities and best practices are important?**

LS I believe there are a number of key capabilities and best practices that all supply chains should embrace to achieve superior performance. I like to think about these in three dimensions: people, process, and technology. I will just comment on several of the major ones here, two of which were highlighted earlier: a strong linkage to the business strategy and creation of a tailored supply chain using segmentation.

When it comes to supply chain key capabilities and best practices, an appropriate place to start is the company's integrated business planning process. This process is the backbone of a company's supply chain. Translating the company's business plan into a good forecast and executable manufacturing plan is extremely important. An effective sales and operations planning process is a key component here as well as strong data management. We all know how difficult forecasting can be, especially for new products. But this is just one of the potential uncertainties the supply chain must be designed for and prepared to manage, which brings me to the need for a solid business continuity program.

Stated in simplest terms, a business continuity plan starts with a comprehensive risk assessment followed by a risk mitigation plan. There are multiple kinds of risks that must be considered in addition to forecast or demand variability. These include product failures, potential competition scenarios, major supply chain disruptions such as natural disasters, and variables around the regulatory process.

Each company needs to be deliberate in setting the risk appetite thresholds deemed appropriate for their business. There are several levers by which risks can be mitigated. A combination of approaches are often employed that can entail products that are dual sourced across facilities and suppliers, strategic inventory, and/or agile lead times to shorten time of recovery. An important point here is that risks can be significant and the associated mitigation plans expensive, so decisions should be made cross functionally with executive management understanding and endorsement.

Next, there is the need for a well-thought-out supply network strategy. Most companies do not have the luxury of starting with a "clean sheet of paper" when it comes to their supply network strategy; they already have their legacy network, which often is not optimally designed to support current and/or future business requirements. Questions around site locations, scope, and technology platforms all need to be addressed. Multiple decision-making criteria go into designing the ideal supply network, and this can involve balancing competing priorities. For example, maximizing asset utilization to optimize cost may conflict with installing redundancy in order to mitigate risks to ensure business continuity.

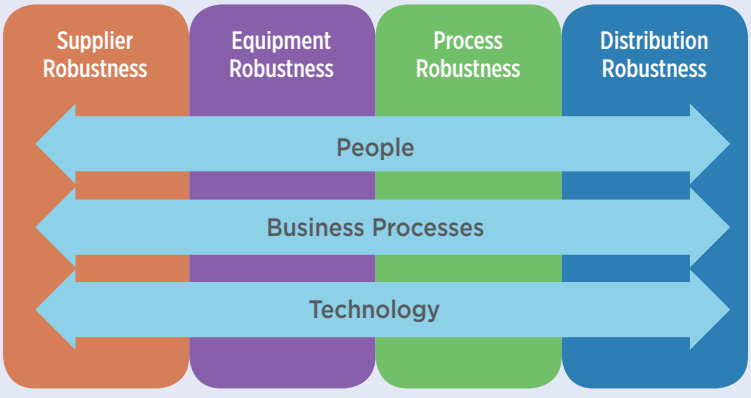
*In Devens, Massachusetts, the company expanded its Biologics Manufacturing site by adding development capabilities.*

Requirements for local manufacturing can further complicate decision making. Another important strategic decision here is determining what operations and activities to perform internally vs. externally. Outsourcing can be driven by a number of factors. It might be desirable when there is a need for external proprietary technology, backup capacity, a necessary geographical presence, incremental scalable capacity, or cost leverage. Over the past decade, progressive supply chain organizations have focused on new external manufacturing paradigms to achieve a more integrated and seamless relationship with their contract manufacturing partners. The bottom line in all of this is that the ideal supply network should be fit for purpose.

Two attributes for the supply chain organization that have become more and more important are agility and flexibility. With the increasing number of disruptions, uncertainty, and volatility, these two attributes are both necessary core capabilities and a potential source of competitive advantage as well. An initial assessment of where these capabilities are most needed is a good place to start. This activity should be undertaken with an end-to-end view of the supply chain. Then the effort needs to turn to the building of these capabilities for the targeted functions and processes. Having the ability to "look around corners" to sense, detect, and respond to events in a timely manner is important. The focus should cut across the supply chain and include product development, purchasing, production and planning, and logistics. Some of the relevant programs that supply chain organizations have implemented with great success are lead time reduction initiatives, late-stage customization or postponement, flexible multi-product operations, scalable variabilized capacity, and supplier contingency planning. I would also add here that external focus, or looking outside the industry, is an invaluable exercise. Especially in this area of agility and flexibility where there is much to be learned and best practices to be replicated from automotive, high tech, consumer goods, and other industries.

Lastly, there are a few other areas that could be particularly relevant to a given business. One is the area of complexity. Complexity is increasing

**GMS Product Robustness Approach**



*The company is constructing a new state-of-the-art, large-scale biologics manufacturing facility in Cruiserath, County Dublin, Ireland, that will produce multiple therapies for the company's growing biologics portfolio.*

and a major challenge for the supply chain. Complexity management can greatly improve supply chain efficiency and effectiveness. Through a cross-enterprise pragmatic approach, the elements of complexity can be best managed. Main elements to evaluate can include the number of products and SKUs, geographies and different regulatory requirements. The second area is that of measurement. We are all familiar with the saying "you can't manage what you don't measure." Having a complete and balanced scorecard, incorporating leading and lagging key performance indicators, that measures results as well as capabilities internally and externally is central. And the third area is collaboration from end to end. I emphasized alignment earlier. Supply chain management is a team sport. An integrated approach, shared objectives, transparency, and communications are all key success factors.

## Vision and strategy without execution is just hallucination.

**PE You stated earlier that quality was a basic and foundational element. What is your view of the linkage between quality and supply chain excellence?**

LS Enemy number one of the supply chain is variability, so a primary goal needs to be the identification and minimization of all forms of variability. Reducing variability is synonymous with improving and attaining high quality. You cannot hope to have a reliable, agile, and cost-effective supply chain without high quality. So pursuing high-quality outcomes and getting it right first time should be viewed as an investment and not a cost.

For many years, the Juran Trilogy Model for quality management has been fundamental to my view of high quality. It consists of three important management tools that work together: quality planning, quality control, and quality improvement. In Six Sigma terms, the related process is called DMAIC.

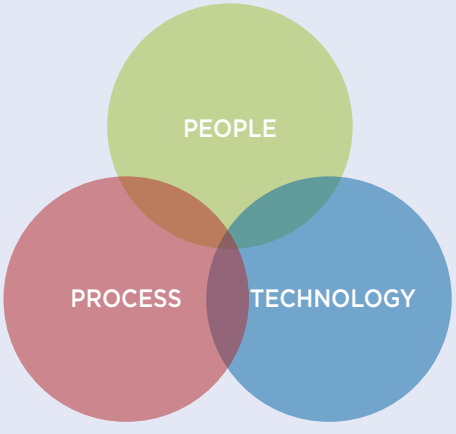
Dr. Joseph Juran was a pioneer in emphasizing the important role of statistics in manufacturing, which I like to refer to as the language of variability and quality.

Originating from all his work was the concept of cost of poor quality, and it is in this concept that the business case for high quality and its linkage to supply chain excellence is made. This is all about understanding the cost of providing poor quality and service. By focusing on root cause and prevention, you maximize return on quality (ROQ) and drive down non-value-added failure and appraisal costs that can be significant.

**PE How is that put into practice at BMS?**

LS Our aspiration has been to move from a reactive to a proactive mindset and thereby realize the greatest ROQ. This is at the heart of our quality system and plan. A main component of our approach is our product robustness program. The vision for this program is the certainty and ability to prove that any product, at any time, in any place, from any site (internally or externally), meets BMS's high-quality standard and is available when and where it is needed. It has four pillars: supplier, process, equipment, and distribution robustness with process, technology, and people elements common to each pillar. Program scope includes the full product life cycle, from development to late life cycle and discontinuation. We set targets for CpK across the portfolio and for each of our supply nodes with a goal to exceed 1.33 for all critical quality attributes.

**Three Dimensions of Supply Chain**




This robustness work, coupled with our "inspection ready everyday" philosophy, has been pivotal to raising the reliability and performance of the supply chain. In addition, BMS has been very engaged with our peer companies, regulatory partners, and ISPE on both the drug shortage and quality metrics topics. Our supply chain and aligned quality efforts are obviously key to our methodologies for both of these.

Lastly, I want to just briefly comment on the "soft" side of attaining quality excellence: the people and culture aspects. As with any business-critical priority, the tone must be set from the top and reinforced by every leader in the organization. Painting a vivid picture of the future state for quality and the associated expected behaviors is very important. It is then incumbent on leadership to create an environment in which people are empowered to identify and raise issues and then be provided with the training and tools to resolve them. At BMS, our people strategy, which focuses on engagement

and development, in concert with our operational excellence (Continuous Improvement-Lean Six Sigma) program are integral to this.

**PE Perhaps you could conclude by speaking about a few of the major trends and challenges you see the industry's supply chains facing as we look to the future?**

LS A very important question. The first one that comes to mind is the need for the supply chain to be able to support the increasing R&D productivity, shift from primary to specialty care portfolios, and the associated growth in biologics. Let's consider some of the implications. A related issue is the advent of accelerated regulatory review and approval. Supply chain organizations need to revisit their development and launch processes. The new time-constrained development environment makes ensuring robustness more challenging given limited process experience and data. In addition, legacy supply networks will need to be restructured for the new specialty care products. The trend toward personalized medicines could indicate an increase in smaller-batch production and complexity.

Today, biologics sales are approximately 20% of total worldwide industry sales with a forecasted 15% annual growth rate. The continued growth in biologics is certainly a challenge for the industry's supply chain organizations. An estimated 40% of the industry's R&D pipeline are biologics. The introduction of biosimilars into the market will place added demands on already-constrained global capacity. In response, the industry has increased global capacity by over a third over the past six years and will be investing in excess of an additional $20 billion over the next six years. In addition to capital expansion, bioprocess optimization should continue to play a significant role in creating new capacity as it has over the past two decades. It is also worth noting that some companies now have a growing need for added pharmaceutical API and formulation capacity, which have not been seen for some time.

There are several other areas that I think are noteworthy. I mentioned external manufacturing earlier, and I believe this is a trend that will continue. Business development activity has been fast and furious of late but is now slowing a bit. That said, supply chains will need to be prepared for the possible merger, acquisition, or the acquiring of new assets. I expect the further globalization of supply chains and the need for manufacturing in developing markets will also continue. In addition, with the ever-increasing cost pressures on governments and health care providers, cost containment will become more and more important.

Supply chains will need to become more efficient. Of course, the new technologies coming out of R&D and those for commercial application, such as antibody drug conjugates or disposable single-use technology, will present both opportunities and challenges. Lastly, preparing for the workforce of the future will need to be a top priority. Major trends will sweep across and radically change the landscape of workplaces and the makeup of the workforce. The industry will need to address issues such as the significant diversification of the workforce, requisite new skills, and the pervasive impact of growing globalization.

**Strategy is about choices and tradeoffs.**

## Closing

There was one recurring theme throughout our discussion, leadership. Schmukler has a deep passion for the subject. At times he speaks about it as a seasoned senior executive and others a business school professor. His primary view is that culture and performance are a direct reflection of leadership. So when it comes to improvement and change, leadership effectiveness is where you must start.

He articulated four traits he thought vital for future leaders: the ability to see the big picture, having change agility, adeptness at talent development and authentic leadership. He then described the leadership dimensions he regarded as crucial for the successful 21st century supply chain leadership team: the need for alignment, external focus, fast high-quality decision making, risk taking and experimentation and the ability to move horizontally and vertically across roles and levels. It was very clear that leadership development is a key focus for him and BMS.

Schmukler talks easily about his personal lessons learned and that both successes and mistakes have been equally valuable. In describing those lessons he references a Max DePree quote: "The first responsibility of a leader is to define reality. The last is to say thank you. In between, the leader is a servant." Exemplified in all his comments is a leader with a tremendous respect and admiration for his people. ■

## References

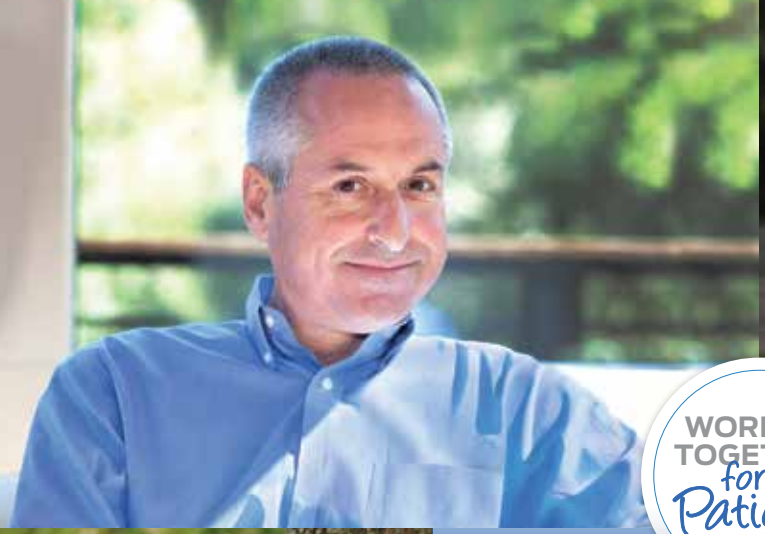

Thomas Ebel, Ulf Schrader, and Ketan Shah (2014). McKinsey & Company, Finding opportunity in uncertainty: *A new paradigm for pharmaceutical supply chains*.

Eric Langer (editor), (2015). BioPlan Associates, Inc., *12th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production: A Study of Biotherapeutic Developers and Contract Manufacturing Organizations*.

Roselinde Torres, Martin Reeves, and Claire Love (2010; updated 2014). Adaptive Leadership. *BCG Perspectives*.

Roselinde Torres, Nneka Rimmer (2011). The Five Traits of Highly Adaptive Leadership Teams. *BCG Perspectives*.

Joseph Defeo, and J. M. Juran (2010). Juran's Quality Handbook: *The Complete Guide to Performance Excellence*.



WORKING TOGETHER *for* Patients

At Bristol-Myers Squibb, we are working together for patients.

Our mission is clear—we discover, develop and deliver innovative medicines that help people prevail over serious diseases. And our sense of urgency is real—we work every day in every part of our company to make a meaningful difference in the lives of patients.

It's what we do. It's why we do it.

Visit **www.workingtogetherforpatients.com** and **www.bms.com** to learn more.

To learn more about the opportunity to change lives, including your own through a rewarding career at Bristol-Myers Squibb, visit **www.bms.com.**

Bristol-Myers Squibb

# How to Fight a Bully

## Compassionate Use Policy Offers Options When None Exist

Four years, five craniotomies, and 26 surgeries ago, Gavin Pierson was diagnosed with a rare condition: intracranial growing teratoma syndrome, a brain tumor that wouldn't stop growing. A short week after his tenth birthday on May 26, one final surgical intervention, the twenty-sixth, took a blade to all the years of suffering, and ablated the last of his tumor, Joe Bully.

*The Pierson family*

**The summer of 2016** is one Gavin Pierson will not soon forget: It is his first, cancer-free, in more than four years. His mother, Nicole Pierson, is an advocate for pediatric brain tumor research, and a guest author for Caring Bridge and Children's Hospitals of Minnesota. She is also a mathematics teacher with a master's degree in education and an education specialist degree in brain-based teaching. Her memoir, *Be Strong and Be Brave*, a memoir about Gavin's journey, will be published in August 2017. Nicole and her husband, Steve, live in Ramsey, Minnesota with their three children.

"The number-one reason Gavin is here today," says Nicole, "is because of his spirit and his faith: he has always said he would survive this. And we wondered how that was going to happen," she says, "but he just believed."

**When we told him, "Buddy, we have your Joe Bully medicine," his response was, "Let's do it. Let's get rid of Joe Bully."**

### A Last Resort for Dire Situations

"Compassionate use is very much viewed as a last-resort option for doctors and the patients they treat," explains Nicole. As both an advocate and a parent, she believes patients and their families need to be made aware of it by their team of doctors. "I was inquiring about different clinical trials, and doing research on my own, when I found an adult trial for growing teratoma syndrome," she says. Her aunt, Dr. Lisa Bishop, a pediatrician at the National Institutes of Health in Alina, Minnesota, gave Nicole access to medical journals and would "explain cellular processes to me."

That was in 2012. Nicole brought this information to the attention of her son's medical team, and they reacted very positively and suggested getting Gavin on a pediatric trial for the drug. A good idea, says Nicole, "but there

*Gavin Pierson*

weren't any. At that point, had I known about compassionate use, I would have asked for it."

Nicole and her husband Steve were told their son had run out of surgical options, and only had months to live, in January 2013. Gavin's surgeon, Dr. Joseph Petronio, told them, "I cannot cure this tumor." It was then that Nicole and Steve found out about compassionate use. "I wish it had been brought to my attention before that moment."

Dr. Kris Ann Schultz, the neuro-oncologist, immediately filed the necessary paperwork with Pfizer (the maker of palbociclib, the compound that Dr. Schultz was requesting be tried for Gavin), and submitted the biopsy results and application to the FDA. Within two weeks Dr. Schultz was notified of the approval.

During that two-week period of waiting, Gavin had said to his parents, "Mom and Dad, don't give up on me, I'm going to make it." Yet his conviction was put to the ultimate test once he was accepted as the first pediatric patient for Pfizer's experimental drug palbociclib, undergoing scientific evaluation in adults with a different type of tumor. "He wasn't concerned he'd be the first child to in the world to try palbociclib," says Nicole. "He trusted that we were looking out for him. When we told him, 'Buddy, we have your Joe Bully medicine,' his response was, 'Let's do it. Let's get rid of Joe Bully.' "

On February 6, 2013, Gavin received his first dose of palbociclib. Within weeks, his formerly fast-growing teratoma had stopped growing, allowing him time to recover from repeated brain surgeries. With this time, his neurosurgeon was able to acquire a minimally invasive laser technology that could access the tumor and ablate tissue.

# Pfizer's Compassionate Use Policy

*Pharmaceutical Engineering* spoke with Allyanna Anglim, a Pfizer spokeswoman, about compassionate use, and the role it has played in Gavin's life.

**PE: What is Pfizer's compassionate use policy and how does it work?**

**Pfizer:** Pfizer's policy on compassionate access, formally known as Pfizer's "Policy on Investigational or Unlicensed Product Use Outside of a Clinical Trial,"[1] describes basic circumstances each request must meet for it to be considered. There are three in all, which must be present:

1. The patient must have a diagnosis of a serious or immediately life-threatening disease or condition;
2. There are no available treatment options in the country of the request, or no remaining/untried treatment options; and
3. The patient is not eligible for participation in any ongoing clinical trial of the investigational drug.

For Pfizer to consider a compassionate access request, there must be scientific evidence to suggest that the drug might provide clinically meaningful benefit, in the patient's case.

It's important to note that the country regulatory agency, such as the FDA, has final approval of compassionate access requests. However, in many cases, regulators agree with a company's decision.

**PE: The challenges inherent in making those decisions must be great. Can you talk a little about the bigger ones Pfizer faces with each request?**

**Pfizer:** Last year, Pfizer received more than 1,000 compassionate use requests and approved the majority.

The biggest challenge is striking a just balance among four important factors: first, patient safety; second, the scientific evidence, as I mentioned earlier; third, we need to consider the impact approval may have on Pfizer's ability to carry on with clinical trials of the product requested; and finally, logistics preparedness to meet the request. We have to consider whether providing compassionate access to a single patient may hinder our potential ability to help greater numbers of patients.

**PE: What prompted Pfizer to approve Nicole Pierson's request?**

**Pfizer:** Pfizer approved Nicole Pierson's request because there was scientific evidence to suggest that the drug, palbociclib, might provide clinically meaningful benefit in treating the particular tumor type identified in Gavin's biopsy, and it met the requirements outlined in Pfizer's Compassionate Use policy.[1] Giving the drug to Gavin was not without potential risk: He was the first child in the country to receive it, and, as an investigational drug, we did not know palbociclib's full safety and effectiveness. And that is a risk we may incur with each request. The full medical rationale has since been documented in an article[2] published in 2015, by Wiley.

**PE: How can patients better avail themselves of this option?**

**Pfizer:** For patients who have a serious or life-threatening illness and who have tried all available treatment options, a next step may be to explore a clinical trial. If an appropriate trial isn't available, a treating physician may be able to request access to an investigational drug before it is approved through compassionate use or expanded access. That is what occurred in Gavin's case. Although Gavin's story, happily, has had a positive outcome so far, it's important for people to understand that there's no way to predict what the outcomes may be. It's not without risk, and each case is carefully reviewed by Pfizer scientific experts.

By law, treating physicians must submit compassionate access requests on behalf of a patient. Physicians can visit our request portal, PfizerCAReS.com, to submit a request or inquiry. At Pfizer, we have medical experts dedicated to ensuring that compassionate access requests are handled fast and fairly. We try to respond to requests as quickly as possible and commit to do so within five business days at most, and usually we respond much sooner. ■

"When I think back (to before), I felt so empty because I didn't know our son had any options or any chance to live," remembers Nicole. "The moment we found out he was accepted for compassionate use, I was filled with hope. After feeling we were losing, we were ready to fight again."

So was Gavin.

In the summer of 2016, Gavin relearned how to ride a bike, attended karate camps, and was able to finally get a reprieve from treatment. After many summers of hospitals and treatment, he was able to relax, enjoy his family, and just be a child.

Life, after Joe Bully, is good. ■

*Anna Maria di Giorgio*

## References


1. Pfizer Inc. "Policy on Investigational or Unlicensed Product Use Outside of a Clinical Trial." 1 October 2015. http://www.pfizer.com/research/research_clinical_trials/compassionate_access_policy
2. Schultz, Kris Ann, Joseph Petronio, Anne Bendel, Richard Paterson, MD, and David J, Vaughn. "PD 0332991 (Palbociclib) for Treatment of Pediatric Intracranial Growing Teratoma Syndrome." *Pediatric Blood & Cancer* 62, no. 6 (November 2014).

# The new world of patient engagement

McKinsey & Company, Pharmaceuticals & Medical Products, July 2016

The CEO of Acorda Therapeutics, Ron Cohen, explains how the biotechnology company's relationship with patients is changing and what that means.

How is the relationship between patients and pharma businesses changing? In this interview, Ron Cohen, the CEO of biotechnology company Acorda Therapeutics, explains how digitization is changing the nature of consumer engagement and how he has sought to embed new technologies and create a culture of risk taking within his organization. An edited transcript of the interview follows.

## Interview transcript

When I grew up in the industry, things were pretty well set in terms of how pharmaceutical companies engaged with patients—which is to say that you didn't engage all that much.

But now, for various reasons, that has changed. It's changed because various patient groups have insisted that it change—and rightly so. Today, patients are demanding more of a say in the type of care they get, the type of medicines that are being developed, how the medicines are going to be applied to them, and what the regulatory pathway should be.

When you put all this together, it's clear that there needs to be a brand-new level of deep engagement with the patients for your drugs, starting at the very early parts of development all the way through to commercialization and beyond. The good news is that all of this is coinciding with a revolution in digital technology and social media—in the ability to reach people with particular characteristics all over the world.

## Digitizing collaboration and engagement

At Acorda Therapeutics, we have been approaching this need to integrate the patient in a number of ways. One of them is not digital—one of them is good old-fashioned face-to-face engagement with patient groups and patient ambassadors. We can interact with them to learn about their needs and also educate them about what we're doing. Just because we have digital, it doesn't mean that there isn't a need for the other piece. In fact, you need them both to be successful.

A few years ago, I started a digital-innovation-and-strategy group at the company because it was clear that we could integrate digital into everything we were doing, including our internal operations, as well as our clinical development, our commercial marketing, and our drug development.

I engaged with the leadership team, such as the head of commercial, the head of clinical and medical, the head of R&D, and our internal creative staff—all the people who report to me. And over time, we identified the areas that we wanted to focus on. For example, the medical-affairs team engaged with the digital-strategy group to develop a way to integrate more closely with our patient community.

And so our group developed a self-health application called MS self, and it's one of the most popular apps now for the multiple-sclerosis community. Users can track various metrics about what's going on with their health—how they are walking, how they are thinking that day, what their diet is like, how much exercise they're getting, and so on. It has provided a tool for our patient community to use, and thousands of people have already downloaded the app. Second, they get to know Acorda, so we then have a contact point with the community.

## Embracing the digital vision

So it starts with the leadership. I believed this as CEO of the company. My job was to go and talk to the leadership team. And, yes, there was resistance. The commercial group, say, came out of the historical school of how you market a drug—for example, you take out advertisements in the journals. Digital was not part of their world as they grew as professionals and excelled and became executive vice presidents of commercial and chief commercial officers.

However, if you have the right people in the leadership on your teams, that shouldn't matter so much. Because if they're the right people, they are focused on "How can I get this job done the absolute best I can? And what tools are available, even if I've never used them before?" Because your job is always to think about how do we do it better. And if new tools come in, you better embrace those tools and try them and see if they'll work for you. Well, our chief commercial officer was willing to do that, and she made sure that her team was willing to do that.

You also need a culture that not only forgives failures and mistakes but embraces them and encourages risk taking. That sort of culture really helps when you're trying to get digital integrated.

## Setting up your digital team for success

For the first two years we had the digital-innovation-and-strategy group, I had the executive director report directly to me. When people see that something's important enough to the CEO that [a team is] reporting to him or her, they begin to pay attention. And furthermore, in those two years, I was able to craft the vision for what I wanted digital to do in the company together with the team, because it was reporting directly to me.

## Adopting a test-and-learn approach

The old saw about advertising is "I know half of my budget is wasted. I just don't know which half." Well, with digital marketing, we have, for example, much better ways of tracking the efficiency and effectiveness of the different concepts that we try online. And we've actually extended that into other areas in the company.

So, for example, we are now recruiting for our clinical studies with the help of digital marketing. We've taken the same multichannel techniques and we've turned them on to find people with a particular condition—let's say, Parkinson's disease or stroke—to inform them about the clinical trial. And then the individual can click through and figure out how to get into the trial. We've had hundreds of people call in to be in our trials as a result. This is something brand new.

So we can measure that, right? We launch a campaign, and then you see how many people are calling in. That's pretty clear. Even with our commercial efforts for our drug AMPYRA, we can try different campaigns and measure each channel used and the tweaks on each one. And you can track who's clicking through and what are they doing when they get there. Then we look to determine whether these behaviors are likely to predict an action that's beneficial. This means that patients will go and talk to their doctors about whether the drug is right for them. ■

*Ron Cohen is the president and CEO of Acorda Therapeutics. For more on how digitization is revolutionizing the relationship between patients and pharma and how companies can respond, see "Pharma 3D: Rewriting the script for marketing in the digital age," Pharma 3D, April 2016, pharma3d.com.*

# FOYA 2017

## Facility of the Year Awards

It's an exciting time in our industry. Thanks to your innovative designs, we're changing the way we work and deliver quality medicines to the people who need them.

**SUBMIT YOUR PROPOSAL TODAY.**

2017 Deadline: 21 November 2016

Innovation.
By Design.

www.facilityoftheyear.org

ISPE®

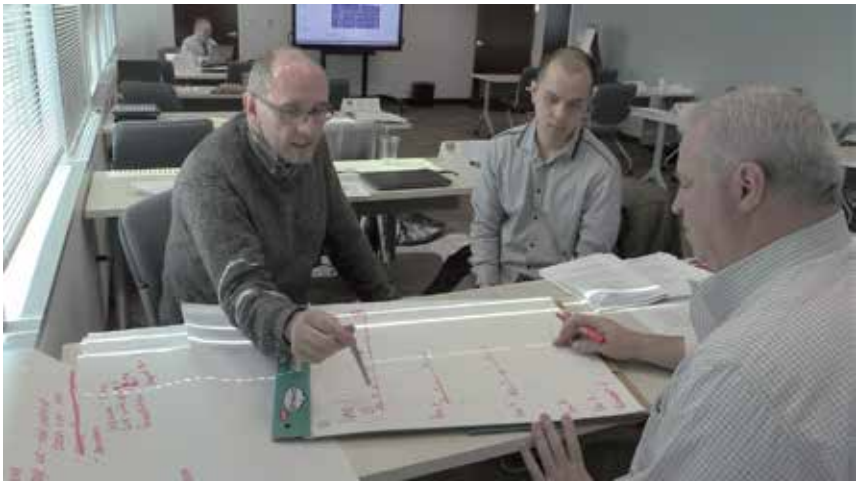
Also in this section



# ISPE Training Institute Marks First Anniversary

## Meeting Members' Needs at Home and Abroad

**After nearly 20 years, ISPE's robust body of knowledge has become the go-to resource for manufacturing professionals and regulators. But as regulations and manufacturing GMPs change with increasing speed, the pharmaceutical industry has seen a growing need for training and education. So how does the industry's best training get better?**



**The ISPE Training Institute opened its doors in 2015 and celebrates its first anniversary this fall**

"Adding a bricks-and-mortar facility not only offers an alternative learning experience, it firmly establishes ISPE's footprint in Tampa," says Alicia Montes, Senior Director of Training. The ISPE Training Institute opened its doors in 2015 and celebrates its first anniversary this fall. ISPE has been offering courses since 1998, online and in off-site locations.

Located within the ISPE offices in Tampa, Florida, the ISPE Training Institute offers Members more of what they have come to expect from ISPE: expert-facilitated training that helps industry meet its cGMP regulatory requirements and support Members' professional development goals. The ISPE Training Institute is well located, less than 3 miles from Tampa International Airport, with several hotels within walking distance.

High-tech amenities make teaching and learning even easier. "ISPE uses an interactive display system designed to provide smooth and effortless communication in a wide range of contexts," says Montes. "Using touch pens, for example, allows several people to write on the screen at the same time; the software also enables multifaceted wireless communication and promotes a more participant-centered teaching environment."

Randy Perez, an instructor who recently retired from Novartis, likes the setup. "The room was well appointed to support a collaborative atmosphere for the students," he told Pharmaceutical Engineering, "and it let me as an instructor foster an interactive session."

### Instructors Make the Difference

What makes ISPE's training (both content and facilities) so worthwhile? "The ISPE training classes are developed and delivered by people who work in the industry," says Kate Townsend, an instructor who teaches several GAMP courses, "so they have hands-on knowledge and experience. Sharing this knowledge with the audience

and facilitating discussions via workshops is what makes ISPE training so special."

Courses include lectures, group exercises, and case studies that provide tangible takeaways for on-the-job application. Students who took the HVAC course came away impressed: "The material and the way it was presented was very complete," says Elden Lainez, Facility Manager at Moderna Therapeutics.

Kevin LaPlante, Mechanical Engineer at Design Group Facility Solutions, says "The instructor kept the content interesting and encouraged lively discussions."

One government employee who attended the OSD course says she was impressed that the instructor was able to answer questions about her unique manufacturing niche. "Other participants in the class were excellent resources but they couldn't help with some of my more specific needs," she says, "The instructor's broad knowledge and experience was helpful and informative in these areas."

"This was an excellent broad overview that covered tablets and capsules. I couldn't find any other courses that covered both."

She also appreciated the course's comprehensive approach. "This was an excellent broad overview that covered tablets and capsules. I couldn't find any other courses that covered both."

Other students in the OSD course were equally pleased.

Coral Ramos, Manager, Global Quality Compliance SWAT at Mylan, says "I was very pleased with the outcome. It will help my knowledge of the area improve by understanding and applying what I learned."


Roberto Aponte, Manufacturing Product Quality Assurance–Program Manager at Takeda Pharmaceuticals took the Cleaning course. He liked the "small class and direct interaction with the speaker," and commended the instructor as "very knowledgeable and a good communicator" who kept the participants engaged. "She presented a lot of important details about the requirements needed in a cleaning validation protocol and specifications," he says, "and provided examples of the theory presented, so we could understand how it is useful and required. She answered questions in terms that we all understood. In summary, it was a very good seminar."

## GAMP® 5

Perez, a member of the global GAMP® Council Chair from 2013 to 2015, and ISPE Chair from 2011 to 2012, adds that instructor expertise is true for GAMP courses, as well. "They really know the material," he says, "and are able to discuss variables in a manner that fosters thoughtful consideration of the question."

Adam Lomas, Quality Lead at Nulogy who attended the Basic GAMP 5 course, praised the instructor's "incredible industry knowledge and the context-building that kind of experience allows."

Kip Kyprianou, Project Manager at Rhodes Technologies who took the Basic GAMP 5 course, agrees. "The instructor was a member of the global GAMP council and a core team member that led to the development of GAMP 5,"," he says. "That was really very helpful. I don't think we could have asked for a better instructor. Sometimes instructors in in other courses aren't as experienced."

His classmates also added value to the training. "Most participants were actively working in or had job functions that were related to the course," Kip says. "This allowed us to have really good discussions on the various aspects of GAMP."

But the best part of the course was what he took away with him: "confirmation that our approach to risk-based computer systems compliance is within broadly accepted industry guidelines and best practices."

When asked which 2017 GAMP courses he was looking forward to, Perez says the 2017 Data Integrity, Electronic Records and Signatures, and Operation of GxP Computerized Systems courses should be highly worthwhile. "It's a very hot topic for regulators and will benefit from the work that GAMP is currently putting into the guide under development. This guide should be available early next year and will be the best, most authoritative treatment of the subject as well as the basis for the ISPE course."

**For those who can't travel, ISPE brings its in-person courses to the big screen—your computer**

## A Global Footprint

In addition to the Training Institute courses in Tampa, in 2017 ISPE will also offer courses in San Diego, California; in Boston, Massachusetts; at NIBRT (National Institute for Bioprocessing Research and Training) in Dublin, Ireland; at the Institute of Technology Management at the University of St. Gallen (ITEM-HSG) in Switzerland; in Copenhagen, Denmark; in Manchester, UK; and in Amsterdam, Netherlands," Montes notes. For more information about ISPE Training, go www.ispe.org/training-courses. ■

*Amy R. Loerch*

## eLearning

For those who can't travel, ISPE brings its in-person courses to the big screen—your computer. ISPE's eLearning offerings now include more than 140 products, with continuing education units for each course taken. Find more information about ISPE eLearning at www.ispe.org/elearning.

**Expanded online training:** Many two-day classroom courses are now available online. These courses deliver the intensity of face-to-face training at your keyboard. Demo buttons let you preview a course: www.ispe.org/expanded-online-training-courses.

**Fundamental industry knowledge online courses:** Developed and reviewed by expert instructors and international regulatory advisors, these are designed to cover topics product development through manufacturing, help meet annual training requirements. Learn more at www.ispe.org/elearning/fundamental-industry-knowledge-online-courses.

**General industry knowledge courses** provide industry overviews, historical background to understand more advanced and specific industry topics. See course offerings at: http://www.ispe.org/elearning/general-knowledge-online-courses

**GMP training on the US FDA's systems-based GMP inspection approach:** GMP compliance is widely accepted as the best way to conduct business, putting product quality first. See the course offerings at www.ispe.org/gmp-online-training-courses.

**Webinars** span 20 topics pertinent to global pharmaceutical manufacturing professionals and provide in-depth knowledge to share best practices. Find case studies with in-depth knowledge as well as best practices from seminars and ISPE Guidance Document authors. See what's available at www.ispe.org/webinars.

# Japan Affiliate Annual Meeting Focused on New Manufacturing Trends

*Hiroshi Yamaguchi*

*David Churchward , MHRA Expert GMDP Inspector*

*Dr. Daniel (Yingxu) Peng, Lead Chemist in the US FDA Office of Pharmaceutical Quality*

*Dr. Masayuki Mitsuka, President, Mitsubishi Tanabe Pharma Corporation*

**Since its founding in 2002,** ISPE's Japan Affiliate has been a source of global information for the country's pharmaceutical community. The Affiliate held its fourteenth annual meeting, focused on Manufacturing Trends "Beyond the New Horizon" on 14–15 April in Tower Hall Funabori, Tokyo. The meeting, which drew about 400 participants, featured presentations from regulators and industry leaders from Japan, US, and Europe, as well a series of workshops.

## Day 1: Presentations

**Mr. Shigeru Nakamura**, Chair of ISPE Japan opened the meeting by stating that the Affiliate's goal in 2016 is to further broaden and deepen ISPE Japan activities. He said that " more" is the keyword in executing this plan. Mr. Nakamura revealed that there would be eight planned Young Professional seminars this year as part of an ongoing effort to develop talent and networking. He also outlined various measures to send more intelligence and information from the Japan Affiliate to ISPE's global audience. He closed with a commitment to address more of members' requests.

**Dr. Masayuki Mitsuka**, President of Mitsubishi Tanabe Pharma Corporation, presented "Becoming the First to Deliver Differentiated Value" on the drugs of the future and his company's strategic direction. In his lecture, he commented that global market and technology trends mean that we are now subject to significant changes, both overseas and domestically.

**Dr. Naoyuki Yasuda**, Office Director, Office of International Programs, Pharmaceutical and Medical Device Agency (PMDA), discussed the agency's regulatory science initiative, outlined measures PMDA has taken to resolve drug shortages, and discussed key goals described in the 2015 PMDA International Strategic Plan. He also explained PMDA's strategic intent to contribute to an international regulatory environment that leads to future regulatory harmonization.

**Dr. Theodora Kourti**, Senior Vice President, Global Regulatory Affairs, ISPE, reviewed the current status of continuous manufacturing (CM), discussing technical and regulatory considerations, and the hidden traps when developing the control strategy in CM.

Dr. Kourti also discussed CM in relation to:

- US Food and Drug Administration's (FDA) Emerging Technologies Team and European Medicines Agency's (EMA) Innovation Task Force
- FDA's breakthrough therapy designation and EMA's priority medicines (PRIME) scheme
- Drug shortages

**Mr. David Churchward,** Expert GMDP Inspector at Medicines & Healthcare Products Regulatory Agency (MHRA) presented "Regulatory Developments in Data Integrity: Trends and Strategy for a Global Supply Chain." Mr. Churchward discussed harmonization, trends, and strategy on the international hot topic of data Integrity. He explained the influence of organizational behavior and risk management on the success of data integrity controls in the context of a company's quality system and supply chain partnerships.

He also spoke about the evolution of existing international good manufacturing practice (GMP) requirements, referring to data integrity guidance published by MHRA and the World Health Organization in 2015. He also shared his experience as an inspector about issues that continue to challenge the industry.

**Dr. Daniel (Yingxu) Peng,** Lead Chemist in the US FDA Office of Pharmaceutical Quality, began by defining and identifying the driving force for product and process robustness, then discussed strategies to achieve them. He also presented some useful tools for evaluating and monitoring the state of robustness, including control charts and process capability analysis.

## Day 2: Workshops

### Regulatory Committee

Under the banner of "ICH Harmonization and Japan's Globalization," this workshop featured a series of lectures followed by a panel discussion.

The first four lecturers, one of whom was the Q12 Implementation Working Group topic leader, discussed ICH harmonization, particularly devel-

*Dr. Naoyuki Yasuda, Office Director, PMDA*

*Dr. Theodora Kourti, Senior Vice President, Global Regulatory Affairs, ISPE*

opment of quality guidelines, and recent topics about QICH 12. The next section discussed PMDA's globalization initiative both from inspection and examination perspectives. The final part discussed issues of life cycle management, expectations on Q12, and the current status and future possibilities of continuous manufacturing, which could affect life cycle management.

Following these presentations, the speakers participated in a panel discussion about Q12 and Q3D. The conversation that followed noted that Q12 described differences in regulations as the differences in change process, and these do not hinder the development of guidelines. Once established conditions (ECs) are agreed upon, implementations can be straightforward. Japanese approval points can be regarded as ECs in a Q12 framework. Further discussion focused on implementing Q3D domestically in Japan, as it is being discussed by the pharmacopeia committee. Because immediate pharmacopeia change would generate confusion, parallel adoption of ICH and Japan pharmacopeia is being contemplated.

This workshop, which sparked very active discussions, helped share a great deal of current information about Q12 and other topics, and greatly enhanced expectations on the globalization of the Japanese pharmaceutical industry.

**Dr. Toru Kawanishi**, Director General, National Institute of Health Sciences, closed the workshop with a closing address.

### CoP Workshops

Five CoPs held workshops on the second day of the meeting. Each featured intense discussions and were active forums for technology information exchanges.

- Sterile Products Processing (SPP) CoP: Issues of RABS [restricted-barrier access systems], Isolators, and HEPA filters
- Containment CoP: Risk-based Approach for Handling Pharmaceutical and Chemical Products
- Pharmaceutical Process Systems Engineering (Pharma PSE) CoP: Pharma PSE for realizing "Excellence by Design"
- Investigational Products (IP) CoP: A New Era for Clinical Supply—Enhancing Globalization in Japan
- Workshop for Young Professionals: Engineering and Validation Activity Applied for Risk-Based Approach and Group Work

## Japan Affiliate CoPs

The Japan Affiliate has 16 active CoPs with a total of 520 members. Given the total Affiliate membership of 850, this represents an impressive rate of involvement.

### Manufacturing Management

*Kentaro Fujii, Marusan Pharma Biotech Corporation*

One of Japan's unique CoPs, the MM CoP was established in 2009. The group improved the GMP pest control standards in pharmaceutical plants with the publication of the *Pest Control Handbook*, published in 2010. It became a best-seller and broke downloading records. The *Pest Control Maintenance Guide*, published the following year, helped Japan win the 2011 Affiliate of the Year Award.

Following the Fukushima earthquake of 2011, the CoP also developed business continuity planning strategies and countermeasures for human error at pharmaceutical plants. Both were presented in workshops at the Affiliate's tenth annual meeting

### Investigational Products

*Zene Matsumoto, Manager, Head of Quality Control, Production & Supply Chain, Saitama, UCB Japan Co., Ltd.*

The IP CoP was established in May 2008 to create best practices in clinical supply activities by identifying similarities and gaps between best practices in Japan, the United States, European Union (EU), and China. The CoP has three activities:

- Challenge interaction to PIC/S GMP on blinding randomization of IP under Japanese good clinical practice.
- Establishing IP good distribution practice (GDP) in Japan.
- Site and patient survey of current clinical supplies and material usage. During the 2016 annual meeting in 2016, the Japan Affiliate invited IP CoP members from the China, EU, and US to discuss a patient-centric approach to clinical studies. In 2013 the CoP translated and published the "Comprehensive Guide to Clinical Materials (A Handbook for Training Clinical Materials Professionals)."

*–continued on next page*

## The Japan Affiliate has 16 active CoPs with a total of 520 members

*Shigeru Nakamura, President of ISPE Japan (left), Mr. M Arnold (center)*

*Regulatory Committee panel members*

### Packaging

*Makoto Saotome, GlaxoSmithKline K.K.*

The Packaging CoP is comprised of professionals from the pharmaceutical and engineering industries, as well as equipment suppliers and consultants working in the area of packaging.

The CoP initially focused on understanding the guidelines in the *ISPE Good Practice Guide: Packaging, Labeling, and Warehousing Facilities* (PACLAW). After publishing a Japanese version of the guide, the CoP conducted a seminar in July 2014 to introduce the PACLAW concept and share information on the latest packaging technology.

While the pace of activities in the CoP has slowed at the moment, we are exploring topics on packaging technologies and best practices that would provide opportunities for members to learn from.

### Active Pharmaceutical Ingredients

*Akira Kunimatsu, Yonezawa Hamari Chemicals, Ltd.*

The API CoP was established in 2003 on the occasion of the *API Baseline® Guide* revision; the group published a Japanese version of the second edition in 2007. Today, 28 members are involved in activities such as studying and disseminating the guide, collecting and sharing up-to-date information, and establishing interpersonal networks. Recent activities include seminars on API life cycle management, a technical salon and free discussion space for hot issues on API, facility tours as case studies for the Baseline® Guide, and monthly face-to-face discussions. In the last three years, these activities and discussions have led us to the 2016 publication of a mockup design of an API multi-purpose manufacturing facility, including "HMCIN," a virtual API.

### Oral Solid Dosage

*Yuichi Miura, Senior Manager, DAI-DAN Co., Ltd.*

In the OSD CoP, members discuss predesignated topics and help each other enhance related knowledge and insights. Topics include interpretations of various regulations, history and future outlook of production automation, and design principles of HVAC.

### Scientific Approach to Manufacturing & Good Manufacturing Practice

*Fumio Kishimoto, Shin Nippon Yakugyo Co., Ltd.*

The SAM&GMP CoP was established in April 2014 as a Japanese original CoP. We have activities on:

- API life cycle management
- New regulatory guidelines
- Translation of Baseline Guides and Good Practice Guides
- SAM & GMP conference facility visits
- Education seminars

In collaboration with the API CoP, for example, we have been investigating life cycle management case studies of "HMCIN," a virtual API, and have also undertaken a comparative study of EU, US, and Japan process validation guidelines. The study achievements were presented at a 2015 Japan Affiliate Annual Meeting workshop and a series of "API Lifecycle Management Seminars" in Tokyo, Yamaguchi, Shizuoka, and Osaka. Ongoing case studies include continuous process verification, cleaning validation, and other API life cycle activities. We translated the *ISPE Good Practice Guide: Technology Transfer* second edition into Japanese and published the e-book in January 2016.

### Biopharmaceuticals

*Sei Murakami*

The Biopharmaceuticals CoP was organized in 2006 to discuss biopharmaceutical manufacturing technologies and propose meaningful insight into the biopharmaceutical industry. The CoP's 24 current members have backgrounds and expertise in biopharma R&D; production; chemistry, manufacturing, and controls; and plant engineering and equipment manufacturing.

In April 2009 the Biopharma CoP integrated with the ASME-BPE CoP. Major activities and achievements include:

- Translating the 2006 and 2014 *Biopharmaceutical Manufacturing Facilities Baseline Guides* into Japanese and adding Japan-specific notation.
- Organize biopharma manufacturing seminars involving ISPE Baseline Guide topics.
- Provide Japanese perspective to each ASME-BPE standard revision.
- Translating "A-Mab: A Case Study in Bioprocess Development" into Japanese.

- Submitting public comments to the Japanese government's biopharma-related regulation proposals.
- Contributing to the article "Approaches to Quality Risk Management When Using Single-Use Systems in the Manufacture of Biologics" (*AAPS PharmSciTech* 16, no. 5, October 2015).

### Pharmaceutical Sterile Products Processing

*Koji Kawasaki, President, Airex Co.,Ltd.*

This CoP comprises about 75 active members drawn from both industry (pharma firms, engineering companies and equipment supplier) and academia (including PMDA). Our mission is to share awareness of what is going on in global GMP, especially in sterile products processing. We mainly collect and interpret new and revised EU and US GMP guidelines to improve our understanding of SPP issues via monthly Q&A sessions and face-to-face discussions on several kinds of topics.

We also have also four other projects:

- Environmental monitoring and risk-based approach
- RABS: the ideal state, which can be recommended by the SPP CoP
- Study of single-use technology from the engineering point of view
- HEPA filter testing methods, including suitable air velocity and air-flow measurements

### Containment

*Morihiko Takeda*

The Containment CoP provides a forum those involved in the safety of patients and people from exposure, contamination, and cross-contamination of hazardous compounds. We interact with all appropriate stakeholders to share, influence, and change knowledge, guidance, and regulations for the good of all.

Our activities:

- Disseminate *ISPE Baseline Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)* concepts for product quality and flexible use of manufacturing assets in the Japanese pharmaceutical industry and regulatory agency. We have translated the guides and held some seminars for Risk MaPP or setting acceptable daily exposures.

*Note:* Risk-MaPP provides a scientific risk-based approach based on ICH Q9 for setting health based cross-contamination, cleaning validation, and operator safety limits. These limits drive the risk controls that are implemented on case-by-case bases to maintain product quality and operator safety.

- To provide scientific information on risk-based manufacturing for highly potent products, we have introduced risk-assessment methods for industrial hygiene and preventing cross-contamination using FMEA sheets, classification of containment systems, and the physical properties of surrogates, as described in *Assessing the Particulate Containment Performance of Pharmaceutical Equipment Good Practice*

*Guide* or the pharmaceutical equipment exposure measurement database.

## Process Analytical Technology

*Munetaka Hattori*

Established in 2004, the PAT CoP's initial was to evaluate PAT tools, mainly near-infrared spectroscopy. After this initial study, we developed how to describe PAT on the common technical document before EMA issued a Reflection Paper on this theme in 2006; some results were reflected in the ISPE Product Quality Lifecycle Implementation® guidance documents.

Recent studies have shifted our focus to newly developed PAT tools, such as testing incoming raw materials outside of paper containers, predicting drug release from modified-release film-coated tablets based on the thickness and density of coated film, and assay of low-dose formulations. We will disclose the results of those studies at future Japan Affiliate meetings.

## Commissioning and Qualification

*Tadashi Inatani, Engineering, Planning and Administration, Technology, Astellas Pharma Inc.*

The C&Q CoP aims to achieve effective and efficient risk-based C&Q approaches in compliance with related regulations and guidelines.

C&Q CoP activities are:

- Investigate pharmaceutical engineering and risk-based C&Q activity flow
- Investigate practical activities for user requirement specifications, risk assessment, design review/design qualification, and verification (acceptance tests and qualifications).
- Case study of a risk-based C&Q approach for drug substance manufacturing process

## Engineering Management

*Koichi Miyake, Deputy General Manager, Obayashi Corporation*

During pharmaceutical facility engineering and construction projects, the ordering party and contractor sometimes understand the scope of work, specifications, and contract conditions differently. To remove or minimize these misunderstandings, the EM CoP was established in 2006. We research and analyze these gaps in understanding, and discuss how to resolve the issues that account for them. The CoP currently consists of 51 members and two groups: one focused on project turnover and the other on a Japanese translation of *ISPE Baseline Volume 4: Water and Steam Systems*, 2nd edition.

## Maintenance

*Yohei Hayashi, Azbil Corporation*

Maintenance directly affects pharmaceutical quality, supply, and cost It is also associated with:

- Maintenance personnel management and training
- Management of suppliers and partner companies
- Improving cost reduction, trouble reduction, and operational efficiency

The Maintenance CoP aims to strengthen the competitiveness of various sites, in addition to complying with relevant regulations.

Current investigations are:

- Maintenance program
- Risk-based approach in maintenance
- Risk-based approach in calibration

## GAMP®

*Hirokazu Hasegawa*

The Japan GAMP Forum was established in January 2003 as a special interest group (SIG) to study computerized system validation (CSV). In the years since then, it has translated various documents and references, including *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*. In 2016, five new SIGs were established:

- SIG 1: Translation of QC laboratory system and GAMP® Good Practice Guide
- SIG 2: CSV for GDP
- SIG 3: Applying GAMP® 5 for CSV in GCP
- SIG 4: Quality risk management to apply CSV effectively during project phase
- SIG 5: Electronic signature guidance and compliance

## Tissue Engineering and Regenerative Medicine

*Seiji Takahashi, Life Scientia Ltd.*

TERM, the Japan Affiliate's newest CoP was established in September 2015. Its mission is to contribute to the life science industry and international society by researching state-of-the-art technologies as well as the global regulations and standards and practices applied to regenerative medicines. We currently have 19 members and hold a meeting on the fourth Thursday of each month at the ISPE Japan office. To accelerate our activities, we have organized two study groups: One is for investigating regenerative medicine manufacturing processes, and the other is for interpreting applicable regulations. We hope to present our research results at the next of Japan Affiliate Annual Meeting.

## Pharmaceutical Process Systems Engineering

*Hirokazu Sugiyama, Associate Professor, The University of Tokyo*

This new CoP aims to practice the concepts and methodologies of Pharma PSE in drug development and manufacturing. Pharma PSE is an academic discipline that our leader, H. Sugiyama, has been developing in the field of chemical engineering since 2013. Since its initiation in 2015, the CoP has deployed four projects:

- Process design systematization
- Business process improvement
- Comparison of single- and multi-use technologies
- Systems approaches for unused medicine

Our initial results were presented at the Japan Affiliate 2016 Annual Meeting. The CoP numbers around 30 active members from both industry and academia. ■

# ISPE Ireland YPs Host Summer Seminar and BBQ

*Joseph Hanna*
*All photos by Kinlan Photography*

*Joseph Hanna*

**I am currently working on placement** in Mylan (Dublin, Ireland) and preparing for the final year of my chemical engineering degree at UCD (University College Dublin). As well as focusing on academic development, I am also using this time to seek out as much industry experience as possible. I have found one of the most rewarding ways to be through learning from those around me, as this placement is affording me the opportunity to be exposed to excellent people who are clearly achieving great things in the pharmaceutical industry.

Learning about possibilities for career progression is one thing, however, looking at those in senior roles here is also teaching me about the personal skills and attributes that are vital in taking your career to the next level. In my search for connection with like-minded students and professionals, I found the ISPE Ireland Young Professionals (YPs). It is a branch of the Irish Affiliate of the International Society for Pharmaceutical Engineering. The group aims to bring together those who are planning to or have recently started to work in the pharma sector in Ireland. I took the plunge and attended my first YP event in June: the inaugural summer seminar and BBQ entitled "Reading the Trend: Pathways to Success."

*Lynn Gallagher (Pfizer)*

format always includes speakers who are experts in the topic as well as time to network with other attendees. This style of event aims to fulfil the mission statement of the ISPE Ireland YP group which is:

> *To create a welcoming, comfortable environment at all levels of ISPE wherein young professionals have unrestricted opportunities to network with peers, mentors, and other professionals, gain fundamental and advanced knowledge about the industry and their areas of professional interest, and grow their skills as needed to become industry professionals and the ISPE leaders of tomorrow.*

The June event took place in the trendy glass-clad Gibson Hotel in the Docklands of Dublin City, Ireland. Four industry leaders at the forefront of major recent investments into the pharmaceutical industry in Ireland, from global concept to local construction, gave an insight into these projects as well as into their own individual career paths. In addition, the speakers were asked to offer the YP audience one piece of advice, insight, or inspiration that they themselves would have found beneficial when progressing through the early stages of a career in the pharmaceutical sector.

The format of the sessions saw George Francis (Senior Director of EMEA Engineering at Mylan), Lynn Gallagher (Manager of Technical Services, Pfizer), Ciarán Grimes (Senior Program Manager at Shire) and John Deasy (Process Engineering Manager, Bristol-Myers Squibb) each present for thirty minutes, followed by an energetic Q&A session with the YP audience.

This was the Ireland Affiliate's largest Young Professionals event to date, with 96 people registering and 30 different companies represented that evening. The event was free to attend and was supported by three cosponsors, namely the engineering companies Jacobs, Sisk, and M+W Group.

One of the main things that struck me about each of the speakers was the number and diversity of roles through which they had progressed in a relatively short period of time to reach their current positions.

Lynn Gallagher began her career in contract validation after she obtained her degree in science from Trinity College Dublin. Lynn is now a Manager of Technical Services. George Francis started his career as a trainee accountant before taking on the role of a building services engineer. George is now the Senior Director of Global Engineering at Mylan. The trajectory experienced by the speakers was well depicted by John Deasy when he told the audience that he "hadn't spent more than 24 months on a single project over the last 14 years."

## The event was enormously interesting, enjoyable, and hugely beneficial

It was clear to me that with rapid role changes early on in your career comes an opportunity to get a better understanding and different perspective on a broad variety of projects. This opportunity probably reduces as your career progresses and you become more focused on one specific area or subject matter. However, one of the greatest benefits of quick progression and role changes seems to be the exposure to such a range of different projects and environments, allowing you to learn what areas you are really passionate about.

It would appear, from the experiences of our guests, that throughout a professional career we will all reach a point where a tough decision will have to be made. For Lynn Gallagher, this was "taking the plunge" into the drug product area of her career and for George Francis this was taking a job in France when he had two young children back home in Ireland.

George Francis and Ciarán Grimes both referred to that period in your career where you become comfortable in your environment, working with the same familiar processes and same familiar faces. If you really want to reach your full potential as a professional, this is the time to make the tough decision, take the plunge, and begin a new project. Although new projects bring along new experiences and challenges, which may be uncomfortable, demanding, and frustrating at times, this is when you are learning, adapting, and improvising at a maximum, which will enhance your professional growth no matter where your career path leads you.

*Left to right: Anne-Marie Murphy (Crest Solutions), Dermot McMorrow (SL Controls), James McSweeney (Pfizer), Samusideen Ogunyemi (ESP), Paul O'Sullivan (University College Dublin), Stephen Ferguson (University College Dublin), Conor Eighan (Prochem), and John Clarke (Pfizer)*

Ciarán Grimes began his speech with an exuberant reenactment of the best goal he ever scored, in which he described in detail all the steps up to his shot. This sporting analogy successfully made the point that you perform at your very best when you "play to your own strengths and those of your team members for a common goal." He urged the audience to take the time to establish their own aptitudes as individuals by applying themselves to the job at hand and continuously learning from assignments, to discover what they enjoy working at. John Deasy firmly believes in developing people and their attitudes. He said that when you have a team of people that have positive attitude towards the challenges that they themselves and their team face, it makes the task half the problem it could pose.

George Francis had a rather simple but extremely important piece of advice. He told us not to chase the money, not to chase the certificates, but to chase our passion. Once we do this we will enjoy a long, satisfying, and successful career.

Following the seminar, the inaugural ISPE Ireland Summer BBQ took place on the hotel's rooftop terrace, which gave everyone an opportunity to meet and network with others, speak one-to-one with the industry leaders, meet the ISPE Ireland YP committee members to learn about becoming more involved—and of course enjoy some good food!

*Left to right: George Francis (Mylan), Ciarán Grimes (Shire), and John Deasy (Bristol Myers Squibb)*

*Left to right: Conan Mulraine, George Francis, Kealan Reid, and Joseph Hanna (all Mylan)*

The ISPE Ireland YP committee members actively encouraged everyone to network, and I found this section of the evening particularly enjoyable. Everyone welcomed the opportunity to break the ice and get to know some new faces. People conversed and shared their own experiences, prompted by the guest speakers' contributions earlier. It should never be underestimated how important networking is from the very beginning and throughout your entire career. A friendly welcoming environment such as this provides a rich and fertile ground for the exchange and sharing of ideas. It also provides an opportunity to meet with old acquaintances as well as developing new ones. Plenty of contact details were exchanged and new LinkedIn connections made on smartphones by people at the event.

Overall, the event was enormously interesting, enjoyable, and hugely beneficial. I would highly recommend getting involved in a YP group in your region. If there is none yet established, why not start one?! I'm sure the folks at YP Ireland would be happy to give some pointers to get you started. Also, don't let the title "YP" put you off! This group is ideal for anyone who is embarking on a career in the pharmaceutical sector, regardless of previous experience. The group will provide you with the ideal opportunity to meet, share, learn, and develop with like-minded professionals at all stages of their careers in the pharmaceutical industry. ■

*The next ISPE Ireland YP event will run in November 2016. To add your name to the group's mailing list and/or find out more about the ISPE Ireland YPs, drop an email to Caroline Rocks at YPsireland@ispe.org.*

## Acknowledgements

*Many thanks to Anne-Marie Murphy of Crest Solutions for her help and input toward the final article.*

## About the Author

**Joseph Hanna** is a new member of the ISPE Ireland Young Professionals group. Joseph is a fourth-year student in the BSc programme in chemical and bioprocessing engineering at University College Dublin and is currently undertaking an internship programme at Mylan Ireland, one of the world's leading global pharmaceutical companies.

# Hot Off the Presses

## Good Practice Guide for Management of Engineering Standards

Harmonization may not be a new idea, yet it is one that demands rigorous attention in today's global, diverse, and highly regulated landscape.

ISPE has just released the *Good Practice Guide for Management of Engineering Standards*, which presents tried and tested methods for establishing and managing standards, and implementing them across a pharmaceutical/biopharmaceutical organization. Additionally, the 52-page guide identifies processes for keeping content current and compliant through periodic review, and success factors for integration with third-party designers/integrators.

An engineering standards program provides peace of mind to professionals, by helping to assure that their facilities and processes worldwide are in compliance with a given regulatory environment.

"ISPE's intention in creating this Good Practice Guide is to provide a common understanding and approach to the management of engineering standards, typically set at the corporate level, for manufactures, designers, and builders of pharmaceutical plants and processes," explains Wendy Sturley, Vice President, Marketing, Communications, and Membership.

Designed as a compilation of best practices developed with input from peer organizations, the *ISPE Good Practice Guide for Management of Engineering Standards* addresses a broad variety of themes, subjects, problems, and issues in pharmaceutical design, maintenance, and operation. The Guide is intended to be read in conjunction with other ISPE guidance, International Council for Harmonisation (ICH) guidelines, and industry recognized standards. Although written for engineering standards programs, its principles also apply to other document types.

The Guide describes how best to set up and govern a standardization program and also offers tools and templates to help to create engineering standards. As a reference tool, it can be used daily to inform SMEs or project owners on the process used to manage engineering standards.


The *ISPE Good Practice Guide for Management of Engineering Standards* is written by and for professionals who work with standards within a pharmaceutical/biopharmaceutical organization, across all levels. Its key concepts include governance, maintenance and application of engineering standards as well as understanding who your organizational sponsor should be, and where your engineering standards fall in your document hierarchy.

To order your copy today, visit http://www.ispe.org/ispe-good-practice-guides/management-engineering-standards. ■

# Appointments

*Mark E. Hernick*

### Chief Financial Officer and Vice President of Administration

A veteran financial executive with over 20 years' progressive experience in for-profit and not-for-profit organizations, Mark E. Hernick is ISPE's new Chief Financial Officer and Vice President of Administration.

"I'm honored to have been selected for the position," he told *Pharmaceutical Engineering*, "and I look forward to collaborating with the talented leaders, members, and staff at ISPE to continue their outstanding scientific, technical and regulatory work across the entire pharmaceutical lifecycle."

Mark comes to the ISPE from the American Geophysical Union (AGU), where he served as CFO for more than seven years and was directly responsible for safeguarding the organization's $100 million in assets. Mark lead the AGU's $30 million "net zero" building renovation project, and served as executive liaison to the organization's board of governors on matters relating to audit, budget, business model analysis, financial forecasting, investments, and the legal affairs committee. His many accomplishments include a proven track record of increasing revenues, cost analysis and reduction, improving process efficiency, and raising member/partner satisfaction levels.

He previously served as vice president of operations and director of finance at the American Land Title Association, where over an eight-year period his responsibilities included oversight of finance, human resource, meetings, membership, information technology, marketing, fundraising, research, and communication programs. Mark received a master's degree in financial management in 2002, and a bachelor's degree in accounting in 1993, both from the University of Maryland, University College. He became a member of the Maryland Society of Accountants in 1991, and is an active member of the American Society of Association Executives member where he earned the Certified Association Executive (CAE) designation in 2014.

Mark has a passion for aviation and is a veteran of the United States Navy, where he served as a naval air crewman for 11 years. He later earned his private pilot's license and currently flies Cessna 172s recreationally. Mark is an avid runner and biker and has completed multiple sprint triathlons. ■

# THE MAIN EVENT
## FOR LIFECYCLE SOLUTIONS

PHARMA EXPO™

**Processing & Packaging Conference and Tradeshow**

November 6–9, 2016 • Chicago, Illinois USA

JOINT VENTURE

PMMI ISPE

### More answers for every production question.

With the safety, security and quality of your products on the line, you need to be sure you will find the right solutions.

At Pharma EXPO 2016, you will see all of today's most advanced machinery in action—technologies from **more than 250 exhibitors**—and learn about industry best practices from experts in a world-class conference program.

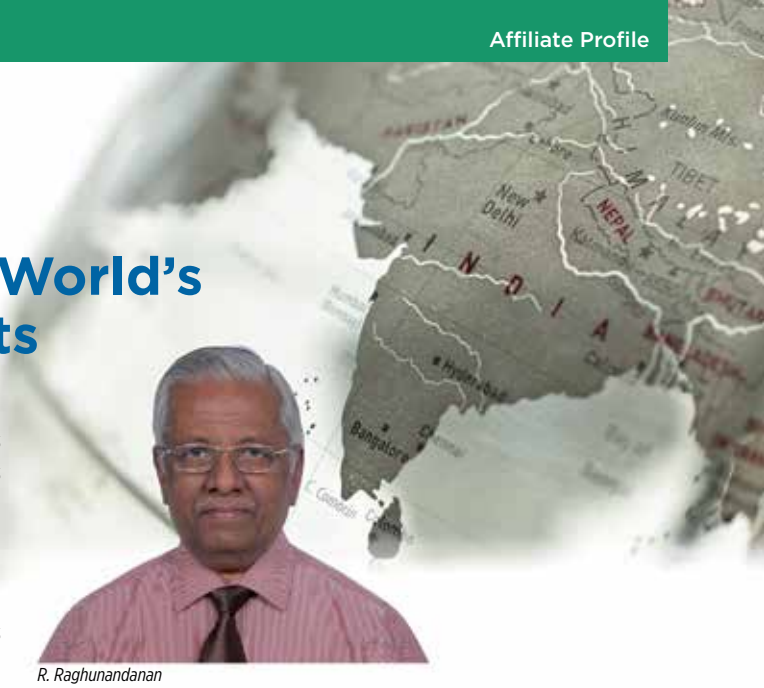
**Don't miss it—November 6–9 2016.**

**Register today at pharmaexpo.com**

Co-located with: PACK EXPO® INTERNATIONAL

Produced by: PMMI

# ISPE India Affiliate: Supporting One of the World's Leading Pharma Markets




*R. Raghunandanan*

**For the global pharmaceutical industry,** there is little doubt that India is recognized as a powerhouse. In terms of production volume, India ranks third in the world and fourteenth in terms of value. It is one of the fastest growing pharmaceutical markets in the world, with a domestic market valued at almost $14 billion. And according to ISPE India Affiliate Chairman, R. Raghunandanan, the Indian pharma industry will need experienced leadership from individuals and associations like ISPE to help work out the issues that inevitably come with growth.

## ISPE's History in India

The ISPE India Affiliate was founded through the notable efforts of Ajit Singh, founder and Chairman of the India-based company ACG Worldwide, one of the world's largest hard-gelatin capsule manufacturing firms, along with senior management at ISPE. Today, the Affiliate's headquarters are located in India's financial capital, Mumbai. An office is provided by Singh's company, where an Affiliate Manager and one assistant manage the Affiliate's daily business.

Over the years, the Affiliate has grown to serve the pharmaceutical industry in all parts of the country. Over the last five years, three Chapters were formed, each in an area considered a pharmaceutical hub: the first and largest was formed in 2010 in Hyderabad, a city in the south of India where there is a conglomeration of several API companies; a second in 2013 in Ahmedabad, which is located in northern India and is home to many large pharmaceutical companies; and also in 2013, a third in Bangalore, located in the south, home to a number of pharmaceutical companies and several pharmacy colleges. The Affiliate also has a Student Chapter, which they are hoping to expand.

The Affiliate is currently led by Raghunandanan, an industry veteran who worked 35 years at GlaxoSmithKline, and where until his retirement he was Vice President, Quality for the South Asian region. Now 69, Raghunandanan has spent the last 10 years as a freelance pharmaceutical consultant. He joined ISPE 12 years ago and became Chairman of the India Affiliate in 2014.

"My two-year term as Chairman comes to an end in August 2016," says Raghunandanan. "We will have an annual general body meeting where the new Chairman will take over. By convention, the Vice Chairman will step into the role of Chairman and I will continue to be a Board member."

## Looking for Membership Stability and Growth

With membership currently hovering around 300, Raghunandanan admits it is not at the level he would like to see. As with other Chapters and Affiliates around the world, the India Affiliate has experienced membership surge as high as 500 members, only to fall back again. "Two years back, when we would conduct our annual conference, any nonmembers attending the conference got a membership along with their conference fee," he explains. "However, it was only for 12 months and these people often didn't renew it, so our numbers would unfortunately go down." The Affiliate has since stopped the practice and no longer takes any extra membership fee for the annual conference.

"One of the big challenges we are facing is to attract more members," he says. "Annual membership fees are approximately 8,000 Indian rupees (approximately $120), which is not a very small amount for the people in India because the middle mid- or lower-level managers may find it difficult, and not all of the companies are reimbursing their membership fees. That could be a reason why our membership is not going up." Annual membership fees of 8,000 rupees represent almost a quarter of an average worker's monthly take-home paycheck.

**The main objective of the Affiliate is to provide knowledge sharing and networking opportunities**

Still, Raghunandanan remains optimistic. "If people really want to take the benefit of what ISPE can provide, and that's what we are telling people, then it is worth paying this money because you have a lot of knowledge there. During our annual conference, we have a 20-minute session on why they should become a member, what membership means, what the benefits of membership are, and the knowledge that is available with ISPE."

ISPE India is not alone in the search for attracting and retaining new members. "People go to work in the morning, and including their travel time, they work for 12 hours each day and most only get Sunday off, so they work 6 days per week," says Raghunandanan. "People find it really difficult to devote time to go to ISPE and find out what is available there; and then there are so many other organizations like the Indian Pharmaceutical Association, but membership is a problem for most of these professional organizations as well."

## Ongoing Objectives

While membership levels remain an ongoing concern, Raghunandanan acknowledges that the main objective of the Affiliate is to provide knowledge sharing and networking opportunities.

Those opportunities often take place at ISPE-sponsored events and the India Affiliate's schedule features several each year. The annual conference, a two-day event, is usually held in Mumbai between January and April, and features international speakers on topics such as GAMP, quality metrics, aseptic processing, continuous manufacturing, or process validation. "We also make every effort to get an FDA speaker because that gives an opportunity for the participants to hear about the current expectations directly from the regulators," says Raghunandanan.

In addition to the annual conference, the Affiliate also holds young professional programs, which are one-day events held in different parts of the country, such as Ahmedabad, Bangalore, or Hyderabad.

ISPE-sponsored training is an area that the Affiliate hasn't ventured into yet. "We recently tried having one training program on Goa (a state in southwest India) that was supposed to be spread out over eight Saturdays and eight Sundays," explains Raghunandanan. "But we couldn't go ahead with that because people were not happy about the eight weekends, so for the time being we have not yet launched it. So, while training is an area that we have not ventured into, probably there is some scope there. We want to help fill the gap between the increasing regulatory expectations and the current practices in the industry here."

Ongoing engagement with students is also considered an important objective. "Students are tomorrow's professionals for our industry," says Raghunandanan. "We conducted a couple of programs for students from leading universities in Mumbai. Again, the issue is that if you conduct a program for students in Mumbai, then the participants will only be from the Mumbai colleges. In Bangalore, there are several pharmacy colleges, so the Bangalore Chapter has initiated some student programs there with some of the pharmacy colleges. But this is an area where we should consolidate more, so we have recently taken one of the research students from one of the universities in India as one of our executive committee members so that he can work for our Student Chapter."

## Current Challenges

As important as student engagement is to the India Affiliate, so too is building stronger relationships with regulators, according to Raghunandanan. "In the Indian setup, there is a central regulator that is based in the capital of the country, Delhi, and then in every state we have separate regulators," he says. "We give them complimentary membership and a good number are members. Some of them contribute, some of them participate, some of them speak of the conferences and some of them come as the guest of honor at the conferences. So, engaging the regulators is an ongoing thing, but it's a challenge for us to get many of them."

Looking ahead, Raghunandanan hopes to get some additional help from ISPE headquarters. "The support we are getting from ISPE headquarters is good, but I think there is some scope for improvement in that area," he says. "Of course, there are procedures that we have to follow because we are an organization, and an organization cannot work without procedures. For example, they recently sent a directive saying that if we want an FDA speaker, we have to inform them six months in advance; I think that is an FDA requirement and obviously we will have to comply with that. So, that is one area where we require support from headquarters; in finding good speakers." ■

*Mike McGrath*

**India is one of the fastest growing pharmaceutical markets in the world, with a domestic market valued at almost $14 billion**

### Officers

**Emeritus Chairman:** Ajit Singh
**Chair:** R. Raghunandanan
**Vice Chair:** Kapil Bhargava, Retired, Dy. Drugs Controller, Central Drugs Standard & Control Organization
**Treasurer:** Jawahir Sipahimalani, Chem-Med Analytical Laboratories
**Secretary:** Vijay Kshirsagar, TRAC Pharma Consulting
**Past Chair:** Gopal Nair, GRASP Enterprise

### Directors

Someshwar Mudda, Micro Labs Limited
Dr. Anil Singal, Consultant

### Membership Chair

Vijay Kshirsagar, TRAC Pharma Consulting

### Executive Committee Members

Satish Bhadri, Envirochem Tech Solutions (I) Pvt. Ltd
Dr. V Bhalla, Carlton Pharmaceuticals & Chemicals Pvt. Ltd
Sudhir Bhandare, Mylan Laboratories Limited
Salim Veljee, Director, FDA, Goa
Rajendra Dadhich, IPCA Laboratories Limited
Dr. Uday Shetty
Anuvrat Singal, Glatt (India) Engineering Pvt Ltd

**Affiliate Manager:** Ravi Nair, India Affiliate
**Staff Project Manager:** D. Tracey Ryan, ISPE

LETZNER
Pharmawasseraufbereitung

## Pharmaceutical Water and Pure Steam Systems

- 316 L
- DIN 11864
  Hygienic Design
- Anti Rouging Concept
- Green Planet Concept

## Online Total Organic Carbon Analysis

- Multichannel (7)
  NDIR-Detection
- One system for
  hot and cold samples
- CFR 21 Part 11
- JP 16 compliance


Made in Germany
www.letzner.de

# New Opportunities for a Young Professional

We all remember the optimism we had when we started our first job. The prospect of the amazing things we will accomplish, the smart people with whom we will work, and that we will change the world. After the first five years in the middle of your young professional career, you look back at what you have accomplished: the first projects you were able to manage and the learned lessons from your mistakes along the way. You already visited different places around the world, you are earning more money, but you are also spending more. Further, you start getting your first wrinkles and slight little gray hair and start wondering about living in the calm countryside instead of the city. Facing these different issues at this point in life can cause some uncertainty, but I can assure you everybody experiences it.

**Everybody, regardless of career level and socioeconomic status,goes through periods of "mid-career crisis"**

## What Is My Next Step?

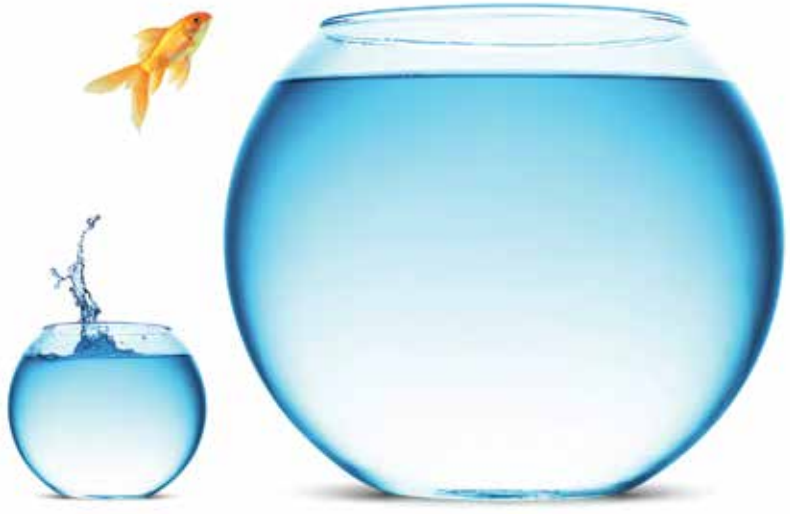
Having experienced your first career promotions and having achieved great things, you reach a point of constancy in life for the first time. Since entering school as a child you have always been trying to learn more and more. Now after your first years in your career you have the feeling you achieved those lifelong goals.

So what's next?

You will definitely want to spend some of your hard-earned money. You will go and try out new things, like doing a triathlon, driving an electric car, and traveling to an exotic place.

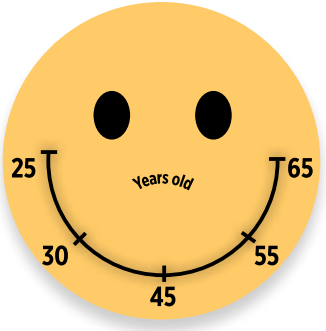
After you try out the new electric car everybody is talking about, you look at the price tag and ask yourself, "Isn't there something better I can do with the money?"

- Should I buy a car?
- Do I want to live in the city or country side?
- Which job can I do next?
- Should I do an additional degree?



## The "U-Curve" Theory

During your lifetime you will always have phases where you have the feeling of a crisis, even though you have reached your goals and have everything you wished for. A unique longitudinal German survey that followed 23,000 individuals from 1991 to 2004 was done. People reported their current life satisfaction as well as their expected satisfaction in five years' time.




The results were that everybody, regardless of career level and socioeconomic status, goes through periods of "mid-career crisis."

It seems to be part of a natural developmental process, driven by biology rather than the specifics of a particular job. Hence, drastic career changes are unlikely to make you better off. If the burned-out Wall Street lawyer and the dissatisfied NGO activist were to change seats, perhaps neither would end up more content.

## What Can I Do?

Despite the fact that everyone goes through the same process, you should definitely act if you're going through a mid-career crisis. There are different ways of approaching it:

At the individual level, you should accept the fact that you reached a period of "mid-career-crisis," but also be aware that it's temporary and that there is going to be a way out, which will specifically work for you. It's also OK to regret some past decision; that's life. You will move on and with every step you are getting smarter in being the captain of your own life.

**It always helps to look for a mentor outside of your company and build with him or her a trustworthy and honest relationship**

At a mentoring level, you should look into ISPE, which provides you the unique opportunity to learn from our industry's leaders. It always helps to look for a mentor outside of your company and build with him or her a trustworthy and honest relationship. The mentor is a good source of guidance and reassurance that he or she also went through the same process.

## Bringing It All Together

While the midlife crisis of a young professional seems unbelievable, it does happen. You should face it as an opportunity to make a self-assessment as described in my March/April 2016 column, "Three Goals for YP Development," reevaluating your personal strengths and weaknesses. Be assured that in the "U-curved model" there is always the way up again. ■

*This article is based on "Why So Many of Us Experience a Midlife Crisis" (Harvard Business Review, 20 April 2015), by Hannes Schwandt, then a postdoctoral research associate at Princeton University's Center for Health and Wellbeing.*

**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.

# Consulting: A Young Professional Perspective

*Lindsey Daniel, PE*

*Lindsey Daniel*

As a young professional in the consulting world, I am frequently asked why I chose consulting. Coming out of college I had an offer from a manufacturing company and a consulting company. With a degree in chemical engineering, I felt a passion for the biotech industry but struggled to decide what part of the industry I wanted to engage. A year-long co-op in college allowed me to gain experience in manufacturing, design, business analysis, and supply chain work, but I still was not sure which suited me best to start my career. As I pondered over my two job offers, I became more and more enamored with the thought that the consulting world could provide me the opportunity to learn and explore a broad range of the biotech field, including different processes, equipment, companies, and even countries. After four years as a consultant, here is my story.

## The Opportunities

Working as an engineering consultant exposed me to a variety of unit operations, systems, equipment, and industries, as well as cultures and ways of thinking. Every company has a different way of designing its operations, running projects, and working with project teams and consultants. I have seen various design philosophies, project motives (budget, quality, schedule, etc.) and company cultures, all of which have their own unique effect on the end product.

My first projects were for a major biotech company that developed cancer-fighting monoclonal antibody drugs via mammalian cell lines. I learned about cell culture and purification design, as well as sterilization methods. More recently I have been involved with clean-in-place and buffer system start-ups, where I gained hands-on experience in the field. Aside from the process side, I have worked on electrical, HVAC, safety, environmental, and even architectural designs. These experiences allowed me to understand different processes and systems and how they tie together to make the final product. I learned about the importance and variety of the stakeholders and how they are critical to project success including quality, safety, manufacturing operations and engineering.

After my first couple of years and projects, I was even more confused about where I wanted to focus. The experiences I had thus far were so diverse and engaging. I enjoyed all of them. I asked myself, do I want to be a technical expert in a specific unit operation, or would project management and business development be a more suitable career path? I was not ready to settle down into a single manufacturing company or role without more exploration of various unit operations, equipment, and management styles. Consulting continued to give me the opportunity to try out different jobs and see what path I wanted to go down.

During the last two years, I focused on broadening my experiences outside of process engineering design and tackled new challenges. I got involved in project management, business development, validation, commissioning, plant start-up, and process improvements—all without having to change companies. On some projects I held more of a coordination or project management role where I was responsible for budgets, schedules, and coordinating work. On others, I worked more on the technical side, designing multiple systems and processes and implementing those designs. This diverse exposure taught me to understand the design and project from varying perspectives as well as the big picture of how products are manufactured, which is an important aspect regardless of what path you choose. As a project manager you have to understand the deliverables you are committing to and what they entail; as an engineer you need to understand how a project is executed, what the phases of the project are, and what is expected of you.

Another great aspect of consulting is having access to a variety of industry leaders and experts. Having these types of mentors creates a great culture for young engineers to absorb a wealth of technical knowledge in a relatively short amount of time. Every project is made up of different teams, including owners and consultants, so you are continually exposed to a range of expertise. This allows junior engineers to grow their networks and knowledge, learn to work on diverse teams, and be exposed to successful troubleshooting/management techniques. In my opinion one of the biggest challenges for most engineers is working with others and communicating effectively. By being continually challenged working with different teams and people you will be forced to learn how to communicate and work with different personalities.

## The Challenges

As wonderful as consulting is, it does come with challenges. When I first joined my company I was told that I would never be forced to travel but the best projects that would develop me the fastest would not always be local. For me, this was an exciting aspect as I love to travel, but not everyone does well flying somewhere on a weekly basis or being away from home for extended periods of time. Traveling can also be scary as it takes you out of your comfort zone and exposes you to new environments.

Travel requirements vary from project to project. I have been on projects where I worked out of my office the entire time, where I flew for occasional meetings during design, and where I was on a plane every weekend. My projects to date have taken me to California, Boston, Ireland, Atlanta, and Minneapolis—all within four short years. I have learned that traveling can wear out even the most energetic person, so it is important to find a balance that works for you.

**How do you design something you have not yet operated, and how do you operate something you have not designed?**

My biggest challenge as a junior engineer has been the lack of hands-on experience. How do you design something you have never seen or operated? As a consultant, I work with a lot of drawings and pictures but rarely get the opportunity to run the equipment. Visualizing how something works or runs if you have never physically seen it is difficult. Facility and equipment start-up opportunities are the best way to learn about equipment and processes. Starting up something you have designed is even better. I was fortunate to gain this hands-on experience during a start-up experience in a large facility, but those opportunities are rare and usually require a significant amount of travel.

Someone once told me that the greatest opportunity missed is the opportunity to learn from your mistakes. Consulting typically requires you to get in and get out, which sometimes results in missed opportunities for lessons learned. Once the design is completed you are on to the next project. Often the senior engineers are responsible for reviewing equipment submittals and solving challenges in the field. The feedback that results in lessons learned often does not flow down to junior staff. I believe that it is important to learn from your mistakes—otherwise you are bound to make them again.

One additional possible challenge with consulting is lack of control and decision making. As a junior engineer, I did not have enough knowledge or expertise to "know better." As you grow and develop your knowledge, however, there will be times when you disagree with a client. I have watched senior engineers feel strongly and advise against a certain design or approach, but in the end the client decides they want it their way, and we have to make it work. As a consultant, it may be a challenge to not always have complete control over the design or the process. You will have to learn to accept and do your best with clients' requests, even if they are not how you would solve the problem.

## Consulting: The Millennial Opportunity

In my opinion, consulting can offer the highest potential for accelerated career development opportunities for young engineers. Consulting is hard work and requires drive, organization, patience, and a lot of energy. Engineers fresh out of school are usually enthusiastic and have a great thirst for knowledge. They are often excited about the opportunity to travel out of state or overseas and gain new experiences.

Young engineers often struggle to generate a career plan, however, due to their many interests and lack of experience. It is rare that I meet a student or someone recently out of college who knows exactly what he or she wants to do. There are many career options within this industry, and most students do not even know about half of them. Consulting is a great opportunity for young engineers to take on a variety of roles, equipment, companies, and cultures that will help them determine the direction in which to navigate their career.

Consulting will sometimes consist of long hours, travel, and challenging projects, but it is also the fastest way to grow and develop as a junior engineer if you have the right mindset. The work associated with being a consultant should never be boring. It will require you to be adaptable, flexible, and ready to learn. It will provide optimal exposure to a diverse landscape of equipment, roles, experts, and cultures. This variety builds a solid foundation for your career. Coupling a young engineer's energy, thirst for knowledge, and motivation with the learning opportunities provided by consulting is an optimal pathway to a career foundation that will help you discover your passion in our industry. ■

## About the Author

**Lindsey Daniel, PE**, is a Process Engineer with CRB, where she is responsible for process design and coordination, construction management, commissioning, project startup, and business development. She has over four years of experience in the biotech and pharma industries. Lindsey has worked with top biotech and pharma companies, offering a wide range of designs and troubleshooting solutions. She is a member and Past Chair of ISPE's Young Professionals Committee, past Young Professionals Chair of the San Diego Chapter, and a current member of the Midwest Chapter. Lindsey graduated from Virginia Tech in 2012 with a BS degree in chemical engineering; she earned her Professional Engineer license in early 2016.

# What Makes a Qualified Candidate?

*David G. Smith*

*David G. Smith is Senior Recruiting Partner for Biogen's manufacturing and quality organizations in the United States.*

**As a Young Professional or a new graduate evaluating job postings, what level of position should I consider? How can I know if I would be a qualified candidate?**

**This is a common question** for new grads and young professionals in the industry. The functional areas in which newly graduated scientists and engineers frequently get their start are manufacturing operations and quality control (QC). With the proper education or training in place, many of these opportunities require minimum to no previous career experience. Associate-level job titles are common in these categories, such as manufacturing associate, QC associate I, associate scientist, or associate engineer. For candidates that do not have internships or other direct hands-on experience in manufacturing or QC, temporary or contract assignments may be a great opportunity to gain the experience required to be considered for full-time roles.

Most organizations write job descriptions very carefully, and often include minimum degree and experience requirements. When you see that certain credentials are "required," these should be viewed as the absolute minimum needed to be considered qualified. While "preferred" skills and training are more of a like-to-have, candidates possessing these qualifications will have clear advantage in the overall consideration for the role. Internships and co-ops are often considered work experience, while academic research and projects are not. As long as you meet the minimum requirements, the job level should be in the general ballpark of what you are targeting.

You may find that opportunities within the functional areas you are pursuing require experience you do not possess. "How do you get experience when all the opportunities require experience?" you may wonder. You may need to consider a bridge position to gain the skills necessary to be a competitive candidate as a stepping stone to your ultimate career destination. LinkedIn can

**Consider a bridge position to gain the skills necessary to be a competitive candidate as a stepping stone to your ultimate career destination**

be a very powerful tool in gaining career-path knowledge.

Let's say that you are interested in being a process engineer at an operating company. You have been exploring job descriptions, but you see that all openings require minimum experience that you do not possess. Try searching LinkedIn for individuals that are currently employed at the company in the position you are considering. Their profiles will allow you to see what kind of credentials these individuals possess, and more importantly, what positions they held prior to landing the job you want. With this data, you should be able to see trends that indicate how the people in those roles got their start, and how they were able to leverage their experience to move their career forward.

While the information you find online will help you a great deal, there is no substitute for networking. As an ISPE Member, you have access to some of the best events in the industry, each of which will allow you to network with other Members that can help you understand careers in the industry. Many chapters offer career events to give Young Professionals insight to career paths and what "a day in the life" might look like in various functional areas. The more knowledgeable you are about the roles you are pursuing, the better you can prepare and present your capabilities as a candidate. Who better to give you this knowledge than individuals currently in the positions you are pursuing? To find out more information about upcoming events, visit www.ispe.org/globalcalendar.

Finally, it is important to be realistic about positions for which you would be considered qualified. Employers are flooded with highly qualified applicants, and it is a risky proposition to consider people who do not possess the experience and training necessary to do the job. You will need to carefully target jobs at which you can prove you'd be successful—not just jobs where you think "I could do that."

Try putting yourself in the hiring manager's shoes: What would make them excited about hiring you? If you can't figure out why they should be excited about hiring you, this should be an indication that you need to move on to a different opening—one where you can make a compelling case for yourself. Ultimate success will be driven by your ability demonstrate specific evidence that you would excel in the role. ■

## 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!**

ISPE

SANOFI

ISPE Europe Conference on

# BIOTECHNOLOGY

**Reinventing Commercial Biomanufacturing**

**24 – 25 October 2016**
**Industriepark Höchst, Frankfurt**

**Bridging Regulatory and Quality, Process Science, Knowledge Management, and Innovation Using Case Studies**

**Why attend?**

- Learn about GMP challenges and opportunities for biomanufacturing
- Understand the implications of the new regulations, like Annex 1 and 2, for biopharmaceuticals
- Discuss and explore success factors of knowledge management and technology transfer in Bio Pharma
- See first-hand innovative solutions in process development

**Plant Visits at Sanofi**

Four options available at the Industriepark Höchst:

- Multi-Insulin Plant
- Lantus (Insulin) Plant
- Cell Culture Pilot Plant for Development
- Höchst Industry Park Tour (History and Current Operation)

**REGISTER NOW!**
**www.ISPE.org/2016-Europe-Biotechnology-Conference/Register**

ISPE

# Biopharmaceutical Manufacturing Conference

## 5 – 7 December

**InterContinental Mark Hopkins**
**San Francisco, CA**

***Getting Ready to Grow: Delivering on Our Promise to Patients***

Tap into the expertise of industry leaders to ensure that your company can successfully navigate through this time of unprecedented growth in the biopharmaceutical sector.

This growth is driven, in large part, by:

- Robust clinical pipelines
- Innovations in product development
- Next-generation manufacturing platforms/ technologies
- New regulatory pathways for breakthrough and fast-track status on new molecular entities
- Introduction of biosimilars

Learn how to operationalize your investments to meet rapidly expanding patient demands; understand potential supply constraints to implementing new and emerging technologies; and work in tandem with colleagues and thought leaders to effectively solve issues before they become unmanageable. Be prepared to deliver on our promise to supply life-changing medicines to patients around the globe.

**www.ISPE.org/2016-Biopharmaceutical-Manufacturing-Conference**

**Exhibit and On-Site Branding Opportunities Available**
**Contact Chris Galione at cgalione@ispe.org or +1-301-364-9212**

## EARLY BIRD DISCOUNT

Register before 4 November 2016 and **SAVE!**

Discounted rates apply for groups of three or more.

# Water is Expensive. Why Waste it?

## High Efficiency **BioPure LSX**

### Up to 95% Water Recovery. Economical Price.

The BioPure LSX USP Purified Water System for Pharmaceutical applications features a High Recovery Operating Mode that automatically adjusts the system for optimal production flow rate while recovering up to 95% of the feed water. This standard feature can save the user tens of thousands of gallons of water and reduce discharge of waste to drain. High Recovery Operating Mode is only one of the many features that make the BioPure LSX the logical choice for a pharmaceutical research and manufacturing USP water system.

VISIT US AT THE **2016 ISPE ANNUAL CONVENTION & EXPO** AT **BOOTH 515.**

**Visit www.mcpur.com to find out more about the BioPure LSX.**

MAR COR
A Cantel Medical Company

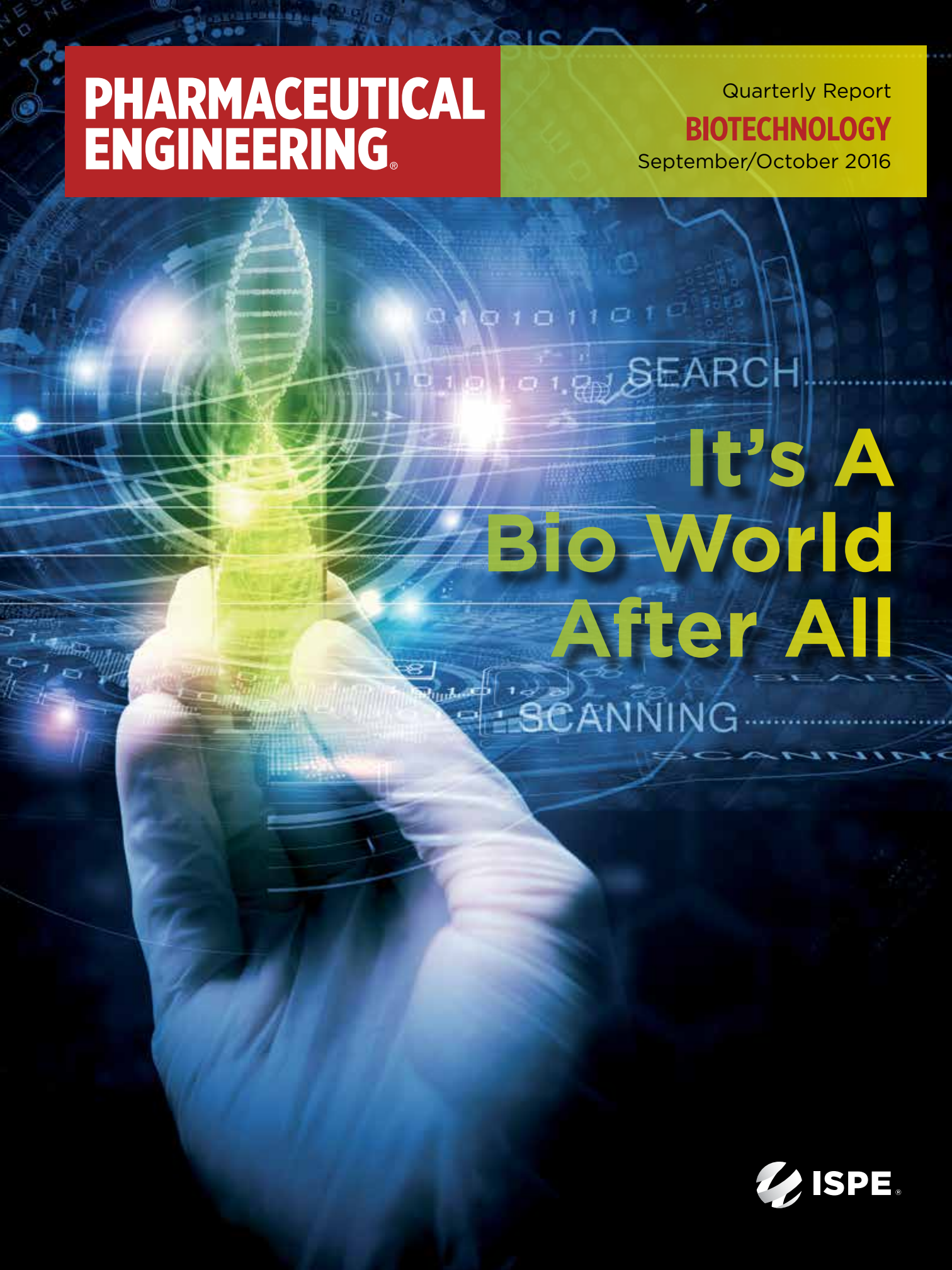
ISO 9001 & ISO 13485 Certified · US: 800-633-3080 · Canada: 800-268-5035
For more information email us at info@mcpur.com or visit **www.mcpur.com**

PHARMACEUTICAL ENGINEERING®

Quarterly Report

BIOTECHNOLOGY

September/October 2016




# It's A Bio World After All

ISPE®

in this section



# Every Patient, Every Time

## Assessing and Planning for Biologics Supply Chain Risks

*Andrew D. Skibo*

**At the 2015 ISPE/FDA/PQRI Quality Manufacturing Conference held in Washington, DC, Andrew D. Skibo gave a keynote address titled "Biologics Supply Chain Risks: Point and Systemic Risks." This article is based on his presentation.[1]**

**Consider this hypothetical scenario:** A healthy woman gives birth prematurely, at 34 weeks. ("term" means "full term"). Although she is distressed to have her newborn transferred to the neonatal intensive-care unit (NICU), she is comforted to know that the NICU at her county hospital is designed to deal with preemies this age and even much younger. Her son's vital signs are monitored constantly. He is susceptible to infection by a virus called RSV because his lungs aren't fully developed. He should be given a vaccine that is routinely administered to preemies during RSV season to prevent this infection.

Unfortunately, there is a shortage of the RSV vaccine—a sole-asset-in-class product—due to a supply chain problem at our manufacturing plant. The supply base is narrow. Bulk mammalian cell drug substance production is always at risk of sporadic but lengthy interruptions due to particularly difficult-to-clear contaminations such as murine retroviruses. The drug that could save this baby's life is at risk of becoming unavailable. Fortunately, we know our supply risks and we manage accordingly. In this instance we maintain enough inventory to bridge a full season's worth of production of this very specialized product.

I know that the market for a drug like this cannot be shorted. In this case, the math representing human health outcomes is implacable. I don't ever want to wake up in the morning having to do that math. I don't take risks managing its supply chain.

### Taking Our Industry's History

#### The Risks to Quality of Cost-Cutting

Three years ago, while thinking about the general risks to supply in our industry, I was reading a review by a leading consultancy that recommended that pharma could learn from the supply chain models and supply chain efficiencies of the big automotive companies. They noted one manufacturer in particular as a best-in-class example. I also happened to have the Business Section of that Sunday's *Washington Post* on my desk. The headline article highlighted the despair of key auto suppliers in Japan that were having to move production offshore to offset the cost pressures and just-in-time scheduling being mandated by this very same automobile manufacturer. These suppliers could no longer ensure that their products would be produced to the standards of quality that were historically associated with their family name.

The juxtaposition of these two articles startled me. One suggested we learn from the auto industry while the other demonstrated the adverse effects that this manufacturer's relentless cost cutting was having on supplier quality.

*Andrew D. Skibo*

Fifteen years ago, pharma industry supply chains were fat. We had largely internal production, controlled the quality, maintained deep inventory, and had an average utilization of only 54%. What followed was streamlining and cost-cutting by all of big pharma. Concomitant with this, drug shortages and quality alerts both went up significantly. Many firms with previously stellar quality records were having quality issues, near misses, and unpleasant conversations with the FDA. Had pharma's attempts to streamline our supply chains created a different problem?

We at first thought of these as disconnected events. I would argue that they were not. Like those Japanese automotive manufacturers, as we streamlined our supply chains to reduce costs, did we increase the risks of being able to manage quality or supply product?

### The Risks to Supply of Cost-Cutting

As an industry, there was no doubt that we had to streamline our networks, but in retrospect were we stumbling into risks that we weren't aware of? We were migrating from a supply chain that relied on three or four internal sources and end-to-end internal sourcing—in plants that had been making pharmaceuticals in our home bases for 15 years. If there was a challenge in one of those plants—an old piece of equipment that went down, for example—the market never saw it. You could move production around in the rest of your network, which was totally under your control. You had deep inventory. There was incredible resilience in the supply chain as it existed then.

Starting in 2010, drug shortages doubled in just over two years. The FDA believed this was connected to quality control. In 2013 it started a quality metrics and drug shortage initiative with major support from the ISPE. The thinking was that if we could get a handle on the quality metrics of any one plant, we would have a sense what the risk might be of product shortages from that plant.

But this was generally not the root cause issue, as demonstrated by two hypothetical scenarios. First, consider a perfect plant, the poster child for quality metrics. Yet it operates at 95% capacity, the supply chain maintains only two months of inventory, it is manufacturing a sole-asset-in-class specialty care pharmaceutical, and it is located in a difficult part of the world. This is a high-risk scenario for drug shortage despite the plant's superb quality metrics.

Alternatively, consider the example of the same product manufactured in three older plants in our home base. The plants are fully in compliance but rely on equipment that is 20 years old. There are three nodes, all internal, operating at 54% capacity, and with 14 months of inventory. I'd argue that's a much lower overall product supply risk situation even though anyone of those older plants might have a higher probability of an equipment failure.

## Diagnosing the State of the Supply Chain Today

### The Perfect Storm

A confluence of factors accounted for this focus on cost. We've seen increases in:

- Patent expirations.
- Drug development costs—In the mid-1980s it cost $75-100 million to get a drug from concept to approval. Today that number is $1.8 billion, or more than $7 billion if you factor in the cost of unsuccessful products.
- Regulatory uncertainty—Regulators are becoming more conservative, especially for lifestyle drugs or a me-too product such as a third-generation product, for which the approval data would need to be impeccable.
- The bar for reimbursement and access is high—The pool of insurance company money is limited and a product has to offer a material advantage over what's already on the market for it to be reimbursable.

These have been accompanied by decreases in:

- R&D productivity—The success rate for small molecule launches 15 years ago was about 6%. Today, that number is under 2% (10% for biologics). This is not a fundable business model, were we requesting venture capital to start our business today.

Many supply chain leaders in pharma came to the industry from high manufacturing cost, must-be-efficient supply markets such as apparel, footwear, or automotive. They used their experience and met this perfect storm of factors, streamlining operations and reducing costs through:

- Outsourcing—An increased reliance on CMOs (contract manufacturing organizations). Many big pharmas brag that they've achieved 100% outsourcing for APIs (active pharmaceutical ingredients). Sixty percent or more of all APIs are currently outsourced to emerging markets.

**Since 1990, R&D and all other costs except for manufacturing operations have come close to doubling.**

- Increased utilization rates to chemical company levels, approaching 85%–90%
- Reduced inventories, sometimes by as much as a factor of five
- Reduced investments in internal networks

This focus on supply chain cost was absolutely necessary. Since 1990, R&D and all other costs except for manufacturing operations have come close to doubling. If supply chain leaders hadn't stripped out 40% of cost by streamlining the supply chain, the rising expenses of the rest of the business would have made earnings go down in relation to revenue.[2]

## The Industry Prognosis

### There's a Growth Spurt, Especially Within Biologics

We are entering a new era in which new BLAs (biologic license applications) are being submitted at an historic rate and approvals are doubling from what they were a few years ago. Nine of the top 10 drugs are forecast to reach over $1 billion in sales in the US five years post launch.[3] Growth of the pharma market is expected to grow, year on year, until 2020 when sales are expected to reach $1 trillion, which is double that of 2006.[4] This growth is coming from a few markets.

### Large Molecule

There is clear growth in the biologics space. R&D productivity is high. With 15%-20% of total R&D going into bio over the last 15 years, large molecules represent half of the pipeline in the industry. On a sales basis the portion of revenues for bio is expected to grow from 14% in 2006 to 27% in 2020.[5] Some projections suggest that 70%-80% of the pipeline in 2020 will be biologics.

### Oncology

The oncology space shows the largest and fastest growth, especially immune-oncology products targeting the PD-1/PD-L1 pathway.[6] These breakthrough therapies see pipeline acceleration of as much as five years, which is enormous.

### Biosimilars

We used to think that biosimilars would merely replace the bio-novels and that the capacity of one would decline while the other increased. That has turned out not to be true.[7] Among other reasons, biosimilars will be used in co-therapies with novels, at least in the oncology space. The value demand for a bio product doesn't collapse after a patent expires, as it frequently can for small molecules.

### Emerging Markets

Southeast Asia and Latin America are expected to lead the growth in pharmaceutical sales among emerging markets, which will grow from 30% to 40% of worldwide sales by 2017.[8] These are markets we can no longer ignore.

### Personalized Drugs

The predictive personalized drug market is expected to double from 2013 to 2019, which is what is partially driving the oncology space.[9]

**As we streamlined our supply chains to reduce costs, did we increase the risks of being able to manage quality or supply product?**

### Impacts of Cost-Cutting and Projected Growth on the Supply Chain

As mentioned earlier, as an industry we have made our phama supply chain lean. We are now at a low point of capacity agility and resilience.[10] Our industry's overall agility to support a return to growth with new products may be constrained. This is particular true for biologics, where there are at least 17 large bio drug substance plants in development right now. It takes five years to design, build, and commission one of these plants. As an industry, we are clearly facing potentially constrained bio drug substance supply until this wave of new plants are commissioned and licensed. We will watch the years 2017 through 2020 with caution as we plan for bio supply.

For the past 10-15 years big pharma has operated with a mature product portfolio focused more so on primary care rather than specialty care markets. We operated in the efficient / mature end of the supply curve.

Now we are moving into the agile end of the supply chain curve: new product launches, more specialty care products, highly variable and unpredictable first years demand. Variables such as the number of patients, the dose per patient, and production titer dictate a wide range of potential plant capacities that may be required. For new oncology products, the launch volumes required are notoriously difficult to project and can vary by a factor of as much as 17. How do you plan for that? Agility and flexibility are key.

As we said before, it takes about five years to design, build, commission, and license a big biologics manufacturing facility. The product development cycle used to be approximately seven to nine years. Now we see product developments cycles of three years. Yet it still takes five years to build a plant if you need one. Suddenly we're in a position where we are risk mapping for products we don't even have yet because they will come before you can get that plant designed, built, and licensed. It's a very different world.

It costs $750-$800 million to build a 4 × 15,000 l plant today. If you don't have the capacity, and you're not able to share capacity with another big pharma—a previously common occurrence—you could end up with a significant shortage. More importantly, we're not in this just for dollars; there are patients on the other end of that supply chain. If we short a statin, it will be meaningful in terms of lost revenue to our companies, but no patient suffers because there are other suppliers. If we short a PD-1/PD-L1 product, patients suffer. Many of these breakthrough therapies are saving lives, yet there is not 5x surplus capacity for these products available in the marketplace. If we get the launch / early year volumes versus supply wrong, there will be health care consequences, not just dollar consequences.

## The Way Forward—Supply Chain Modeling

Supply chain agility is now a buzzword in the industry,[11] with over three-quarters of businesses in big pharma agreeing that they need to change their supply chain model. Tellingly, only 7% have completed that change.[12]

Two years ago at AstraZeneca, we developed a proprietary capacity model for our biologics products. We run this model for hundreds of demand scenarios to assess whether the actual capacity of our current network needs to be augmented to meet future demand. The model allows us to tell our executive committee and our Board not only what we're asking them to build to meet future capacity, but very importantly what is the white space above that for which we are not planning to build. If the extreme upside demand hits and we're not prepared, as a company we need to understand what we may not be able to provide that capacity on short notice, given the constraints in the industry. We can't build to all the upsides—there aren't enough very large plants available or the dollars to build them. How much of the wide-range of potential demand that we are planning to supply should be an executive decision, not just a supply chain decision.

**It takes about five years to design, build, commission, and license a big biologics manufacturing facility.**

### Modeling Supply Chain Risk

When we change a manufacturing process in our industry, we routinely do a quality risk assessment. Since supply chain risk has as much impact on drug supply as quality risk, we need to be doing the same risk assessment for the supply chain. For this reason we are developing a model to assess supply chain risks.

Supply chain management requires mental thinking that is like nine-dimensional chess. If you're good at it you can see that when you make a change here, and put that constraint in over there, then somewhere else in the matrix something happens that may create risk. Understanding this subjectively is helpful. When you approach your board and ask for $800M to cure that risk, boards expect more than subjective judgement. Boards like hard numbers.

Our model allows us to quantify risks so we can go to our CFO with actual projections of risk mitigation versus cost. Quantification allows us to sell objective modeling instead of appearing to base need on personal preference.

Modeling also helps us identify risks that we may not subjectively see. As an example, in our flu vaccine franchise, we are very good about projecting incoming raw material needs, understanding the plant capacities, packaging, and shipping and in-house testing needs. But we missed the risk associated with limited capabilities of outside testing labs. Missing that risk could have had the same consequence for us as not ordering the raw material. We had backup plans that fortunately mitigated the issue. But that conceptual miss was one of the issues that made it clear that we needed an end-to-end risk model that would flag a risk if we didn't see the risk ourselves.

Eventually the model will respond dynamically, be live and self-correcting, and offer solutions to identified risks.

### What Determines Risk?

Supply chain risk is determined by inventory policy, network utilization, redundancy, and visibility.

#### Inventory policy

If inventory is reduced to free up cash while someone else is reducing utilization and someone else is optimizing the number of nodes in the supply chain, we could collectively be building a weak supply chain.

#### Network utilization

With 95% utilization there is little room for equipment malfunction or other risks. With 50% utilization production is inefficient and expensive. How do you balance these options?

#### Redundancy

Remember our example of 15 years ago. Three plants in our home base, primarily insourced under our control with our quality systems, low utilization, and high inventories. The redundancy of this network leads to virtually no risk to the supply chain. Compare that to today—do we have that redundancy in our supply chain?

#### Visibility

Outsourcing means that we can't shine a spotlight on production the way we could when all plants were under our control. If we treat these supply contracts as commodity purchase orders, we have no visibility into our true supply chain. We discover a risk only when there is a problem. We may have a dual source structure, but suppose both suppliers use the same intermediate material supplier for a key step. What looks like two outsourced nodes is in reality only one. What if one of them is in a difficult part of the world, operating at 95% utilization, and we have greatly reduced inventory? This is a high supply risk that we may not see.

These variables have to be considered together. Optimizing them independently puts the drug supply at risk. Understanding the risks associated with a single production site (i.e., quality metrics) alone is of marginal value in evaluating overall supply risk. It's not correct to think that a company with outstanding quality metrics needn't worry about supply chain risks.

Takeaway: Quality metrics do not equal supply chain risk metrics.

### Anticipating Supply Chain Risks—Two Real-Life Examples

We find that the output from our risk model has high value for measuring risks such as what impact would the failure of a particular node have on on-time delivery. Here are two examples where we used the model to successfully anticipate supply risks.

**The value demand for a bio product doesn't collapse after a patent expires, as it frequently can for small molecules.**

We had two supply sources providing DP for a key clinical material, one internal and one external. The external supplier unexpectedly received a warning letter and had to close its plant. At the time it was our planned sole source of this clinical trial material. This could have materially affected our trials. However, we never eliminated the internal node. When the warning letter hit, we were able to easily call upon the internal node. We produced the drug product internally with less than three weeks notice. Because we had planned for that potential risk we averted an issue on a major clinical program.

As another example, increasing volumes of a frozen supply chain product lead to potential constraints on air shipment, the historical method of choice. We planned to move to ocean ship for the next year. Ocean ship start-up proved to be less robust than expected. Fortunately, our risk model told us that this was a potential risk and, instead of cancelling the air shipment option, we had held it in reserve. It was reactivated it immediately with no interruptions to supply.

## What will supply chain risk assessment allow?

Modeling the supply chain risk ensures two things: First, we see the risk; second, that we have hard data to support requests or plans that will add cost to our network to mitigate the risk.

The supply chain doesn't operate in a vacuum. We need to communicate with our colleagues in clinical, finance, regulatory, commercial, R&D, and manufacturing to understand the whole network. Then we can make these decisions together. We really want our executive committee to be aware of what we're doing.

Cost-to-benefit analysis of de-risking is easier to implement before a shortage, but harder to sell to the CFO without concrete facts. Modeling tells us these costs versus benefits. Solutions may include white space in plant. A 70% utilization adds flexibility across products without adding inventory. This is especially true if we're in the agile, or growth, part of the supply curve. It does add cost. Is the balance, right?

### Moving Beyond Efficiency

Until recently, most texts and journal articles regarding supply chain structures focused only upon efficiencies. Supply chain efficiency tools such as simplification, higher utilization, and the 3 Vs (visibility, variation and velocity) were discussed in depth. Many of the early texts about supply chain modeling are full of complicated formulas, focused upon these issues. There are factors for the number of nodes, leanness, and inventory. But most of the texts, most of the math, included no factors for risk. We weren't measuring risk; we were measuring how lean we could make the supply chain.

Bayesian risk analysis is frequently used for quality analysis. Few people have used it for supply chain analysis. It's complex, but it can be done, as E.D. Soberanis discussed in her PhD thesis regarding Bayesian network approaches for SCD.[13]

## Conclusions

Big pharma does quality risk assessments for any process change. We should also do risk assessments for supply chain design and change. They have as much impact on product supply as a poor quality plant.

We must understand that analyzing the quality or product supply risk of a single node is of marginal value in understanding overall supply risk. Quality metrics have to lead to supply chain risk metrics.

I want us to assess and plan for supply chain risks because it's good for our industry. Just as importantly, none of us personally want to risk having a supply chain upset that affects our patients' health or lives.

## References


1. "Biologics Supply Chain Risks: Point and Systemic Risks" Author: A. D. Skibo, ISPE/FDA/PQRI Quality Manufacturing Conference, Washington, DC, 2 June 2015.
2. Mckinsey and Company, October 13, 2014 – ISPE Presentation
3. Evaluate Pharma, June 2014
4. Evaluate Pharma, June 2014
5. Evaluate Pharma, June 2014
6. Evaluate Pharma, June 2014
7. IMS Health
8. IMS Market Prognosis, Global 2013 – 2017, V1.0
9. 2013 DR/Decision Resources LLC
10. Adapted information: Gartner Hype Cycle
11. Price Waterhouse Coopers "How to Build an Agile Foundation for Change" February 2008
12. Deloitte: Logi Pharma 2015 Life Sciences Supply Chain Benchmarking Survey 2015
13. Dr. E.D. Soberanis: "An Extended Bayesian Network Approach for Analysis, Supply Chain Disruptions" University of Iowa (2010) PhD Thesis.


## About the Author


**Andrew D. Skibo** is Head of Global Biologics Operations & Global Engineering at MedImmune/AstraZeneca, where he affects changes in manufacturing operations, quality oversight, and cross-functional relations throughout the company. He is also responsible for AstraZeneca's Global Engineering and Real Estate functions. Previously he has worked in other senior leadership roles at Amgen, Genentech, and Foster Wheeler, among others. In these roles he has been responsible for significant aspects of the companies' operations including operations, engineering, construction, and validation for large-scale capital projects related to biopharmaceutical manufacturing. He is a member of the International Leadership Forum, the Materials Technical Advisory Committee of the US Department of Commerce, and the Editorial Advisory Board of Life Science Leader. A Past Chair of the ISPE International Board of Directors, Andy has been an ISPE Member for 24 years. He has served on the judging panel for the Facility of the Year Award, as a conference leader, and as a member of several committees. Andy holds a BS degree in organic chemistry and an MS degree in chemical engineering, both from MIT.

# Comprehensive Compliance Solutions

Navigating the complicated and changing regulatory environment of the drug and device industries across the globe can be very challenging. ProPharma Group brings clarity and breadth of experience across the full lifecycle of your products. Let us be your single source with our complete suite of services:

- COMPLIANCE & QUALITY ASSURANCE
- COMMISSIONING & QUALIFICATION
- PROCESS & CLEANING VALIDATION, AIQ & EM
- COMPUTER SYSTEMS VALIDATION
- TECHNOLOGY TRANSFER & CMO SELECTION
- PHARMACOVIGILANCE
- MEDICAL INFORMATION

ProPharma Group

For more information, call **1-888-242-0559**
or visit us at **propharmagroup.com/ispe**

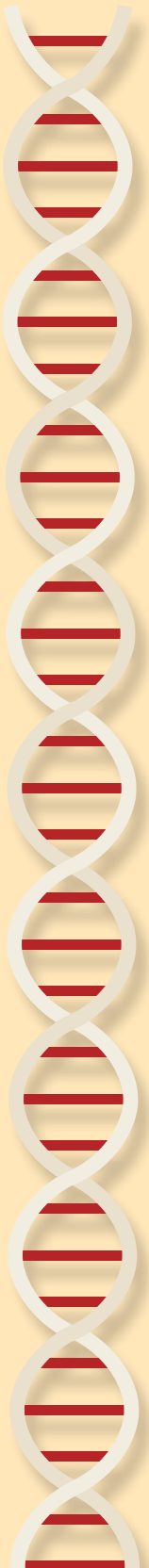
# A Brief History of Medical Biotechnology

**To paraphrase Newton, the latest revolutionary innovation in biotechnology—clustered regularly interspaced short palindromic repeats (CRISPR)—was only possible because its architects were standing on the shoulders of giants. A long list of great scientists and their discoveries has brought us to the current state in which the production of biologics, and the application of gene therapies are changing the biomedical landscape.**

**Culturing cells**—whether bacterial, yeast, mouse, or human—has been a constant technique of biotechnology, the origins of which can be traced back to industrial microbiology and the fermentation of beer. Cell cultures allowed the production of compounds that were in short supply, such as the yeast that provided 60% of feed for livestock in Germany during World War I. Penicillin, which was the first miracle drug, was manufactured using deep fermentation in the 1940s and fermentation allowed the industrial-scale production of steroids, such as cortisone, in the 1950s. Culturing cells in bioreactors continues to be important for modern biopharmaceutical manufacturing, allowing the production of complex engineered proteins that save lives and are worth billions of dollars.

Twenty years after the structure of DNA was elucidated in 1953, Herbert Boyer and Stanley Cohen used bacterial restriction endonucleases to create a recombinant plasmid that was introduced into a cell and replicated. Recombinant DNA technology was born; linking it with large-scale fermentation, the way that penicillin and cortisone were manufactured, allowed the production of large amounts of a wide variety of engineered proteins that could be used as medicine.

## A Few Highlights of the History of Modern Biotechnology



### 1952
A continuous human cell line was created from a patient with cervical carcinoma, Henrietta Lacks. HeLa cells were used for medical research for decades after this.

### 1953
James Watson and Francis Crick discovered the structure of DNA, using critical data from Rosalind Franklin and others.

### 1955
Jonas Salk developed the polio vaccine using cultured monkey cells.

### 1958
DNA was manufactured in a test tube for the first time.

### 1961
The genetic code of DNA was deciphered by Marshall W. Nirenberg and Har Gobind Khorana, providing an understanding of how RNA is translated into protein.

### 1970
Restriction enzymes were discovered that recognize and cleave a specific DNA sequence.

### 1973
Cohen and Boyer used bacterial restriction enzymes to construct a recombinant plasmid that was replicated in a cell. Boyer founded the first biotechnology company, Genentech.

### 1977
Faster DNA-sequencing techniques were developed by Frederick Sanger and Walter Gilbert.

### 1978
The first synthetic hormone, Humulin (human insulin), was produced at Genentech; the technology was sold to and commercialized by Eli Lilly. The first baby conceived via in vitro fertilization was born.

### 1980
Biogen produced interferon. The US Supreme Court ruled that organisms can be patented, and Exxon was awarded the first patent for a genetically modified organism.

### 1981
The first transgenic animal was created.

### 1982
The first US Food and Drug Administration (FDA) approval of a recombinant drug, human insulin, took place.

### 1983
Kary Mullis invented the polymerase chain reaction, which allows DNA sequencing from miniscule amounts of DNA.

### 1986
The first recombinant human vaccine, for hepatitis B, was approved. The FDA approved recombinant interferon for the treatment of cancer.

**1988**
The Human Genome Project to map and sequence the entire complement of human DNA began.

**1989**
Lap-Chee Tsui discovered the gene that, when mutated, causes cystic fibrosis.

**1990**
The first successful gene therapy was developed. A four-year old girl was treated for adenosine deaminase deficiency, an immune disorder.

**1994**
Mary-Claire King identified the breast cancer gene, BRCA1.

**1995**
Georges Köhler and César Milstein created fusion cell lines capable of producing monoclonal antibodies for the first time.

**1996**
Dolly the sheep was the first cloned mammal and resulted from the transfer of the nucleus from an adult mammary gland cell into an unfertilized egg.

**1997**
The FDA approved the first monoclonal antibody, Genentech's Rituxan (rituximab), for the treatment of some non-Hodgkin lymphomas.

**1998**
Personalized medicine for cancer patients began with the approval of Herceptin (trastuzumab), a monoclonal antibody. It is used for the treatment of metastatic breast cancer that overexpresses the HER2 gene. Embryonic stem cells were cultured for the first time in a laboratory.

**2002**
Rapid DNA-sequencing techniques allow sequencing of the genomes of hundreds of species.

**2003**
The Human Genome Project is completed. The entire human DNA sequence became available to researchers.

**2004**
The FDA approved Avastin (bevacizumab; Roche/Genentech) for the treatment of certain metastatic cancers.

**2006**
The first preventive cancer vaccine, Gardasil (human papillomavirus quadrivalent vaccine; Merck), is approved for protection against some human papillomaviruses.

**2010**
Craig Venter's laboratory created the first life-form, using a synthetic genome capable of replication in a bacterium.

**2011**
Sequencing tools improved to the point where a human genome can now be sequenced in a few days for less than $2,000.

## Culturing cells in bioreactors continues to be important for modern biopharmaceutical manufacturing

Genetic engineering alters the DNA sequence of an organism to affect gene expression. In the early days, it required finding segments of DNA —often entire genes—inserting them into a plasmid, and introducing them into a different organism. This was a hit-or-miss process that took great skill and a lot of time. With the development of rapid and cheap DNA sequencing techniques beginning in the late 1980s, the ability to store huge amounts of sequence data, including entire genomes, in databases, and the development of gene-editing technologies such as CRISPR, genetic engineering has become much cheaper, quicker, and is accessible to any scientist with a laboratory.

CRISPR is now used by an estimated 50,000 scientists worldwide, promising to provide gene therapies for diseases such as Duchenne muscular dystrophy, cystic fibrosis, cancers, Huntington's disease, and many others. Gene-drive technology, which uses CRISPR to insert sequences of DNA into an organism that then spread through all subsequent generations, is being contemplated as a means to alter entire populations of mosquitoes to prevent the transmission of malaria and the Zika virus.

We've come a long way from fermenting beer and the discovery of the double helix. Along with the plethora of biologics that are currently available and in development, groundbreaking applications of these advances in biotechnology—the potential for germline editing of DNA in human embryos is one that comes to mind—continue to push the frontiers of science. ■

*Scott Fotheringham, PhD*

### References

Amgen website. "Timeline of Medical Biotechnology." http://biotechnology.amgen.com/timeline.html

Biotechnology Innovation Organization website. "History of Biotechnology." https://www.bio.org/articles/history-biotechnology

# Breaking the Paradigm

## New Technologies, Ideas, and Adaptations for Biotechnology Facilities

*Nissan Cohen*

**For over 30 years,** biotechnology production was based on the transference of traditional pharmaceutical production and support systems. These tried-and-true pieces of equipment and technology were adapted to biotechnology production. The equipment was known, familiar, and could be commissioned, qualified, and validated based on the then-current modes of thinking and acceptance.

Today, 30 years later, there is a great opportunity to change the existing paradigm and shift to new technologies, new ideas, and new methodologies oriented to biotechnology without traditional pharmaceutical influences. The paradigm shift is in recognizing the uniqueness of biotechnology approaches and the possibilities to manage, operate, and develop economic savings models for production, "green" applications, and environmentally compliant solutions while being an outstanding corporate citizen with no compromise in production or quality.

Contained in this editorial are ideas and physical changes that can be incorporated readily into a biotechnology facility.

Biotechnology water systems are identical to pharmaceutical water system in terms of design and performance. Why is this? 316L stainless steel (SS) piping and hot-water sanitizable pharmaceutical water systems are ubiquitous. These systems are sanitized on a routine basis by heating the water to 80°C or higher to kill microbials in the water. Sometimes chemicals are added to enforce sanitization and microbial kill. Maintenance and operation of a 316L SS system is expensive. This is a tried-and-true model for pharmaceutical systems but not an ideal model for biotechnology.

Biotechnology systems use ambient purified water or WFI (water-for-injection) as makeup for their tanks. Nutrients, media, and sometimes buffers are added to the water to encourage the proliferation of bacteria and the production of genetically infused material to produce proteins, enzymes, and organic material. The entire process revolves around organic chemistry, which is carbon based. The chemicals used in the clean-in-place (CIP) system are acids, caustics, and surfactants with rinses of purified or WFI water. Why are we using inorganic chemistry in the CIP for an organic chemistry–oriented system?

The best system would be the following: A purified water or WFI system produced at ambient temperatures with ozone administration to keep the water free of microbials and TOC (total organic carbon). This system would use nonmetallic piping of PVDF (polyvinylidene fluoride), which once installed has no maintenance issues. The installation would include a pump with PVDF impellers. This system would be devoid of metal. A nonmetallic system also means no corrosion or rouge. No hot-water sanitization or heating is needed. No production downtime at night due to sanitization intervals. No issues with hygienic clamping, gasketing or leakage, and easy maintenance. Ozone can be administered at ambient temperatures in a properly lined or specified tank. The system will use the ozone for microbial and endotoxin destruction, prevent biofilm development, and maintain a pristine water system with very-low-to-no microbials in the water system. Ozone can be maintained at a concentration of 50–60 parts per billion with very pristine water. Ozone can be destructed by a UV-254 nm lamp installed in the distribution piping system, preventing ozone interference with the point-of-use products.

> Thirty years later, there is a great opportunity to change the existing paradigm and shift to new technologies, ideas, and methodologies oriented to biotechnology without traditional pharmaceutical influences.

The CIP system can be simplified by using ozone. Ozone oxidizes all organics to $CO_2$ in water. Ozone will destroy all organisms and organics. There will be no cell bodies left over, no organic film, organic residue, no BOD, and most importantly, no disposal costs. Ozone, when properly applied, can keep a water system very pristine and free of microbials, biofilm, and extremely low TOC content. The fermentation and production tanks are full of organic material. The ideal method to rid the tanks of any organic residue is by ozone. The CIP skids' process steps can be simplified and become more economical with little wastage by continual rinsing of purified or WFI water after each process step for chemicals, surfactants, or acids. Cost savings include the elimination of chemicals, surfactants, acids, handling, purchasing, neutralization, storage, and personnel costs for all tasks.

Ozone can be used to destroy all organic waste. This means getting rid of the autoclaves for bacteria kill. To ensure that the bacteria used in

**The use of online instrumentation with elimination of laboratory methods offers immediate knowledge of the status of the production, its limits, operational parameters in real or near real-time, and recognizes trending towards possible OOS conditions long before specification limits are reached.**

the production process, after extraction and purification, are benign, the bacteria is subjected to autoclaving. How much does it cost to dispose of bacteria in this manner? Thousands of dollars per day? Autoclaves are expensive to purchase, maintain, service, and operate. A simple organic slurry, in a confined tank with ozone, can be oxidized in a very short period of a few minutes. Studies have shown 5–6 log reduction in *E. coli* bacteria in 2–3 minutes using ozone at only 1–2 ppm concentrations. Destruction of the bacteria to $CO_2$ in water also means no disposal costs and no wastewater treatment issues with the local municipality's wastewater treatment plant. No organic waste disposal is an excellent example of "green" technology.

Rapid microbial monitoring (RMM) is a perfect application for biotechnology water and CIP systems. Today, most microbiological sampling is based on manual sampling and incubation for 48–72 hours or longer using single-use petri dishes with R2A media. According to one AstraZeneca source, manual sampling of microbials costs $200 per point. This includes all costs for personnel, labor, incubation, laboratory analysis, single-use devices, cleaning of sampling containers, etc. If there are 20 use points that are sampled every other day, then the total yearly cost of manual sampling is 20 points × 150 days × $200 = $600,000 per year. When the water is classified as WFI, the usual microbial reading is "no counts." The company is spending $600,000 a year to get "no counts." RMM is less expensive by a factor of 10 and gives near-real-time data. The delay in manual sampling, incubation, and analysis is at least a 72-hour procedure. Meaning, the "clean" fermentation tank is idle until the microbial data is issued by laboratory personnel. How much lost production time is due to waiting for laboratory results? What does this cost the company in lost revenue? Tens of thousands of dollars per day? Hundreds of thousands of dollars per day or more? Can you afford this idle time?

RMM can be used regardless of the microbial detection method employed and integrated to your production facility. Guidelines for alternative microbial monitoring methods can be found in PDA TR33, USP <1223>, and EP 5.1.6. Use RMM to release your water and fermentation tanks to production without having to wait for laboratory confirmation over the next few days while saving hundreds of thousands of dollars in manual sampling.

Process analytical technology was released by the US Food and Drug Administration in September 2004. In 2016, almost 12 years later, this excellent method for process knowledge and feedback, which eliminates traditional validation methods, is used by only two or three biotechnology companies. This methodology can greatly increase continuous process knowledge and monitoring. The use of online instrumentation with elimination of laboratory methods offers immediate knowledge of the status of the production, its limits, operational parameters in real or near real time, and recognizes trending towards possible OOS (out-of-specification) conditions long before specification limits are reached.

The above examples are a short list of possibilities to break the current paradigm. There are other ideas and technologies that are applicable to biotechnology facilities. Overall, it is the recognition of the uniqueness of biotechnology production and manufacturing with insight to new technologies; new methodologies; adoption of new online instrumentation; and institution of "green" technology, which can decrease the cost of manufacturing, increase throughput, increase revenue production, and reduce downtime due to maintenance and idleness while creating a forward-thinking corporate entity. ■

## About the Author

**Nissan Cohen** is a pharmaceutical water consultant and lecturer with 40 years' experience in total organic carbon, high-purity, ultrapure, reclaim and recycle water systems, specializing in instrumentation, automation, and organic contamination oxidation systems using ozone, UV, ion exchange, and catalysts. Previous positions include vice president, Anatel Corporation; director of business development, Rohrback Cosasco Systems, Inc.; and principal scientist, high purity water systems, Commissioning Agents, Inc.

Nissan has written over 35 technical articles, is a technical editor for the *Journal of the Institute of Environmental and Science Technology*, a member of the Pharmaceutical Engineering editorial review board, Chair of the ISPE Water and Steam Forum, and Founder/Chair of the ISPE Discussion Forums.

He earned a BS degree in agriculture and genetics from the University of Wisconsin and the Ruppin Institute, Israel, with graduate studies in agricultural water systems. He has been an ISPE member since 1994.

# ELETTRACQUA

*pure water technologies*

SINCE 1966

## PHARMACEUTICAL WATER SYSTEMS

OSMOSIS + EDI UNIT HOT WATER SANITIZABLE


DOUBLE PASS REVERSE OSMOSIS

HIGH TEMPERATURE SANITIZATION + CONCENTRATE RECOVERY SYSTEM


MULTIPLE EFFECTS DISTILLATION UNIT

PURE STEAM GENERATOR

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES • DOUBLE PASS REVERSE OSMOSIS • R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE • ULTRAFILTRATION • MULTIPLE - EFFECT DISTILLATION UNITS • PURE STEAM GENERATORS • STORAGE AND DISTRIBUTION LOOP • COMPLETE TURN KEY PROJECTS • VALIDATIONS IQ, OQ

**www.elettracqua.com**

# The State of Biopharmaceutical Manufacturing in Ireland

**Beginning in the early 1990s, when Schering Plough (now MSD Animal Health) opened the first biotechnology facility in the Republic of Ireland—a microbial drug substance and fill-finish plant[1]—to today, when most Big Pharma firms have offices and facilities in the country, Ireland has earned renown as a hot spot of biotechnology and biopharmaceutical R&D and manufacturing.**

The biopharmaceutical industry has invested $8 billion in new facilities, mostly in the past 10 years[2] while exporting $44 billion in drugs last year, making it the largest exporter of pharmaceuticals in the European Union (EU).[3] While Ireland's competitive corporate tax rate draws foreign investment and mergers—notably the attempted union of Pfizer and Allergan that was recently foiled by a change in the US tax code—there are many other incentives to invest in Ireland. With access to a young and well-educated workforce, proximity to Europe, a history of innovation, and strong government support, Ireland is seen as a strategic place to do business.

## Brexit Storm Clouds Gather

The recent vote to leave the EU has cast uncertainty over the biotechnology industry in the UK, which had been recovering nicely since a major downturn about seven years ago.[4] How Brexit will affect manufacturing in the Republic of Ireland, which is independent from Britain and thus eligible to remain in the EU, remains to be seen. There is concern that talent might react warily, either looking for positions outside the UK and Ireland or not going there in the first place.[5] **Alexion** provided a significant boost post-Brexit when it recently announced an additional €100 million investment to expand its biologics manufacturing site in Athlone.[6] And the Irish health minister would like to see the headquarters of the European Medicines Agency (EMA), which is currently in London, but will have to move once Britain leaves the EU, relocated to Dublin.[13]

Nine of the top 10 pharmaceutical companies operate in the country, according to IDA Ireland.[2] Firms located in and around Dublin and Cork often work together, sharing knowledge and assets. A prime example of this is a collaboration among four of the bigger firms—**GlaxoSmithKline**, **Janssen Biologics**, **Novartis**, and **DePuy Synthes**—on a sustainable energy project in Cork, including the installation of a wind turbine at each site. The four firms employ 4,000 people in Ireland and have spent more than €2 billion ($2.2 billion) over the past 20 years.[7] Additional clusters of biopharmaceutical companies are developing around Sligo, Waterford, and Mayo.[2]

The Irish government had the foresight that investing in biopharmaceutical manufacturing—product development, cell culture, and protein purification—would provide a higher rate of return than continuing to expand stainless steel capacity.[1] Government invested €60 million ($66 million) to form the National Institute for Bioprocessing Research and Training (NIBRT), which trains 4,000 people a year and includes board members from IDA Ireland—the government agency responsible for foreign direct investment into Ireland—and Alexion, Sanofi, Johnson & Johnson, and BioMarin.[1] This facility, with a molecular biology laboratory, downstream processing laboratories, and much more, collaborates with University College Dublin, Trinity College Dublin, Dublin City University, and the Institute of Technology, Sligo.[8] NIBRT, which won an ISPE Facility of the Year Award in 2012 for novel collaboration,[9] will focus on downstream processing and innovative manufacturing equipment to produce biologics.[1]

**Ireland has earned renown as a hot spot of biotechnology and biopharmaceutical R&D and manufacturing.**

This is a partial list of the 75 pharmaceutical companies involved in biotechnology in drug discovery and development in Ireland. In addition to these companies, a large number of biotech companies are involved in medical and pharmaceutical assays, medical devices, veterinary drugs, and bioanalytical services.


With its proximity to Europe, a history of innovation, and strong government support, Ireland is seen as a strategic place to do business.

## DUBLIN and Environs

**Pfizer Biotechnology Campus** at Grange Castle is a facility that focuses on product development of biologics and vaccines. **Science Foundation Ireland** and Pfizer jointly fund biomedical research through their "SFI-Pfizer Biotherapeutics Innovation Award Programme able to conduct research at Pfizer's Grange Castle facility.[10]

**MSD** (known as Merck in North America) employs 2,300 people at eight sites, including MSD Animal Health in Dublin, which provides vaccines and drugs for livestock, and Carlow (near Dublin), which is a biologics and human vaccine facility.

The **Amgen** facility at Dún Laoghaire (Dublin) focuses on secondary manufacturing processes such as formulation, fill, lyophilisation, and packaging of small molecules and biologics.

**Bristol-Myers Squibb** invested $900 million in a manufacturing and R&D facility for immune-oncology products in 2014.[1]

**Alexion** plans to spend €450 million ($495 million) to build a biologics manufacturing facility by 2019 at its site outside Dublin.[11]

**Shire** is investing $400 million in a biologics manufacturing plant to complement its US facilities.[12]

**Solvotrin Therapeutics** is headquartered in Cork, with laboratories in Dublin. It focuses on therapeutics such as its candidate drug, ST0702, aimed at colorectal cancer.

**Allergan**, which was acquired by **Actavis** in 2015, has its headquarters in Dublin and aims to lead in the biosimilar sector. In addition to medicines and products for eye care, neurosciences, and obesity intervention, Allergan works with Amgen on four oncology biosimilars.

**Amarin** is headquartered in Dublin. The biopharmaceutical firm focuses on drugs for cardiovascular health.

**Genable** (acquired by Spark Therapeutics) is a development-stage gene therapy company. Its lead product in development, which has orphan drug status, is for the treatment of retinitis pigmentosa.

**Heart Metabolics** has its headquarters in Dublin and develops treatments for diseases that include hypertrophic cardiomyopathy.

**Horizon Pharma**, whose global headquarters are in Dublin, is a biopharmaceutical company with nine medicines including synthetic hormones.

**Ipsen** has a facility focused on the development and production of peptide and small-molecule active pharmaceutical ingredients (APIs).

**Jazz Pharmaceuticals**, with corporate headquarters in Dublin, is a global biopharmaceutical firm that specializes in drug products that treat sleep problems and hematology/oncology.

**Leo Pharma** manufactures dermatology and ophthalmology products for this global company, which is headquartered in Denmark.

**Opsona Therapeutics** is a drug development company, focusing on biologics for autoimmune disorders and cancers.

**Prothena** specializes in the discovery, development, and commercialization of immunotherapy products for potential treatment of amyloid diseases. It has three monoclonal antibodies (mAbs) in development.

## CORK

**Eli Lilly** has a plant in Kinsale, County Cork, that manufactures APIs for both small molecules and biologics, including mAbs.

**Novartis** operates a manufacturing plant in Ringaskiddy, Cork, and has offices in Dublin as well.

**GlaxoSmithKline** operates manufacturing facilities in Cork, Dungarvan, and Sligo.

**Johnson & Johnson** manufactures as DePuy Synthes and Janssen Biologics in Ringaskiddy and Little Island. Its Irish headquarters is in Dublin.

**MSD** (Merck) also operates a facility at Brinny (near Cork), which specializes in fermentation, purification, and filling of biologics for the treatment of hepatitis C and rheumatoid arthritis.

**Gilead Sciences** manufactures biopharmaceuticals at its facility in Cork.

**AbbVie** has a bulk tablet finish plant in Cork.

**BioMarin Pharmaceuticals**, with a plant in Shanbally, Ringaskiddy (Cork), is a biopharmaceutical manufacturer that aims to provide treatments for rare genetic diseases such as Morquio A syndrome.

## SLIGO

**AbbVie** has two manufacturing plants in Sligo.

## ATHLONE

**Alexion** has a fill-finish plant in Athlone, which it plans to expand.

**Alkermes** has a 505,000 square-foot manufacturing facility in Athlone to produce solid oral dose medications. It has a number of products in clinical trials, including ones for the treatment of schizophrenia and cancer.

## WATERFORD

**Sanofi Genzyme** has a manufacturing facility in Waterford for fill finish, vial filling, and lyophilization for Genzyme's medicines.

**EirGen Pharma** has a biologics manufacturing facility in Waterford with analytical laboratories. It functions also as a CMO.

## LIMERICK

**Regeneron** has a 400,000 square foot biologics production facility in Limerick responsible for production and packaging of the company's APIs.

## BALLINA

**Charles River Laboratories** has a facility in Ballina, dedicated to drug discovery, research animal models, and preclinical research.

## TULLAMORE

**Nexvet Biopharma** has a facility in Tullamore to produce mAbs for veterinary care.

## CLARECASTLE

**Roche** manufactures APIs in Clarecastle and has its Irish headquarters in Dublin. ■

*Scott Fotheringham, PhD, and James Hale*

## References


1. Heavey, B. "A Tale of Irish Biopharma." *The Medicine Maker*, June 2016. https://themedicinemaker.com/issues/0616/a-tale-of-irish-biopharma/
2. IDA Ireland. http://www.idaireland.com/business-in-ireland/industry-sectors/bio-pharmaceuticals/
3. Keown, A. "BIO2016: Ireland Still Attracting Biotech, Pharma Companies to Set up Shop." *BioSpace*, 9 June 2016. http://www.biospace.com/News/bio2016-ireland-still-attracting-biotech-pharma/422798?type=sm&source=twitter_060916irelandbio
4. Carroll, J. "What's Ahead for UK Biotechs in the Wake of Brexit? It's Not a Pretty Picture." *Endpoints News*, 24 June 2016. http://endpts.com/whats-ahead-for-uk-biotechs-in-the-wake-of-brexit-it-may-not-be-pretty/?utm_medium=email&utm_campaign=5%20Brexit%20Top%205%20Phase%20III%20Sanofi%20CRISPR&utm_content=5%20Brexit%20Top%205%20Phase%20III%20Sanofi%20CRISPR+CID_41d9739ae448959392dbd0be3b15fe6b&utm_source=ENDPOINTS%20emails&utm_term=Whats%20ahead%20for%20UK%20biotechs%20in%20the%20wake%20of%20Brexit%20Its%20not%20a%20pretty%20picture
5. Osborne, K. "Brexit Implications for British Pharma ... A Month On." *The Pharma Letter*. 23 July 2016. http://www.thepharmaletter.com/article/brexit-implications-for-british-pharma-a-month-on
6. Hilliard, M. "Alexion Announces New €100M Facility in Athlone." *The Irish Times*, 7 July 2016. http://www.irishtimes.com/business/health-pharma/alexion-announces-new-100m-facility-in-athlone-1.2713541
7. Sustainable Energy Authority of Ireland. http://www.seai.ie/lienreport/company-cork-lower-harbour-energy-group.html
8. National Institute for Bioprocessing Research and Training (NIBRT). http://www.nibrt.ie/aboutnibrt
9. International Society for Pharmaceutical Engineering. Facility of the Year Awards. "2012 Facility of the Year Awards Category Winners!" http://www.facilityofthyear.org/index.php/ci_id/1881/la_id/1.htm
10. Engineers of Ireland. "SFI and Pfizer Announce Biotherapeutic R&D Programme for Ireland." Engineers Journal, 18 April 2016. http://www.engineersjournal.ie/2016/04/18/sfi-and-pfizer-announce-rd-programme-for-ireland/
11. Alexion. http://alexionpharma.ie
12. Gleeson, C. "Pharma Group Shire to Create 400 Jobs in Co Meath." *The Irish Times*, 15 April 2016. http://www.irishtimes.com/business/health-pharma/pharma-group-shire-to-create-400-jobs-in-co-meath-1.2612014
13. O'Carroll, L. "Ireland Calls for EU Drug Agency to be Moved from London to Dublin." *The Guardian*, 1 August 2016. https://www.theguardian.com/business/2016/aug/01/ireland-calls-eu-drug-medicines-agency-moved-london-dublin

# CRISPR: Genome Editing to Aid Drug Discovery

**We have known for nearly 30 years that Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene that lead to an absence of a protein required to keep muscle intact. Onset begins in early childhood for the roughly one in 3,600 boys who are affected, and their life expectancy, although rising due to advances in care, remains only approximately 25 years. Merely reading the DNA sequence of normal and mutant dystrophin genes has been of little help in producing an effective treatment. The latest technology to revolutionize genetic engineering—a tool called CRISPR that can actually edit what we've read—promises to change that.**

CRISPR—Clustered Regularly Interspaced Short Palindromic Repeats—was discovered and applied in 2012 by Jennifer Doudna, Emanuelle Charpentier, and Feng Zhang. Who discovered what first is the subject of an ongoing patent fight that won't be decided until at least November.[1] Meanwhile, each of these researchers has cofounded their own companies and forged licensing deals with DuPont, Novartis, Bayer, Regeneron Pharmaceuticals, GE Healthcare, and others.[2]

There are an estimated 50,000 scientists using CRISPR,[3] a testament to the fact that although CRISPR is not the first sequence-specific DNA modification technology—zinc finger nucleases and transcription activator-like effector nucleases came before—it is by far the most powerful, fastest, cheapest, and easiest to use.

It has already been used to correct mutations that cause DMD both in mice[4] and in human cells,[5] although experts believe we won't see a gene repair treatment of that disease for at least 10 years. In addition to DMD, researchers have corrected mutations in mice that cause hereditary tyrosinemia,[10] Huntington disease,[11] a rare liver disease,[12] and retinitis pigmentosa in human stem cells.[13]

Although engineering out disease-causing mutations in patients attracts considerable attention, most researchers agree that a more immediate benefit of CRISPR is the acceleration of the drug development pipeline.

> **"The real opportunity of CRISPR is in drug discovery"**
>
> — Riley Doyle, Desktop Genetics CEO

"When it comes to applying CRISPR, people think first of cell line engineering or gene therapy," said Riley Doyle, the CEO of Desktop Genetics, a company that works with scientists to perform gene editing experiments using CRISPR. Desktop Genetics designs libraries, delivers transfection-ready material, and analyzes data. "But the real opportunity of CRISPR is in drug discovery."

## A Guided Missile System for Cutting DNA

It has become routine for scientists to manipulate modular chunks of DNA like LEGO blocks, reassembling them, and introducing them into an organism or cultured cell line to achieve a desired outcome. Gene editing extends this manipulation, allowing in vivo correction of a mutation, insertion of a novel gene for the production of a protein, or knockout (disruption) of a gene to discover its function or to create an animal model.

One of these scientists is Ellen Jorgensen, PhD, a molecular biologist and the cofounder of Genspace, a not-for-profit in Brooklyn, New York, that aims to improve science literacy, specifically in molecular and synthetic biology. She and her team deliver CRISPR workshops – basic knowledge as well as hands-on genetic engineering laboratories – for lay people and scientists.

"CRISPR is a guided missile that makes a double-strand break in DNA at a specific point in the genome," she said. "Then, the cell's natural repair processes rush in to repair the break. During that repair, there's an opportunity for us to direct it to make the alteration we want, either an insertion, a deletion, or repair of a mutation."

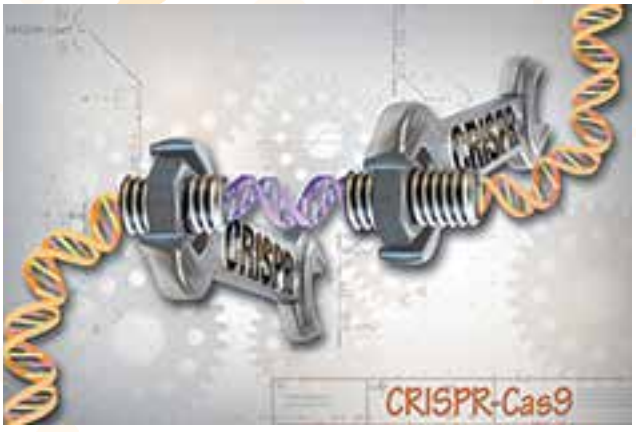
CRISPR, derived from the bacterial immune system of *Streptococcus pyogenes,* has two parts: a guide RNA (gRNA) and an enzyme called Cas9 that cuts DNA. (The system is sometimes referred to as CRISPR/Cas9 to signify that it is made up of two parts.) The guide is a short piece of RNA that directs the Cas9 to a complementary sequence where it introduces a precise double-strand break in the DNA. Jorgensen refers to Cas9 as the missile warhead and the gRNA as its guidance system.

Putting the broken DNA back together depends on the cell's two endogenous DNA repair systems. Nonhomologous end joining sticks the two ends of the double-strand break together. It occurs after a random sequence is inserted between the two ends, which leads to inactivation of the gene. Homology-directed repair (HDR) uses a complementary sequence as a template to repair the break. The matching sequence can either come from the genome or is introduced exogenously into the cell. Correction of a mutation can result by HDR if a complementary sequence containing the nonmutated sequence is available.

Jorgensen sees the biggest contribution of CRISPR being the acceleration of all basic and biomedical research. "CRISPR radically changes the timeline of experiments. The turnaround time is now days instead of the months it used to be. You can custom order a short piece of DNA that has been cloned into a plasmid, and codes for a guide RNA, and receive it almost overnight from a gene-synthesizing company."

The market for genome editing is projected to be worth $3.5 billion by 2019, which includes biomedical, bioenergy, and agricultural uses.[6] Caribou Biosciences, Editas, Intellia, CRISPR Therapeutics, and the Parker Institute are some of the main players in the race to bring gene-editing technology into clinical trials. Cellectis SA (a Pfizer partner) is using it to make CAR-T candidates, while AstraZeneca is applying CRISPR in its drug discovery and development units.[7]

**The market for genome editing is projected to be worth $3.5 billion by 2019**




*CRISPR-Cas9 – By Ernesto del Aguila III, NHGRI [Public domain], via Wikimedia Commons*

## Uses in Drug Discovery

Some of the first biomedical CRISPR applications will be to make animal models of human disease. To produce a diabetic mouse, for example, the first step would be to use CRISPR to change the mouse genome so it is more like the genome of the diseased human.

Some of the most enthusiastic adopters of CRISPR include Chinese scientists who have used it to engineer monkeys with the goal of developing primate models of Alzheimer disease and other neurological diseases.[8]

"One of the most interesting things people are doing with CRISPR is creating better drug-testing models, both at the cell line level and in animals," said Doyle. "They can create humanized mice, rats, pigs, and monkeys to act as models for their precise biologics." This is necessary because a company can't test a drug, such as a humanized antibody, in a monkey or a mouse because it will be immunogenic to that species and won't give an accurate result.

CRISPR can be used to knock out a gene as part of the drug development process. Prior to CRISPR, it was time-consuming to discern gene function for genomes as large as the human one, with its tens of thousands of genes.

"Before CRISPR, knocking out a specific gene to create an animal model of human disease was a laborious process," Jorgensen said. "You can multiplex cheaply by generating multiple 20-nucleotide guide RNAs for the one Cas9 protein. This way, CRISPR hits multiple targets at once. And once you have an animal model, then you can test drugs."

This is how George Church and his team at Harvard University simultaneously knocked out 62 different endogenous retroviral genes in the porcine genome with the goal of producing an animal source of human heart valves.[9]

"We've generated libraries containing 80,000 guide RNAs for clients because they wanted to knock out every gene in the genome," said Doyle. "If you've got the data analysis capabilities, which is where we come in, then you can pull out a lot of interesting information.


*Crystal structure of Streptococcus pyogenes Cas9 in complex with sgRNA and its target DNA at 2.5 A˚ resolution – By Hiroshi Nishimasu, F. Ann Ran, Patrick D. Hsu, Silvana Konermann, Soraya I. Shehata, Naoshi Dohmae, Ryuichiro Ishitani, Feng Zhang, and Osamu Nureki [CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0)], via Wikimedia Commons*

"Gene function can be elucidated using CRISPR, but it's often of secondary concern." Instead, researchers use the first screen to identify whether or not the gene is essential to survival. If the gene is essential under certain conditions and it's known to be involved in some pathways and the disease biology seems to make sense, then the next step is to find a druggable locus.

"CRISPR also allows you to target specific sequence motifs of a gene with programmable negative selection, then look at the influence on the cell with or without drug present," Doyle concluded.

This requires the design of a library of gRNAs to target specific motifs or regions of the target gene. The gRNAs are synthesized, delivered into cells along with a gene encoding Cas9—using virus vectors, electroporation, or lipid-based carriers—and observed under specific conditions. For example, the cells might be grown in the presence of an experimental drug. If a specific gRNA leads Cas9 to cut a gene that is essential for survival in the presence of the drug, that gRNA will be depleted over the course of the assay as the cells in which it functions die. Depletion of that specific gRNA indicates that an essential function has been targeted.

"A fancier experiment would be to target promoter regions or target functional domains of a gene exclusively," said Doyle. "You could target a set of genes in a particular pathway. You could target one gene in detail, say with one hundred guides targeting one gene. You're going to find the active sites. Because CRISPSR is fast and cheap, the sky's the limit."

## Bottlenecks

As powerful as this new generation of gene-editing tools is, it's worth keeping in mind that it is only four years old. As with any hot new technology, companies that produce reagents are scrambling to get CRISPR products out and some have not performed as advertised.

**Most researchers agree that a more immediate benefit of CRISPR is the acceleration of the drug development pipeline**

"CRISPR doesn't work as well as people say it does right now," Jorgensen admits. "The media use the words 'easy and cheap' so often, and the people who have pioneered it have been such great advocates, that scientists can be embarrassed to admit that they tried it and it didn't work in their labs. It's not fully plug-and-play yet."

Despite this, Jorgensen is optimistic about its prospects. "We'll figure out more of the rules we need to get it to work in different cell types and organisms, each of which has a unique DNA repair pathway."

Three hurdles to applying CRISPR to human disease are delivery of the CRISPR system to cells, ethical objections, and off-target mutagenesis.

"These therapies suffer from the same bottlenecks as any gene therapy," Jorgensen said. "You have to deliver CRISPR into the cell and deliver it locally to the right cell. You need accessible tissue. In cystic fibrosis, you could potentially load it into a virus that infected lung cells. Once you get it into the cell the edit is made efficiently and precisely."

The ethical concerns, although not limited to human embryo manipulation, begin there. When alterations are introduced in germ line cells or embryos, the changes are permanent. In an experiment that raised red flags in the scientific community and beyond, Chinese scientists used CRISPR to modify nonviable human embryos.[8]

"I don't know when editing the human germ line will happen, but I think it will eventually," Jorgensen said. "Proponents of CRISPR point to the scepticism that people had for in vitro fertilization when it was introduced. Now it's a completely acceptable technology."

Technical difficulties specific to the CRISPR system are another holdup, and have to be worked out in each case. One is off-target mutagenesis, which are mutations that occur in genes other than in the intended one. These need to be minimized, especially in therapeutic applications.

The problem of off-target hits is exacerbated when researchers design their gRNA libraries based on published genome sequences and not a particular cell line.

"You have to take into account the genotype of the human or mouse cell line you're using," said Doyle. "Ideally, you'd do them in primary cell lines, such as cancer patient–derived cell lines. Research lines or real-world clinical cell lines do not look like the reference genome. They have copy number

variations, polyploidy, all sorts of crazy stuff going on, which affects the design of experiments. If your cell line has four copies of an essential gene, do you have to knock out all four?"

The pace of gene-editing research continues to ramp up. Zhang and his colleagues recently announced the discovery of a new CRISPR system that targets RNA instead of DNA, using a protein called C2c2.[14] Like Cas9, C2c2 uses a gRNA, but unlike Cas9, it seeks out and degrades cellular RNA. It promises to be a new way to use RNA interference to manipulate intracellular levels of RNA and, thus, gene expression, in a process known as gene knockdown that can be used to study and treat diseases.

"These tools are going to have a lot of impact on how we test our drugs, discover targets, and validate those targets, all of which are really important to the overall discovery process," Doyle concluded. "Biologics fail usually because the disease biology is wrong. Where CRISPR can really help is to make sure we're making the right products."

Whether it's applied to drug development or gene-repair therapies, CRISPR is going to have wide-ranging effects for the biopharmaceutical industry. Hopefully, in 10 years, we'll look back and see CRISPR as the beginning of a number of success stories in biologics and gene therapies. ■

*Scott Fotheringham, PhD*

**CRISPR can be used to knock out a gene as part of the drug development process.**

## References


1. Begley, S. "In the CRISPR Patent Fight, the Broad Institute Gains Edge in Early Rulings." *STAT*. 18 March 2016. https://www.statnews.com/2016/03/18/crispr-patent-dispute/
2. Garde, D. "A Lucrative Wrinkle in the CRISPR Patent Fight." *STAT*. 7 July 2016. https://www.statnews.com/2016/07/07/crispr-patent-fight-evotec/
3. Riley Doyle, pers. comm. According to Desktop Genetics, using data from Addgene.
4. New release. "Gene-editing Technique Successfully Stops Progression of Duchenne Muscular Dystrophy." UT Southwestern website. 31 December 2015. http://www.utsouthwestern.edu/newsroom/news-releases/year-2015/dec/duchenne-muscular-dystrophy-olson.html
5. Al Idrus, A. "Using CRISPR/Cas9, UCLA Team Corrects Duchenne Mutation in Human Cells." *FierceBiotech*. 17 February 2016. http://www.fiercebiotech.com/r-d/using-crispr-cas9-ucla-team-corrects-duchenne-mutation-human-cells?mkt_tok=3RkMMJWWfF9wsRokuq%2FOce%2FhmjTEU5z16u0vW6Oxh5l41El3fuXBP2XqjvpVQcZkN7HIRw8FHZNpywVWM8TILtkUt9hsLQziDW0%3D&utm_medium=nl&utm_source=internal
6. Markets and Markets. "Genome Editing/Genome Engineering Market by Application (Cell Line Engineering, Animal & Plant Genetic Engineering), Technology (CRISPR, Antisense, TALEN, Zinc Finger Nuclease) & End User (Biotechnology & Pharmaceutical, CRO) - Global Forecast to 2019. Report BT3380. April 2015. http://www.marketsandmarkets.com/Market-Reports/genome-editing-engineering-market-231037000.html
7. Taylor, NP. "AstraZeneca Taps CRISPR to Extract Value from Genome Data." *FierceBiotech*. 1 February 2016. http://www.fiercebiotech.com/genomics/astrazeneca-taps-crispr-to-extract-value-from-genome-data
8. Larson, C. "China's Bold Push into Genetically Customized Animals." *Scientific American*. 17 November 2015. http://www.scientificamerican.com/article/china-s-bold-push-into-genetically-customized-animals/
9. Wyss Institute. "Removing 62 Barriers to Pig-to-Human Organ Transplant in One Fell Swoop." 11 October 2015. http://wyss.harvard.edu/viewpressrelease/222/removing-62-barriers-to-pigtohuman-organ-transplant-in-one-fell-swoop
10. Yin, H. et al. "Genome Editing with Cas9 in Adult Mice Corrects a Disease Mutation and Phenotype." *Nature Biotechnology*. June 2014. 32(6): 551-553. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157757/pdf/nihms615982.pdf
11. Armitage, H. "Gene-Editing Method Halts Production of Brain-Destroying Proteins." *Science*. 20 October 2015. http://www.sciencemag.org/news/2015/10/gene-editing-method-halts-production-brain-destroying-proteins
12. Yang, Y. et al. "A Dual AAV System Enables the Cas9-Mediated Correction of a Metabolic Liver Disease in Newborn Mice." *Nature Biotechnology*. 1 February 2016. 34:334-338. http://www.nature.com/nbt/journal/v34/n3/full/nbt.3469.html
13. Press release. "CRISPR Use to Repair Blindness-Causing Genetic Defect in Patient-Derived Stem Cells." Columbia University Medical Center. 27 January 2016. http://www.eurekalert.org/pub_releases/2016-01/cumc-cut012616.php
14. Broad Institute. "New CRISPR System for Targeting RNA." *MIT News*. 2 June 2016. http://news.mit.edu/2016/new-crispr-system-targeting-rna-0602

# Using the Power of Biotechnology to Deliver Affordable Health Care

## Biocon's Innovation Mission in India

*Biocon Park*

**One has the impression, in speaking with her, that Kiran Mazumdar-Shaw asks herself "What else can I do?" several times a day. Those who have observed her career over the last four decades know her answer is always a variation on "Make health care affordable."**

**Gender barriers prevented her from pursuing a dream** of becoming a brewmaster in an Indian brewery. So when opportunity knocked and proposed a biotech startup, Kiran Mazumdar-Shaw, chair and managing director of Biocon, replied with "OK, that's something else I can do with my knowledge of enzymes and fermentation." That practical decision has shaped not only her business philosophy—it has put India on the path to becoming a global biotech innovation hub.

Over twenty years, what began as an Indo-Irish joint venture that made enzymes for diverse sectors including food, beverages and textiles evolved into a new answer to "What else can we do with fermentation technology?" This time the answer was biopharma. In the mid-1990s, India was "the epicenter of diabetes," and much-needed human insulin produced from recombinant DNA was so expensive it eluded the reach of those who needed it most. Mazumdar-Shaw saw the opportunity to change the equation.

"So I said, "why don't we try to develop recombinant human insulinusing our technology ?" recalls Mazumdar-Shaw. "That decision fueled a passion that burns still today: that of providing affordable access to life-saving drugs among those in need." The impact of that decision on India, both directly and indirectly, has been significant. Over the following decade, into the early noughts, Biocon expanded the market tenfold and reduced prices by 90%. Biocon, with Mazumdar-Shaw at the helm, challenged the Western business model of "low volume, high prices." This decision in the 1990s has made Biocon the fourth-largest insulin producer in the world. The company is expanding capacity by setting up Asia's largest integrated insulin manufacturing and R&D facility in Malaysia to address the global need for biosimilar insulins, which was commissioned in 2015 and is getting ready for commercialization

While Mazumdar-Shaw was driving Biocon's fermentation technology applications, she was also fostering a sustainable culture of innovation through strong investment in research and development, as well as building a cutting-edge ecosystem. Biocon sustains innovation in two ways, she says: "On the one hand, we strive to balance the business with evolutionary innovation to develop technologies that can deliver affordability, which enables us to develop biosimilars in a cost effective manner, On the other hand, we've made huge investments in breakthrough innovation for our novel biologics programs. Among them is the world's first oral-dosage insulin under development by Biocon.

"Most companies make their insulin using the *E. coli* bacteria," says Mazumdar-Shaw, "We make it using a proprietary patented technology that uses yeast, *Pichia pastoris*." In fact, by the end of March 2016 Biocon had more than 1,200 patents filed, of which 984 were granted. "Proprietary platforms may be imitative," says Mazumdar-Shaw, "yet they are nonetheless innovative."

Biocon has also developed novel yet affordable monoclonal antibodies that treat psoriasis as well as head and neck cancer, of which there is a high incidence in India, due to the prevalence of tobacco chewing.

*Biocon Academy*

*In the lab*

## Turning Education into Knowledge

Education plays a critical role in sustaining innovation at Biocon and developing a cutting-edge ecosystem. For Mazumdar-Shaw, what matters most is not what you learn, but how you apply what you have learned. "Translating education into high-end competitive knowledge, that's what it's all about," she says. And so she has set about developing the capabilities and competencies of talent in India and nearby Malaysia.

Biocon Academy, a Center of Excellence for Advanced Learning in Applied Biosciences, was established in 2014, with the US-based Keck Graduate Institute. Its mission is to develop high-end talent to create a globally competitive biotech ecosystem in India. Its programs offer a broad-based curriculum that includes classroom sessions, hands-on training, and practical industry exposure. This industry-oriented approach is designed to unlock the true potential of life sciences students, helping them build successful careers as biotechnologists, microbiologists, molecular biologists, and biochemists.

Last year it added two programs to its flagship certificate program in biosciences; one in biosciences management and another in applied industrial microbiology. The academy has collaborated with the Birla Institute of Technology & Science, Pilani in India for its program in Applied Industrial Microbiology. The academy is a CSR initiative of Biocon and it supports all the students for a major portion of their fee.

"There is vested self-interest in this academy, I don't deny that, but our objective is to develop this talent not only for Biocon but for all the players in the industry. In fact more than ten companies have hired Biocon Academy students, and they are extremely happy with the quality of talent developed at the Academy," says Mazumdar-Shaw. "India has what it takes to become a global biotech innovation hub. And Biocon is committed to make that happen and will do what it takes to achieve that goal and thrive."

## Breaking Barriers with Credibility

While Mazumdar-Shaw's journey, and that of Biocon's, have not been without obstacles, she maintains that credibility is key to breaking through barriers—of gender, of racism, and of cultural bias. "Once you achieve success, you cross the credibility barrier and immediately negate skewed perceptions," she believes, "and that is as true for individuals as it is for organizations, and, even, countries."

India has had a relationship fraught with "perception hurdles" when it comes to the biopharmaceutical industry and regulation. While Mazumdar-Shaw concedes there have been problems in some areas, those same issues of data integrity and quality appear in Western countries as well. The difference, she says, is that what may be overlooked in the Americas or even Europe is scrutinized in India.

"Indian companies are going through a rough patch," she says. "Inspections that used to be regular and routine are now almost forensic in nature and heavily weighted against India.

"Yet, there is much at stake for Indian companies as well, and they are investing huge amounts of money to improve their quality systems." With

### Focused on Affordable, Available, and Accessible Innovation

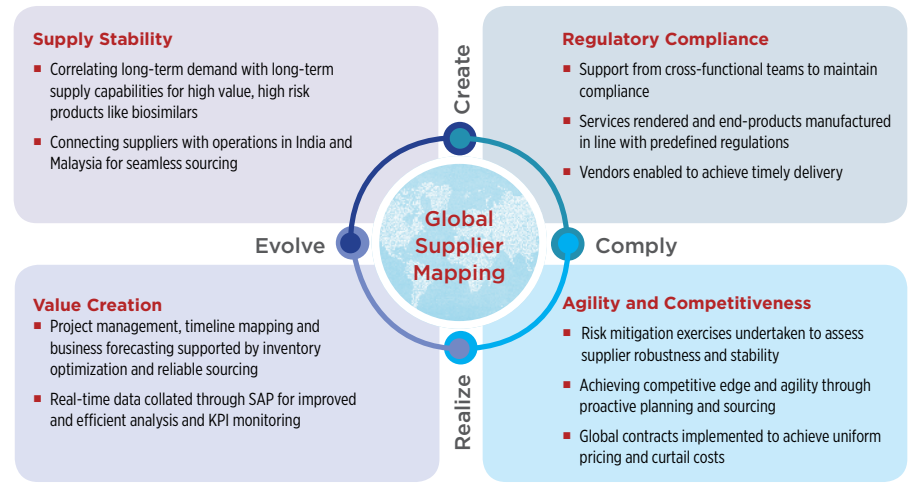
As an emerging global enterprise, Biocon addresses the needs of patients by taking a range of novel biologics, biosimilars, differentiated small molecules, and affordable recombinant human insulin and insulin analogs, from "lab to market." Investment in cutting-edge research has lowered therapy costs for chronic conditions like diabetes, cancer, and autoimmune diseases.

For diabetes patients, Biocon pioneered the development of Insugen, a recombinant human insulin based on proprietary fermentation technology, as well as Basalog, a long-acting insulin glargine.

In the anticancer therapy segment, patients now have access to BIOMAb EGFR, India's first indigenously produced novel monoclonal antibody for head and neck cancer . And for the treatment of HER2-positive breast cancer, Biocon produced CANMAb, an affordable trastuzumab follow-on.

Biocon also developed ALZUMAb, the world's first novel anti-CD6 monoclonal antibody for the treatment of chronic plaque psoriasis. This molecule also holds promise for a range of other autoimmune diseases.

**Robust Sourcing Strategy**




**Proprietary platforms may be imitative, yet they are nonetheless innovative**

India owning one-third of the generics market, similar success in biosimilars is entirely plausible.

Biocon enjoys strong track record with regulatory agencies, including the FDA. "We have had a strong focus on quality from day one, and we have a highly compliant culture mindset at Biocon. We wouldn't be able to succeed without it." In fact, Biocon's injectable 'ready to use' insulin glargine pen received approval and was launched in Japan, in what Mazumdar-Shaw calls "a great endorsement of our approach to quality."

## Proof Is in the Pudding

Compliance with quality standards and maintenance of data integrity are strong guarantors of a stable and healthy drug supply. But what happens when quality metrics are tied to the supply chain? Does it suffer? Mazumdar-Shaw's colleague, Prasad Deshpande, Biocon's Vice President and Head of Supply Chain believes quality metrics extend to the complete value chain of biopharmaceutical manufacturing and supply.

"At Biocon, our team knows that 'good quality of a drug manufactured' is not enough to ensure long-term supply stability. Supply chain excellence is critical to maintain the quality of drugs until they reach the patient.

"We understand the risks posed to supply stability due to an overlapping quality metric—such as supply shortages caused by frequent rejections—and cost pressures resulting from cost of compliance, increased cost of input, and cost of delivery, which are prevalent in the pharma industry. However, at Biocon our supply chain function operates on a well-crafted balanced supply stability plan, which works with cross-functional teams on various fronts. A collaborated effort toward business forecasting, planning, material sourcing and supply ensures a seamless inward and outward operation."

Some 400 people work 24/7 to ensure quality across the manufacturing process from testing to distribution, says Deshpande, so that "global regulatory benchmarks are achieved and surpassed." Investments in protocols, regular training, and upgrades of analytical labs and quality controls have helped Biocon maintain a strong compliance track record with no critical observations.

## Entrepreneurship and Innovation

Entrepreneurship is as much a state of mind as creativity is a state of being. Biocon is in the enviable position of being a leader in a growth industry in a burgeoning market. And that, says Mazumdar-Shaw, can present some very exciting opportunities for young professionals. "We are living in an ideas economy, where there is room for experimentation."

The inherent risk in innovation is failure, of course. "However," says Mazumdar-Shaw, "at Biocon we are fortunate that in our biopharma journey so far, the cost of failure has been affordable, since we are based in India and have leveraged our past expertise in the area of biotechnology." ■

### Maintaining an Agile Supply Chain

Ensuring an agile supply chain in a high-growth industry like biologics is complex. Consistent effort and presence in the ecosystem helps, says Deshpande. "We have leveraged our prudent risk-management capability to develop and sustain a dynamic supply chain that is compliant, efficient, and flexible, and [this] makes it possible for our drugs to be affordable and first to market."

Deshpande identifies four factors that help Biocon maintain supply chain agility:

1. **Actively managed raw material supply and regulatory-compliant suppliers** developed through active business relationships with key suppliers, supply quality monitoring, and continuous supplier evaluation
2. **Supplier risk assessment and plans for mitigation** created by multivendor and multisite manufacturing capabilities within the supplier base to address extended supply chain interruptions
3. **Effectively managed inventory monitoring systems** maintained by appropriate operational and strategic stock levels
4. **Robust and secure logistics/distribution networks** maintain biologics product quality and integrity with temperature-controlled environments throughout storage and transportation

# Fostering the Next Generation of Biotech Entrepreneurs

## JLABS Opens Incubator Space at Texas Medical Center

*Melinda Richter, Head of Johnson & Johnson Innovation, JLABS*

**Melinda Richter believes that the design and production of biopharmaceuticals, medical devices, and consumer health care products require a culture of innovation reminiscent of what is seen in Silicon Valley.**

**In localized hubs of life science entrepreneurship**—places like San Francisco, Boston, and Research Triangle in North Carolina—like-minded visionaries can rub shoulders, living and breathing drug and medical device development in the way their counterparts in software development do. Yet pioneering a new product or service in the health care space takes more than a community of complementary activity; it requires mentoring, huge amounts of capital, and expensive equipment.

"Let's say you have what you think could be a drug," said Richter, who is the head of Johnson & Johnson Innovation, JLABS. "Before you turn the lights on, it takes at least a year to get the money for equipment, to get a specialized operation team in place, and to get permits and licenses. Then it can take eight to 12 more years, and potentially billions of dollars, to bring your product to market. As an entrepreneur, which industry would you rather enter? You'd go into tech, unless someone could help make commercialization in health care just as quick, and just as easy, to get started."

JLABS aims to do just that with its model of "incubators," which house start-up companies that need support to get from the conceptual stage of a good idea to development.

*JLABS @ SSF*

**JLABS @ TMC will eventually house up to 50 startups.**

"Great technology is just as likely to come from outside the walls of J&J as inside," said Richter. "But outside, those discoveries face many more hurdles before they can become a viable commercial entity. It's in the industry's best interest to help remove those hurdles and foster an environment where innovation thrives. And when you do this together with entrepreneurs, you create a community in which there is not only collaboration and cooperation, but also healthy competition."

*JLABS@SSF*

JLABS opened its fifth life sciences incubator in March at the Texas Medical Center (TMC) in Houston, known as JLABS @ TMC. While most of the 26 companies accepted into the new facility are involved in the development of biologics, there are also start-ups looking to produce medical devices or consumer health applications. JLABS @ TMC will eventually house up to 50 start-ups. There are an additional two JLABS in San Francisco, one each in San Diego and Boston, and a sixth in Toronto that just opened in May—the first outside the US.

By embedding facilities in localized regions rich in medical research and health care services, JLABS aims to accelerate the translation of ideas and research into commercial entities through education, funding, and networking events.

"We want to instill a sense of confidence in entrepreneurs," Richter said. "We want them to know that they can be in locations beyond the San Francisco Bay area or the Boston/Cambridge area and be successful."

In addition to facilities and equipment, JLABS provides partners with access to on-site operations teams that allow scientists to focus on research; to business services that support them as they create and run a business; and to partner services, like HR, finance, insurance, and more; to mentors across J&J from different areas of expertise.

"This is where the big-company advantage comes in," Richter said. "Most of these entrepreneurs have never gone through development and manufacturing, have never had to think about the commercial side of things or regulatory concerns. We can provide that kind of support for early-stage companies."

Richter refers to it as a pay-for-play model that comes with no strings attached to J&J, such as first right of refusal, rights to the IP, or equity. Partners are able to choose whatever configuration of space fits their needs. The model is flexible and can grow with companies as they continue to succeed and grow.

"Our goal is to catalyze the ecosystem so that it produces a higher volume and better quality of innovator," she said. "In the end, we hope we get to know each other better; and when it's right for them, and for us, we hope we'll do a deal. But that's not a precondition to be at JLABS."

**Our goal is to catalyze the ecosystem so that it produces a higher volume and better quality of innovators**

Companies can sign traditional deals with J&J, such as collaborations, licenses, or equity investments, or enter into nonconventional arrangements. Richter gives a hypothetical example of a start-up that doesn't have enough data to secure additional capital. "We might suggest a contract for three months and $100,000 to conduct an experiment that will tell us what to do next. This can be pivotal for early-stage companies that don't have the money to do those things and won't get venture capital without demonstrating that the science and technology are viable."

Xycrobe Therapeutics, a partner company at JLABS San Diego that hopes to use the microbiome to treat inflammatory skin conditions, recently inked a deal with J&J Innovation. Together, they will collaborate to obtain a proof of concept of Xycrobe's platform.

JLABS partners are supported by Johnson & Johnson Innovation science leads for therapeutic areas that include immunology, neuroscience, cardiovascular/metabolics, infectious disease/vaccines, and oncology. There is also a medical device science lead and a consumer science lead.

"Our experts take a look at a company to determine if the science and technology are exceptional, and have the potential to become a critical solution," Richter said. "If so, they get accepted into JLABS."

## The Attractions of Houston

Half of the 34,000-square-foot JLABS @ TMC facility is shared lab space filled with state-of-the-art equipment that would typically cost a company $5 to $10 million. The other half is separated into individual labs, private offices, and support services provided by JLABS. A rental space can be as

*Entry and event space at JLABS@TMC*

small as a five-foot bench that would give someone access to all the equipment and other services.

"This is a flexible model that gives start-ups the option to grow," Richter said. "They can start with a minimal investment, get proof of concept, then go and get millions of dollars of additional capital once they have something viable to show investors."

Houston caught Richter's eye for a number of reasons. Topping the list is the TMC—JLABS is located within the TMC Innovation Institute—the innovation hub of the Texas Medical Center, which is the largest medical center in the world, with 56 coordinated member institutions offering research and healthcare services. All the organizations connected with the TMC share a centralized internal review board, which streamlines applications for clinical trials. She was also attracted to the more than 160 life sciences companies in the city; the $1.8B in academic research investments that occur annually in the city; the presence of Baylor College, which is a leader in genomics and one of three large-scale sequencing centers in the US; and that the governor of Texas recently approved $3 billion in funding for oncology research over the next ten years to such institutions as the MD Anderson Cancer Center.

"Put all this together, then add on the top-notch executive team that is taking the TMC to a whole new level," Richter said. "Dr. Robert (Bobby) Robbins, president and CEO of the TMC, came from Stanford and brought that 'Silicon Valley spirit' with him to Houston. We knew that if we brought JLABS there, we could not only make an impact in that region, we could also make an impact for patients around the world."

For Richter, JLABS is as much about encouraging the next generation of leaders as it is about supporting today's biotechnology entrepreneurs.

"We want to make these facilities as hip and cool as Apple's or Google's," Richter said. "They're futuristic places designed for today's eighth grader, so that by the time they graduate they will still want to work here. We want to inspire young people to get into STEM [science, technology, engineering, and mathematics] programs. When you provide a platform that makes it much easier, more of a recipe, and less of an unknown, suddenly creating great solutions that make a difference becomes achievable." ■

# Environmental Footprints of a Flexible Pharmaceutical Production Facility:

## A Life Cycle Assessment Analysis

*Johannes Tvrdinić and David Estapé, PhD*

**In recent years,** the industry has been experiencing a noticeable surge in the demand for manufacturing facilities designed to be more resource and energy efficient. Fueled by green policies, the growing environmental consciousness of stakeholders, or the sheer awareness that it is good for business, companies continue to push to enhance their sustainability performance. It has become evident that sustainability has reached mainstream and is here to stay.

Attaining a better understanding of the key factors responsible for the environmental impacts of a manufacturing facility, therefore, becomes increasingly relevant. This is particularly important to target sustainability efforts effectively.

In this case study, a holistic approach is applied to capture and analyze the impact of a biopharmaceutical production facility in its entirety. Therefore, the whole life cycle—from construction to operation and demolition—is examined using life cycle assessment (LCA).[1,2] Impacts that occur directly onsite and offsite are equally considered. These include, for instance, impacts related to the manufacturing of materials, transportation of goods, and energy used in the facility or connected with the disposal of waste.

A parameterized facility model is used to simulate and compare different facility configuration production scenarios. For instance, the number of production bioreactors, their batch volume and batch frequency per year, and the facility lifetime are varied. These scenario variations enable one to determine key environmental impact drivers and acquire a better understanding of relationships between facility systems.

The results indicate that the key drivers for the environmental sustainability are not necessarily found directly at the facility, but rather in the supply chain.

## Model Facility and LCA

### The Facility

The model production facility was specifically selected to represent current trends in the biopharmaceutical industry that aim for more flexibility at a smaller scale. The facility employs exclusively single-use bioprocess systems up to a 2,000-L scale and is built up using modular construction. The production is based on a typical process for monoclonal antibodies (mAbs) with a titer of 3 g/L. China was the preferred location to be evaluated.

The parameterized facility model enables analysis and comparison of various possible facility configurations. For instance, the number of production bioreactors, the process scales, or the batch frequency can be varied. Table A lists the parameters that can be modified and their value ranges considered in the facility model.

The process itself follows a generic mAb process flow. Upstream operations include media preparation, seed train, production bioreactors, and a clarification step. Downstream activities are composed of buffer preparation, capture, intermediate and polishing chromatography steps, ultrafiltration/diafiltration systems, and virus and bulk final filtration operations. The upstream and downstream process trains are operated in cleanrooms class D and class C, respectively.

**Table A: Overview of the Facility Model Paramet**

| Parameters | Value Range |
|---|---|
| Number of production bioreactors | 1 – 4 |
| Production bioreactor volume | 500 L, 1,000 L, 2,000 L |
| Number of batches per bioreactor per year | 1 – 25 |
| Facility footprint (area) | Small, medium, large* |
| Facility lifetime | 1 – 30 years |

*Total facility area in the range of 2,200 – 2,700 $m^2$ (24,000 – 29,000 $ft^2$)

## LCA and System Boundaries

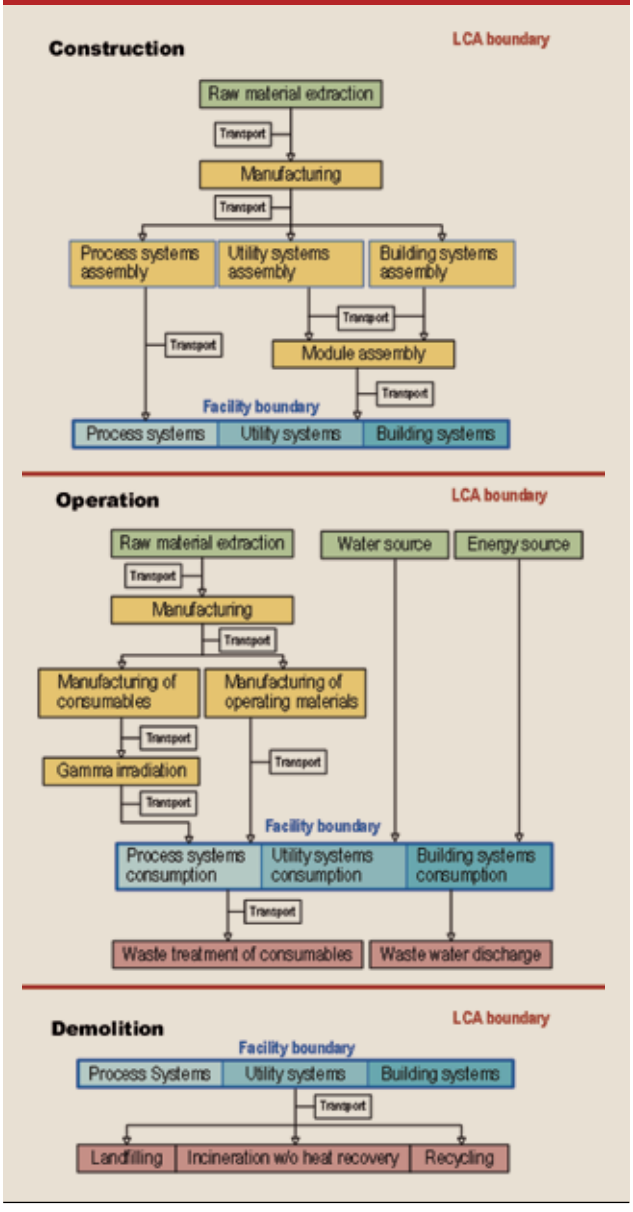
The LCA was carried out in accordance with ISO 14040 and ISO 14044 requirements.

The assessment was not limited to the facility site. It considers all materials and resources utilized and waste and emissions generated worldwide as a result of the facility's existence. The environmental impact evaluation was also not limited only to the operational phase of the facility. It included the construction and, in the supposed case, it reaches the end of life, the demolition impacts. In this way, the transportation of the facility modules during the construction phase was also considered. Moreover, the facility lifetime (i.e., years of operation) was defined as a parameter in the model. Figure 1 is a schematic illustration of the LCA boundaries for each life cycle phase. The assessment encompasses the whole facility building. This entails process, utility, and building systems:

1. Process systems include all production equipment to actually run the process, from media and buffer preparation to all unit operations including production bioreactors, chromatography systems, tangential flow filtration and filtration systems, etc.
2. Utility systems provide process support. It includes supply systems such as purified water and water-for-injection (WFI) generation units but also waste treatment systems such as decontamination autoclaves or neutralization systems.
3. Building systems refer to the technical units that provide building services, for instance, heating, ventilation, and air conditioning (HVAC) units but also lighting and sanitary facilities. It also covers all cleanrooms (e.g., gowning, upstream and downstream process rooms, buffer and media preparation and holding, etc.) and technical areas.

The model is further organized combining the life cycle phases with the three system types. Following this structure, a detailed overview of all material, resources, and activities considered in the environment impact evaluation is presented in Table B. This entails, for instance, the manufacturing of construction materials, process equipment or consumables, sterilization of single-use consumables in a gamma irradiation facility, and transportation of all materials to and from the site, as well as the disposal of waste in waste treatment facilities. Moreover, geographic specific factors, such as yearly energy consumption of HVAC systems, energy mixes, and industry standard waste treatment technologies[3] are considered.

**Figure 1: Schematic illustration of the LCA boundaries per life cycle phase**




## Basic Assumptions and Data Sources

Process demand data, such as electrical power consumption, WFIs, or single-use bags, were collected on a per-batch basis, for all unit operations, at the 2,000-L process scale. For the 500-L and 1,000-L batch size, it is assumed that the process demand scales proportionally to the batch volume, except for the disposables and electrical power consumption. Data on electricity and consumables use at these volumes were collected independently. Furthermore, data for manufacturing of the entire process equipment, for every process scale, were also acquired from the equipment manufacturers.

The building systems consumption and construction material data (e.g., electricity and water use for HVAC or the steel and piping amount) were gathered for a medium-sized facility. These are assumed to scale linearly with the facility footprint (area).

Life cycle data on the used materials, resources, and technologies are based on GaBI,[4] ecoinvent 3.2 databases,[5] and environmental product declarations.

## Limitations

The case study does not consider the direct environmental impact from construction and demolition activities at the facility site. Construction and demolition are then based on the exhaustive material takeoff for the building and all systems.

**Table B: Overview of Materials, Resources, and Activities Considered in the Environmental Impact Evaluation**

| | Construction | Operation | Demolition |
|---|---|---|---|
| **Building Systems** | Manufacturing and transportation of:<br>■ **HVAC built-in parts**, such as: piping, piping trays, air handling units, filter fan units, insulation materials, silencers, fire dampers<br>■ **Media supply and waste treatment built-in parts**, such as: piping for potable water, steam and wastewater, sanitary facilities, insulation materials, fittings, pumps<br>■ **Building materials**, such as: steel structures, exterior plaster, insulation materials, flooring, cleanroom walls, steam brakes, gypsum fiberboard, wall covering<br>from the manufacturing site to the module assembly site, as well as:<br>■ Transportation of assembled modules to the facility location | Energy, resource, and utility consumption of:<br>■ HVAC units<br>■ Filter fan units<br>■ Hot water, chilled water, softened water, and water supply systems<br>■ Steam generation system<br>■ Lighting<br>■ Lifts<br>■ Sanitary facilities<br>■ Rainwater runoff | Disposal of all building systems' materials from the facility site, by:<br>■ **Waste incineration, without heat recovery** for high-calorific materials, e.g., plastics<br>■ **Recycling:** in particular for metals<br>■ **Landfilling** of inert waste, e.g., rock wool<br>including transportation of the materials to the waste treatment plant locations |
| **Process Systems** | Manufacturing and transportation of:<br>■ **Process equipment**, such as: production bioreactors, filter systems, chromatography systems, mixers, scales, pumps, single-use bags, tubing, connectors, bag assemblies, filter cartridges, chromatography columns<br>to the facility location. | Energy, resource, and utility consumption of each<br>■ Process step/unit operation in use<br>including:<br>■ Manufacturing of consumables, packaging, and operating materials<br>■ Sterilization of consumables at a gamma irradiation facility<br>■ Waste treatment of consumables and packaging waste in waste incineration plants and landfills<br>■ Transportation of consumables, operating materials, and wastes to and from the facility | Disposal of all process systems' materials from the facility site, by:<br>■ **Waste incineration, without heat recovery** for high-calorific materials, e.g., plastics<br>■ **Recycling:** for metals<br>■ **Landfilling** of inert waste<br>including transportation of the materials to the waste treatment plant locations |
| **Utility Systems** | Manufacturing and transportation of **utility equipment**, such as:<br>■ Purified water generation unit<br>■ WFI generation system<br>■ Thermal inactivation unit<br>■ Neutralization system<br>■ Decontamination autoclave<br>from the manufacturing site to the module assembly site | Energy, resource, and utility consumption of all:<br>■ Utility equipment<br>including:<br>■ WFI storage and distribution<br>■ Compressed air generation | Disposal of all utility equipment materials from the facility site, by:<br>■ **Waste incineration, without heat recovery** for high-calorific materials, e.g., plastics<br>■ **Recycling:** for metals<br>■ **Landfilling** of inert waste<br>including transportation of the materials to the waste treatment plant locations |

Moreover, commuting of personnel to and from work, as well as maintenance activities during operation of the facility, is not considered.

## Environmental Impacts

The study concentrates on the most relevant environmental impact categories. These are the climate change impact (in kg $CO_2$-equivalents), commonly known as carbon footprint, the primary energy demand (in MJ), and blue water use (in $m^3$).

In this article only, the climate-change impact is presented. Very similar trends were observed in the other two impact categories. For calculation of the climate-change impact, the IPCC 2007[6] impact assessment method was applied.

## Results and Discussion

### Total Environmental Impact

The total carbon footprint for a model facility over the entire lifetime is shown in Figure 2. It includes the total amount but also a breakdown into each life cycle phase: construction, operation, and demolition.

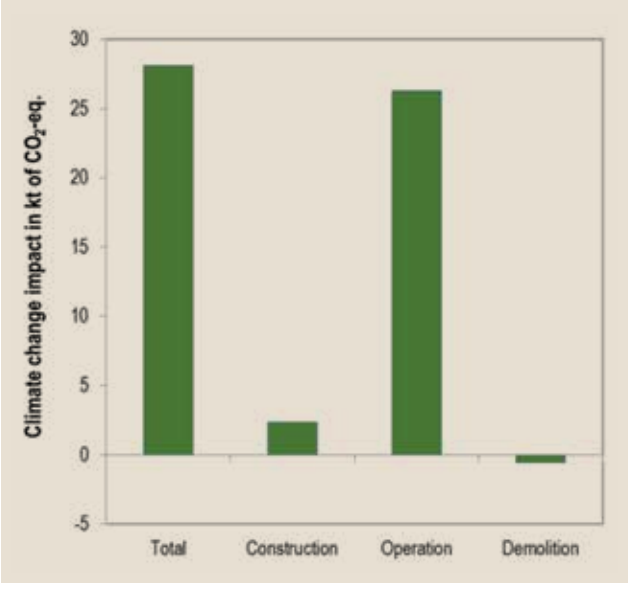
The overall carbon footprint totals close to 28 kilotons of $CO_2$-equivalents ($CO_2$). The absolute value will however strongly depend on the facility case study (i.e., batch size, titer, batch frequency, total number of bioreactors, years of operations, etc.). For instance, for a facility configuration with a four-times-higher yearly production capacity, the overall footprint reaches 64 kilotons of $CO_2$. In summary, one can expect that a higher facility capacity and longer lifetime lead to a higher overall carbon footprint.

The resulting specific construction impact of 116 kg $CO_2$ per $m^3$ is similar to 46 calculated for a prefabricated industrial building of similar volume.[7] The higher value could be attributed to the different building shell structure (i.e., modular vs. prefabricated) and the larger total floor and clean room wall area, apart from the difference on the scope definitions of both studies. The study for the prefabricated industrial building also reports lower specific values for the demolition (-2 instead of -43 kg/$m^3$ for this study) as well as for the transportation (1 instead of 37 kg/$m^3$ for this study). In both cases, the values are strongly dependent on the recycling level as well on the transportation distance (100 km by road instead of >21,000 km by road and container ship). These are expected to be much higher values for this model.

The operational phase can also be compared to previous studies. In this case, the 26 kilotons of $CO_2$ for the operational phase corresponds to 44 tons of $CO_2$ per batch or 7 kg of $CO_2$ per gram of product for a 3-g/L titer. These values are in the range of previous described carbon footprints for similar biopharmaceutical facilities. For instance, in a study performed by GlaxoSmithKline (GSK)[8] for a mammalian process at a clinical scale, the resulting carbon footprint benchmark is 65 tons of $CO_2$ per batch and 59 kg of $CO_2$ per gram of product. In another study published by GE Healthcare,[9] where single-use and stainless-steel systems are compared for a mammalian process, the climate change impact can be calculated as 22 tons of $CO_2$ per batch or 2 kg of $CO_2$ per gram of product. The differences between all three studies strongly depend on the definition of each case study (i.e., bioreactor volume, titer, batch frequency, etc.) but also on the scope definition (e.g., systems taken into account). Overall, the order of magnitude for all three studies seems to be in agreement, GE Healthcare and GSK being at the lower and upper ends, respectively.

Looking at the three life cycle phases, it is apparent that the major impacts occur during operation. This behavior can also be observed in office[10] and commercial[11] buildings. It is the result of the accumulated recurring impacts of activities over a long operational phase. With an average impact of approximately 1,900 tons per year and a facility lifetime of 15 years, the impact of the operational phase accounts for 94% of the total. For a longer facility lifetime, a larger proportion will be related to the operational phase. However, for a shorter facility lifetime such as 5 years, the operational phase still accounts for 83% of the impact. These values are slightly higher than the values reported for an office or commercial building where the operational phase accounts from 80%–90% of the total impact after 50 years of service time. This implies a larger impact of the operation for the biomanufacturing facility by the added energy and resources that are necessary to run a complex process in highly controlled environments.

**Figure 2: Total carbon footprint and distribution over the entire life cycle for a model facility.**




Model parameter settings: 2 × 2,000-L bioreactor volume, 20 batches per bioreactor and year, 15 years operational time.

Construction amounts just for 8% of the total impact, whereas the demolition offsets the overall impact by 2%. The "negative impact" of the demolition has to be understood as credits won through the recycling of material in the demolition phase, especially metals.

The impact in the construction phase is mainly related to the manufacturing of the construction materials for the building (57%) as well for the process equipment and utilities (28%). Even if the transportation of an entire facility, building modules, and equipment from Europe to China may appear controversial, it represents a very small portion of the total environmental impact (1%).

## Operational Phase

The analysis of the operational phase becomes essential to understand the environmental performance of the facility. In particular, it is necessary to examine the relationship between the three basic types of systems that define the operational phase as described previously (see Table B). These are process, building, and utility systems.

The comparison of three different facility configurations each with a different production output allows determining the relative impact between the different systems. The three bioreactor configurations analyzed are

2 × 1,000 L, 2 × 2,000 L, and 4 × 2,000 L. The number of batches per production bioreactor per year and the facility lifetime are the same across all configurations. Accordingly, the production doubles between configurations: for 4 × 2,000 L, the amount of mAbs produced is twice that of 2 × 2,000 L, or four times the amount of 2 × 1,000 L in the same time frame.

Figure 3 shows the breakdown of the impact for the operational phase for the three facility configurations. It can clearly be seen that with an increase in the production output, the carbon footprint grows significantly. By doubling the production output, the carbon footprint increases by approximately 25% and 60%.

Process system's impact grows at a very high pace every time the capacity doubles, between 40% and 100%. The result comes to indicate that the 2,000-L configuration is more efficient than the 1,000-L. Utilities system impact also increases but at a slower pace, between 38% and 55%. However, the increase of the production output has a limited influence on the environmental impact of the building systems, with a relative growth of 20% between a low and high output configuration. This is true even if a slightly larger facility were considered to accommodate four production bioreactors instead of two.

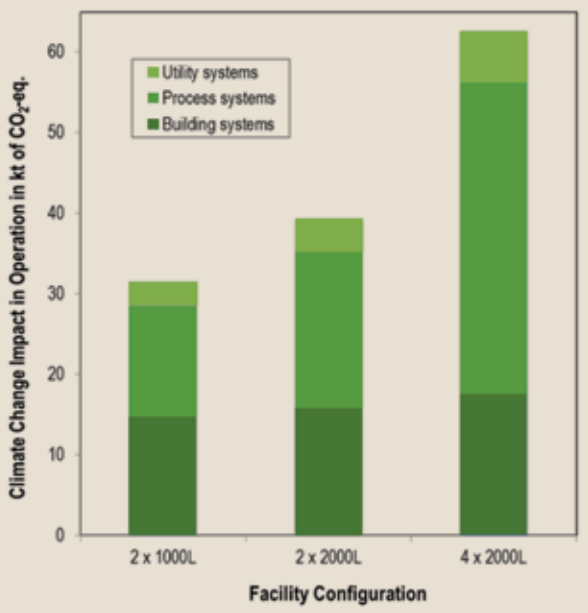
The increased production output also shows that the overall shares of the process systems rise from 44% to more than 60%. At the same time, the contribution of the building system decreases from 47% to just less than 30%. Utility systems remain almost constant at around 10%. These results point out that the building and process systems are the main contributors to the overall environmental impact. They also indicate that to mitigate the environmental burden of a manufacturing facility, more than just efficient design of HVAC systems is important. Also, the impact generated by process systems, particularly at high production outputs, needs to be considered and optimized.

These results also demonstrate the relevance of the functional units when different values or studies are compared. For instance, on a per-batch basis, the 1,000-L batch size shows a lower or similar environmental efficiency with 32 tons of $CO_2$ per batch, compared to 31 or 39 tons of $CO_2$ per batch for a 2,000-L scale. However, on a per-product basis, the 1,000-L batch with 11 kg of $CO_2$ per gram of product is higher than the 5 – 7 kg of $CO_2$ per gram of product for the 2,000-L batch. However, the authors' recommendation would be to compare results based on per gram of product basis when different scenarios or studies are compared. This seems to be more plausible, taking into account that the total impact is more logical to depend on the total product output (i.e., total mass of product) than on the number of batches per year, when this can have a different size and, consequently, different mass and energy demands or relative impact.

## Economy of Scale

The environmental impact caused by process systems was further examined to determine if it can be reduced at a larger process scale, as indicated in the previous analysis.

**Figure 3: Breakdown of the carbon footprint of the operation phase for three facility configurations, with increasing production output.**




Model parameter settings: 25 batches per bioreactor per year and 20 years facility lifetime for each facility configuration. This represents the highest production capacity for all three configurations enhancing the impact of the process systems.

For that, the process impacts of three configurations were compared:

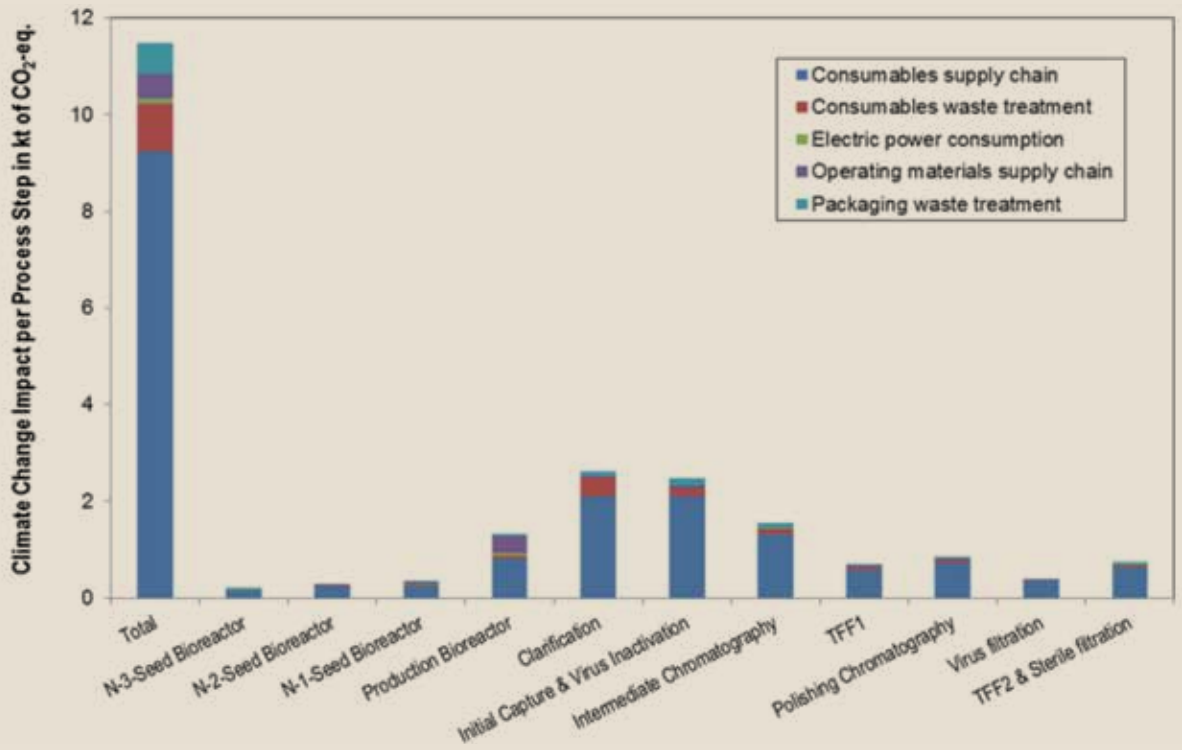
- 2 × 500 L, 24 batches per bioreactor per year
- 2 × 1,000 L, 12 batches per bioreactor per year
- 2 × 2,000 L, 6 batches per bioreactor per year

The three cases have the same production output over their lifetime (i.e., 72 kg of mAbs per year).

The calculated values are 7, 5, and 3 kg of $CO_2$ per gram of product for the 500-L, 1,000-L, and 2,000-L configurations, respectively. The results show that bigger-process scales lead to considerable environmental savings.

These savings do not necessarily originate from a reduced process demand (e.g., electric power consumption, etc.), but rather from the amount of used consumables and their size. The amount of plastic waste from consumables, excluding packaging, generated for a 500-L, 1,000-L, and 2,000-L batch are 357, 478, and 660 kg, respectively. Therefore, the relative amount of waste per kilogram of product is clearly reduced by increasing the batch size: 238, 159, and 110 kg plastic waste per kilogram of product. At larger process scale, the number and volume of the single-use bags are used more efficiently, resulting in a reduced overall demand for consumables.

**Figure 4: Breakdown of the process systems carbon footprint by unit operation in the operational phase according to process flow.**




Model parameter settings: 2 × 2,000-L production bioreactors, producing 20 batches per bioreactor per year over a 15-year facility lifetime.

## Process Systems by Unit Operation

The process systems carbon footprint breakdown by unit operation, following the process sequence, is shown in Figure 4. The impact per unit operation is further divided to identify the main impact causes. These include consumables (e.g., plastic bags) and operating materials (e.g., raw materials) supply chain, electric power consumption, waste treatment of consumables, and packaging waste. Supply chains hereby include the manufacturing, gamma irradiation at a different location if required and all transportation routes to the facility site.

It is important to note that just four unit operations—the production bioreactors, clarification, initial capture, and intermediate chromatography steps—are responsible for 69% of the environmental burden of the process systems in the operational phase. None of the remaining unit operations represents more than 7%. This impact distribution over the process flow corresponds to the unit operations with the largest size or volume. The handling of larger process volumes demands a larger size or number (i.e., total mass) of consumables, such as bags, tubing, connectors, or filter cartridges.

This is confirmed by looking at the total process systems breakdown per impact sources. The consumables supply chain is, by far, the major part of the environmental impact for each unit operation. In total, it is responsible for 81% of the impacts of the process systems that occur during the operational phase of the facility.

Considering that:

- 94% of the overall impacts of a manufacturing facility happen in the operational phase,
- 50% of those impacts are related to the process systems for a medium/average production output, and
- 81% of those impacts can be traced back to the consumables supply chain,

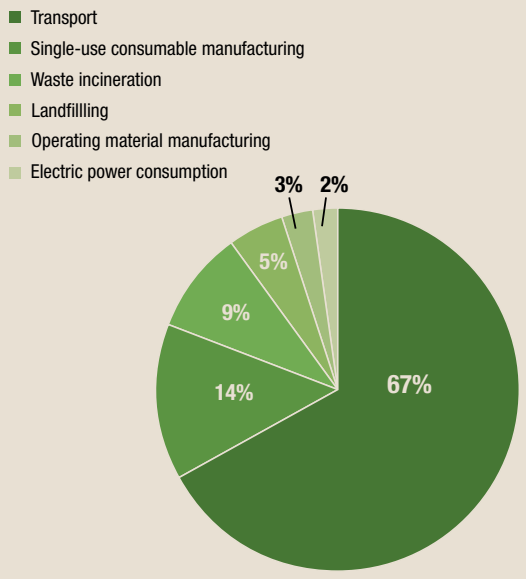
It can be reckoned that 38% of the total environmental impact of a facility, over its entire lifetime, is related to the consumables supply chain alone.

## Process Systems by Impact Sources

Process systems' operational footprint was further analyzed to identify key impact sources. This time, the supply chain impacts were split into manufacturing and transportation. Thereby, consumables manufacturing also includes packaging manufacturing and gamma irradiation of consumables. All waste treatment is broken down in waste incineration, without heat recovery and landfilling. Electric power consumption covers just the electricity necessary to run the process equipment, whereas transport considers all transports that occur (e.g., from the manufacturing site of consumables or operating materials to the biopharmaceutical facility or from the facility to the waste treatment location).

Figure 5 shows the impact breakdown following this approach. Although consumables are basically a mix of different kinds of plastics, their man-

**Figure 5: Breakdown of the carbon footprint for process systems in the operational phase by impact sources.**




Model parameter settings: 2 × 2,000-L production bioreactors, 20 batches per bioreactor per year and a 15-year facility lifetime.

ufacturing, including packaging and further treatment, has just a limited effect on the overall process systems' carbon footprint, with a share of 14%.

An important focus on the discussion around consumables has always been on their disposal, in particular considering that usually 478 and 660 kg of plastic waste, excluding packaging, are generated per a 1,000-L and 2,000-L batch, respectively. In this regard, the results show that the impacts related to their waste treatment only play a limited role (9%), even if it is comparable to their manufacturing impact (14%).

Nevertheless, the impact of consumables is very significant in relationship to their transportation. With a share of approximately 67%, the transportation impact clearly dominates the carbon footprint in the operational phase of the process systems. The reason for this is largely rooted in the huge transportation distances from the consumables manufacturing plant to the biopharmaceutical manufacturing site, which are located on different continents. Therefore, the consumables are often transported by plane over more than 12,000 km (7,456 miles). In contrast, the transportation impact for operating materials is much lower, due to the possibility to source operating materials regionally and with alternative modes of transportation.

It can be concluded that the location of the facility relative to the consumables manufacturing site plays a key role on the overall environmental impact of the facility. It also points out the challenging task of reducing the impact by optimizing the supply chain or the transportation system. Moreover, it demonstrates the need to understand the worldwide environmental impact of the facility more fully instead of focusing on the local impact around the facility site.

## Conclusions

Full modeling allows a holistic understanding of the environmental impact of a biopharmaceutical facility across its entire life cycle. This should allow us to define where to focus the effort if we intend to be more sustainable.

On the one hand, it confirms that the biggest impact occurs during the operational phase of the facility and all sustainability efforts should focus on this phase more effectively. On the other hand, it reveals that the largest impact (31%) of the operational phase relates to transportation and has little to do with the actual production process. As a consequence, it limits any sustainability improvement done at the site and challenges the supply chain or the facility location. Finally, it demonstrates that the efforts on HVAC optimization will have a larger contribution than, for instance, looking at alternative waste treatments of consumables, where a large part of the discussion is focused. ■

## References


1. International Organization for Standardization. ISO 14040: "Environmental Management—Life Cycle Assessment—Principles and Framework." Geneva, Switzerland, 2006.
2. ———. ISO 14044: "Environmental Management—Cycle Assessment—Requirements and Guidelines." Geneva, Switzerland, 2006.
3. Wells B., et al. "Guide to Disposal of Single-Use Bioprocess Systems." *BioProcess International* 5, no. 8 (2007): S24–S27. http://www.bioprocessintl.com/manufacturing/supply-chain/guide-to-disposal-of-single-use-bioprocess-systems-183977
4. Thnkstep. GaBi Software-System and Database for Life Cycle Engineering, copyright 1992–2016 thinkstep AG. (Compilation 7.0.0.19, DB version 6.110). www.gabi-software.com.
5. Swiss Centre for Life Cycle Inventories. ecoinvent Database (v. 3.2), 2010. www.ecoinvent.org.
6. United Nations. Intergovernmental Panel on Climate Change. "Climate Change 2007: The Physical Science Basis." Contribution of Working Group 1 to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change, by S. Solomon, et al. Cambridge University Press, Cambridge UK and New York. https://www.ipcc.ch/publications_and_data/publications_ipcc_fourth_assessment_report_wg1_report_the_physical_science_basis.htm
7. Bonamente, E., and F. Cotana. "Carbon and Energy Footprints of Prefabricated Industrial Buildings: A Systematic Life Cycle Assessment Analysis." *Energies* 8 (2015): 12,685–12,701.
8. Snyder, M, and D. Etherington. "Carbon Footprint Benchmarking, Biopharmaceutical Process Carbon Modeling and Optimization." Presented at the ISPE Annual Meeting, 12–15 October 2014, Philadelphia, Pennsylvania.
9. Flanagan, W. P. "An Environmental Life Cycle Assessment: Comparing Single-Use and Traditional Process Technologies for MAb Production." *BioProcess International* Special Report 13, no 11i (2015):10–16. www.bioprocessintl.com/manufacturing/single-use/toward-sustainable-engineering-practices-in-biologics-manufacturing.
10. Airaksinen, M., and P. Matilainen. "A Carbon Footprint of an Office Building." *Energies* 4 (2011): 1,197–1,210. file:///C:/Users/aloerch/Downloads/energies-04-01197.pdf.
11. Peng, Changhai, and Xiao Wu. "Case Study of Carbon Emissions from a Building's Life Cycle Based on BIM and Ecotect." *Advances in Materials Science and Engineering* 2015, article ID 954651 (2015).


## About the Authors


**Johannes Tvrdinić** is a project engineer at M+W Central Europe GmbH in Stuttgart, Germany. He graduated as an environmental engineer. His work focuses on the life cycle assessment of high-technology production facilities for diverse industries including pharmaceuticals, batteries, and microelectronics. He is a co-author of the ISPE Sustainability Handbook.

**David Estapé, PhD,** has over 20 years of international experience in facility design and GMP consulting within the biotechnology, vaccine, and blood plasma pharmaceutical sectors. He is currently Technology Manager for Life Sciences at the Global Business Unit Life Sciences and Chemicals in the M+W Group based in Stuttgart, Germany. At the corporate level, he focuses on gathering overall manufacturing and engineering knowledge, especially new technology trends and regulatory requirements, to enhance facility design and engineering. He also focuses on technology transfer and strategic developments for the group worldwide. He is a member of the ISPE biotechnology community of practice.

# Sustainability's Relevance to the Pharmaceutical Supply Chain

*Dr. Clarice Hutchens*

**Establishing a robust and transparent supply chain** is a critical element of a sustainability strategy that encompasses the entire value chain: supply chain, manufacturing and operations, logistics, patient use, and final disposal. Corporations seek to partner with suppliers that have transparent sustainability programs and pursue continuous improvement. By leveraging corporate purchasing power to establish sustainability goals beyond their internal borders, pharmaceutical companies can mentor their suppliers and instill sustainability throughout the supply chain to drive further positive impact.

**Environmental stewardship and positive social impact throughout the value chain can further drive innovation**

Voluntary sustainability standards such as the Global Reporting Initiative (GRI), the Carbon Disclosure Project (CDP), Dow Jones Sustainability Index, and Sustainability Accounting Standards Board include metrics for supply chain performance and operational data. GRI's "G4 Sustainability Reporting Guidelines"[2] also include supply chain metrics. Section 6.3, "Supply Chain Related Standard Disclosures," succinctly summarizes these supply chain metrics: standard, economic, environmental (energy, emissions, environmental assessment), and social (labor practices, human rights, impact on society) disclosures. GRI has a linkage document that outlines how CDP relates to GRI standards;[3] CDP Supply Chain questionnaires,[1] however, address only water and climate change. Sustainability Accounting Standards Board's supply chain metric is "percentage of facilities and Tier I suppliers participating in the Rx-360 International Pharmaceutical Supply Chain Consortium audit program or equivalent third-party audit programs for integrity of supply chain and ingredients (e.g., APIs, chemical, raw material, excipients, etc.)."[5] Whilst some commonalities are detected between these standards, significantly different approaches are offered by the voluntary standards that are relevant to supply chain.

Relevant supply chain sustainability topics for the pharmaceutical industry include: natural resource consumption, recycled content of materials, sustainable packaging, manufacturing effluent, wastewater and greenhouse gas emissions, pharmaceuticals in the environment, labor concerns, human rights, accidental hazardous material releases into the environment, and adverse environmental impacts on the local community. The pharmaceutical industry is affected by global chemical regulatory developments such as REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) in the EU. Companies should monitor their suppliers for compliance with global regulations to ensure that suppliers do not have banned or restricted materials in their products.

In 2005, the Pharmaceutical Supply Chain Initiative (PSCI)[4] was formed by the major pharmaceutical companies to help suppliers operate sustainably, in accordance with industry expectations with regard to labor, health and safety, environment, ethics, and management systems. These criteria are covered in PSCI's Pharmaceutical Industry Principles for Responsible Supply Chain Management ("the Principles"). The hope of member companies is that application of these principles will result in better social, economic, and environmental outcomes for all involved in the pharmaceutical supply chain. PSCI resources include: "A Risk-Based Approach to Managing APIs in Manufacturing Effluent," "The Principles," "PSCI Audit Guidance," "Guidance for Implementing the Principles," and "PSCI SAQ & Audit Report Template for Core Suppliers, External Manufacturers, Component and Material Suppliers."

Suppliers ready to be transparent with their sustainability programs may be more desirable partners with a competitive advantage over other busi-

**Suppliers ready to be transparent with their sustainability programs may be more desirable partners with a competitive advantage over other businesses**

nesses. This can start with becoming educated in the sustainability standards previously discussed and sustainability-related certifications. Example certifications relevant to the pharmaceutical industry are Leadership in Energy and Environmental Design (LEED), ISO 24000 – Social Responsibility, and ISO 14000 – Environmental Management. Third-party audits can facilitate the development of a sustainability strategy for businesses. A typical audit takes an inventory of current sustainability programs and benchmarks them against industry's best practices.

With a growing emphasis on supply chain management as critical to a corporation's long-term resilient business strategy, sustainable supply chain management is increasingly linked to business value and reputation. The goal is that environmental stewardship and positive social impact throughout the value chain can further drive innovation and a better world for future generations. ■

## References


1. CDP Worldwide. Carbon Disclosure Project. "CDP Supply Chain Program." www.cdp.net/en-US/Programmes/Pages/CDP-Supply-Chain.aspx.
2. Global Reporting Initiative. "G4 Sustainability Reporting Guidelines." www.globalreporting.org/resourcelibrary/GRIG4-Part1-Reporting-Principles-and-Standard-Disclosures.pdf.
3. ———. "Linkage Documents and Supporting Publications." www.globalreporting.org/standards/Resources/Linkage%20documents_and_supporting_Publications/Pages/default.aspx.
4. Pharmaceutical Supply Chain Initiative. https://pscinitiative.org.
5. Sustainability Accounting Standards Board. "Pharmaceuticals Sustainability Accounting Standard." August 2013. www.sasb.org/wp-content/uploads/2013/09/SASB_Standard_Pharma.pdf.


## About the Author


Clarice Haigh Hutchens is a Director in CMC Regulatory at Pfizer, Inc., supporting biotech R&D and commercial licensing opportunities. She serves on Pfizer's Global Environmental Sustainability Council and Green Chemistry Steering Committee, represents Pfizer on ACS's Green Chemistry Initiative Biopharma's Roundtable, and serves on the Nanomedicine Alliance's Board of Directors. She has 25 years of experience in the pharmaceutical industry and holds a doctorate of management degree focusing on environmental and social sustainability. Dr. Hutchens has been an ISPE member since 2007.

# Shire plc: Expanded Facility in Italy Responding to Increased Market Demand

**Every day, patients around the world suffering** from autoimmune disorders rely upon plasma-derived therapies to manage their illness. Shire is a worldwide leader in the development of such therapies, and their plant in Rieti, Italy, recently acquired via a combination with Baxalta Inc., has completed a significant expansion that has positioned it to meet the ever-increasing global demand for these products.

Baxalta was a pioneer in plasma fractionation and one of the world's largest providers of plasma-derived therapies. It was formerly the Biosciences Division of Baxter Healthcare, until a decision was made in 2015 to spin it off into a stand-alone company as part of an effort to create value for all stakeholders, including employees, investors, and patients alike. As it turned out, the value and the opportunities involved with the Baxalta operations were quickly recognized by Shire, who acquired the company in June 2016 as part of its focus on rare diseases and highly specialized conditions.

## Dramatic Increase in Global Demand

In recent years, the demand for plasma fractionation—the precipitation of plasma proteins with ethanol at various pH levels in a cold environment—has increased dramatically. To meet the demand, Shire significantly extended the capacities at its plant in Rieti, Italy, located in the Apennine Mountains, 60 kilometers northeast of Rome.

"The Rieti site was established as part of the Baxter Bioscience network in 1972," says Sam Kitchell, Head of Engineering at Shire. "It was small for a volume standpoint, but a critical part of our plasma fractionation network that supplies the critical biotherapeutics that we are able to purify from plasma. As we looked at the expanding need for patient supply, it became apparent that we needed to add manufacturing capacity to keep up with the demand. We took a look at our network of plants and identified an attractive opportunity to expand the operations in Rieti."

The project was envisioned to take place in two phases, beginning in 2008. The first phase was to double the plasma production capacity and the second to bring an incremental capacity increase.

Phase 1 consisted of a four-story 780-square-meter expansion that included new process tanks, filter presses, high-speed centrifuges, and ultrafiltration units. It doubled the capacity in Rieti from 600,000 liters to 1.2 million liters of plasma per year, and became operational in 2012. Integration into the existing facility's critical and support systems and operations was important in order to share resources and minimize cost.

**The accelerated design and construction methodology allowed for rapid change with exemplary safety results**

Phase 1 was not without its challenges. The L'Aquila earthquake in April 2009 was one of Italy's deadliest, with more than 300 people who are known to have died. The epicenter was less than 30 miles from the Rieti construction site. The scientific community, government, and construction companies immediately began to consider construction code changes to reduce the possibilities of repeating the L'Aquila quake's deadly impact. Because of this, Shire entered into multiple discussions and coordination meetings with Italian regulators to adjust the construction timelines and design in light of potential construction code changes.

"Fortunately the earthquake itself did not have a significant impact on the facility, but this event caused an extensive review of building codes and of the design itself," says Kitchell. "As it turns out, there were not many modifications that we needed to make, but it was a significant exercise of due diligence to ensure that we adapted as the world changed around us."

## Adapting to Ensure Continuous Supply

In Phase 2, a 520-square-meter four-story structure was planned to increase the capacity in Rieti by an additional 500,000 liters, or up to a total of 1.7 million liters of plasma per year. With cost control in mind, Phase 2 was initially conceived to integrate into Phase 1 during a prolonged shutdown period during which the supply chain would be compromised. As Kitchell explains, however, those plans needed to change.

"We are in a dynamic industry where the patient needs are changing and growing," says Kitchell. "In our original plan, we were very proactive in developing capacity in order to have it in place ahead of the demand. As we launched the project, we took a project plan where we would take advantage of a shutdown period in the second phase. As it turned out, the demand requirements shifted and it became apparent that if we followed our initial project plan, we would take some of our capacity offline for a period of time. To ensure that we could maintain the critical supply, we took a step back and looked at the project plan and determined how we could

modify it so that we could minimize any impact to the existing supply while still successfully executing the project."

The project team managed to almost eliminate downtime during Phase 2 by repurposing the transfer panels installed during Phase 1 (see Figure 1). The design team was able to develop revised piping paths to accommodate the new equipment being installed as part of Phase 2. This provided the ability to transport product between fractionation process steps (unit operations) through a closed system, minimizing potential contamination, improving product quality, and minimizing product loss between steps (less product pipe loss, less protein degradation, and more harvest). This flexible system also allowed integration between existing and new piping systems for process assurance.

The accelerated design and construction methodology allowed for rapid change with exemplary safety results. The system's design provided improved protein harvest, higher recovery and increased yield, which is critical, based upon the limited supply of plasma.

"I think what was unique and significant was that we had to integrate a project plan on a daily basis with the manufacturing operations, because it was critical that we did not disrupt the manufacturing operations. Very close coordination was required so that we could have an active construction site directly adjacent to manufacturing operations and ensure that we did not negatively impact manufacturing operations. It really became a project that was interwoven and a great cross-functional collaboration to keep the operation running while we changed the project plan."

Phase 2 began commercial operations in July 2015, two months ahead of schedule, below budget and without the extended nine-month shutdown.

## Early Adoption of Standards and New Technologies

The Rieti project's success can be credited to many factors, including the project team's adoption of the ASTM E2500 (Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment) approach.

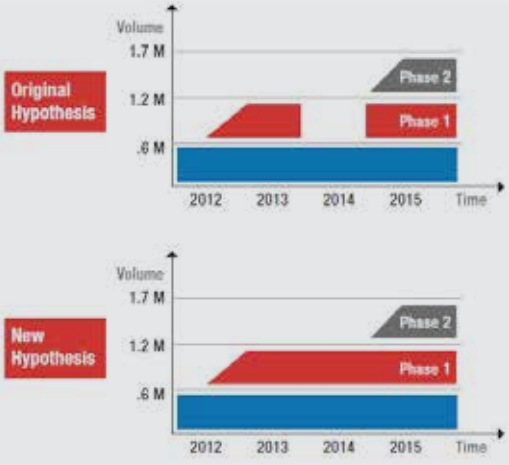
"Nowadays, ASTM E2500 is a pretty well recognized approach, but in the days of this project, it was new approach to validation," says Kitchell. "We implemented it very quickly, which allowed us to shorten some of the windows associated with bringing the capacity online and getting it qualified. That was a key strategy for us."

On the software front, the team utilized a process of "virtual validation," where they created scenarios of how the system would be operated, refining and adjusting the processes while moving toward validation. This allowed team members who were unfamiliar with the system and not working on-site to start working with the process and build their expertise. As this was done in parallel with construction, it saved considerable time and allowed Shire to meet milestone deadlines.

### Shire

| | |
|---|---|
| **Project:** | Baxalta Rieti Capacity Expansion |
| **Location:** | Rieti, Italy |
| **Mission:** | Increase production capacity from 600,000 liters/year to 1.7 million liters/year |
| **Site information:** | Total land: 48,200 square meters |
| | Total covered area: 10,724 square meter |

**Implementation strategy**




grated skids at the manufacturer, which allowed us to do a lot of the qualification at the manufacturer's site," says Kitchell. "Then when we brought it into the facility we could leverage that work and very quickly bring it online."

Leveraging the equipment vendors for skid design and factory acceptance testing allowed for faster installation, as well as qualification and operational readiness. Three-dimensional design models assisted fabrication of major equipment platforms. Process and instrumentation diagram documents were designed in-house by lead Shire engineers with experience in current processes and existing facility operations.

For the actual equipment, each preassembled module was thoroughly tested offsite at the manufacturer's location before installation. Modular construction and equipment included sanitary cleaning skids, process tanks skids, buffer skids, transfer panels skids, and centrifuges.

By validating the equipment in smaller units, once the pieces were brought on site and installed only the connection and installation required validation. A skid system strategy was used with skid-supplied process controls.

"Those were some of the techniques we used to ensure that we were keeping the project on track while dealing with the challenges of increasing demand and ensuring that we maintain supply for our patients," says Kitchell.

### Strategic Staffing

Attracting and retaining highly qualified staff is a serious challenge, and training that staff to conform to the validated processes within the facility represents a significant effort to establish and maintain operational excellence. The local conditions at Rieti, which is in a remote location, added to that challenge.

"We had a unique opportunity to think about how we manage talent to successfully construct the project, but also transition seamlessly into operations," says Kitchell. "We spent a lot of time thinking about how we could build our workforce and how we could leverage our technical resources globally to support the project from its early stages, when there is not necessarily a workforce there to do the project work, and then transition into building an operations team. In this project, we were successful at transitioning a very large percentage of technical staff that supported the project work into positions operating the new facility. And I think that was a unique opportunity where, rather than hire a bunch of external firms and then watch a lot of the experience walk out the door at the end of the project, we used internal resources from our broad manufacturing network and were able to build a great team that transitioned into the operations staff."

Once the project was completed, approximately 90% of the internal engineers who designed the facility and developed and validated the systems, software, and processes were retained to fill critical roles in both operations and quality assurance. New staff hires were dedicated for this effort during early design, carried through construction, and ultimately became lead operational and quality assurance staff after validation efforts were completed.

As a result, there was little need to transfer knowledge because these team members were already fully aware of the approved and validated processes and highly knowledgeable about the systems and equipment being used. By maintaining and redistributing this "institutional memory," Shire was able to reduce downtime for training, increase efficiency, and reduce cycle time. This was a major contributor to ensuring the success of the facility's ramp up.

"This project was envisioned and brought online to support the growth of the plasma business, originally as part of the Baxter Biosciences," says Kitchell. "As we have continued to grow and increase our ability to serve patients, we are now integrating our manufacturing capabilities between the two companies, Baxalta and Shire; both with tremendous capabilities and both with great pipelines that will allow us to bring new medicines to new patient groups. As we put these networks together we are really building a very strong and diversified manufacturing network across the globe." ■

*Mike McGrath*

# ISPE 2016 - 2017 TRAINING

Industry's Trusted Source of Knowledge

## OCTOBER 2016

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

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

## NOVEMBER 2016

ISPE Training Institute, Tampa, FL

- 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 2016

ISPE Training Institute, Tampa, FL

- 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.

## JANUARY 2017

ISPE Training Institute, Tampa, FL

- GAMP® 5, Annex 11/Part 11 (T45), 23 – 25 Jan.
- QRM (T42), 30 – 31 Jan.

ISPE Members attend training programs and other events at a discount. Visit www.ISPE.org/Membership for details.

## FEBRUARY 2017

ISPE Training Institute, Tampa, FL

- Clean In Place (T03), 13 – 14 Feb.
- GAMP® 5 Data Integrity (T50), 6 – 7 Feb.
- HVAC (T14), 8 – 10 Feb.
- Process Validation (T46), 1 – 3 Feb.
- Science and Risk-based C&Q (T40), 23 – 24 Feb.
- Water Generation (T04), 6 – 7 Feb.
- Water Storage, Delivery, and Qualification (T23), 8 – 9 Feb.

## MARCH 2017

ISPE Training Institute, Tampa, FL

- Auditing (G07), 13 – 14 Mar.
- Cross Contamination (Risk-MaPP) (T41), 13 – 14 Mar.
- Facility Project Management*(T26) 6 – 7 Mar.
- GAMP®5 Process Control Systems (T21), 9 – 10 Mar.
- Process Validation in Biotechnology (T32), 27 – 28 Mar.
- Technology Transfer (T19), 30 – 31 Mar.
- Verification of Facilities, Systems, and Equipment Workshop (T48), 27 – 28 Mar.

Manchester, UK

- GAMP® 5, Annex 11/Part 11 (T45)

## APRIL 2017

ISPE Training Institute, Tampa, FL

- GAMP® 5, Annex 11/Part 11 (T45), 26 – 28 Apr.
- Cleaning Validation (T17), 6 – 7 Apr.
- OSD (T10), 3 – 4 Apr.
- Biomanufacturing Overview (T24), 3 – 4 Apr.
- Q7A (T30), 5 – 6 Apr.

ISPE®

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

**Register Today at ISPE.org/Training**

# Overachiever.


**Analytical performance at pilot and production scale. And more.**

LEWA EcoPrime® LPLC achieves accuracy and precision better than 99% with linear gradients from 1 to 99%. That's analytical performance that delivers:

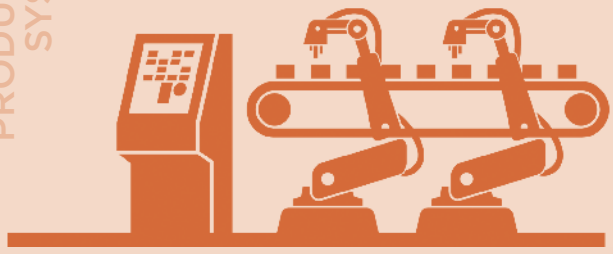
- Increased purity and yield
- Superior batch-to-batch reproducibility
- A flow range of 2 conventional systems in a single skid

Add to that the versatility of our on-board buffer in-line dilution system, and you've got all the makings of a real chromatography wunderkind.

**www.lewapt.com**

LEWA
Creating Fluid Solutions

PRODUCTION SYSTEMS



# Characterization of Silicone Tubing: Effect of Pressure and Irradiation on Tubing Diameter

*Pietro Perrone, Csilla Kollar, Andrew Diehl, and Ernie Jenness*

A single-use assembly consists of flexible components connected via heat seals, overmolds, or mechanical fasteners. The integrity of such a system requires an internal surface that is continuously sealed and free of disconnects between the various components. For this reason, it's important to know the diameter of the flexible tubing during manufacture of the assemblies and the tubing expansion at operational pressures.

The aim of this study was to characterize four different tubing types under various pressure conditions before and after gamma irradiation. Understanding these factors can help design assemblies that maintain their integrity throughout their use at operating conditions.

The inner lumen of the tubing was exposed to pressures up to one-third of the measured burst pressure. As the internal pressure increased, internal tubing diameter increased up to 15%. While irradiation generally makes tubing stiffer and less likely to expand, this effect was found to be minor. For all tubing durometers, the difference in diameter expansion before and after irradiation was under 1% with the exception of the pump tubing, where the difference was approximately 2%.

## Materials and Methods

We tested non-irradiated and gamma-irradiated tubing. Irradiated tubing was exposed to gamma radiation levels of 27–35 kilograys.[2]

- Tubing diameter: ¼-inch internal diameter (ID), ½-inch outer diameter (OD)
- Tubing type: Pump tubing, 50-, 65-, and 80-durometer (Shore A hardness)
- Connection: Fittings machined to match tubing inside diameter
- Laser micrometer system: Laser digital micrometer model LS-7500 (Keyence)
- Linear slide: Precision slide, Model 5242A21 (McMaster Carr)
- Displacement gauge: Starrett electronic indicator model 2900-3-1 (McMaster Carr)

Tubing was mounted onto a pressurization apparatus fitted with stainless steel connections that matched the ID of the tubing being tested (Figure 1).

The fastener that kept the tubing in place was positioned approximately 5 mm onto the fitting—just far enough to safely prevent slipping during pressurization. The intent was to minimize the impact of the fitting on the expansion of the tubing. Figure 2 shows the method used to fasten the tubing onto the fitting. All displacement measurements (x axes) started at the edge of the fastener.

The pressurization system was fitted with a movable laser micrometer system (Figure 3) that measured the OD without touching with the tubing. This provided detection capability with the accuracy essential for the tests. The laser micrometer was mounted onto a linear slide that included a displacement gauge used to define the location of the laser micrometer as it travelled coaxially. The testing system as it was arranged for these experiments is shown in Figures 4 and 5.

Tubing types and diameters were chosen based on the frequency of use in assemblies. While this report is specific to ¼-inch-ID tubing as shown in Table A, similar results were observed for ⅜-, ½-, and ¾-inch-ID tubing. The pressure range tested was specific to each tubing type and was based

**Figure 1: Fitting used for connection to tubing. Fitting was machined to an external diameter equal to the ¼-inch internal tubing diameter.**


**Figure 2: Tubing and fitting connection**

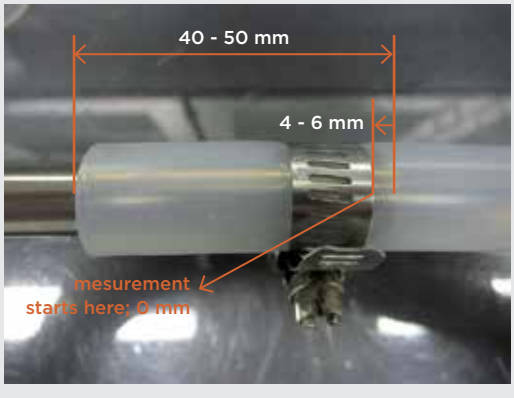


**Figure 3: Laser micrometer**

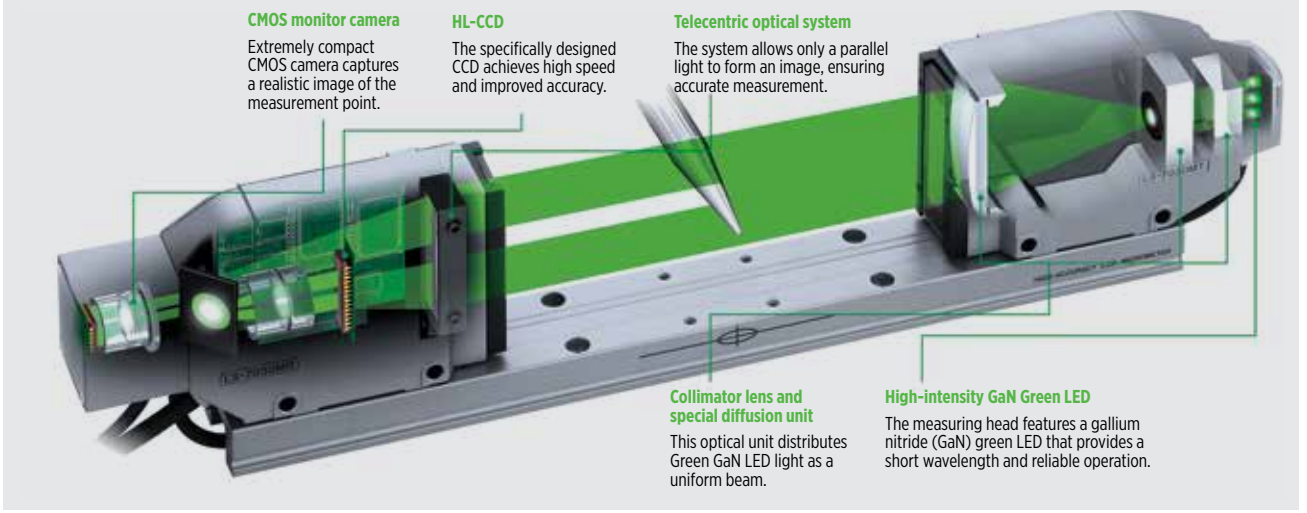



Image courtesy of Keyence Corporation, www.keyence.com

**Figure 4: Test system showing displacement gauge for laser micrometer lateral movement, top view**

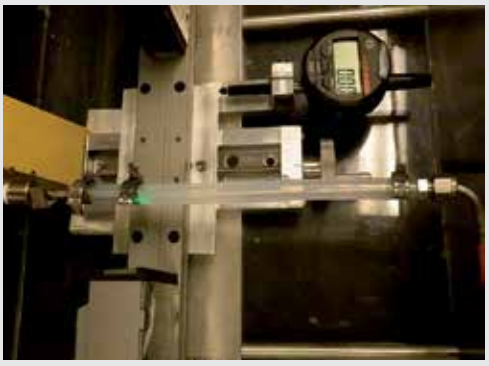
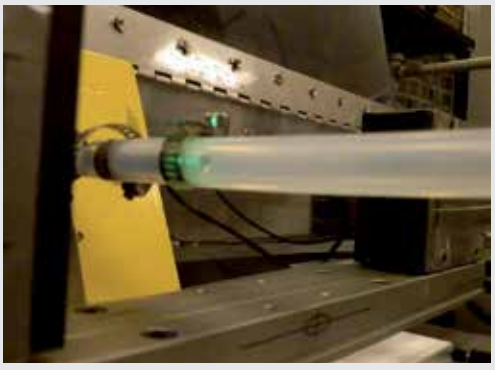


**Figure 5: Tubing position relative to laser heads, side view of test system**



on a maximum pressure one-third the typical burst pressure[1] for each. Study sample burst pressure information and the burst pressure typically measured for each tubing type are presented in Table B.

The pressure range for the study was consistent for both irradiated and non-irradiated tubing.

## Results

### Tubing diameter profile under pressure

Typical tubing OD profiles for 50- and 80-durometer tubing are shown in Figures 6–9. In Figures 6 and 8, the profile at zero pressure shows the effect of the fastener squeezing the tubing. Also noticeable in Figure 2, this effect does not depend on pressure.

To appropriately analyze the effect of pressure on tubing, the effect was extracted from the data for all pressurized conditions. Figures 7 and 9 exclude this effect via normalizing the OD by the profile experienced at zero pressure. Pump and 65-durometer tubing had similar profiles to those shown here.

Hysteresis can be observed in Figures 6–9, especially for the diameter measurements at higher pressures. While all OD measurements discussed in this article for each pressure condition were taken within a 10-minute interval, we also conducted extended tests where the tubing was kept at a specified pressure for up to one hour. These data on the impact of time were consistent with the hysteresis effects observed above.

Operations with single-use systems rely on a continuous sealed surface within the assembly. This requires a tight contact between the barb fitting and the tubing ID. The critical contact point between these two components typically occurs several millimeters away from the position of the fastener. For this reason, we analyzed the diameter measurements a distance from the fastener, focusing our analysis on the latter four points measured at each pressure condition.

While outer tubing diameter characteristics are more readily measured, ID characteristics are of more interest and significance, as that's where the tubing contacts the barb fitting. Expansion under pressure stretches the wall of the tubing and decreases wall thickness. This has an additional impact on the ID of the tubing relative to the measured OD.

**Figure 6: OD profile of pressurized ¼-inch-ID 50-durometer tubing**

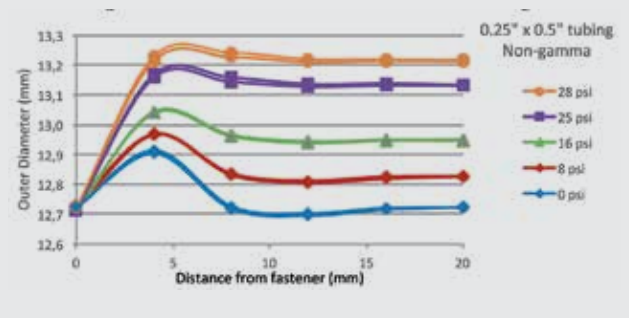
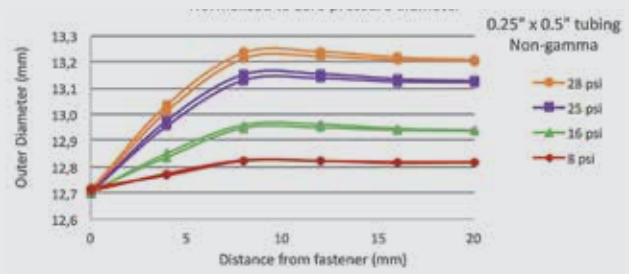



**Figure 7: OD profile of pressurized ¼-inch-ID 50-durometer tubing normalized to eliminate effect of fastener.**




Therefore, we converted the OD measurements into a calculated ID by developing a conversion equation:

$$D_{2i} = \sqrt{D_{2o}^2 - D_{1o}^2 + D_{1i}^2}$$

Where:
Condition 1 is at ambient pressure
Condition 2 is at test pressure
$D_{2i}$ = Inside diameter at condition 2 (test pressure)
$D_{2o}$ = Outside diameter at condition 2 (test pressure)
$D_{1i}$ = Inside diameter at condition 1 (zero pressure)
$D_{1o}$ = Outside diameter at condition 1 (zero pressure)

The equation is based on a constant density for the polymer at the two pressure conditions. Because the applied pressure is very low and the expansion is not constrained, it was assumed that the density of the cured silicone tubing did not change during the expansion test. In addition, since pressure forces are concentrated in the radial direction, the axial length change at the measuring point is considered negligible. All charts and the analysis presented in this article are based on the calculated IDs using the respective ODs measured at the locations between 8mm and 20 mm.

**Figure 8: OD profile of pressurized ¼-inch-ID 80-durometer tubing**

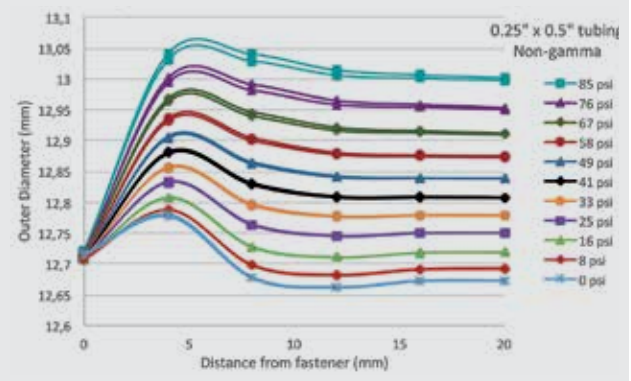
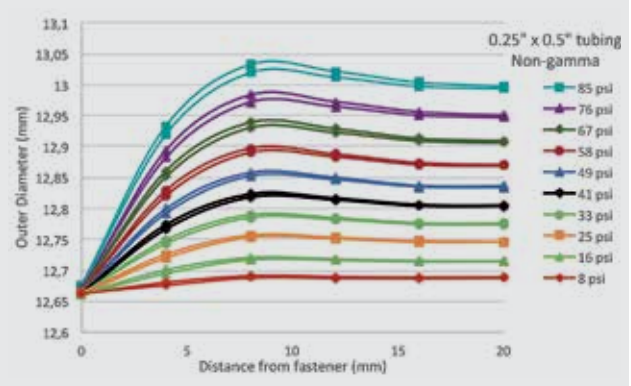



**Figure 9: OD profile of pressurized ¼-inch-ID 80-durometer tubing normalized to eliminate effect of fastener**




## Effect of Pressure

Figures 10 and 11 show the percent change in ID for each tubing type. Figure 10 shows that lower-durometer tubing reaches an ID expansion of 15% at pressures of about 25 pounds per square inch gauge (psig). As expected, higher-durometer tubing types (65 and 80) have lower expansion rates and reach significant expansion levels only at higher pressures.

**Table A: Tubing used in tests**

| **Tubing type** *Sterilized at Steris, Northborough, Massachusetts* | **Pump*** 50 durometer 65 durometer 80 durometer |
|---|---|
| Internal diameter | ¼-inch |
| Wall thickness | ⅛ inch |

*When pump tubing is specified, it is not referenced by its durometer. Pump tubing has a Shore hardness of approximately 50 durometer.

**Table B: Burst pressure information**

| Tubing type | Average measured burst pressure | | Typical burst pressure (psig) |
|---|---|---|---|
| | Non-irradiated tubing, psig | Gamma-irradiated tubing, psig | |
| Pump | 75 | 89 | 75 |
| 50 durometer | 87 | 98 | 85 |
| 65 durometer | 186 | 209 | 147 |
| 80 durometer | 290 | 328 | 254 |

**Figure 10: Pressure increases tubing ID**

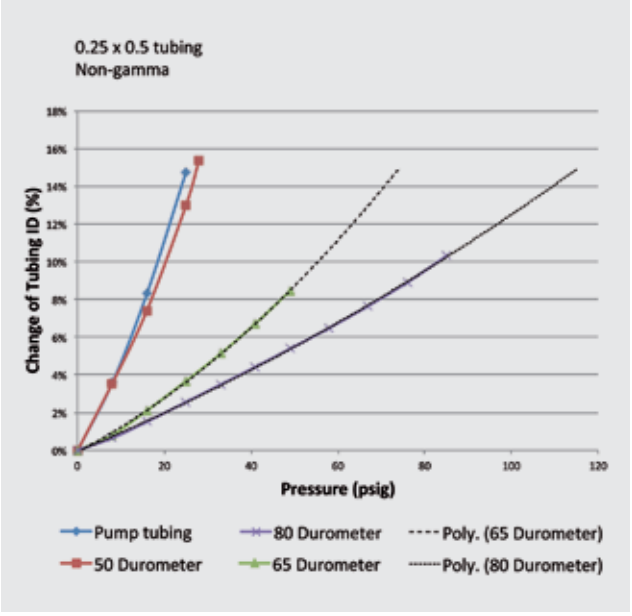



**Figure 11: Pressure increases tubing ID based on burst ratio for each tubing type**

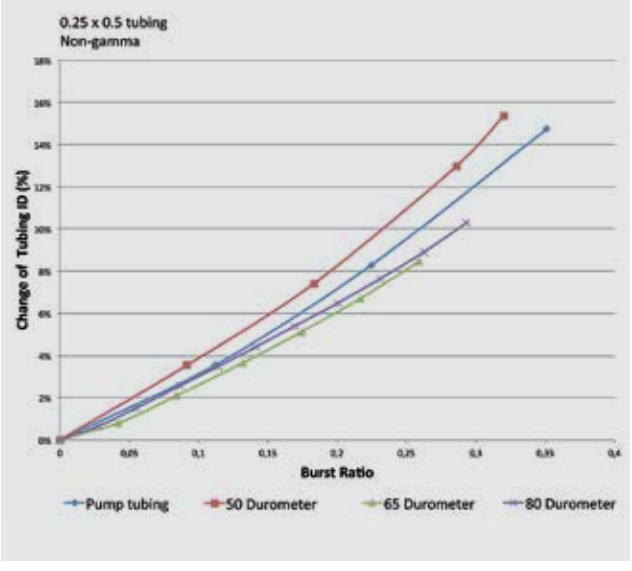



**Figure 12: ID lot-to-lot variation relative to the effect of pressure on pump tubing**

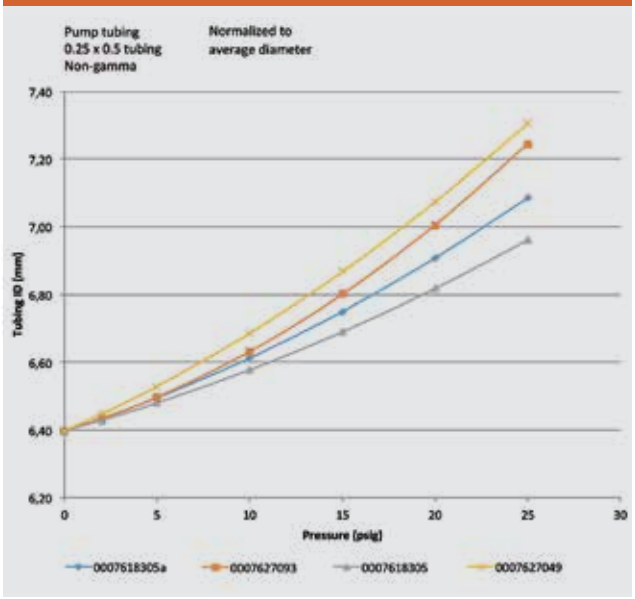
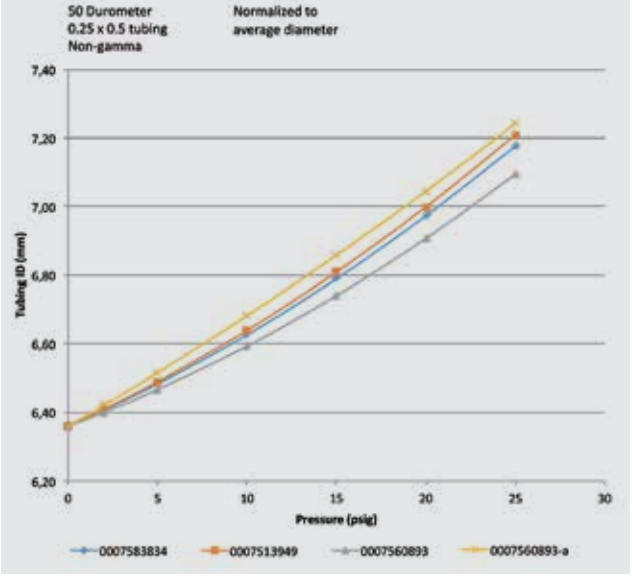



**Figure 13: ID lot-to-lot variation relative to the effect of pressure on 50-durometer tubing**




When the diameter data is plotted on a chart where the abscissa is the burst ratio (Figure 11), one observes alignment of the expansion between the various tubing durometers. (The burst ratio correlates the measured pressure and the tubing burst pressure.) The burst ratio metric helps assess the diameter expansion relative to a proportionally equivalent stress level on the tubing.

## Lot-to-Lot Variation

As in most production processes, a range of specifications must be met before the product is acceptable. Table C shows internal diameter and wall thickness acceptability criteria for the ¼-inch ID tubing and the respective acceptable range of ID and wall thickness. The table also shows that variations in the starting diameter (at ambient pressure or non-pressurized condition) are within the acceptable range. The measured range data are based on measurements from both irradiated and non-irradiated tubing.

Variation in diameter as a function of pressure between tubing lots is shown in Figures 12–14. While in most instances multiple lots were tested, in some cases only one lot was tested; in other cases multiple units from the same lot were tested. These charts cover the range of tubing materials: pump tubing, 50-, and 65-durometer tubing. The variability chart for 80-durometer tubing is not shown, as only one lot was tested due to the availability of this type of tubing.

**Figure 14: ID lot-to-lot variation relative to the effect of pressure on 65-durometer tubing**

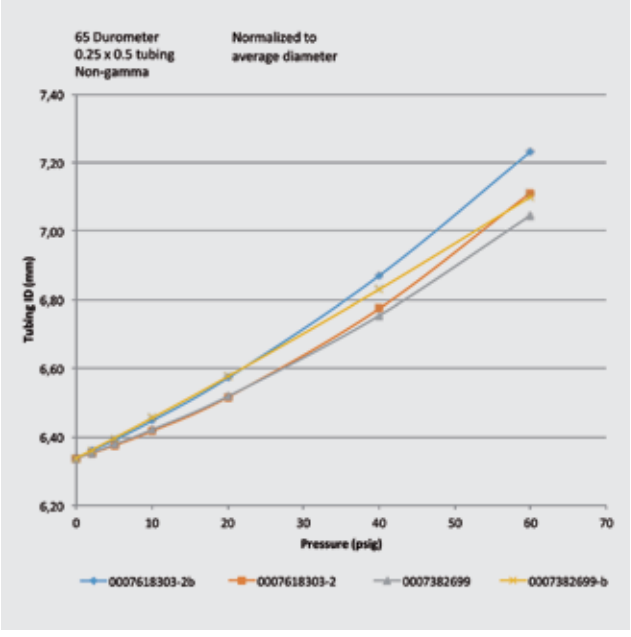



**Figure 15: ID of 50-durometer tubing with and without irradiation when exposed to internal pressure**

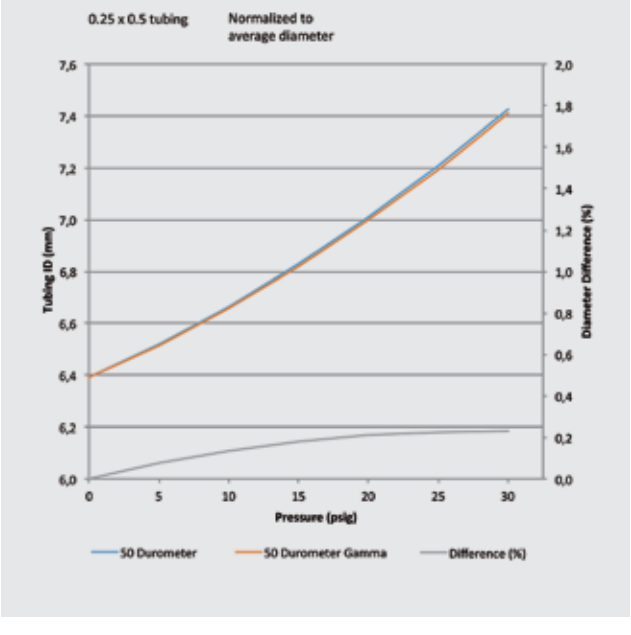



**Figure 16: ID of 65-durometer tubing with and without irradiation when exposed to internal pressure**

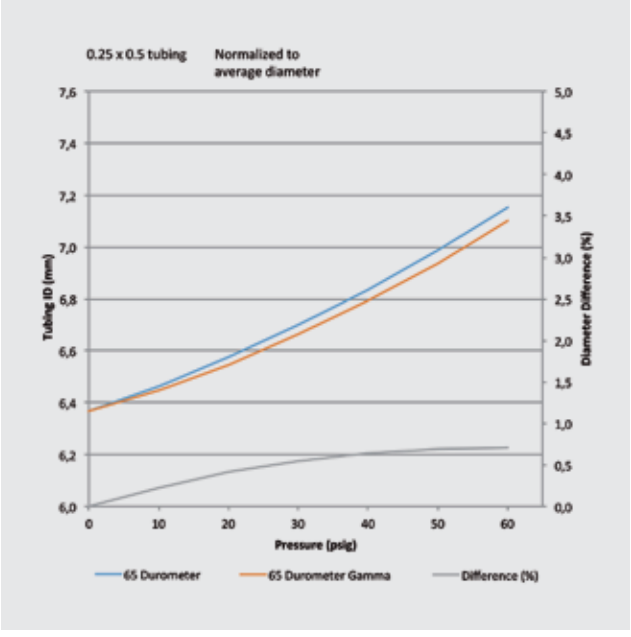
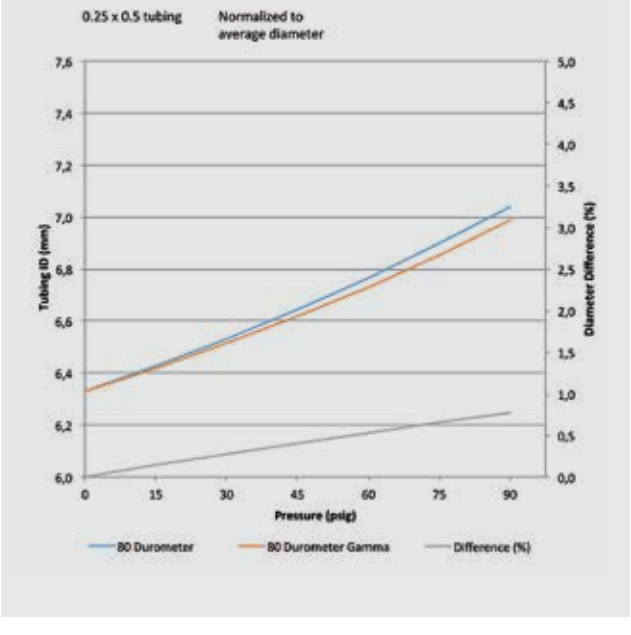


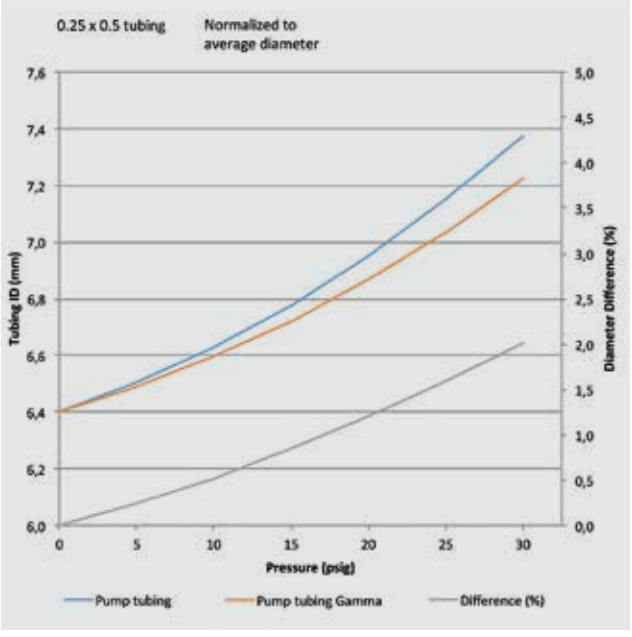

**Figure 17: ID of 80-durometer tubing with and without irradiation when exposed to internal pressure**




To minimize the effect of normal manufacturing variation and highlight variation caused by pressure, diameters in Figures 12–14 are normalized to average ambient pressure diameter. We did this by adjusting the measurement for each tubing lot relative to the average diameter of all of tubing lots tested. This yields a common starting point when the tubing is not pressurized.

Internal diameter variations that arise from the effect of pressure could be due to differences in wall thickness. At lower-pressure conditions, small variations in wall thickness do not have a significant impact on tubing response to pressure. When pressure rises, however, there is a pronounced variation in response between and within tubing lots. Correlating wall-thickness variation and ID expansion under pressure would be worth analyzing as more data become available.

**Figure 18: ID of pump tubing with and without irradiation when exposed to internal pressure**




## Impact of Irradiation

Figures 15–18, based on average data from all lots for each tubing type, show the differences between irradiated and non-irradiated tubing types when exposed to pressure: about 2% for pump tubing and below 1% for all other types. These results show that irradiation has a minor effect on the expansion of tubing when exposed to pressure.

## Discussion/Conclusions

Increasing the pressure to one-third of the burst pressure increases the ID by 10%–15%. The lower-durometer tubing types (50 durometer and pump tubing) show increases closer to 15% (at 25 psig) while the 65- and 80-durometer tubing types show an increase closer to 10%. To obtain an equivalent 15% ID equivalent for the 65- and 80-durometer tubing, the necessary pressure is extrapolated as 70 psig and 110 psig, respectively. Analyzing the response to pressure by evaluating the ID change as a function of burst ratio shows alignment between all the durometer types. This supports the hypothesis that tubing durometer is a good characteristic for defining the tubing's pressure-handling capability.

There are small variations in tubing wall thickness between lots, but these are well within the acceptable range of the manufacturing specifications for the tubing. At lower pressure conditions, these small variations do not significantly affect the tubing's response to pressure. However, wall-thickness variations are considered a significant contributor to the tubing's response to higher pressures. As the pressure rises, there is a pronounced variation (via diameter change) that arises out of the small variations in wall thickness.

The impact of gamma radiation on the tubing diameter changes attributed to pressure changes is in the 1%–2% range. Considering the pressure effect (10%–15%) and the inherent variation in diameter of the tubing, the impact of irradiation can be considered minor and insignificant.

**Table C: Nominal tolerances and range of the ¼-inch (6.35 mm) ID tubing with ⅛-inch (3.175 mm) wall thickness**

| | Nominal tolerance | Acceptable size range | Measured size range of the study samples |
|---|---|---|---|
| ID (mm) | ±0.4318 | 5.92–6.78 | 6.12–6.48 |
| Wall thickness (mm) | ±0.3048 | 2.87–3.48 | 3.12–3.25 |

Expansion of the tubing diameter at the operating pressure is a critical characteristic that should be assessed when designing connections. To reduce the probability of leaks during operation it is important to consider how the tubing expands at connection points and to maintain operating pressure conditions within the characteristics of the tubing, barb fitting, and fastener placement. ■

## References

1. For specific tubing characteristics, please contact the authors.
2. Tubing products were sterilized at Steris (Northborough, Massachusetts).

## About the authors

**Pietro Perrone** is a Professional Engineer registered in Massachusetts. He has a bachelor of science degree in chemical engineering from Tufts University and master of science degree in biomedical engineering and biotechnology from the University of Massachusetts. Pietro has more than 20 years of purification/separation technology experience in process development/optimization, equipment scale-up, and project management. His experience is in applications using both traditional (stainless steel) equipment and single-use technology equipment. Pietro chaired the Disposables Community of Practice of ISPE for several years and is a member of the Pharmaceutical Engineering review board. As part of his activities with the Boston Chapter of ISPE, he is the Industry Advisor to the Tufts University Student Chapter. He has led educational sessions on single-use technology at local and national industry events. Pietro participates in the BioPhorum Operations Group and is a member of ASTM Committee E55.

**Csilla Kollar** serves as an Application Engineering and Technical Specialist for Dow Corning's silicone products manufactured for the pharmaceutical and biopharmaceutical processing industries. Csilla has been with Dow Corning for 17 years and has worked in a wide range of technical roles within various technology platforms, and product development. Prior to her health care role she gained expertise in surface modification technologies, formulation, rubber development, and managed the US external analytical service. Csilla holds an MS degree in chemical engineering from Budapest University of Technology and Economics. In addition, she has been granted 19 US patents and coauthored 49 internal Dow Corning Technical Information Reports and six external publications. She has presented at 10 technical conferences. She is an active member of ASME-BPE, BPSA, and ASTM task groups.

**Andy Diehl** is a Senior S&T Technician at Dow Corning. He received his BS degree from Central Michigan University in electronic engineering technology. In his early career he worked in the information technology field for 13 years and he has been with Dow Corning Healthcare since 2006, taking various roles in the tubing manufacturing and S&T environment. He obtained Six Sigma Black Belt certification and as a senior S&T technician he works with members of the commercial team, product development, marketing, and manufacturing.

**Ernie Jenness** is a Senior Product Manager for Mobius Single-Use Products at Millipore Sigma. Ernie joined Millipore in 1990, and has held positions in manufacturing, applications, research and development, and product management. His focus for the last 13 years has been in single-use systems. Prior to Millipore, Ernie worked in the micro-electronics industry. Ernie holds a BS degree in mechanical engineering as well as an MBA degree. He has published several articles related to single-use systems. He is a member of PDA, ISPE, and BPSA.

# Predictable.


## We honor your schedule.

Delayed departures, late arrivals, change of plans - we have all experienced how frustrating it is when we have important meetings and deadlines to keep!

In our industry it's vital to keep schedules – to get your new pharmaceutical manufacturing facility up and running on time, to ensure your critical process systems perform as specified and you are able to satisfy your commitment to the patients dependent on life saving therapies.

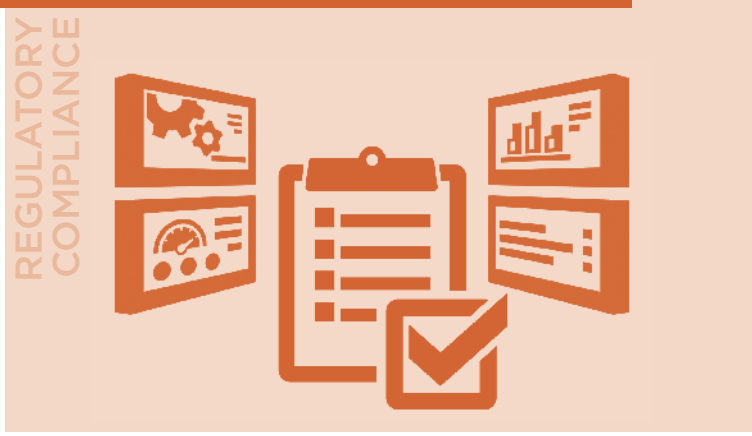
Pharmadule delivers solutions, from concept design through start-up and qualification. Our predictable and well-proven delivery model, based on our modular concept and off-site construction, will ensure the success of your project – meeting the market demand and maximizing your return on investment.

For us it's a matter of honoring deadlines – continuing to deliver the values that Pharmadule has been recognized for over the last 25 years.

On Time , On Budget - The Modular Way

pharmadule

www.pharmadule.com




# Balancing Pre- and Post-Market Control of Health Supplements

*Chan Lai Wah, Benjamin Tan Zhi Yang, Vimal Sachdeva, and Sia Chong Hock*

Regulatory authorities (RAs) worldwide employ different terminologies to describe various medicinal and health products. According to the definition by the Association of Southeast Asian Nations (ASEAN), Health supplements (HS) are products used to supplement a diet as well as to maintain and improve the healthy function of human body.[1] They contain one or more active ingredients such as vitamins, minerals, and fatty acids, as well as substances derived from animal, botanical, or synthetic sources. HS are presented in dosage forms such as capsules, tablets, or liquids, but do not include sterile preparations.[1] Similar products are known as food supplements (FS) in the European Union (EU)[2] and dietary supplements in the United States (US).[3] Other terminologies include nutraceuticals, nutritional supplements, natural health products, complementary medicine, health food, and functional food. The products defined by these different terminologies are generally similar but the way they are regulated varies from country to country (Table A).

Currently, the demand for HS is increasing rapidly. Global sales of HS in 2013 was estimated at US$84.5 billion, a considerable increase from $62.5 billion in 2008.[4] Reasons for consumption of HS include seeking improvements in general well-being, "boosting" the immune system, filling perceived nutrient gaps in diets, and improving joint functionality.

The public may have misconceptions that HS are inherently safe on the basis that many active ingredients of HS are derived from natural sources.

## Current Problems

### Inconsistent quality

Recently, the New York State Attorney General's Office reported that 80% of herbal HS from major global companies tested did not contain any of the herbs listed on the label. Instead, these products contained undeclared fillers such as powdered legumes and wheat.[5] A review on the quality of HS sold highlighted that the actual content of active ingredients in HS products often did not match the labeled content.[6] These inconsistencies and quality problems can lead to unintentional overdosing of the active ingredient(s), poisoning, and allergic reactions. Inconsistent quality is due mainly to the HS manufacturer's poor compliance with good manufacturing practices (GMPs) and unethical practices.

### Adulteration

A study was conducted on the frequency and characteristics of HS recalls in US from January 2004 to December 2012; active pharmaceutical ingredients (APIs) accounted for all of the 237 HS recalled. Most of the HS recalled were marketed as products for body-building, weight loss, or sexual performance.[7] The unapproved items were usually potent APIs such as sildenafil and corticosteroids, which can cause serious consequences if taken without medical supervision. There were cases in which the consumption of adulterated HS led to severe impairment of vital organs and even death.[8] Some unscrupulous manufacturers sought to avoid detection of the unauthorized ingredients by using analogues of these compounds or by incorporating these potent unauthorized ingredients in the capsule shells to avoid detection during regulatory or routine quality control tests.[9]

### Inappropriate claims

Most HS lack scientific evidence of efficacy. And despite guidelines established by RAs, some companies continue to market their products with inappropriate claims, such as treatment of cancer and prevention of coughs, colds, and flu.[10] Both fly-by-night companies and established companies have engaged in such malpractice. These erroneous claims can pose serious health problems, as they may cause consumers to forgo prescribed medicines in favor of HS with dubious claims of efficacy.

## Current Regulatory Controls

### Oversight

RAs may implement pre- or postmarket regulatory controls for HS, or enact a combination of both approaches. In premarket regulatory controls, the product is assessed by the RA before it is manufactured or sold. For postmarket regulatory controls, the RA may audit HS manufacturers as well as implement product surveillance programs.[11] Companies are generally prohibited by most RAs from marketing their HS with medicinal claims to treat, diagnose, or prevent disease.

### Harmonization and international collaborations

As mentioned in Table A, each country has its own regulatory requirements for HS. In recent years, several regions and international organizations including ASEAN (section 3.2.2) have begun to harmonize regulatory requirements to facilitate transnational movement of HS across participating countries.

### Codex Alimentarius Commission

The Codex Alimentarius Commission (CAC) was established by the World Health Organization (WHO) and the Food and Agriculture Organization to promote harmonization of regulatory requirements for food supplements.[20] Like the EU, CAC uses the term "food supplement," which it defines as a concentrated form of nutrient(s) used to supplement the normal diet, and is presented in dosage forms such as tablets and capsules. It has established guidelines that address the maximum and minimum daily

consumption levels of vitamins and minerals, appropriate claims for such products, packaging, and appropriate choice of vitamins and minerals. The guidelines state that claims of treatment, alleviation, or prevention of disease are prohibited for FS containing vitamins and minerals.

### ASEAN

ASEAN is a regional organization that consists of 10 member states: Brunei, Cambodia, Indonesia, Laos, Myanmar, Malaysia, Philippines, Singapore, Thailand, and Vietnam. ASEAN is currently harmonizing HS regulatory requirements to facilitate their transnational movement among member states as part of the integrated ASEAN Economic Community formed on 31 December 2015.[21] The ASEAN Traditional Medicines and Health Supplements Product Working Group is currently developing an ASEAN regulatory framework, including the harmonization of product technical requirements and GMP compliance. Already harmonized regulatory controls include the list of prohibited active ingredients, maximum limits of vitamins and minerals in HS, labeling requirements, pesticide control, additives and excipients, and the risk of transmissible spongiform encephalopathy.

### EU

The EU implemented the Directive 2002/46/EC, approximation of the laws of the member states relating to food supplements, with the goal of facilitating transnational movement of FS among EU Member States.[22] Currently, these regulations only apply to FS containing vitamins and minerals. FS containing ingredients other than vitamins and minerals will be regulated by the legislature of individual member states. The FS company has to apply for authorization from European Commission (EC) of the EU if the products contain vitamins or minerals that are not present in the list or if they contain any novel ingredients; these are ingredients that have no history of significant use before 1997. If, however, the company is able to demonstrate that the novel ingredient is significantly equivalent to an existing ingredient, the authorization process can be accelerated.

All FS sold in the EU can only contain claims approved by the EC, and claims relating to disease risk reduction will require higher level of scientific evidence. Companies are also prohibited from marketing their FS with any claims of treating, diagnosing, or preventing diseases.[22] Another regulation, Directive 2004/24/EC, covers traditional herbal medicinal products, which in Europe, are generally regulated as medicines.

### Effect of differing regulatory frameworks

There is no worldwide agreement on the definition of HS, and the differing regulatory controls across countries have proven to be a challenge for companies marketing their HS globally. As shown in Table A, HS have been regulated as food, medicinal products (MP), or "intermediate" products that straddle both categories. Product categorization helps determine the level of regulatory controls required; regulatory controls for food are usually less demanding than those for MP. The regulatory framework for HS may differ from country to country. For example, Malaysia Drug Control Authority and Health Canada have more stringent regulatory frameworks: Premarket approval is required before sale or manufacture of such products can occur. However, many RAs categorize HS as food products; these HS are regulated under food product laws.

**Inconsistent quality is due mainly to poor compliance with GMPs and unethical practices**

Some countries such as China and India have yet to establish a legal definition for HS. These countries categorize HS under the broad category of "health food."[23] Despite the legal definitions of HS in many countries, specific GMP standard for their manufacture have yet to be established. The UK Food Standards Agency, for instance, requires manufacturers to comply with GMP meant for manufacture of food.[24]

Some countries also have different requirements regarding substantiation of claims used by companies to market HS. For example, the Japanese RA requires clinical trials to be conducted for any claims made by the company before these HS can be marketed. On the other hand, animal tests are sufficient for certain HS claims in China. To further complicate matters, there have been claims for HS that are accepted by EC but rejected by US Food and Drug Administration (FDA).

## Recommendations

### Premarket ingredient approval

A regulatory framework incorporating a premarket approval process can help avert situations such as the one involving ephedra-containing dietary supplements in the US about 20 years ago. Between 1995 and 1997, US FDA received over 900 reports of adverse events due to ephedra-related toxicity.[25] Other botanical ingredients such as kava-kava and yohimbe have been reported to cause liver failure and cardiovascular disorder respectively.[24] These adverse events could have been averted with premarket assessments.

Over the years, EU Member States have implemented premarket regulatory controls for HS with the underlying principle that HS must be proven safe for human consumption before they can be sold. On the other hand, some HS companies opine that the EU regulatory system is too stringent and have raised this issue to the European Court of Justice. It was ruled, however, that such a regime is necessary to ensure consumers' safety. Countries such as Canada and Malaysia have recognized the advantages of pre-market regulatory controls and have adopted similar regulations.

In contrast, premarket regulatory controls for such products are minimal in the US, where the products are presumed to be safe unless proven otherwise with consumers' access taking center stage.[26] There have been counterarguments lamenting the lack of protection of consumers' safety under the current regulatory framework in the US. In recent years, US FDA has recognized the lack of consumer protection and is reconsidering the current regulatory controls for novel ingredients in such products.[27]

The premarket approval system adopted by EU is a feasible form of pre-market regulatory control to safeguard consumers of HS. RAs could issue a positive list of ingredients that HS are allowed to contain, and companies would be required to submit the composition of the products for approval before they could be sold. If the HS contain active ingredients not present in

**Table A: Regulatory controls by agency**

| Regulatory Agency | Term and definition | Details |
|---|---|---|
| **China Food and Drug Administration** (China FDA)[12] | **Health food**<br>Products meant for providing vitamins and minerals. They are also used for modifying physiological functions. They should not contain any claims of treatment of disease. | ■ Products must be registered with China FDA and undergo technical examination by authorized laboratories for safety and efficacy before they can be sold or manufactured in China.<br>■ China FDA has only approved 27 functional claims, and use of these claims requires validation by animal or human studies or both.<br>■ The raw materials should conform to the national standards on physical, chemical and microbiological agents.<br>■ Manufacturers should comply with GMP for health food. |
| **US Food and Drug Administration** (US FDA)[13] | **Dietary supplements**<br>Products consumed orally and contain a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" may include vitamins, minerals, botanicals, amino acids, and substances such as enzymes and metabolites. | ■ No premarket approval is required.<br>■ However, if the product contains any new "dietary ingredients", a premarket notification containing relevant information must be sent to US FDA.<br>■ Manufacturers must register with US FDA but approval is not required. Manufacturers should comply with GMP for Dietary Supplements established by US FDA.<br>■ Claims of treating, preventing or diagnosing diseases are prohibited.<br>■ Premarket approval by US FDA is only required for claims of disease risk reduction.<br>■ Companies should inform US FDA of any complaints of severe adverse events. |
| **United Kingdom Food Standards Agency** (UK FSA)[14] | **Food supplements**<br>Products meant to supplement the normal diet; a concentrated source of a vitamin or mineral or other substance with a nutritional or physiological effect, alone or in combination. | ■ Only novel products are required to undergo safety assessments; these are products without a significant history of consumption in EU prior to 1997 or produced in a novel manner.<br>■ The Food Supplements Directive contains the list of permissible vitamins and nutrients that can be present in the product. If the vitamin or nutrient is not listed in the directive, the product cannot be sold.<br>■ Claims of treatment or prevention of diseases are prohibited.<br>■ Premarket approval of product claim is done at the EU level. |
| **Singapore Health Sciences Authority** (HSA)[15] | **Health supplements**<br>Products used to supplement the diet, with benefits beyond those of normal nutrients and/or to support or maintain the healthy functions of the human body. | ■ Products must not contain any substances controlled under the Poisons Act.<br>■ No prior approval required for manufacture and sale of HS.<br>■ There is no mention of any GMP standard specifically for the manufacture of HS.<br>■ No premarket approval of claims is required.<br>■ Products are prohibited from claiming treatment or prevention of diseases. |
| **Australia Therapeutic Goods Administration** (TGA)[16] | **Complementary medicine**<br>Products consist of one or more designated active ingredients such as vitamins, minerals, herbal materials, etc., and each active ingredient has a clearly established identity and traditional use. | ■ Risk-based approach on assessing products.<br>■ Lower-risk products will be listed on the Australian Register of Therapeutic Goods (ARTG) and evaluated on safety and quality.<br>■ Higher-risk products should be registered on the ARTG and evaluated for safety, quality and efficacy.<br>■ If the product contains a novel ingredient, the company must demonstrate its safety during assessment.<br>■ Australian manufacturers are required to have a license and comply with GMP established by TGA.<br>■ If the manufacturing process occurs outside of Australia, the company must demonstrate compliance with GMP established by TGA.<br>■ Listed products are prohibited from containing claims of treatment as well as restricted representations. Registered products are allowed to make restricted representations. Premarket approval is required for restricted representations used by companies to market registered products. |
| **Health Canada** (HC)[17] | **Natural health products**<br>Products used for:<br>a) Diagnosis, treatment or prevention of disease in humans<br>b) Restoring or correcting organic functions in humans<br>c) modifying organic functions in humans to Maintain or promote health | ■ Require a product license. Evidence of product safety and efficacy is required for the application of the license.<br>■ A site license is required for manufacture and the company needs to demonstrate compliance with Health Canada Guidance for Natural Health Products GMP.<br>■ Premarket approval of claims is required. Companies that wish to make more serious claims of disease treatment or disease risk reduction are required to provide additional scientific evidence. |
| **Malaysia Drug Control Authority** (Malaysia DCA)[18] | **Health supplements**<br>Products used to supplement the diet and may contain:<br>a) Vitamins, minerals, amino acids, probiotics, and other bioactive substances<br>b) Substances derived from natural sources, including animal, mineral and botanical materials<br>c) Synthetic sources of aforementioned ingredients may only be used if safety has been proven | ■ Require premarket approval. Products have to fulfil safety, quality and appropriateness of claim before it can be approved.<br>■ Manufacturers have to comply with GMP for HS established by Malaysia DCA in order to obtain the license and product approval.<br>■ For products that contain disease risk reduction claims, the GMP must be established by Malaysia DCA, PIC/S or RA in the country of manufacture with GMP similar to that of PIC/S.<br>■ Any claims of treatment, cure or prevention of disease are prohibited.<br>■ Disease risk reduction claims require human intervention, toxicology and pharmacological studies. |
| **Food Safety and Standards Authority of India** (FSSAI)[19] | **Health supplements**<br>Products used to satisfy dietary requirements which exist due to a disease or condition. They may contain the following ingredients:<br>a) minerals, vitamins, proteins, metals or their compounds, amino acids or enzymes<br>b) botanicals<br>c) substances of animal origin<br>d) a dietary substance used to supplement the diet | ■ Require approval if the products contain any ingredients or additives that are not included in the Rules and Regulations of the Food Safety and Standards Act.<br>■ Need to obtain manufacturer's license from FSSAI.<br>■ Products cannot bear claims of curing or alleviating disease.<br>■ Products can bear claims of disease risk reduction.<br>■ Claims must be substantiated with scientific evidence.<br>■ No GMP established specifically for the manufacture of HS. |

## Harmonization of HS regulatory requirements could enhance consistency, efficiency, and cost-effectiveness

the list, the ingredients would be subject to safety assessments before the products could be sold. Instead of subjecting every product to individual assessment, premarket approval by ingredients is more practical. Such a regulatory system, based on a positive list of ingredients, would require fewer resources, and would hopefully result in a smaller backlog. In China, where the FDA subjects each product to premarket approval, it is estimated that it can take up to 5 years for a new product to be registered in the country.[23] In comparison, it takes an average of 3 years to approve novel HS ingredients in the EU.

As for HS that contain ingredients that are not in the positive list, approving them on the basis of historical use may be unwise. Historical use may not be a good indicator of safety, as evinced by the adverse events associated with supplements containing kava-kava and ephedra, which have a long history of use as "traditional medicines."

The US Committee on the Framework for Evaluating the Safety of Dietary Supplements also highlighted that historical use may not always be relevant in assessing the safety of ingredients due to issues such as differences in indications and dosage forms.[28] Prohibiting the sale of these products can severely impact consumers who need them. Two possible approaches may be adopted to avoid excessive inconvenience to consumers: The first would require affected companies to engage in safety testing akin to Phase IV clinical trials of new drugs. The companies would be allowed to sell their products while necessary safety tests are being conducted. The products would be withdrawn only when found unsafe. The second approach would allow restricted sale of products to consumers, subject to assessment and verification by physicians, similar to the system for supply of prescription-only medicines. Both approaches, however, would imply that there would still be consumption of products despite the incomplete safety assessment of the ingredients.

As safety is very important, neither approach may be acceptable. To avoid adverse effects, the sale of potentially harmful products should be prohibited during the safety evaluation period. consumer safety should always take precedence over accessibility and business considerations. Moreover, these are not lifesaving products, and the lack of such products is not life-threatening. Therefore, if RAs were to implement a form of premarket framework for HS, the approval of any HS product or ingredient should not be based just on historical use. It has been argued that premarket regulations may reduce consumers' access to HS by raising economic barriers to market entry. However, it is a minor drawback compared to the risks from the consumption of potentially harmful HS. A premarket regulatory system would also improve the ability of RAs to detect adulterated HS before they are sold, and to deter companies from producing such products.

### Premarket claims approval

Inappropriate claims of HS made by companies are a major problem. RAs in countries such as China and Malaysia require companies to submit claims for approval before the HS can be sold; in contrast, this is not required in countries such as the US and Singapore. The onus is on the HS industry to act responsibly and avoid making inappropriate claims. There are unethical companies, however, that will seek to boost sales by making inappropriate claims. These companies may abuse the lack of oversight by making claims that appear legal and deceive consumers into believing the HS products can treat or prevent disease.[26, 29] Premarket interventions can prevent inappropriate claims as the RAs would be able to reject such claims before granting market authorization.

An ideal premarket regulatory regime should require all companies to prove HS efficacy via randomized clinical trials (RCTs), similar to the premarket regulatory framework for pharmaceutical products. This would allow only products with proven efficacy to reach the market. However, RCTs can be costly, and HS companies may not have the economic resources as there are no avenues to patent their products. Additionally, it may not be practical to expect RCTs to be conducted for all types of claims. Instead, it would be more prudent for the various HS claims to be substantiated by appropriate levels of evidence, based on the nature of the HS and their risk profiles.

### Establishing GMP

GMP-compliant companies are better able to assure HS quality and safety as they have consistent manufacturing processes and cross-contamination


*ASEAN Traditional Medicines and Health Supplements Product Working Group*

prevention programs in place. Currently, there is a lack of national and international GMP standards specifically for manufacture of HS. It is essential to establish internationally acceptable GMP standards to avoid quality issues. The manufacture of HS requires appropriate process controls, suitable equipment, specialized skills, and knowledge.

The occurrence of several quality-related incidents convinced US FDA to establish GMP specifically for the manufacture of HS. The US FDA also noted that because HS, unlike food products, were packaged into dosage forms such as tablets and capsules, it would be inappropriate for HS manufacturers to adopt GMP established for food manufacturers. Although GMP compliance will increase manufacturing costs, it will help improve consumers' confidence in HS. In the long run, this will benefit the HS industry, the RA, and the consumers. Upon implementation of the GMP inspection standard, there should be periodic audits by RAs to ensure continued GMP compliance by the manufacturers. Periodic audits are necessary as HS companies were still found to be noncompliant to GMP during ad hoc audits conducted by the US FDA despite the establishment of GMP standard for HS manufacturers.[30] The 2003 Pan Pharmaceutical debacle in Australia in is a classic example of the importance of regular GMP audits.

RAs can also explore other options beside implementing regulatory controls to address quality problems. These include encouraging HS companies to undergo voluntary third-party (independent) GMP certification, coordinated by industry associations. Currently, reputable third-party organizations such as the US Pharmacopeia (USP) and NSF International conduct quality testing of products as well as GMP inspection of manufacturing facilities.[31–32]

HS products that bear these organizations' stamps indicate that the manufacturers are GMP compliant. These voluntary independent certifications may provide a form of quality assurance to HS consumers. RAs can encourage companies to undergo such certification by educating the public and health care professionals about the important role such organizations play. They could also provide guidance to assist HS companies in selecting the correct organizations[33] and to single out products that are legally misbranded, or do not comply with the certifying organization's specifications.[34]

These certifications could also help ease the strain on the limited resources by complementing the RA efforts in market surveillance and GMP audits, especially for overseas HS manufacturers. Organizations such as USP have established offices in countries such as India and China to facilitate the certification of HS manufacturers in these countries. RAs can also help encourage some form of industry self-regulation through formation of associations such as the Health Supplements Industry Association of Singapore, Food Supplements Europe, and the Council for Responsible Nutrition in the United States. The associations could establish their own code of ethics and mutual agreements on GMP and quality standards, thus increasing the likelihood that companies will be GMP compliant. In some cases, the associations have established their own GMP standard specifically for the manufacture of HS despite the lack of a regulatory GMP standard. Overall, industry initiatives may complement the efforts of RAs to safeguard public health and help to ease the strain on the limited resources of RAs.

## Harmonization of regulatory requirements

Most regulatory standards for HS are currently not harmonized. In some countries such as China and Australia, HS are required to be registered with the RAs while in many other countries, premarket licensing or approvals are not mandatory. This leads to a diverse range of regulatory requirements for the HS industry to manage.

Harmonization of HS regulatory requirements could enhance consistency, efficiency, and cost-effectiveness for both RAs and the industry. It would facilitate cooperation and collaboration among different RAs in a highly globalized world with interconnected trade. Sharing information among different RAs can facilitate the detection of adulterated or poor quality

HS and help avoid public health crises. Harmonization is also beneficial for companies as it can reduce number and amount of regulatory submissions required and hence, reduce registration time and regulatory cost.[35] It has been shown that harmonized requirements and the resulting reduced cost of product registration have encouraged pharmaceutical companies to invest more in research. The same outcome may apply to the HS industry if the regulatory requirements for HS are harmonized.

However, harmonization may create economic issues for countries that have insufficient resources or expertise. Moreover, the large variation of HS products and formulations in different countries may compound the difficulty of achieving harmonization. Nevertheless, harmonization should be pursued.[35] International organizations such as the WHO and the Food and Agriculture Organization of the United Nations as well as countries with relevant expertise can help countries that are lacking, through training of the regulators. ASEAN member states have been harmonizing their regulatory requirements for HS and collaborating actively with one another. Despite differences in cultural, political and socioeconomic background among ASEAN member states, significant progress has been achieved, indicating that harmonization of HS regulatory requirements at the regional or international level is possible.

## Conclusion

The demand for HS is expected to grow considerably, attracting many companies to have a slice of the growing market. It is still largely a caveat emptor (buyer beware) market where tighter worldwide regulatory control for HS appears necessary. RAs should implement appropriate HS regulatory schemes to safeguard public health, but without severely affecting the consumers' access to affordable products. As all RAs have limited resources in terms of manpower and funds, an appropriate risk-based regulatory scheme is critical. ■

## References


1. Singapore Health Sciences Authority. "ASEAN Guidelines on Labeling Requirements for Traditional Medicines and Health Supplements." www.hsa.gov.sg/content/dam/HSA/HPRG/Complementary_Health_Products/Annexes/ANNEX%20IX%20ASEAN%20GL%20on%20Labeling%20Requirements%20for%20TMHS.pdf.
2. European Commission. Food Safety. Labeling and Nutrition: "Food Supplements." http://ec.europa.eu/food/safety/labelling_nutrition/supplements/index_en.htm.
3. US Food and Drug Administration. "Dietary Supplements." http://www.fda.gov/Food/DietarySupplements.
4. Feldman, Monica. "The Impact of Regulation on the Market Value of Nutraceuticals." Presented at Discover Global Markets: Healthcare and Life Sciences Business Forum Series, 17–18 November 2015, Minneapolis, Minnesota. http://export.gov/minnesota/build/groups/public/@eg_us_mn/documents/webcontent/eg_us_mn_080867.pdf.
5. O'Connor, Anahad. "New York Attorney General Targets Supplements at Major Retailers." *New York Times*, 3 February 2015. http://well.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers/?_r=2.
6. Lockwood, G.B. "The Quality of Commercially Available Nutraceutical Supplements and Food Sources." *Journal of Pharmacy and Pharmacology* 63, no. 1 (2011): 3–10.
7. Harel Z, et al. "The Frequency and Characteristics of Dietary Supplement Recalls in the United States." *JAMA Internal Medicine* 173, no. 10 (May 2013): 926–928.
8. Singapore Health Sciences Authority. "HSA Alerts Public to 'OxyELITE Pro'—an Unregistered Medicinal Product Linked to Serious Liver Injuries." www.hsa.gov.sg/content/hsa/en/News_Events/Press_Releases/2013/OxyELITE_Pro.html.
9. Venhuis B.J., et al. "Capsule Shells Adulterated with Tadalafil." *Forensic Science International* 214 nos.1–3 (2012): 20-e22.
10. US Food and Drug Administration. "FDA Issues Warning Letters to Dietary Supplement Firms in Colorado and Texas for Promoting Unapproved Products as Drugs." FDA News Release, 6 September 2012. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm318445.htm.

11. US Food and Drug Administration. "Overview of the Implementation of the Current Good Manufacturing Practices for Dietary Supplements Guidance for Industry." A prepared script for satellite broadcast, 24 October 2007. http://www.fda.gov/Food/GuidanceRegulation/CGMP/ucm173996.htm.
12. China Food and Drug Administration. Laws and Regulations. http://eng.sfda.gov.cn/WS03/CL0758.
13. US Food and Drug Administration. "Dietary Supplements." http://www.fda.gov/food/dietarysupplements/default.htm.
14. UK Food Standards Agency. www.food.gov.uk.
15. Singapore Health Sciences Authority. "Health Products Regulation." www.hsa.gov.sg/content/hsa/en.html.
16. Australia Therapeutic Goods Administration. http://www.tga.gov.au.
17. Health Canada. www.hc-sc.gc.ca/index-eng.php.
18. Malaysia National Pharmaceutical Regulatory Agency. "About the Drug Control Authority." http://npra.moh.gov.my/index.php/about-npcb/drug-control-authority-dca/information.
19. Food Safety and Standards Authority of India. www.fssai.gov.in.
20. World Health Organization. Codex Alimentarius International Food Standards. www.codexalimentarius.org.
21. Association of Southeast Asian Nations. "Harmonising Regulation of Traditional Medicines and Health Supplements Ahead of ASEAN Integration." http://asean.org/harmonising-regulation-of-traditional-medicines-and-health-supplements-ahead-of-asean-integration.
22. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. *Official Journal of the European Union* L. 183, 12 July 2002. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:183:0051:0057:EN:PDF.
23. US-China Health Products Association. "China's Dietary Supplement Sector and Key Issues." 3 April 2014. http://uschinahpa.org/wp-content/uploads/2012/01/China%E2%80%99s-Dietary-Supplement-Sector-and-Key-Issues-2014.pdf.
24. US Government Accountability Office. Dietary Supplements: *FDA Should Take Further Actions to Improve Oversight and Consumer Understanding*. GAO-09-250. January 2009. www.gao.gov/assets/290/285372.pdf.
25. National Center for Complementary and Alternative Medicine. "Ephedra." http://nccam.nih.gov/health/ephedra.
26. Azizi Rahi. "Supplementing the DSHEA: Congress Must Invest the FDA with Greater Regulatory Authority over Nutraceutical Manufacturers by Amending the Dietary Supplement Health and Education Act." *California Law Review* 98, no. 2 (30 April 2010): 439–479.
27. Cohen P.A. "Assessing Supplement Safety—The FDA's Controversial Proposal." *New England Journal of Medicine* 366, no. 5(2012): 389–391.
28. Institute of Medicine, and National Research Council of the National Academies. *Dietary Supplements: A Framework for Evaluating Safety*. Washington, DC: The National Academies Press, 2004.
29. US Office of Inspector General. "Dietary Supplements: Structure/Function Claims Fail to Meet Federal Requirements." https://oig.hhs.gov/oei/reports/oei-01-11-00210.pdf.
30. Whitsitt V., et al. "The Role of Good Manufacturing Practices for Preventing Dietary Supplement Adulteration." *Analytical and Bioanalytical Chemistry* 405, no. 13 (2013): 4,353–4,358.
31. NSF International. "Dietary Supplement Safety." http://www.nsf.org/services/by-industry/dietary-supplements/supplement-safety.
32. US Pharmacopeial Convention. "USP Verified Dietary Supplements." http://www.usp.org/usp-verification-services/usp-verified-dietary-supplements.
33. US Food and Drug Administration. "Voluntary Third-Party Certification Programs for Foods and Feeds." Application Process. www.fda.gov/RegulatoryInformation/Guidances/ucm125431.htm#IVA.
34. US Pharmacopeial Convention. "USP Comments on FDA's New Dietary Ingredient Draft Guidance." http://www.usp.org/node/2682
35. Riviere J.E., and G.J. Buckley, eds. *Ensuring Safe Foods and Medical Products through Stronger Regulatory Systems Abroad*. Appendix H: "Strengthening Core Elements of Regulatory Systems in Developing Countries: Identifying Priorities and an Appropriate Role for the US Food and Drug Administration." Washington, DC: National Academies Press, 2012. www.ncbi.nlm.nih.gov/books/NBK201164.


## About the Authors


**Chan Lai Wah** has a bachelor's degree in pharmacy, as well as a doctoral degree in pharmaceutics from the National University of Singapore. She is an Associate Professor with the department of pharmacy at the National University of Singapore, where she lectures and carries out research in pharmaceutical science, technology and microbiology. She has published close to 100 research papers, many more conference papers and a few book chapters. She also serves as an editorial board member and reviewer for scientific journals.

Chan Lai Wah is a registered pharmacist in Singapore. She is particularly concerned about the quality, safety, and efficacy of pharmaceutical products and takes a keen interest in their formulation, manufacture, and regulatory control. In addition to her academic activities, she provides consultancy in pharmaceutical formulation and has served as an external specialist to the Health Sciences Authority of Singapore.

**Benjamin Tan Zhi Yang** has just graduated with a bachelor's degree in pharmacy with honours from the National University of Singapore. He has a strong interest in the regulatory control of health supplements, particularly their safety and quality, good manufacturing practices, adulteration, and supply chain integrity.

**Vimal Sachdeva** has been working as a Technical Officer (Inspector) with the World Health Organization (WHO) office in Geneva, Switzerland, since 2010. As a WHO Technical Officer, Vimal performs inspections of various facilities such as contract research organization (CROs), manufacturers of finished pharmaceutical products and active pharmaceutical ingredients, as well as quality control laboratories in accordance with the WHO GCP, GMP, and GLP standards, respectively. Prior to joining WHO, Vimal had worked with the Singapore Health Sciences Authority for more than 7 years as a senior GMP auditor and senior quality reviewer.

**Sia Chong Hock** holds a bachelor's degree in pharmacy from the University of Singapore, as well as a master's degree in healthcare management (with distinction) from the University of Wales. He has worked about 30 years in various positions in the pharmaceutical and healthcare sectors, including manufacturing and quality assurance of medicinal products, product quality review and good manufacturing practice inspection.

At present, Sia Chong Hock is an Adjunct Associate Professor with the National University of Singapore. From time to time he contributes review articles to ISPE's Pharmaceutical Engineering and other international scientific journals in the field of comparative pharmaceutical regulations, traditional and herbal medicines, process analytical technology, control of APIs and pharmaceutical excipients, supply chain integrity, and ASEAN harmonization.

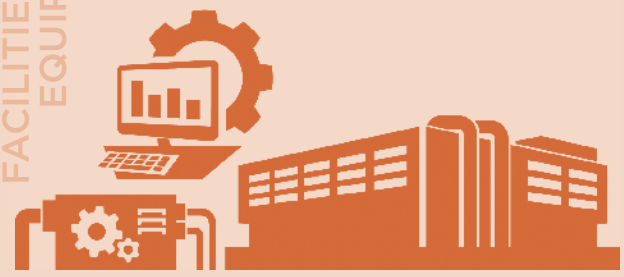

## THE FUTURE OF CONTAINMENT AND STERILE TRANSFER TECHNOLOGY.

As world leaders in product transfer solutions we are specialists in our field. Driven by innovation, our valve technology is created without compromise to meet even the most demanding levels of quality and safety.

**thechargepoint.com**

ChargePoint TECHNOLOGY

FACILITIES AND EQUIPMENT



# Manufacturing and Packaging Line Clearance in an OSD Manufacturing Facility

*Michael DeBellis, Jim Cahir, and Robert Matje*

For filling and packaging line operations, line clearance is a growing concern in pharmaceutical and nutraceutical oral solid dosage (OSD) manufacturing facilities. These operations utilize types of equipment that have many hidden or shrouded areas into which tablets/pills, caplets, gel caps, and capsules can find their way. This increases the risk of mix-ups and cross-contamination, which have serious consequences. Several cases have been reported where different products have ended up in the same bottle.

General "housekeeping" cleaning between product and product format changeovers is often insufficient. To assure that the last product filled is completely removed prior to the start of a different product, regulatory requires validated cleaning and decontamination procedures between changeovers. All potential particulate contamination must be safely removed and all product contact surfaces must be properly cleaned.

Establishing standard cleaning and inspection procedures that operators can follow on a daily basis could save manufacturers from quality issues on the shop floor, costly recalls due to cross-contamination of products, health risks to patients, and potential citations or penalties issued by a regulatory agency (i.e., FDA Form 483).

Toxic, cytotoxic, and other hazardous products have other concerns and requirements in line clearance, decontamination, and cleaning; they are not the focus of this article. This article discusses common areas that are typically found to be trouble spots on shared filling and packaging equipment lines, and presents some commonly used industry procedures that prevent material from one production batch from getting into another.

## Main Drivers

For most OSD manufacturing companies, internal process reviews or failure mode and effect analyses (FMEAs) are the main drivers of a risk-based approach to identify potential manufacturing and packaging problems. Once these are identified then they can begin to develop mitigation plans to minimize the risk that they will occur.

Tablets, caplets, or capsules left behind from previous runs have the potential to create a failure pathway. The next run could be a different product, a different concentration of the same product, a different packaging configuration of the same product, or different quantities of the same product. Whatever the case, if the wrong item ends up in the wrong place it can lead to a compliance issue or, in the worst case, product contamination.

Some commonly reported line-clearance inadequacies originate from:

- In-house quality assurance (QA) audits finding tablets in the line. This could lead to cross-contamination if a different product was packaged prior to the current product.
- Customer complaints citing mixed products or incorrect quantities in a product package.

These observations may become evident during regulatory reviews of cleaning and standard operating procedures (SOPs), and may lead to line clearance uncertainty and the potential for cross-contamination between products and associated packaging components such as labels, information inserts, leaflets, and medical guides.

In accordance with the *FDA Compliance Program Guidance Manual*, when production systems or packaging and labeling systems are inspected, an inspector will look for a firm's adherence to written procedures and verify this through observation. Adherence to preprocessing procedures (cleaning, setup, line clearance, etc.), should be demonstrated to the FDA, but this may be difficult given the lack of current good manufacturing procedures (cGMP) guidance and regulations regarding line clearance. Depending on the inspection's findings, the level of scrutiny and depth of analysis may vary.

## State of Control

A manufacturing firm is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of the cGMP regulations that pertain to their systems. A firm in a state of control produces finished drug products for which there is an adequate assurance of quality, strength, identity, and purity.

A firm is out of control if any one system is out of control. A system is out of control if the quality, identity, strength, and purity of the products resulting from that system or those systems cannot be adequately assured. Examples of this are:

- Companies found to have multiple incidents of line-clearance issues without signs of remediation of these issues
- Demonstrating a "pattern of lack of control"

Factors that may challenge a system's state of control of are:

**Line changes:** The trend in the pharmaceutical industry, in order to stay competitive, is to manufacture in smaller, more specialized batches. As batch sizes get smaller, product changeovers occur more frequently and the filling, packaging and labeling runs get shorter. This promotes the need for leaner operations and lean fundamentals, which drive faster changeover times for:

- Products (as well as fills of the same product in different quantities)
- Packaging sizes
- Labeling

**Machine designs:** Equipment—especially older equipment—is not typically designed to address line clearance issues, so beware of these following areas of concern:

- Pinch points create spaces in which product can get trapped or remain hidden, even during cleaning and inspection.
- Compressed air used during cleaning can force product into areas not visible during cleaning and inspection.
- Some types of conveyors (such as those with starwheel designs) have openings where product can hide and get trapped.
- Flat surfaces on the machine are problematic. Slanted surfaces can help get tablets to the machine base or into catch basins or other collection areas.
- Open holes in the horizontal deck of the equipment frame have the potential to swallow up product that might not be found until it is too late.
- Equipment support feet should provide adequate clearance above the floor for cleaning and inspection. Detection of a stray product under the line could trigger a quality investigation that will cost money and time.
- Rolled or bent sheet metal on panels and conveyors can promote product hang-up. Be careful to eliminate any horizontal surface, either visible or hidden.

**If the wrong item ends up in the wrong place it can lead to a compliance issue or, in the worst case, product mix-ups and contamination**

- Encourage the supplier to provide hinged parts so that the entire system can be exposed quickly during cleaning and line clearance.
- Waste system design: If the equipment includes a reject system, its design must make it easy to verify that rejected product is not left behind.
- Avoid colored panels so that line clearance is obvious. Blue glass panels might look nice on a packaging line but seeing a blue pill through them might not be so easy.

**Line maintenance and setup:**

- Proper line setup to prevent bottles from binding or tipping
- Positive seal on filling head to bottle
- Appropriately tensioned and maintained belts and conveyor rails/guides to prevent spillage during conveyance

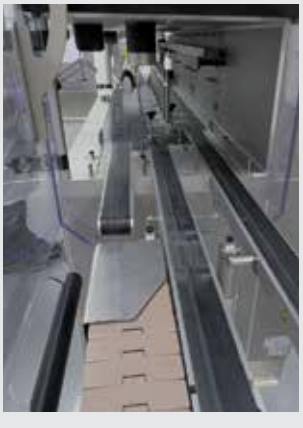
## Recommended Changes

Make the following recommended machine design changes, or ask the manufacturer to redesign problem areas wherever possible:

- Seal areas completely to prevent tablets from entering.
- Use Lexan covers to make areas where tablets may get lodged more visible during inspections.
- Minimize horizontal surfaces.
- Eliminate holes or crevices on horizontal surfaces.
- Install clear enclosure panels with hinges and good lighting to expose the entire machine and provide maximum visibility.

**Figure 1: Typical bottle packaging line**

**Figure 2: Potential areas of entrapment within packaging equipment**



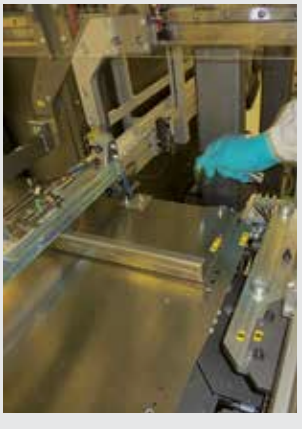


**Figure 3: Pinch points on a typical packaging machine**

## General "housekeeping" cleaning between product and product format changeovers is often insufficient

Use newer equipment:

- New equipment is designed for line clearance ease; older equipment must often be retrofitted with solutions like catch bins, sealed panels, etc.
- New machines have better conveyors and are designed to eliminate pinch points. The result is fewer line clearance issues.

Identify high-risk areas:

- Use appropriate tools (flashlight and jigs) to ensure hard-to-reach areas can be accessed and cleared of all materials.

Implement remedial procedures:

- Identify problem areas discovered during cleaning and inspections on a plan drawing of the entire packaging line; use stickers to indicate where these areas are.
- Create a picture book of photographed areas; use stickers on photos to indicate where hiding spots exist.
- After cleaning and inspection of lines, perform a second QA inspection before reassembling the line.
- List or show all known trouble spots in operator sign-off logs.
- Prohibit use of compressed air after cleaning to prevent blowing product into hidden or already checked areas; use vacuum cleaning instead.

**Figure 4: Inspection method: Use of additional lighting**

**Figure 5: QA inspection of disassembled slat-style bottle filler**

Establish line-clearance procedures that include:

- Checking all problem areas to verify that everything from the previous operation has been removed, including:
  - Materials and residues
  - Utensils and accessories
  - Containers
  - Waste product, if the system includes waste collection
  - Paperwork
  - Preprinted items such as labels, cartons, shippers, etc.
- Ensuring all equipment is cleaned and properly status labeled
- Ensuring all areas are clean and status is displayed

# Development of SOPs with operator sign-offs for each step involved with line clearance and inspections is recommended


## Summary

While the US Code of Federal Regulations Title 21 Parts 210[1] and 211[2] sets forth equipment cleaning and maintenance requirements, it is not as prescriptive regarding line-clearance requirements. Many filling, packaging, and labeling operations utilize two levels of cleaning: a minor cleaning between same product batches, which is the line-clearance level; and a major cleaning, which is a detailed cleaning wash-down and set up to run a completely difference product. Good manufacturing practices require that manufacturing and packaging lines shall allow for the reconciliation of all elements in the production process (such as tablets, capsules, various labels generated and applied, and product leaflets). Reconciliation shall be possible for all sections of the inspection and packaging line (IPL) where it is possible to reject or "lose" a tablet or other element. In addition to full reconciliation of all elements, the IPL shall be configured and equipped to enable proper line-clearance verification before and after batch processing as part of segregation within batches (such as for changes to labeling), and wherever else line clearance may be required. Reconciliation and line clearance shall be safe, robust, and effective.

Development of SOPs with operator sign-offs for each step involved with line clearance and inspections is recommended, and their usage enforced. The FDA will look for evidence that these SOPs are being followed and implemented into each day's activities. ■


## References


1. US Government Publishing Office. Electronic Code of Federal Regulations. Title 21, Chapter 1, Subchapter C, Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General. http://www.ecfr.gov/cgi-bin/text-idx?SID=43fb2935d4392a4d54fe49f53100f769&mc=true&node=pt21.4.210&rgn=div5.
2. US Government Publishing Office. Electronic Code of Federal Regulations. Title 21, Chapter 1, Subchapter C, Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals. http://www.ecfr.gov/cgi-bin/text-idx?SID=43fb2935d4392a4d54fe49f53100f769&mc=true&node=pt21.4.211&rgn=div5.


## About the Authors


**Michael (Mike) DeBellis** is a Lead Process Mechanical Engineer for Jacobs Engineering. He has over 32 years of diversified experience in the engineering and design of pharmaceutical and biotechnology manufacturing facilities as well as secondary packaging and end of line packaging systems. Presently he is on the ISPE *Oral Solid Dosage Forms Baseline Guide* Committee as a repeat Co-Chapter Leader and author of the "Products and Processing Chapter" (2nd and 3rd editions) and is Co-Chair of the Steering Committee for the ISPE OSD Community of Practice (CoP). He is also the lead for the Manufacturing subcommittee within the OSD CoP. He has been an active member of the Delaware Valley Chapter's Programs Committee and an ISPE member since 1997. Mr. DeBellis earned his BS degree in mechanical engineering at New Jersey Institute of Technology.

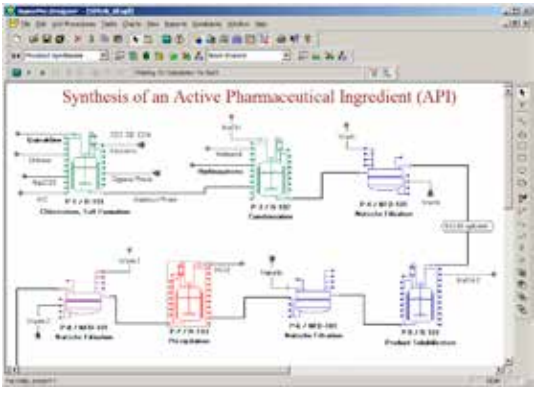
**Jim Cahir, PE**, is the Engineering Manager–Life Sciences at Barry Wehmiller Design Group's regional office in King of Prussia, Pennsylvania. He worked at AstraZeneca between 2004 and 2011. Positions included capital project manager, maintenance engineer– sterile product facility, and maintenance facilitator/engineer for OSD bottle packaging lines. Duties included maintenance and reliability, implementation of lean principles, and identification and elimination of tablet migration mechanisms. Before that, Mr. Cahir spent 17 years with Day & Zimmermann with roles as plant engineer, lead process engineer, and validation engineer. He has worked with many area pharmaceutical clients, including McNeil, GSK, Mallinckrodt, Merck, Wyeth, Pfizer and Novartis. He is a member of the Oral Sold Dosage sub-committee. Mr. Cahir earned a BS degree in engineering from Lehigh University, an MS degree in engineering from the University of Notre Dame and an MBA degree from Wilmington University. He is a Registered Professional Engineer in Pennsylvania.

**Robert (Bob) Matje, PE, CPIP**, is a pharmaceutical consultant specializing in project and program management services as well as management consulting. He was formerly the vice president of technical operations at Qualitest, Endo's generic manufacturing division. Prior to that he was the vice president and general manager of both oral solid dosage facilities within Qualitest where he had full responsibility for manufacturing, materials management, site engineering, and site EH&S. He has also held the position of senior director of engineering at Endo, which included reliability and maintenance, environmental, health and safety, automation, capital, and qualification. Robert Matje worked at Pfizer (then Wyeth) between 1999 and 2012. He held numerous positions, including program manager for Pfizer's Global Serialization Project Management Office and program director for PNS projects in Puerto Rico. Mr. Matje has been a Member of ISPE for 14 years and is Past President of the Delaware Valley Chapter. He currently chairs the ISPE Awards Committee and serves on the Quality Metrics Team and the Oral Solid Dosage CoP Steering Committee. He is also an author of the *Oral Solid Dosage Forms Baseline® Guide*. He was elected to the ISPE Board of Directors in 2013. Mr. Matje earned a BS degree in engineering at Lafayette College and an MS degree in engineering at Villanova University. He is a Registered Professional Engineer in Pennsylvania and was awarded his CPIP designation in 2012.

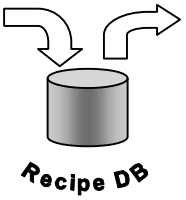
# Intelligen Suite®

## The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Multi-Product Facilities

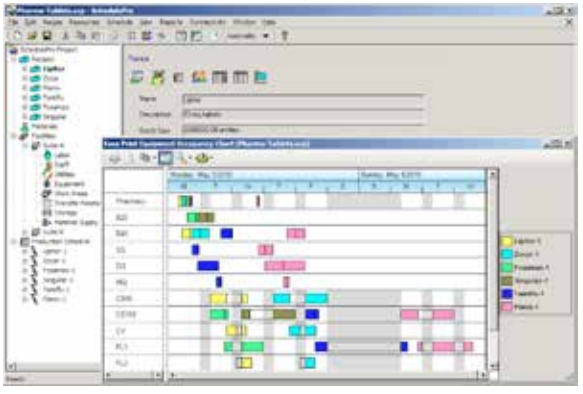
## SuperPro®



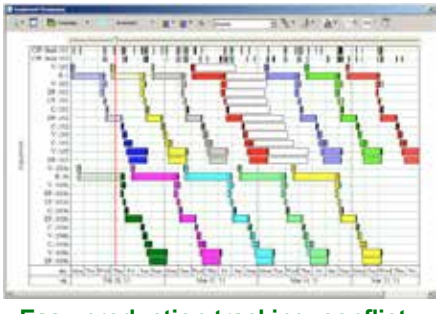

Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



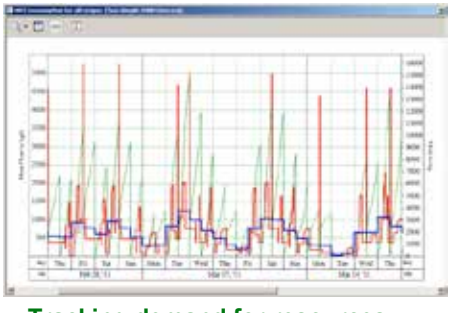

## SchedulePro®



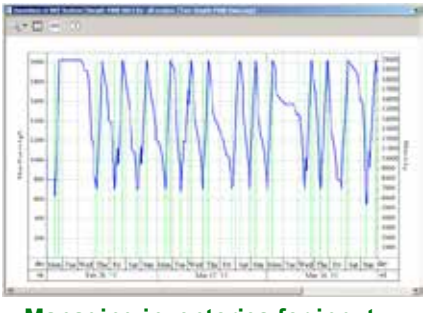
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling



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



Managing inventories for input, intermediate, and output materials

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

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

***Visit our website to download detailed product literature and functional evaluation versions of our tools***

**INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA**
**Tel: (908) 654-0088 • Fax: (908) 654-3866**
**Email: info@intelligen.com • Website: www.intelligen.com**
***Intelligen also has offices in Europe and representatives in countries around the world***

## Advertisers' Index



## Classified Advertising

*Please see the ads for each of our advertisers in this issue.*

### Analytical Instruments

GE Analytical Instruments
6060 Spine Road
Boulder, CO 80301 USA
+1 800-255-6964

### Architects, Engineers, Constructors

CRB
7410 NW Tiffany Springs Pkwy.,
Suite 100
Kansas City, MO 64153 USA
+1 816-880-9800

NNE Pharmaplan
Nybrovej 80
DK-2820 Gentofte, Denmark
+45 4444 7777

Pharmadule Morimatsu AB
DanvikCenter 28
SE-13130 Nacka, Sweden
+46 (0)8 587 42 000

### Biopharmaceutical

Bristol-Myers Squibb
1 Squibb Drive
New Brunswick, NJ 08901 USA
+1 732-227-5168

### Construction

Fluor
100 Fluor Daniel Drive
Greenville, SC 29607 USA
+1 864-281-4400

### Containment

ChargePoint Technology
80 Venture Point West
58 Evans Road
Liverpool, L24 9PB
United Kingdom
+44 151 728 4500

### Dust Collection Systems and Equipment

Camfil Air Pollution Control
3505 S. Airport Drive
Jonesboro, AR 72401 USA
+1 870-933-8048

### Electric Dry Steam Generators


### Facility Engineering and Maintenance

Valsteam
Rua da Guia, 3105-467
Guia PBL, Portugal
+351 236 959 060
See our ad in this issue.

### Filling and Packaging Equipment

Optima Packaging Group GmbH
Steinbeisweg 20
74523 Schwäbisch Hall, Germany
+49 791 9495-0

### Information Technology

Ing. Punzenberger COPA-DATA GmbH
Karolingerstrasse 7b
Salzburg, Austria 5020
+43 662 43 10 02-0

### Instrumentation

Bürkert Werke GmbH
Christian-Bürkert-Strasse 13-17
D-74653 Ingelfingen, Germany
+49 (0)7940 10 0

Particle Measuring Systems Inc.
5475 Airport Boulevard
Boulder, CO 80301 USA
+1 303-443-7100

### Machinery Design & Construction

Gericke AG
Althardstrasse 120
CH-8105 Regensdorf, Switzerland
+41 44 871 36 36

### Pumps

Alfa Laval, Inc.
5400 International Trade Drive
Richmond, VA 23231 USA
+1 804-222-5300

Fristam Pumps USA
2410 Parview Road
Middleton, WI 53562 USA
+1 800-841-5001

LEWA-Nikkiso America
132 Hopping Brook Road
Holliston, MA 01746 USA
+1 508-893-3218

Watson-Marlow Fluid Technology Group
37 Upton Technology Park
Wilmington, MA 01887 USA
+1 800-282-8823

### Software Products

Novatek International
2537 Rue Guenette
Montréal, Québec
Canada H4R 2E9
+1 514-668-2835

### Software Simulation and Processing Systems

Intelligen, Inc.
2326 Morse Avenue
Scotch Plains, NJ 07076 USA
+1 908-654-0088

### Validation Services

Commissioning Agents, Inc.
652 N. Girls School Road
Indianapolis, IN 46214 USA
+1 317-271-6082

ProPharma Group, Inc.
10975 Benson Drive., Suite 330
Corporate Woods Bldg. 12
Overland Park, KS 66210 USA
+1 913-661-1662

### Valves/Fittings/Hoses/Tubing

AGRU Kunststofftechnik GmbH
Ing.-Pesendorfer-Strasse 31
A-4540 Bad Hall
Austria
+43 7258 790

GEMU Valves, Inc.
3800 Camp Creek Parkway
Bldg. 2600, Ste. 120
Atlanta, GA 30331 USA
+1 678-553-3400

### Water/Steam Systems

Letzner Pharmawasseraufbereitung GmbH
Robert Koch Str. 1
42499 Hückeswagen, Germany
+492192/92170

MECO
68375 Compass Way East
Mandeville, LA 70471 USA
+1 985-249-5500

Stilmas SpA
Viale delle Industrie, 14
Settala (MI) 20090 Italy
+39 02 9508061

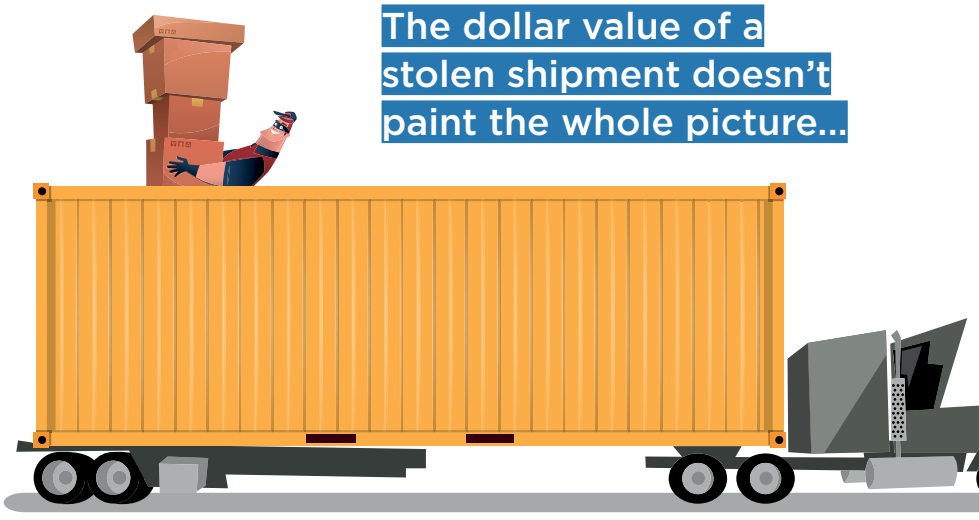
### Water Treatment and Purification

Elettracqua Srl
Via Adamoli 513
16165 Genoa, Italy
+39 010 8300014

Mar Cor Purification
160 Stedman Street
Lowell, MA 01851 USA
+1 978-453-9600

Mettler-Toledo Thornton Inc.
900 Middlesex Turnpike, Bldg. 8
Billerica, MA 01821 USA
+1 800-510-7873

# Keeping the Mice at Bay



**The dollar value of a stolen shipment doesn't paint the whole picture...**

**An audacious theft** at an Eli Lilly warehouse in Connecticut in 2010 was a watershed moment for the pharmaceutical industry. Thieves cut a hole in the roof; lowered themselves into the building; disabled alarms; and drove away with over $70 million worth of Prozac (fluoxetine), Zyprexa (olanzapine), and other drugs. Enhancements in security since then have prevented another warehouse robbery on that scale, although drug theft remains an industrywide concern.

The theft of pharmaceuticals will increase globally this year, according to a British Standards Institution (BSI) report.[1] There were 31 reported cargo drug thefts in the US last year, with an average value of about $240,000.[2] Truck theft is on a steady decline,[6] although significant global disparities exist, with the problem being most acute in Europe,[3] where truck robberies increased over fivefold between 2010 and 2012 in Italy.[4] There has been at least one "open sunroof" theft in China, in which acrobatic thieves boarded a moving truck, cut holes in the top or back of the trailer, and threw goods to accomplices in a vehicle behind.[5] Elsewhere, organized gangs in India have removed goods from stolen trucks without breaking custom seals, and there has been a sharp increase in truck hijacks in South Africa, where the trend is toward violent thefts.

The dollar value of a stolen shipment doesn't paint the whole picture, according to Charles Forsaith, the Chair of the Pharmaceutical Cargo Security Coalition (PCSC). "Not only did you lose the shipment, but you have to replace those drugs, incur additional cargo insurance because of the loss, and there can be damage to customer confidence," he said. "An apparent $250,000 loss, when it shakes out in the end, could easily triple."

Theft can also lead to shortages of critical drugs and the chance that mislabeled, adulterated, less potent, or toxic products can reenter the legitimate market as thieves reintroduce contraband either by rerouting it through another country; through online pharmacies; or through legitimate pharmacies with new, fake labels.[8]

The global nature of the supply chain—from the manufacturing facility, through a wholesaler, delivery to pharmacies and hospitals, and on to the consumer—is long and wide, with potential vulnerabilities throughout.

"Until the delivery stage, there isn't a particular product that is stolen more than another," Forsaith said. So-called last-mile thefts commonly involve controlled substances, like opioids. "There are two ways thieves, looking to sell stolen products, look at pharmaceutical thefts. Prescription narcotics have a higher value, but are much more difficult to reintroduce into a legitimate supply chain because of all the regulatory complexities. Over-the-counter drug and nutritional products, such as laxatives or infant formula, have lesser values, but are much easier and have fewer risks when attempting to reintegrate them into a supply chain."

Technology is helping secure the supply chain, with fleet monitoring systems providing door sensors, panic buttons for drivers, and detection of GPS signal jammers. The latter is important because, as with any cat-and-mouse game, criminals look for ways to evade the latest traps and have, on occasion, jammed these GPS signals. Last year, GPS tracking was credited in the recovery of a truckload of stolen drugs within 1 hour.[9]

Initiatives like the PCSC—a collaboration of industry professionals, law enforcement, and government groups—have helped improve security throughout the supply chain in the US; pharmaceuticals are absent from a list of the most commonly stolen goods among 312 cargo thefts recorded by BSI in the first quarter of 2016.[7]

When asked how to prevent stolen goods from reentering the market, Forsaith said it best: "The best prevention is to keep [the] product from leaving the legal supply chain in the first place." ■

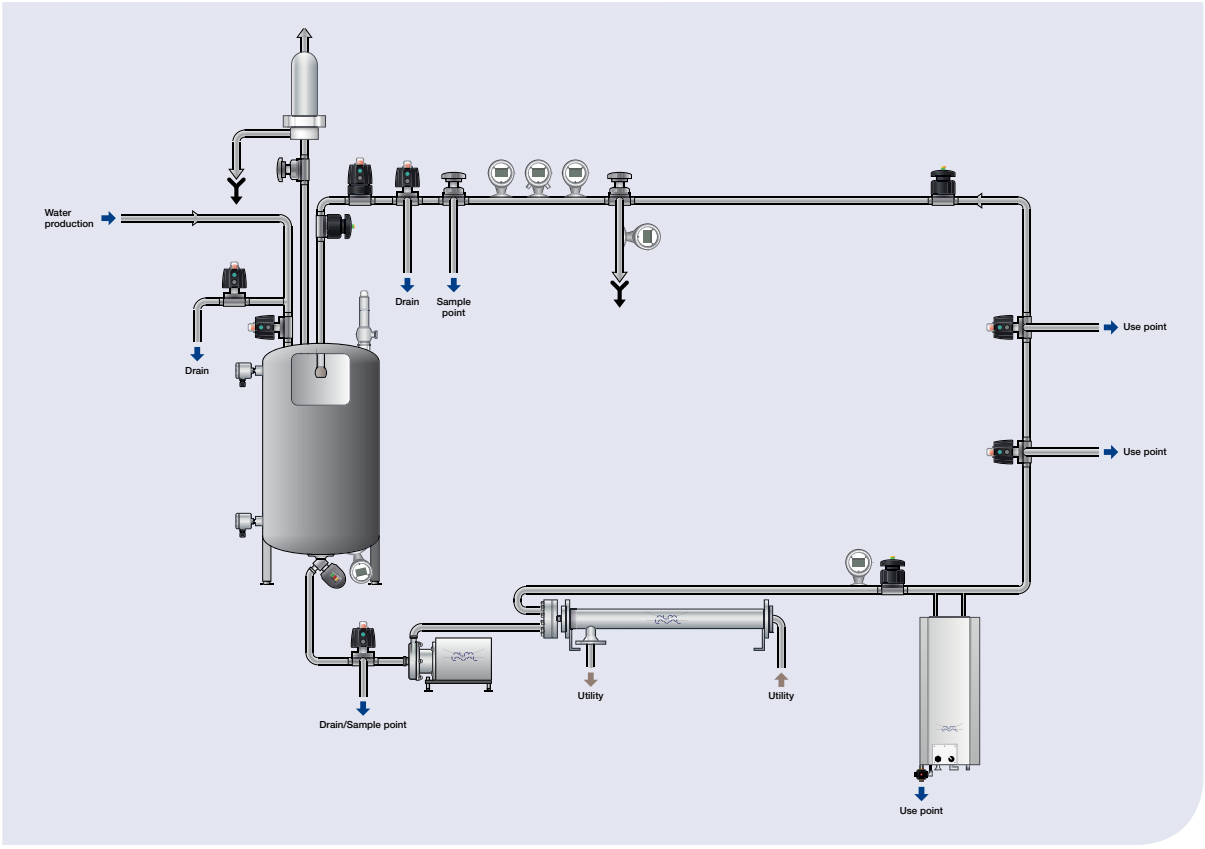
## References


1. BSI Supply Chain Services and Solutions. "BSI's Global Supply Chain Intelligence Report Reveals 2015 Top Supply Chain Risks." 23 March 2016. http://www.bsigroup.com/en-GB/about-bsi/media-centre/press-releases/2016/March/BSIs-Global-Supply-Chain-Intelligence-report-reveals-2015-top-supply-chain-risks-/#.V4e-mEKMlsg.
2. David Blanco, Marketing Communications Coordinator at FreightWatch International. FreightWatch International data. Personal email communication, 21 July 2016.
3. Ekwall, D., H. Brüls, and D. Wyer. "Theft of Pharmaceuticals during Transport in Europe." *Journal of Transportation Security*, October 2015. http://www.unitrans-us.com/newsroom/Attachments_Uploads/TheftofPharmaceuticals.pdf.
4. Riccardi, M., M. Dugato, and M. Polizzotti. *The Theft of Medicines from Italian Hospitals*. Transcrime Joint Research Centre on Transnational Crime, 2014. https://www.researchgate.net/publication/260487710_The_Theft_of_Medicines_from_Italian_Hospitals
5. Taylor, P. "China Sees Rise in Cargo Theft from Moving Trucks." Securing Industry, 20 March 2016. https://www.securingindustry.com/china-sees-rise-in-cargo-theft-from-moving-trucks/s112/a2721/#.V4fDH0KMlsh
6. Charles Forsaith, Chair of the Pharmaceutical Cargo Security Coalition. Telephone conversation, 15 July 2016.
7. BSI Supply Chain Services and Solutions. "SCREEN: United States Cargo Theft Report Q1 2016." http://bsi-supply-chainsolutions.com/en-US/resources/special-reports/
8. Eban, K. "Drug Theft Goes Big." *Fortune* 31 March 2011. http://fortune.com/2011/03/31/drug-theft-goes-big/
9. Grisolano, G. "GPS Tracking Device Credited for Pharmaceutical Load Recovery." *Land Line*, 24 July 2015. http://www.landlinemag.com/Story.aspx?StoryID=29482#.V3vQM0KMlsh

# OUR NEW **MS 10 SERIES** IS WELCOME

The treating machine with high flow rate of 20 tons and over, **less than 15 minutes to be operational,** supplying water of the highest quality standards and the lowest consumption.
Stilmas has top innovation secrets to disclose. **www.stilmas.com**

STILMAS
MASCO GROUP




# Pharmaceutical water systems

Water is an essential ingredient to the manufacturing of pharmaceutical products. Proper design, installation, commissioning and validation of hygienic equipment is critical in order to ensure the safe, continuous and efficient operations of the pharmaceutical manufacturing facilities as well as the quality of the final end products. Alfa Laval hygienic equipment combines sustainable performance with significant cost savings and comes with Alfa Laval Q-doc our cutting-edge documentation package for the pharmaceutical industry making validation exceptionally easy.
Optimize your water system: **alfalaval.com/pharmawatersystems**

Alfa Laval
Pharma-line

This high quality shell and tube heat exchanger offers reduced risk of contamination and is available with a unique inspectable inner tube package.

Alfa Laval
DV-ST UltraPure

Compact and modular, this diaphragm valve delivers reliable performance. The range includes 2-way, T-port, tandem, tank outlet and multi-port body options. Available in forged, block and cast options.

Alfa Laval
Sani SB

Ideal for the holding tank in a pharmaceutical water system, this rotary spray head is easy to install, validate and minimizes the risk of rouge.

Alfa Laval
LKH UltraPure

Reliable and energy efficient, this centrifugal pump is ideal for facilitating continuous circulation. Its external shaft seal provides easy and safe leak detection and prevents contamination. The open impeller design prevents biofilm buildup.