PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

September-October 2017 | Volume 37, Number 5

CAR T-CELL THERAPY BREAKTHROUGH

Patent Battles in the Age of CRISPR

Finding Relationships between Clinical Batch Quality Data and Patient Outcomes

Microbiome Treatments for Recurrent *C. Difficile* Infections

SPECIAL REPORT — BIOTECHNOLOGY

Rendering of a T-cell lymphocyte with receptors for cancer cell immunotherapy research

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THE NEW NORMAL

Anna Maria di Giorgio
Editor in chief

Many spend their summer relaxing, perhaps traveling, but generally trying to "put their feet up." Others change the course of health care as we know and practice it.

Gilead's 28 August purchase of Kite Pharma, one of the companies developing chimeric antigen receptor (CAR) T-cells, a therapy that harnesses the body's own immune system to recognize and attack malignant cells, sent strong signals across the markets. Learning that the United States had joined China in gene-editing human embryos using CRISPR made headlines, as did the 13 July unanimous recommendation of the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) that the FDA approve CTL019, Novartis's CAR T-cell therapy.

These events were transformative enough. But then, on 30 August, this industry's equivalent of the first moonwalk took place: Novartis was granted approval, an FDA first, for its CAR T-cell therapy, Kymriah (CTL019).

The subject of our cover story, CAR T-cell therapy will not only transform the pharmaceutical industry, it has the potential to breathe life into dying patients and restore normalcy to their family lives. Cell therapy may possibly be this century's most extraordinary medical development thus far.

Author Scott Fotheringham, PhD, speaks with Tom Whitehead, whose daughter Emily went into remission 23 days after treatment with the experimental Novartis therapy. Dr. Fotheringham also interviews Dr. Stephan Grupp—who you may have heard at last year's Annual Meeting & Expo in Atlanta—about his clinical trials in pediatric oncology testing CAR T-cell therapies, and his hopes for immunotherapy in solid tumors. Finally, Dr. Fotheringham talks to Spencer Fisk of Novartis and Dr. Mihaela Simianu of Pharmatech Associates about the challenges that surround the manufacture of biologics.

THE REST OF THE ISSUE

Our feature story is penned by lawyers Ainslie Parsons and Carmela De Luca, who look at CRISPR patent battles in the United States and demystify the proceedings for us.

Robert Dream, PE, CPIP, PhD, and member of the *Pharmaceutical Engineering* Committee is our guest editor for the Special Report on Biotechnology, which examines the role of engineers in biopharmaceutical manufacturing, why China is ahead of the GMP game in biotech, and how closed production systems improve the sterility of equipment and the facilities in which they are located.

On the ISPE front, we hear from leaders at the ISPE/FDA/PQRI Quality Manufacturing Conference, and showcase the category winners of the 2017 Facility of the Year Awards. Christopher Potter, member of the ISPE Quality Metrics Core Team, reports on a recent meeting with FDA Quality Metrics team members, and author Mike McGrath takes a close look at the ISPE Turkey Affiliate and the work it is doing in a country fraught with political turmoil.

In the technical realm, authors Valérie Vermylen, Jean-Etienne Fortier, Eric Rulier, Alain Bernard, Carl Jone, and Justin Neway explore the link between clinical batch quality and patient outcomes. Marzena Ingram, Ajay Babu Pazhayattil, Naheed Sayeed-Desta, and Galina Desai make the case for a life cycle approach to ensure manufacturing excellence.

And to wrap it all up, Dr. Fotheringham explores the possibilities presented by fecal microbiota transplantation for refractory *C. difficile* infections.

My humble self believes we have crossed the threshold of disruption and that biotechnology and its myriad variants are becoming the new normal. What do you think?

I look forward to hearing your point of view on this and many other topics at the 2017 Annual Meeting & Expo in San Diego. Until then, take good care. ‹›

ISPE

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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.

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

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

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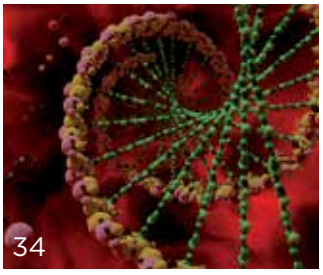

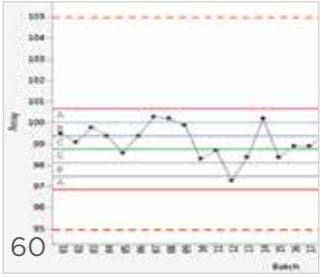

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HEROES MAKE US STRONG

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

A hero is someone who has given his or her life to something bigger than oneself.

—"The Hero's Adventure," in *The Power of Myth*, by Joseph Campbell with Bill Moyers, 1988

Of all the definitions of a hero, this one from Joseph Campbell is my favorite. You met one such hero at our 2016 Annual Meeting, when I introduced you to Gavin Pierson. His mother Nicole was a keynote speaker who shared her family's journey in their fight to save Gavin, who was suffering from a rapidly growing teratoma, a type of brain tumor (see *Pharmaceutical Engineering*, November-December 2016, page 20). Gavin was in remission when you met him and I'm happy to say he still is—and is about to get his brown belt in karate!

As she ended her presentation, Nicole called you heroes for the work you do in advancing medicine to improve patient outcomes. I said you were heroes not only for creating medicines that save lives, but for finding ways and improvements to reliably manufacture high-quality medicines, when many attempts fail after years of hard work.

Some notable examples of these efforts include discovery and approval of pediatric CAR T-cell therapy—a treatment that genetically engineers a patient's immune cells to target and destroy cancer cells (see page 12), advancing biotechnology and biosimilars, and alliances with technology firms. These efforts are being applied toward the achievement of a single goal: the improvement of patient care.

WHAT A DIFFERENCE A YEAR MAKES!

Over the past 13 months I've had the opportunity to work closely with many of you who are discovering new medicines. On behalf of the International Board of Directors and ISPE staff, I offer my sincerest thanks to you, our members and volunteers, for finding time in your busy schedules to volunteer with ISPE and lend your continued support. It's simply amazing. You are my heroes.

When you accept the role of Chair, you know you have a fixed period of time to help move things forward. You know that you must foster stability, maintain continuity, and support ISPE's relationship with its community. You also want to grow the organization, ensure an effective infrastructure, and prepare it to meet future demand.

In my first column for this magazine, I wrote that I would focus on four primary areas: transparency, business diversity, collaboration, and strengthening our core. In this, my final column, I would like to discuss the outcome of that focus.

TRANSPARENCY As Chair, I shared 21 messages with you: seven via my "View from the Chair" editorial in this magazine, and 14 via "Chairman's Chatter" on the ISPE Blog. These communications covered global celebrations, society successes, ISPE core values, Young Professionals, Board activities, organizational decisions, plus highlights of conferences and other events.

BUSINESS DIVERSITY The Board has been busy looking at how we can diversify ISPE activities to better serve you and our mission. I asked some Board members to share their thoughts on our accomplishments.

Thomas Hartman, Board Director, and Vice President of GMP Operations, Biopharm CMC, GlaxoSmithKline

"The Business Development Team was established in January 2017 with a remit to identify and assess new ISPE focus areas with the intention of increasing membership, member value, and further industry engagement. Multiple initiatives were evaluated using a tool developed by the team that weighs potential benefits against effort and member needs. From these evaluations, the concept of the ISPE Foundation emerged. The idea was approved by the Board and is currently being developed. Information about the foundation will be shared in San Diego at the 2017 Annual Meeting & Expo."

Fran Zipp, Board Director, and President and CEO, Lachman Consultant Services

"ISPE Women in Pharma (WIP) provides women in the manufacturing sector of the pharmaceutical industry a community of mentors, resources, and educational sessions for career success and work-life balance. WIP held its inaugural session at the 2016 ISPE Annual Meeting & Expo in Atlanta, Georgia, with nine panelists from industry and FDA and about 70 attendees. It has since grown remarkably, with well over 120 attendees at the 2017 Women in Pharma breakfast at the ISPE/FDA/PQRI Quality Manufacturing Conference. Since 2016 WIP has received $5 donations for ISPE Women in Pharma buttons; proceeds have been awarded to the University of Georgia Department of Pharmaceutical and Biomedical Sciences to women pursuing degrees in the field. Monies are earmarked for ISPE student memberships, registration fees for ISPE events, purchase of an ISPE Guidance Document, or attendance at an ISPE training course."

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2017 CALENDAR

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

SEPTEMBER

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

8 Singapore Affiliate
Go-Karting Challenge
Singapore

10 Nordic Affiliate
Critical Utilities CoP Network Meeting
Copenhagen, Denmark

Nordic Affiliate
PAT CoP Autumn Meeting
Malmo, Sweden

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

12 India Affiliate
India and ISPE GAMP India Efficient Pharma Computer Compliance
Goa, India

12 Delaware Valley Chapter
Pump Manufacturing Plant Tour
Telford, Pennsylvania

UK Affiliate
York Racecourse Facilities Tour and Networking Drinks
York, England

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

12–14 2017 Process Validation Conference
Bethesda, Maryland

13 DACH Affiliate
DACH CoP GAMP and D/A/Ch Forum mit vortragen (with presentation)
Frankfurt, Germany

14 Canada Bike and Hike Networking Event
Joliette, Quebec, Canada

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

14–15 2017 Process Validation Statistics Conference
Bethesda, Maryland

18–20 Brazil Affiliate
GAMP 5 Training
São Paulo, Brazil

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

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

25–26 **Biotechnology Manufacturing Facility Design (T31)**
Cleaning Validation Principles (T17)
Amsterdam, Netherlands

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

Process Validation (T46)
ISPE Training Institute
Tampa, Florida

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

Chesapeake Bay Area Chapter
2017 Golf Tournament
Ijamsville, Maryland

26–27 ISPE 2017 Europe Biotechnology Conference
Dublin, Ireland

27–28 **Commissioning & Qualification (T40)**
GAMP 5 GxP Compliance (T21)
GMP Sterile Pharma Manufacturing Facility (T12)
Amsterdam, Netherlands

28 DACH Workshop: OSD-Produktion als Ultra-Fast-Track-Projekt (Production as an ultra-fast-track project)
Ingelheim, Germany

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

OCTOBER

2–3 **Overview Biotechnology Manufacturing Processes (T24)**
ISPE Training Institute
Tampa, Florida

4 Boston Area Chapter
Annual Product Show
Foxboro, Massachusetts

5 San Diego Chapter
Technical Meeting
San Diego, California

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

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

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

France Affiliate
IPIL Conference: Externalisation (Outsourcing)
Lyon, France

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

12–13 **GAMP 5 GxP Compliance (T21)**
ISPE Training Institute
Tampa, Florida

14 Nordic Affiliate
GAMP Networking Meeting
Copenhagen, Denmark

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

18 France Affiliate
Workshop: Operations Management
Paris, France

18–19 Brazil Affiliate
Annual Conference
São Paulo, Brazil

Poland Affiliate
YP and SME Global Systems and Data Integrity
Lodz, Poland

19 France Affiliate
GAMP Francophone Workshop: IT Infrastructure
Paris, France

IChemE Singapore Awards
Singapore

Rocky Mountain Chapter
Fall Educational Event

23–24 **Biotechnology Manufacturing Facility Design (T31)**
Cleaning Validation Principles (T17)
Pharma Water Generation USP WFI & PW (T04)
Boston, Massachusetts

Pharmaceutical Water Systems (T35)
Manchester, England

24–26 Malaysia Affiliate
ASEAN Guideline GMP for Traditional Medicine
Petaling Jaya, Malaysia

HVAC CGMP Regulations (T14)
Boston, Massachusetts

25–26 **Pharmaceutical Facilities Management (T26)**
Storage/ Qualification of Pharma Water (T23)
Boston, Massachusetts

26 DACH Affiliate
Pharma 4.0 Digital Transformation Ideation Workshop
Ismaning, Germany

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

30 Oct–1 Nov
Singapore Affiliate
Pharmaceutical GMP Course
Singapore

31 Brazil Affiliate
Validation of Electronic Spreadsheets
São Paulo, Brazil

NOVEMBER

1–2 **Process Validation in Biotech Manufacturing (T32)**
ISPE Training Institute
Tampa, Florida

1–3 **Basic GAMP 5 Annex 11/Part 11 (T45)**
ISPE Training Institute
Tampa, Florida

6–7 **Managing Cross Contamination Risk MaPP (T41)**
ISPE Training Institute
Tampa, Florida

8–9 Brazil Affiliate
Project Management for Life Sciences
São Paulo, Brazil

9 Belgium Affiliate
Young Professionals Event
Lille, Belgium

Nordic Affiliate
Annual Conference
Stockholm, Sweden

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

13–14 **CIP Design, Integration and Chemicals (T03)**
ISPE Training Institute
Tampa, Florida

ISPE 2017 Asia Pacific GAMP Data Integrity Conference
Singapore

13–15 **GAMP Data Integrity 21 CFR Part 11 (T50)**
Manchester, England

14–15 Philippines Affiliate
Seminar on PIC/S Updates and Project Management
Quezon City, Philippines

15 Greater Los Angeles Chapter
Evening with Industry Executives
Pasadena, California

16 San Diego Chapter
Technical Meeting
San Diego, California

16–17 **ICH Q7A GMPs for API (T30)**
ISPE Training Institute
Tampa, Florida

18 Brazil Affiliate
Requisite Regulations for Calibration
São Paulo, Brazil

20–21 **Pharmaceutical Technology Transfer (T19)**
Manchester, England

20–22 Brazil Affiliate
GAMP 5 Training
São Paulo, Brazil

22 Belgium Affiliate
Annual Seminar
Mechelen, Belgium

23 France Affiliate
Integrité des Données (Data Integrity)
Paris, France

23–24 ISPE 2017 Europe Pharma 4.0 Conference
Pescantina, Verona, Italy

27 India Affiliate
Containment of High Potent APIs
Mumbai, India

28–30 Poland Affiliate
Water in Pharmaceutical Industry
Lodz, Poland

30 UK Affiliate
Annual Conference
Bridgefoot, England

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Antonio Moreira, Board Director, and Vice Provost for Academic Affairs, University of Maryland, Baltimore County

"The Academic Outreach Subcommittee of the Business Development Committee recently joined forces with the WIP Academic Subcommittee to foster initiatives to recruit and retain student memberships in ISPE, including specific efforts aimed at reaching female students and faculty, followed by conversion to YP membership.

"During the past summer, the Academic Committee interviewed YP and Student Activity Committee leaders in the Boston Area, Carolina–South Atlantic, New Jersey, and San Francisco Bay Area Chapters. From these interviews, we are compiling information on activities and processes that produce a strong and sustained student chapter. These best practices will serve as the foundation for establishing three new student chapters at universities, which have yet to be selected. This pilot exercise will guide the development of a package of information to be made available to all chapters and affiliates."

Brody Stara, YP Committee Chair, and Engineer at Amgen

"2017 was a year of growth and organization for YPs. We put a new committee structure in place to serve membership around the world. We added YP regional leaders for North America and Europe, and held the YP Hackathon at the 2017 Europe Annual Conference in Barcelona. Europe's YPs have also begun to hold regular conference calls to engage members and support local chapters."

COLLABORATION I am happy to report there has been good progress on this front. Throughout 2017 we identified partnerships with other organizations and fostered opportunities to share and promote knowledge with chapters and affiliates.

We've had successful business events with the Ireland Affiliate, Singapore Affiliate, and the Great Lakes Chapter; we also started an active conversation with the India Affiliate on opportunities for collaboration. Additionally, the ISPE Board approved the creation of ISPE Affiliates in China and Russia (Eurasia). Launch of the ISPE Eurasian Economic Union Affiliate is slated for October 2017.

We began discussions with the Parenteral Drug Association to work together on overlapping initiatives and identify other collaborative activities that align with ISPE strategy. We also met with the US Pharmacopeia regarding business prospects.

We continued to pursue our relationship with the FDA, providing input on several initiatives, including quality metrics. We also proposed quarterly strategy meetings to be facilitated by the ISPE Regulatory Steering Committee.

STRENGTHENING OUR CORE As robust and efficient business systems and processes are essential for success, this area received a great deal of the Board's attention in 2017. We worked closely with ISPE staff to do the following: Update and approve Governance Documents, assess and implement new business process automation tools (accounting), redesign and launch a new website, restructure the organization, and establish an ISPE Regulatory Steering Committee and Voice of the Customer Committee—interviews and feedback.

Joanne Barrick, Board Director, and Advisor in Global Validation Support, Eli Lilly and Company

"The Guidance Document Committee and document authoring teams have had an extremely productive year: Five new or updated Guidance Documents and two Concept Papers were issued. Over 8,000 Guidance Documents were sold through 31 July, with the GAMP® *Records and Data Integrity Guide* selling more than 700 copies in the first four months after publication. Guidance Document member authors are now being recognized on the ISPE website. ISPE staff has been bolstered with additional personnel to assist in editing draft documents and implement improvements focused on facilitating document development. ISPE has also invested in a new publisher platform, Tizra, which will improve delivery and searchability of ISPE publications."

Chris Reid, Board Director, and CEO, Integrity Solutions Ltd.

"The Voice of the Customer Committee is charged with soliciting feedback from key ISPE stakeholders: industry leaders, ISPE volunteers, Board members, affiliates and chapters, young professionals, staff, and regulators. Their feedback is vital to ensure that we are meeting the needs of ISPE members, and will influence the way we operate, communicate, and move our strategy forward." Customer feedback has contributed to several of our business decisions in 2017.

A FINAL NOTE

When I first wrote this column 13 months ago, I indicated we would be faced with both opportunities and challenges. Challenges, I predicted, would arise from the complexity and competitiveness of our environment. I also said that ISPE must embrace these challenges head-on as we prepared for the future.

Embracing them made for a very busy year for our Board, staff, and volunteers! As a result, our business is better positioned to meet future demands, our membership continues to grow, and our finances remain strong and directionally correct. Our income continues to rise, as does our contribution to the reserve funds; supporting our 2017 investments in infrastructure and technology.

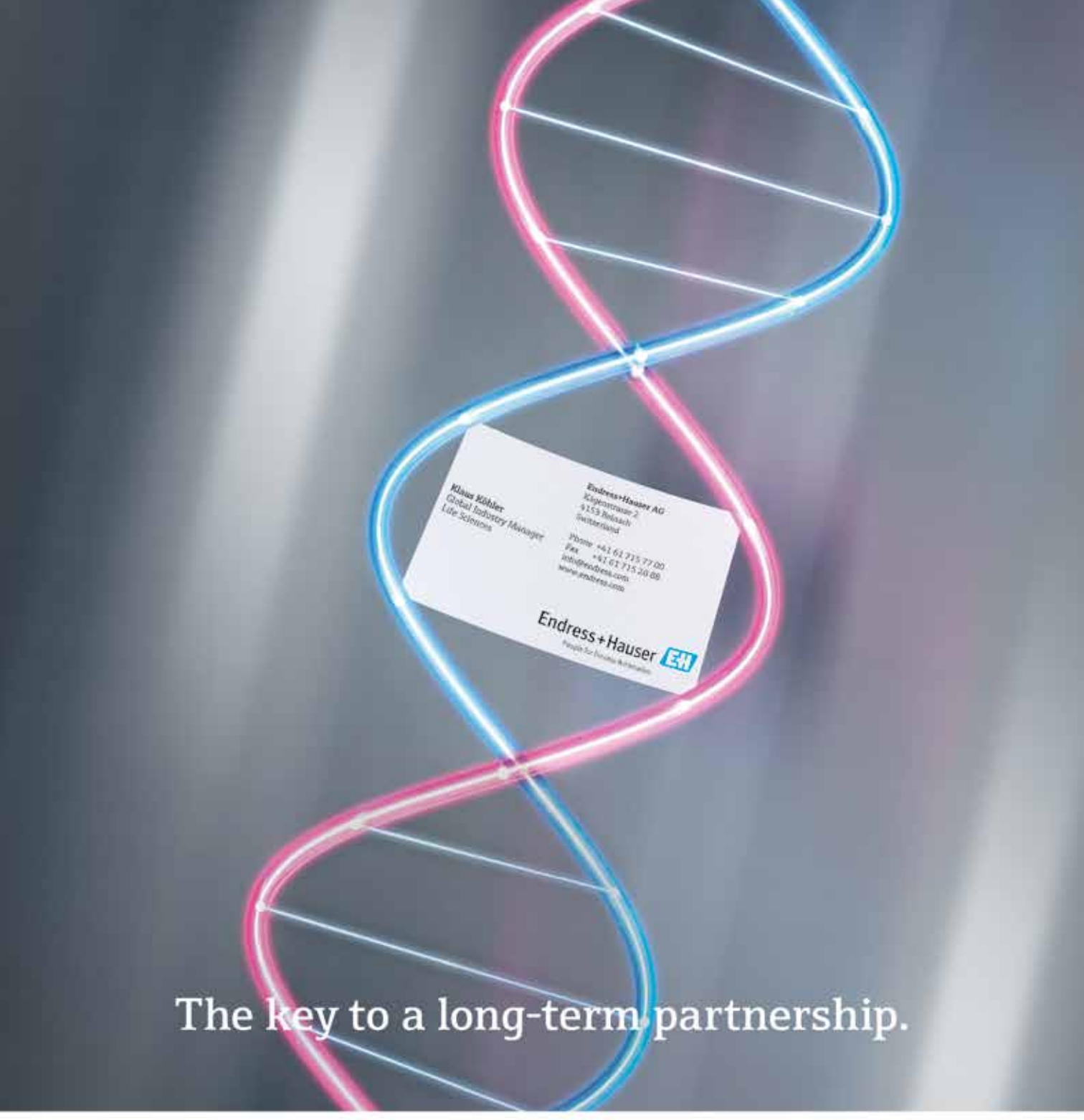
Although we've made significant progress this year, more remains to be done. By building on this year's changes, we can concentrate on other important business opportunities.

In closing I would like to thank the Board members for their unwavering support, strategic input, and counsel. Their tireless efforts have made 2017 a year of tremendous effort and accomplishment.

To our 18,456 members I want to express my sincere gratitude for your intellect, personal time commitment, and passion for ISPE. As an organization, ISPE is the world's largest, financially sound, highly respected, and professional nonprofit organization serving the pharmaceutical industry. You make us strong!

To Tim Howard, our incoming 2017–2018 Board Chair, I wish you great success in the coming year, and I pledge to you my continued support.

Thank you for the opportunity to be your leader for the past 13 months; I wish you all continued success in the years to come. ‹›



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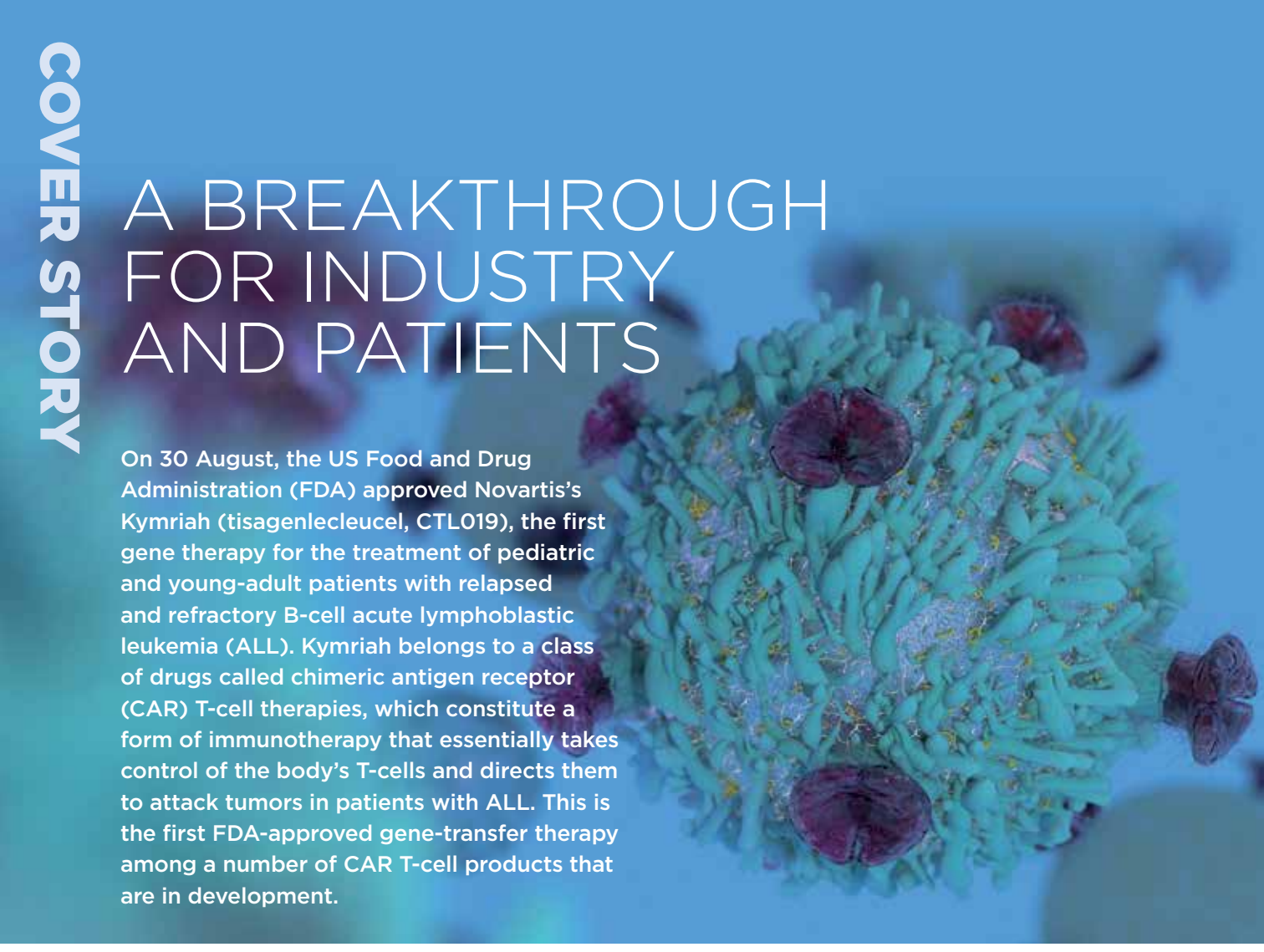

On 30 August, the US Food and Drug Administration (FDA) approved Novartis's Kymriah (tisagenlecleucel, CTL019), the first gene therapy for the treatment of pediatric and young-adult patients with relapsed and refractory B-cell acute lymphoblastic leukemia (ALL). Kymriah belongs to a class of drugs called chimeric antigen receptor (CAR) T-cell therapies, which constitute a form of immunotherapy that essentially takes control of the body's T-cells and directs them to attack tumors in patients with ALL. This is the first FDA-approved gene-transfer therapy among a number of CAR T-cell products that are in development.

Emily Whitehead and her family were in the right place at the right time to save her life. The Pennsylvania girl was five when she was diagnosed with ALL in 2010 and treated with extensive chemotherapy. Chemotherapy works for 85% of children with ALL; it didn't work for Emily, however. By February 2012, when she was scheduled for a bone marrow transplant, she relapsed for a second time and no longer qualified for the procedure. Her doctors held no hope that she would survive and recommended that her family set up palliative care in their home.

"I couldn't picture a day in my life without Emily and we could see her slipping away," said her father, Tom Whitehead. "But I always believed she would beat it and she always believed she would beat it."

The Whiteheads knew of a therapy being tested at the Children's Hospital of Philadelphia (CHOP), which is located four hours from their home, and called to see if the clinical trial was open. "We said we were transferring to CHOP no matter what they had available," said Whitehead. "We were willing to try whatever they recommended."

In 2012, Emily became the first pediatric patient in the world to be treated with CTL019 (tisagenlecleucel), an experimental CAR T-cell therapy. She was treated by a team at the University of Pennsylvania (Penn) and Novartis Pharmaceuticals Corporation also entered into a global collaboration with Penn in 2012 to further research and develop CAR T-cell therapies.

When doctors administered the therapy, Emily's temperature soared, and her blood pressure collapsed: she fell into a coma, and was on a ventilator for two weeks. She was suffering from cytokine release syndrome (CRS), likely due to a spike in interleukin-6, for which she was given an immunosuppressant monoclonal antibody (Mab), tocilizumab. She came out of the coma a few days later, on her seventh birthday.

Twenty-three days after receiving CAR T-cell therapy, Emily was cancer-free. She went home three months later, in June, and was back in school two months later. She has been cancer-free ever since.

Now, only a few weeks after the Oncologic Drugs Advisory Committee (ODAC) unanimously recommended that the FDA approve CTL019, the agency has done so, making Kymriah the first treatment based on gene transfer to be approved. At the same time, the FDA expanded the approval of Roche's tocilizumab to treat the kind of cytokine storm that Emily Whitehead and many other patients experienced with CAR T-cell therapy.[6]

HOW DO CAR T-CELLS WORK?

"Cellular therapies are a complete disruption of the traditional way we think about treating disease, using the body's own cells as the catalyst to tackle the most challenging illnesses," said Spencer Fisk, Vice President and Global Head of Cell and Gene Technical Development and Manufacturing at Novartis.

CTL019 is an adoptive cellular therapy, a living drug that uses a patient's own T-cells to fight cancer. The process has three main steps: First, T-cells are filtered out of a patient's blood by a process called

leukapheresis and frozen. Second, the cells are shipped to a lab, where they are genetically modified by virus transfection so they express a chimeric antigen receptor that recognizes an antigen on tumor cells. In the case of CTL019—and many other CAR T-cell products in development—the antigen is the CD19 protein expressed on B-cells. Third, the modified CART-cells are cultured, then frozen* and shipped back to the medical center, where they are reinfused into the original patient. In the body, the CAR T-cells are activated when they bind to the CD19 antigen on the surface of tumor cells, release cytokines to kill the tumor cells, and proliferate after receiving an internal signal.


Dr. Stephan Grupp

Hematological cancers are the easiest to target with CAR T-cells, which is why the first drug candidates are those for leukemias and lymphomas. ALL is the most common childhood cancer, making up a quarter of all pediatric cancer cases. There are 3,000 new cases of pediatric ALL in the United States every year, of which roughly 15% relapse after standard treatments.[1]

NOVARTIS–PENN COLLABORATION

CTL019 was researched and developed at Penn, which entered into an exclusive research and licensing agreement with Novartis for CAR T-cell therapies in 2012. Testing of the therapy began that year.

The Novartis clinical trial enrolled 88 patients and 68 patients were infused with CTL019. They were treated at 25 global medical centers in 11 countries, including the United States, Canada, Japan, Australia, and seven in the European Union. After one treatment, 83% of patients in the phase 2 clinical trial went into complete remission, with a survival rate at one year of 79%.[2]

Despite the treatment's success, CAR constructs and CAR T-cells are difficult to make, can have significant side effects and toxicities, are challenging to scale, and are expensive. Even when they do work there is the concern that patients will relapse as their cells become resistant or evade the therapy.

SAFETY CONCERNS

As with any new medicine, safety is a concern. Juno Therapeutics's CAR-T product, JCAR015, was in phase 2 clinical trials for adults with relapsed or refractory ALL when five patient deaths in 2016 put the study on hold. The company has since announced it is ceasing development of the therapy.[3]

According to Stephan Grupp, MD, PhD, the baseline against which the safety and efficacy of CTL019 is measured is the mortality from the alternative, which is a bone marrow transplant. "A small number of ALL patients are eligible for a bone marrow transplant, for which the mortality rate in the United States is between 10% and 30%. The treatment-related mortality for cell therapy is much lower, but it's not zero." Dr. Grupp, Director of the Cancer Immunotherapy Program and Director of Translational Research for the Center for Childhood Cancer Research at CHOP, is on the Penn team that led the development of CTL019 and treated Emily Whitehead.


Dr. Mihaela Simianu

CAR T-cell therapies can lead to an overstimulation of the immune system. Of patients in the Novartis clinical trial, 47% developed moderate to severe CRS, though there were no deaths due to refractory CRS.[2] Following their experience treating the first patient in the trial, Dr. Grupp's team developed a treatment protocol—which included the use of tocilizumab—for all the medical centers taking part in the study.

"The doctors performing this treatment are bone marrow transplant specialists, so we're starting from a high baseline of knowledge and experience," said Dr. Grupp. "We've rolled this out to multiple centers around the world and have done that with an extraordinary degree of safety."

Another side effect of the treatment is B-cell aplasia, which occurs because CTL019 recognizes both healthy and cancerous B-cells, all of which express the CD19 antigen. This leaves patients without antibodies and thus vulnerable to infections. The aplasia lasts as long as the modified T-cells are in the patient's body and requires regular infusions of immunoglobulin G, such as the subcutaneous immune globulin product Hizentra.

MANUFACTURING CHALLENGES

Dr. Grupp compares the state of manufacturing CAR T-cell products to where the industry was when it first used cultured cells to make biologics. "It was hard to start, but the industry now knows how to make biologics amazingly well and how to do it at scale," Dr. Grupp said. "Everybody is learning how to manufacture CARs at scale right now."

"The challenges that come with manufacturing CAR-T therapies lie at the heart of their novelty," Spencer Fisk agreed. "One critical challenge area is in scalability for immunotherapy products."

The industry seems to be meeting the challenge. The Novartis facility in Morris Plains, New Jersey, has already manufactured CTL019 for more than 250 patients in global clinical trials. Novartis expects that the time from manufacture start to product release (including quality assessments) will be about 22 days. Kite Pharma, another company with CAR T-cell products in clinical trials, has comparable delivery times and estimates the capacity of its manufacturing plant at as many as 5,000 doses per year.[4]

"The experience gained at the Novartis facility will be a foundation for commercial manufacturing of CAR-T therapies," Fisk said. "We continue to make investments in our unique CAR-T manufacturing facility to ensure we can meet the needs of patients being treated with these therapies."

Dr. Grupp is optimistic about what the pharmaceutical industry can accomplish. "It's amazing to see the handoff from academic good manufacturing practice (GMP) to commercial GMP and to watch how Novartis can pull off worldwide logistics for something as complicated as a cell therapy."

While the techniques for manufacturing biologics are well developed, adoptive cell therapies have unique technical, regulatory, and logistical challenges.

"Though the same quality by design (QbD) principles that apply to biologics are used for cell-based therapy products, there are significant challenges that require new approaches to define and 'design quality in' during the development of such products. The process for autologous cell-based

* Both inbound and outbound cells are frozen. The Novartis manufacturing process uses cryopreserved leukapheresis, which enables patients to be apheresed early in their course of therapy, giving physicians the flexibility to schedule apheresis at a time that is in the best interest of their patients, including times in advance of manufacturing. It also gives Novartis flexibility on when to start manufacturing CTL019 for the patient and allows for manufacturing and treatment of patients from around the world. In addition, cryopreservation ensures that CTL019 maintains its integrity from the time it leaves the manufacturing facility to the time it's ready for infusion.

therapy starts with patients and doctors at medical centers as suppliers of the starting living biological material that will be used in the manufacturing process. The attributes selected for control of identity, purity, potency, and safety during development need to be defined specifically for each product," said Mihaela Simianu, PhD, Director of Regulatory Compliance at Pharmatech Associates. "For biologics, the active ingredient is a nonliving biological modality isolated or produced at large scale using biotechnological methods. In this case, living cells are genetically engineered and used to express at scale the desired active ingredient. With cellular therapy, the starting active ingredient and the product are living cells."

The patient's white blood cells are frozen after collection, which allows physicians to schedule leukapheresis at a time that they determine.

The complexities go beyond safety and manufacturing to include the need to maintain stability and chain of identity for product shipped from a medical center to the Novartis facility and back again.

"Cell activity and other functional attributes are sensitive to time and conditions used during transit across locations and points in the process; expedited and controlled transit of these living cells is a critical success factor," said Dr. Simianu. "For example, one may need to ensure that cells arrive at the manufacturing site within an 18- to 48-hour time frame. Specific containers, data loggers to keep track of samples, chain of custody, and carriers that can do this without a flaw are needed. All the details impacting cell-material stability during the closed-loop supply chain must built into the development of the product; it can't be an afterthought."

STANDARDIZING CELLULAR THERAPIES

One of the stumbling blocks to regulating cellular therapy, particularly one using autologous medicines unique for each patient, is how to standardize product and measure efficacy between and within manufacturing facilities.

"What we can do in an academic manufacturing lab might not be possible in a pharma setting," said Dr. Grupp. "They have to apply additional rigorous regulatory control processes for which there is not yet a good regulatory mechanism."

"The characterization of living cells requires different methodologies than we use routinely for a biologic active pharmaceutical ingredient," said Dr. Simianu. "You need to search and adapt techniques used by cytology, cytogenetics, cellular biology, histology, virology—combine different medical research techniques to select the best tools to analyze those molecules. It's not that we're using something completely new, it's just new to the biopharmaceutical sector."

So how will companies standardize products and how will regulators measure and compare products?

"We start with a target product profile," said Dr. Simianu. "What is it for? What is it made of? What do we need the activity to be? How will it be delivered? How stable does it need to be to reach and treat the patient? Based on the target product profile, you decide what are the critical quality attributes (CQA) that the product needs to have. From the CQAs you define the way you control these attributes and the control strategy: those are the same QbD elements that we apply successfully today to biologics.

"In transferring from the lab to a commercial site, or from site to site, there are challenges in understanding what is critical and what is important to maintain the CQAs, then define these attributes well from the beginning. You have a different facility, different equipment, environment, and staff. Everything starts with defining what's important, what process to use, and how to do different parts of the process."

Take potency assays as an example. "There is no proven assay for a cell-therapy product that predicts whether it will work in a patient," Dr. Grupp said. "Yet the FDA requires you to have one." The danger, he says, is that a potency assay will get invented—even one with great parameters—but they won't know if it correlates with the desired outcome, which is whether the therapy actually works.

Fisk is confident that Novartis can overcome these hurdles. "For each patient treated with CTL019 during a clinical trial, we performed comparability and equivalency testing to demonstrate that each batch was standardized. We have a highly reproducible manufacturing process with demonstrated manufacturing success. Novartis uses well-established standards to maintain a rigorous chain of identity from leukapheresis at an approved site, through manufacturing, to patient infusion. These standards seamlessly integrate with a Novartis quality system dedicated to managing chain of identity of patient material and final product."

Fisk points out that the Novartis facility in Morris Plains will be the manufacturing location for commercial product. "Furthermore, Novartis has successfully transferred and demonstrated equivalency of the CTL019 process to our partner in Europe, demonstrating the robust and reproducible process we have developed."

Dr. Grupp recommends that a lot more patients be treated before specific manufacturing rules are applied. "The field is being created on the fly. The danger is that once a rule is established it will be difficult to change. The companies that are doing it first—Novartis, Juno, Kite, all of which have single manufacturing streams—are going to define the regulatory context and they'd better be certain about the manufacturing rules before they suggest them to regulators."

"Because this characterization is so important to the success of the product, there is a lot of investment during the discovery phase to establish this methodology," said Simianu. "This is a flip from biologics, where we know what we're looking for and we have standardized techniques. In cell therapy, you have to invest a lot in defining how you will characterize the product. There may be some general techniques, but there aren't as many tools that are nonproprietary. The goal is to establish this early on so that, if you make changes to the way you produce or test the cells and there's impact on com-

parability, you don't have to start over. Significant changes in characterization will require comparability protocols. When a company enters phase 1 they need to be readier with these tests than they usually are for biologics."

"Global health authorities have expertise and standards in place that were established specifically to evaluate clinical research and manufacturing of CAR T-cell therapies," Fisk said. "We saw this process in action for the first time in July 2017, when ODAC unanimously recommended approval of CTL019. Through the ODAC process, the committee was able to review and hear from experts in the field of CAR-T science and product development."

THE COST OF A CURE

Given that autologous therapies are unique for each patient, the global supply chain, and manufacturing challenges, this technology will be expensive. Novartis indicated that the one-time treatment will cost $475,000.[6]

To put this estimated price in perspective, the National Institute for Health and Care Excellence, which provides guidance and advice for the National Health Service in the United Kingdom, pegged the benefit of CAR T-cell therapies as a curative for ALL at $650,000.[5] Most children with leukemia respond well to standard therapies such as a bone marrow trans-

IN GOOD COMPANY

The success of Novartis's CTL019 in treating relapsed or refractory pediatric ALL, including FDA approval of the company's biologics license application, makes it the first adoptive cell therapy to reach the market. While Novartis is also seeking approval of CTL019 from the FDA and the EMA for another disease, diffuse large B-cell lymphoma in adults,[7] there are many other CAR T-cell products in development and clinical trials.

One contender is Kite Pharma's KTE-C19 (axicabtagene ciloleucel). Originally developed at the National Cancer Institute (NCI),[1] this CAR T-cell therapy also targets the CD19 antigen on B-cells and is in clinical trials for patients with refractory aggressive non-Hodgkin lymphoma (NHL). In a phase 2 study, 36% of patients were cancer-free at six months.[2] KTE-C19 received priority review from the FDA earlier this year; the agency plans to announce its decision on whether to approve the drug 29 November.[3] Kite Pharma also filed a marketing authorization application with the EMA for KTE-C19 in July 2017, the first CAR T-cell therapy application in Europe.

KTE-C19 is also in phase 2 trials for the treatment of ALL in both adults and children, with data due in 2018. The adult trial has shown promising results, with 73% of patients having complete remission.[12] Another phase 2 study is testing the drug for the treatment of mantle cell lymphoma, which accounts for 6% of NHL cases.[1]

Juno Therapeutics had a major setback during the phase 2 trial of its lead candidate JCAR015, when three patients died. After a reset, two more patients died and the company pulled the plug on the study.[4] Juno has other CAR T-cell products in phase 1 and 2 clinical studies for the treatment of NHL, ALL, and multiple myeloma.[5] One of these, JCAR017, has shown positive response data in NHL, but the experimental treatment was linked to one death and severe neurotoxicity in 18% of patients.[6]

Another promising target for CAR T-cells is the B-cell maturation antigen (BCMA), expressed on mature B lymphocytes, with the potential to treat multiple myeloma. Nanjing Legend Biotech presented promising phase 1 results for its candidate LCAR-B38M at the annual meeting of the American Society of Clinical Oncology in June.[8] Another contender is Bluebird Bio, whose partner Celgene had good phase 1 data for its anti-BCMA drug bb2121. This includes positive safety data with no moderate or severe CRS or neurotoxicity observed.[9]

While biotechnology and pharmaceutical companies are joining forces to develop and bring CAR T-cell products to market, many academic institutions continue experiments that are key to development.[10] In addition to its success with CTL019, the University of Pennsylvania is partnering with Novartis to develop a CAR T-cell construct that targets the epidermal growth factor receptor EGFRvIII antigen for the treatment of recurrent glioblastoma, a solid brain cancer tumor that currently has no curative treatment.[11] Significant progress is also being made at the NCI, Memorial Sloan Kettering, Fred Hutchinson, and Baylor College of Medicine in developing CAR T-cell therapies.

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plants, which cost roughly $500,000.

Novartis announced that it has entered into a collaboration with the US Centers for Medicare and Medicaid Services to use an outcomes-based approach that permits payment only if patients respond to Kymriah within the first month of treatment.[7]

Brad Loncar, CEO of Loncar Investments, a company that focuses on cancer immunotherapy, sees this as a good-news story for the pharmaceutical industry after a couple years of negative press. "This shows the pharmaceutical industry at its best and shines a light on why this industry exists. The results we're seeing in these blood cancers are extraordinary."

It's also good news for investment in the industry. "Any time a new technology makes it across the finish line at the FDA it's meaningful," said Loncar. "People are skeptical when things are developmental and the regulatory path is not clear. But when a treatment moves from the theoretical to the real, a lot of investors take note."

Novartis shares on the New York Stock Exchange were up almost 2% the next day.

FUTURE OF CELLULAR THERAPIES

Novartis plans to file an application for market authorization with the European Medicines Agency (EMA) later this year.[2] Kite Pharma filed a Marketing Authorization Application with the EMA for axicabtagene ciloleucel in July 2017, the first CAR T-cell application in Europe. Dr. Stephan Grupp and his Penn team will be instrumental in continuing to provide training to designated medical centers. Beyond that is the need to improve the efficiency of the manufacturing process.

"What I'm looking forward to from our pharma colleagues is significant innovations in manufacturing cells so it can be less expensive and time-consuming," Dr. Grupp said. "That's something that the pharma folks should be awesome at and is super important."

There is a push to develop CAR constructs that target antigens other than CD19 and to apply them to solid tumors, which, other than glioblastoma, have been refractory to immunotherapy.

"Pediatric patients with relapsed solid tumors have very bad outcomes and there isn't anything out there for them," said Dr. Grupp. "But we have to overcome the solid tumor problem, which is significant. That's the work of the next five years."

THE EMILY WHITEHEAD FOUNDATION

The mandate of the Emily Whitehead Foundation (EWF) is to help fund immunotherapy research and build awareness.

"Everything about our normal life before cancer has changed," said Tom Whitehead, who established the foundation with Emily and his wife Kari. "Since Emily's treatment got worldwide coverage we get offers to travel and talk about our experience to help inspire the workers and to raise money for cancer research."

The EWF will hold a "Believe Ball" in King of Prussia, Pennsylvania, in October, to which all the other children who have received the Novartis CAR-T therapy are invited, along with their doctors, the families of children in other T-cell trials, and celebrities.

One of those doctors is Stephan Grupp, who admits that pediatrics is as much a calling as a career choice. He gets the patients for whom standard therapies don't work. "It can be very challenging to deal with patients with potentially fatal diseases and families who are desperate to help their kids, but I feel that I'm engaged in something that really matters.

"My patients are what inspire me. The great thing about being a pediatrician is that you are dealing with kids. Seeing a child who is critically ill get better and watching them get back to their lives is the most inspirational thing I have done in the last 25 years."

"Stephan and his team are amazing," Whitehead said. "One of the things my wife and I learned from our forced education in oncology is that these doctors are as great people as they are great scientists and doctors."

He has a message for all the doctors, engineers, and scientists working in this field to create lifesaving medicines.

"Each time you have a success, it changes a family dynamic. Our whole family would never have been the same if Emily hadn't had a good outcome. You don't realize the importance of all this work, even the paperwork, that it takes to get to the point you can treat somebody. Each day you make a difference and you can save a life. It took everyone getting it just right to keep Emily alive.

"This treatment kept our family whole." ‹›

—Scott Fotheringham, PhD

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Also in this section

ISPE/FDA/PQRI QUALITY MANUFACTURING CONFERENCE

ALIGNING WITH REGULATORY PRIORITIES

This is an important event for quality professionals," said Marianne Bock, ISPE's director of continuing education, describing the fifth annual ISPE/FDA/PQRI Quality Manufacturing Conference, held 5–7 June in Arlington, Virginia, United States.

"This year's program was developed jointly by a team of FDA regulators and industry quality experts. Content was driven by priorities of both industry and FDA's Office of Pharmaceutical Quality (OPQ) to focus attention on significant issues facing both entities," she continued.

In response to attendee feedback, the event had a new format that was built around four interactive workshops, with topics chosen from the FDA's priority list for 2017: Linking Quality to Clinical Relevance, Modernizing Pharmaceutical Manufacturing through Emerging Technology and Innovation, Designing Proactive Approaches to Facility and Life Cycle Quality Management, and Implementing Next Steps for Quality Metrics.

Workshop sessions were designed to encourage frank discussion and identify real solutions to current challenges. Following a short introduction, participants broke into groups to share perspectives, explore best practices, and discuss the future of these important initiatives.

"The workshops allowed for a very high level of engagement among delegates, industry leaders, and regulators," said Bock. "Participants in each session interacted with industry experts and regulators who led the discussions, working with each group to answer questions and share best practices." Key findings and results from each topic were presented by the facilitators and regulators during the Workshop Reports on the final day of the conference.

A WORKSHOP LEADER'S PERSPECTIVE

James McGlade, Science Market Leader
BHDP Architecture

When I was first asked to be a workshop leader for the Quality Manufacturing Conference this past June, I accepted thinking my workshop assignment would be directly related to my professional field of architecture. Instead, I was completely out of my comfort zone as I helped guide the Facility and Lifecycle Quality Management Workshops—assisted by a team of "true" experts in the field, thank goodness!

I fully expected to learn more about an area of the manufacturing process of which I had only a cursory knowledge. By the end of the two-day conference, however, I had two other unexpected learnings for which I could see parallels in my sphere of influence.

First, multiple attendees noted that a "supportive management culture" is critical to finding true root causes to errors. If the goal is to always find a person to blame, I realized, then the truth will always be difficult to find. A supportive culture allows for a team approach to discovery and learning rather than avoiding what is true to evade any repercussions. This is also a reality when dealing with facility design and construction. A collaborative and mutually supportive team always provides improved results.

My second takeaway was discovering that knowledge transfer of consequences to operators is critical. In my world, "operators" would be the equivalent of design architects and engineers, but in both spheres, these are the people on the front line of effort. Their day-to-day responsibilities can have an enormous influence on product outcome—patient safety in the biopharma world. Ensuring that potential process consequences are effectively communicated was a discussion theme that emerged repeatedly.

The Quality Manufacturing Conference was a unique experience for me. The workshop format created two days of energetic discussions while I gained a deeper understanding of what quality management entails. Many of the conference attendees I spoke to also told me they had gained new ideas and perspectives that they can incorporate in their organization's quality approach.

DATA INTEGRITY WORKSHOP

"Control of your data is the foundation of all pharmaceutical manufacturing processes," said Frances Zipp, President and CEO, Lachman Consultant Services, as she welcomed attendees to the Data Integrity Workshop, a special half-day event held on Sunday, 4 June.

Data Integrity Workshop ATTENDEE FEEDBACK

- *The process mapping session was extremely informative and very interactive.*
- *I am convinced that by understanding and preventing data integrity events across the entire supply chain, we not only enable our companies to deliver the life-enhancing, life-saving therapies we make to our patients more efficiently, we reduce drug shortage risks.*
- *Panel discussion with FDA and industry experts allowed opportunity to interact, understand the current thinking and enforcements from regulatory agency*

Following Zipp's opening remarks, Michael Rutherford, Consultant–Laboratory and Quality Systems, Medicines Development Unit, Eli Lilly and Company, and Data Integrity Program Committee member, presented an overview of the new ISPE GAMP® *Records and Data Integrity* Guide (published April 2017), which includes sections on regulatory focus, data governance framework, and quality risk management.

After the opening plenary, attendees divided into three breakout groups: Process Workflows and Data Mapping, Data Review and Forensic Tools (with one session focused on Laboratory and one on Manufacturing), and Data Integrity Governance Maturity Model and Cultural Model.

"This was the second year the Data Integrity Workshop was held in conjunction with the Quality Manufacturing Conference," said Rutherford, "and this year we focused on providing tangible tools that taught skills the participants could take back to their companies and apply. We listened to their feedback from last year and really tailored the program to meet their needs."

The workshop concluded with a regulatory and industry panel discussion led by Stephen Mahoney, Senior Director in Global Quality and Compliance at Genentech, Inc. The workshop leaders were by FDA representatives Sarah Barkow, PhD, Team Lead, Manufacturing Quality Guidance and Policy Staff at CDER's Office of Manufacturing Quality, and Karen Takahashi, Senior Policy Advisor at CDER's Office of Policy for Pharmaceutical Quality.

"One topic that really sparked a lot of discussion," said Rutherford, "was oversight for third parties and the importance both parties play in ensuring data integrity. This linkage and the importance of managing our suppliers and third parties was further emphasized by Thomas Cosgrove during his keynote presentation during the conference." Other questions included quality assurance periodic review, how firms can improve data integrity, what companies should look for when auditing suppliers, and how to prepare for an audit.

The bottom line, Rutherford concluded, is that "the bulk of data integrity problems occur where technology and people intersect."

KEYNOTE REVIEW: OPQ PROGRESS UPDATE

George Millili, Senior Principal Technical Advisor, Genentech, and Conference Planning Team Chair, 2017 ISPE/FDA/PQRI Quality Conference Program Committee

This annual conference is one of the most important conferences of the year. Cosponsored by ISPE, FDA, and PQRI, it allows many opportunities to interact with FDA regulators. Dr. Michael Kopcha, Director, Office of Pharmaceutical Quality, FDA, CDER, presented an informative keynote entitled "OPQ Progress Update." Some of the highlights were:

- The new OPQ structure has been operational for a year; he feels that there has been improved oversight of quality throughout the quality life cycle.
- He commented on the agency's successful efforts to reduce redundant inspections by the various FDA offices. They accomplished this by clearly outlining roles and responsibilities of each FDA group in detail, and by enhancing the communication process of all involved.
- The New Inspection Protocol Project is standardizing how inspections are performed so industry better understands agency expectations.
- He thanked industry for its comments on the draft Quality Metrics Guidance. The FDA took them seriously, he said, and incorporated many of the suggestions into the second draft. Once all the comments have been reviewed more interaction and discussion will be required on how to implement this guidance and standardize definitions.
- He encouraged the development of emerging technologies and underscored the importance of early communication with the FDA emerging technology team when working with a novel or innovative technology. A good number of companies are already doing this, and he encouraged more of these interactions.
- "Like any other organization, we need to continuously improve," he concluded. "We're working together to achieve the vision of 'a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.' The key is 'without regulatory oversight.' We need to advance manufacturing sciences to know that quality issues have been addressed. Review must be done on a risk-based basis. Hopefully this dream will be realized in my lifetime." ›

MARK YOUR CALENDARS

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Arlington, Virginia,
United States

If you have not had the opportunity to attend one of these conferences, I encourage your participation next year. This is a simple way to remain current with FDA and industry priorities, expand your professional network, and enjoy spending time with colleagues, both during the sessions as well as in the numerous breaks and receptions.

WOMEN IN PHARMA BREAKFAST

Conference participants gathered for the Women in Pharma (WIP) breakfast on Tuesday, 6 June. Chair Fran Zipp, President and CEO, Lachman Consultants and ISPE Board Member, welcomed more than 100 attendees.

"Women in Pharma began as a small idea for the ISPE Annual Meeting last year," she said. "The response was terrific so we decided to formalize the group, and here we are."

Emily Stump, Director of Operations, Pacific Northwest, Commissioning Agents, Inc., introduced the panelists and facilitators: Mihaela Simianu, PhD, Director, Regulatory Compliance, Pharmatech Associates, Inc.; Kellie Schoolar Reynolds, PharmD, Deputy Director, OTS/OCP/DCPIV, US FDA, Center for Drug Evaluation and Research; Tammie Champlin, Senior Director, Quality Engineering, Johnson & Johnson; and Valerie Jensen, Capt., RPh, Associate Director, Drug Shortage Staff, US FDA.

The event began with a panel discussion on the characteristics that lead to success and career-defining or pivotal events. Table discussions on assigned questions followed, after which Zipp asked for a volunteer to share each group's summary.

In her closing remarks Zipp thanked ISPE CEO and President John Bournas and Board Chair Mike Arnold for their support, and expressed gratitude to sponsors Johnson & Johnson and Pharmatech. ‹›

Celebrating FOYA 2017 Winners

BEST OF THE BEST

ISPE celebrated the thirteenth annual Facility of the Year Awards (FOYA) banquet on Tuesday, 6 June, with a lively group of participants from the ISPE/FDA/PQRI Quality Manufacturing Conference and beaming category award winners in attendance. Guests mingled for cocktails and conversation before the main event, emceed by Dave DiProspero, Associate/Director, Pharmaceutical Process Technology, CRB Consulting Engineers, and Chair of ISPE's FOYA Committee

DiProspero began by introducing ISPE CEO and President John Bournas. "Tonight," he said, "we highlight the best of the best—exemplary projects that epitomize the spirit of FOYA." The evening's honorees hailed from the United States, Puerto Rico, Ireland, as well as Indonesia, which, Bournas noted, was receiving the country's first FOYA award. "We are proud to honor these facilities for their shared commitment to innovation—for advancing pharmaceutical technology by demonstrating creativity and excellence in facility design, construction, and operations."

Mike Arnold, ISPE Board of Directors Chair and Investigational Product Business Process Owner, Pfizer Global Clinical Supplies, also addressed the gathering, noting FOYA's significance to ISPE. He applauded the winners for being "creators of disruptive innovation."

Jim Breen, Vice President and Lead, Biologics Expansion, Janssen Pharmaceuticals, and current Chair of the FOYA Judging Committee, welcomed incoming Committee Chair and ISPE Board member Tony Crincoli, Executive Director and Head of Global Engineering Services, Bristol-Myers Squibb. Together they presented awards to the 2017 Category Winners and Honorable Mention recipients.

Cook Pharmica won in the Equipment Innovation category for its Flexible Filing Line project. Designed to add flexibility and capacity within an existing cGMP space by leveraging new technologies, this project was a collaborative development between owner, suppliers, and engineering experts. Together, they delivered a novel application of commercially available and custom-developed equipment manufacturing solutions. Project sponsor and COO Ryan Hawkins accepted the award, thanking his "great partners" and "talented team that made the difference."

The Facility Integration category award went to **Bristol-Myers Squibb** for its Biologics Development and Clinical Manufacturing Building project, an example of how to integrate new capabilities within an existing plant through careful design, good collaboration, and creative engineering. The results were impressive, integrating the facility within the company's broader mission and network of the assets. As Morrey Atkinson, PhD, project owner and Vice President, Biologics Development and Clinical Manufacturing accepted the award, he explained that he was doing so in memory of a friend who had died from melanoma. "I'm working to make that [melanoma] a thing of the past," he said.

Eli Lilly and Company earned two FOYA awards for its Continuous Direct Compression Manufacturing Kits 2 and 3 project. With a mission to design and implement a network of continuous manufacturing process facilities, Lilly was recognized with its first award in the Facility of the Future category for process development, production platform commitment, and deploy-

2017 CATEGORY WINNERS

Abbott
Operational Excellence
Operational Excellence—A New Quality Approach
Longford, Ireland

Bristol-Myers Squibb
Facility Integration
Biologics Development Building and Clinical Manufacturing Building
Devens, Massachusetts, US

Cook Pharmica
Equipment Innovation
Flexible Filling Line
Bloomington, Indiana, US

Eli Lilly and Company
Process Innovation
Facility of the Future
Continuous Direct Compression Manufacturing Kits 2 and 3
Indianapolis, Indiana, US (CM2) and Carolina, Puerto Rico (CM3)

Jazz Pharmaceuticals
Project Execution
Project Rock
Monksland, Athlone
Co. Roscommon, Ireland

Honorable Mention
Nephron Pharmaceuticals Corporation
Nephron SC
West Columbia, South Carolina, US

Novartis and University of Pennsylvania
Novartis-Penn Center for Advanced Cellular Therapies
Philadelphia, Pennsylvania, US

PT. Kalbio Global Medika
Biotech Facility
Jakarta, Indonesia

Abbott—L to R: Michael Cryan, Ellen Muldoon, Helena Warnock, Everett Tucker, Ciaran Corcoran, Stephen Kelleher, Ciara Mulleady, John Williams

Bristol-Myers Squibb—L to R: Muris Kobaslija, Dan Post, Bryan Mann, Dave Wilson, Morrey Atkinson, Anthony Haskell, Norm Stoffregen, Mike Borys, Tony Crincoli

ment of three replicate operational continuous oral solid dosage (OSD) production facilities. Bret Huff, Vice President of Small Molecule Design and Development accepted the award. Noting the team's refusal to compromise on speed, quality, or costs, he called the project a "win for everyone, but especially for the patients."

›

Cook Pharmica—L to R: Hamid Farzad, Brok Weichbrodt, Lauren Smith, Alex Haig, Kavya Kumar, Ryan Hawkins

Eil Lilly and Company—L to R: Ian Leavesley, Ken Weerts, Peter Waite, Bret Huff, Kevin Trivett, Paul Collins, David Pappa, Tim Pletcher

The winner in the Operational Excellence category went to **Abbott Diagnostics** for its New Quality Approach project to create a sustainable continuous improvement culture. The facility has increased productivity, improved changeover efficiencies, eliminated backorders, and enhanced product quality while also reducing cost per unit, cycle times, equipment downtime, and inventory holdings. Everett Tucker, executive sponsor for the program and Division Vice President, Operations Strategy and Engineering, accepted the award, praising the "industry-leading body of work on display" among the honorees' projects, and thanked his team for their "exceptional job delivering real results."

Jazz Pharmaceuticals was the Project Execution category winner, for its "Project Rock." The project team—which had never built a pharmaceutical facility before—resolved to create a fully operational FDA-approved manufacturing plant in two years. The approach was highly pragmatic, and a model for lean project execution and integration of the investment from project phase to licensed GMP operations. Accepting the award, Alan Mac Neice, Executive Director and site leader, said that the team "did something truly remarkable by not recognizing where boundaries were."

Eli Lilly and Company's second award for its Continuous Direct Compression Manufacturing Kits was awarded in the Process Innovation category. The company's forward-thinking approach was recognized for the implementation of continuous direct compression and other process innovations in OSD facilities across its manufacturing network. Bret Huff also accepted this second award saying, "This is much more than just a facility—it's all of the systems that go into it."

Three projects earned Honorable Mentions.

Jazz Pharmaceuticals—L to R: Alan Mac Neice, Bob Chew, Lee Arnold, Ronan McGrane, Jennifer Lauria Clark, Jeremy Freeman

Nephron Pharmaceuticals—L to R: Bryan Beck, Hunter Gordy, Sandra Watson, Lou Kennedy, Lindsey Miles, Lance Rogers, Jonathan Burgess, Hank Jibaja

UPenn/Novartis —L to R: Erik Terry, Stephan Blair, Joseph Palombit, Myung Kim

Kalbio—L to R: Christopher Sweeney, John Bournas (ISPE)

Nephron Pharmaceuticals was recognized for its South Carolina project which integrated industry-leading technologies such as laser-guided vehicles, automated warehousing, robotics, and track-and-trace technology. CEO and Owner Lou Kennedy also wanted to create a plant that would inspire children to want to learn about technology and science, so viewing and access areas were designed to facilitate visitor exposure to the pharmaceutical industry and advance pharmaceutical manufacturing careers.

Kennedy accepted the award with obvious delight. "It's like an Oscar! Thank you so much!" she said.

Novartis and University of Pennsylvania were honored for their Center for Advanced Cellular Therapies Project, an innovative center to advance personalized medicine that leverages pharmaceutical engineering principles to merge academic, corporate, and medical considerations. The project advances the development of new operating models to harness the potential of personalized cancer treatments. Joseph Palombit, MBA, RA, LEED-AP, Senior Project Manager for Real Estate, Design, and Construction for the University of Pennsylvania Health System accepted the award, thanking his team for working through the challenges of construction in an occupied facility.

The young and highly motivated project team on the **PT Kalbio Global Medika** biotechnology facility project in Indonesia exemplifies the can-do spirit and the potential for biomanufacturing in Southeast Asia. A point of pride for the company is its quality management system, designed in accordance with PIC/S standards, which integrates all aspects of manufacturing. Christopher Sweeney, Senior General Manager, praised his "very young, hardworking, and dedicated team." Noting that biotech is taking off in Asia, he also asked ISPE to "help bring knowledge and skills to the region." ‹›

The Overall FOYA Winner will be announced at the ISPE 2017 Annual Meeting & Expo on 31 October 2017 in San Diego, California, United States.

FDA QUALITY METRICS PROGRAM CONTINUES

Christopher Potter, on behalf of the ISPE Quality Metrics Team

ISPE's new online course on implementing a QM program onsiders FDA 2016 draft guidance

At a meeting with ISPE staff and Quality Metrics Team members on 1 August 2017, FDA confirmed their plans to progress a quality metrics (QM) and data-driven surveillance program. FDA will maintain its commitment to the goals communicated in their 2015 and 2016 draft guidances[1–2] and associated Federal Register Notices.

The agency acknowledges while industry changes have occurred since the QM program began, its overarching goals remain: quality oversight, continual improvement, informing risk-based inspection scheduling, making inspections more efficient by focusing on higher-risk products, and the potential for indication of drug shortages. The regulators agreed that all of these goals will not be accomplished during the initial program phase.

The agency expressed strong appreciation for the value and learning derived from the ISPE Quality Metrics Initiative Waves 1 and 2,[3–4] which they indicated had helped shape the QM program. FDA also reinforced its commitment to product-based reporting and standardized definitions.

Waves 1 and 2 were based on data from 28 companies and 83 sites, including contract manufacturing organizations, laboratories, and drug substance manufacturing sites representing a wide range of technologies. All considered themselves in a good state of compliance and already had mature internal quality metric programs.

DEFINITIONS

One of the most significant conclusions from Waves 1 and 2 is that harmonized definitions are a challenge. The proposed definitions in FDA's 2016 draft guidance drew considerable industry feedback.

In comments submitted to the agency,[5] ISPE noted that many of the proposed terms and definitions and metric calculations were:

- Atypical and different from those commonly used in industry
- Not sufficiently clear despite exemplification
- Open to interpretation due to the use of nonstandard definitions

ISPE also commented that different and unclear definitions combined with inappropriate metric calculations can lead to wide variations in data element values, and comparisons of calculated metric values between time periods, sites, companies, and technologies. This, in turn, removes the ability to make logical conclusions from or derive potential relationships between metrics.

ISPE further suggested that the definitions in its Wave 1 and 2 Pilot Programs could be a starting point for industry-wide harmonization.

At the 1 August meeting with FDA, ISPE indicated a willingness to share further recommendations and illustrative examples for certain definitions. For its part, the agency expressed a strong desire to ensure that any definitions it adopted would bring value to both industry and FDA, and drive continual improvement. ISPE proposed that FDA consider these definitions in a pilot designed with industry representatives to clarify requirements and value relative to the burden of standardizing them.

QUALITY CULTURE

Perhaps the most important finding from the Wave 1 and 2 Pilots was confirmation that culture is very important and a crucial foundation for quality excellence or good quality performance. For example, quality culture scores had statistically significant relationships with internal (e.g., lot acceptance rate) and external quality outcomes (e.g., complaints and recalls). As a consequence, ISPE has established a very successful quality culture program, which produced its *Cultural Excellence Report* on 25 April 2017.[6] The report also includes practical tools, training, and templates that companies can adopt immediately.

ONLINE COURSE

FDA has indicated clearly that a reportable QM program is on the horizon.

Using its knowledge of quality metrics programs using standardized definitions, ISPE created *Operationalizing a Quality Metrics Program: Critical Success Factors*,[7] a new online course that explains how to implement a quality metrics* program considering FDA 2016 draft guidance.

Course objectives are:

1. Learn how to develop and standardize a collection process for data from various sites, including definitions, defining data elements to minimize gaming, and understanding how regulatory metrics fit into a wider quality metrics program.
2. Articulate the need for standardization to acquire real and comparable data.
3. Apply information gained from harmonized quality metrics.
4. Understand the relationships and where there may be leading indicators and cultural indicators. These factors can inform understanding of change within a site, and consequently affect inspectional risk.
5. Learn the value of recurring deviations as a potential leading indicator metric.

The course provides insight into establishing a harmonized metrics program, with industry examples about how a well-thought-out program can provide substantial knowledge that drives continual improvement. It also includes the finding from the Wave 1 and 2 Reports that the recurring deviations metric, although very hard to define across sites and companies, has the potential to be a leading key performance indicator.

The course provides practical steps to implement a metrics program and drive continual improvement; it is an excellent resource for a company at any stage of its quality metrics journey. ‹›

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* A good review of metrics programs is given in the *ISPE Operations Management Good Practice Guide*.[8]

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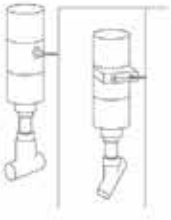

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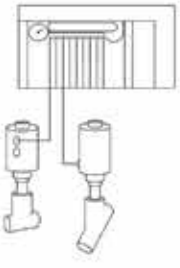

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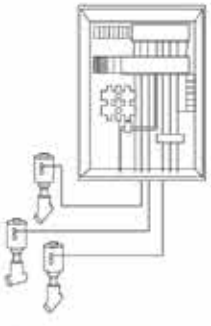

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Training Turkey's Regulators

AN AFFIRMATION OF GLOBAL CITIZENSHIP

Antonio Moreira, PhD, is unequivocal about ISPE's need to encourage members and colleagues around the world. "They have their challenges regarding travel and sometimes political unrest, so anything we can do that demonstrates ISPE's commitment to support all who count on us, regardless of location, for scientific and technical knowledge transfer is essential," says the ISPE Board member and Vice Provost for Academic Affairs, University of Maryland, Baltimore County. He calls this obligation "an affirmation of ISPE's global citizenship."

Fellow Board member Fatma Taman, Chair of the ISPE Turkey Affiliate and based in Istanbul, concurs. "We are Turkey's leading association for technical pharmaceutical training. Every effort we can make, every gesture, makes a difference," she said.

Taman and Dr. Moreira have spearheaded a training video initiative with the Turkish Medicines and Medical Devices Agency (TMMDA). Their first session, which lasted five hours, was hosted on 20 March at ISPE headquarters in Bethesda, Maryland. A group of 35 new and experienced professionals participated from TMMDA's office in Ankara, Turkey's capital, and the overwhelmingly positive response will result in the creation of a training program for the agency.

"There is interest in a course on inspections," said Taman, "and Tony and I are developing one for a follow-up session." In fact, Taman and Dr. Moreira are developing a curriculum for intensive and short courses, with a focus on biotech.

TIMING WAS JUST RIGHT

With Turkey's recent boom in biologics—there are currently 18 companies investing in biotech—the TMMDA requested training in biologics, biosimilars, and their registration procedures. "When the ISPE colleagues from Turkey approached the Board of Directors for support, a number of us responded positively," said Dr. Moreira.

Once the political environment became more precarious, however, and corporations imposed travel embargos, the Board had to think of alternatives. Dr. Moreira, who has extensive experience with a variety of training media, suggested videoconferencing. "Fatma and I started talking about developing a program around biotech; we developed an outline, and presented it to the Turkish regulators." The TMMDA liked what they saw, and both teams coordinated the Bethesda–Ankara videoconference session.

The program was focused on biotechnology: registration of biologics, differences between FDA and EMA biosimilar registration procedures, biosimilar product development, and studies of FDA-approved biosimilars. There was also a translator on hand to lend support. "We had more material than we could cover, and more questions than we could answer in one day of training," said Taman, "yet the level of engagement was overwhelming."

Following the session, which included Taman's introduction of ISPE and the Turkey Affiliate, the 35 TMMDA participants and Dr. Hakkı Gürsöz, the head of the agency, became ISPE members. ‹›

ISPE Turkey Affiliate

A DECADE OF ACHIEVEMENT

Since the Turkish pharmaceutical industry began applying good manufacturing practices and other international standards in 1984, its performance has been strong. Today, Turkey is home to 300 pharmaceutical companies and 31,000 employees, which produce more than 11,000 products at 67 production facilities and export to 160 countries—largely the European Union, Commonwealth of Independent States, Middle East, and North Africa.

In many ways, the Turkey Affiliate's performance has been equally strong. Its 11-year history has been filled with growth, accomplishment, and an unrelenting commitment to deliver maximum value to members.

INTERNATIONAL RECOGNITION

Founded in late 2005, the affiliate has garnered recognition both from ISPE and the Turkish pharmaceutical industry. At the 2016 ISPE Annual Meeting & Expo, ISPE Turkey was a co-recipient of the annual Affiliate and Chapter Excellence Award—the second time in its brief history to receive this award. In 2007 ISPE recognized the affiliate for its rapid growth in membership and commitment to the society's global objectives. It also received a 2011 Golden Mortar Award, the "Academy Awards" of the Turkish pharmaceu-

tical sector. In addition, Affiliate Chair Fatma Taman, was recently appointed to ISPE's International Board of Directors.

ISPE Turkey has also been instrumental in developing educational programs to help build the country's next generation of pharmaceutical technicians and engineers. The affiliate first helped introduce a pharmaceutical technician curriculum at the vocational high school level in 2008, followed by a project to develop a university-level pharmaceutical engineering curriculum with Istanbul University's Faculty of Pharmacy. "This was a national education project conducted with the consent of the country's Higher Education Council," says Affiliate Secretary Buket Hekiman Bayraktar. "It was established for the future of our industry." The affiliate additionally supports a student chapter at Istanbul University's Faculty of Pharmacy.

FULL SPECTRUM OF INDUSTRY PROFESSIONALS

Having celebrated its tenth anniversary in 2015, the affiliate has benefitted from increased exposure in the media, including trade magazines and websites, as well as a live television interview on *Bloomberg Turkey*. The resultant publicity boosted membership to 150 members at the end of 2016, more than a 20% increase.

According to Bayraktar, the affiliate's membership is a good representation of the spectrum of pharmaceutical industry professionals in Turkey. "It is not just colleagues from pharmaceutical companies that are present in our affiliate; we also have suppliers and academicians," she says. "ISPE is based on the necessity for pharmaceutical industry, suppliers, academicians, and authorities to meet on a common platform. So, we have this representation at our affiliate as well."

The affiliate has also developed a strong relationship with the Turkish Medicines and Medical Devices Agency (TMMDA), the regulatory body for pharmaceuticals in Turkey. "We are now on the official list at the Ministry of Health, resulting in very successful and interactive participation at all related meetings," says Affiliate Chair Fatma Taman. "The TMMDA now consults with us frequently, because they respect ISPE as an objective and trustworthy organization that benefits the pharmaceutical industry." Following a videoconference training organized for TMMDA, 36 delegates—including the head of the agency—applied for ISPE membership and now regularly attend the affiliate's educational events.

Seminars, workshops, and networking events are held about once every two months. Seminars involve globally recognized speakers and are based on hot topics—either engineering or quality—depending on current regulations or upcoming requirements. The affiliate also has working groups on topics such as process analytical technologies and quality by design. In 2016, two new working groups were started on quality metrics and data integrity; this was followed by the "excellence in pharma engineering" working group founded in 2017.

In 2016, the affiliate also introduced industry sector meetings. "These are conducted as afternoon meetings by professionals in the pharmaceutical and related industries," explains Bayraktar. "We discuss current topics. The last one, for example, was about Industry 4.0, which is something that will influence the whole industry and is quite important for our country's development as well."

LOOKING AHEAD

Both Taman and Bayraktar acknowledge ongoing challenges, such as limited industry training budgets. In addition, unfavorable exchange rates between the Euro and Turkish Lira translate into unusually high fees for Turkish members. "We are an emerging economy and foreign exchange rates are high, so companies are reluctant to send their employees to trainings outside of Turkey," says Taman.

They are optimistic nonetheless.

"One of our aims for 2017 is to really establish the Young Professionals group in Turkey," says Bayraktar. "We expect to be more active with our working groups and will provide more training on a variety of subjects. We already have strong interaction with our regulatory authority and we will continue to highlight this going forward."

"In the next two to three years, we want to strengthen our relationship with TMMDA to obtain a sustainable contribution of the regulators at ISPE's global activities," says Taman. "We will also reach out to Young Professionals and intend to establish a 'Women in Pharma' chapter of our affiliate, and try to meet their technical and managerial training needs."

Taman points out that the affiliate's activities with YPs and women will feature more than training. "Our goal is to bring peers together and create networking possibilities that each and every one of them can use for the benefit of their companies and their own careers," she says. ‹›

—Mike McGrath

ISPE TURKEY AFFILIATE: QUICK FACTS

Founded: 2005
Region: Turkey, Eastern Europe, and Western Asia
Membership: 200+
Events: At least 6 per year

Chair
Fatma Taman, Member, ISPE International Board of Directors

Vice-Chair
Buket Aksu, Istanbul Kemerburgaz University

Secretary General
Buket Hekiman Bayraktar, PharmaVision

Turkey Affiliate Office Manager
Gizem Yeğen

Members
İlknur Gümüşeli Hırçın, Bayer Türk Company
Devrim Çavuşoğlu, Pfizer
Havva Çınar Aşar, Bayer Türk Company
Figen Ergin, BTS
Tanju Cepheli, BASF Türk
Prof. Dr. Yıldız Özsoy Erginer, Istanbul University
Fahrettin Kazak, PharmaVision
Banu Refik, Convalgroup
Hülya Uslu, Consultant

Members of the Turkey Affiliate, 2016 Affiliate and Chapter Excellence Award co-recipient, with Joe Famulare, outgoing Board chair (second from right) and John Bournas, ISPE CEO and President (right)

Second Edition ISPE Baseline Guide Available

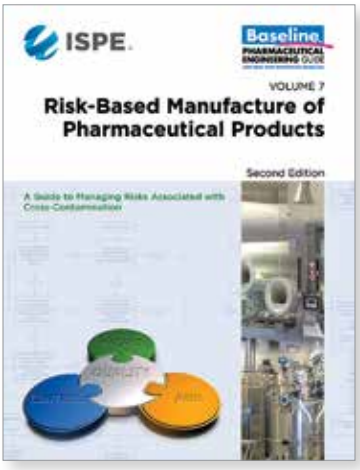
RISK-BASED MANUFACTURE OF PHARMACEUTICAL PRODUCTS

The ISPE Baseline® Guide: *Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)* (second edition), provides a scientific risk-based approach based on ICH Q9: "Quality Risk Management," for managing the risk of cross-contamination within shared facilities. Risk-management processes should be used to determine and document reasonable and acceptable risk in order to maintain product quality and operator safety and to satisfy regulatory requirements.

This second edition provides a process that allows manufacturers to assess risk and determine where control strategies are necessary to meet acceptable limits for cross-contamination. The control strategies to manage risk can vary from administrative to full dedication or segregation. Typically, some combination of control strategies may be necessary. This Guide is intended to provide a consistent approach on setting acceptable limits to assess the potential of cross-contamination, thus enabling implementation of appropriate controls to facilitate safe and affordable drug product manufacturing.

The ISPE Risk-MaPP Baseline Guide (Second Edition) acknowledges that the overall principles presented in the first edition are still valid, but includes several changes to support ongoing developments:

1. Information has been added to support significant changes in regulations and the application of regulations. These include:
   - Updated EU GMPs relative to the use of quality risk management principles in managing the risk of cross-contamination.
   - EMA-issued guideline on setting health-based exposure limits (HBELs) for use in the risk management process for shared facilities. This guidance also states that PDE (permitted daily exposure) and ADE (allowable daily exposure) are effectively synonymous.
   - ICH-issued M7 guideline "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk," which sets a threshold of toxicological concern (TTC) for mutagenic impurities in drug substances and drug products when there is insufficient data to calculate the acceptable limit.
   - Adoption by US and EU regulators of a life cycle approach to process validation incorporating three stages of process design, process qualification, and continued process verification. The process validation life cycle approach recognizes that validation is an ongoing control strategy to manage risks and maintain process control. The concept of ongoing assurance of cleaning process efficacy is one of the keys to the control of cross-contamination outlined in this Guide.
   - Implementation of risk-based approaches to managing the risk of cross-contamination and sharing lessons learned.
2. Information has been relocated, so that the layout of the Guide aligns with the ICH Q9 process.
3. Updated application example has been added, based on an increased understanding and more experience with quality risk management, and more specifically with risk assessments for cross-contamination.



For more information, or how to order, visit http://www.ispe.org/publications-guidance-documents/risk-mapp-management-plan-second-edition. ❮❯

Join the Discussion

BE A CHAMPION

Do you want to connect with your colleagues around the globe? Are you seeking information on current trends, hot topics, or how to solve a problem? Then look to the ISPE Communities of Practice! CoPs are virtual libraries, a group of online communities available only to ISPE members offering access to a vast body of knowledge:

- Browse archives for information
- Join an existing conversation or start a new one
- Post links and references to enhance discussions
- Receive email notifications to stay up-to-date on issues and trends

These interactive forums host a variety of discussions, with a broad range of questions and answers from colleagues in the field. They're also a great way to share your own knowledge and experience. Sample topics include:

- C&Q: Package integrity testing
- GAMP®: What is your #1 data integrity concern?
- Critical Utilities: Heated vent filters on WFI systems
- HVAC and Sustainable Facilities: Airflow pattern studies for Class 8 OSD facility

CoPs also provide networking opportunities for members in every corner of the world:

- Search ISPE profiles to connect with colleagues around the globe
- Create a profile populated from your ISPE membership information, and customize it with your photo, links to other social networks, videos, companies, articles, and more

Visit www.ispe.org/communities-practice or contact communities@ispe.org to join the discussion. ❮❯

CO-OPS AND INTERNSHIPS: MASTER THE BASICS FOR MAXIMUM BENEFIT

David G. Smith is Talent Acquisition Lead, PO&T North America, Biogen

Hi David: I've landed a great co-op job that will start soon. Do you have any tips on how to maximize this opportunity?

Congratulations! Internships and co-ops are great opportunities that can enhance your résumé and build a strong relationship with the organization. How do you make a good impression while adjusting to a new work environment—especially given the limited time of an internship or co-op?

MASTER THE BASICS

As Woody Allen said, "Showing up is 80% of life." Start with the basics:

- Be on time and be prepared: Tardiness is a surefire way to make a bad impression.
- Smile and show energy: If you aren't excited and ready to engage, why should your teammates want to work with you?
- Dress the part: Match the attire of people around you.
- Hit your deadlines: This will go a long way toward making a positive impression.
- Limit distractions: Resist the temptation to let outside responsibilities creep into your time at work.
- Follow the rules: Learn company polices and follow them to the letter.

MAXIMIZE YOUR EXPERIENCE

Many internships focus on projects that are important to the organization. Whether yours is mundane or exciting, make sure your attitude reflects your drive and determination to produce quality work, and complete each task to the best of your ability. If you're asked to schedule a meeting, have all materials prepared and ready to go. If you're asked to prepare a presentation, make it visually appealing and accurate; be especially vigilant about bad grammar and typos.

Review the materials you've been given (SOPs, SharePoint sites, and training materials) before asking for help. Being resourceful will show that you respect your manager's busy schedule, and that you're engaged with your job. If you ask for help, make sure the question shows that you've done your homework. During meetings, listen and learn from others, take notes, and organize the information so you don't ask the same question twice.

Don't avoid or decline tasks. If you have extra time, volunteer for assignments others may not want to do or that may require skills you need to develop. Your ability to deliver beyond expectations will not only enhance your professional development, but can become a real differentiator when new opportunities arise. Remember: Your consistent, passionate ability to deliver excellence will create the foundation for your future.

NETWORK

Many companies allow you to participate in activities such as facility tours, training sessions, networking, or community events. These can help you learn more about the organization's culture and values, as well as provide opportunities to interact with the broader organization and develop key relationships:

- Meet fellow co-ops and interns: Like you, many of your peers will be standout students, but with different skillsets and backgrounds. They may have the potential to help solve work-related problems, or refer you to hiring managers later.
- Get outside your group: Learning more about different functional groups in the company can help you develop your career. Most leaders are open to meeting with co-ops or interns who want to learn, so don't be shy about asking. Do some research ahead of time so you can ask great questions, and don't forget to say thank you!
- Join organized activities: Many companies have sports teams, charity events, and employee outings that you may be able to join as well. These allow you to mingle with people that you would not meet otherwise, and can be a great way to learn about other groups and leaders.
- Enjoy a lunch break: While you may be tempted to eat at your desk, don't. The lunch hour is often when your colleagues are the most available and easiest to talk to. Use this time to connect with others and develop better relationships.
- Find a mentor: Identify a mentor or sponsor before the end of your project. He or she should be well connected, in good standing with the company, and someone you can trust. Finding a leader that can advise you on how to grow your career and recommend you to others is invaluable.

LEARN THE HIRING PROCESS

Ask your manager which recruiter supports hiring for the team, then find out if you can get a meeting with him or her. Your discussion should include how to find and apply for a job, identify entry-level opportunities, and what recruiters look for when considering candidates. You might also want to ask about other programs for which you may be eligible as a current or former intern, and if you should meet with other recruiters as well.

Thank you for your question—I wish you the best of luck in this important first step. ‹›

If you have a question about career development, send it to me at david.g.smith@biogen.com, and I will answer it in a future column.

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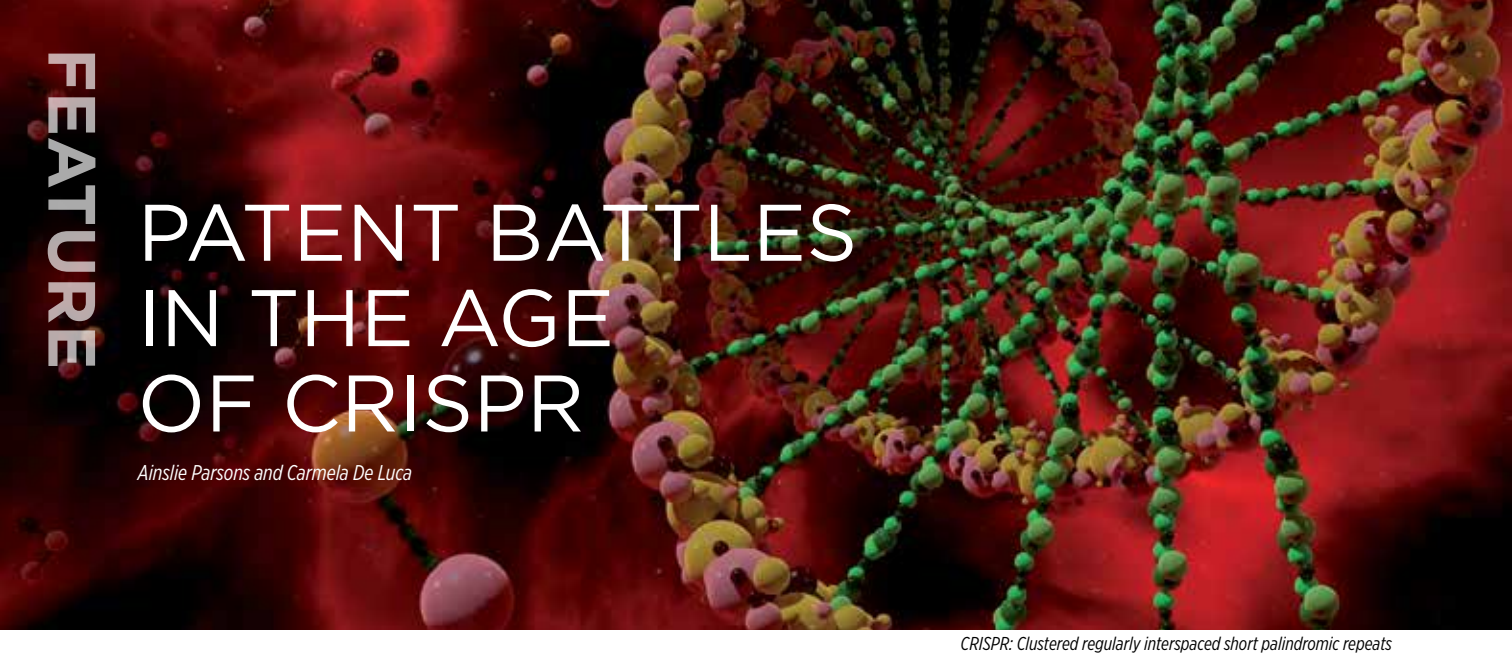
FEATURE

PATENT BATTLES IN THE AGE OF CRISPR

Ainslie Parsons and Carmela De Luca



CRISPR: Clustered regularly interspaced short palindromic repeats

The CRISPR/Cas9 system (CRISPR) developed for gene editing only a few short years ago* has already revolutionized genomic engineering, and clinical trials for targeted cancer therapies have recently commenced in China and the United States.

CRISPR's power lies in its relative simplicity and precision, and it is expected to have profound implications for agriculture and the treatment of disease. No surprise, then, that the groundbreaking technology is already beset with controversy ranging from ethical issues associated with the technology† to a highly publicized and public US patent dispute.

CRISPR's nucleic acid sequences are part of a naturally occurring bacterial defense system in which repeating sequences of genetic code are interrupted by "spacer" sequences. The spacer sequences represent remnants of genetic code from past viral invaders. Using enzymes of the CRISPR system, the bacteria snip out parts of the virus DNA and keep a portion of it behind to help them recognize and defend against the virus next time it attacks, much like an immune system.

This bacterial defense mechanism has been adapted by scientists to form a number of related gene-editing systems, yet the CRISPR/Cas9 system has been the main focus of attention to date. Here, two key molecules are used to modify a DNA molecule: guide RNA and the enzyme Cas9. Guide RNA (gRNA) is a piece of predesigned RNA sequence about 20 bases long, located within a longer RNA scaffold. The gRNA has RNA bases that are complementary to those of the target DNA sequence, which allow it to find and bind to that specific DNA sequence (Figure 1A). Cas9, which is in a complex with the gRNA, follows the gRNA to the same location in the DNA sequence. Together they bind to the target DNA site, a process that also requires the presence of a sequence called the protospacer adjacent motif that facilitates Cas9 binding.

Cas9 then makes a cut across both strands of the DNA, resulting in a double strand break (Figure 1B). At this stage, the cell recognizes that the DNA is damaged and tries to repair it. Scientists can then use DNA repair "machinery" to introduce specific changes in the host DNA sequence, such as a new mutation, a sequence addition, or a sequence deletion (Figure 1C).

CRISPR can be designed to target virtually any DNA sequence. So far it has been adapted to alter genomes that include yeast, worms, fruit flies, zebra fish, plants, mosquitoes, mice, monkeys, and human cells.

PATENT PROCEEDINGS

Not surprisingly, CRISPR's wide-reaching and powerful potential applications have led to significant interest in protecting the intellectual property associated with this technology.

As with many important scientific advances, both individuals and research groups were involved in identifying the CRISPR system in nature, recognizing that it could have far-ranging applications, and then adapting it as a genome-editing technology.‡

In June 2012 a group of researchers led by Jennifer A. Doudna of the University of California (UC), Berkeley, and Emmanuelle Charpentier of Umeå University in Sweden published a seminal paper in *Science* describing a CRISPR/Cas9 system that could cut DNA *in vitro*.[5] By the time the paper was published, the researchers had already filed a patent application with the United States Patent and Trademark Office (USPTO) claiming methods and compositions for modifying DNA (the "UC application").[6]

In December 2012, a second group of researchers, led by Feng Zhang of the Broad Institute, filed a patent application with the USPTO (the "Broad application"). Unlike the UC application, which described the use of CRISPR/Cas9 only in prokaryotic cells (unicellular organisms that lack a nucleus or organelles), the Broad application showed that the CRISPR/Cas9 system could be used in eukaryotic cells (those that have a membrane-bound nucleus and other organelles) to modify DNA *in vivo*.

While the Broad application was filed after the UC application, it requested and received accelerated examination and issued to patent first, in April 2014.[7] The Broad patent claims cover methods of editing genes in eukaryotic cells using CRISPR/Cas9.

The UC application was filed under the "first to invent" patent system in the United States.

* For one a review of the timelines and scientists involved in developing CRISPR, see reference 1 at the end of this article.

† The ethical issues associated with gene editing are not discussed here. For one review, See reference 2 for one perspective.

‡ Briefly, repeated sequences of 30 bases separated by spacers of approximately 36 bases were identified in an archaeal microbe by Francisco Mojica in 1993 (see reference 3). Over a decade later, Mojica realized that CRISPR loci are part of an adaptive defense system that protects microbes against specific infections (see reference 4). Encouraged by these initial discoveries, scientists began to explore ways by which this natural process could be adapted to edit genes.

While the United States has now switched to a "first to file" patent system, consistent with the majority of patent systems around the world, the older system awards a patent to the first person to invent a new technology. When questions arise under this system with respect to which party first invented a commonly claimed invention, administrative proceedings known as "interference proceedings" are held. These proceedings are now obsolete under the current system.

In early 2016, UC (and related parties) requested that a patent interference proceeding be initiated. They claimed that the Doudna/Charpentier team invented the CRIPSR/Cas9 system and that the disclosure in the Broad patent and related patents and applications that the system worked in eukaryotic cells was merely an obvious extension of Doudna and Charpentier's work. Essentially, UC's position was that both the UC application and the Broad patent were directed to the same invention and that the Doudna/Charpentier team were the first inventors. According to this rationale, the Broad family of patents and applications were invalid.

In a decision released on 15 February 2017, however, the USPTO's Patent Trial and Appeal Board (PTAB) rejected the UC argument. The PTAB agreed with the Broad Institute's position that one of ordinary skill in the art would not have reasonably expected that a CRISPR/Cas9 system as described in the UC application would work in eukaryotic cells. Thus, according to the PTAB, the UC and Broad applications are directed to two different inventions and there is no interference between the two patent families.

Because that issue was determinative of the interference, the PTAB declined to decide any other issues and terminated the interference. In summary, the PTAB found that:

> *Broad provided sufficient evidence to show that its claims, which are all limited to CRISPR-Cas9 systems in a eukaryotic environment, are not drawn to the same invention as UC's claims, which are all directed to CRISPR-Cas9 systems not restricted to any environment. Specifically, the evidence shows that the invention of such systems in eukaryotic cells would not have been obvious over the invention of CRISPR-Cas9 systems in any environment, including in prokaryotic cells or in vitro, because one of ordinary skill in the art would not have reasonably expected a CRISPR-Cas9 system to be successful in a eukaryotic environment.* [10]

Practically, this means that the Broad patent remains valid, and that the UC application can proceed.

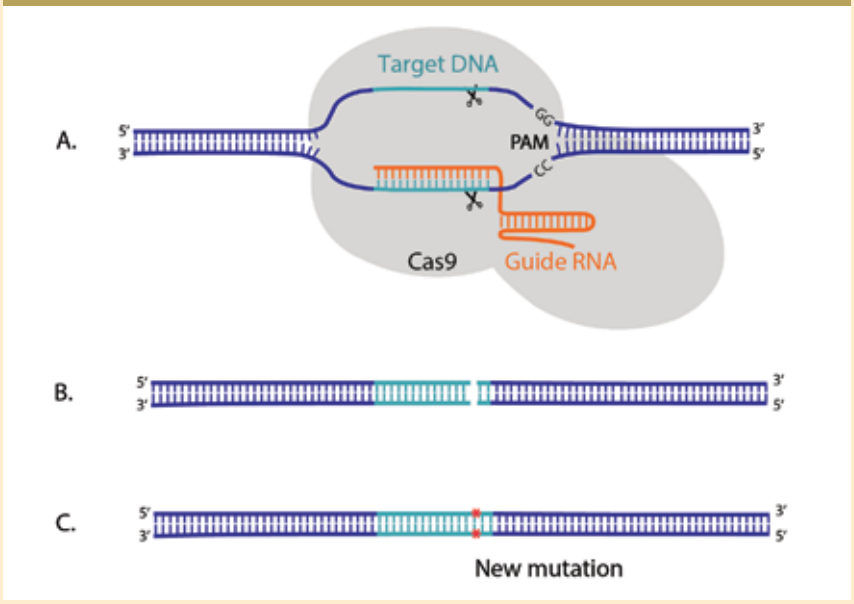
At time of publication, the case has not yet been settled. On 13 April 2017, the UC filed an appeal of the PTAB decision to the United States Court of Appeals for the Federal Circuit, so there is a possibility that the decision itself could be overturned.§ [11] Even if the decision is upheld, it is still unknown what patent claims will ultimately issue from the UC family of applications.

HIGH STAKES

If, as expected, CRISPR proves to have diverse applications in agriculture and medicine, the holder of any key patent stands to gain a pretty sum. In spite of the ongoing patent dispute, companies have moved quickly

§ The Broad Institute's opening brief in the case is due 25 October 2017.

Figure 1: The CRISPR/Cas9 system



1A. Guide RNA (gRNA), which is in complex with the DNA cutting-enzyme Cas9, aligns with a target DNA sequence.

1B. Cas9 makes a cut across both DNA strands, resulting in a double strand break.

1C. This triggers cellular DNA repair, and enables the introduction of specific changes such as mutations in the target DNA sequence.

to license CRISPR patent portfolios, and several CRISPR biotechs went public in 2016 with initial public offerings worth $90 million and more.[8] For third parties wishing to license the CRIPSR-Cas9 technology, the current licensing landscape remains murky at best.

For example, even if the Broad Institute's patents covering the use of CRIPSR-Cas9 in eukaryotic cells (i.e., including human cells) are upheld, it is possible that the UC application will issue with broad claims to the use of CRISPR-Cas9 in any cell. Depending on the claims that issue for the UC patent, a third party hoping to edit eukaryotic cells using CRISPR (e.g., in the development of human therapeutics) would potentially need to license both the Broad and UC patents. In addition, both patent portfolios are already licensed to a number of different parties under a variety of arrangements including, in some cases, exclusive licenses, adding further layers of complexity.

Furthermore, it is likely that improvements and alternatives to CRIPSR-Cas9 will be developed. Searching the USPTO database for pending applications that include "CRISPR" in the title identifies 86 applications published in 2016 and 2017.** For example, alternatives that do not use the Cas9 enzyme may also work. In particular, the Cpf1 endonuclease has been shown to be a CRISPR effector.[9]

CONCLUSION

The CRISPR system is an exciting, groundbreaking, and game-changing technology. It has already revolutionized laboratory science and, if expectations are realized, will have profound effects on the treatment of cancer and genetic diseases. In addition, the technology is expected to have big implications for food, pest control, and livestock, and will likely have many as of yet unforeseen applications. The patent battles for control of CRISPR technology are underway, but it will be some time before it is clear whether the victory will be shared or if it will be a case of "winner takes all." ‹›

** Based on a USPTO patent application database search on 13 June 2017 for entries containing "CRISPR" in the title. The search results were not reviewed. It should be noted that patent applications are not typically published until 18 months after filing, so there may be many more applications pending that are yet to be published.

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About the authors

Ainslie Parsons is an associate with Bereskin & Parr LLP. A lawyer and registered patent agent in Canada and the United States, Parsons's practice focuses on biotechnology and pharmaceutical matters, including patents, plant breeders' rights, licensing, and related litigation. She has authored a number of professional papers published in *Cell* and *Nature Biotechnology*. Parsons is also the recipient of the Canadian Institutes of Health Research Canada Graduate Scholarship Doctoral award and the Natural Sciences and Engineering Research Council of Canada Post-Graduate Scholarship.

Carmela De Luca is a partner with Bereskin & Parr LLP. A lawyer and registered patent agent in Canada and the United States, De Luca practices in all areas of intellectual property, focusing on patent matters. This includes advising clients on strategic global aspects of obtaining and managing patent portfolios, as well as in the preparation and procurement of patents and industrial designs. She works closely with clients, including start-ups, universities, and multinationals, in preparing and prosecuting patent applications relating to biotechnology, pharmaceuticals, biologics, diagnostics, green technologies, and other areas in the life sciences. De Luca is also active in the analysis of patent issues such as validity, infringement, and freedom to operate. In addition, she has experience advising on regulatory compliance and on plant breeders' rights.

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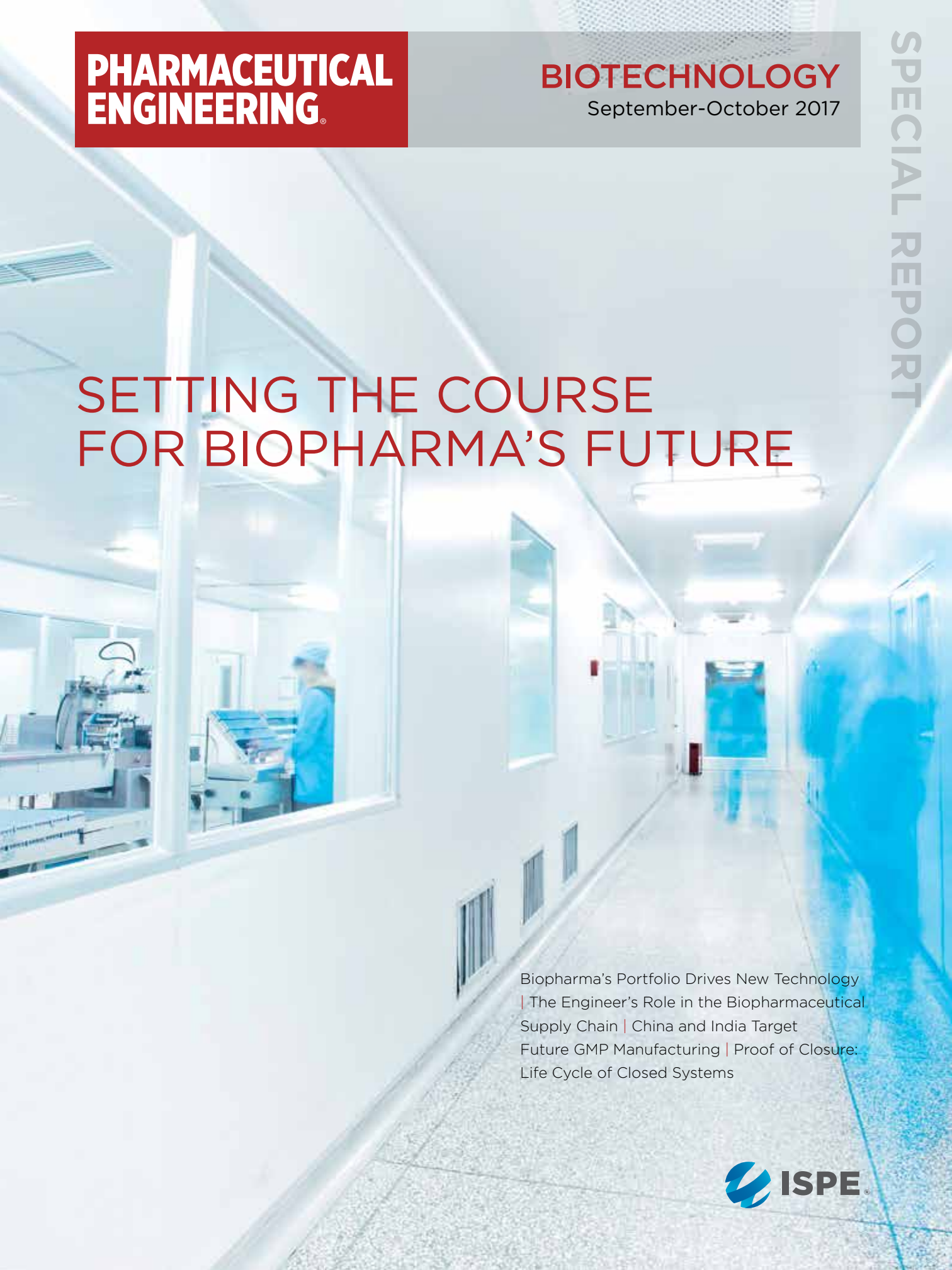

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BIOPHARMA'S PORTFOLIO DRIVES NEW TECHNOLOGY

Robert Dream, PE, CPIP, PhD Principal, HDR Company LLC , and guest editor, Biotechnology Special Report

The portfolio sold by today's global biopharmaceutical industry is fundamentally different than it was even a decade ago. This shift is a reflection of today's global market, which features greater competition, more treatments for orphan diseases, an increase in large-molecule drugs, and personalized or targeted medicines. The result has been genotype-specific biopharmaceutical products produced in extremely limited production runs under tightly controlled manufacturing specifications. This new product mix, combined with the industry's drive to improve production efficiency, is stimulating the development of new technologies and processes that are helping to improving economic outcomes, flexibility, and quality in biopharmaceutical manufacturing—all while benefitting patients.

What are some of these new technologies?

- Gene therapy replaces defective genes by inserting new, functional genes into patients' cells. The field has flourished since the first clinical trials in the 1990s.
- Stem cells are unspecialized cells that can be guided to develop as multiple types of tissue- or function-specific cells. Stem cells offer great potential for chronic diseases like heart disease and diabetes, but much work remains to be done before they are fully understood.
- Nanomedicine works at the atomic level using microscopic particles called nanoshells; some are being studied for their ability to convert infrared light into heat energy that will destroy cancer cells.
- New drug delivery systems include biodegradable microspheres that dispense targeted drugs as the sphere degrades. These are being studied as possible treatment mechanisms for cancers and other diseases.

While regulators seek assurance of technically sound, risk-based, reliable, and predictive processing that is relevant to product quality, today's regulatory environment also provides traction for the ongoing advancement of innovation. Authorities in the three ICH regions and beyond are encouraging industry to adopt new technology as supported by ICH Q8(R2), Q9, Q10 and Q11, along with the introduction of quality by design concepts.[1] This may lead manufacturers to adopt cleaner, more flexible, and more efficient closed systems.

Many biopharmaceutical manufacturers are investing in:

- Continuous manufacturing, which can improve scalability, shorten time to market, and enhance quality, while reducing capital and operating costs
- Process analytical tools that streamline and fortify processes, accelerate production scale-up, and ensure resources are used efficiently
- Single-use systems that improve flexibility and reduce production lead times, yet reduce capital investment and energy consumption
- Alternative downstream processing techniques that increase yields and reduce costs
- Adopting green chemistry to diminish waste
- Improving capacity, scalability, and flexibility with new vaccine and therapy production methods
- Products that increase patient compliance and increase the effectiveness of medicines, such as drug-device combinations or improvements in drug-delivery systems

These products require new manufacturing techniques both at the facility and throughout the supply network. When combined with changes in biopharmaceutical portfolios, these new technologies affect biopharmaceutical companies in several ways:

- They look for increasingly specialized employees. Some organizations are working with university biomanufacturing centers to design training programs that teach relevant skills.
- They collaborate on manufacturing innovation with academic institutions and diagnostics developers as well as production equipment and medical device manufacturers.
- They consider location and ecosystem advantages in strategic manufacturing decisions as a result of the new portfolios and technologies required to produce them.

Biopharmaceutical drugs have become standard therapy for multiple diseases, a trend that has spurred both increasing demand for biotechnology and the emergence of small biopharmaceutical manufacturing companies.

Companies hoping to ride the wave created by these trends will face new challenges, however. The world's regulatory agencies are expected to further tighten their guidelines and will continue to call for the serialization of drug production.[2]

But as the global market continues to expand, the future looks bright. Indeed, market research firm IMS Health estimates the global sales of biological products will reach $390 billion by 2020, as much as 28% of the worldwide pharmaceutical market.[3]

Biotechnology CoP Committee members are participating in the following activities:

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- Publishing papers in the specific area of biomanufacturing
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THE ENGINEER'S ROLE IN THE BIOPHARMACEUTICAL SUPPLY CHAIN

John Balchunas, Chris Smith, and Lucas Vann

As the industry evolves in its quest to increase quality, productivity, efficiency, and safety, engineers must be equipped with skills that enable them to meet new and challenging demands. This first in a two-part series focused on biopharmaceutical manufacturing explores a few of the exciting roles engineers play to drive continuous improvement. Part 2, slated for* Pharmaceutical Engineering*'s November-December 2017 issue, will focus on how engineers working in the traditional pharma industry can leverage their background and gain new skills to transition into the biopharma sector.

Biopharmaceuticals are the fastest-growing segment of the pharmaceutical industry, with global sales that are projected to grow to $445 billion by 2019. In the United States alone, the biopharmaceutical workforce is comprised of 854,000 direct jobs and 1.7 million indirect jobs across a diverse supply chain of vendors supporting the industry. Future growth and success of the biopharmaceutical industry will depend on a highly educated and trained workforce, with engineers playing a critical role in driving innovation.

While the chemical processes that underpin traditional pharmaceutical manufacturing processes are predictable, biopharmaceutical manufacturing processes—which are grounded in the use of biological systems—are inherently more mercurial and complex. Products include monoclonal antibodies, vaccines, and cell- and gene-based therapies—a quickly emerging product line.

The complexity of biopharmaceutical manufacturing processes has driven the need for a highly skilled cross-functional biopharmaceutical workforce that spans the life sciences (such as microbiology and molecular biology), engineering (chemical, mechanical, electrical, and biomedical), medicine, and business.

Engineers are an integral part of the entire product life cycle and occupy many different roles. Some roles are quite similar to those in the pharmaceutical industry and easy to understand: Engineers, for example, play a fundamental part in the design and construction of facilities.

After design engineers leave the facility in the hands of manufacturing, quality, and business teams, however, several critical engineering functions remain to be filled:

- Process engineering, to develop and optimize processes as well as execute tech transfer and scale-up
- Facility engineering, to qualify new equipment and ensure existing equipment is maintained
- Automation engineering, to drive process efficiency and cost reduction by leveraging sensors, multivariate data analytics, and advanced process control

To shed light on the role of engineers in biopharmaceutical manufacturing, this article presents three "virtual round tables" featuring engineers that work in each of these positions.

PROCESS ENGINEERS: REVOLUTIONIZING OPERATIONAL OPPORTUNITY

Engineers focused on process engineering and process development are responsible for the conceptual design and optimization of new operations, taking a product from bench-scale to full-capacity production using the most efficient means possible. Equipped with a blend of scientific, technical, and engineering expertise, these specialists must understand how a specific process fits within an organization's large-scale production plans. Process engineers boast a skill set that's sought after by both large and small organizations, as well as contract development and manufacturing organizations and consulting firms. Indeed, most have a bachelor's degree and several years of industry experience. As is evident from the discussion below, process engineers possess, above all, a lifelong passion for continual learning that allows them to keep up with modern technologies and trends.

Participating in this discussion:

- Oscar Bernal, PhD, Process Development Scientist, MilliporeSigma
- Marisol Hydock, Integrated Solutions Sales Manager, Southeast, Sartorius Stedim Biotech
- Kayla Peck, Fermentation Process Engineer, Ajinomoto

Can you tell us about your job?

BERNAL As a field-based process development scientist, I proactively pursue and perform process-development studies for the purification of antibodies, vaccines, viral vectors, and all kinds of therapeutic proteins; I provide technical support as well as drive technical collaborations between MilliporeSigma and the client.

HYDOCK As part of the integrated solutions team, I develop and implement rapid and cost-effective solutions from early-phase development through scale-up to commercial manufacturing. This includes close collaboration with customers and other preferred solution providers to consult on conceptual designs and process capabilities and to provide implementation support for hybrid and single-use equipment and services.

PECK In representing a manufacturing company, my role is a little different from Oscar's and Marisol's. I track current batch performance, troubleshoot issues, and analyze fermentation data to drive improvements, make recommendations to management to secure buy-in, and complete projects.

Which emerging technologies and trends are interesting to you professionally?

BERNAL As the scale of titers is increasing and pushing the limits of older purification technologies, I am seeing a lot of interest in single-use technologies and continuous bioprocessing.

HYDOCK Cell and gene therapy, full implementation of single-use and continuous bioprocessing. We help growing companies realize that single use is a very robust solution for them—with the knowledge that no single solution fits every process.

PECK I am very interested in using automation to measure many points across a process and having that information converted to a specific action.

What has been your career trajectory?

BERNAL I completed my bachelor's degree in chemical engineering and microbiology in Colombia, and then came to the United States for my doctorate in chemical engineering. I spent a year doing chromatography process development on flu vaccines and then transitioned to my current role as a purification Subject Matter Expert covering Southern California at MilliporeSigma.

HYDOCK While in school, I interned in quality control for a solid-oral-dosage facility. After graduation, I was hired as a bioprocess technician at a start-up vaccine manufacturing site, where I learned the fundamentals of good manufacturing practice (GMP) and had opportunities to work on special projects in many departments. Due to this variety of experiences, I was offered a position as a process engineer for a contract manufacturer. There, I gained more experience, working with big pharma, start-ups, and on R&D projects. I was eventually recruited to work with Sartorius Stedim Biotech. I believe it was due not only to my varied experience but also because I enjoy working with people, can manage change well, and am an active member of ISPE.

PECK I graduated with a degree in chemical engineering and a minor in biomanufacturing. I was hired as a general production support engineer overseeing issues across the entire plant, and later offered the opportunity to be the fermentation process engineer so that I could focus my skill set.

What do you think the future will bring?

BERNAL The future looks very diverse. A myriad of start-ups with aggressive timelines are popping up all over the country and they're developing the new generation of genetic therapies and antibodies. This translates into a highly competitive and innovative environment that will benefit patients worldwide.

HYDOCK Increased scrutiny over autologous medicine and high scrutiny for pricing. One autologous treatment can cost a million dollars. The challenge will be reconciling high-priced technologies with the overarching need for personalized medicine.

PECK At many manufacturing facilities, there are still a lot of unnecessarily manual operations. I suspect that the future will bring complete automation to fermentation.

What advice would you give to individuals interested in your area?

BERNAL Stay awake! This industry is evolving permanently and you need to stay up to date. There is a shortage of highly qualified individuals overall, but the turnaround rate is also high as people move between companies quite frequently. Most importantly, everyone knows everyone, so it is critical not to burn any bridges.

HYDOCK Build your network and your experience by joining professional organizations such as ISPE. Any experience that you can get in other roles such as quality control, manufacturing, validation, and process development will help lay a strong foundation for being able to speak technically and proficiently.

FACILITY ENGINEERS: SECURING THE FUTURE OF BIOTECHNOLOGY

New technologies are being introduced to our industry at an ever-increasing rate. How do we build new facilities and introduce new equipment to keep pace with today's changing technology and expectations? Enter the facility engineer. Facility engineers have a solid understanding of current GMP regulations and advancements in technology; they also have the ability to work with other technical disciplines to understand an organization's complete business needs.

Participating in this discussion:

- Chris Dela Cruz, Validation Engineer, Commissioning Agents, Inc.
- Tim Stark, Director of Operations for the Pacific Region, Commissioning Agents, Inc.

Can you tell us about your job?

DELA CRUZ Commissioning, qualification, and validation, with a focus on greenfield projects and older facilities requiring equipment upgrades/retrofits. Building off my time as a validation engineer, in which I completed projects in quality control, plasma fractionation, albumin manufacturing, and oral solid dosage, I am able to bring new best practices, ideas, and approaches in problem solving.

STARK My expertise is in aseptic bioprocessing and biotech facility design. I connect skilled individuals with client needs. I spend my days understanding and anticipating what customers need and finding engineers to fulfill those needs.

What emerging technologies and trends are interesting to you professionally?

DELA CRUZ There is a push to digitalize the previously paper-intensive validation process as "execution on glass." Instead of taking hundreds or even thousands of pages to the field, this can all be done with a tablet. This is similar to how the industry has migrated from written batch records to electronic batch records.

STARK Significant is the move from tradition, the somewhat duplicative process of commissioning and qualification to the ASTM E2500 verification standard.

What advice would you give to individuals interested in your area?

DELA CRUZ Many are unsure about what area they want to work in. Working for a company that provides contract validation work will allow someone to experience a variety of roles.

STARK Try to gain experience that will help you see different points of view, such as the difference between working in an R&D or manufacturing environment, or the difference between working for a manufacturer or service provider. The ability to help your customer requires different skills than does the ability to help your boss/team. I would also say that if you desire a breadth of experience and a chance to see the world, you should choose consulting.

AUTOMATION ENGINEERS: BRINGING AUTOMATED CONTROL SYSTEMS TO PRODUCTION

Current automation and control systems to produce biologics and pharmaceuticals are well behind those found in other highly automated industries, such as semiconductor manufacturing. Routine monitoring and proportional integral derivative (PID) controllers do not provide control of many important critical parameters that impact critical quality attributes. Establishing a robust control strategy during process development that can be scaled up and transferred to manufacturing is crucial to ensuring quality throughout the product life cycle. While advanced monitoring tools are available, utilizing them effectively is challenging since advanced control solutions must be capable of predicting what might occur within a batch or unit operation and act accordingly to correct it. To meet current demands as well as be positioned to anticipate and overcome future challenges in automation, engineers must be equipped with the necessary skill set.

The following questions were posed to three engineers with various jobs and backgrounds. Each of these engineering roles, while different, are required to drive a complete automation control solution.

Participating in this discussion:

- Saly Romero, Senior Manager at Biogen in manufacturing sciences; has extensive experience in data analytics and modeling
- Thomas Jacobsen, Automation Engineer at NNE; works as a team leader for the company's automation infrastructure
- Amos Dor, CTO of the Automation Product Group at Applied Materials; works to provide enterprise solutions for both the semiconductor and pharmaceutical industries

Can you tell us about your job?

ROMERO I lead a small team of data analysts performing data-driven modeling in the areas of process performance as well as advanced sensor calibrations. Based on my experience, I bring a strong skill set in data analytics, including real-time analysis and modeling, related to characterization and optimization with the overall goal of generating process intelligence, knowledge, and control.

JACOBSEN I work in automation for pharmaceutical and biopharmaceutical companies, where I help to provide infrastructure for plant-wide turnkey installations including building management system, distributed control system, and supervisory control, and data acquisition systems.

DOR I evaluate current technology platforms for both the semiconductor and pharma industries and work to promote new technologies and markets. I've managed to combine my software engineering education with entrepreneurial business and management skills to add a unique perspective in both a large company and start-up settings.

What has your career trajectory been like?

ROMERO While pursuing my bachelor's in chemistry at Purdue University, I had the opportunity to work for a university research center and developed calibration models for near-infrared as well as Raman applications, which was my introduction into chemometrics and data analytics. I then went on to work for a number of large pharma companies supporting both small- and large-molecule manufacturing by modeling for advanced sensor strategies as well as building multivariate analysis models to troubleshoot, identify process characteristics, and help with investigations. My experience enabled me to start my own consulting company, which led me to the job I have now.

JACOBSEN As an undergraduate, I had the opportunity to work in a fermentation lab, where I began doing PID tuning and other automation and control activities on bioreactors. When I graduated, I began working for Novartis in statistical analysis but always wanted to do more in automation. I went back to school and earned a master's from the Biomanufacturing Training and Education Center at North Carolina State University, completing an automation-centered project that led to my current job.

What emerging technologies and future trends are interesting to you professionally?

ROMERO I see biopharma becoming less technology-conservative and more open to adopting advanced manufacturing technologies. It is a different way of thinking, as well as working, when compared to the classic approach in that it is knowledge-based rather than only skill-based.

JACOBSEN Automation is a very expansive area in manufacturing and requires so many segments. This creates silos of dependencies in those areas, such as equipment programmable logic controllers (PLCs), user human-machine interfaces, and computer servers, to name a few. The future of automation must be one where these are integrated in a more seamless manner. This also includes security, which I feel is a specific area to focus on for the future as more systems become networked and more virtual-based systems are used.

DOR The emerging trend of enterprise software solutions and machine learning to provide enhanced process understanding and prediction capabilities. Also, Industry 4.0 concepts of cloud-based integration and connectivity to enable mobile data collection and aggregation. I also envision more connectivity between the supply chain and more end-to-end integration for advanced decision-making. Eventually, I see the industry becoming like the semiconductor industry in that it will be more "lights off," meaning automation practices have been implemented to the point that the facilities can run themselves without significant human presence.

What is your proudest professional accomplishment?

ROMERO I would say I am proud of my overall career path. I went from a bachelor's in chemistry to becoming an advanced manufacturing expert. I am proud that I have had, and continue to have, the strength and desire to be able to keep up with this dynamically evolving area of the industry, and that throughout this process I have developed a strong network that appreciates my background and trusts me and my skills. ›

JACOBSEN I am one of the youngest managers at NNE and I believe one of the reasons for this is how I have been able to learn and expand to keep up with how fast automation is growing.

DOR Building a great network of people that has enabled me to grow professionally as well as build amazing teams of individuals. I am also very proud of being part of a start-up team that began and grew a multimillion-dollar company.

What advice would you give someone interested in automation engineering?

ROMERO Never lose perspective of the physical world or process where the model will be applied. Any type of modeling or automation will require math skills, but the more knowledge one has of the process, the better one will be at performing their job duties.

JACOBSEN Students fresh from university don't seem to have a good grasp of input/output (I/O) and how controls work from the ground up. Programming PLCs is one thing but actually making the correct connections, programming the I/O points, and tying everything together to make a control system function as a whole is something that would be a great benefit.

DOR I feel there are two main types of individuals: those who are extremely focused in one area and whom I would advise to make sure they are doing what they love, and those who are more holistic in nature and like to know about multiple areas, whom I would advise to always continue seeking to learn new things to be able to improve their overall capability to increase productivity.

What do you wish you had been able to learn as an undergrad?

ROMERO More practical hands-on training. I learned a lot of math and theory but very little in terms of practical application.

JACOBSEN I also feel there was not enough practical training in my undergrad degree. Learning how the equipment actually functions from the standpoint of understanding where the numbers on a control screen are coming from would go a long way. More focus on that helps an engineer to question data and not just blindly trust numbers that are being displayed

DOR I would answer this more from the perspective of what skill set I feel is missing from recent graduates when they are looking for employment. I am always looking for good chemometricians, and there are very few students in the United States learning these skills in a practical way. Data is key, so the skill set required to make use of data that is being generated is crucial. ‹›

China's biological pipeline may take the lead

CHINA AND INDIA TARGET FUTURE GMP MANUFACTURING

Vicky Xia, Leo Cai Yang, and Eric Langer

China and India have demonstrated their capability in good manufacturing practice (GMP) manufacture of small-molecule drugs for decades. But production of biological therapeutics has, until recently, not been done to GMP standards due to the greater complexity of bioproduction and the need for highly trained staff, regulatory expertise, and quality management systems. This is changing, and both India and China have moved their domestic bioproduction forward rapidly with the intent of challenging US and EU dominance. It is not likely a question of if, but rather when these regions, which include nearly 40% of the world's population, will be manufacturing biologics for their domestic populations and global export as well.

Whether this happens in 5, 10, or 20 years, it is clear from our recent research that GMP export-quality biomanufacturing is in the sights of most biopharma facility managers in these regions. This article reviews our white paper research [1–2] comparing the Chinese and Indian biopharma industries' perceptions of their efforts to globalize, what is yet missing, and when success will be achieved.

The domestic markets for biologics in these two countries represent a remarkable opportunity, and domestic biologics manufacturing is clearly important for both health policy and economic reasons. But the payoff may be seen in future export opportunities, and both countries are attempting to create positive investment climates to expedite domestic biomanufacturing capabilities so they can evolve their competence to permit export to more lucrative markets in Europe and North America. This, of course, will require manufacturing to GMP standards.

We recently queried professionals at bioprocessing facilities in China and India to identify their current capabilities and ambitions for the

export of biological therapeutics. We interviewed 50 biopharmaceutical manufacturing executives in China and 104 executives in India. All were members of BioPlan Associates, Inc.'s Biotechnology Industry Council panel of regional and global bioprocessing experts. These surveys confirmed that both China and India are making efforts to become global bioprocessing centers.

Data about total biopharmaceutical manufacturing capacity (on-site bioreactor volume), drawn from BioPlan's Top 1,000 Global Biopharmaceutical Facilities Index [3] and directory of Asian biomanufacturers, [4] show that India and China today have relatively comparable manufacturing capacities. Both countries also have a number of facilities owned by major Western biopharmaceutical companies. There are very significant differences, however. Chinese companies tend to be more oriented toward development and investment in innovative domestic products, for example, while Indian companies are investing in Western facilities and pursuing a more international strategy.

FINDINGS: CHINA VS. INDIA

In our research, we assessed critical areas where Chinese and Indian biomanufacturing executives recognize they lack capabilities required to participate globally. These executives clearly recognize their companies' regional shortcomings and shared their perspectives on how they plan to move toward GMP export-quality bioprocessing.

Biopharmaceutical professionals in both countries believe they will achieve the required quality operations required by the United States, European Union, and other regions with stricter guidelines and enforcement of GMP, quality control, and documentation. In fact, nearly 90% of responding Chinese biologics managers indicated their companies plan to target global distribution of GMP-produced biologics within 10 years. Indian managers, in comparison, also recognize that they lack capabilities required to participate on the global stage. But among Indian biopharmaceutical professionals, 100% of biologics managers indicated their company plans to target global GMP production of biologics within 10 years.

Study respondents were asked to identify the top criteria for expanding their presence in global biopharmaceuticals. A country's overall "quality image," one of 17 tested in the survey, was deemed by almost 70% of Chinese survey respondents to be the most important criterion for competing globally in a GMP environment, with Chinese biopharmaceutical managers stating that overall quality image was a key weakness. Other criteria identified were:

- Overall quality image (68% selecting as a top attribute)
- More innovative biopharmaceutical pipeline (62%)
- Scientific/technical expertise (52%)
- Compliance track record/expertise (52%)

Figure 1. Chinese bioprocessing facilities: Objectives for biologics production, 2016 vs. 2026

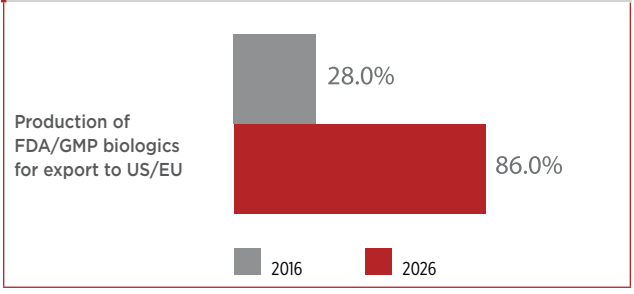


Figure 2. Indian bioprocessing facilities: Objectives for biologics production, 2016 vs. 2026

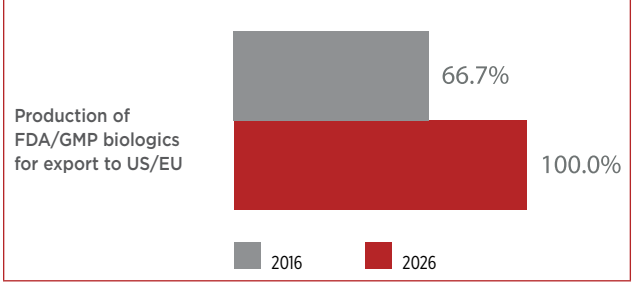


Table A: Comparison of biologicals, mAbs and the vaccine market in China (2014)

Category	Market size (USD)	Growth rate
Vaccines	$3.1 billion	8.3% (from 2010–2014)*
mAbs	$0.42–$0.96 billion	20.3%**
All biologicals	$6–8.5 billion	~20%***

* Ldhxcn.com
**0.42 is IMS data (2014), 0.96 is 2014 data from the Zhongkang CMH
***IMS estimates the market size as $6 billion; Livzon projects to be $7.2 billion

In comparison, fewer Indian than Chinese respondents—over 40%—perceived the country's quality image to be a key weakness in its ability to compete globally. Although image was, again, a top attribute, it was noted by a lesser percentage:

- Overall quality image (41% selecting as a top-five attribute)
- Scientific/technical expertise (37%)
- Audit results (35%)
- Timeliness/scheduling/reliability (33%)

We also asked respondents what should be done to ensure their domestic industry develops the systems required for global-quality biomanufacturing. This question was intended to outline perception of what is needed to become competitive in a GMP environment.

In China, over three-quarters of respondents mentioned that having the ability to develop a more innovative biological product pipeline, with better R&D competence, will help establish global competitiveness within 10 years.

- Innovative biologics/better R&D (76%)
- Improve legal/regulatory compliance (44%)
- Better quality management systems (20%)

China's pipeline development in recent years has shown rather rapid growth. In 2016 alone, the China Food and Drug Administration (CFDA) registered nearly 200 new biological pharmaceuticals entering clinical trials. BioPlan's own analysis shows over 170 monoclonal antibody (mAb) therapeutics alone under clinical development in China, including a number of biosimilars: CD20, HER2, EGFR, VEGF, and TNF-alpha.

In India, over one-third of respondents stated that having the ability to develop marketable, innovative biological products tops the list of they need to help establish global competitiveness within 10 years. These prerequisites may be challenging to build from the ground up in India, given the relatively limited availability of biologics R&D expertise. Options for acquisition of these innovations may exist, however. Required core competencies identified by the Indian biopharmaceutical manufacturers included:

- Innovation/R&D product pipeline
- Production quality improvements
- Education, expertise, skills
- Regulatory expertise/audits

In our studies we asked respondents to indicate their facility's primary objectives for biologics production today and in 10 years. In China today, 70% of biopharma facilities focus on production for domestic consumption. The Chinese biopharmaceutical industry is seeing relatively strong domestic demand as economic growth and expansion of national health insurance coverage creates demand. Multiple studies suggest the biological market in China will be the second-largest such market globally by 2020.

In 10 years, 86% of Chinese biopharma managers expect they will be focused on exporting to the United States and European Union. In other words, the great majority of Chinese biomanufacturers plan to produce biologics for both domestic and export consumption in 10 years (Figure 1).

Indian respondents are also primarily focused on production for domestic consumption (81%) today. In 10 years, however, the focus will have shifted from domestic production to production for exports, particularly biosimilars. And 100% agreed they would also be focused on export production for US and EU markets (Figure 2).

DISCUSSION

China appears to be better prepared for GMP export over the next 5 to 10 years. Chinese companies seem to be more oriented toward development of their own biological pipeline compared to India, perhaps due to bigger domestic market demand, government support, as well as more investment from the local venture capital industry. China's pipeline development, especially in mAbs, shows strong growth potential for biological therapeutics. Although China started rather late, it is making rapid progress. In 2014, the biological market in China was worth some $5 billion. According to Vincent Xie, former Director of CMC at Livzon mAbPharm, Inc., it is expected to grow to around $21 billion by 2020 at a compound annual growth rate of 20%.

Despite this, a major gap exists between China, the United States, and the European Union when it comes to prescribing mAbs as therapeutics. While mAbs are the largest class of biologics globally, they currently make

up only 7% of the Chinese biologics market, according to IMS Health. The gap may be due to several factors:

- The price of imported mAbs can be prohibitive to many Chinese patients and the national health insurance does not currently cover many of them.
- A lack of lower-cost biosimilar mAbs from domestic drug makers is bottlenecking demand. Biosimilar and bio-better drugs from domestic drug makers are more likely to be listed in the national health insurance list and more affordable to Chinese clients.

Domestic companies are actively filing for clinical trials of mAbs in China. The Chinese market has strong demand for mAb products, but, at present, a large proportion of this demand is being filled by imports from developed countries. China imported $950 million worth of mAbs in the first half of 2015, according to estimates by Zhongkang CMH and others. Many domestic drug makers are working to seize this opportunity for future growth. Dr. Zhou Xinhua, CEO of Genor BioPharma, stated that with expanding national health insurance coverage and reimbursement rates, combined with the patent expiration of many mAbs developed by multinational companies, the mAb market in China will increase rapidly in the near future.

As noted above, the CFDA reports that close to 200 drug makers had submitted applications for mAb clinical trials to its investigational new drug (IND) application process by the end of 2015. It is estimated that over 600 drug makers in China are planning, at some level, to have therapeutic mAbs in the development pipeline. By the beginning of 2016, over 280 mAb clinical trial applications had been filed with the CFDA, according to Pharmacodia.com. Among these, were 132 from multinational companies with 148 from domestic drug makers.

Contract research organizations or contract manufacturing organizations (CMOs) involved in biologics are also targeting international clients, some of which have therapeutic mAb projects under development. Innovent Biologics is representative of this category. The most ambitious Chinese companies are already conducting clinical trials in regulated markets; Genor BioPharma, for example, has started phase 1 clinical study of its anti-HER2 mAb in Australia, and Teruisi Pharmaceutical, an antibody-therapeutics company founded by returnee scientists (Chinese scientists returning to China after working abroad), also plans to file an IND for one of its projects in the United States this year. We expect to see a more robust biological pipeline from Chinese companies in the near future.

Government and industry are working together to support the development of the Chinese biological pipeline. While we see the concern related directly to China's limited R&D investments—especially insufficient investment in early-stage research on products and platforms—there have been signs in recent years of coordinated efforts to address the issue. In the past decade, China's Ministry of Science and Technology has undertaken several projects, including the National Mega-Project for Innovative Drugs program, which funds development of biological pipelines from domestic companies. In 2016, Biodiscover.com reported a total of 32 biological products (from all but four domestic pharmaceutical companies) were in the last round of evaluation for the megaproject program, among them 18

mAbs, three vaccines, and two cell-therapy programs.

Regulatory authorities in China have also pursued reforms in recent years and are planning additional reforms that will facilitate growth of a more innovative biopharmaceutical industry. These reforms are intended to speed up the evaluation and approval process for more innovative therapeutics. Such reforms are essential if the industry is to shift from biogenerics to more innovative biopharmaceuticals.

China also initiated reforms in 2015 to remove the regulatory restrictions on contract manufacturing in the pharmaceutical industry, which mandated that drug developers must also be in charge of the manufacturing of the drug products they have developed. This is no longer the case country-wide with a trial marketing authorization holder program under which holders of drugs with CFDA drug-approval numbers are required to market and take the responsibility for the drug products while having the option to either manufacture them on their own or use contract manufacturers instead. This reform not only provides growth opportunities for CMOs but also makes it possible for biotech companies that are drug research-intensive but lacking in manufacturing infrastructure or expertise to focus on pipeline R&D, as they are no longer forced to spend significant resources to develop their own production facilities.

Local venture capital firms in China are also helping biotech company growth with pipeline development. This source of funding is relatively new. In the past, venture capital investors in China tended to shun biotech companies, since due to their limited exit options such investments were not easily sold or liquidated. BeiGene's successful venture-capital-backed NASDAQ initial public offering and the first public offering in the United States by Hutchison Medi Pharma showed Chinese venture capital investors that exit can generate significant returns from biotech companies. Akeso Biopharma, an innovative biotechnology company founded in 2012 by a group of entrepreneurial returnees, for example, focuses on discovering and developing innovative biologics with international intellectual rights. The company got venture capital investment from Shenzhen Capital Group and CCB Principal Capital Asset Management Corporation and others in 2016 to develop a rich product pipeline targeting oncology plus autoimmune, inflammatory, and cardiovascular diseases. That same year, Qiming Ventures and Lilly Asia Venture invested in CanSinoBIO, a Tianjin-based biotech dedicated to developing an innovative vaccine pipeline. Analysts expect that exit routes via NASDAQ as well as China's stock market (specifically the China's Growth Enterprise Market) will attract more venture capital interest.

China's ambition in GMP exports of biologics differs from India's strategy of making investment overseas. As noted from our recent surveys, in 10 years 70% of Chinese biopharma facilities will focus on production for domestic consumption while the great majority, 86%, will be manufacturing for export to developed countries—a scenario made possible by China's GMP regulations, updated in 2010, which demand higher manufacturing standards. In early 2017, the CFDA also announced plans to replace the current five-year GMP certification cycle by a dynamic unannounced inspection system. These moves are intended to bring China's GMP code in line with European and American codes and regulations. Multinational pharmaceutical companies such as Boehringer Ingelheim and Pfizer Inc. are taking notice and have set up biologics manufacturing facilities in China. In fact, scarcely a month passes without a Chinese company announcing plans to build a biologics manufacturing center.[4]

India, in comparison, has long been home to many pharmaceutical companies that export small-molecule active pharmaceutical ingredients to regulated markets, but we do not find a similar trend for biologics. We are witnessing a reduction in foreign investment in India. At the same time, major Indian biopharmaceutical manufacturers are increasingly investing more overseas, often by expanding their manufacturing capacity and distribution networks in the United States and European Union, and by building new biopharmaceutical manufacturing facilities in other Asian countries. According to recent reports, Indian companies invested $1.5 billion in 2015 and more in 2016 in overseas facilities rather than investing in India's domestic infrastructure. As an example, Aurobindo Pharma, which makes most of its drugs in India, is planning a second US facility. Its first US plant was established in August 2016, and the company will build a second sterile-injectables plant in New Jersey. In addition, due to increasing regulatory pressure from the FDA over quality problems in India, some companies are planning to enter the US market with US facilities and US-trained staff as it is seen as easier than trying to achieve the level of quality acceptable to the FDA in India.

SUMMARY

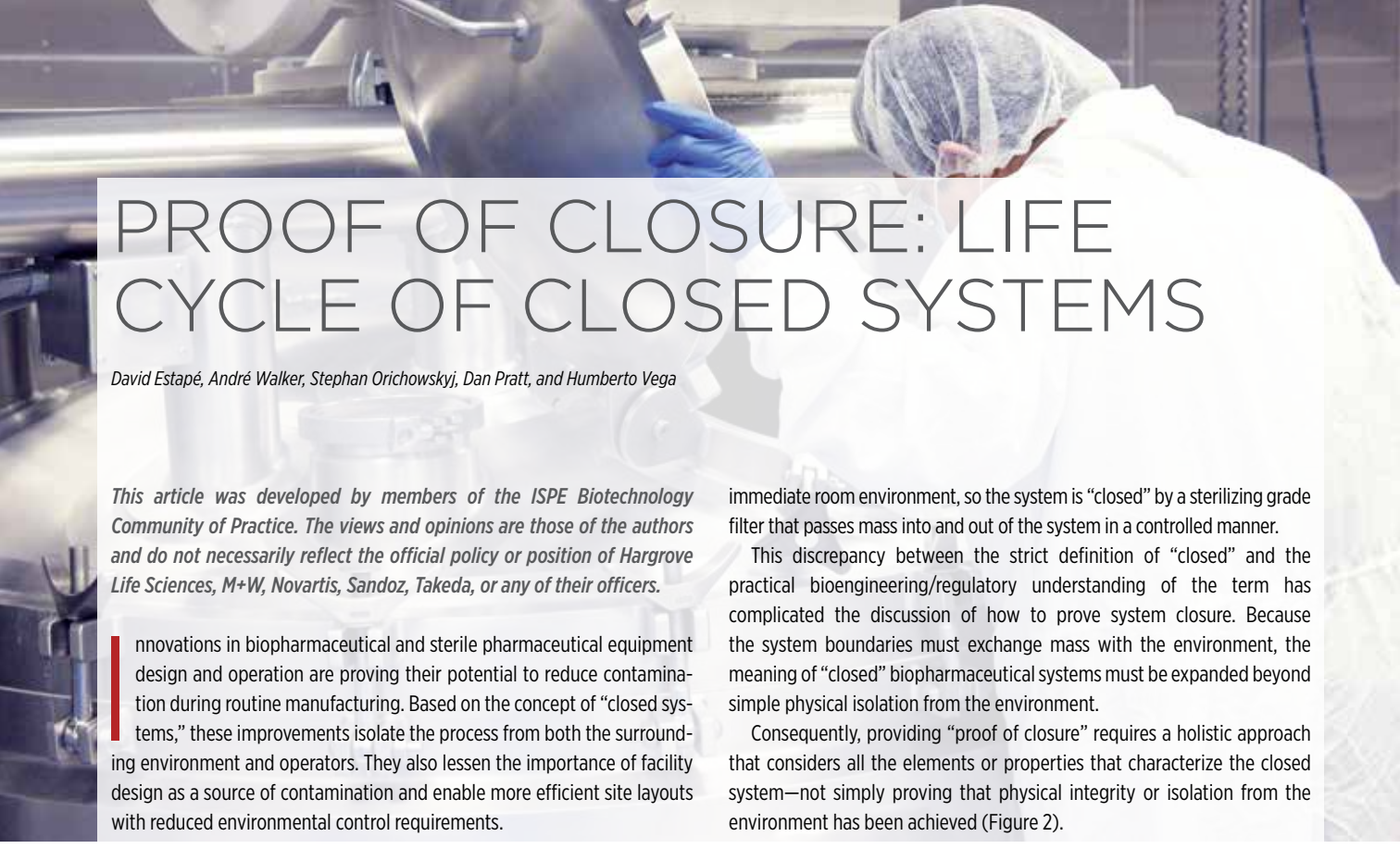
Domestic demand in China and India for biopharmaceuticals has been growing, by various estimates, by between 15% and 20% annually, due to rising incomes, access to health care and insurance, and the availability of more products. Biopharma companies, especially those in China, are ramping up operations to serve emerging domestic markets, which will help develop the quality systems and competence required to enter Western markets. Biosimilars are beginning to play a role in India's bio-industry development as several large companies now manufacture a handful of GMP-grade products approved in Western markets. In terms of profitability, however, a pipeline of biosimilars will not provide the same level of return that domestic innovative biologics would bring.

China continues to take steps toward aligning with global GMP requirements. However, China is not currently, and likely in the future will not be, among the lowest-cost destination countries for biopharmaceutical manufacturing. Our studies indicate that costs for the manufacture of typical mAb biosimilars in developing countries will continue to be higher than large-scale Big Pharma reference product facilities and typical new facilities coming online (e.g., Samsung and Celltrion in South Korea).

The Chinese biopharmaceutical industry appears to be investing in long-term global opportunities in biologics, including in bioproduction. With domestic Chinese manufacturers' rational view of what the necessary investments in R&D, quality and regulatory systems, infrastructure, IP reform, health care, and workforce development will be within 10 to 20 years, it is likely China's biologics may compete effectively in major markets, including the United States and Europe. ‹›

Portions of this article were originally published as:

1. BioPlan Associates, Inc. "China's Advances in Global Biopharma and Bioprocessing: A 10-Year Projection on Need for Innovation and Quality Improvements." White paper, January 2016.
2. BioPlan Associates, Inc. "India's Importance to the Global Biopharma Industry: Quality Improvements Targeting International Markets; Expect Production by 2025 to Impact Global Bioproduction." White paper, October 2016.



PROOF OF CLOSURE: LIFE CYCLE OF CLOSED SYSTEMS

David Estapé, André Walker, Stephan Orichowskyj, Dan Pratt, and Humberto Vega

This article was developed by members of the ISPE Biotechnology Community of Practice. The views and opinions are those of the authors and do not necessarily reflect the official policy or position of Hargrove Life Sciences, M+W, Novartis, Sandoz, Takeda, or any of their officers.

Innovations in biopharmaceutical and sterile pharmaceutical equipment design and operation are proving their potential to reduce contamination during routine manufacturing. Based on the concept of "closed systems," these improvements isolate the process from both the surrounding environment and operators. They also lessen the importance of facility design as a source of contamination and enable more efficient site layouts with reduced environmental control requirements.

PRODUCTION AS A CONTINUUM

Closed production can be considered a continuum of closed systems (Figure 1), each of which can be further divided into subsystems. The interfaces between systems are integral parts of the proof of closure; each one should be evaluated individually to demonstrate that it does not break the integrity of the production process. Manufacturers using closed systems must demonstrate not only that a system is ready for use, but that it will remain closed during routine production.

Separating the entire production into multiple systems reduces the complexity of this analysis. Moreover, it allows the closure strategy to be adjusted (e.g., engineering, validation) to specific characteristics of the unit operation, considering the product requirement at each production step.

This article provides practical guidance on closed systems, focusing on:

- Managing process closure across unit operations; closed production as a continuum of connected closed systems
- Understanding closed systems, including characteristics, life cycle, elements, and materials
- Documenting the strategy that ensures system closure

UNDERSTANDING CLOSED SYSTEMS

If you ask people in the biopharmaceutical community to describe a closed system, they'll more than likely tell you it's a system that protects a product or process from the environment beyond the system boundaries or, more precisely, a system that does not exchange matter with its surroundings. The latter definition is analogous to the container closure concept already established for the integrity of primary packaging (e.g., vials, cartridges, ampules) of final drug product. It would be difficult, however, to apply this analogy to a bioprocess system, which always exchanges materials with the environment. Even if we were to focus only on isolating a rudimentary system from the surrounding room environment, the container closure analogy is not sustained. As an example, a closed holding tank must "breathe" air from the immediate room environment, so the system is "closed" by a sterilizing grade filter that passes mass into and out of the system in a controlled manner.

This discrepancy between the strict definition of "closed" and the practical bioengineering/regulatory understanding of the term has complicated the discussion of how to prove system closure. Because the system boundaries must exchange mass with the environment, the meaning of "closed" biopharmaceutical systems must be expanded beyond simple physical isolation from the environment.

Consequently, providing "proof of closure" requires a holistic approach that considers all the elements or properties that characterize the closed system—not simply proving that physical integrity or isolation from the environment has been achieved (Figure 2).

Characteristics

There are three criteria that define the readiness of a closed system: bioburden level, cleanliness level, and degree of environmental segregation or integrity. Bioburden refers to the level of viable microorganisms; cleanliness is the level of nonviable chemical or particulate residue. Controlling bioburden and cleanliness prevents contamination that could affect the process or product going through the system. The degree of environmental segregation reflects the system's ability to maintain cleanliness and bioburden levels before and during use, and to control release of contaminants to the environment after use.

Bioburden and cleanliness levels should be defined per allowed limits for the product that will be manufactured or process that occurs in the system. For example, cell culture requires axenic conditions (containing only a single, intended organism) so bioburden control is critical. In contrast, this is not the case in early purification steps, but requirements again return to stringent levels in the final formulation tank.

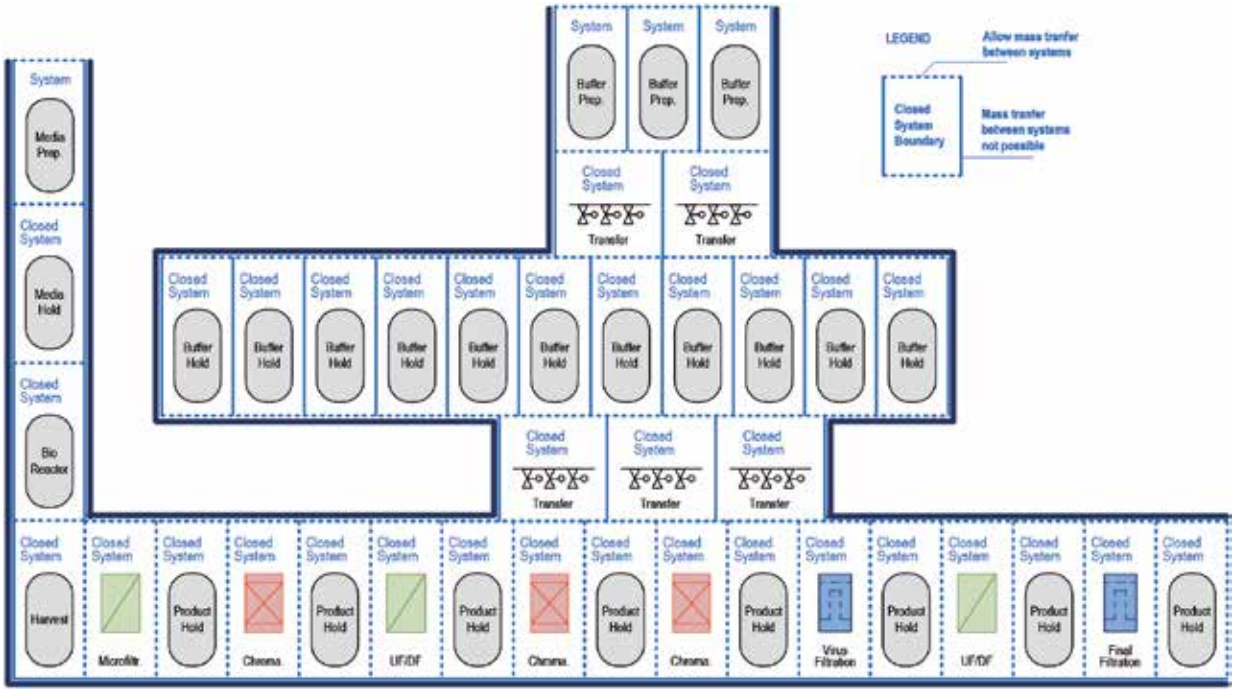
Similarly, system integrity should ensure the level of environmental isolation necessary to maintain required levels of bioburden and cleanliness during the system's life cycle. For example, although a stainless steel bioreactor should be pressure tested before each use to ensure integrity, a purification intermediate hold tank could be tested at extended intervals or after maintenance, because process requirements for axenic cell culture are more stringent than for low-bioburden purification.

Taken together, bioburden, cleanliness, and integrity define the closed status.

System closure = f(bioburden, cleanliness, integrity)

If for any reason it is not possible to guarantee or maintain one characteristic, then it is not possible to claim that the system is closed. A physical breach may have affected system integrity, or an addition may have introduced a

Figure 1: Closed production process as a continuum of connected closed systems:



contaminant. Other failures, such as ineffective transfer line steaming, may have occurred as the system was being prepared for closure. This highlights the importance of considering the entire life cycle of a closed system.

Life Cycle

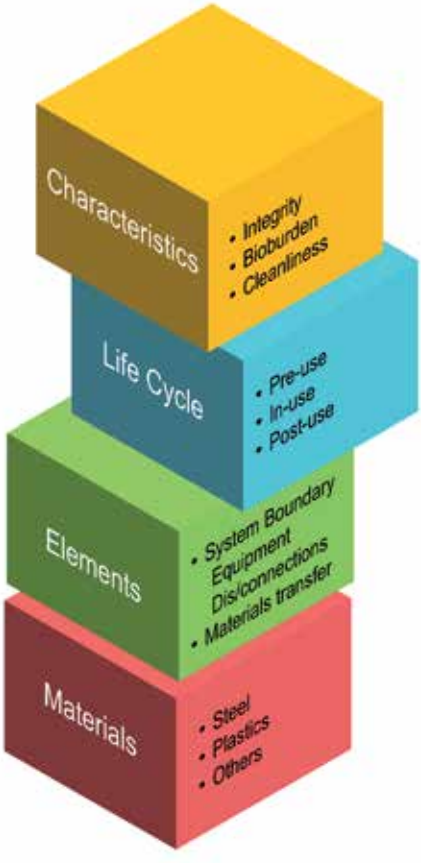
A closed system is assembled and prepared from subassemblies, components, or materials in a manner that achieves a state of readiness (closure) prior to normal process operation. Closure is maintained during the process until material is transferred to the next unit operation. At this point the system either remains closed and stays idle, or is disassembled and no longer closed.

To confirm system closure, a variety of process parameters/conditions are used or tests are conducted over this entire life cycle, which has three phases: pre-use, in use, and post-use. Cleanliness, bioburden, and integrity must be controlled at each step. This is achieved through activities that extend beyond cleaning, sanitization, and assembly.

It may seem logical to associate achieving closure to the pre-use phase, and maintaining integrity to the in-use phase, and to see the post-use phase as somewhat irrelevant. Reality, however, is much more complex. For example, connections performed during the in-use phase will require cleaning and bioburden reduction to reestablish closure, and the integrity of a chromatography column must be maintained both during (in use) and after processing (post-use). The proposed three-phase life cycle is a good way to understand that the closed system must be created, used, and removed from use in a controlled manner, according to the guidelines below (Figure 3):

Pre-use: System is prepared to the required level of integrity, cleanliness, and bioburden. Cleaning may be performed before and/or after assembly, or completed post-use and maintained by controlled storage conditions. Sanitization or sterilization is usually the last step before use; if the system

Figure 2: Closed system breakdown



is not used immediately, the closed state must be protected. The important concept is understanding when things are clean, how the clean state is maintained, and how assembly may affect that cleaned state.

In use: The closed system is in production. This phase may also be called "closed processing," even though in many cases mass is transferred across the system interface (e.g., through sterilizing grade filters). During connections and disconnections to expand or retract system boundaries, materials are added or removed in a safe manner to avoid contamination from the environment, operators, or materials.

Post-use: The process stream is no longer in the system. Measurements (e.g., filter-integrity tests, confirmation of noncontamination) should verify that closure was maintained during processing. The environment should be protected from residue in the equipment through careful decontamination processes or physical/temporal segregation. If the system or its components are cleaned and sanitized, storage and/or transport should protect their closure. Single-use systems or components can be discarded.

Elements

When analyzing proof of closure, it is important to consider all parts of the system that play a role in achieving and maintaining closure (acceptable bioburden, cleanliness, and integrity). One approach is to identify the closed-system boundaries and mass transfers required during operation. To facilitate this analysis, system boundaries could be further divided into equipment and connections/disconnections.

Methods must be developed to ensure equipment integrity and prevent uncontrolled material exchange with the surroundings. It is possible, for instance, to conduct a pressure hold test to ensure that there are no losses through seals and valves in a stainless steel tank.

When connecting or disconnecting systems it is necessary to prove that there is no risk of contamination. For instance, a challenge test of a single-use sterile connector can confirm that no contamination occurs in the process.

Correct material addition and removal must also be verified. Integrity testing of sterilizing grade vent filters on tanks, for example, verifies controlled addition and/or removal of air, and quality control testing ensures raw materials are fit for purpose. Following this structure allows a more systematic approach to a risk assessment for system closure.

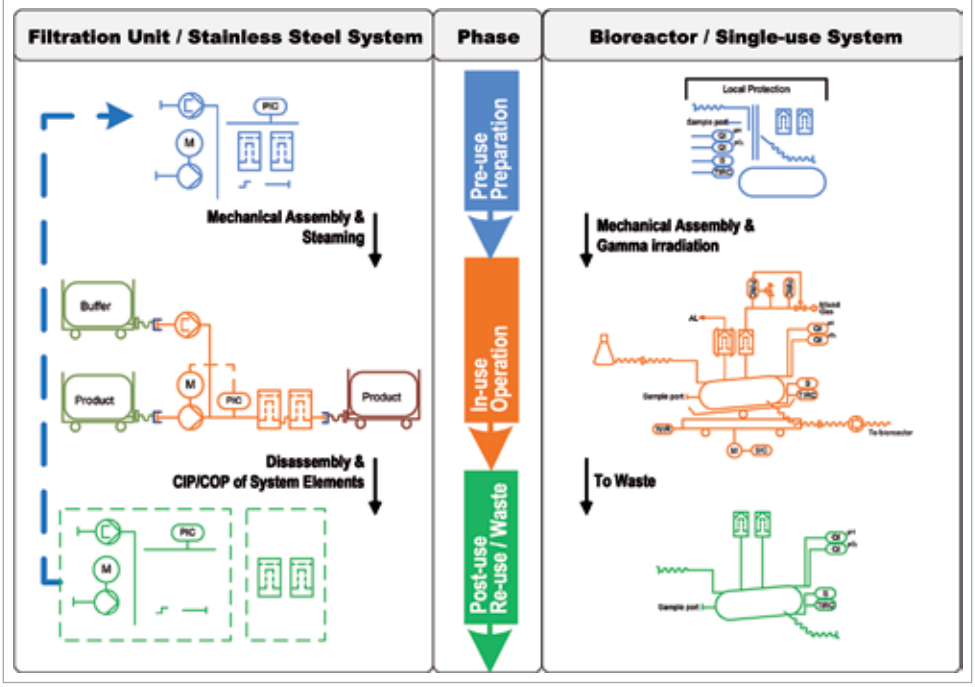
Materials

Materials of construction have a major influence on how closure is attained, maintained, and proven. The ISPE *Biopharmaceutical Manufacturing Facilities Baseline® Guide* (2nd edition) presents single-use bags as an example of a "closed system." Multiuse stainless steel systems are defined as "functionally closed," meaning the system is open and "rendered closed" through cleaning, sanitization, and/or sterilization processes.[1] Single-use systems are comprised of materials and components that are manufactured and assembled in a clean environment at the supplier's facility and then gamma irradiated to reduce bioburden. Although these are very different processes, closure occurs in both cases and must be understood and controlled.

Single- and multiuse systems have distinct life cycles. In the pre-use phase, the single-use system is brought to a state of closure at the supplier's facility. The final user is responsible for qualifying the supplier through a quality agreement and inspections. In contrast, multiuse systems are under direct control of the manufacturing site, at which closure is attained through controlled procedures.

In-use material transfers between steps require a connection that protects the process from the environment. Single-use systems can employ manual aseptic connectors or automated sterile tubing welders to achieve closure. Multiuse stainless steel systems require cleaning and bioburden reduction, which can rely on manual or fully automated procedures. Hybrid systems, in which there is an interface between a single- and multiuse system, rely on disposable valve assemblies that can be steamed at the interface between the two.

Figure 3: Closed system life cycle



In the post-use phase, the single-use system will be discarded but the multiuse system will go through disassembly and cleaning procedures.

In all cases, regardless of the materials of construction, each system must be closed through controlled procedures and operated throughout its life cycle in a manner that fulfills the system closure characteristics required for the process. The techniques utilized to achieve, maintain, and prove closure clearly diverge due to the difference of the material properties.

PROOF OF SYSTEM CLOSURE

Since system closure encompasses three attributes (cleanliness, bioburden, and integrity), proving system closure requires much more than ensuring a system has sufficient isolation from the environment. Methods for ensuring all three attributes must be in place for each stage of the system's life cycle. A direct measure of system closure for each one is ideal—such as a filter-integrity measurement, or pressure hold test on stainless equipment. These are completed for each use of the system or continuously during use.

Indirect measures are also employed to confirm closure, especially in cases where a direct measure is not possible. Indirect measures are indicative of system closure, but do not verify it. Like direct measures, they occur before each use or continuously during use. Typical cell culture health parameters (e.g., viable cell density), for example, are indicative of correct sanitization, and a manual or automatic verification of cleaning or sanitization equipment performance (time, temperature, concentration) indicates that the cleaning and/or sanitization were likely effective.

Finally, quality system methods ensure correct system closure. These consist of validation studies and vendor quality agreements documenting that the systems and materials utilized are fit for use.

Taken altogether, a structured and complete account of direct, indirect, and quality system methods should form a web of confidence and sufficient proof of closure for a given system. A partial list of typical direct, indirect, and quality system verifications is shown in Table A. A suggested format for documenting these methods, shown in Table B, contains the following elements:

1. Describe the system to be assessed. A variety of scopes are possible, ranging from a single component (e.g., sterile connector), to a complete system (e.g., bioreactor with attached feed vessels).
2. Describe each part of the system life cycle (pre-use, in use, post-use):
   a. Describe the sequence of operation for each phase of the system life cycle
   b. List the materials that must pass through the system boundary
   c. Define the system boundary
3. Itemize proof-of-closure activities:
   a. For each part of the system life cycle
   b. For each closure attribute (cleanliness, bioburden, integrity)

Proof of Closure Matrix

This proof of closure matrix is an invaluable tool for risk assessments, investigations, and audits. It also aligns well with the "closure analysis" described in Section 4.4.1 of the ISPE *Biopharmaceutical Facilities Baseline Guide*. The matrix is the natural outcome of phases 1 and 2, where the system is defined, risks identified, and control measures documented. It provides succinct guidance for the risk-rating assignment in phase 3, and data to justify the assessment of residual risk via the fault tree analysis presented in the Guide.

Once completed, the closure matrix retains a lasting utility. It provides a focal point for deviation investigations, especially those dealing with an excursion of in-process bioburden or potential cross-contamination in dual-product facilities. It facilitates hazard and operability studies and other risk assessments for both new facilities and retrofits; it lets technolo-

gy-transfer teams determine if new processes are compatible with existing facilities, and helps compose procedures for new processes. At a license holder's discretion, it could also be used to justify operations to external auditors.

In summary, to reap the benefits of closed processing systems, firms must prove that the equipment and operations in use isolate the process from the environment. The natural inclination to rely merely on measures and procedures that ensure system integrity is insufficient; the system's life cycle and cleanliness and bioburden attributes must also be considered. A thorough assessment of a system's closure must consider the following:

- Closure = *f* (cleanliness, bioburden, integrity), i.e., closure is attained only when a system has acceptable levels of cleanliness, bioburden, and physical integrity.
- Closed production is performed in a sequence of closed systems.
- Closed systems have a life cycle: pre-use, in use, post-use.
- Despite being "closed," systems must permit the addition, removal, and transfer of mass in a way that maintains system closure.
- Different processes have different closure requirements; the system should meet those requirements.

Table A. Direct, indirect, and quality system proof of closure measures

Direct	Indirect	Quality System
□ Visual inspection of system integrity □ Filter integrity test □ Pressure hold test □ In process bioburden sample □ Confirmation of noncontamination □ Adventitious virus testing □ Helium leak testing □ Conductivity (e.g., real-time CIP return)	□ Verification of cleaning/sanitization cycle □ Cell culture health measures □ Positive pressure monitoring □ Pre-inoculation media hold verification □ Cleaning record review	□ Cleaning validation □ Sanitization/sterilization validation □ Vendor quality agreements □ Clean hold validation □ Challenge testing of sterile connectors □ Media hold and other process simulation studies □ In-process hold simulation studies □ Leachables/extractables testing □ Destructive incoming testing for integrity/performance

Table B: Proof of closure matrix template

System Description	
System	
Materials	
Cleaning methods	
Bioburden reduction	
Sequence of Operation	
Pre-use	
In use	
Post-use	
Mass Transfer	
Pre-use	
In use	
Post-use	
System Boundaries	
Pre-use	
In use	
Post-use	

Attribute	Proof Type	Method	Pre-Use	In Use	Post-use	Remarks
Environmental segregation	Direct					
	Indirect					
	Quality system					
Cleanliness	Direct					
	Indirect					
	Quality system					
Bioburden	Direct					
	Indirect					
	Quality system					
General						

- Creating and proving closure differs by equipment type, connections to adjacent systems that must be made, and materials of construction.
- Proof of closure includes direct and indirect measures of closure, as well as quality system activities.

When this assessment has been completed for all unit operations and systems, it is possible to document a facility-wide proof of closure strategy matrix that will prove a useful reference for a variety of activities within the engineering, development, and operations functions. ‹›

EXAMPLES

This section presents sample proof of closure matrices for two equipment types and unit operations. It illustrates the concepts presented in this article, but is not comprehensive.

Nutrient hold tank, stainless steel vessel, automated CIP & SIP

Consider a simple stainless steel tank for holding a cell culture nutrient feed. It is a fixed tank with automated clean in place (CIP) and steam in place (SIP), fed by a filter transfer skid, and connected to the bioreactor by a steamed transfer line. It has a 0.2-micrometer (µm) vent filter, CIP and SIP inlets, bottom drain, and a variety of ports for sensors and sterile sample devices.

Pre-use activities include assembly of any cleaned-out-of-place components and installation of the spool piece that enables vent-filter-line CIP. Cleanliness level is created through the automated CIP process, but the vent filter spool piece must be replaced with the filter housing, which is cleaned out of place, assembled, integrity tested, and then dried with compressed dry air. Automated SIP establishes the bioburden level, which is protected by maintaining the system at a positive pressure.

When in use, the system receives filtered nutrient from the filter transfer skid through a cleaned and sterilized transfer line. Bioreactor feed is delivered through a similar cleaned and steamed transfer line and is controlled by an automated on/off diaphragm valve. Motive force is provided by isolating the vent filter and pressurizing the tank headspace with sterile, filtered, compressed air.

Post-use the system is drained, the vent filter removed and replaced with a spool piece, and a CIP cycle completed.

What direct, indirect, and quality system measures should be in place to ensure closure of this simple stainless steel system? If the focus is on system integrity (segregation from the environment) then a pressure hold test is a common direct measurement, although acceptance criteria are likely to be set at values typical for that system rather than a defensible engineering study that relates pressure loss to meaningful system integrity. Another is a documented system walk down. An in-use failure of the system boundary might be indicated by leakage.

Recall that cleanliness and bioburden levels must also be met to prove closure. Although direct measurement of these attributes could be obtained through sampling, this is impractical and increases risk to the system closure. In this case, quality-system-based assurance verifies closure through validation of the CIP and SIP processes, including sterile hold and clean hold studies. During use, indirect measures such as vessel pH monitoring and cell culture health will indicate that closed-system attributes are maintained acceptably (Figure 4, Table C).

Single-use bag

Consider a simple single-use bag assembly that will be used to deliver cell culture nutrient to a bioreactor. It has an inlet tube with integral sterilizing grade filter, outlet tube with sterile connector, and the entire assembly is gamma irradiated to control bioburden. The inlet tubing is installed in a peristaltic pump and connected to a mix tank containing the nutrient solution. The pump provides the motive force to move the nutrient solution through the sterile filter into the bag. The inlet tubing is then thermally sealed near the bag and the sterilizing filter assembly removed. After transport to the bioreactor, the outlet tubing is installed in a peristaltic pump and connected to a matching sterile connector on the bioreactor. Pump speed is controlled over several days to meter the nutrient into the cell culture as indicated by procedure and culture health. Once depleted, the outlet tubing is disconnected from the bioreactor and the bag discarded.

System boundaries are the bag wall, tubing walls, sterilizing filter, and sterile connector. The mass that must transfer across the boundary is the nutrient solution, which enters through the sterilizing grade filter and leaves through the outlet tubing sterile connector. Pre-use (assembly) is completed by the vendor, where the levels of cleanliness, bioburden, and environmental segregation are established. In-use procedures and technology (sterile connectors, automated tubing sealers) maintain environmental segregation and thus cleanliness and bioburden levels. Post-use, the benefit of single-use technology is most evident, as the bag assembly is simply discarded once the integrity is confirmed as part of its removal—e.g., there is no evidence of leaks or damage, proper disconnect procedure is typically confirmed by visual inspection (Figure 5, Table D).

Figure 4: Nutrient hold tank system

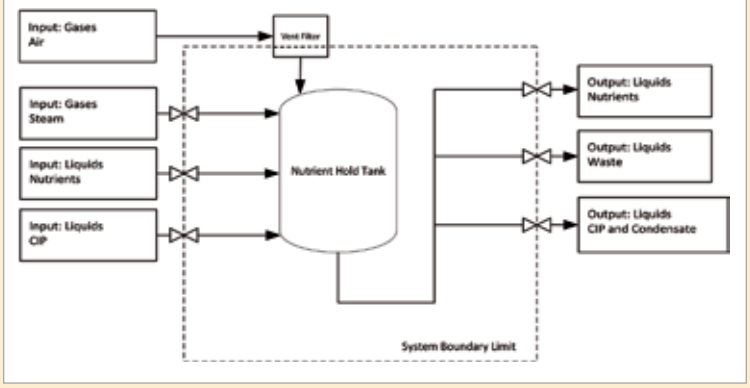


Figure 5: Nutrient hold single-use bag system

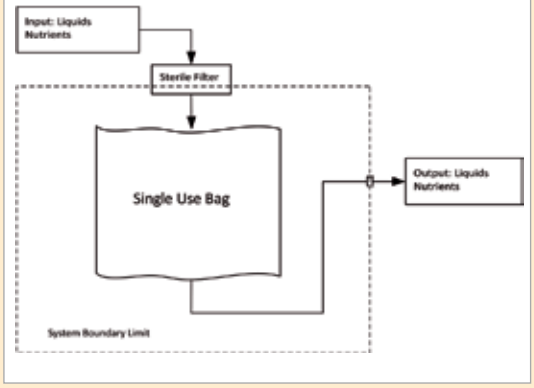


Table C: Proof of closure matrix for a nutrient hold tank

System Description	
System	Nutrient hold tank including inlet from filter transfer skid and outlet to bioreactor
Materials	Stainless steel vessel, Teflon elastomer valve closures, sterilizing grade filters (vent and liquid inlet), Viton O-rings
Cleaning methods	• Some components cleaned out of place with automated ware washer • Automated CIP of vessel with spool pieces in place of filter housings
Bioburden reduction	• SIP of assembled vessel
Sequence of Operation	
Pre-use	Assemble any components cleaned out of place. Install spool pieces enabling CIP of the vent filter line and inlet transfer line. Run automated CIP process. Replace spool pieces with vent filter assemblies cleaned off-line, with tested and dried filter installed. Run automated SIP. Maintain at positive pressure during cool down with filtered compressed air and/or condensate.
In use	Receive filtered nutrient from the filter transfer skid through the transfer line. Close transfer line valve after transfer. Maintain vessel at slight positive pressure. Feed the bioreactor as required through automated on/off diaphragm valve. Motive force is provided by tank positive pressure.
Post-use	Isolate from the tank from the upstream and downstream systems. Vent to atmospheric. Remove filter assemblies and replace with spool pieces. Post-use CIP vessel and maintain at slight positive pressure. Integrity test filter assemblies and then clean out of place.
Mass Transfer	
Pre-use	• Steam during SIP • Clean air to maintain vessel pressure post SIP
In use	• Nutrient addition from filter transfer skid through sterilizing grade filter • Nutrient removal through the automated diaphragm valve • Air (room or pressurized clean, dry, oil free) in and out of vent filter as tank level changes or to maintain desired tank pressure
Post-use	• CIP fluids and air blow down
System Boundaries	
Pre-use	• Components cleaned, assembled, or sanitized out-of-place that are protected during storage and transport. • Open ports, fittings, or transfer lines protected from the environment After SIP: • Stainless vessel walls, inlet piping from filter skid, outlet piping to bioreactor • Valves at sterile boundary, sterilizing grade final filter of filter skid, sterilizing grade filter on vent
In use	• Same as pre-use • After tank filling: system contracts with closing of the inlet line isolation valve
Post-use	• Components removed from the vessel to be cleaned out of place are managed to avoid release of process soils to the facility. • Components cleaned, assembled, or sanitized out of place are protected during storage • Open ports, fittings, or transfer lines on the vessel must be protected from the environment

Attribute	Proof Type	Method	Pre-Use	In Use	Post-use	Remarks
Environmental segregation	Direct	Visual inspection	X	X		
		Filter integrity test	X		X	
		Pressure hold test	X			
		System boundary, Confirm Valve Position		X		
	Indirect	Human factor error proofing	X	X		
		Positive sys press control	Post SIP	X		
	Quality system	2nd visual inspection	X			
Cleanliness	Direct	Visual inspection	(1)		X	(1) Per expired clean hold
		Conductivity test			X	
	Indirect	E/L studies	(2)			(2) Leachables and extractables could be seen as an external contaminate
		Automated cleaning	(1)		X	(1) Per expired clean hold
		Manual cleaning			(3)	(3) Possible manual cleaning of spare parts
	Quality system	Cleaning validation	(1)		X	(1) Per expired clean hold
		Maximum clean hold time	X			
		Cleaning record review	(1)		X	(1) Per expired clean hold
		Maximum soiled hold time			X	
Bioburden	Direct	N/A				
	Indirect	Automated sanitization/sterilization	X			
		Cell culture health/visual inspection		X	X	
		Process performance/parameter trending		X		
		Confirm noncontaminated samples			X	
	Quality system	Sanitization/sterilization validation	X			
		Sanitization/sterile hold studies	X			
General		SOPs	X	X		
		Operator training	X	X		
		SOP verification	X	X		

Table D: Proof of closure matrix for a nutrient hold single-use bag

System Description	
System	Single use: media/nutrient sealed sterilized (gamma-irradiated) bags
Materials	Various polymers in the bag, tubing, filter, and fittings.
Cleaning methods	Manufactured in environmentally controlled rooms at the supplier.
Bioburden reduction	Gamma irradiation, certified sterile.
Sequence of Operation	
Pre-use	At the bag vendor, polymer films are fused into a multilayer sheet. The sheets are assembled into bags with tubing, filters, and fittings. The filter is integrity tested and dried before assembly. Welding process is validated. Assembly is gamma irradiated using validated sterilization process. Bag is shipped and stored according to procedures and expiration date assigned.
In use	Remove bag from shipping container and place bag in support structure. Clamp outlet tubing. Connect inlet tubing to mix vessel through peristaltic pump. Fill bag with nutrient through 0.2 µm sterilizing grade filter. Thermal seal inlet tubing near bag and remove filter. Connect liquid outlet to bioreactor through sterile connector. Install tubing in peristaltic pump. Feed bioreactor as required.
Post-use	Disconnect from bioreactor. Confirm integrity of bag (e.g. no evidence of leaks or damage, proper disconnect procedure.) Remove excess material in a controlled manner. Remove filter and discard bag. Integrity test filter.
Mass Transfer	
Pre-use	None
In use	Nutrient/media flows in through the sterilizing filter and out through the sterile connector line
Post-use	Residual or used materials removed from the bag before disposal
System Boundaries	
Pre-use	Bag, sterilized tubing from bag to 0.2 µm liquid inlet filter, sterilized tubing from bag to liquid outlet sterile connector
In use	Filling: no change from pre-use. Discharge to process: bag system boundary connected to bioreactor system boundary
Post-use	Aseptic disconnect or sealing of tubing while disconnecting the bag from the bioreactor. Maintain system integrity until controlled discharge of residual material.

Attribute	Proof Type	Method	Pre-Use	In Use	Post-use	Remarks
Environmental segregation	Direct	Visual inspection	X	X	X	
		Filter integrity test	X		X	
	Indirect	Human factor error proofing		X		
		Use of validated dis/connectors		X		
	Quality system	Dis/connectors validation		X		
		Training and SOPs	X	X	X	
		Handling and housekeeping procedures	X	X	X	
		2nd visual inspection	X	X	X	
		Vendor quality agreement	X			
		Certificate of analysis/conformance	X			
Cleanliness	Direct	Visual inspection	X			
	Indirect	E/L studies	(2)			(2) Leachables and extractables could be seen as an external contaminate
	Quality system	Vendor quality agreement	X		X	
		Certificate of analysis/conformance	X			
		Qualified environmental controls at supplier	X			
		Training and SOPs	X	X	X	
		Handling and housekeeping procedures	X	X	X	
Bioburden	Direct	N/A				
	Indirect	Sanitization/sterilization by supplier	X			
		Cell culture health/visual inspection		X	X	
		Process performance/parameter trending		X		
		Confirm noncontaminated samples		X	X	
	Quality system	Sanitization/sterilization validation	X			
		Sanitization/sterile hold studies	X			
		Vendor quality agreement	X			
		Certificate of analysis/conformance	X			
		Qualified environmental controls at supplier	X			
		Training and SOPs	X	X	X	
		Handling and housekeeping procedures	X	X	X	
General		SOPs	X	X	X	
		Operator training	X	X	X	

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THE ENGINEER'S ROLE IN THE BIOPHARMACEUTICAL SUPPLY CHAIN

About the authors

John Balchunas is Assistant Director, Professional Development Programs, at North Carolina State University's Biomanufacturing Training and Education Center (BTEC), where he has responsibility for program management, business development, and partnership. Balchunas previously served as the director of workforce development for the North Carolina Biotechnology Center, an internationally recognized nonprofit corporation charged with creating jobs through support of research, education, and business. In an earlier career, John worked as a technical writer in the biotechnology and medical diagnostic industries. John holds a master of science degree in technical communication and a bachelor of science degree in microbiology from North Carolina State University.

Chris Smith, an ISPE member since 2014, serves as Graduate Programs Coordinator and Instructor of two graduate-level courses at North Carolina State University's Biomanufacturing Training and Education Center (BTEC). He has been involved with developing BTEC's academic programs and increasing industry ties since joining BTEC in 2011. Smith holds a master of science degree in molecular physiology and an MBA in marketing; he currently serves as the NCSU Student Chapter ISPE Faculty Advisor.

Lucas Vann manages the automation and engineering group at North Carolina State University's Biomanufacturing Training and Education Center (BTEC). He has over 15 years of experience in upstream process development, scale-up and automation. He is founder of Biozaivan LLC, a consulting company specializing in advanced automation, process development, data analytics, and predictive maintenance and control. Vann leads the process analytical technology initiative at BTEC and is currently completing his PhD (ABD) in bioprocessing at North Carolina State University. He holds bachelor's and master's degrees in biosystems engineering from McGill University in Montreal, Canada.

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About the authors

Vicky Qing Xia Project Director, BioPlan Associates, has a master of science degree in biology from the University of Texas–Houston, Health Science Center, Graduate School of Biological Science, and an MBA from the University of Pittsburgh. She has experience in consulting, business development, as well as alliance management in China's biopharmaceutical industry. Her expertise includes developing research and analysis on multiple global market segments, and she has managed a team of industry experts and projects.

Leo Cai Yang, Project Manager at BioPlan Associates, has business development experience in biotech and pharmaceutical segments and 10 years in market research. He graduated from East China Normal University with a bachelor's degree in biotechnology in 2006, and has worked with equipment manufacturers in pharmaceutical and medical device industries in Switzerland, Austria, and Germany. He has also project-managed studies involving new biopharmaceutical technology applications in China, including analysis and strategy development.

Eric S. Langer is President and Managing Partner at BioPlan Associates, Inc., a biotechnology and life sciences marketing research and publishing firm established in Rockville, Maryland, in 1989. He is editor of numerous studies, including "Biopharmaceutical Technology in China," "Advances in Large-Scale Biopharmaceutical Manufacturing," and many other industry reports. He can be contacted by email at elanger@bioplanassociates.com.

PROOF OF CLOSURE: LIFE CYCLE OF CLOSED SYSTEMS

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About the authors

David Estapé, an ISPE member since 2007, is Technology Manager at the Global Life Sciences & Chemicals Business Unit of M+W Group, a leading global engineering and construction partner for technology-based clients in segments like pharmaceutical and biotechnology. Estapé holds a PhD in chemical engineering from the University of Barcelona, Spain. He has been at M+W Group since 1996. He has over 20 years international experience in facility design and GMP consulting within the biotech, vaccine, and blood plasma pharmaceutical sectors for start-ups to lead pharmaceutical companies. His corporate function in the M+W Group focus on strategic developments in the different areas worldwide, technology transfer, regulatory requirements and new technologies.

André Walker, BSChEng, CPIP, and an ISPE member since 1997, is a consultant with over 30 years' experience providing engineering and technical support for manufacturers of biopharmaceuticals, medical devices, and consumer products, including 13 years in director roles for Biogen, with postings in the US and Europe. Walker has led teams that support every aspect of manufacturing operations including facilities, utilities, maintenance, metrology, technical support, label and pack, qualification, and process validation. His broad experience and leadership help teams balance engineering, operations, and compliance. A passionate ISPE volunteer, he served as the Chair of the International Board of Directors in 2011, is currently the Chair of the Biotechnology Community of Practice, and Co-Chair of the upcoming Biopharmaceutical Manufacturing Conference in December. Andre enjoys sharing and discussing hot topics in the industry through presentations, articles, and as a guest instructor at Worcester Polytechnic Institute's Biomanufacturing Education and Training Center.

Stephan T. Orichowskyj, PE, CPIP, an ISPE member since 1996, is Senior Director of Biotechnology for Hargrove Life Sciences in Philadelphia, Pennsylvania. He has 30 years of experience in the biotech industry as a process development engineer, engineering consultant and project manager. This includes domestic and international projects for start-up biotech companies and major biotech/pharmaceutical companies, as well as experience in the food, dairy, and biofuels industries. Orichowskyj'sprior experience includes process development work with Lawrence Berkeley Laboratories, Hoffmann-La Roche and Microlife Technics. He is a chemical engineer with a BS from Rutgers University in New Brunswick, New Jersey, and an MS from the University of California, Berkeley.

Dan Pratt, an ISPE member since 1995, is Director of Engineering and Project Management in Takeda Pharmaceutical's Global Oncology and Biologics Group. A favorite part of his current responsibilities is searching for new and innovative technologies to advance Takeda's manufacturing processes. He is currently working with Takeda's Grange Castle Ireland site to build a high potent facility to manufacture Ninlaro, which treats patients with multiple myeloma. Pratt has over 25 years of experience developing and manufacturing both small-molecule and biologics pharmaceuticals from drug substance through secondary packaging. He has a broad scope of experience, including: leading technical transfer, constructing and commissioning facilities, process and equipment validations, and facilitating product and process improvements. Pratt cofounded the start-up Neurological Models Inc., and has worked for DuPont and Bristol-Myers Squibb, and is a member Boston Area Chapter's Educational Program Committee.

Dr. Humberto Vega, an ISPE member since 2014, is Associate Director of Novartis, External Supply Operations–Manufacturing Science & Technology, based in Princeton, New Jersey. He has been in the pharmaceutical and food industries for over 27 years in multiple roles including research assistant, process and manufacturing head of sterile and nonsterile pharmaceutical operations, senior scientist and associate director of validation sterile, vaccine and biologics, and technology head–vaccine manufacture. He holds BS and MS degrees in chemical engineering from the University of Puerto Rico and a PhD in engineering science from Washington State University.

FINDING RELATIONSHIPS BETWEEN CLINICAL BATCH QUALITY DATA AND PATIENT OUTCOMES

Valérie Vermylen, Jean-Etienne Fortier, Eric Rulier, Alain Bernard, Carl Jone, and Justin Neway

Understanding how variability in biopharmaceutical product quality, manufacturing, and controls (CMC) affects both safety and efficacy is a major goal in pharmaceutical quality. The increasing number of software packages available to manage "big data" has greatly improved the ability to assess the criticality of biopharmaceutical product quality attributes. These advances in technology have not gone unnoticed by regulatory agencies, which now require greater understanding of critical quality attributes in relation to patient safety and drug efficacy.

Yet industry-wide technical and organizational difficulties frequently prevent correlations between CMC data and patient outcomes, production processes, and product quality. It's important to understand why this is so:

- Biopharmaceutical companies, partially in response to regulatory drivers, generate increasing amounts of data through initiatives such as quality by design, process analytical technology, process characterization, and continued process verification, along with new manufacturing and measurement technologies.
- Drug developers require better ways of using their process and quality data for statistical investigations and analyses, such as correlations that can help support patient-focused business decisions.
- Even today, in organizations of all sizes, much data is still captured manually and stored in spreadsheets. In addition, structured data often reside in separate and mutually incompatible databases, making aggregation difficult.

Consequently, it has been difficult to gather, organize, and contextualize data to improve knowledge of process and production operations, maintain and share this knowledge, and ensure appropriate levels of privacy. The US Food and Drug Administration (FDA) acknowledges as much in its "Process Validation: General Principles and Practices" Guidance for Industry:[1]

> *Focusing exclusively on qualification efforts without also understanding the manufacturing process and its variability may lead to inadequate assurance of quality. Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product.*

The same guidance presents the following list for manufacturers:

- *Understand the sources of variation*
- *Detect the presence and degree of variation*
- *Understand the impact of variation on the process and ultimately on product attributes*
- *Control the variation in a manner commensurate with the risk it represents to the process and product*

A report by Shashilov and Neway that explored the link between upstream process parameters and downstream product quality outcomes, noted the following:

> *[A]n important benefit of being able to easily perform upstream/downstream correlations in complex manufacturing processes is that significant barriers are removed to identifying potential cause-and-effect relationships between upstream process conditions and downstream process outcomes. Such relationships drive the formation of hypotheses that can be confirmed, extended or refuted using mechanistic knowledge and/or experimentation. The information thus gained about the relationships between upstream process parameters and downstream process outcomes is a major component of process models used for process control, and also contributes in the development of sophisticated process models for use in real time adaptive control (RTAC).*[2]

The aim of this study was to leverage the work of Shashilov and Neway, to explore the link between product quality (specifically impurity levels) resulting from manufacturing process variability, and patient outcomes. Specifically, the authors wanted to better understand:

- Whether process parameters driving product quality profile outcomes matched the clinical needs
- Whether quality attributes impacted patient responses
- Whether immunogenicity (safety) could be correlated with quality attributes
- Whether the levels of product related impurities that were administered to patients could be estimated reliably

METHODOLOGY

This article reports on a retrospective study using historical CMC and clinical data sets. We chose this approach because:

- It had a relatively low cost compared to a designed study, as it could

use existing data without the expense of changing the clinical study design and/or data-gathering requirements.
- It was a pilot, and a proactive approach is needed before the design of a clinical study.

CMC data

The data sources used were:

- GMP pilot-scale batches producing drug product used in clinical trials. We collected release-testing and some process-execution information from paper batch records.
- Process development batches: We collected most of the laboratory experiment data from spreadsheets.
- CMC: Internal and external contract manufacturing organization (CMO) data, including:
  - General batch data, including raw materials, cell lines, and associated quality attributes (critical material attributes)
  - Critical process parameters
  - Release data and in-process control (key and critical quality attributes)
  - Stability data (e.g., purity)
- Supply chain data to confirm that the drug product was maintained within specifications during transport to the clinic
  - Temperature excursions during transport

Clinical trial data

- Lists of kits used in clinical trials (individual kits contained one or more syringes to meet a total active ingredient quantity, as required in the clinical trial plan); each kit contained drug product from one or two production and/or placebo batches
- Clinical trial plans listing planned and actual individual patient treatments and the kits used
- Patient characteristics (e.g., age, sex, body mass index)
- Treatment type and details (visit dates, doses injected, etc.)
- Adverse events (number and type)
- Individual patient treatment response
- Physiological data (e.g., immunoglobulin G levels)

Clinical teams extracted specific data on demand to be incorporated in this study. This ensured that patient confidentiality and anonymity were maintained and clinical data sets were interpreted correctly.

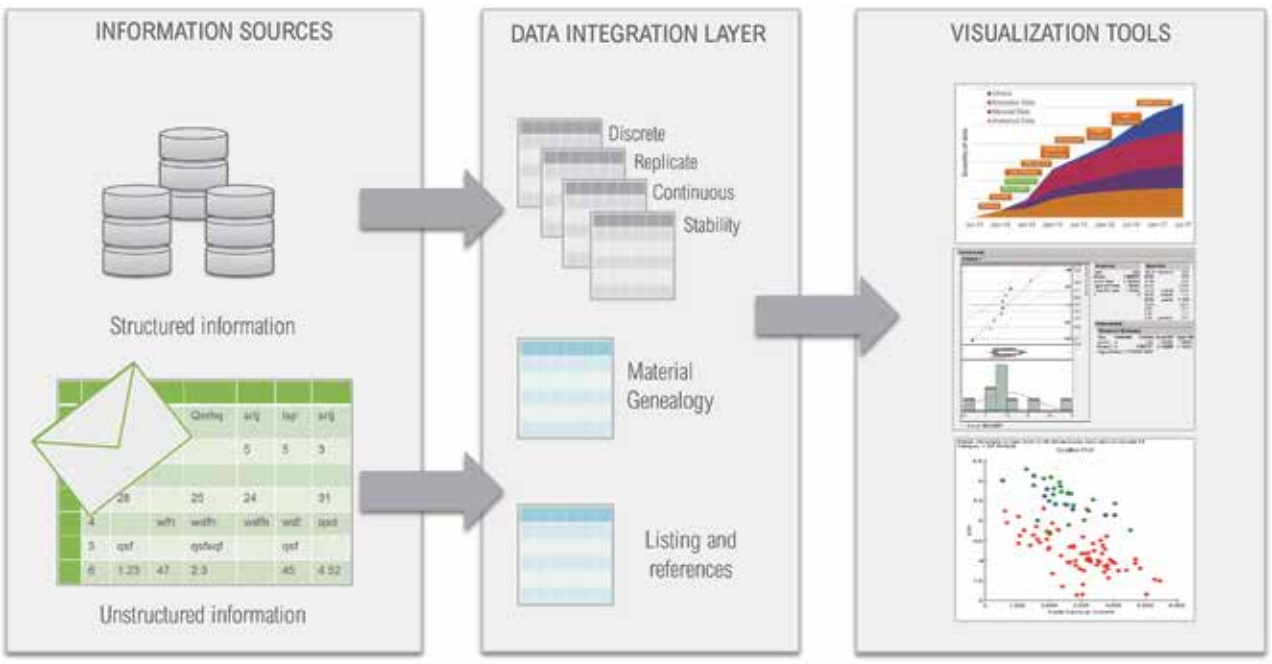
Establishing data set genealogies

We used a commercially available fully integrated data access, aggregation, contextualization, analysis, and reporting software system to align data from multiple sources to a single organizing principle (e.g., a process batch). This created a single data structure that could be used for meaningful comparisons independent of various data elements origins (geographic locations, data sources, and business functions).

To simplify data integration, we designed an intermediate data layer that was integrated according to its format rather than its content (e.g., discrete, replicate, continuous, stability, batch, and genealogy data). This ensured that no context was lost, regardless of the original data source, even when taken from paper records and spreadsheets (Figure 1). The number and type of metadata could come from different sources. A typical analytical result is linked to a specific analytical method, method component, equipment, etc., as appropriate. Materials will be linked to a supplier, grade, etc., as appropriate. To allow easy data aggregation, we defined a structure in which all data could be loaded and retrieved by querying its metadata. Tables always refer to a manufacturing or clinical unitary item (e.g., batch number or patient identification code).

Five tables in the database were constructed to ameliorate simultaneous

Figure 1: System architecture and data organization in data integration layer



searches by different users:

1. **Discrete:** Unique single-instance measurements (e.g., patient age, batch manufacturing date)
2. **Replicate:** Single unit in a series of repeated measurements (e.g., injection dates for one patient)
3. **Continuous:** Series of measurements that relate to a single batch of product (e.g., time-based pH profile during the batch manufacturing process)
4. **Stability:** Single unit in a series of measurements over time and conditions (e.g., change in aggregate levels of the active ingredient in a biopharmaceutical over the duration of a stability study)
5. **Genealogy:** Linked inputs and outputs of processed materials over a sequence of process steps (e.g., upstream drug substance lots that contributed to one batch of downstream drug product)

This approach preserved the links between data values and metadata across the organizing principle, and enabled users to trace lots used in the clinic to individual vials from the working cell bank.

Meaningful conclusions and correlations cannot be drawn from data without being able to account for the genealogy of the process stream. Using automated genealogy-mapping tools provided in the same commercially available software system as used above, we linked up- and downstream critical process parameters to product-critical quality attributes in processes where drug product splitting and pooling occurred.

Data sets were in both electronic and hard copy form. Hard copy historical CMC data (usually from a CMO) was transcribed, double-checked to verify correctness, and entered into an electronic database using the browser-based data entry capability also provided in the same commercially available software system used above.

The single data repository was disconnected from the original data source and data-processing applications. Metadata was perpetuated in a data integration layer so it could be extracted, saved, and shared through self-service access without affecting the original source data. This created a plug-and-play system that generated queries and process algorithms automatically.

With the tools and methodology in place, CMC/technical data analyses were conducted independently from the clinical trial process. These were separate from and did not interfere with clinical data processing, since all analyses were conducted in the absence of any clinical data.

To verify data linkages, clinical data sets also included a dictionary to define each parameter for which a measure was reported. We used process modeling and data organization tools to determine correlations between process conditions, product characteristics, and clinical results. Clinical data sets included: 1) information related to the product used (finished goods), such as kit numbers and use dates, and 2) information related to individual patients, such as identification codes and recruitment dates.

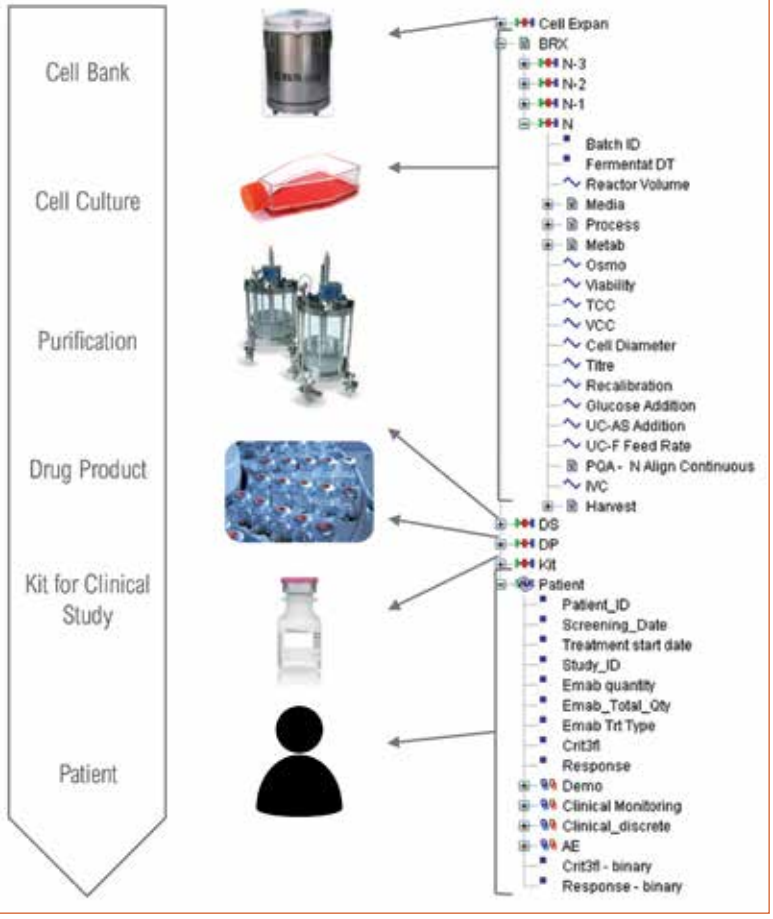
In many companies, CMC/technical and clinical teams operate independently of each other due to their different experiences, expectations, locations, business objectives, and key performance indicators. Our methodology was designed to link the two data families and help the teams work together. It also enabled an integrated data analysis that included the process genealogy, tracing back to early drug production process steps from individual kits of clinical trial material. A single active drug product batch, for instance, could generate up to 1,000 product kits for clinical use, and each patient could be exposed to up to four different product kits over multiple visits.

Product process performance is typically evaluated by measuring outputs such as process yield, product purity, and cycle times. In this study, clinical outcomes were the major outputs. Nevertheless, the same mathematical, statistical concepts, or information technology systems and tools were used to analyze process outputs in this different paradigm.

Figure 2 illustrates the complexity of the material genealogy over the process manufacturing steps from raw materials to patient responses, as well as the data model organization used for this study. It appears for an end-user as an activity-based organized data map, ensuring an easy-to-use interface. The process data model configuration enabled analysis across process set-up, production process operations, in-process controls, materials genealogy, product stability, product release, clinical observation, adverse events (AEs), and product/patient linkage (as genealogy).

To enable correlation of multistep manufacturing processes and clinical data, complete traceability across process steps is required. Our platform was configured to analyze each material transaction individually as a single

Figure 2: Superimposition of the complete process with data model



parent-child couple, allowing fast data retrieval and analysis by branch-and-leaf-type filtering as a specific parent or child category. In addition, it removed recycling processes that often create endless query loops and generate lengthy retrieval times.

Each type of transaction has a unique genealogy table. Filtering batch metadata (steps, product name, or number) links successive steps.

Table A: Genealogy table

Linked steps	Genealogy origin	Genealogy links	Cardinality
Cell expansion/N-3 N-3/N-2 N-2/N-1 N-1/N N/API	Excel (in lab) and paper batch record (in mfg)	Batch number to batch number	From 1:1 to 1:10 (between steps N-1 and N)
API/bulk drug product	Electronic records (internal mfg)	Batch number to batch number	1:1.6 (average)
Bulk drug product/kit	Excel records	Batch number to kit number	1:1,000
Kit/patient	Excel records	Kit number to patient identification number	4:1

Understanding the CMC data connection to clinical data

Clinical populations were divided into groups according to treatment outcomes:

1. Responders to treatment:
   - Yes: A positive response to treatment
   - No: A negative response to treatment
2. Patients who stayed for the duration of the clinical study:
   - Yes: The patient completed the clinical study
   - No: The treatment was stopped. (Note that a patient not completing a treatment is automatically considered a negatively responder.)
3. Adverse event: The number of AEs in different classes:
   - None
   - Limited number (1–5)
   - Significant number (> 6)

Note: Certain specific AEs (e.g., rashes) and clinical measures (e.g., C-reactive protein) were checked but not reported in this study.

To correlate physical parameters in the patient population, we determined quality attributes that influenced clinical observations and later specification limits by performing the following process data analyses:

- Parameter characterization and distribution description: Provides basic descriptive statistics and shape analyses
- Unifactorial correlation verification: Checks whether an input parameter influenced an output parameter (e.g., analysis of variance), correlation matrix, nonparametric tests, dimension reduction: principle component analysis with selection of the most influential parameters
- Multiple regression: Uses a list of selected input parameters in a stepwise multifactorial regression. Stepwise procedures alternatively include and exclude parameters to retain only influencing parameters and quantify parameter influences.

RESULTS

Critical quality attributes

To define the product quality profile, we estimated the evolution of quality attributes between the dates of drug manufacture and drug administration, then correlated the model of the quality profile with clinical outcomes. This approach provided a more realistic assessment of the effect of individual quality attributes on treatment efficacy.

A stability model for each quality attribute was used to predict its evolution until the time of administration to the patient. Constant and correct storage conditions (5°C) were used to determine the predicted value.

Stability studies performed on drug substance and drug product (at –70°C, +5°C, +25°C, and +40°C) identified three types of relationships between measured values evaluated during product testing and at the estimated time of administration to patients (Table B):

Table B: Quality attributes evolution model, based on stability outcomes

Stability outcome	Relationship equation
No evolution	Yinj = Ymfg
Linear evolution	Yinj = A + B.Ymfg × time
Nonlinear evolution	Yinj = B.f(time, Ymfg)

Where:
Ymfg is the quality attribute level at testing
Yinj is the estimated quality attribute level at injection
Time is the elapsed interval between testing and injection

Prediction: The real-time evolution of specific impurities during product storage (Figure 3) were used to develop the process model, which was then used to predict a quality profile of the clinical material on the date of drug intake (Figure 4). This was achieved by combining the date of drug manufacture, the impurity profile at release time, and the evolution of the impurity profile measured during stability studies. This model was used to predict the quality profile on the date of patient administration for individual kits after a variable period of storage from manufacturing to patient administration.

Quality attributes were assessed as a function of three criteria:

- Individual patient treatment response
- Patients remaining for the study duration
- Adverse events: Scoring the number of AEs in different classes

To investigate relationships between clinical responses (e.g., AEs, responders, and nonresponders), we looked at the total patient population, the population that completed clinical trials, dosage, and quality parameter values. Figure 5 compares the variability of a specific parameter value, under different conditions. The figure can be divided into two groups: "Patient global response to treatment" (A and C) and "Patient completing clinical study" (B and D). Variation analyses were performed for all treatment types (A and B), with doses of active pharmaceutical ingredient (API)ranging from 100 to 1,800 milligrams (mg), and for treatment type 3, which corresponds to a 1,200-mg dose (C and D). Observation of these subgroups removes an important source of variability, but also decreases the statistical significance of the study.

Figure 3: Real-time evolution of a specific impurity during drug product storage

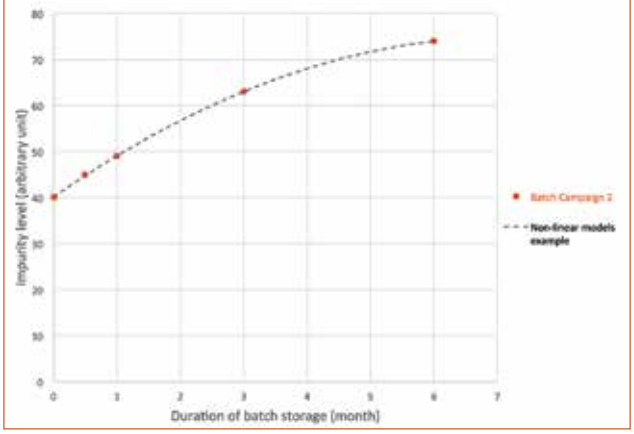
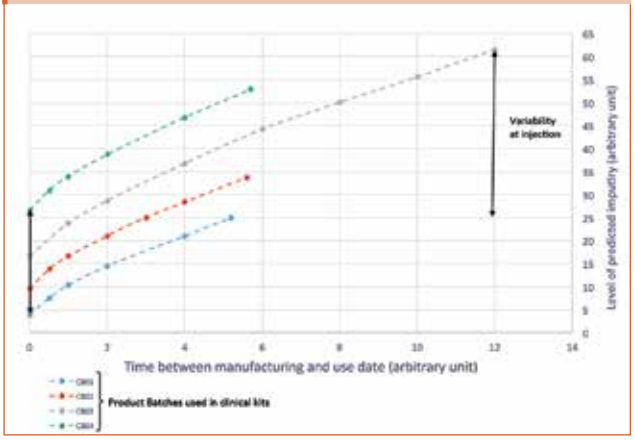


Figure 4: Prediction of the same impurity levels at date of administration



To analyze this correlation, we used multiple tools, such as:

- Box and whisker plot: Evaluates the different distributions of quality attributes between groups
- Regressions: Evaluate quality attributes that influence clinical measurements. The variability range of each quality attribute showed no correlation between responder and nonresponder patients, or between patients who completed the treatment and those who left the study.

Using a formal statistical approach, we concluded that there was a statistical difference between those patients who left and those patients who completed the type 3 treatment (1,200 mg API, *P* value = 0.04). However, the size of the subgroup (patients receiving treatment type 3 and leaving the trial) was limited, and the observed statistical difference was not significant.

Quality profile effect on AEs

Clinical results can be expressed in different ways:

- Quantitative: Number of AEs observed in an individual patient attributed to treatment
- Qualitative: "Yes" if AEs observed, "No" if no AEs observed
- Semiquantitative: Number of AEs observed during treatment (0, 1–5, or > 6)

The semiquantitative method distinguishes group effects better than numerical correlation and is recommended to highlight adverse events and identify group homogeneity.

To analyze this correlation, we used statistical tools.

- Figure 7A: Box-and-whisker plot and cluster analysis on the quality attributes to evaluate the distribution differences between qualitative and semiquantitative groups (patient responses, patient leavers, AEs) (Figures 5 and 6)
- Figure 7B: Principal component analysis multifactorial regression on the quality attributes and combination of quality attributes to measure their impact on quantitative factors (frequency of adverse event, biological measures)

Neither analysis showed any correlation between quality attributes and clinical observations.

We were unable to isolate quality attributes as influencing clinical observations for either efficacy indicators or adverse events.

CONCLUSIONS

The objective of this pilot study was to develop an approach to understanding relationships between product quality attributes and clinical patient outcomes. A carefully designed data architecture was combined with a commercial software system for fully integrated data access, aggregation, contextualization, analysis, and reporting to assess possible links between clinical outcomes and manufacturing process data.

By following this approach we were able to evaluate relationships between quality and clinical metrics (single or combined) more easily, as compared to the manual methods used in the past.

No significant correlation was found between product quality attributes and clinical outcome of the drug product in terms of treatment efficacy, treatment tolerance, or AEs. The value of this result represents (to the best of our knowledge) the first published instance of such a demonstration.

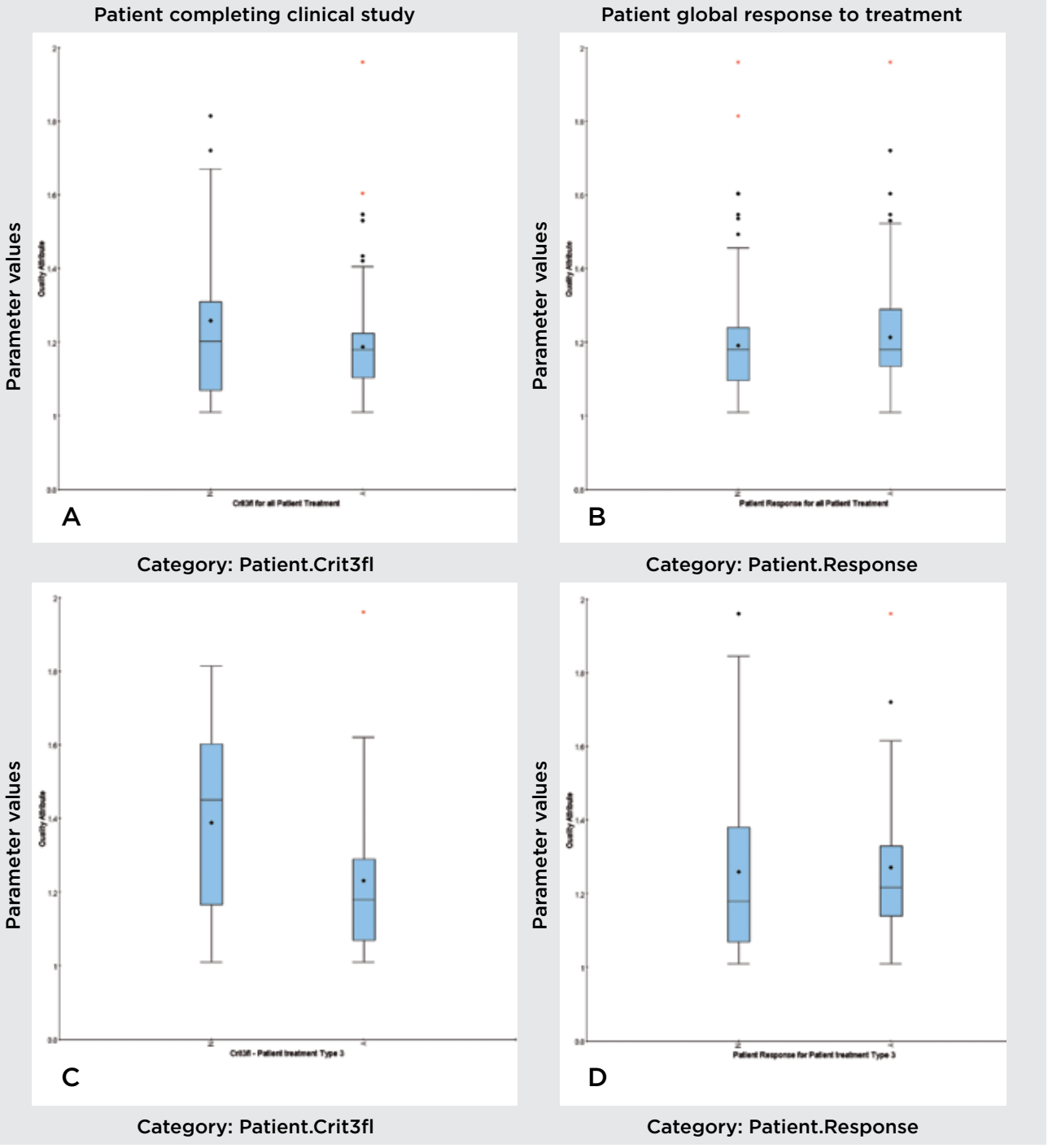
This study used software systems instead of manual data aggregation and contextualization methods, dramatically reducing the potential for human error. It provided systematic analysis for 10 to 1,000 batches. The knowledge gained can easily be leveraged and connected with other sets of data.

Making the link between manufacturing process and product quality data and patient outcomes was the most important step forward, since lower patient risk translates to lower costs and faster times to market for new drugs.

We believe that the processes and tools described in this study offer a useful path to link the quality of manufactured product to improved treatment safety and efficacy that will improve the data-driven determination of critical quality attributes and their relationship to meaningful clinical qualification of specifications.

The process of progressing a pharmaceutical product from clinical trials to successful launch and delivering consistent product to the patient requires analysis and understanding of vast amounts of data. Analyzing of such large data sets (commonly referred to as "big data") is often a complex and arduous way to demonstrate that a pharmaceutical product meets expected standards of quality, safety, and efficacy.

Figure 5: Critical parameter variability comparison



Establishing data-driven quality specifications (product and process limits) based on scientific understanding of the pharmaceutical, its stability, characteristics, and manufacturing capability is reasonably straightforward. Linking product quality metrics to safety and efficacy data, however, is still not typically a facile endeavor. Advances in "big data" methods, as shown in this study, offer the potential of achieving science-based clinical qualification of specifications.

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About the authors

Valérie Vermylen is Director for Knowledge Management at UCB, where she develops methodologies and supervises projects to improve tacit and explicit knowledge management in technical operations. She joined UCB in 2002 as Automation and Process Control Director. Previously, she worked at Dow Corning as a chromatography expert to support development and manufacturing projects. She holds a PhD in chemistry from Université Catholique de Louvain, Belgium.

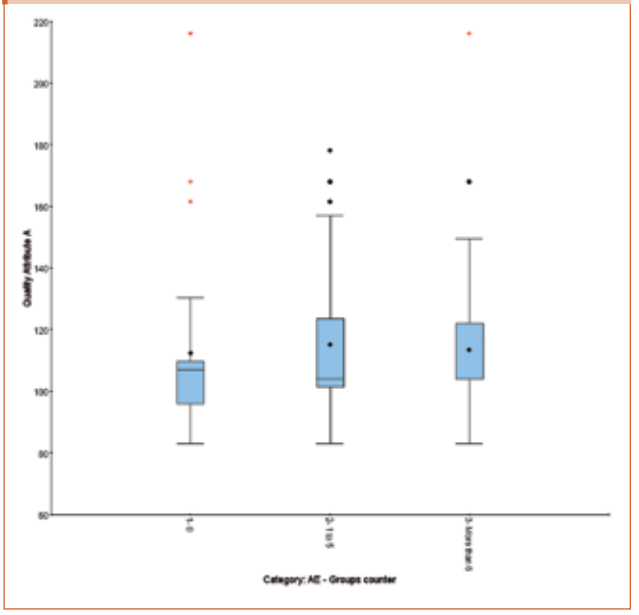
Jean-Etienne Fortier is Associate Director for Scientific Data Management at UCB, where he organizes support and develops methodologies to get insight from data in technical operations. He joined UCB in 2008 to introduce new technologies for manufacturing. Previously, he was a site manager and endorsed quality assurance as a Qualified Person for IBA Molecular (now Curium Pharma). He holds a PharmD from Université de Lorraine, France, and a process engineer master's degree from École nationale supérieure des industries chimiques, Nancy, France.

Eric Rulier joined UCB in 2010; he has been Senior Manager IT Labs Management & ELNs since 2014. Before taking that position, he gained extensive experience in laboratory information systems (LIMS, ELNs, CDS, labs standalone system, and SDMS) during the 20 years he spent within GSK on both the IT and business side. His background allowed him to be a key player to put in place Advanced Analytics tool within UCB for BioPharma & Pharma Development Labs and QC Labs. Rulier earned his postgraduate certificate in physiological engineering, cell biology, cell physiology and computer science at the University of Poitiers, France.

Dr. Alain Bernard, an ISPE member since 2012, is the former Vice-President, Biopharmaceutical Process Sciences at UCB, overseeing process developments for new chemical and new biological entities as well as for life cycle management of marketed products. He joined UCB in 2006 following eight years at Serono, where he served as director of process development and was responsible for the R&D biotechnology department. Prior to that move, he had worked at the Glaxo-Wellcome Institute of Molecular Biology. Dr. Bernard holds a PhD in biochemical engineering and worked both in the United States and Europe on process and product development and reactor design for a variety of biotechnological processes. He has authored or co-authored many publications in biotechnology.

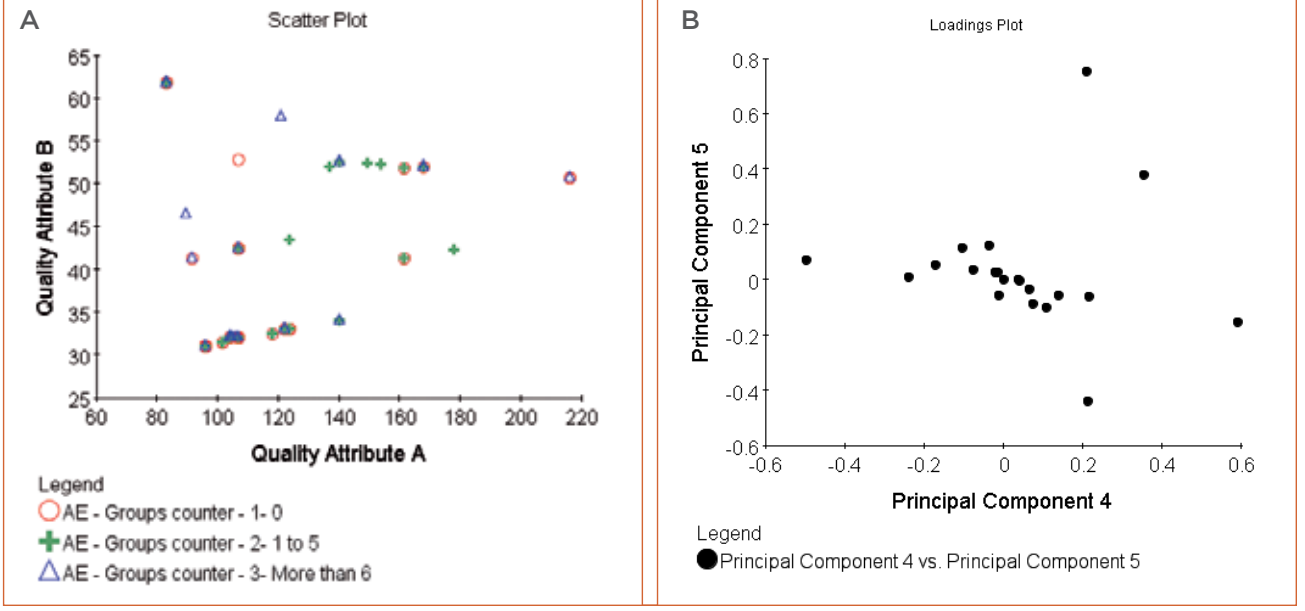
Carl Jone joined UCB in 2009, initially setting up the Knowledge Management team before taking responsibility for Analytical Sciences for Biologicals. He has had an international career (working in Europe, Japan and Australia) in both academia (University of Western Australia) and the biopharmaceutical industry (Ciba-Geigy, GSK, Serono, Merck, UCB). He began his interest in knowledge management applied to analytical sciences at Glaxo in the 1990s; this interest has continued throughout his career at Serono and UCB. He holds a PhD in protein chemistry from Tokyo Science University, (Tokyo Rika Diagaku), Japan.

Figure 6: Critical parameter variability between AE groups



Justin Neway, an ISPE member since 1998, is Vice President and Managing Director, Process Production Operations, and Senior Fellow, BIOVIA Science Council, at Dassault Systèmes. He has over 35 years of experience in biotechnology and pharmaceutical process development and manufacturing, and in the application of software solutions to operational issues and quality compliance. He received his PhD in biochemistry from the University of Illinois, US, in 1982, before holding various process development and manufacturing leadership positions at Wyeth BioSciences, Novartis Vaccines, and Baxter BioSciences. In 1997, Dr. Neway was founder of Aegis Analytical Corporation, creator of the Discoverant software system for integrated data access, aggregation, contextualization, analysis and reporting. Aegis became part of the BIOVIA Life Science division of Dassault Systèmes in 2014.

Figure 7: Quality attributes and clinical outcomes correlation



MANUFACTURING EXCELLENCE UTILIZING A LIFE CYCLE APPROACH

Marzena Ingram, Ajay Babu Pazhayattil, Naheed Sayeed-Desta, and Galina Desai

The emergence of "big data" has allowed pharmaceutical organizations to harness the vast amount of information they generate. By collecting equipment, facility, and manufacturing data (process parameters, calibration, qualification, environmental conditions, etc.) companies can improve process development, apply continuous improvement initiatives, and reduce failures on the floor.

Knowledge gained on sufficiently similar products and processes at commercial scale can further provide confidence of product quality. Process validation guidance from the US Food and Drug Administration (FDA),[1] along with process validation guidelines[2] and Annex 15[3] from the European Medicines Agency (EMA) mandate commercialization only when data has established a high degree of product and process understanding and has demonstrated adequate process controls. FDA's Q8, Q9, and Q10 Questions and Answers (R4)[4] further clarify that like the product itself, process validation also has life cycle stages:

Stage 1: Process design
Stage 2: Process qualification
Stage 3: Continued process verification (CPV)

Knowledge management (KM) is a method of capturing, storing, distributing, and utilizing explicit, implicit, and tacit knowledge to improve product knowledge and process understanding.[6] KM is also an enabler for implementing ICH Q10, "Pharmaceutical Quality System,"[5] and supports manufacturing excellence by assuring product realization, robust control strategies, and continuous improvement.

Finally, KM applications are imperative to support a life cycle approach for any given product or process. This article reviews three case studies in which effective product and process KM from all three stages of the process validation life cycle enabled risk-based and data-driven decision-making.

CASE STUDIES

1. Addressing variability in uniformity for a legacy product

During annual product quality review of an immediate-release solid-dose product, the Quality Unit observed out-of-statistical-control (OOSC)[7] results during powder blend uniformity (BU) trending. Berman, et al. suggest that if the product passes but the blend fails, further evaluation is necessary as a significant sample error may be affecting the results.[8] We initiated an investigation to determine the likelihood of blend segregation, including review of the extended content uniformity testing results. The data and tight relative standard deviation indicated that powder blend segregation was not the most likely root cause; sampling bias was suspected. Per Berman, the results are applicable to statistical inference B, which is:

> *... indicative of sampling bias. Significant differences exist between the means of the blender and product indicating a high probability the samples were not taken from the same population. The standard deviation of the blender is greater than that of the product providing further evidence of sampling bias. These are the conditions most frequently seen when sampling bias is occurring.*[8]

It was essential, therefore, to confirm that the sample size provided adequate representation of the entire blend batch.

Purutyan and Carson suggest that sample size has a profound impact on the variable blend uniformity results.[9] Since the product was a legacy molecule with minimal stage 1 quality by design data on blend sampling

sizes, understanding application of sample sizes for similar products was critical. Because data was available across multiple products at all stages of the life cycle, the KM system was able to perform an ad hoc query.

Sample size, blend data, and associated information came from sources such as the laboratory information management system (LIMS) (i.e., results), quality management system (QMS) (i.e., investigations), and enterprises resource planning system (ERP) (i.e., batch genealogy). All were integrated into the life cycle KM system. Sample sizes used for similar formulations with similar physical characteristics of the blend were identified and used.

A verification batch performed with the suggested sample size was successful, which confirmed the investigation hypothesis of sampling bias. A new sample size was suggested for future batches. In addition, parameters that affect BU results, such as particle-size distribution, were evaluated to determine if there was a correlation. Application of existing data eliminated the need for experiments, prevented delays, reduced failure, and limited additional cost of material. The approach also reduced the need for production resources and ensured continued commercial supply of the product.

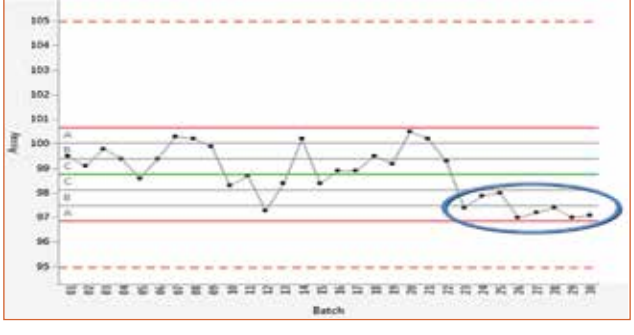
2. Site transfer and scale-up

For a site transfer of an existing solid-dose formulation, the manufacturing process and equipment at the sending site were compared to those at the receiving site. Review of the formulation, equipment comparability, and risk assessment of the proposed process showed that the blend process should be scaled-up to meet volume demands, because multiple similar scale bin blenders were not available. It was further determined that apart from scale, the blend process, bin blender geometry, and mixing dynamics between the proposed bin and the bin blender at the sending site were similar. As a result, scale-up risk therefore was estimated to be low.

We therefore decided to leverage the life cycle KM system to understand the process parameters of similar products to establish optimal blend process parameters prior to a demonstration batch. Identifying products and processes with comparable formulation (percent active), raw material physical characteristics, blend batch size, bin fill, blend bulk density, and blend uniformity results allowed review of potential issues. The blend process parameters were established and confirmed during the demonstration batch.

The ability to retrieve essential information through the life cycle KM system negated the need for additional manufacturing floor trials and additional resources. Data compilation, analysis, and trending were performed by the life cycle KM system, integrating LIMS, QMS, and ERP. This ensured that blend parameters were based on sound science and overall product and process understanding prior to initiating stage 1 verification studies. Per FDA process validation guidance, it is not typically necessary to explore the entire operating range at a commercial scale if assurance can be provided from credible experience with sufficiently similar products and processes.[2]

Figure 1: Statistical process control chart



3. CPV trend

Figure 1 shows continued monitoring of assay results, a critical quality attribute (CQA) for an immediate-release solid-dose product, where the specification is 95.0%–105.0%. The control chart includes zoning by a standard deviation of 1 sigma. This identifies unnatural patterns by applying commonly accepted test rules.* [10]

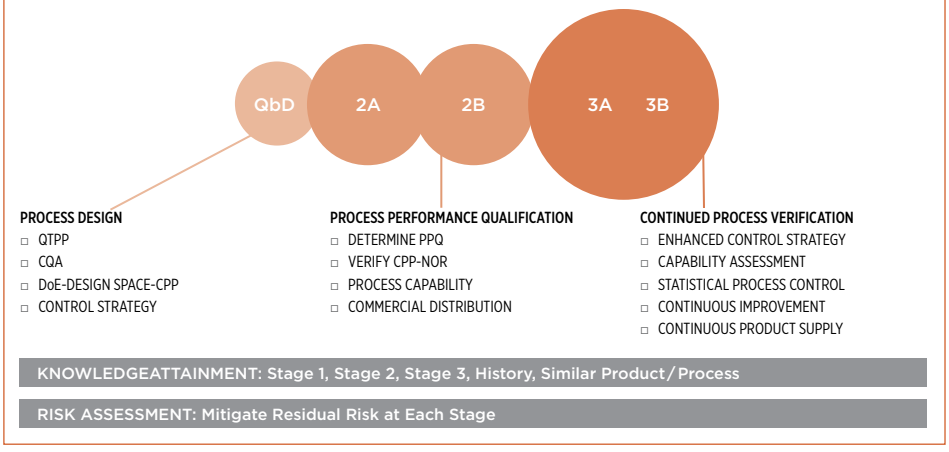
Figure 1 depicts eight consecutive assay data points on one side of the mean value (WECO rule 4). This highlights an unnatural pattern, indicating small sustained shifts or trends; the results, however, are well within the specification limits. Assay results were retrieved from LIMS and trended in the life cycle KM system. Further investigation identified a root cause: Corresponding analysis of weight variation indicated that batches were being compressed below target weight (although still within specification). Corrective and preventive measures were enacted to ensure target weight was maintained prior to further processing, resulting in an uninterrupted production cycle.

Trending near and/or real-time quality attribute and process parameter data to ensure compliance with FDA process validation guidance[2] is of paramount value, adding assurance that the process remains in a state of control during routine commercial production of drug products. Through life cycle stage 1, critical material attributes and CQAs are established; critical process parameters (CPPs) and process control strategies are defined. CPPs and CQAs are verified in stage 2. As the product moves to stage 3, the body of data grows significantly.[11] In stages 3A and 3B, CPV data continues to be generated until the product is discontinued.[17] Control mechanisms such as ensuring notifications for out-of-trend or OOSC data are established as part of the CPV program. Trend detection is easily visible and alerts can be generated for further evaluation. Special attention is required to detect false alerts—those not process related—to curb overreaction and focus only on significant trends. As data is available in near real time, it allows immediate action upon signal detection.

Information in the life cycle KM system may include elements such as detailed manufacturing processing stages, equipment used, and process parameters, which can generate automated outputs such as manufacturing process flow charts. A well-maintained product history, including change control summaries, validation statuses, investigations, complaints, field alerts, and stability data, lends itself well to an automated annual product quality review report.[12] Integrating typical pharmaceutical document, content, and workflow management systems such as LIMS, ERP, and QMS are essential to managing the process validation life cycle stages.[13] Data must be accessible, gathered, interfaced, and delivered to continually support all life cycle stages. New FDA guidance on emerging technology applications[14] promotes the adoption of innovative technology; other regulatory agencies have provided further clarity on data integrity, cGMP compliance,[15] and current thinking on data creation and handling.

* Western Electric (WECO) rules, Nelson tests, ISO 2859 tests, Boeing ASQ rules, and Trietsch rules

Figure 2: Product knowledge and process understanding at various life cycle stages



CONCLUSION

Product and process knowledge about all process validation life cycle stages must be captured, organized, managed, stored, and shared. It must also remain easily accessible to promote data-driven, science- and risk-based decision-making. Available, reliable data that can be evaluated statistically at any time ensures that each stage of the life cycle is in control. This enhances both regulatory compliance and product/process confidence, and improves product understanding.

Metrics developed may be submitted as defined in the FDA's "Request for Quality Metrics" draft guidance.[16] Near-real-time trending of quality attributes, and process parameters ensures early signal detection and presents opportunities for manufacturers to act before a process failure occurs. The greatest benefits of a well-implemented life cycle KM system include reduction of product-remediation costs, lower cost of quality, and above all, consistent delivery of quality products to the patient.

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About the authors

Marzena Ingram has more than 16 years of pharmaceutical industry experience with quality assurance and technical operations teams at Apotex Inc., where she currently holds the position of Senior Manager Continued Process Verification. Ingram developed a specialized continued process verification team and spearheaded the implementation of a stage 3 CPV program to meet the company's global regulatory requirements. She also introduced statistically driven product assessment processes as part of process validation stages 3A and 3B, and has been the lead on implementing a comprehensive PV life cycle management solution. Ingram also has authored multiple pharmaceutical journal articles. She holds a BSc in biology from the University of Western Ontario, Canada.

Ajay Babu Pazhayattil, an ISPE member since 2007, is Associate Director, Process Validation, at Apotex Inc. has held leadership roles with brand name, generic, and contract manufacturing organizations. Pazhayattil is an industrial pharmacist and has successfully delivered tangible results in multiple segments of pharmaceutical operations. He has conducted extensive GMP audits of raw material, formulation, medical device and clinical sites across the globe. Pazhayattil holds a BS in pharmacy and an MS in pharmaceutical chemistry; he has also has authored multiple pharmaceutical journal articles, developed and implemented a comprehensive PV life cycle management program, and introduced novel product and process assessment methodologies.

Naheed Sayeed-Desta,an ISPE member since 2016, has more than 16 years of pharmaceutical industry experience in product development and technical operations for generic and contract manufacturing organizations. In her current capacity as Senior Manager, Process Validation at Apotex Inc., Sayeed-Desta is responsible for providing strategic direction on PV life cycle management for more than 300 molecules. Sayeed-Desta, who earned a BS in biology from the University of Western Ontario, Canada, is an active speaker at several industry forums and lead author of multiple pharmaceutical journal articles.

Galina Desai,an ISPE member since 2017, has more than 15 years' experience in the pharmaceutical industry and is Site Head of Quality and Compliance at Apotex Inc.'s Etobicoke Solid Dose Manufacturing Plant in Ontario, Canada. A graduate of Voronezh State University, Russia, Desai championed implementation of Labware LIMS in manufacturing to facilitate the "real-time" gathering and reporting of relevant in process quality control results from Apotex solid-dose and liquid-dose operations to support annual product review process and PV life cycle management.

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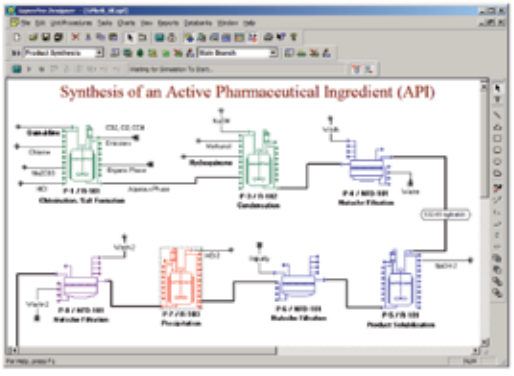

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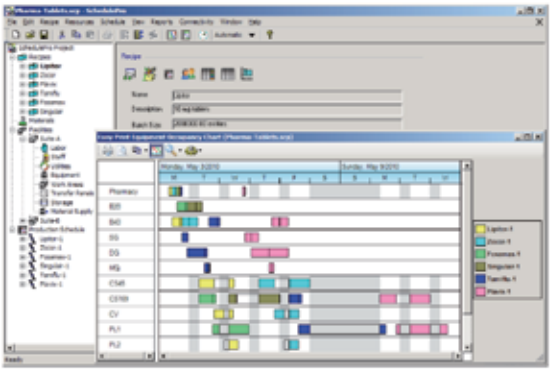

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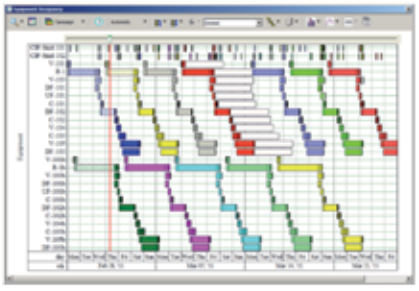

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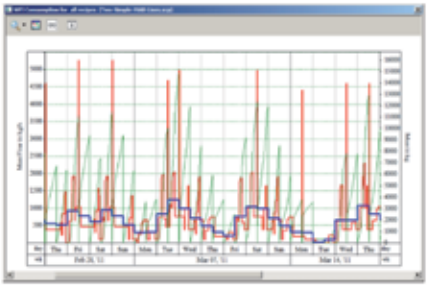

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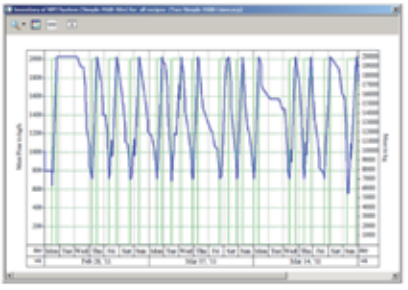

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MICROBIOME TREATMENTS FOR RECURRENT *C. DIFFICILE* INFECTIONS

Roughly 29,000 Americans die of *Clostridium difficile* infections every year. This gram-positive bacterium produces severe intestinal disease, with fatality rates ranging from 6% to 30%. Because the spores are hard to kill and can remain viable for years, infections are easily passed to patients, especially in medical facilities.[1] While metronidazole and vancomycin are the treatments of choice, about 30% of patients will suffer at least one relapse.[3]

One low-tech alternative involves the transfer of stool from a healthy donor to the bowel of an ill recipient, known as a fecal microbiota transplant (FMT). This centuries-old treatment, recently rediscovered, is surprisingly effective for recurrent *C. difficile* infections, with a 90% cure rate.[6]

"Our FMT patients have a life-threatening condition for which nothing else has worked," said Michael Silverman, MD and chief of infectious diseases at Western University in London, Ontario, Canada. "These transplants help revert them to a healthy microbiome over a short time. The alternative is a lifetime of taking vancomycin."

MICROBIOME

The microbiome, the population of microbes in and on our bodies, is a virtual organ that not only affects gut and skin health, but mood and mental health as well. In addition to *C. difficile*, the microbiome is being used to test treatments for cancer, inflammatory bowel disease (IBD), immunotherapy, cardiac and respiratory diseases, and even obesity. As many as 70 start-ups and research institutes are developing mixtures of cultured microbes to use as microbiome drugs. Instead of a stool sample, live cells or spores are packed into capsules and taken internally or applied topically to treat skin conditions such as acne and eczema.

TREATMENTS

Seres Therapeutics is testing an oral capsule for recurrent *C. difficile* infections. While initially promising, SER-109, which has breakthrough status and an orphan drug designation from the US Food and Drug Administration (FDA), failed phase 2 trials last year. Seres reviewed its data and incorporated learnings and feedback; SER-109 has now entered a phase 3 clinical trial.[4]

Other companies with biotherapeutics in the pipeline include Azitra, with preclinical dermatological treatments; Finch Therapeutics, which is partnering with Takeda on a microbial mixture to treat IBD; and Vedanta Biosciences, which has a licensing deal with Johnson & Johnson to develop candidates to treat allergies, infections, and cancer.

Unlike new technologies being used to develop biologics such as antisense RNA and gene therapy, there aren't huge technical hurdles to manufacture microbiome medications other than standardizing culturing techniques to ensure cell or spore viability. There is a concern among some industry experts, however, that regulatory agencies might not have the expertise to judge these treatments.[2]

DELIVERY

"The incidence of *C. diff.* and the percentage of people who have multiple relapses has been going up," said Silverman, who was one of the first to use FMT to treat *C. difficile* in North America. In 2003, prior to regulation by Health Canada, he developed a self-administered enema procedure for patients. His clinic now treats two or three patients each month with FMT for recurrent *C. difficile*.

Stool samples are delivered to patients in one of three ways: enema; colonoscopy, which gets the microbes into the upper large colon; or via a nasogastric tube that delivers fecal matter to the small intestine. It is unknown which route is the most effective. Enemas are easier, although multiple FMTs are usually necessary if this approach is taken.

"A low-volume enema is the most practical procedure," Silverman said. "It can be done by the patient and is the least expensive alternative."

IND

While the FDA considers fecal microbiota an investigational new drug, the agency issued an exception that allows physicians to perform FMT for recurrent *C. difficile* infections.[5] In Canada, FMT is regulated as a new biologic drug, but can be used for infections that are refractory to standard treatments. In both countries stool samples must be screened for pathogens.

For a separate study investigating the effects of FMT on metabolic syndrome, Silverman had to screen 42 donors to find one that was suitable. Each required a physician consult, stool samples, and tests to ensure donors weren't carrying multidrug-resistant microbes or other pathogens. It's a huge amount of work.

"It would be better for everybody if we had a commercial product for *C. diff.* and we didn't have to do fecal transplants," said Silverman, who noted that his clinic will be part of the next Seres trial. "Beside the 'ick' factor, if we had a capsule free of pathogens, it would be easier and less expensive than having to do all this screening." ‹›

—Scott Fotheringham, PhD

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