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Is Asia the new frontier for biotech?

Industry leaders weigh in:
Kiran Mazumdar-Shaw, CEO, Biocon
Dr. Sei Murakami, Japan Affiliate Bio COP
Dr. Chris Chen, CEO, WuXi Biologics

ALSO IN THIS ISSUE:

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The Next Final Frontier?

Anna Maria di Giorgio, Editor in chief

When I think of frontiers, I think of traumatic border crossings, the Wild West, and outer space. The latter two, a colleague tells me, are the major premise of *Star Trek*. "Space is the final frontier," she says, "and part of its appeal is the idea of discovering new planets, new life forms, etc." *Star Trek*'s creator Gene Roddenberry wanted the series to present a world free of bigotry and conflict, albeit in another galaxy in the twenty-third century.

How does all this relate to pharmaceutical engineering, and more specifically to this issue's cover? Quite well, as a matter of fact.

The pharmaceutical industry continually pushes into new territories so that patients have the medicines they need to heal and science continues to evolve. The industry crossed the border into biotechnology in the 1970s, a breakthrough that is now beginning to be bear fruit across most of the globe.

This is particularly true in Asia, which seems to be gaining speed after a slow start. To learn more, we reached out to leaders in India, Japan, and China for their perspectives. Their stories provide an inside look at how and why Asia is, indeed, the new frontier for biotechnology.

Another frontier is matter and how we build it. Freelancer Scott Fotheringham looks at modular construction and prefabricated facilities, both of which are making inroads in the pharmaceutical industry. He also highlights 3D printing, which is being used to produce everything from capsules to bridges to buildings, transforming the way we think about manufacturing in the process.

Architects and engineers have had, at least anecdotally, very definite boundaries around roles and responsibilities—architect Louis Kahn (the first to use prefab concrete) and engineer August Komendant (who pioneered the use of reinforced concrete) come to mind. Their lifetime collaboration was one of give and take, heated discussion, and absolute creativity, which produced some of the world's most memorable buildings. ISPE member and architect Mark Brooker speaks to the important role of process architect in the pharmaceutical industry, and how it relates to that of the process engineer.

Managing editor Amy Loerch met with Novo Nordisk about their new $2 billion 833,000-square-foot plant in North Carolina, the company's first API plant outside Denmark. It will produce APIs for both current and future GLP-1 and insulin products. Their specific frontier? Time: The facility must be operational in five years.

Here at the *Pharmaceutical Engineering* editorial offices we're expanding our horizons too: Inside you'll find a pull-out Knowledge Brief on wet granulation. Look for more of these overviews on processes and technologies that affect the pharmaceutical industry in future issues.

This month's magazine also includes the 2016 FOYA Report, which celebrates the 2016 Category Winners and Honorable Mentions. Breaking down barriers and reaching new goals is at the heart of the FOYA program and this year's winners have set the bar high. Please join us in applauding them and their accomplishments.

Last, but not least, our special report explores another new frontier: the Facility of the Future and how emerging technologies and opportunities can help make tomorrow's facilities even more agile and responsive. The timing of this report is not accidental: "Facility of the Future" will debut as a FOYA category in 2017.

Back to Rodenberry and his intentions with *Star Trek* ... We may not be in outer space, but our thinking should be, so that we can continue to produce and deliver the best quality medicines to patients around the world.

Quch (happy) reading. ■

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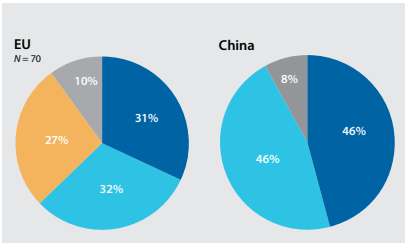

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May 2016

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

New Jersey Chapter
Student Poster Competition
Johnson & Johnson
New Brunswick, New Jersey

4–5 Australasia Affiliate
Cleaning Validation & Contamination Control Practices Seminar
Sydney, Australia

9 Boston Area Chapter
Annual Spring Golf Tournament
Seekonk, Massachusetts

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

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

Singapore Affiliate
ISPE Singapore Affiliate Statistics for Validation Workshop
Singapore

10–11 DACH Affiliate
Pharma 2025 Containment
Heidelberg, Germany

11–13 Singapore Affiliate
Training Event
Practical Implementation of Process Validation Life Cycle Approach (T46)
Singapore

12 Italy Affiliate
Data Integrity Normative & Linee Guida
Rome, Italy

Pacific Northwest Chapter
Life Science Forum
Bellvue, Washington

Chesapeake Bay Area Chapter
Thermo Fisher Tour

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

13 Delaware Valley Chapter
Volunteer Day

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

New Jersey Chapter
Golf Outing and Winery Tour
Neshanic Station, New Jersey

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

17 Brazil Affiliate
Training Event
GAMP 5
São Paulo, Brazil

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

18 Belgium Affiliate
Networking Event
Brussels, Belgium

19 Boston Area Chapter
ISPE Single Use: From Toddler to Adolescent
Shire
Lexington, MA

Midwest Chapter
TechEd Day
St. Louis, Missouri

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

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

26 Boston Area Chapter
ISPE Single Use: From Toddler to Adolescent (Reshowing)
Worcester, Massachusetts
Providence, Rhode Island
Portsmouth, New Hampshire

Nordic Affiliate
Annex 15 Updates & Continuous Process
Stockholm, Sweden

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

June 2016

2 Belgium Affiliate
Young Professionals Networking Event
Wilrijk, Belgium

5 ISPE Data Integrity Workshop
North Bethesda, Maryland

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

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

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

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

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

UK Affiliate
Latest Developments to Guidelines & Regulations
Birmingham, England

16 France Affiliate
Conférences: Confinement pour Formes
Paris, France

France Affiliate
Annual General Meeting
Paris, France

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

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

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

Midwest Chapter
YP Thirsty Thursday
Kansas City, Missouri

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

27 Italy Affiliate
Summer Night — Drug Shortages Prevention

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

July 2016

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

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

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

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

Pacific Northwest Chapter
Annual Golf Tournament
Redmond, Washington

21 San Francisco/Bay Area Chapter
Fun Day
Napa, California

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

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The new biotech frontier?

Biotechnology Can Transform India into a Global Innovation Hub

Kiran Mazumdar-Shaw

India's biotechnology industry has, over the past few decades, built a robust portfolio of products and services based on a strong platform of technological capabilities. The country has emerged as the world's largest vaccine producer, an insulin manufacturer with global scale, and the largest supplier of genetically modified cotton globally. India is also one of the world's most attractive destinations for life sciences research, with about 800 companies currently valued at over $10 billion and a sustained growth of about 20% compound annual growth rate over the past decade. With a favorable business environment, the biotechnology industry could generate revenues of $100 billion by 2025.

India is now ranked among the top 12 biotechnology destinations in the world and second in Asia. Already a biotechnology hot spot, India also has what it takes to become a global biotechnology innovation hub. Its competitive edge lies in its large, qualified, English-speaking scientific talent pool, production costs that are roughly a third of that in the West, a network of distinguished research laboratories and state-of-the-art pharmaceutical labs, global-scale manufacturing facilities, and biodiversity.

In fact, biotechnology can be a powerful enabler for transformational socioeconomic change as it can spur not only economic growth and provide much-needed jobs but also ensure that we find answers to modern challenges in health care, energy, food security, and environmental sustainability. This transformative innovation combines new technologies, new methods, and new knowledge that can lead to an inclusive and enlightened economy that ensures a better quality of life for all of India.

India's biopharmaceutical companies have achieved global reputations by helping to increase access to drugs like insulin, erythropoietin, monoclonal antibodies, and other recombinant proteins that offer lifesaving therapies for a host of diseases from diabetes to renal disorders to autoimmune disorders to cancer. Companies like Shantha Biotechnics and Bharat Biotech have pioneered a vaccine revolution, and today two out of every three children in the world are immunized with a vaccine made in India.

The biopharmaceuticals segment, which accounts for nearly two-thirds of Indian biotechnology industry revenue, offers a huge prospect for growth. Given its global manufacturing scale and biology, process development, and engineering skills, India can tap the estimated $250 billion to $300 billion global biopharmaceutical opportunities and emulate its earlier success with affordable chemistry-based generic drugs.

Going forward, biosimilars, biomedical devices, genomics, bioinformatics and 3D bioprinting, synthetic biology, gene editing using clustered regularly interspaced short palindromic repeats (CRISPR) technology, contract research services, and agricultural biotechnology offer new growth opportunities for the industry.

Biosimilars

The unfolding biosimilars opportunity in emerging markets in the near term and developed markets long term will give Indian biopharmaceutical players the next big bolus of growth. From $1.3 billion in 2013, the biosimilars market is expected to reach nearly $24 billion in 2019.

India is well poised to play a significant role in the biosimilars area where companies like Biocon, Dr. Reddy's Laboratories, Intas Pharmaceuticals, Zydus Cadila, and others are developing high-quality biosimilars to provide affordable access to complex biologics.

Indian patients have had access to some of the biosimilars, such as recombinant human insulin, insulin analogs, and filgrastim since the early 2000s; more recently, complex antibodies such as trastuzumab, rituximab, and adalimumab have also been introduced. This early experience with developing biosimilars will pave the way for Indian players to capitalize on this unfolding global opportunity. India's experience with chemistry-based generics could also allow Indian biosimilars players to offer affordable cutting-edge biotherapeutics to patients and health care systems around the world.

Kiran Mazumdar-Shaw, Chair and Managing Director, Biocon Limited

Biomedical devices

The government's recent decision to allow 100% foreign direct investment (FDI) in medical devices through the automatic route has opened an opportunity for manufacturing world-class biomedical devices in India. Relaxation of the FDI regime has also made it attractive for overseas players to leverage India's cost advantage to tap the $400-billion medical device market globally.

With India's medical device market projected to grow from its current $5 billion in sales to $50 billion by 2025, the country offers the industry a huge opportunity for growth and expansion.

Genomics, bioinformatics, and 3D bioprinting

As technological advancement has brought down the cost of genome sequencing, genomics and big data analytics are other emerging opportunities. Already, genome sequencing is being combined with molecular diagnostics, imaging, and data analytics to decipher the cellular structure of malignant tumors and tailor treatment regimens. Given their technological prowess, Indian companies like Strand Life Sciences are leveraging the potential of bioinformatics through big data to find answers to the challenges in translational medical research. Some, like Ganit Labs, are successfully bringing down the cost and time required for sequencing, analyzing, and interpreting genome data. India has the potential to emerge as the key provider of high-end analytics based on genomics-related big data.

There is tremendous growth potential in the area of biomarkers and companion diagnostics. This area is the future of new medicine; it will personalize therapy and optimize the benefits of biotech drugs. A new range of advanced yet affordable health care monitoring devices is being developed by Indian companies like XCyton Diagnostics, and Bigtec Labs.

Pandorum Technologies, a Bangalore-based tissue-engineering start-up, recently made India's first artificial human liver tissue with the help of 3D printing technology. This is a significant milestone that showcases the tremendous potential of 3D printing technology to develop organs and save lives.

The biopharmaceuticals segment, which accounts for nearly two-thirds of Indian biotechnology industry revenue, offers a huge prospect for growth

Synthetic biology

Synthetic biology is gaining global prominence in developing new diagnostics, novel vaccines and drugs, and a number of value-added nutritional and food ingredients. Indian researchers' recent success in sequencing the genome of the medicinal plant tulsi (*Ocimum tenuiflorum*) has opened opportunities for using synthetic biology techniques to synthesize the plant's bioactive compounds for use in treating human diseases.

Gene editing

CRISPR–Cas gene splicing allows scientists to edit genomes with precision, efficiency, and flexibility, and to do so cheaply, quickly, and accurately. In a country like India, such a tool holds tremendous potential for treating and eliminating a number of genetic diseases specific to the country's population. This technique can be used to genetically alter mosquitoes and limit the spread of mosquito-borne diseases like malaria, dengue, and chikungunya. Similarly, it can also be used to create hardier indigenous varieties of plants that are resistant to certain diseases and pests.

Contract research services

Indian biotechnological companies are also well positioned to offer contract research services to multinational corporations, which increasingly outsource R&D work to third-party service providers. Indian players are well positioned to tap the $67-billion global contract research-service opportunity for discovery and development services.

Agricultural biotechnology

Agricultural biotechnology can be leveraged to usher in a second green revolution with unprecedented opportunities to ensure food security for both India and the world. India has only 2.3 percent of the world's land area but must ensure food security for 17.5 percent of the world's population. Biotechnology offers scientific techniques that optimize the use of available resources without placing additional demands on land or water to boost yields—which is just what India needs. These solutions, which can easily be scaled across the country, can also improve the quality of the produce with disease-free and nutritionally enhanced crop varieties.

Indian farmers who opted for genetically modified Bt cotton* are reaping the early benefits of agricultural biotechnology through increased crop yields. Bt cotton has made India the largest cotton producer in the world and converted the country from a net importer to a net exporter of this important cash crop. Over 90% of the country's cotton-growing areas today grow Bt cotton, which has doubled cotton yields over the last decade.

Apart from genetically modified crops, agricultural biotechnology is leveraging molecular markers in crop breeding for the selective propagation of genes that improve yields and resist disease. Micropropagation is another area where biotechnology is helping to produce pathogen-free plants and address soil-imbalance issues.

* Pest-resistant cotton engineered with a gene from the bacteria *Bacillus thurengiensis* to produce a toxin that kills bollworms

India's experience with chemistry-based generics could allow Indian biosimilars players to offer affordable cutting-edge biotherapeutics to patients and health care systems around the world

Beyond cultivation, biotechnology also provides value-added economic opportunities in the area of biopesticides and biofertilizers, which have the potential to help farmers reap more profit from their crops.

The way ahead

The Indian government's "Make in India" initiative, which aims to transform the country into an attractive cost-effective global manufacturing hub, has identified biotechnology as a thrust area. The government has also unveiled the National Biotechnology Development Strategy (NBDS) to provide a strategic road map for creating an optimal ecosystem that encourages innovation in biotechnology. Some of the sector's immediate needs—access to capital, quality infrastructure, and high-end talent—are likely to be eased with the implementation of this road map. NBDS, therefore, will set the biotechnology agenda for the country and help its evolution as a biotechnology hub and preferred destination for innovation.

India needs to unleash the power of biotechnology to promote socioeconomic progress by transforming agriculture, health care, energy, and the environment. This will lead to the dawn of a new economic era that can aptly be called a "bioeconomy." This new era will offer India the opportunity to emerge as a leading bioeconomic power and also drive inclusive growth. ■

About the author

Kiran Mazumdar-Shaw, a pioneering biotech entrepreneur, is the Chair and Managing Director of Biocon Limited, Asia's leading biopharmaceuticals enterprise. Named among *TIME* magazine's 100 most influential people, she is recognized as a global thought leader for biotechnology. Under her stewardship, Biocon has evolved from an industrial enzymes company to a fully integrated, innovation-led, emerging global biopharmaceutical enterprise committed to reduce therapy costs of chronic conditions like diabetes, cancer, and autoimmune diseases. Ms Mazumdar-Shaw is an Independent Member of the Board of Infosys, a global leader in consulting, technology and outsourcing solutions. She is also the Chair of the Board of Governors of the Indian Institute of Management, Bangalore.

Is Japan the New Frontier for the Biopharmaceutical Industry?

Dr. Sei Murakami and the Japan Affiliate BIO CoP

In 2014, Japan joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of good manufacturing practice (GMP). PIC/S's mission is "to lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products."[13] Japanese regulatory authorities applied for PIC/S membership in March 2012, and Japan became the 45th PIC/S participating authority as of 1 July 2014.[1]

Japan's participation in PIC/S not only enables its international GMP harmonization but will also provide more opportunity to extend its biotechnology and biopharmaceutical innovations globally. In this article, we introduce and examine recent biopharmaceutical industry achievements, and review Japanese focus on biologicals, regenerative medicine, and manufacturing technology.

Biologicals

Japan's long history with fermentation technology began centuries ago with the discovery of fermented foods. Today it includes microbial pharmaceutical production and clinical monoclonal antibody with continuous innovation. The following are examples of current Japanese pharmaceutical manufacturers' proprietary technologies.

Kyowa Hakko Kirin Co., Ltd.

Eliminating fucose from sugar chains on an antibody enhances antibody-dependent cellular cytotoxicity (the critical factor in antitumor activity) by up to a hundredfold both *in vitro* and *in vivo*. Kyowa Hakko Kogyo Co., Ltd., (now Kyowa Hakko Kirin Co., Ltd.) developed this technology and named it POTELLIGENT Technology. Several POTELLIGENT monoclonal antibodies are currently in ongoing clinical trials.

Kyowa also developed COMPLEGENT Technology, which enhances complement-dependent cytotoxicity (CDC), a major mechanism of action in an antibody. By introducing portions of IgG3 into corresponding regions of IgG1, COMPLEGENT Technology significantly enhances CDC activity beyond that of either IgG1 or IgG3 alone, while retaining the desirable features of IgG1.

Kyowa has licensed both POTELLIGENT and COMPLEGENT technologies to biopharmaceutical companies around the world through BioWa, Inc.[2]

Chugai Pharmaceutical Co., Ltd.

Recycling antibodies are engineered so that a single antibody molecule can bind to an antigen multiple times. It targets previously untargetable antigens, and achieves a product profile that could not be realized with a conventional antibody.

Sweeping antibodies are recycling antibodies that has been further engineered to bind to FcRn at neutral pH. A sweeping antibody can be administered in smaller doses with longer-dosing intervals than can be achieved by conventional antibodies.

Bispecific antibodies (BiAbs) have two different binding sites—two different heavy chains and two different light chains—that can respectively bind to two different antigens. Chugai's large-scale BiAb manufacturing technology has produced ACE910, a bispecific antibody granted breakthrough therapy designation by the US Food and Drug Administration in

Kobe GMP manufacturing site.

2015. ACE910 will be investigated for the prophylactic treatment of hemophilia A.[3]

Ono Pharmaceutical Co., Ltd.

Opdivo (nivolumab), codeveloped by Ono and Bristol-Myers Squibb, is the world's first immune checkpoint inhibitor blocking the PD-1/PD-1 ligand pathway, proven to extend overall survival in patients with advanced non-small cell lung cancer previously treated with chemotherapy. It received regulatory approval in Japan for the indication of unresectable melanoma in July 2014, and currently has regulatory approval in more than 40 countries.[4]

Regenerative medicine

With the invention of induced pluripotent stem cells (iPS cells), Japanese industry, government, and academia have put monumental efforts into the application and development of regenerative medicine.

iPS cells

iPS cells are immature cells that can develop into any type of body tissue. The method of making iPS cells was established by Professor Yamanaka Shinya at Kyoto University.5 He and Sir John Gurdon were awarded the 2012 Nobel Prize in Physiology or Medicine for the discovery that mature cells can be reprogrammed to become pluripotent. The Center for iPS Cell Research and Application (CiRA) was established at Kyoto University in April 2010 to serve as a global leader in iPS cell research, conduct basic and applied research of iPS cells with the goal of developing new regenerative medicine, and train future leading scientists and promote research collaboration with Kyoto University's Institute for Integrated Cell-Material Sciences, Graduate School of Medicine, and University Hospital. Advanced goals include producing clinical-grade iPS cells, preparing for clinical studies on Parkinson's disease and blood diseases, and developing iPS-cell-based personalized medicine for intractable diseases such as Alzheimer's disease.[6]

CiRA and Takeda Pharmaceutical Company Limited formed the Takeda-CiRA Joint Program for iPS Cell Applications (T-CiRA) in April 2015.[7] The program combines CiRA's expertise in iPS cells with Takeda's expertise in drug development. The center will conduct research to develop clinical applications for iPS cells and innovative iPS-cell-based medicines, including treatments for heart failure, diabetes mellitus, neuropsychiatric disorders, cancer, and intractable muscle diseases.

Regenerative Medicine Promotion Act

The Japanese Diet (parliament) enacted the Regenerative Medicine Promotion Act on 10 May 2013.[8] The act is a comprehensive promotion of policies on regenerative medicine from R&D to implementation.

The Act on the Safety of Regenerative Medicine, which came into force on 25 November 2014, established standards for institutions providing regenerative medicine and cell culturing, as well as processing facilities for medical treatment and clinical research. The act enables medical institutions to outsource cell culturing and processing. It also specifies three categories of regenerative medicines and stipulates necessary procedures for each category:

- Class I are high-risk, such as those not previously used in humans (ES and iPS cells, for example)
- Class II are medium risk, such as those currently in use (somatic stem cells, for example)
- Class III are low risk (such as the processing of somatic cells)

Based on these risk levels, procedures for submission of plans, standards of cell culturing and processing facilities, and licensing procedures for regenerative medicine are required.

Another piece of legislation affecting marketing of regenerative medicine is the Revised Pharmaceutical Affairs Act, which came into effect on 25 November 2014. This act established an approval and licensing system for regenerative medical products that accommodates the early implementation of regenerative medicine. It also adopted post-marketing safety measures, such as obtaining informed consent from patients on the use of the product and the recording and storing of information on treated patients.

With these acts, the swift and smooth implementation of safe regenerative medicine, as well as the delivery of various products as early as possible, is expected.

Manufacturing Technology

Recent advancements in biopharmaceutical manufacturing are enormous. The following are instances of R&D activities in biopharmaceutical manufacturing in Japan.

Manufacturing Technology Association of Biologics

In 2013, the R&D partnership Manufacturing Technology Association of Biologics was established to develop key technologies for the discovery and manufacture of pharmaceuticals for next-generation treatments and diagnoses. The project was sponsored by Japan's Ministry of Economy, Trade, and Industry. In 2015, the Japan Agency for Medical Research and Development (AMED) joined the project. Over 40 MAB research results were presented at the 67th Annual Meeting of the Society for Biotechnology in Japan in 2015.[9]

In Japan the single-use systems market is constantly growing

In 2015, with the support of Kobe University and many other organizations, MAB completed construction of the Kobe GMP manufacturing site at the Integrated Research Center of Kobe University (Figure 1). Among facility's purposes are application of developed technologies and products into actual GMP-conformed manufacture, the accumulation of novel process data for establishing process platforms, and manufacturing operations education.

Single-use systems

In Japan, the single-use systems market is constantly growing. To ensure the quality of biologics manufactured in single-use systems, an appropriate risk assessment and a stable supply of biologics are necessary. Risk control strategies based on the risk assessment—including selection of appropriate single-use components and qualification of the single-use system—are important.

Although the number of Japanese single-use manufacturers is still limited, many novel technologies and products are emerging. Japanese pharmaceutical manufacturers, together with engineering firms, members of academia, regulatory authorities, and Japanese/global single-use suppliers, have discussed the risks of single-use systems and established control strategies to assure the quality of biologics. These results were published in a white paper entitled "Approaches to Quality Risk Management When Using Single-Use Systems in the Manufacture of Biologics" in 2015.[10] This study will be useful in promoting the development of biologics as well as in ensuring their safety, quality, and stable supply.

Conclusion

What drives this intense Japanese pharmaceutical R&D effort?

In Japan, the number of people aged 65 and over became the highest in the world in 2005,[11] and reached 33 million in 2014, its highest point to date. This pushed the percentage of the population aged 65 and over to 26 percent. By 2060, one in 2.5 people is expected to be 65 or older, and one in four will be 75 or older. Although Japan has successfully established advanced technologies and systems to address these problems, still more are required. These demographics will further drive the development of pharmaceuticals in "Japan as a forerunner of finding answers for emerging issues."[12] ■

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The next 10 years should be a golden age for the Chinese biologics industry

China: the Next Frontier for Biologics

Dr. Chris Chen and Dr. Sheng Yin

Led by development of monoclonal antibodies (mAbs), the biologics industry has witnessed phenomenal growth in the past 20 years. The emergence of mAbs has produced significant breakthroughs in the treatment of cancer and autoimmune diseases. In 2015, seven of the top 10 best-selling drugs were biologics, including six mAbs.[1] Recently approved immuno-oncology mAbs such as Keytruda (pembrolizumab) and Opdivo (nivolumab) and an exciting immuno-oncology pipeline are set to drive the growth of antibody therapeutics in the years to come.

In 2014, the mAb industry accounted for $68 billion in global pharmaceutical sales. By contrast, total mAb sales in China were merely $0.9 billion, despite over 40% average growth during the past 5 years.[2] MAb treatments for autoimmune diseases accounted for 20% of global biologics sales, but only 4% in China.[3] In China, expensive treatments—including mAbs—are usually paid by patients out-of-pocket, so affordability is a major challenge in adopting these new medicines.

China's outdated regulatory system, designed mainly for small-molecule generics, has not been able to provide the necessary support for innovative products from either domestic companies or multinational corporations. It is estimated that new products are typically launched in China 5–9 years later than in the United States. Approximately 30% of US-approved cancer treatments, for example, are not yet available in China. Availability of these novel treatments poses another significant challenge for the Chinese pharmaceutical industry.

As China is the largest developing country with a dramatically aging population, the need for new medicines to treat cancer and other diseases is becoming urgent. Regulators, the pharmaceutical industry, and policy makers are working together to address both affordability and availability of these new medicines—especially mAbs.

CFDA guidelines

Dr. Chris Chen

The first wave of changes came from recent top-down regulatory reforms. In March 2015 the China Food and Drug Administration (CFDA) published its first guidance on the development and evaluation of biosimilars, which is much welcomed and puts an end to many discussions and debates over whether biosimilar standards in China should be consistent with global guidelines. It is anticipated that biosimilar companies in China will now adapt quickly to develop biosimilars to global regulatory standards. Thus, select companies in China may play expanding roles in the development and introduction of biosimilars to the global drug market.

Besides issuing the biosimilars guideline, the CFDA also implemented major reforms to drive innovation. In February 2016, the agency announced comprehensive overhauls and stated that it would give fast-track status to innovative products that fill the gap of unmet medical or clinical needs in the country. Equally important, the agency plans to significantly reduce Investigational New Drug (IND) application review time. This is expected to reduce IND review for oncology products from 18–24 months to 2 months, and closely align CFDA review process with other global regulatory agencies. These reforms will generate great excitement from the Chinese biotech industry to develop both biosimilar and innovative biologics.

To address the affordability of biologics with no or expired patents, a cluster of domestic companies are focused on the development of biosimilars. Due to limited resources in talent, good manufacturing practice, manufac-



turing to global regulatory standards, and financial support, as well as the lack of return in the near-term, Chinese companies naturally selected biosimilar investments that generate potentially higher returns with lower risk.

Booming biopharmaceuticals

Per Reuters' reports, China now boasts the second-highest number of biosimilars in development after the United States. As of April 2016, it is estimated that 27 companies are developing a biosimilar to Humira (adalimumab). Alphamab, a Suzhou, China–based biologics drug company, claimed to have 28 biosimilar programs in development (the most in China), followed by Qilu Pharmaceuticals with 10 programs.[4] Many of these companies are collaborating with global contract research organizations (CROs) to gain access to high-producing cell lines and deep process knowledge to leverage the CROs' integrated talent, technology platforms, and research and manufacturing facilities, in addition to minimizing upfront financial investment (Table A).

This biosimilar development is a direct reflection of China's booming biopharmaceutical industry. China-based biosimilar developers are expected to compete fiercely with global companies to drive down treatment cost; this will somewhat address the affordability challenge in China. If history can repeat itself, current development of mAb biosimilars could mimic biosimilar erythropoietin (EPO) and human growth hormone (HGH) development in China in the 1990s, where more than 20 companies had products on the market and pricing was driven down by over 60%. As a result, the Western EPO and HGH innovator companies gave up the Chinese market to these domestic companies and today, after continued intense competitive pressures, four or five local companies now dominate the Chinese market for these drugs.

There are also three biosimilar versions of Enbrel (etanercept) approved in the Chinese market, which are priced at 30%–50% of the originator product. The domestically manufactured etanercept generated approximately $113 million sales in 2014, accounting for approximately 62% of Chinese market share. This suggests that with a sound biosimilar strategy both Chinese biosimilar developers and foreign companies aiming for the Chinese biosimilar market can be successful and at the same time help drive down health care costs in China (Table B).

Strategic pillars

Since 2012, the Chinese government has named the biopharmaceutical industry as one of seven "strategic and pillar industries." The government created mega research grants with an average $1 billion per year to support of technology platform development that will spur pharmaceutical innovation. The class of anti-programmed cell death protein 1, (anti-PD-1) mAbs and antibody-drug conjugates (ADCs) were listed as separate megaprojects.

As a result, there are already five companies with novel anti-PD-1 mAbs filed with the CFDA for clinical trial approval or in Phase I trials. In December 2015, China's very first anti-PD-1 antibody by Shanghai Junshi Biosciences was approved for clinical trials by the CFDA, almost at the same time as Bristol-Meyers Squibb's anti-PD-1 mAb Opdivo. Throughout China an additional 15 anti-PD-1 or anti-programmed death-ligand 1 (anti-PDL-1) programs are in preclinical development. It is hoped that this strong support for both local innovation in China and global innovation worldwide will gradually address China's availability challenge by bringing in novel biologics to treat diseases in patients who need them most (Table C).

Table A: Biosimilars in development by Chinese companies[5]

Name	Brand Name	Chinese Biosimilar Development Projects
Adalimumab	Humira	27
Bevacizumab	Avastin	18
Etanercept	Enbrel	15
Infliximab	Remicade	13
Rituximab	Rituxan	25
Trastuzumab	Herceptin	24

Table B: 2014 Tumor necrosis factor blocker sales in China[6]

Brand Name	Biosimilar	Company	2014 Sales
Etanercept	Yisaipu Qiangke	3S Bio (CPGJ) Shanghai Celgen	$113 million
Enbrel	Etanercept	Pfizer	~$10 million
Remicade	Infliximab	Janssen	~$50 million
Humira	Adalimumab	Abbvie	~$10 million

China now boasts the second-highest number of biosimilars in development after the United States

One of the reasons the market space in biosimilars and anti-PD-1 mAbs is so crowded is that the Chinese pharmaceutical market is still fragmented by the types of drug bidding and insurance plans provided by each province. It is possible that any company could have a strong hold in one or several provinces. In addition, a local Chinese biologics company only needs to receive approximately 15%–20% market share to be profitable, due to the lower cost basis and lower margin expectations. This crowdedness will not disappear until the Chinese pharmaceutical market consolidates and several dominant companies emerge.

Golden age

With innovation in great demand, Chinese companies are also looking abroad to beef up their biologics pipelines quickly—and to some extent more cost-effectively. Table D outlines recent cross-border deals focusing on innovative biologics. Most companies are sourcing innovation from the United States, Europe and South Korea. In particular, there are several interesting and complementary collaborations between Korean and Chinese companies. Korean companies tend to invest more in research and early discovery, while Chinese companies consider development and manufacturing as their core expertise. A number of cross-border biosimilar deals were also recently announced. This trend is expected to continue at an even faster pace as companies continue to invest in biologics in China.

Table C: Anti-PD-1 mAbs pending IND approval or in clinical trials[7]

Official Name	Sponsor	Status
Nivulomab	Bristol-Myers Squibb	Phase I clinical trial
Pembrolizumab	Merck Sharp & Dohme	Clinical trial application filed
Humanized PD-1 mAb	Junshi	Phase I clinical trial
Humanized PD-1 mAb	Hengrui	Phase I clinical trial
Humanized PD-1 mAb	BeiGene	IND filed
PD-1 mAb	Genor	IND filed
Fully human PD-1 mAb	Gloria	IND filed

Besides sourcing innovation abroad, local innovations are bubbling, and several collaborations with US companies have been announced, as well: Innovent–Eli Lilly and Hengrui–Incyte partnerships are centered on anti-PD-1 mAb assets available from Chinese companies. Interestingly, a third such partnership between Merck Sharp & Dohme and Akeso Bio also

Table D: International collaboration in innovative biologics[8]

Licensee	Licensor	Licensor Region	Product
Simcere	Apexigen	USA	VEGF mAb
3S Bio	Alteogen	Korea	HER2 ADC ALT-P7
Zhejiang Medicine	Ambrx	USA	HER2 site-specific ADC (ARX-788)
Eddingpharm	Prima BioMed	EU	LAG-3-Fc fusion protein
3S Bio	PharmAbcine	Korea	Tanibirumab
Chemo Wanbang Biopharma	Genexine	Korea	EPO-HyFc (GX-E2)
Jinghua	Kadmon	USA	Fully human PDL-1 and VEGFR2 mAbs
3S Bio	Alteogen	Korea	HER2 ADC ALT-P7
Beike Biotech	Altor Bioscienes	USA	Immunotherapy
Galaxy Bio	Oncoimmune	USA	Immuno-oncology portfolio including CTLA4 mAb
Zai Lab Ltd	UCB	EU	Undisclosed first-in-class autoimmune program
CANbridge	APOGENIX GmbH	EU	CD95R Fc fusion protein
Tasgen	Genexine	Korea	A portfolio of five products
CANbridge	Aveo	USA	HER3 mAb
Shutaishen	InflaRx	EU	Novel infectious disease target

Table E: Chinese companies' biologics out-licensure or codevelopment partnerships[9]

Licensee	Licensor	Product
Eli Lilly and Company	Innovent	Anti-PD1 mAb and bispecifics involving anti-PD1 mAb
Incyte	Hengrui	Anti-PD1 mAb
Merck Sharp & Dohme	Akeso Bio	Immuno-oncology mAb

focused on another immuno-oncology asset. All three innovations were originally derived from global CROs, indicating strong global CRO–biologics company partnerships in China (Table E).

Although there will be plenty of challenges, the next 10 years should be a golden age for the Chinese biologics industry, both in terms of innovative biologics and biosimilar mAbs. With investment pouring in, the regulatory process bottleneck expected to disappear, and private insurance emerging to pay for expensive biologics, entrepreneurship in China is poised to become wildly successful. This, in turn, could trigger even more excitement for the biologics industry. It is not surprising that IMS Health predicts that China could be the world's second-largest biologics market by 2020.[3]

China *is* the next great frontier of the biologics industry! ■

China's biosimilar development is a direct reflection of its booming biopharmaceutical industry

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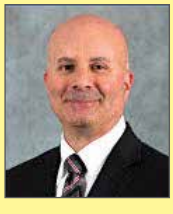

Michael Kopcha, PhD
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Steven Solomon, PhD
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Appointments

ISPE's Third European Annual Conference

Frankfurt, Germany, 7–9 March 2016

Dr. Thomas Zimmer, Vice President European Operations, ISPE

Dr. Thomas Zimmer

Pr. Manfred Schubert-Zsilavecz

Joe Famulare

Three hundred thirty-two attendees gathered at the ISPE 2016 Annual European Conference, held 7–9 March 2016 in Frankfurt, Germany, to explore the theme of "innovation, integration, and integrity." Experts conferred on challenges to quality, compliance, cost, and continuous supply, and discussed topics like knowledge management, single-use production, data integrity, and digital connection of production processes. The conference presented four education tracks—regulatory, facilities of the future, data integrity, and investigational products—with 56 presentations.

Dr. Thomas Zimmer, Vice President of ISPE's European operations, presented "Key Drivers and Future Challenges for the Pharmaceutical Industry." He explained that "Industry 4.0" is a concept of complete integration of automation in the process industry. It has been partly realized in biopharmaceutical manufacturing, where new products with high margins can pay off investments in this highly complex concept.

"Industry 4.0" also means that new skills and capabilities will be required for future employees in the biopharma industry. Beyond traditional education as a chemist or pharmacist, there will be an increasing demand for biologists, microbiologists, and virologists. On the managerial side, a holistic view of the end-to-end supply chain is of utmost importance.

Executive forum

More than 80 attendees came to a kind of "pre-conference" called the Executive Forum to learn about best practices used in other branches and topics of strategic relevance for pharmaceutical production.

Professor Manfred Schubert-Zsilavecz, Vice President of Goethe University in Frankfurt, Germany, opened the forum with a presentation about innovation called "Close the Current Gap in Drug Development by Strengthening the Sociopolitical Acceptance of Life Sciences." Innovation in Europe, however, is subject to classification according to the benefit for the patient. This will determine the price for a new drug in the market and represents a high pressure on manufacturing cost; it's one of the main drivers for innovation in productivity, process development, analytics, and modern quality-control concepts. Culturally, pharma operations must be considered as a "value" for the societies in Western European Countries, not only as a "cost factor" in the health care system.

Regulators spoke about recent developments and updates in the EudraLex Volume 4, EU Guidelines to Good Manufacturing Practice, Annex 1. A complete renovation of these guidelines for aseptic and sterile manufacturing will be issued this summer.

Participants listened to excellent presentations from pharma manufacturers, suppliers, regulators and other stakeholders of the pharmaceutical supply chain, and had opportunities for networking and creative exchange of ideas. The overall positive feedback from the various


Pr. Thomas Friedli


Paul Rutten


Dr. Franz Lärmer


Dr. Graham Cook


Paige Kane


Dr. Theodora Kourti

participant groups encourages ISPE in Europe to continue with this structure of the annual conference.

Joe Famulare, current chair of ISPE's international Board of Directors, explained future challenges for pharma operations and highlighted the changing educational skillset required for employees. Biotechnology workers, for instance, need a different education than those in small molecules. It is estimated that biomanufacturing would require a further 45,000 experts within the next decade. ISPE is filling the gap with industry support for training, offering technical guidance, seminars, webinars, and conferences.

Professor Thomas Friedli from the Institute for Technology Management in St. Gallen, Switzerland, gave insight into the opportunities and limits of cross-industry benchmarking. Very often, branches are compared without looking at their different decoupling points in the value chain of their products and processes. Rightly applied, however, the pharmaceutical industry can learn about product individualization from the automotive industry, safety concepts from the aircraft industry, and cleanroom management from the electronics industry. All are champions for living excellent quality culture.

Paul Rutten, partner at McKinsey & Company and involved in the FDA initiative on metrics, gave an overview of the second wave pilot project on metrics in pharma operations. The more details are investigated, the clearer becomes the need for common definitions and interpretation of measured KPIs. Data must be condensed to information, information to interpretation, and interpretation to conclusions, and conclusions to management decisions. Only common insight and alignment between all stakeholders can lead to meaningful use of metrics.

Four education tracks—regulatory, facilities of the future, and data integrity

Dr. Franz Lärmer, Project Director at Bosch GmbH, Stuttgart, Germany, explained "Industry 4.0" as the next industrial revolution, where machines and processes interact and employees are basically removed from production. His playing field is the production of sensors, used everywhere from smart phones, cars, and houses to highly complex production processes. Sensors are to a certain extent "mass products" and must be of high quality, as their functionality can be easily tested by the customer. Making high-quality mass products with zero failure rate is a must in this business. The same principals should be applied to pharmaceuticals.

Dr. Graham Cook, Senior Director, Process Knowledge and Quality by Design at Pfizer and Chair of the European Federation of Pharmaceutical Industries Associations' Technology and Development Expert Group (TDEG) Committee led the audience back to pharmaceuticals. What does an executive need to know about ICH standards, what is new, and what has affects pharma operations?

Keynote sessions

Paige Kane, Director of Knowledge Management at Pfizer, opened the keynote session addressing a key success factor for future operations: knowledge management. This very complex topic is manageable only if driven by the right cultural mindset. Hot spots are knowledge transfer from development to production and from one manufacturing site to another, but also ensuring and maintaining knowledge through retirement, job rotation, or when key people leave a company. She noted that not all knowledge can be codified, and that people's experience is another form of knowledge.

Dr. Theodora Kourti, ISPE's Senior Vice President for Regulatory Affairs, drew on her history in industry and academia to highlight the opportunity that continuous manufacturing presents to reduce time to market and manufacturing cost. She also identified the need for definition in quality assurance concepts and quality risk management.

Mark Birse of the Group Manager Inspectorate at MHRA gave an overview of EU and global inspectorates' current focus: regulatory changes and closer coordination between agencies.


Mark Birse


Dr. Bruno Mouton

Dr. Bruno Mouton, Vice President of Quality Auditing and Compliance, Merck Serono, Darmstadt, Germany, addressed additional high-level success factors for pharma operations, noting that people are the drivers for execution and excellence in pharmaceutical production. He explained how Merck organizes continuous development of people's abilities to understand complex pharma manufacturing processes, from both technical and business perspectives. Systematic job rotation, defined qualifiers for reaching the next level in management responsibility, lessons-learned exercises, ex-pat assignments, and a knowledge portal are some of the tools that help increase employee capabilities at different levels in the organization.

Plant tours

The conference also included three guided plant tours to Merck Darmstadt, Corden Pharma Heidelberg, and Lufthansa Cold Chain Management Facility. ■

2016 Aseptic Conference

Ryan Hawkins
VP Operations, Cook Pharmica, LLC, Barrier Track Lead
Joerg Zimmermann
VP Development Service, Vetter Pharma-Fertigung GmbH & Co. KG, Aseptic Track Lead
Rameeza Shaikh
ISPE Continuing Education Program Manager

The 2016 Aseptic Conference was held from 29 February to 1 March at the Crystal Gateway Marriott in Arlington, Virginia, United States. This year ISPE celebrated the twenty-fifth anniversary of this signature event.

The total number of attendees was 318, which included 154 education attendees, as well 118 exhibitors (representing 49 companies), speakers, and representatives from the regulatory community.

Barrier track highlights

- We heard from regulators that clear, early, and frequent communication is the biggest key to successful resolution of challenges including, but not limited to, facility design, process changes, and regulatory submission content.
- The platform of ready-to-use components, including vials, syringes, and cartridges has strengthened. Newly designed robotic, sometimes modular filling equipment is creating yielding greater flexibility in products and presentations, simplifying design processes, and reducing project and life cycle costs.
- Several case studies demonstrated how modifying existing facilities can transform them into long-term reliable facilities using modern technology.

Sessions were well attended by a knowledgeable and engaged audience

Aseptic and disposables track highlights

The presentations in this track gave a good overview of the state of the art for disposables/single-use equipment.

Review from a regular attendee

Dear Rameeza,
I always enjoy the Aseptic Processing/Barrier Isolation Conference! I consider that the exchange of more technical, more directly applicable information happens with a high frequency at this conference, every year. I believe this is more useful to manufacturers directly than what is found at many other conferences that I have been to. The format lends itself directly to great dialogue, both in question-and-answer sessions, and informally at the breakout sessions and during the networking breaks. I would recommend this conference to anyone wishing to hear about real-life situations regarding aseptic processing/barrier isolation, as well as other CGMP matters. In fact I have recommended it often to both regulators and my clients.

Best regards,
Destry Sillivan, Owner
TCubed Regulatory Consulting, LLC

Speakers covered the subject from many angles:

- Development of aseptic fill-finish processes using disposables
- Standardization of disposable equipment
- Extractables risk assessment and testing of disposable equipment
- Change control strategies with suppliers of disposables
- Manufacturing processes and technology for silicone tubing
- Using 2,000-liter disposable bioreactors in fermentation at commercial scale
- Developing a disposable dispensing isolator
- Using disposable equipment in fill-finish processes

Sessions were well attended by a knowledgeable and engaged audience; lively discussions

ISPE celebrated the twenty-fifth anniversary of this signature event

with participants complemented the information presented in the workshop. Overall, the presentations showed that there is no single "right" answer. It is not "disposables or stainless steel," but rather the clever combination of both to create the best possible process. The speakers were very realistic with their views.

General sessions

- The industry panel discussion was well received. A concise opening statement by panelists on the use of robotics in aseptic processing was followed by a lively one-hour discussion that captivated the 300-member audience. It was a great quick overview of who is thinking about and doing what.
- Discussion groups helped accelerate benchmarking and learning.
- FDA Q&A at the regulatory panel was exceptionally good, with a record number of questions and answers thanks to preparation and organization by FDA and facilitation by Bob Sausville. ■

Unleashing Innovation: When Pharma Meets Techno

John Bournas, ISPE President and CEO

Photos: Agoria; ©Triptyque

On March 10, 300 attendees from the pharmaceutical and technology industries gathered for "Unleashing Innovation: When Pharma Meets Techno," sponsored jointly by Pharma.Be, the Belgian Pharmaceutical Industry Association; Agoria, the federation of the technology industry in Belgium; and the ISPE Belgium Affiliate.

Baudouin Corlùy, Director of Business Communities for Agoria, the federation of the technology industry in Belgium, explained: "Only by working together can the pharma and technology industries realise the full benefits of digital health and industry 4.0. To boost this collaboration, we organized this event with pharma.be and the ISPE Belgium affiliate, the members of which will be at the forefront of advances in both tech and pharma."

John Bournas spoke on the importance of technological innovation in the pharmaceutical industry during the plenary session:

"Given the constantly changing landscape of our global pharmaceutical and biopharmaceutical industry, innovation is critical. To recognize key innovators in our industry, ISPE has introduced a new Facility of the Future Award Category in 2017, as part of the widely recognized Facility of the Year Awards (FOYA) Program. The new Facility of the Future Category will recognize innovative design concepts, new technologies, and unique solutions that exemplify the next generation of agile and flexible life sciences facilities.

"Continuing focus on FOYA and Facility of the Future, collaborative partnerships with the National Institute for Bioprocessing Research and Training and the Institute of Technology Management at the University of St. Gallen, and the new ISPE *Sustainability Handbook* all demonstrate ISPE's relentless commitment to innovation in our industry.

Dr Thomas Zimmer

Photos: Agoria; ©Triptyque

"Traditional manufacturing and quality functions will struggle to keep pace with the digital revolution and need for more personalized medicine. By embracing 'Industry 4.0' and by adopting new technologies and partnerships to make their production infrastructure more efficient pharmaceutical and life science companies will be able to better cope with the increasing market and regulatory demands and thus enable the future of pharmaceutical production."

In addition to Bournas, Dr. Thomas Zimmer, ISPE Vice President of European Operations, appeared as part of the "Pharmaceutical Production: The Road to Pharma Factory 4.0" panel. ■

ISPE Broadens Training Footprint in Europe

ITEM-HSG and NIBRT to Offer Training In 2017

ISPE Members around the world will soon be able to choose between three locations for professional training and skills development. St. Gallen, Switzerland, and Dublin, Ireland, have joined Tampa, Florida, as brick-and-mortar training spots; this makes training even more accessible for ISPE Members and the regional pharmaceutical industry.

ISPE and the Institute of Technology Management at the University of St. Gallen (ITEM-HSG) signed a contract on 7 March 2016, in Frankfurt, Germany, during the ISPE European Annual Conference. ITEM-HSG focuses predominantly on the development of problem-and-application research. It maintains close ties to industry through intense collaboration with European and global organizations such as ISPE through major research and consulting projects, the results of which flow directly into courses.

Dr. Thomas Zimmer, ISPE's Vice President of European operations, is thrilled with the news. "The ITEM-HSG has a fantastic cross-functional database of operational excellence benchmarks in various branches of the process industry, which can be leveraged by the pharmaceutical manufacturing industry," he said.

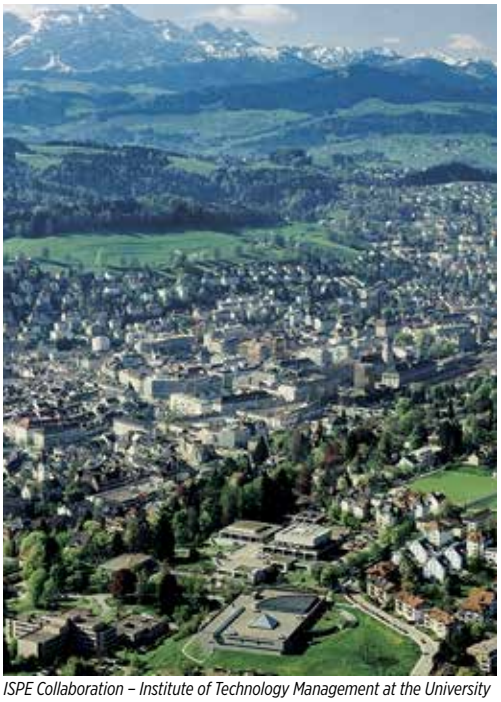
Operational excellence, a complex management concept that can be difficult to teach, is one of ITEM-HSG's key areas of research and consulting. "Combining ITEM-HSG's management training in operational excellence with ISPE's technical training in pharmaceutical manufacturing means ISPE members have a European learning base, in particular to know the levers that make manufacturing processes more efficient, agile, and in compliance," Dr. Zimmer added.

Designed to ensure the safety of the world's supply of medicines, ISPE training uses a body of knowledge viewed as the leading resource by manufacturing professionals and regulators around the world. Classroom training gives participants two to three days of topic-specific in-depth learning and skill building. Courses include lectures, group exercises, and case studies that provide participants with practical information they can apply immediately to their job.

ISPE has also signed a memorandum of agreement with the National Institute for Bioprocessing Research and Training (NIBRT), in Dublin, Ireland, for a similar collaboration. NIBRT is a world-class institute that provides training and research solutions for the bioprocessing industry. Its mission is "to support the bioprocessing industry by providing a unique learning experience for trainees in an environment that replicates the most modern industrial bioprocessing facility."

Ali Montes, ISPE's Senior Director of Training, said this is all part of ISPE's plan to increase the organization's training reach. "In 2017, we have two six-course training events in Europe," she noted, "in addition to the courses we plan to hold at the NIBRT and ITEM-HSG.

"Now, with a base in continental Europe and one in Ireland in addition to the Tampa Training Institute in the United States, ISPE is solidifying its global training footprint, and in so doing, is making it easier for members to reach us." ■



ISPE Collaboration – Institute of Technology Management at the University of St Gallen, Switzerland (ITEM-HSG)

ISPE President and CEO John Bournas (left) and NIBRT CEO Dominic Carolan

National Institute for Bioprocessing Research and Training (NIBRT), Dublin, Ireland, is a world-class institute that provides training and research solutions for the bioprocessing industry.

International Board of Directors Elections

Email ballots arrive this month

The 2016 International Board of Directors Election will open in mid-June. You can help shape the Society's future by voting for representatives to fill open seats.

The Board is ISPE's ultimate authority: It establishes the Society's vision and mission, articulates strategic priorities, and ensures that business operations are consistent with its policies, best practices, and laws. We count on Members to vote for candidates that best represent the ideas and priorities that are important for ISPE.

Election to the Board comes with considerable responsibility and is never undertaken lightly. Candidates on the ballot were nominated by ISPE Members and have been vetted by the Board Nominating Committee and Board Officer Nominating Committee through a demanding process. Learn more about this year's candidates by visiting www.ispe.org/board-election/meet-the-candidates.

If you are a current ISPE Member, you will receive an official electronic ballot by email from Intelliscan, Inc., our independent election partner. Please add @intelliscaninc.net to your safe senders list to ensure that you receive your ballot. If we do not have your email address on file, you will receive a postcard and voting instructions by mail. Please be sure to cast your vote; the election closes at 11:59 PM EDT on 20 July 2016. ■

Erratum

We neglected to credit the photographer whose work appeared in our January/February 2016 profile of George Millili. The photos were taken by Rick Brady Photography, Riva, Maryland.

Guidance Documents

Good Practice Guide

Operations Management

ISPE is pleased to announce the publishing of the *Operations Management Good Practice Guide*.

This Guide establishes a framework for all major topics in operations management in a ready-to-use "toolbox." The multidisciplinary document provides a 360-degree review of everything involved in the manufacturing and supply of life sciences products in pharmaceuticals, biotechnology, and medical devices. *The Operations Management Good Practice Guide* also defines a common language with which to discuss operations management, and introduces lean concepts—a pharmaceutical industry first. Learn more about the guide and how to purchase by visiting http://www.ispe.org/guidance-documents.

Concept and Discussion Papers

Process Validation Lifecycle Implementation for Existing ("Legacy") Products

For many companies, the most urgent issues in aligning with a process validation lifecycle center are the ongoing verifications of existing, or "legacy" products. The ISPE Process Validation (PV) Team has drafted a discussion paper addressing the concerns of companies attempting to implement the process validation lifecycle as a whole and, more specifically, the ongoing process verification phase.

It may be problematic for firms simply to increase monitoring of all attributes to "statistical" levels, especially in the absence of a well-developed knowledge base or pharmaceutical quality system to support the implementation of enhanced monitoring. A "road map" to implementation may be needed. This paper is intended to help plan that journey for legacy products and provides a perspective for both company-wide and individual product strategies. Download this paper and provide feedback by visiting http://www.ispe.org/publications/discussion-papers.

Considerations for a Corporate Data Integrity Program

Regulatory agencies, as well as industry, rely on accurate information to ensure drug quality and patient safety. If the information associated with a drug product is not accurate, complete, or reliable, a company cannot ensure the safety and efficacy of their product for the patient. Data integrity has become one of the hottest regulatory and compliance topics in years and pharmaceutical companies are being driven to implement or review corporate data integrity compliance programs.

To help understand the critical success factors for a corporate data integrity program, the ISPE GAMP Community of Practice (CoP) released a concept paper that addresses the topics of executive sponsorship, cross-functional ownership, risk-based prioritization, planning for continuous improvement, and the data integrity lifecycle. It also provides some practical insights into ensuring the sustainability of the program and the data integrity lifecycle. Download this paper by visiting http://www.ispe.org/publications/concept-papers.

How Should Clinical Supply Chain Performance Be Measured? An ISPE Discussion Paper/Survey

Clinical supply chain management includes unique but important elements that are worth measuring. The investigational products community in general has not yet homed in on the most relevant KPIs, conducted benchmarking, or targeted a common set of metrics with associated performance standards.

The ISPE Investigational Products CoP has created a discussion paper/survey that establishes a framework for standardizing key performance indicators for the clinical material/investigational product supply chain. With this discussion paper/survey, we encourage the community of clinical supply chain professionals to provide input on the importance and prioritization of the most relevant metrics, potential challenges, and solutions to overcome them, along with how each metric should best be captured for purposes of standardization.

Your feedback matters! Participate in the survey by visiting http://www.ispe.org/publications/discussion-papers. Deadline for completing the survey is 15 June 2016. ■

NEW Release

ISPE Good Practice Guide: Operations Management

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

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

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

Topics considered by this Guide include:

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

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

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www.ISPE.org/guidance-documents

ISPE VP and CFO Victoria Smoke Retires

Victoria Smoke has made the decision to retire after 20 years of service with ISPE. We are extremely grateful for the dedicated years that Victoria has provided to our organization. She has ably managed its operations and worked hard to bring us back to fiscal health. She has been a true asset to ISPE and an outstanding professional.

During her tenure she has made many friends within the organization among volunteers, members, and those who have had the chance to interact with her. She will be truly missed as a colleague but most of all as a friend.

I hope you join me in thanking Victoria for her service and in wishing her all the best on her new path.

John E. Bournas

Notes in a Bottle, from ISPE's Administration and Finance Department

—Victoria is dedicated, insightful, and gracious. While we are losing a CFO at the end of May, for many of us who have worked closely with Victoria, she is also a mentor, an empathetic ear, and an inspiration. God bless you in your future endeavors, Victoria. You will be sadly missed!

— I have had the privilege of working with Victoria for 20 years. Her dedication to ISPE has been unwavering and her astute knowledge of ISPE as a whole, along with the expertise to oversee the financial well being of our organization has been extraordinary. She is a woman whose integrity I admire. I will miss her.

— I've learned a lot over the years working under your direction. You are an asset with a wealth of knowledge of the organization that no one could ever replace. You will surely be missed. Enjoy your retirement.

— In terms of profit and loss, your retirement is a loss for your colleagues and a profit for your family.

— Victoria is the epitome of optimism and hard work. Her never-ending library of knowledge is beyond measure. We are surely going to miss having her as our go-to person! Blessings and Happy Retirement!!

— Just like a perfect cake cannot be made without the perfect ingredients, a perfect boss cannot be made without perfect employees. Happy retirement, to a perfect boss from her perfect employees.

— Victoria has the ability to convert mistakes into lessons, pressure into productivity and skills into strengths. She really knows how to bring the best out in everyone around her.

— Victoria has meant so much to ISPE. Her passion for ISPE and its mission is evident in everything she does and she has been a true inspiration to all of us.

— I've really enjoyed working for Victoria. I've learned a lot about this industry and its importance by working for her. She's definitely helped make me a better IT professional. ■

ISPE President and CEO John Bournas presents a plaque commemorating 20 years of service to Victoria Smoke, Vice President of Administration and CFO, Accounting.

Quality Metrics Wave 2 Report to Debut at 2016 Quality Metrics Conference

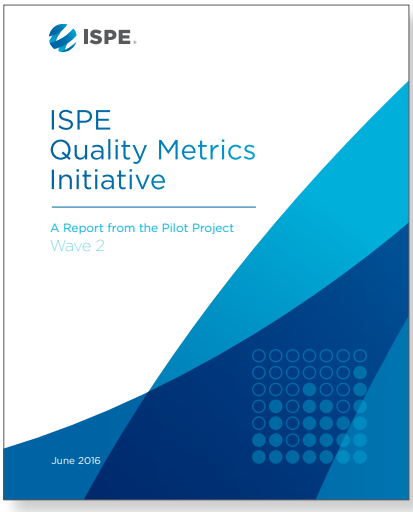
The ISPE Quality Metrics Initiative Pilot Project Wave 2 commenced in July 2015. Like Wave 1, presented a month earlier at the June 2015 Quality Metrics Conference, Wave 2 was a confidential data collection and analysis conducted in partnership with McKinsey and Company.

Each participating site received a confidential benchmarking report that outlined their performance with respect to their peer group(s). Participating companies reported that they derived great value from the metric data they received, and from the confidential benchmarking exercise. ISPE received only aggregated data; individual sites could not be identified.

Preliminary findings from Wave 2 were used to develop ISPE's response to the FDA Request for Quality Metrics Draft Guidance and Federal Register Notice. The final results confirm findings and statistically significant relationships from Wave 1, affirm the importance of quality culture, and identify some further relationships.

"ISPE Quality Metrics Initiative: A Report from the Pilot Project, Wave 2" will be presented at the ISPE/FDA/PQRI Quality Metrics Conference, 8–11 June 2016 at the Bethesda North Marriott Hotel and Conference Center, North Bethesda, Maryland.

Quality Metrics Conference attendees will receive a free copy of the report as part of their registration fee. ISPE Members will be eligible for a free download immediately following conference. The report will also be available for sale alone or in combination with the Wave 1 report. ■



Participants at the 2015 Quality Metrics session

Appointments

Ciara Durkan, Senior Director, Membership and Component Relations

Ciara Durkan joined ISPE on 11 April 2016 as the new Senior Director, Membership and Component Relations. Ciara brings more than 20 years of marketing, communications, and membership experience to ISPE, and we're excited to have her join the team.

Ciara was previously the Director of Membership Development at the Endocrine Society (ES), a professional biomedical association in Washington, DC, where she drove membership growth and retention for almost seven years. From 2011 to 2015, Ciara and her team increased Endocrine Society membership by nearly 30%—from 14,000 to more than 18,000—by focusing on increasing both member retention and international membership. Prior to ES, she worked in membership marketing for a financial professionals' association, managed integrated marketing and communications for B2B clients at two DC-based advertising agencies, and worked closely with Disney on brand management and the development of creative materials for Disney on Ice.

A native of the DC area, Ciara enjoys spending time with her husband and two young sons. She will be located in the Bethesda office and travel frequently to the Tampa office. ■

ISPE 2016 TRAINING

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JUNE

ISPE Training Institute, Tampa, FL

- Auditing (G07), 27 – 28 Jun.
- Bio Process Validation (T32), 13 – 14 Jun.
- Sterile (T12), 6 – 7 Jun.
- Q7A (T30), 20 – 21 Jun.

JULY

ISPE Training Institute, Tampa, FL

- Basic GAMP® 5 Annex 11 / Part 11 (T45), 11 – 13 Jul.
- Cleaning Validation (T17), 25 – 26 Jul.
- HVAC (T14), 18 – 20 Jul.

AUGUST

ISPE Training Institute, Tampa, FL

- C&Q (T40), 11 – 12 Aug.
- OSD (T10), 8 – 9 Aug.
- Process Validation (T46), 22 – 24 Aug.

SEPTEMBER

Barcelona, Spain

- Facilities, Systems and Equipment Workshop (T48), 27 – 28 Sept.
- GAMP® 5 Data Integrity (T50), 26 – 27 Sept.
- GAMP® 5 Process Control (T21), 27 – 28 Sept.
- HVAC (T14), 26 – 28 Sept.
- Technology Transfer (T19), 27 – 28 Sept.
- QRM (T42), 26 – 27 Sept.

San Diego, CA

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

ISPE Training Institute, Tampa, FL

- Application of GAMP® 5 (T11), 12 – 13 Sept.
- Bio Manufacturing Processes (T24), 15 – 16 Sept.
- C&Q (T40), 29 – 30 Sept.

Atlanta, GA

- Cross Contamination (Risk-MaPP) T41, 22-23 Sept.
- Technology Transfer (T19), 22-23 Sept.

OCTOBER

Boston, MA

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

Copenhagen, Denmark

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

NOVEMBER

ISPE Training Institute, Tampa, FL

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

DECEMBER

ISPE Training Institute, Tampa, FL

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

ISPE Members attend training programs and other events at a discount.
Visit www.ISPE.org/Membership for details.

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

Register Today at ISPE.org/Training

Leaders of the Future

As ISPE Young Professionals, we believe in bringing faster and better quality medicines to the people who need them the most. We make it happen by widening our horizons, connecting industry young professionals across the world, and providing technical knowledge to other young professionals in quality, development, and manufacturing.

Widening our horizons

If we as young professionals want to innovate within the space of our highly regulated industry, we have to combine the experienced leaders of today with fresh, new minds.

As an example, young professionals are keen to seek out and understand new technologies like augmented reality and artificial intelligence. With this in mind, I went to the ISPE European Annual Meeting in Frankfurt, Germany. I asked several regulators, quality officials, regulatory affairs leaders, and manufacturing experts what it would take to implement augmented reality technologies in a good manufacturing practice manufacturing setting. It could be used for things like operator training and to help visualize all of the relevant data coming out of the production process.

I had a variety of responses including "there is no FDA or EMA approved process, that I'm aware of," "this would change completely how quality works," and "to do that, we would need to completely change our IT infrastructure."

As a young professional these answers will seem daunting, but I can assure you, you will find like-minded people at ISPE who are willing together with regulators and industry professionals to work on tomorrow's solutions for today's problems.

I urge every young professional to ask to your process development and commercial manufacturing groups about what it would take to implement new technologies you come across in your daily life.

ISPE is the best university in the world for pharma in real time

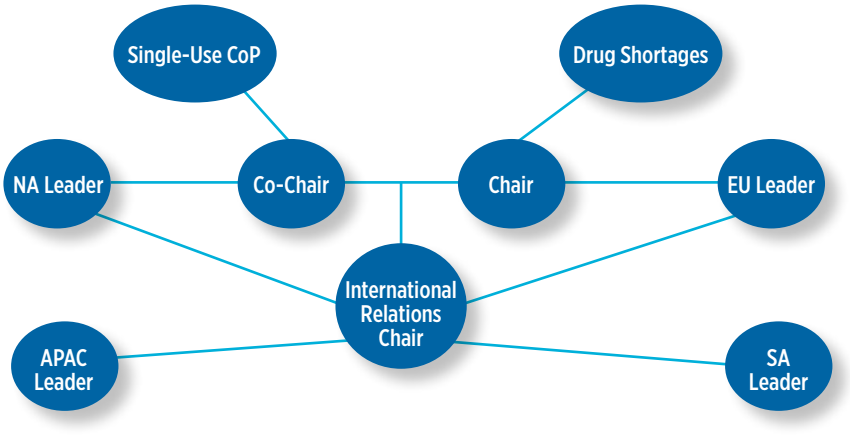
Connecting industry Young Professionals across the world

Through ISPE I was able to connect and work together with incredible young professionals across the world, even though I'm living in Germany. With this network, who all commonly believe in bringing higher quality medicines to people faster, I'm able to know what is going on in our industry in the different places of this world learning from their first hand experiences.

Brody Stara, CPIP, currently works at Amgen as an engineer in single-use systems and technology. He earned his bachelor's degree in chemical engineering from the University of Massachusetts, Amherst, where he first joined ISPE and was student chapter president his junior and senior year. I met Brody at my first ISPE Annual Conference in 2013. It was great to get the insights of a young engineer from the USA and compare it with my experiences. Brody is an active member serving on the Single-Use CoP and as Co-Chair of the Young Professionals Committee.

Brody Stara, YP Co-Chair

Zen-Zen Yen, International Relations Chair



International relations chair connectivity network

Together in our pursuit to build a more international Young Professionals Committee and understanding better the regional needs of young professionals across the world, we created a new volunteer position the "International Relations Chair" As straightforward problem solvers, we went to LinkedIn looking for a young professional from a pharmaceutical company that wanted to join a nonprofit and who could speak Chinese. We contacted quite a few young professionals, but the perfect candidate is Zen-Zen Yen.

Zen-Zen Yen is an International Trainee at Bayer and as of May 2016 she will be working for five months in Buenos Aires, Argentina. Zen-Zen Yen will support the Argentinian and Brazilian Affiliates in building a Young Professional Chair and Co-Chair.

Same technical language for regulatory, quality, and development and manufacturing

From my point of view ISPE is the best university in the world for pharma in real time. We are the ones who sit together with regulators and industry experts building new guidelines and industry initiatives. There is no other place in the world where we can get the most up-to-date news.

We have to start talking the same technical language

It is our responsibility to bring young professionals from the various technical backgrounds and start working together to build our future. We have to start talking the same technical language. A great area of development for young professionals at ISPE is to get more involved within Communities of Practices learning and collaborating with industry experts. From my three years at ISPE, challenges arise in our industry because not everybody has access to the in-depth knowledge that we generate at ISPE.

Bringing it all together

We as young professionals have the unique opportunity to shape our future. From my point of view the best place to do this is the ISPE. Because we literally sit all together and work on industry guidelines. I ask all people in our industry to get at least one young professional to join our cause and support us in shaping our future. ■

Chapters and affiliates with YP chairs

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Belgium
DACH
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France
India
Ireland
Malaysia
Netherlands
Nordic
Philippines
Singapore

US Chapters

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Great Lakes
Greater Los Angeles
Midwest
New Jersey
San Diego
San Francisco/Bay Area

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

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Meet Young Professional Jaywant Pawar

At a very young age, few of us know what we really want to do when we grow up. That was not the case for Jaywant Pawar, who knew from his preschool days that his calling was to become a scientist in the research and development of medicines.

Born in Dindori, a small village of 40,000 residents in the Nashik district of Maharashtra, India, Pawar saw people from his village dying from disease. "Irrespective of the medicines prescribed by doctors, they could not respond to the existing therapy," he says. "From that time, I wanted to do something for all those poor people who couldn't live due to a lack of proper medicines. I wanted to do something for my society, for humanity in India, as well as worldwide."

Today, Jaywant Pawar, 28, is pursuing his PhD in pharmaceutics at the Institute of Chemical Technology (ICT) in Mumbai and is Chair of the ISPE Young Professionals Committee in India. Described by some in ISPE as a "real go-getter," his academic record and accomplishments as a young professional certainly show that he's a driving force for growth in India's pharmaceutical industry.

First PhD from Dindori

Growing up in Dindori, Pawar attended both primary and secondary schools in the village. And he excelled: Upon completing his secondary education, he received the National Talent Scholarship, a program to recognize students with academic talent in India. This was his first academic endeavor in his school days.

"My parents' wish I was that I would become a medical doctor, but that was not my goal," he says. "Given my inclination towards a research-oriented career in biological sciences, chemistry, and medicine, I selected pharmaceutical sciences as the focus of my graduate studies."

He enrolled at the Mahatma Gandhi Vidyamandir (MGV) College of Pharmacy Nashik, University of Pune, after securing the highest ranking in his entrance examinations. In India, entrance exams are administered for entry in the medical and pharmaceutical education fields.

"My undergraduate studies helped me to develop a profound understanding of all aspects of pharmaceutical sciences," says Pawar. "I came to know what medicine is, how it cures diseases, what happens when we take a tablet, how it goes in your stomach, and how it cures the disease. I have come to know the widespread applications."

During his undergraduate studies, Pawar participated in the Young Innovators' Choice Competition conducted by UDCT Mumbai. His team won second prize for their research into problems faced by the pharmaceutical industry. "It was an excellent experimental learning opportunity for me and I tried to develop my investigational skills, critical thinking ability, presentation skills, and my capability to work in a team," he says.

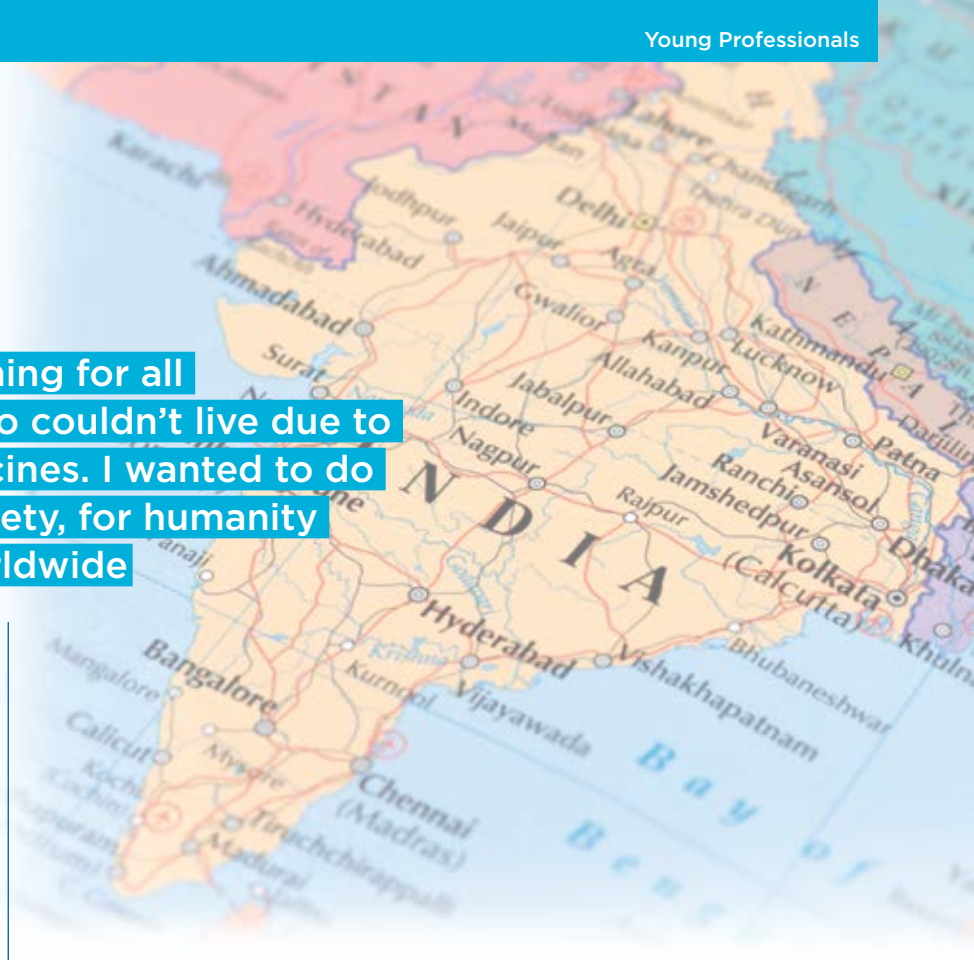
In his final year at MGV's College of Pharmacy, Pawar qualified an entrance examination for the University of Pune. Once again he secured the highest ranking, and enrolled in the Government

Jaywant Pawar, India Affiliate YP Chair

College of Pharmacy to earn his master's degree with specialization in pharmaceutical drug delivery systems.

During his first year of postgraduate studies, Pawar had an opportunity to teach a pharmaceutical science course to undergraduate students at YCMOU University, a private university in Maharashtra, with the collaboration of LUPIN Pharmaceuticals. During his second year, he worked as a Trainee Research Fellow at GlaxoSmithKline on a project studying the compression characteristics of binary blends of antacid drug molecules. "My research was to tackle a problem they were facing on the production side and my findings were successfully implemented," Pawar says. "It was a true pleasure and immensely enriching experience working at GlaxoSmithKline PR&D Nashik under the aegis of Dr. Kisan Chaudhary."

As he completed his master's studies, Pawar had three job offers in hand, but he decided to pursue his PhD degree instead. Once again, he completed his entrance examination and secured the highest ranking. He began his doctoral studies in Pharmaceutics at ICT in Mumbai, one



I wanted to do something for all those poor people who couldn't live due to a lack of proper medicines. I wanted to do something for my society, for humanity in India, as well as worldwide

of India's leading institutes for excellence in academics and research. His PhD research topic, "Approaches for Dissolution Rate Enhancement of Poorly Water Soluble Drugs" focuses on anti-HIV, antimalarial, and antifungal drug-delivery systems.

"Within the next six to eight months," he says, "I shall complete my doctoral studies with the submission of my dissertation and I will become the first doctorate from my home village of Dindori … and that I can say proudly."

ISPE

Pawar joined ISPE in April 2015 and one month later attended annual Europe meeting in Frankfurt, Germany, where he presented and won first prize in the poster competition for his research on "Enhancement of Solubility and Stability of Itraconazole by Formation of Solid Crystal Suspensions Using Hot Melt Extrusion." Pawar published an article on the same topic in the March/April 2016 issue of *Pharmaceutical Engineering*.

At that conference, Pawar and other young professionals met with Robert Landertinger, ISPE Europe's Young Professionals Chair. Landertinger spoke about ISPE YP groups as well as the benefits of ISPE, and Pawar's interest was piqued. By August 2015, Pawar was nominated to be the Chair of the ISPE Young Professionals Committee in India.

"I'm glad to be a part of ISPE, a global organization that has supported and developed my personal confidence as well as helped me grow," says Pawar. "It has given me an international platform to work and I will do my best to grow the ISPE in India by participating in various workshops and organizing seminars to introduce ISPE. I will also be more and more present in various ISPE meetings in India and in Europe and the USA.

"As the YP Chair in India, I'm responsible for internationalization of ISPE with Indian students who are studying at various universities across India, including my colleagues and their friends who are working in various pharmaceutical companies," he says. "I organized one seminar at ICT to introduce ISPE and the benefits of joining, and to date more than 21 of my friends and colleagues have joined ISPE. In the future I am planning to organize workshop meetings for young professionals across India, so that students studying in university as well as professionals who are working in the pharmaceutical industry can come together. I am also planning to start an ISPE India Journal to so that professionals from universities as well as from industry can exchange their ideas and their practical experiences; and that will be helpful in filling the gap between industry and academia. That can develop new platforms so we can collaborate more effectively across different regions of the world and between peers and experts."

A future in teaching

Looking ahead, Pawar sees himself as a teacher, after sufficient industrial experience. "As a professor, like my role model Dr. Purnima Amin, I will contribute to science by doing enormous research in novel drug delivery systems," he says. "I will find innovations and improvements through my curiosity and my creativity. With the help of my research students, I shall explore my research in each aspect of drug delivery so that we can help in the translation of these innovations into novel drug delivery systems that will be helpful to humanity; helpful to bring medicines to the poor people around the world at a reasonable cost."

"I love teaching students because I believe that through teaching we contribute to their development. And as I teach, I am able to understand new aspects of subjects; even interaction with students helps me to generate new ideas," he explains. "And the development of students will ultimately help India's development, because today's youth is the future of our nation." ■

Mike McGrath

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Q&A with the ISPE Japan Affiliate

ISPE® | Japan Affiliate

Pharmaceutical Engineering spoke to ISPE Japan Affiliate Chairman Shigeru Nakamura about the Affiliate's history, its challenges, and its plans for 2016 and beyond.

Shigeru Nakamura

In recent years the Japan Affiliate has held more than 20 events annually

Can you give us an overview of the Japan Affiliate—its history, membership level, geographic coverage, important accomplishments, etc.?

The Affiliate was inaugurated in June 2002, largely in response to rapidly increasing need in the Japanese pharmaceutical industry for a more complete understanding of overseas (notably American and European) regulations and guidelines. It was well recognized that ISPE International would be the ideal conduit for up-to-the-minute information on the quickly evolving demands faced by manufacturers.

Dedicated office space was quickly identified in a central Tokyo location and an ISPE Japan Affiliate Manager hired, with further staff to be added over a period of time. The aim of establishing the office was to gain maximum efficiencies and provide optimized services for a membership that was expected to grow.

The Japanese pharmaceutical market continued to expand as a result of its graying population, and the Affiliate found considerable favor with its program of seminars and conferences. Moreover, we soon began to play a key role in providing translations of technical documents, giving members a further enhanced understanding of international requirements.

To accomplish our goals, in recent years the Affiliate has energetically reorganized itself. Today, the Board of Directors—comprising five Officers, 20 Directors, and three Adjunct Directors—draws widely from Japan's pharmaceutical industry. Most functions are conducted by one or more of the Affiliate's 16 Communities of Practice (CoPs), while certain specialty tasks/events are undertaken by dedicated Committees.

We are proud that approximately 60% of the Affiliate's membership is directly involved in its CoPs. This provides the engine for a successful program of events and tasks. We never fail to recognize the high level of support received from pharmaceutical neighbors both near and far, and we look forward to even greater collaboration in the years to come.

How active is the Japan Affiliate? Do you hold a lot of events?

In recent years the Japan Affiliate has held more than 20 events annually. Typically, these include the Annual Conference, the Winter Meeting, one or two educational seminars (using ISPE International materials), several local CoP training seminars, and quarterly networking events.

In addition, since 2013 a higher level of focus has been on Young Professionals (YP) seminars, which are held six to eight times each year at the Japan Affiliate offices, usually on a weekend evening. This year, for the first time, a YP session will also be held at the Workshop during the 2016 Japan Affiliate Annual Conference.

What are your objectives for 2016 and beyond?

The objectives outlined in our Affiliate action plan for 2016 call for an expanded membership, increased dissemination of ISPE knowledge through a variety of outreach programs, provision of services to our members, and the discovery and nurturing of competent personnel for the continued development of the Affiliate.

As of December 2015, the Affiliate had 852 members with a broad coverage of most pharmaceutical companies, including the industry's big names. We expect further membership expansion will come from the suppliers, consultants, and GDP-associated companies or other firms related to regenerative medicine.

To disseminate ISPE knowledge and provide services to our members, we focus on publishing Japanese translations of ISPE Guidance Documents. From 2004, when we began to publish translated versions of GAMP 4 and Technology Transfer, to the end of 2015, we have translated

Building a good relationship with PMDA is an ongoing objective w

and published 28 titles in total, with 5,900 books purchased, including five Baseline Guides, nine GAMP Good Practice Guides, and 14 Good Practice and ISPE Guides.

In terms of events, we may somewhat reduce the number. We need to analyze the needs of event participants so that hot topics training seminars can be provided in a timely manner. At present all of the 20+ events we hold each year are operated by three Japan Affiliate office members, including the Japan manager, without any outsourced contractors. The key reasons for this achievement are the significant efforts made by the three staff members as well as the availability of the membership management system database, which was adopted in 2010. The office (with its database) offers multiple functions, including member information updates, translated book order processing, acceptance of event applications, admittance certificates, and invoice issuances.

Building a good relationship with the Pharmaceuticals and Medical Devices Agency (PMDA)—Japan's regulatory agency—is an ongoing objective. Since Japan became joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) in 2014, PMDA has drawn more attention to the need for collecting the latest information on a global basis amid advancing internationalization. At PDMA's request, the Affiliate provides lecturers and organizes seminars. Also, when ISPE HQ's seniors or training seminar instructors come to Japan, efforts are made to facilitate a courtesy call on PMDA from the standpoint of continuity of the relationship between PDMA and ISPE.

What challenges does the Japan Affiliate face?

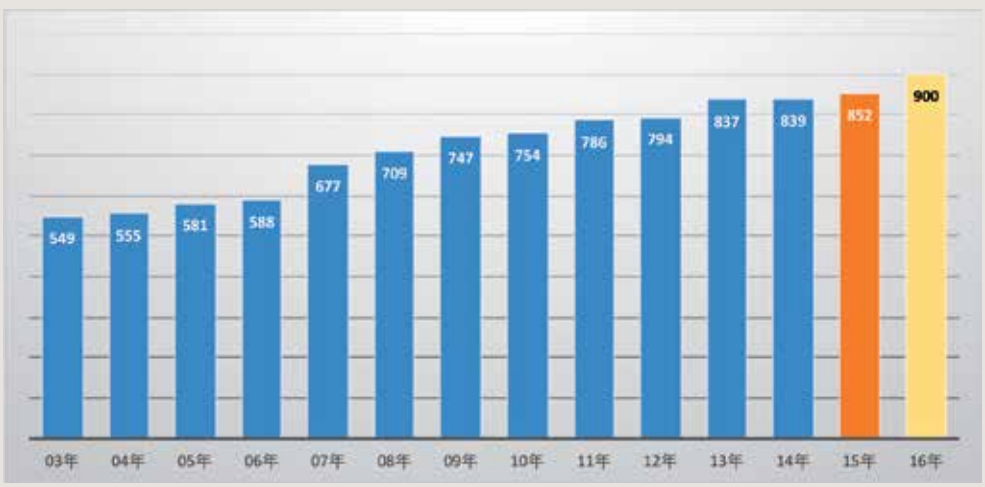
The major challenge the Japan Affiliate faces is how to find competent personnel, specifically members who are innovative and have a volunteer spirit, as well as strong leaders with a sense of balance to help us maintain the continuity of the Affiliate. It is also important that they are able to act while obtaining understanding from their organizations. Finding this kind of human resources is not an easy job, but we keep looking for valuable personnel.

What would you say to someone who is considering joining the ISPE Japan Affiliate?

The first thing we say to someone who is considering joining ISPE Japan is "Please be a member!" Why? Because once you become a member of a nonprofit organization like ISPE that provides state-of-the-art information, communication, and education relating to the manufacture of health care products, you are able not only to obtain the latest information but also network with experts from various areas such as pharmaceutical manufacturers, engineering and construction companies, suppliers, consulting firms, and administration organizations.

We also provide events. One that is planned every year, for example, is the Plant Tour and Annual Meeting in the United States. Twenty industry professionals from Japan participate in the ISPE Annual Meeting each year, and we add tours of a number of US pharmaceutical manufacturing plants and/or laboratories. Each year, about half of the participants are newly registered members. Furthermore, we network with US Chapters during the tour, and this has been warmly welcomed. Participants get a direct feel of the splendor and global atmosphere of ISPE through their participation in the Annual Meeting. And, while we're discussing this tour, we would like to take this opportunity to say that we deeply appreciate the San Francisco/Bay Area, Los Angeles, New Jersey, Boston, and Delaware Chapters, as well as the Canada Affiliate for providing us with networking opportunities.

Membership 2003–2016



And finally, the Japan Affiliate will hold its fifteenth Annual Conference in April 2017; we look forward to support from ISPE international in making speakers available for us. ■

Mike McGrath

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Manufactured Buildings: Embracing Prefab Facilities

When Pfizer won an ISPE Facility of the Year Award (FOYA) this year for development of its oral solid dose (OSD) production facility in Groton, Connecticut, it underscored how modular design and construction are gaining currency in the industry.[4]

Modular and prefabricated construction are examples of the kind of nimble manufacturing that has become necessary due to the growth of worldwide production and outsourcing. "Prefab"—a designation traditionally limited to such components as cabinetry and lighting fixtures—has expanded to include the design and construction of cleanrooms and even entire plants in offsite controlled environments, then shipped and assembled elsewhere.

Architects, designers, software developers, and builders are collaborating to use manufacturing innovations to streamline the design and construction of industrial facilities.[1] The benefits of these replicable and portable systems include a 30%–40% reduction in footprint,[2] lower design and engineering costs, and shorter time to completion, providing the chance to bring products to market more quickly.

"Prefab dates back to at least the 1920s," said Basem Eid Mohamed, an assistant professor of architecture at Abu Dhabi University and an expert in the design and construction of prefabricated housing. "It started with the concept of mass production, borrowed from Henry Ford's Model T by many architects and builders of that era. Since then, prefab architecture and housing has seen ups and downs, but recently has become a more acceptable model."

Mohamed completed his PhD at McGill University School of Architecture, where he developed a digital platform for mass customization of prefabricated housing systems. He laid out the benefits of prefab design and construction in the housing industry in a phone interview with *Pharmaceutical Engineering:*

"Primarily, prefab has the advantage of speed, as site work is completed simultaneously with the production of modules," he said. "Secondly, its offsite location escapes the weather delays that inevitably plague open-air construction. Thirdly, it reduces waste, and thus cost, as the repetition and systematization of specific tasks results in standardization of quantity and quality. Finally, modular homes specifically are built to higher structural standards than most site-built homes due to continuous quality control."

Extrapolating from his experience with housing projects, Mohamed believes that prefab construction can be a perfect fit for any building typology, including industrial manufacturing.

JHL Biotech

A crane places one of the 62 KUBio modular components that will become the GE Healthcare Life Sciences facility in Wuhan, China.

"Prefab construction is not only limited to wood modular types of buildings," Mohamed said. "There are diverse systems that use steel components. I believe these technology-based systems can take prefab construction to a whole new level."

Ulf Danielsson is the COO and executive vice president of sales and marketing at Pharmadule, a Swedish supplier of modular manufacturing buildings for pharmaceutical firms including Eli Lilly and Company, Merck, GlaxoSmithKline (GSK), Genentech, and AstraZeneca. "Modular construction offers benefits such as predictability, standardization and shorter work duration on site," he said. "Properly utilized, this equates to lower overall project implementation cost and reduced risk. Companies will realize this and, as the construction of pharmaceutical facilities matures, we will see more use of modular and prefab solutions."

There are diverse reasons for choosing a prefab or modular structure: the need for a flexible manufacturing facility that can be up and running quickly; the need to produce small amounts of multiple products in various forms (solid, liquid, parenteral); the shift from large-scale production of small molecules like statins to smaller-scale production of personalized medicines and orphan drug development; production planning for breakthrough therapies in oncology and in rare diseases; and the FDA fast-track approval process for experimental drugs to treat life-threatening diseases that can move drugs from Phase 1 to Phase 3 in as little as one year.

Modular construction can range from the assembly of a cleanroom constructed of prefabricated panels all the way to the assembly of an entire prefabricated manufacturing facility that has been shipped from another site.

Modular cleanrooms

"We see modular walls being used almost everywhere now," said Kevin Merrikin, managing principal at Stantec, from his office in Albany, NY. "The reasons for choosing prefab panels vary, but the perception is that they're cleaner and they go together more quickly."

Stantec provides architectural, engineering, and environmental services in a wide range of sectors that includes facility design for biotech and pharmaceutical firms, primarily in North America.

Merrikin points to composite wall and ceiling panels manufactured by AES Clean Technology and used in current good manufacturing practice (GMP) cleanroom environments as an example. They have a 2-inch aluminum core honeycomb structure and are covered with an unplasticized polyvinyl chloride sheath.

"The panels certainly look beautiful and are very cleanable," Merrikin said. "Though prefab material costs tend to be more expensive than stick-built construction, in terms of construction efficiency and safety they have considerable benefits."

Some Stantec projects have used prefab cleanroom ceiling panels that provide a walkable level above ceiling spaces. "Because the ceiling was independently supported, we were able to have crews working at two different levels simultaneously without getting in each other's way," Merrikin said. "One nice feature of this installation was that we extended the wall panels above the ceiling level and used them as the code-compliant fall-protection system so we didn't have to install railings where the ceiling was adjacent to an open technical space."

He cautions that companies will have to consider a plant's potential future uses before locking into any design that may require modifications. There can be limitations to the fixed footprint of either traditional or prefab spaces, preventing, for example, bringing in larger single-use culture vessels.

Alan Orton is a partner at NFOE, an architectural firm in Montréal, Québec, that specializes in the design of high-tech spaces, including those for pharmaceutical and biotechnology companies. One of its recent projects is a vaccine production facility for GSK. While NFOE designs buildings to be constructed on-site, they are fans of prefab cleanrooms where appropriate.

"I think they're an excellent alternative," said Orton. "While this kind of prefab is popular in Europe, it's not as well deployed in North America, where conventional stick-built cleanrooms have remained cost-effective. We would like to have more opportunities to use them."

Part of the cleanroom construction can be prefabricated wall, ceiling, door, and vision panels that come complete with service chases to permit connections to piping and heating, ventilation, and air-conditioning (HVAC) systems.

"I can see an obvious application for a completely prefab manufacturing facility in remote locations where ready material supply is a challenge and good quality of workmanship can be more difficult to achieve," said Orton.

> **"Modular construction offers benefits such as predictability, standardization and shorter work duration on site"**
>
> —Ulf Danielsson, Pharmadule

"If you're building in North Africa or parts of Southeast Asia you might not be able to get the skilled labor or materials needed for conventional construction."

He points out that prefab cleanroom panels or modular facilities are more attractive than stick-built cleanrooms in areas with proximity to European suppliers such as Pharmadule.

Continuous manufacturing applications

In an industry that has lived and breathed batch processing for decades, continuous manufacturing is now gaining traction, and for good reason: The production of oral solid dosage (OSD) drugs can occur in an uninterrupted process to produce tablets in a day. The benefits of continuous manufacturing include leaner and smaller plants, faster production, as well as lower capital and operating costs; inventory needs are lower and yields are higher than traditional batch processing, too.[3]

Despite these pluses, firms can find it challenging to make the move to continuous manufacturing because it's a completely different system, which raises questions about patient safety, compliance, and financial risks. Pfizer, which began using continuous manufacturing for some of its products in 2008, won its FOYA in the equipment innovation category for its portable, continuous, miniature, and modular (PCMM) plant, which transforms raw materials into uncoated tablets in minutes.[4]

The PCMM process equipment fits into a portable unit called a POD, which can be transported worldwide. These enclosed facilities have a smaller footprint than a traditional plant and a reduced startup time that can take less than 12 months.[3]

Pfizer partners with G-CON Manufacturing, which builds and installs the prefab, autonomous PODs.[5] The PODs are self-contained, with HVAC and utilities installed prior to assembly. They have been used to produce vaccines, monoclonal antibodies (mAbs), and personalized medicines.[5] According to G-CON, PODS offer lower capital cost, flexibility to repurpose or relocate the facility for a different application, and potential for expansion.[5]

Pfizer also works with GEA, headquartered in Belgium, which tested the process equipment and shipped it to Groton, where it was installed in the G-CON POD.[6] The Pfizer, GEA, and G-CON consortium, which was expanded in 2015 to include GSK,[7–8] will continue to develop these POD-based mini-factories.[9] GMP benefits from experienced suppliers

JHL Biotech

KUBio modular components are assembled to construct the GE Healthcare Life Sciences facility in Wuhan, China.

Pharmadule's Danielsson sees another benefit of modular: Smaller companies and those in regions that struggle with GMPs can benefit from working with an experienced modular supplier.

"In this case the construction work is completed under controlled conditions in a workshop by people who know how to build a GMP facility," he said. "In fact, it helps with the total delivery, including IQ/OQ [installation and operational qualification]. For IQ you can leverage 90%% of the tests done in the workshop and for OQ about 20%, which makes it much more efficient and predictable on the final site and easier to ensure compliance.

"For international companies moving into new regions or countries, it's perhaps the risk mitigation with modular delivery that is more attractive," Danielsson continued. "There is less dependence on local labor and contractors with questionable experience of construction of a GMP facility."

GE Healthcare Life Sciences realized this benefit in its first KUBio facility, built for JHL Biotech in Wuhan, China. The plant will manufacture biosimilars for the booming Chinese market. Because GE built the prefabricated modules for the facility in Stuttgart, Germany, which has a history of manufacturing expertise, there was no need to source local expertise to build the plant.

The KUBio arrived as 62 modular components, including intact cleanrooms and most of the piping, HVAC system and even the toilets installed. Whereas traditional plant construction can cost between $200 to more than $500 million, GE says these costs can be cut by as much as 45%.[10]

Olivier Loeillot, general manager for GE Asia, asserts in an online video that parallel processes can shave as much as 18 months off the construction schedule.[11] KUBio allows construction steps that are traditionally progressive—site prep followed by frame construction, interior completion and installation of manufacturing equipment—to be done simultaneously.[12] While the modules were being constructed in Stuttgart, the single-use bioreactors for the interior were being tested in Westborough, Massachusetts, and the chromatography system was being produced in Uppsala, Sweden.[10–11] The completed modules travelled from Stuttgart to the JHL site in Wuhan by truck, container ship, and barge. Once they arrived it took a mere eight days to assemble the facility.[13]

"JHL has begun production of clinical batches of two products in its pipeline," said Racho Jordanov, CEO at JHL Biotech. "One is a rituxamib biosimilar and one is an enzyme biosimilar. Using material produced in our Taiwan facility, which has all the same technology as that in Wuhan, we have filed an IND [investigational new drug application] with the UK MHRA [Medicines and Healthcare Products Regulatory Agency]. Our IND has been approved.[14–15]

"JHL is the first company from greater China to receive approval from European authorities to conduct human clinical trials of a biologic drug product," Jordanov said. "This makes us extremely proud. Additionally, in June of this year, we will use KUBio to produce our first batch of clinical product for one of our manufacturing partners."

Because the KUBio prototype uses only disposable equipment—no stainless steel—the factories can be modified quickly to accommodate different mAb products. "The facility is designed for one product at a time," Jordanov explained. "However, changeover from one product to another only takes hours, not days."

It is flexibility like this that makes modular construction attractive to a changing industry. ■

Scott Fotheringham, PhD

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3D Printing in Architecture

Adriaan de Groot/ MX3D

Left to right: The MX3D robot printer; A close-up view of robot welding; A scale-model prototype; Two robot printers construct a bridge; A visualization of the finished product.

When the renowned architect Zaha Hadid, who died earlier this year, collaborated with Stratasys to create a three-dimensional (3D) printed chair in 2014, she was embracing a nascent technology that is now poised to change construction as well as manufacturing and design.[1] In addition to the increasing number of household objects currently being 3D printed are larger structures: a bridge, a pavilion, perhaps even whole houses. It might soon be applied to pharmaceutical manufacturing facilities.

Most building projects currently underway are largely experimental, meant to demonstrate the possibilities of 3D printing in construction. Vulcan, the world's largest 3D printed structure, is a case in point. The Beijing pavilion, measuring 27 feet long and more than 9 feet high, is assembled from 1,086 parts, each of which was 3D printed.[2] Other examples come from Shanghai-based WinSun Decoration Design Engineering, which prints concrete components that can be assembled into single-story houses,[4] and Qingdao Unique, based in the city of the same name, which built a 120-ton prototype printer that may one day be used to print a house in one stage.[3]

These projects exhibit a current tenet of 3D printing for building: It is used to produce individual components that are assembled into a novel structure. In this way, 3D printing is reminiscent of some of the developments in prefab and modular construction. However, to create an entire building, beyond the preliminary trials ongoing in China and elsewhere, is not yet feasible.

It isn't from lack of trying. The Italian engineer, Enrico Dini, considered a pioneer of 3D printing for his techniques and designs, printed large objects using a concrete-like substrate in 2010.[5] His printer, D-Shape, is being used by the Dutch architect Janjaap Ruijssenaars, who has designed a house he intends to build in Amsterdam by 2017. Called the Landscape House, a 1:15 scale model has been printed as a bench[6] (see photos on p. 41). Ruijssenaars plans to use an "ink" that consists of sand and an inorganic binder to print blocks.

Amsterdam is a hotbed of 3D printing experimentation. DUS Architects has designed the Canal House (see photos on p. 41), which will be printed from bioplastics made of 80% vegetable oil. DUS refers to its system as "LEGO for grownups,"[7] with parts that click into place. It also printed bioplastics sections of the Europe Building in the city using its KamerMaker 3D printer, which is large enough that it needs to be kept in a shipping container.[8]

MX3D, another Dutch company that makes robotic 3D printers, is pursuing an alternative technique that prints metals and resins without scaffolding or molds.[9] Together with designer Joris Laarman and software developer Autodesk, the company is currently building a bridge in situ—not out of components. Once the bridge is fully constructed it will be moved to a canal in Amsterdam's Red Light District.[6]

Amsterdam is a hotbed of 3D printing experimentation

One of the more out-there projects (literally) is headed by the European Space Agency, which is working with the architectural firm Foster + Partners to design a 3D-printed lunar base.[10–11]

But what does this mean, if anything, for pharmaceutical manufacturing? The consensus is that while 3D printing is full of promise for building construction, it is not yet ready for prime time. Where it might soon prove beneficial is in areas where construction techniques are not sophisticated, to print individual parts of a single-use facility, or to replace broken parts quickly and cheaply.

Given how far 3D printing has progressed since Dini's early experiments, we won't have to wait too long to find out. ■

Scott Fotheringham, PhD

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Closing the Capacity Gap

Novo Nordisk starts work on a $2 billion API plant

Novo Nordisk has begun construction on a nearly $2 billion 833,000-square-foot plant in Clayton, North Carolina, the company's first insulin active pharmaceutical ingredient (API) plant outside Denmark.

"It's a huge build," says Gary Lohr, Project Director, Site Support and Deputy Site Head for the project, told Pharmaceutical Engineering.

Expected to be operational in 2020, the facility will produce APIs for both oral semaglutide and a range of Novo Nordisk's current and future GLP-1 and insulin products. Oral semaglutide is an investigational glucagon-like peptide-1 (GLP-1) analogue, formulated as a once-daily tablet for the treatment of type 2 diabetes.

An aggressive build

Lohr says that "the company has a high confidence in the product," which is currently in Phase 3A clinical trials. But it's not the only factor in building this facility. "Even without the new medicine," he explains, "future capacity needs justify this new facility just for the insulin alone. Currently insulin comes from Denmark. That adds a few more challenges that we've overcome through design phase. But we're closing the gap of future capacity both for insulin and GLP-1."

The facility is expected to be LEED certified

The technology transfer of Novo Nordisk's core process is equally significant, Lohr adds: "It's one thing to build a new plant; it's another to take 93-year old process and place it in a new transfer. You need a support team as you move knowledge across the Atlantic."

The new site is adjacent to Novo Nordisk's existing 457,000-square-foot facility in Clayton. Expanded several times since it was inaugurated in 1996, it is one of the company's strategic production sites responsible for formulation, filling, and packaging of diabetes medicines.

One of Lohr's biggest challenges is to have the facility operational in 5 years, with a utility building up and running in 3 years. "This is a very aggressive build," he admits. "It's a challenging program that we think we can fully achieve. But it will take a lot of energy."

Lohr, who joined Novo Nordisk in 2005 as the validation project leader for the first major expansion project at the existing Clayton facility, said that the company's determination to minimize environmental impact and improve environmental stewardship on this project is equally assertive. "We have a mandate—not a target—to be CO2 neutral by 2020 as a company." Because the facility is planned to go live in the fourth quarter of 2020, he explains, it will have to meet that standard.

Gary Lohr, Project Director

Computer simulation of the completed facility, aerial view.

Novo Nordisk groundbreaking, 28 March 2016.

From left: Gary Lohr, Project Director-Site Support and Deputy site head for Diabetes API, US project; Tony Braswell, Johnston County Board of Commissioners, Chairman; Pat McCrory, Governor of North Carolina; Lars Rebien Sørensen, President and CEO of Novo Nordisk; Henrik Wulff, Executive Vice President, Novo Nordisk Product Supply; Jody McLeod, Mayor of Clayton, N.C.; and Morten Neilsen, Senior Vice President, Novo Nordisk DAPI US.

Environmental stewardship

The company works hard to meet its social and environmental responsibilities. "We work with the [US Environmental Protection Agency] and the North Carolina Department of Environmental Quality to make sure we're following the correct process and understand the systems. We meet with the Army Corps of Engineers for federal requirements, too. We try to succeed on the first submission."

Lohr added that the building is also expected to be LEED certified. "For a manufacturing facility," he notes, "it's ambitious. That's a high bar to achieve. We're going after that at a very high level."

Another challenge of building for 2020 in 2016, said Lohr, is meeting future cGMPs. "You need to anticipate 5 years ahead," he explained. "We put energy into following regulatory trends. We employ engineering firms that know about building large facilities. The company also coordinates and collaborates with FDA."

Social responsibility

But it's not all bricks and mortar. Novo Nordisk is dedicated to supporting Clayton with neighborhood meetings, public hearings, and local updates. "Novo Nordisk has a 23-year history in this town," explains Lohr, adding that the existing facility already employs 750 people, with another 700 scheduled for the new facility. "We support backpack buddies [for kids] and angel trees for local families on top of sponsorship and employee support for our patient associations; namely American Diabetes Association and JDRF."

We're designing and building and commissioning for the day we open

The company also partners with the Workforce Development Center at Johnston Community College to develop a local talent pool. "Right now we're targeting engineers, QA specialists, subject matter experts," Lohr says, "but as the project develops, we'll hire technicians and operators, too. It'll take time to build, so we can develop the local talent for those positions."

Novo Nordisk's response to social responsibilities and community engagement are big aspects of this build, Lohr adds. That attitude reflects a partnership not only with the local, state, and federal governments, but the private sector and utilities, as well. "We're all working together in a cohesive and collaborative manner," said Lohr. "I've never seen it on any other project."

When asked what else he'd like PE readers to know about the new facility, Lohr doesn't hesitate. "We start with the end—and that's the patients. That's what it's about. Anyone who works here can tell you that. That's the most important part of this.

"When we cut the ribbon in 2020, we'll be standing there for our patients. We're designing and building and commissioning for the day we open. That's our focus." ■

Amy R. Loerch

Process Architects: Bringing value to pharmaceutical projects

by Mark Brooker

Author's note: This article is based on the presentation "Architectural Design Facilitated by Good Engineering: The Role of the Process Architect" by Mark Brooker, architect, and Enrik Blais, engineer, at NFOE, at the 2015 Canada Affiliate Educational & Product Symposium, 21 September 2015 in Ottawa, Ontario.

Mark Brooker

A continuous collaborative effort is critical to the delivery of a well-designed pharmaceutical facility. One of the best ways to create this collaboration is to include process architects at the project onset.

Process architecture

Process architects play a vital role in the design of pharmaceutical manufacturing facilities. In addition to complex architectural requirements, these sites require the integration of essential process engineering, mechanical, electrical, and plumbing (MEP) engineering, and regulatory compliance. Involving a process architect as part of the team from the beginning of the project can help ensure that it is planned, designed, and executed to meet requirements within a limited budget and on schedule.

Architects are trained to be integrators, organizers, and collaborators. As building designers with three-dimensional thinking, they have a global view of all disciplines and are able to link the various players involved in a project.

Trained to work within a technical engineering context, process architects are key to integrating process engineering, MEP engineering, specialized construction requirements, building code compliance, and overall building design.

Facility planning

As with any building, a pharmaceutical facility design must incorporate design elements, functionality (flow and adjacencies), and space (environment and human scale). All of these are balanced against regulatory concerns. To balance these competing concerns, process architects can leverage three-dimensional thinking and building information modeling (BIM) to develop optimal design solutions.

At the Canadian architectural firm NFOE Inc., the design of a pharmaceutical facility begins with an understanding of the company's corporate vision. Aligning these business objectives at the project outset is important. Questions posed at this time may include:

- What products are to be manufactured and what are the target commercial markets?
- Single or multiple products?
- What is/are the proposed product(s)?
- Confinement levels, toxicity, etc.?
- Have regulatory requirements been satisfied to sell the product(s) in the proposed markets?

Once products and markets have been identified, regulatory guidelines—such as FDA good manufacturing practice (GMP), building code regulations,

Process architects are key players in the coordination of project design with engineering requirements and regulatory compliance.

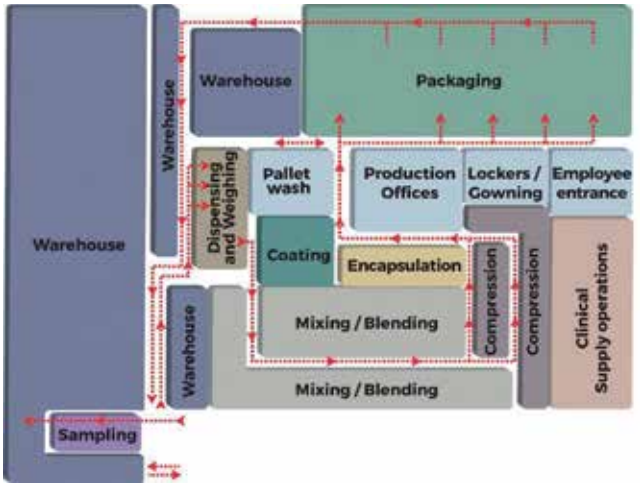
GlaxoSmithKline's (GSK) vaccine production facility in Ste-Foy, Québec, Canada, was the site of several NFOE projects from 1997 to 2014.

local biosafety requirements—and corporate facility guidelines—including health, safety, and environment standards (HSE)—are incorporated into the project design.

Functional design begins with an understanding of product fabrication. At this time the project site masterplan is reviewed, developed, and refined. The existing context and future plans are examined and explored.

The process architect follows the process engineer and the process flow diagram to collect, synthesize, and analyze base information to prepare early functional blocking. The process architect leads the data collection effort, and produces the space program to create a common understanding of the project requirements. Room cards—documents that summarize the functional, equipment, architectural, MEP, and information technology/telecom requirements for each space—are often used to compile this information.

These requirements are distributed to all project stakeholders for review and comment; they serve as base documentation for development of the design. Once this information has been documented and confirmed, the process architect analyzes, synthesizes, identifies, and graphically com-



Example graphic representation of key components in a pharma facility

Process architects integrate product flows and equipment early in the design.

municates the relationships between various building components, space groupings, adjacency relationships, circulations, etc.

It is essential to address equipment integration early in the design process, and get it right the first time—it's expensive if not done properly. Once the equipment has been selected, operating heights, clearance, maintenance access, servicing strategy, and delivery logistics are addressed. Initial design is typically based on generic equipment models or, if the parameters are unknown, by using worst-case scenarios.

Early communication about personnel flow and gowning is essential to promote a common understanding. The process architect shares the protocols of the various gowning steps, together with their related accessories, to all project stakeholders by means of pictograms, diagrams, and plans.

Standard operating procedures such as handwashing or sanitizing and the use of use of personal protective equipment should be defined and simplified. Sterility concerns should be reviewed with all stakeholders, including HSE.

Airlocks and their respective circulation spaces for material and personnel transfer within the facility require significant amounts of expensive space. Planning for an adequate number of airlocks requires accurate information about required current GMP (cGMP) zone classifications, biocontainment, and pressurization. Choices about linens management for airlocks and interlocks will have major effects on project planning and engineering.

Other design criteria to be reviewed include ergonomic design and product manipulations, as well as biological and toxicity levels for dangerous products such as flammable corrosive substances.

Everyone engaged early

A front-loaded design process is based on the "everyone engaged early" axiom. It's an integrative interdisciplinary effort that allows all stakeholders, including the process architect, to share information and work together toward common goals and objectives—not in separate silos.

Involving the process architect early in the design allows him or her to act as an advisor on hazard and operability concerns, "what-if" situations, Lean Six Sigma issues, and GMP reviews. This can help avoid costly process flow diagram redesign, and keep both cost and schedule on track.

Process architects also drive project team coordination and optimize various building elements. Good pharmaceutical manufacturing design should aim beyond integration to promote synergy between systems. 3D BIM can leverage the power of three-dimensional thinking and check for interference among components. Using BIM at NFOE Inc., has helped ensure the success of several pharmaceutical projects.

Quality control facilities

Designing a quality control laboratory requires a design process similar to that of production facilities: listening and gathering information, examining and optimizing sample analysis flows, integrating bench equipment servicing, designing for ergonomics and environmental conditions, as well as envisioning strategies for lab storage and solvent management.

Sampling area design requires an understanding of reception protocols and secure storage. Testing areas should accommodate raw materials active pharmaceutical ingredients, sample testing, as well as laboratory, incubator, cold process, and microbial environmental testing.

Narcotics management requires consideration of regulatory requirements.

Constructability solutions

Once the facility's essential requirements have been determined, the process architect prepares layouts that correspond to the required cGMP classification (Grades A, B, C, D). Major differences in planning are possible depending on which GMP standards (FDA, Health Canada, EU, Japan) are followed; this has important implications for the facility layout.

Exemplary pharmaceutical facility architecture: GSK, Ste-Foy, Québec, Canada.

There is no formal training for process architecture; it is generally learned by field experience.

In addition, different pharmaceutical companies tend to interpret the GMP regulations in various ways. All project team stakeholders should have a common understanding of GMP requirements. Questions to be considered in the GMP review could include "Do airborne particle counts apply to production rooms at rest or in operation?"

Confinement is another important issue in the context of toxic compounds or biocontainment. However, pressurization planning can conflict with confinement requirements. An experienced process architect with a good understanding of the relevant issues can resolve these conflicts.

Segregation between clean and dirty areas should be identified, agreed on, and incorporated into the layouts to avoid impeding product, material, personnel, and waste flows. These flows should be considered in facility design. By documenting them with clear diagrams, circulations can be identified, and pinch points, conflicts, crossovers, or bottlenecks reconciled and resolved.

Interior building systems and material selection involve stick build vs. prefab, flexibility, modularity, and future proofing. Partitions and ceilings should be designed for impact and differential pressure resistances. Spaces should be designed for easy operation and maintenance.

During the design process, it is critical that planning for ventilation and plumbing infrastructure permit easy access to service points. Service rooms can be located in a basement, a mechanical penthouse, or in separate structures. Interstitial spaces can facilitate the relocation and maintenance of services to minimize facility shut-downs.

The process architect, working with the project engineers, confirms that the infrastructure supports production. Full-size panel mock-ups are suggested to ensure optimization of integrated MEP and architectural systems.

Renovations and retrofits

Designing for alterations, renovations, and retrofits presents the process architect with a different set of challenges. These can include negative air pressure zones, erection of temporary partitions, construction in operational plants, decontamination of spaces, dust management, and clean waste removal. "Surprises" are inevitable when working in existing conditions; rapid problem solving is often required.

Creating extraordinary architecture

Although the process architect possesses specialized knowledge in the planning and construction of a pharmaceutical facility, the issues of human scale, workplace aesthetics, and functional productive planning remain foremost considerations, as they do in any architectural project. At its best, a well-planned pharmaceutical facility can be extraordinary architecture that creates a sense of place, facilitated by good engineering and team players.

We see process architects as key team players that bring value to pharmaceutical projects. ■

About the author

Mark Brooker is a senior LEED-accredited architect with more than 30 years of experience in providing design services for highly complex projects, including pharmaceutical and vaccine manufacturing plants, research and quality control laboratories, containment installations, and animal facilities. Since 1997 he has acted as a senior architect and project manager for NFOE Inc., a Montréal, Québec–based architectural firm (founded in 1912) specialized in the design of high technology facilities. Mark graduated from the University of Toronto in 1985 with a bachelor's degree in architecture.

Patient Perceptions of IMPs: An International Perspective

by Esther Sadler-Williams, Lynn Wang, Samantha Carmichael, and Paula McSkimming

Contributions and opinions are based on the individuals' knowledge and expertise; this presentation should not be construed as a statement or opinion by Catalent Pharma Solutions, or any other member of the task team.

Every clinical trial professional faces the same challenge: Get 1) the right product 2) to the right patient 3) at the right time 4) every time. This bar only gets higher when new products with inherent stability challenges (such as biologics or patient-tailored medicines), increasing globalization of clinical trials, and financial constraints are part of the picture. A sound appreciation for the role of clinical site personnel, a commitment to clear instructions for both the patient and the clinical site, and flexibility in IMP design may help address all these concerns.

Traditionally, preparation of investigational medicinal products (IMPs) had been focused on upstream activities compliant with current good manufacturing and distribution (cGMP and cGDP) practices, with little thought for the preferences of the end user—the patient or the clinical site. This may be changing, however, as patient centricity and global perspectives increasingly influence decision making to improve patient adherence and compliance to protocol.

Original study

In 2012, ISPE's Investigational Products Community of Practice (IP CoP) formed a Patient Survey Project Team to conduct what they hoped would be the first industry-sponsored global survey to understand patient experiences with clinical study supplies.[1]

Published in 2013, the "ISPE Project Concerning Patient Experiences with Clinical Trial Materials" surveyed 1,425 clinical trial patients to learn about the suitability of clinical materials, collect patients' opinions about their experiences, and gather suggestions for future improvements. While study findings indicated a good level of reported drug compliance and demonstrated that patients were generally satisfied with the IMPs they received, the results also revealed a number of areas for consideration in improving medicine kit design. A significant challenge, however, was that despite the project team's considerable efforts to recruit a globally diverse study population, almost all (97%) of the respondents were from the United States.

Revised and expanded

To help identify possible geographic differences in patient preferences, regional ISPE Investigational Product (IP) teams decided to adapt and expand the original US-weighted survey to explore detailed feedback from three populations. The first spinoff study was conducted in the United Kingdom (UK) and European Union (EU). In a similar timeframe, the China IP CoP completed a study in China, a region that had never provided feedback on IMPs before. A third arm, conducted in Japan, is still ongoing.

Survey questions for each of the studies were adapted from the original 2013 study, and centered on whether IMP kit design, packaging, and labeling influenced patient compliance with the protocol and retention within the study. These are important cost drivers in clinical trials, where noncompliance can lead to patient failure and unevaluable data. Even a small percentage of failures can be detrimental, since each lost patient has been estimated to cost the study sponsor as much as $42,000 per patient, even if they're not replaced.[2]

All studies went live in the fall of 2015; as before, all were conducted under ISPE auspices. Interim results for the EU and China studies were presented at the ISPE 2015 Annual Meeting, and were published in *Pharmaceutical Engineering* in 2016.[3] Final results for the EU and China studies were presented at the ISPE 2016 European Conference, ISPE 2016 China Spring Conference, and ISPE 2016 Japan Annual Meeting.

This paper focuses on final results from the EU and China surveys and compares some of these results with the original 2013 survey, which for the purposes of this paper will be referred to as the "original US Study," based on the location of most of the respondents.

The vast majority of patients in both studies found their medication easy to use; this is no reason for complacency, however

Objectives

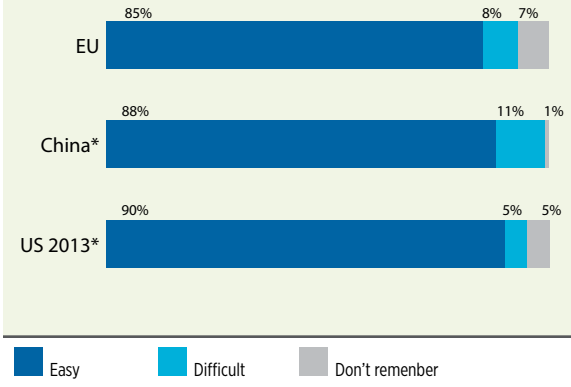
Research teams sought information that could help ensure patient compliance, adherence, and retention in clinical trials. If these new survey results revealed major geographic differences, they could affect how IMP kits are designed, labeled, and packaged for different regions. These are important concerns in clinical trials, which are frequently conducted in multiple countries, languages, and regions.

Goals were to:

- Gather patient feedback on the suitability of clinical materials provided
- Obtain patient suggestions for improvements
- Understand the effect of key patient differentiators

The team hoped to gather results that would support management decisions about IMPs, as well as increase collaboration between global regulatory bodies, sponsor companies engaged in the IMP sector, and facilitator organizations like ISPE so that enlightened global guidance could result.

Figure 1: Overall ease of use

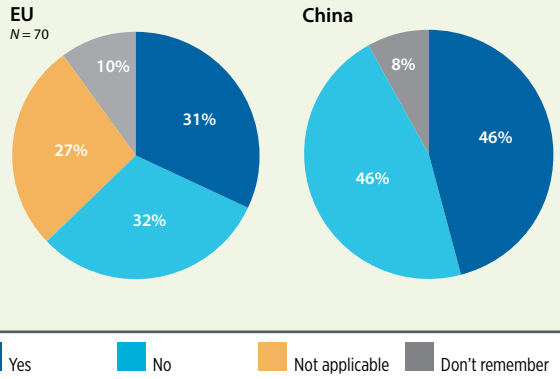


***China and original US study**

Easy = patients that selected options "very easy" + "somewhat easy"

Difficult = patients that selected options "somewhat difficult"+ "very difficult"

Figure 2: Kit design supported taking medicine on schedule



Methodology

Access to appropriate patient populations was instrumental to survey success, with patient anonymity being carefully controlled.

EU

The EU team partnered with three agencies who had access to patient groups:

- UK National Health Service (NHS)
- UK National Institute for Health Research (NIHR)
- European Patients Academy on Therapeutic Innovation (EUPATI)

All had read the results of the original US study with interest and all were actively focused on public and patient involvement in clinical research.

The study was conducted electronically and in English only, with 48 questions adapted from the original US study. ISPE administered the survey and aggregated the responses; NHS, NIHR, and EUPATI disseminated the surveys to patients through clinical trials pharmacies, research nurses, or patient advocacy groups; the Robertson Centre for Biostatistics, University of Glasgow, analyzed and reported on the resulting data.

The final EU analysis contained data on 109 patients out of 543 collected responses. Not all patients responded to every question, thus, charts below show varying *N*s for the EU study population.

China

In China, the ISPE China IP CoP partnered with Drug Information Association China to enlist five site management organizations to collect responses:

- Hangzhou Tigermed Consulting Co., Ltd.
- LinkStart
- Medkey Med-Tech Development Co., Ltd.
- SMO ClinPlus
- WuXi Apptech

The patient survey was also sponsored by seven companies:

- Almac
- Cardinal Health
- Catalent
- Fisher Clinical Services
- Lilly
- Merck & Co., Inc.
- Pfizer

As in the EU, the China survey contained 46 questions modified from the original US study, which were translated into Chinese. Data were collected via mobile or paper versions, depending on the patients' preferences. Surveys were conducted in person at study sites.

Total valid data for analysis was 1,935 out of 2,488 collected responses. Unless indicated otherwise, *N* is always the total study population.

See Table A for study demographics, therapeutic area, and IMP statistics.

Results

Overall ease of use

The vast majority of patients in both studies found their medication easy to use: 85% in the EU study, and 88% in the China arm, which is consistent with the 77% reported in the original US study (Figure 1). This is no reason for complacency, however, as some later results will show.

Kit design supported taking medicine on schedule

In the EU survey, 32% found kit design important—almost the same number that found it unimportant. The Chinese population also split evenly: 46% said the design was helpful, and 46% said it wasn't (Figure 2). This unequivocal result in both EU and China was different from the original US study, where 60% said that the kit design helped them take the medication on schedule.

Investigational Products Community of Practice

Thank You to Our Partners and Sponsors

EU Study Partners

NHS National Institute for Health Research Clinical Research Network

EUPATI European Patients' Academy on Therapeutic Innovation

NHS Greater Glasgow and Clyde

University of Glasgow

China Study Sponsors

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MERCK

Pfizer

What would help the patient take the medicine on schedule?

To delve deeper into this issue, the patients were asked "What would help you take the medication on schedule?" 81% of EU patients stated clear dosing information on the label (58% US) as useful, followed by 66% who chose the provision of individual dosing units in the medicine container, and 64% who said that verbal instructions from site personnel were useful.

In China, 77% cited "instructions from my physician/nurse/pharmacist at every visit" as helpful, followed by 57% who chose medicine kits organized in daily or weekly doses, and 55% who chose dosing information on the label.

Most helpful form of instruction

Despite a stated preference for dosing information on kit labels in the EU study, 73% of patients said that being able to question the medical staff was most helpful in understanding dosage, storage, and other adherence criteria. Results from the China study were even stronger: 78% cited "Someone telling or showing you how to take/use/store the clinical trial medicine" as helpful (Figure 3). In the original US study, 77% of patients said that having someone tell or show how to use, take, and store the clinical trial medicine was very helpful; 76% said that having the opportunity to ask questions on how to take, use, and store the medicine was very helpful.

Medicine form preference

The EU study population showed a strong preference for blister packs (51%). In China, a very small plurality (33%) favored bottles, followed by 27% that preferred blister packs. Overall, these results demonstrated regional differences between the EU, China, and the United States in the preferred presentation for oral medication. This preference for bottles in China was not as strong as in the original US study: 43% bottles vs. 17% for blisters (Figure 4).

Size, storage, and transportation

In the EU survey, 83% of patients said their IMP kit was very easy or OK to store; 90% of patients in the China study said their medicine was easy to store. These results are similar to the original US study, where 82% of patients said their medicine kits were easy or somewhat easy to store. At the outset this was a feature that the survey team was certain would be a concern to patients; the overall consistency and level of patient satisfaction is reassuring.

When asked if the medicine kit size was easy to transport, the answers were similar: 72% of EU patients found the kit was just the right size, compared to 73% from patients in China, and 77% from US patients.

Figure 3: Most helpful form of instruction

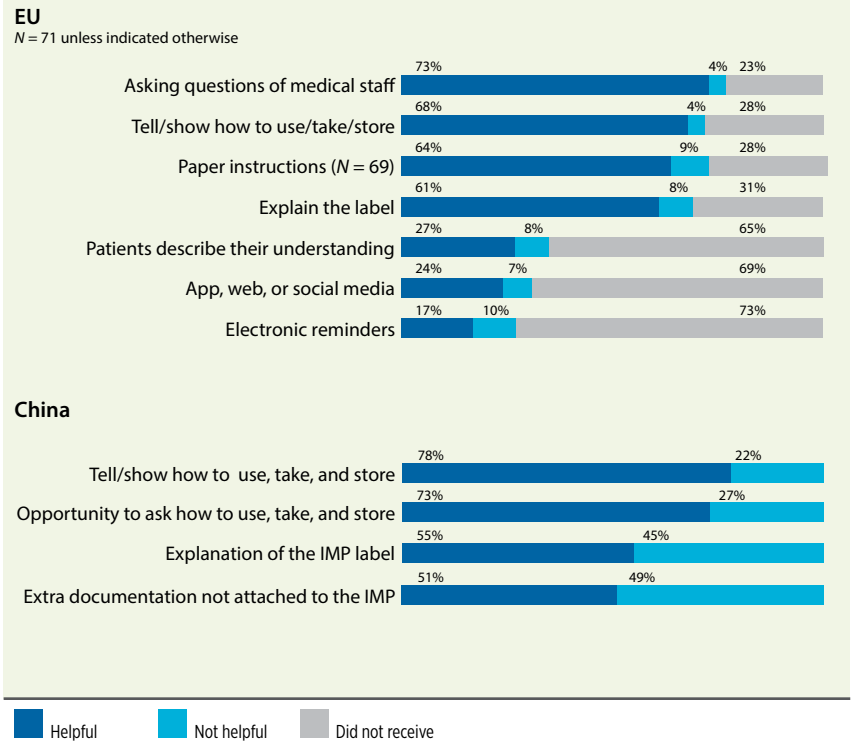
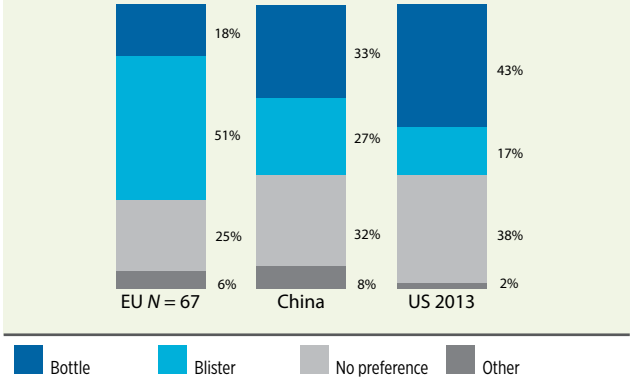


Figure 4: Medicine form preference



Medicine kept in original container

A concern to the industry as a whole is that patients may remove their medication from the clinical trial kit provided, thus risking incorrect dosing. However, patients in all studies reported similarly encouraging responses: 86% of EU patients and 84% of China patients kept their medicines in the original bottles. This corresponds well with the 86% of US patients who did similarly (Figure 5).

Most important IMP characteristics

Patients overwhelmingly rated clear instructions and ease of use as the most important characteristics of their IMP kits: 89% and 85%, respectively,

Figure 5: Medicine kept in original container

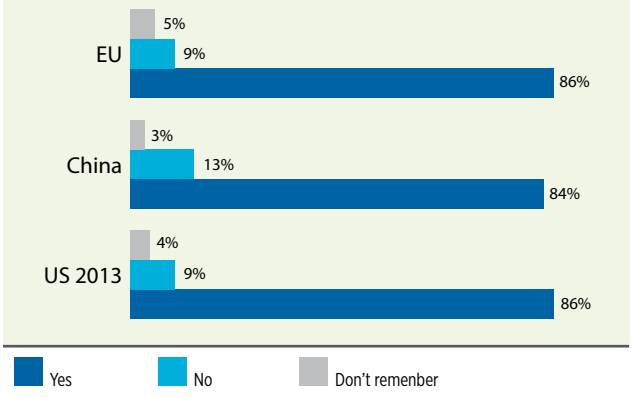
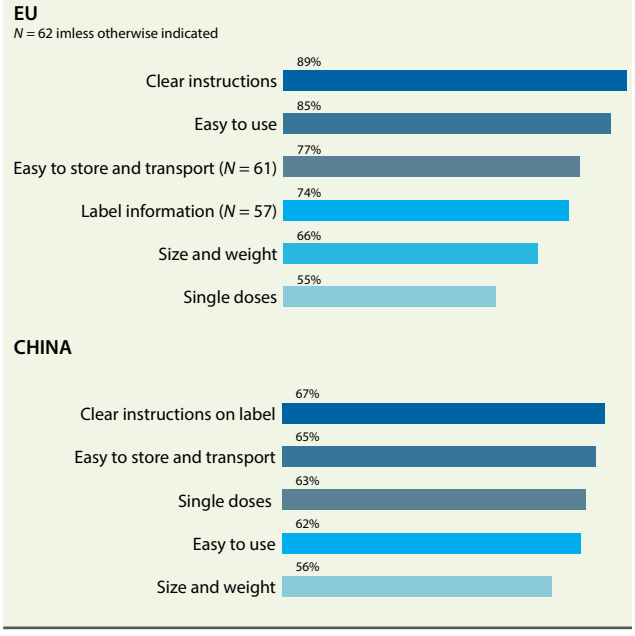


Figure 6: Most important IMP characteristics



in the original US study, and 67% and 62%, respectively, in the China survey (Figure 6). In the US survey, 69% of patients rated clear instructions as most important; 64% cited ease of use.

Return and reuse behaviors

The results from the EU and China were consistent with the results in the original US study, which found that a high percentage of patients did not return unused medication to the clinical sites, with ±20% of patients in all studies at least sometimes keeping the medication for future use, a result that the industry needs to mitigate against globally (Figure 7). The high "on request" results for the China study may reflect the patient's interpretation of the question and represent those patients that returned supplies as they were "requested" to do so by the clinical site.

Home delivery

As patients often have to travel long distances to participate in studies, in order to optimize patient recruitment and retention, there is a growing interest by some sponsors to undertake clinical trials where the IMP is sent to patients' homes. The survey team wanted to gauge patients' future preferences for this. Over 70% of patients in both the EU and China reported that having IMPs delivered directly to their homes would be helpful; these results were very similar to those reported in the original US study (Figure 8).

One interesting finding was that in the EU and China this preference was not significant in any single age group, whilst in the original US survey this preference was much stronger in the younger demographic. This may be a result of increased industry focus in implementing this method of delivery in the two years between the studies.[4]

Booklet labels

In the EU survey, patients were asked if their IMP kit had a booklet label. Less than a third—23 patients out of 80 who responded to this question (29%)—said yes, there was a label; 45% said no. Of those who saw the label, 20 (45 %) opened and read the booklet label on at least one container. Most EU patients (54%) who read the booklet label found it easy or somewhat easy to view their language, and 71% said that the text was large enough to read.

In the China study, 50% of respondents did not see a booklet label on their IMP kit; 41% did. Of those who saw the booklet label, 83% opened and read it on at least one container. Of the Chinese patients who read the booklet label, 75% found it easy or somewhat easy to view their language, a larger proportion than in the EU study (Figure 9).

Figure 7: Return and reuse behaviors

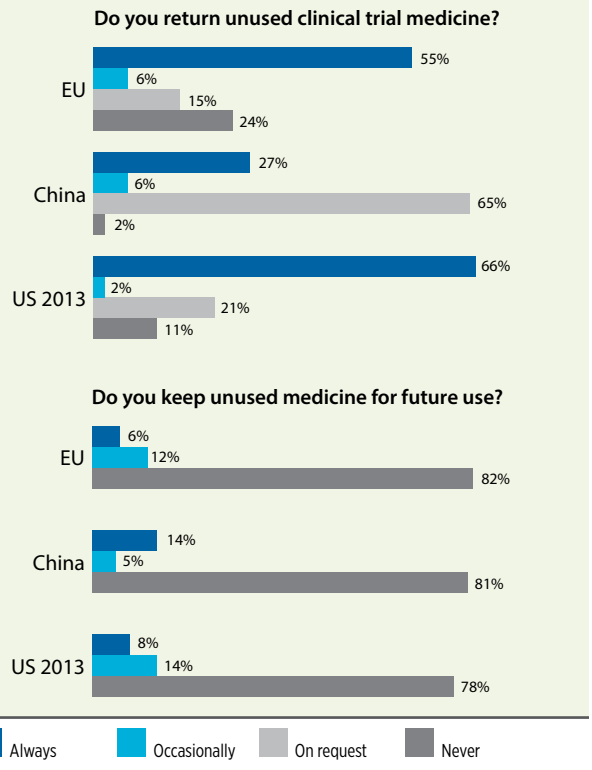
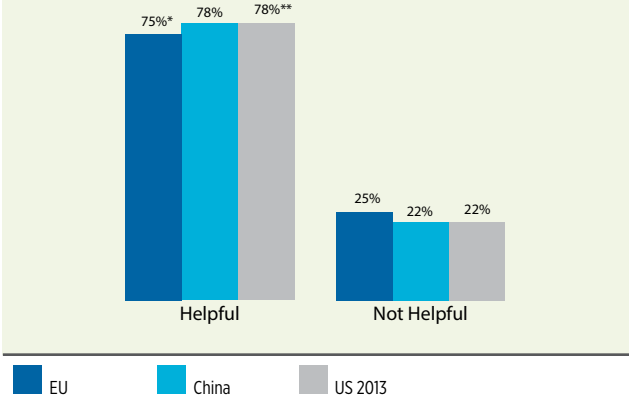


Figure 8: Home delivery of IMPs



* No strong response in any single age group

** Strongest response in younger demographic

Other sources of information

EU patients may have received dosing information on their medicine kit from a source other than the booklet label; the largest alternative source was the receipt of verbal instructions (21%; *N*= 109).

When patients in the China study were asked if they received instructions from a source other than the booklet label, 45% said they had, 55% said they hadn't. Of those patients who received information from a source

Figure 9: Easy to find language in booklet

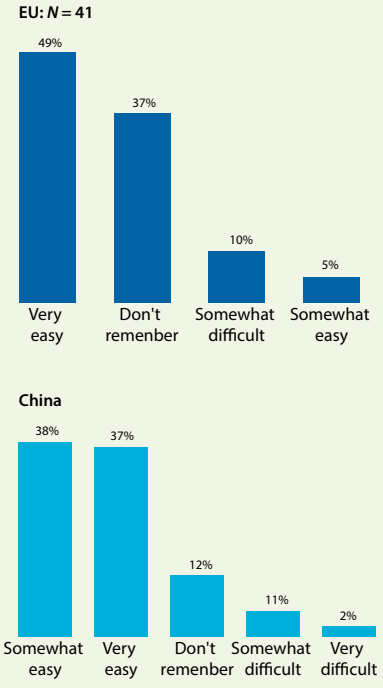
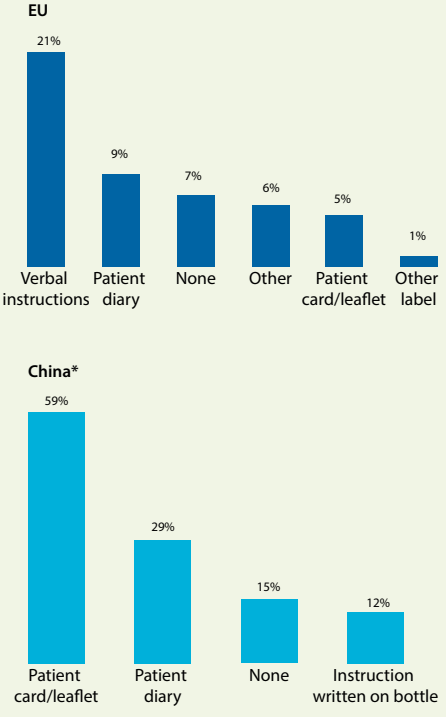


Figure 10: Other sources of information



*China: Patients can provide more than one response

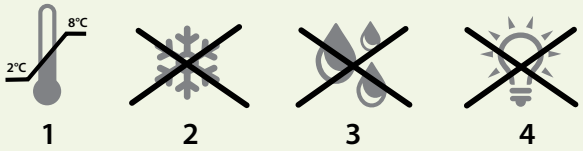
other than the booklet label, 59% received instructions on a patient card or leaflet (Figure 10).

In the original 2013 US study, 34% of respondents reported seeing a booklet label on their IMP kit; 42% did not see a booklet label.

Pictograms

Since pictograms can be used in place of text that would otherwise have to be translated, the survey team wanted to gauge patients' understanding of certain pictograms. Patients were asked to identify each picture in the pictograms below (Figure 11) from a range of provided options.

Figure 11: Pictograms



The correct answers were:

1. Store between 2°C and 8°C
2. Do not freeze
3. Protect from moisture
4. Protect from light

In the EU study, although 75% had not seen pictograms on their kits; for the examples provided, however, 96% (N = 62) identified them correctly.

Patients commented that pictograms to depict storage would be the most useful; 51% of EU patients found text alone helpful, 41% found text and pictogram together helpful, with only 8% preferring pictograms alone. This unequivocal response may reflect current unfamiliarity with pictograms, and could change as the symbols are standardized and adopted more widely. In the China study, > 82% of respondents found the pictograms at least somewhat helpful.

Future information preferences

The survey team wanted to gauge patients' preferences for the way they would like to receive information in the future. The results demonstrated that there are geographical preferences in the way that patients wish to receive information on their medication, clinical trial, or future visits. Patients in all regions indicated a strong preference for text (Table B). It is interesting to note, however, that email was the most preferred method in the EU and US, but least preferred in China, potentially because email is not significantly used as a daily or instant electronic communication tool in China.

Discussion

All of the studies—the original US study as well as the EU and China surveys—suggests an overall high level of satisfaction with IMP presentation. While current IMP kit packaging and labeling conveys a significant amount of information, however, there is no clear message that current designs improve compliance.

In the EU and China studies, as many patients said that the design of the kit did not help with taking their medicine on schedule as those that said it did. This was a stronger message than in the original US study, where < 60% of patients said the design was helpful. It also suggests there is room to improve the design of the kits to improve compliance and adherence. Patient feedback to questions about what would help indicate that more attention needs to be paid to providing individual dosing units within kits where possible, as well as clear and unambiguous label information.

The EU and China studies also confirmed a key finding from the original US study: Personal explanations from clinical research staff are instrumental in ensuring that patients have a positive experience, understand the study protocols, and grasp both the importance of compliance and how to achieve it. This was particularly true for patients in the China study. In view of the importance to the patient, as an industry we may need to consider controlling the way verbal information is provided to patients by the clinical site to ensure that it is provided in a consistent manner across sites and geographies.

The IP team initially expected that patients would complain most about the size, weight, and ease of transporting the kits, but they did not. Transportation and storage of the medicine to their home was not reported as an issue; in both the EU and China surveys over 70% of patients reported that their kit was the right size and over 80% found it easy or fairly easy to store at home, results that were consistent with the US findings. Kit size and weight, in fact, were deemed less important than clear label dosing information and instruction from clinical site personnel.

This general satisfaction with kit size and weight may explain why patients generally did not remove drug from the medicine container. In addition, the fact that size and weight did not feature as one of the most important criteria in "kit characteristics" could be because this is a "given" to the patients that were surveyed in that they believe that the size and weight will be the smallest possible.

These studies indicated that US and Chinese patients favor bottles, whilst patients in the EU prefer a blister format if possible—although in the EU and China there were still a similar number of patients who did not have a preference for either.

These studies were also intended to help evaluate booklet labels, an area of intense focus in clinical trial design. Researchers in the studies wanted to see if the booklet label is an effective way to communicate medical information to patients. This is an important issue for regulators, who are concerned that patients do not read booklet labels; a perception expressed by some is that medicine kits are often returned with unopened booklets.

Although the cohort of respondents who remembered receiving booklet labels was small, 55% of patients in the EU and 17% of patients in China never opened their booklet labels. Although this showed a geographic difference, results from both regions indicated that patients frequently prefer and rely

Table A: Demographics, therapeutic area, and IMP statistics

	EU: *N* = 109		China: *N* = 1,935		US 2013: *N* = 1,425	
Participating in a clinical trial	Currently	40%	Currently	68%	Currently	31%
	< 6 months ago	11%	< 6 months ago	16%	< 6 months ago	23%
	> 6 months ago	49%	> 6 months ago	16%	> 6 months ago	46%
Gender	Female	52%	Female	43%	Female	60%
	Male	48%	Male	57%	Male	40%
Age	17 or younger	3%	24 or younger	4%	17 or younger	4%
	18–34	5%	25–34	12%	18–34	7%
	35–44	11%	35–44	12%	35–44	11%
	45–54	20%	45–54	21%	45–54	23%
	55–74	54%	55–74	48%	55–74	55%
	75 or older	7%	75 or older	4%	75 or older	4%
Region	UK/Ireland	79%	China	100%	US-based	97%
	Europe	21%			Rest of world	3%
Therapeutic area	Neurological	23%	Diabetes	23%	Diabetes	12%
	Cancer	17%	Heart disease	16%	Lungs/breathing disorder	9%
			Cancer	16%	Pain	9%
Form of oral medicine received	Bottle	25%	Bottle	47%	Bottle	42%
	Blister	28%	Blister	37%	Blister	30%

Table B: Future information preferences

Region	Method
EU	1. Email 2. Text
China	1. Text 2. Regular mail
US 2013	1. Email 2. Text

on verbal information from the clinical site rather than booklet labels. On a positive note, however, patients who did read their booklet labels found it easy to find their language and read the information; most EU patients found that the text size was large enough to read.

Pictograms may be another emerging vehicle for communication, especially about storage information. In these studies, nearly all the EU patients were able to identify them correctly, and a majority of China respondents found them at least somewhat helpful. This corresponds to the original US 2013 survey, in which most patients found the same pictograms helpful.

Finally, as in the original US study, these studies confirmed that nearly 20% of patients retain medicines for future use. This remains a concerning statistic in terms of potential patient safety issues; it will be important for the clinical supply community to consider strategies to mitigate against this by defining robust processes to ensure that all unused medications are returned to the clinical site.

In summary, whilst many survey responses were consistent in all of the studies, some regional characteristics were apparent: e.g., medicine form preferences, packaging and reminder methodology preferences.

Conclusions

- Overall patient experience with medicine kits is very positive; patients report strong compliance and a high level of satisfaction with packaging and instructions.
  - Most (> 85%) of patients found IMPs easy to use; > 76% took their medicines on schedule as planned; > 72% said that kit size and weight made the medicine easy to store and transport.
  - EU and China studies show less convincing data than the US study that kit design helped patients take medication on schedule.
  - In all studies, IMP kit size and weight were considered less important than clear instructions.
- Site personnel play a key role in conveying dosage information, explaining medication regimens, and ensuring that patients have positive experience and that they comply
- In the China study, 75% of patients who opened their booklet labels found it easy to find their language; in the EU study, the figure was 54%.
  - Patients rely more on verbal information from clinical site personnel than on information contained in the booklet label, however.
- Technology is not frequently used to support visit and medicine reminders at present, but patients would welcome it. While regional differences among responses were apparent, text reminders were universally liked.

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- EU, China, and US studies all found that ±18% of patients keep IMPs for future use; the industry should mitigate against this globally by improving clinical trial medicine return process.
- Medicine kit design and labeling could play an even stronger role in assisting compliance through the provision of clear:
  - Dosing information
  - Product handling information (e.g., pictograms for storage)
- As in the original US study, most patients in both the EU and China studies said that a home-delivery option for IMPs would be helpful, although unlike the original US study, there was no significant difference between age groups.

Next steps

The EU task team has concluded that it is unlikely that further valuable differentiating information will be obtained from more EU countries by translating the survey. The team are exploring a consolidated analysis of US/EU/China data, however.

The teams are also supporting Japan to increase the level of patient feedback from this important region; assuming it is successful, it is hoped that the Japanese data could be included in the final consolidated analysis.

Within ISPE, a task team is exploring the usefulness of pictograms for IMPs. This task team is due to provide its initial recommendations and suggestions for future study in the near future; suggestions that may include initiating dialogue with regulatory agencies on this important topic.

Finally, the IP CoP is now considering how to create a form of global guidance for sponsors and clinical sites, guidance that will be critical to supporting a patient-centric supply chain of the future. ■

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Silicon Peach: Atlanta Is a Thriving Commercial and Technology Hub

Few American cities are known for as many diverse things as Atlanta, Georgia. Whether it's the city's Civil War history—when General William Tecumseh Sherman ordered it burned—its massive urban transformation in conjunction with the 1996 Summer Olympic Games, or its rise as the cultural center of the South, "Hot 'Lanta" has a story for everyone. And with a metropolitan population of five million, it's a thriving commercial mecca—its share of the nation's gross domestic product makes Atlanta the world's seventeenth wealthiest city.

In addition to being the base of traditional powerhouse companies such as Coca-Cola, Home Depot, UPS, and Delta Airlines, Atlanta has increasingly become a major hub for technology in the South. Nicknamed the Silicon Peach, the city is home to about 85,000 technology workers, making it the fourth-largest center for information jobs in the country.

Atlanta is also home to a growing biotechnology sector. the Centers for Disease Control and Prevention—with a staff of 15,000 epidemiologists, entomologists, biologists, physicians, and others—has its headquarters nearby in DeKalb County, adjacent to Emory University.

Pharmaceuticals

Atlanta's pharmaceutical sector has not grown nearly as quickly, nor has the city attracted the large international names that have gravitated to the Northeastern United States. Most of the 11 significant firms headquartered in the city are homegrown, with at least two having their roots in the region's post-secondary research institutions; many have carved out distinctive niches within the pharmaceutical industry.

Founded in 1975, Mikart is several decades older than most of the others. With more than 234,000 square feet of development and production facilities in the city, the company specializes in contract manufacturing, including the development, manufacturing, and packaging of solid dose and liquid products. Its formulations group specializes in developing product formulas that can be transferred to commercial-level manufacturing.

Also dating to the mid-1970s, SJ Pharmaceuticals focuses on the development and marketing of branded prescription products. The company has a range of drugs in the respiratory, urology, and cardiovascular therapeutic categories, including urinary tract antiseptic capsules and the multivitamin Cardiotek-RX.

GeoVax Labs, founded in 2001, is a clinical-stage biotechnology company that develops human vaccines against infectious diseases and cancer using its own DNA/modified vaccinia Ankara (MVA) platform technology. Current development programs are focused on vaccines against human immunodeficiency virus, Zika virus, and hemorrhagic fever viruses such as Ebola, Marburg, and Lassa fever. The company has also recently initiated a program to apply its MVA-VLP (virus-like particle) vector technology to cancer immunotherapy.

Atlantic Pharmaceuticals has developed a unique place in the market for preventing misuse of prescription drugs. Founded in 2003, it markets Smart/Script, which is an abuse-resistant oral delivery system for short-acting, commonly abused oral medications, such as opioids and amphetamines, as well as a sustained-release injectable depot for opioid maintenance, and a sustained-release injectable depot for analgesia. The company also markets ATLP-0001 for the relief of moderate to severe pain. In 2015, Atlanta-based Celtaxsys—which also has a facility in Brisbane, Australia—made headlines for gaining FDA approval for Phase 2 trials of an anti-inflammatory treatment for lung issues that remain the largest cause of death among people with cystic fibrosis (CF). Founded in 2005, Celtaxsys is a clinical-stage development company that focuses on novel therapeutics to treat inflammatory diseases, including rare and orphan indications. In addition to its flagship CF-related drug candidate Acebilustat, the company is also developing a potential treatment for the rare chronic skin disease called hidradenitis suppurativa.

One of Atlanta's largest drug companies, Arbor Pharmaceuticals has 600 employees and specializes in the research, development, manufacture, and commercialization of prescription products for the cardiovascular, neuroscience, and pediatric markets. The company develops new chemical entities, as well as already approved molecules for new indications or in improved dosage forms. It offers nitroglycerin lingual sprays for prevention of or relief from angina pectoris due to coronary artery disease, angiotensin II receptor blockers that help blood vessels relax so that blood flows through them freely, and isosorbide dinitrate/hydralazine hydrochloride for the treatment of heart failure.

AtlantaPhotos.com

Incorporated in 2007, SpherIngenics commercializes technologies and products for precise delivery of stem cell–based therapies used to treat a broad range of diseases and tissue injuries. Its proprietary microbead technology provides protective capsules for the delivery of cell-based therapies. As the company states on its website: "These microbeads are made using natural materials and ensure that the cells are precisely localized at the targeted area and maintain continued viability after injection. By keeping cell-based therapies localized and viable, SpherIngenics' microbead technology will reduce total treatment costs to patients by eliminating the need for multiple procedures."

Headquartered in Atlanta, with a branch office in Cambridge, Massachusetts, Inhibikase Technologies is developing treatments for orphan indications that arise from polyomaviruses, such as multifocal leukoencephalopathy, BK-virus associated nephropathy, and fungal and bacterial pneumonias. It's also developing small-molecule inhibitors suitable for treatment of infections, for Parkinson's disease and other degenerative disorders, and certain cancers. More than 100 million patients worldwide currently use its products.

The three remaining Atlanta-based companies each has an association with Emory University.

AventaCell BioMedical calls itself one of the world's leaders in developing novel human-derived products for use in cell culture and tissue regeneration. Its products are marketed using the Helios Bioscience brand and are designed to support expansion and production of a broad range of cells including mesenchymal stem cells and multiple immune cell lines. The company's interest in corporate and business development partnerships in stem cell research and cellular therapies development led it to a partnership with Cambium Medical Technologies, which was formed in 2013 by four Emory-based researchers working on the development and commercialization of regenerative therapies derived from novel processed human platelets. Cambium currently markets two products: Elate Ocular for chronic dry eye syndrome, and UltraGRO Advanced, a cell growth culture supplement sold only for research purposes by a Taiwanese company, Zheng Yang Biomedical Technology.

Atlanta has increasingly become a major hub for technology

Metaclipse Therapeutics was founded in late 2010 to develop and commercialize cancer therapy products derived from the work of Professor Periasamy Selvaraj and his coworkers at Emory. Metaclipse manufactures and supplies modified tumor-membrane vesicles that are used to activate the body's immune system to mount attacks against metastatic cancer cells. Its products are used in the treatment of various cancer types, such as breast, prostate, renal, ovarian, melanoma, and lymphoma.

Vibrant academic culture

These collaborations are possible because of Atlanta's vibrant academic culture, which fosters biosciences research that can, and does, offer joint ventures with biotechnology and pharmaceutical interests. The Woodruff Health Sciences Center (WHSC) at Emory University is an academic health center that offers clinical trials to patients at Emory Healthcare. Georgia Institute of Technology has collaborative research with pharmaceutical companies. Its Parker H. Petit Institute for Bioengineering and Bioscience conducts research on ways to improve drug design, development, and delivery for medicines used to treat infections, cancer, AIDS, and other diseases. Georgia State boasts recent research that includes the discovery of new antimicrobials effective against methicillin-resistant *Staphylococcus aureus* and the design of nanoparticles that promise to aid the treatment of inflammatory bowel disease.

These universities have teamed up with health care facilities to facilitate the jump from research to treatment:

- The Atlanta Clinical and Translational Science Institute is a partnership between Emory University, Morehouse School of Medicine, Georgia Institute of Technology, and Children's Healthcare of Atlanta. The institute's mission is to rapidly translate advances in health care research to patients.
- The Marcus Center for Therapeutic Cell Characterization and Manufacturing (MC3M), which launched early this year, aims to improve techniques for the production of living cells that are used in cell-based therapies. It intends to develop standardized processes that mirror what already exists for the manufacture of pharmaceuticals to provide high-quality stem cells and immune cells for cell-based therapies.
- Regenerative Engineering and Medicine is a partnership between Georgia Tech, Emory University, and the University of Georgia focused on regenerative healing, also known as endogenous repair. Its vision is to establish Georgia as a leader in the United States, providing clinical therapies for the regeneration of damaged bone, muscle, nerves, and other tissues. ■

James Hale and Scott Fotheringham, PhD

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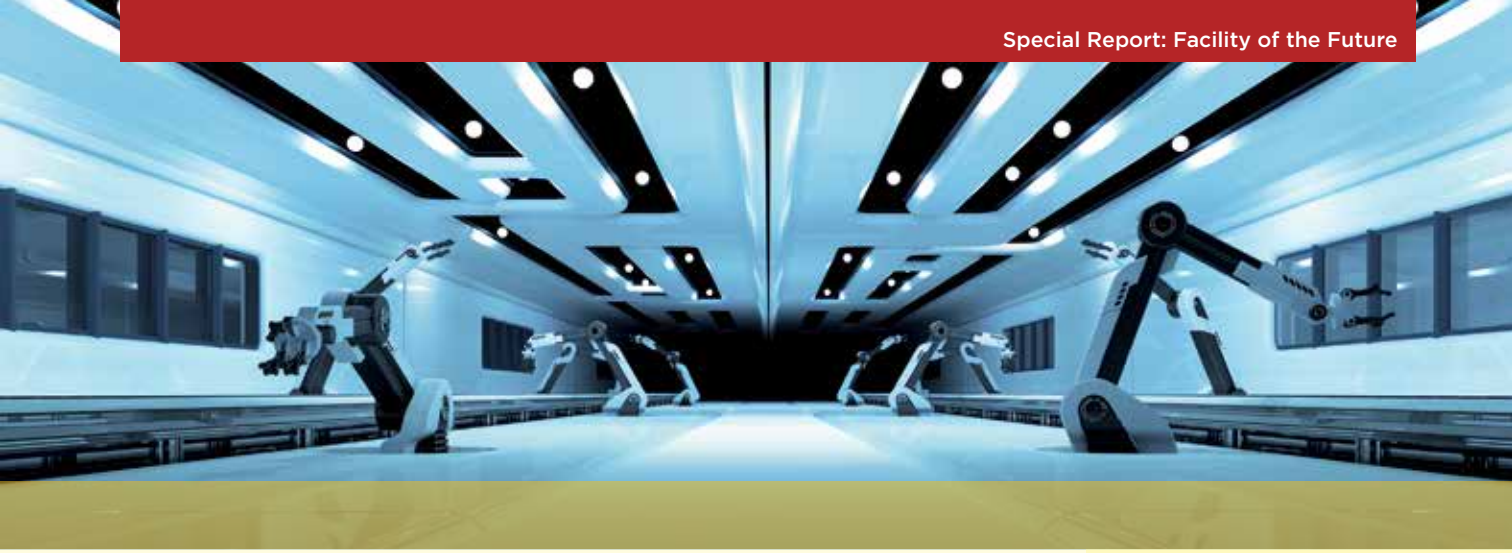

Facility of the Future

Technological advancements such as wearable devices, continuous manufacturing, and 3D printing have significantly improved the products and services available to medical professionals and patients around the world. These and other innovations in numerous industries are the result of advances in materials science and concepts like the Internet of Things. As technology continues to develop, however, many in industry have begun to question if they have the right workforce, facilities, and technologies to produce equally innovative products, processes, and ideas.

Many organizations, including ISPE and the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF), have been preparing for years, discussing and providing information to the pharmaceutical industry on how to handle these new technologies and how to prepare current and future workers to participate in this technological transformation.

The International Leadership Forum (ILF) is a group of 50 to 75 global leaders from more than 30 different companies engaged in the manufacture of key pharmaceutical products, as well as some vendors and service providers. The group meets biannually to address key topics in the pharmaceutical industry. In 2012 the ILF produced a document called the Global Positioning Strategy, which outlined six major elements that would provide platforms for alignment of key areas in the industry.

One of these elements was the Facility of the Future. To ensure that future manufacturing facilities were more agile and responsive to market changes, and focused more on customer's needs, the ILF recommended that the Facility of the Future be designed around the following concepts:

Use more portable and single-use technology, while utilizing flexible production lines, including the use of lean. The need to improve flexibility, increase productivity and efficiency, and reduce overall operating cost will require drastic changes to the pharmaceutical facility of the future if we are to compete successfully in this new and changing environment.

Use modular building strategies that allow for localization and rapid response or relocation to deploy manufacturing where and when needed.

Use quality by design concepts in new facility designs.

Utilize green and sustainable building concepts in the overall life cycle of all manufacturing facilities.

Ensure quick and efficient technology transfer processes so medicines can be delivered to the customer quickly and accurately.

Utilize process analytical technology while ensuring greater data connectivity and usage of analytics to drive improved performance.

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What Is the Facility of the Future?

In 2015, the ILF rebranded itself into an organization known as the Global Pharmaceutical Manufacturing Leader Forum (GPMLF). This group agreed to streamline and continue the focus on three key areas:

1. Supply chain robustness/supply need to rapidly evolve
2. New technology and plant-process design of the future
3. Update workforce of the future

The ISPE Strategic Plan 2016–2020 includes seven areas of prime focus for the organization over the next four years including:

ISPE Strategic Areas of Focus

The inclusion of the facilities of the future as one of ISPE's seven key areas of focus over the next 4 years demonstrates the organization's understanding that agile, efficient, sustainable, and compliant manufacturing facilities are absolutely required to support both patients and customers as we move into the future. ISPE is dedicated to preparing its membership (both individuals and companies) for a major transition as the industry begins to design and implement innovative technologies and concepts that will move the pharmaceutical industry toward the facility of the future.

To further emphasize and ensure the industry clearly recognizes the importance of these new types of facilities, which are focused on customer demand and speed of implementation, the ISPE annual Facility of the Year Award will, in 2017, introduce a new "Facility of the Future" award category. This new award category will highlight organizations and projects that implement new ways of thinking, feature innovative manufacturing of pharmaceutical products, and recognize teams and organizations that employ facility of the future concepts as well as other new technologies to advance the pharmaceutical industry.

As you will see in this series of articles, there are many definitions and assumptions about what a facility of the future includes and how it will better the manufacturer's and customer's daily and long-term goals. To remain at the forefront, an industry must continually examine how things are done and strive to create new ways to be innovative and transform the way of doing business.

Facility of the Future concepts attract the attention of many parties in the development and advancement of diverse industries, including governments, academic institutions, vendors, and service providers.

1. Governments are interested in new ways of manufacturing to ensure sustained employment for a particular industry or area of the state. Federal, state, and local governments succeed and fail based on employment for their constituents. It is well accepted that one manufacturing position usually creates three to four additional positions in a service or support industry. Government organizations in many countries are formatting strategies to help develop Facility of the Future environments for certain key industries they believe will create growth and economic advancement.
2. Academic institutions are continuously focused on Facility of the Future initiatives to ensure they produce graduates with the right technical and analytic skills to compete in the future labor market. Academic institutions also strive to know what future areas of research and development they should be exploring to be ahead of the technology road map.
3. Service providers and vendors want to supply new services, products, training, and expertise that give manufacturers new approaches, skill sets, and technology to improve agility, quality, and cycle time.

In 2017, FOYA will introduce a Facility of the Future category

Only with great collaboration between government, academic institutions, and the private sector can the maximum benefit of facility of the future be obtained. As noted previously, these new technologies will require additional employee training to develop new skills and to understand and implement the new practices brought about by technology advances. Collaboration with academic institutions in new areas of research and development, and working with governments to ensure the right environments are in place will allow these new technologies and methodologies to flourish.

What is clear in the pharmaceutical industry today is that leading industry organizations like ISPE and the GPMLF are putting great energy, effort, and resources into communicating facility of the future concepts and major developments within this field to their members and the pharmaceutical industry as a whole. This is an area of excitement and interest for ISPE leaders and membership.

ISPE has organized Facility of the Future forums in regional meetings around the world throughout 2016. Facility of the Future events or work streams were held in March in Frankfurt, Germany, and Raleigh, North Carolina, and in April in Shanghai, China, with strong participation and interest. ISPE will also conduct an important two-day session focused exclusively on Facility of the Future concepts in November 2016 in Bethesda, Maryland. ■

Jim Breen

Turning Opportunities into Reality

Pharmaceutical manufacturing has been conservative for many years. How conservative? From a manufacturing technology point of view very little has changed in the past half-century. In some selected areas, however, new technologies and regulations have begun to emerge.

A few pharma and biotech companies have shared their visionary strategies; some have even built pharmaceutical "Facility of the Future" concepts that have become operational. These include real-time-release manufacturing, functionally closed systems with low room classification, and continuous manufacturing of pharmaceutical drug products. While only few of these visionary experiences have been shared publicly, they still provide an opportunity to learn new best practices that differ significantly from previous state-of-the-art solutions.

Facilities of the Future initiative

To disseminate this knowledge as widely as possible, ISPE has launched a "Facilities of the Future" strategic initiative, hosting a number of events in Europe, China, and North America. At these gatherings, several companies have shared recent projects and current investments in next-generation solutions that point toward an agile and flexible manufacturing paradigm. With cooperation from regulators and technology suppliers, a number of new solutions and project experiences have been shared, followed by helpful discussions on the lessons learned.

In addition, the US Food and Drug Administration (FDA) has established the Emerging Technology Team—a specialized group within the Office of Pharmaceutical Quality that includes representation from the Office of Regulatory Affairs—to work directly with industry to help identify and resolve scientific issues for new technologies. This provides opportunities for discussion and mutual development between regulators and industry. The ISPE Facilities of the Future initiative is a meeting ground for this cooperation.

From a manufacturing technology point of view very little has changed in the past half-century

Increasing demand

After several years with a low investment levels, project activities are once again high, with increased capacity demand for new or enhanced products, within biotech and chemical active pharmaceutical ingredients as well as injectables and traditional oral solid dosage products. Contract manufacturing organizations are also seeing increased capacity demand as more products are approved for local and global markets.

Some companies are concerned that these capacity demands are more than suppliers and engineering companies can handle, and that they run a risk for a capacity bottleneck. This is probably the new normal for pharma: After years of focus on patent expires and patent cliff concerns, a new wave of product approvals and a new generation of biosimilar products are approaching commercial manufacture.

This new reality also includes regulatory challenges from the world market as some countries establish new regulations or enforce practices that differ from mainstream international regulations. This can challenge the application of new technologies. But if Facilities of the Future are to supply the global marketplace, the challenge should be managed by cooperation with regulators on an international level.

As ISPE continues to stimulate innovation and best practice sharing worldwide, knowledge about current good manufacturing practices will increase. If new technologies are applied with careful consideration and management, they may be able to solve many traditional pharma manufacturing challenges. Pharmaceutical equipment and system suppliers also have many examples to share. And as suppliers often remind us, there's no need to reinvent the wheel: Inspiration may also be drawn from industries outside the pharmaceutical world, as well.

So perhaps the time of the conservative pharmaceutical industry is coming to an end. Pharmaceutical manufacturing technology and solutions are starting to change, and practical experience with new and effective solutions provides a glimpse of the agility, flexibility, and quality envisioned in the FDA's oft-quoted desired state for pharmaceutical manufacturing.

ISPE's Facilities of the Future initiative may be a good way to get there. ■

Gert Moelgaard

The Workforce of the Future

Defining challenges and finding directions

One of the biggest decisions a manufacture r can make is whether its long-term strategic objectives are best served by upgrading existing facilities or by moving to new a location. Making this decision requires answers to a number of questions about the workforce:

- What technical knowledge and process skills will be required to meet future demands?
- How can we transfer them to different regions of the world?
- Do universities in the region teach the necessary scientific and engineering courses?
- How will trainers be trained and/or acquire proper qualification?
- What should we know about regional culture and lifestyle?
- What managerial style works best in each region? Is it contrary to our corporate style and values?
- What is the process for training all levels within organization?
- How will the company analyze workforce demand?
- What will strategy will we use to retain a skilled workforce, especially as the population ages and the industry loses the journeymen who know how to manufacture products?

Workforce development

The biopharmaceutical landscape is changing rapidly. Many multifunctional sites are being repurposed into as-yet-to-be-defined operational units or, in anticipation of product approval, are gearing up to handle new technology that will be deployed at a future date.

Yet while this is happening, 70% of biopharmaceutical industry workers remain stratified in scientific or manufacturing silos, and the industry, which has historically struggled with knowledge transfer, now faces an additional challenge: the emergent divide between technical and process workers. Overlap and cross-functional ability between the two are critical, and that criticality will increase significantly as the industry enters a new age of manufacturing.

Traditional job descriptions must and will change. Employee development programs must prepare workers to fill multiskilled roles that are often unique to each unit. Leaders from both manufacturing operations and the scientific community will be required to identify the skills and knowledge necessary, and ensure that the workforce has the tools they need to be successful. Enabling workforce success will result in success for the operational unit.

Education

Yesterday's workforce required a high school diploma. Today, many workers have college diplomas. Tomorrow's workforce will need postgraduate degrees. The conundrum is how to hire an "overly" qualified workforce, train them to the required skill level, and then retain that workforce to achieve product life cycle stability.

Whatever the employees' educational background, the work culture must offer job satisfaction, a sense of equality, and respect. It's also important to adhere to the region's cultural history. A one-size-fits-all monolithic corporate culture is doomed to fail. Finally, corporate policies addressing workforce culture must be established and strictly enforced; this reinforces the company's commitment to equality.

Millennials

Another factor in workforce development and satisfaction is generational: Millennials define success differently, and have different drivers for career decisions than their predecessors. Many from the United States and Europe have minimal loyalty to the corporation. Industry must learn what these drivers are and strive to create an environment that satisfies both corporate and individual objectives. Failure to do so will only erode employee loyalty and continuity as millennials seek employment elsewhere. Providing a place for employees to work that will improve their way of life and provide satisfaction that they are making a difference is a great place to start.

Leadership

Leadership will also be a challenge for global corporations that manufacture products and do business in different countries. We need to address and answer the following questions:

- How do we determine the ideal global leadership style and assess the gaps we likely have?
- If we examine the attributes of successful leaders in developed economies and compare them to those in emerging economies, can we identify the qualities required to lead a successful global operation?
- Access to huge markets and high profits are offset by the potential for failure. How do we train leaders to be proactive in their approach to leading the region?
- How do we build the succession plan? On what facts should it be based?
- How do we motivate staff so they are less likely to abandon ship?
- How do we create respect between management and workers?
- How can leaders make employees feel like winners?
- How do we convince process operators that producing products that meet specification the first time turns compliance into confirmation?

ISPE task team

The ISPE Global Pharmaceutical Manufacturer's Leadership Forum has been tasked with addressing these and other challenges that surround the Facility of the Future and the Workforce of the Future. These strategic objectives are crucial components of the biopharmaceutical industry's short- and long-term objectives to deliver lifesaving medicines around the world.

Employee development programs must prepare workers to fill multiskilled roles

Case study

My former company, Eisai Co., Ltd., restructured its R&D organization into 12 distinct units, split into therapeutic focus and riskier next-generation drugs. The company had a number of chemical entities that had been discovered years before but were deemed too toxic for human trials. They may now be able to utilize new delivery systems and scientific knowledge to take the drugs from the R&D shelves to next phase of development.

Eisai's reorganization provided the backing and stability of a large company, but by regrouping the workforce in smaller focused units created an entrepreneurial free-thinking environment provided a pathway for employees to expand their knowledge and skill. I don't know if Eisai deliberately established a work environment attractive to millennials, but it definitely provided opportunity and helped satisfy many millennials' desire to gain skill and knowledge.

This organizational setup will work in the process development and manufacturing sector as well, but it must be intentionally structured to best serve the workforce's needs and serve company objectives.

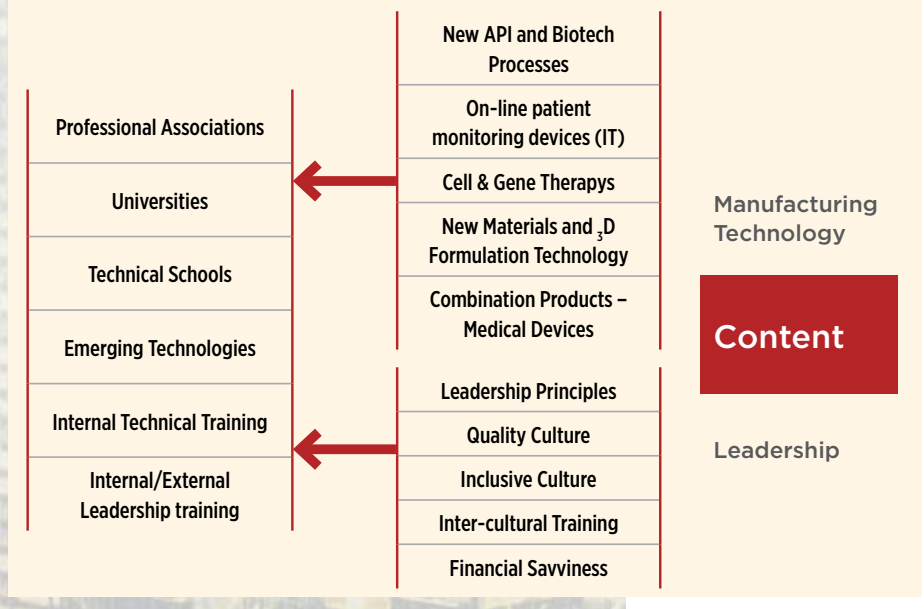


Figure 1: Knowledge sources for manufacturing technologies

Millennials define success differently and have different drivers for career decisions than their predecessors

The task force charter is to:

> *Create a process of ongoing understanding of the many cultural differences, geopolitical activities, national characteristics, and national norms to define diversity in our global "space" so that we can learn and adapt to lead, manage, motivate, and inspire our staff in all the regions of the world in which we do business.*

Figure 1 illustrates knowledge sources (left) for manufacturing technologies (center). Establishing a workforce with the necessary knowledge and skills will require input from many—if not all—of these sources. Employees are also encouraged to never stop striving for knowledge.

The ISPE task team will focus on the knowledge and skills required for process operators, then work backward to process development and R&D. Process operators must know what a CPP is, how it is determined, and how it is related to quality issues. Employees in process development must have a clear understanding of the required specifications for the excipients used, and may even need to identify vendors that meet those specifications. R&D scientists must deliver basic science—and then it is interpreted by process development into the "voice of the product" or the applied science; process development staff uses this information to create technology transfer and training for process operators to insure manufacturing has minimal challenges.

Conclusion

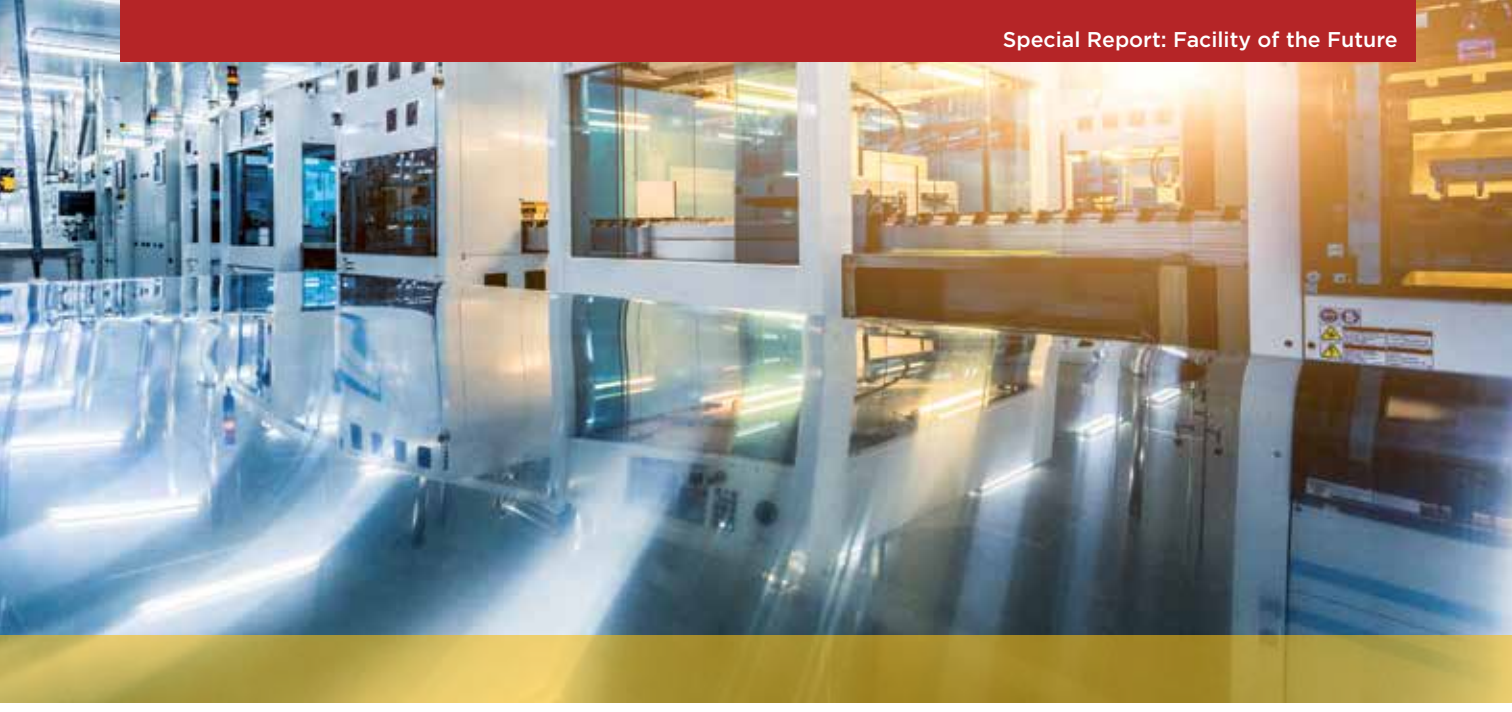
The quest to produce high-quality, low-risk products at lower cost to meet market demand is often addressed through new technology, systems, infrastructure, and asset reliability. Yet a solid and reliable workforce should be established before any of these.

Every company and organizational unit should define the future workforce challenges they face in their region, and identify the strategies and objectives they should develop and execute for long-term success. Since organizational improvement is a journey with no final destination, these objectives will be continuous.

Taking the time to complete this thoughtful planning, however, will provide a road map for today and a GPS for tomorrow. If we neglect to plan for change and improvement, in 10–15 years we will not have achieved the goals for high-quality, safe, pure products and lower unit costs.

Planning for the facility and workforce of the future presents both challenges and opportunities—and that's good news for the patients who depend on us to meet their needs today and tomorrow. ■

Larry Kranking



What Is the Facility of the Future?

"Facility (or plant) of the Future" is a great buzz phrase. Nobody can take issue with it. Why does it resonate with so many people; why are conference sessions on the subject always full? Why is everyone searching for the magic elixir of what it is and how to acquire it? Why is it so elusive? Are we already there? Does our mandate of quality and regulatory compliance help or hinder our ability to achieve efficient, world-class manufacturing operations?

But what are the characteristics of this mysterious facility of the future? What do we have to do to make it a reality, what are the challenges, what are the opportunities?

Pharmaceutical science may be close to entering its own "Moore's Law" era

What are the external forces driving us to FoF?

Pharmaceutical science may be close to entering its own "Moore's Law" era. Our understanding of biochemistry continues to increase—exponentially if you will. Computers are modeling physical chemistry, and our ability to efficiently identify or even to construct therapeutically potent molecules large and small is growing by leaps and bounds. In other words, the productivity of our laboratories—in terms of percent of molecules that prove therapeutic efficacy, will increase. This increase in "hit rate" for clinical trials, if it becomes reality, will drive down discovery costs. But this breakthrough science, if realized, will only put more pressure on engineering and manufacturing to deliver the processes and the facilities more quickly, with higher reliability, more throughput, and lower operating costs.

As costs to develop new drugs presumably declines, as our connected world makes product information more transparently available, as government and private payers demand lower prices for products, and as these new therapies treat previously untreatable and life-threatening or debilitating diseases, demand will only increase and the costs of goods sold will bear increased focus. We have experienced the significant decrease in the cost of computers while their capabilities have grown tremendously; should we not also expect a significant decrease in the cost of drugs in spite of significant increase in therapeutic value?

Diversity is the word when it comes to the global pharmaceutical market. Geography, politics, ethnicity, demographics, infrastructure, and regulatory domains all contribute to this diversity. Certain diseases thrive in certain environments, and in some cases, manufacturing proximity to disease source may drive manufacturing location. In some countries, some or

all manufacturing of drugs must be done in-country. Some diseases are prevalent in a given ethnic population but not others. Population age distributions are shifting, but at different rates in different countries. Different countries have different transportation infrastructure capabilities (road, rail, air, and storage along the way). Global regulators have yet to harmonize, and while progress is being made, regulatory diversity is still an issue for most companies. Lastly, tax rates vary considerably, which often trump all other factors when deciding where to manufacture.

Geographic diversity is reflected in supply chain complexity. Raw material sourcing, reliability of a given source, quality and variability of the source, and exposure of the source to natural or man-made disruptions are all important considerations. Raw material and finished goods protection, from storage conditions, transportation, to anti-counterfeiting, must be incorporated into the acquisition, manufacturing, and distribution processes.

It may not be easy to acquire the workforce that is needed to manufacture. In certain countries, aging populations mean expertise is retiring, and for too long companies have under-invested in transferring that expertise to the next generation, under-invested in developing and retaining talent, and under-invested in the health of their organizations, preferring to "rent" the expertise on an as-needed basis. Will that expertise be available, either in-house or on a contracted basis?

Companies will need to "up their game" when it comes to acquiring, training, and qualifying their manufacturing staff—both operations and maintenance. The good news is technology today offers a variety of methods to impart the necessary process understanding, equipment design, operating and maintenance principles, quality risks and control thereof, procedural requirements, and associated quality system controls—paper or computerized. In addition, some localities offer targeted university programs to help meet this challenge.

All these factors taken together are a wake-up call for factories that are "nimble": they can accommodate manufacturing flexibility due to product diversity, they can adapt to new technologies, they can be delivered quickly, and they are robust—they can tolerate variability small and large. Some will need to produce high volumes of a single product while others may be producing personalized doses.

How do we bridge the "canyon" of technological differences between basic sciences that are light years ahead of applied sciences?

What do we want from FoF?

How might we define this mystical facility of the future? Key attributes might include:

Achieve high tech metrics for process availability, process capability (Cpk): Most of us will admit that the pharmaceutical industry is not at the top of the performance list when it comes to common manufacturing quality and productivity metrics such as Cpk, availability, reliability, or batch rejection rates. Clearly, good manufacturing practice (GMP) regulatory compliance does not equate to world-class manufacturing measured against today's tech industry standards.

Automation without tears: Fifteen years ago at the ISPE Annual Meeting plenary session, GlaxoSmithKline offered a video illustrating the potential integration of automation, information management, supply chain flexibility, and a global manufacturing network. One would think that fifteen years later, the vision portrayed in that movie would have become reality. For most companies, it is still a vision, if that. Companies spend a lot of time and money to implement distributed control systems and manufacturing

execution systems, yet most struggle mightily to achieve significant benefit from this investment.

Data analytics for process improvement: Our industry collects and reports process information and changes in an annual report to regulators. How many of us collect and analyze data to implement improvements on a continuous basis at the quality engineer and machine operator levels? Or do we only focus on that which regulatory filings demand? Do sister factories making the same products share information for common improvement? Are manufacturing observations, trends, problems readily shared as improvement opportunities, or covered up unless required for regulatory compliance?

Compliance at the push of a button: Compliance reporting cannot be avoided. Even today, however, companies are only beginning to take steps to automate the collection, analysis, and reporting from across their manufacturing network.

Flexible: Can easily accommodate multiple products requiring common manufacturing platforms and technologies. Most generic manufacturers find this challenge easy to overcome, and producers of personalized medicine will need to reinvent the quality system to control large-scale small-volume manufacturing. For those with a "campaign" mentality, can we reduce what is often an arduous changeover process?

Reliable: Can we schedule production runs with confidence that equipment will operate reliably? Can we predict machine failure? Do we know where we are exposed to single-point failure, and can we accept such failure based on business or quality critical factors? Are we overly reliant on detecting the occurrence of failure vs. preventing failure? Do we ignore anything that is not "GMP critical" at the risk of impacting our cost of goods sold?

Resilient to operator error: Operators are perhaps the least reliable part of a manufacturing operation. Can the manufacturing equipment and process withstand most operator errors, either through compensation by other means or at least identification when it happens before the impact reaches cost of goods sold? Do the equipment design, automation employment, and operating strategy work together to reduce the potential for operator errors?

Ease of implementing change: Considerations including flexibility, continuous improvement, etc., mean we want to implement change: frequently and easily. Do we have an IT-based change process, the supporting product and process knowledge, quality risk information, and competent internal resources that allow us to quickly assess and implement change as soon as the need is identified? Do we collect information that allows us to pinpoint root causes of problems and laser focus on the right change to improve the situation?

Low maintenance: How often do we have to shut down for routine or corrective maintenance? Some companies today have initiatives to shorten the duration of planned maintenance shutdowns, or increase the time interval between such shutdowns, or even eliminate them altogether. This requires a well-founded asset management strategy, synchronized with the specific manufacturing demands to minimize life cycle capital, operations and maintenance costs and reduce costs of goods sold. Unified communication devices and robust analysis algorithms can continually diagnose asset performance during use. This gives us new challenging issues for improving the efficiency of asset operations. One obvious result is condition-based maintenance that makes a diagnosis of the asset status from continuously monitored data and predicts an asset's irregularities, and alerts operators to execute specific maintenance actions before serious problems happen.

Low energy usage: While energy costs may have plummeted globally over the past year or so, designing and operating an energy efficient plant will always be a driver. From passive solar heating and cooling, to production and operation of WFI systems, designing for energy conservation is an omnipresent consideration. Using a combination of geothermal and other techniques, modern factories can achieve minimal to zero net energy consumption.

Low environmental impact: Along with low energy usage comes low environmental impact: What does the process discharge to the environment, or what demands does the process place on a waste treatment system? This applies not only to liquid or gaseous discharge, but also the impact of component waste and gowning cleaning or disposal.

Easy to design, construct, commission, validate, operate: Simple designs, cookie-cutter factories, plug-and-play equipment modules, reusable automation, standardized design, procurement, fabrication, and commissioning processes, project information management systems, and use of paperless approaches all impact the cost and time required to deliver a facility. How can standardization help the human performance element? How can a sophisticated and highly automated facility help train the operators and maintenance staff using state-of-the-art knowledge management solutions?

Continuous processing and real-time release: The drivers for continuous processing include smaller equipment, higher utilization, lower costs, and more consistent quality. The amount of data collected, and the use of sophisticated process models and adaptive process control strategy will allow us to use real time release in most cases. Separately, industry is moving to product serialization, which should facilitate the acceptability of continuous processing. This "linkage" can be made by considering individual serialized packages time-stamped with time of manufacture, allowing traceability to the processing conditions and raw materials applicable to the product in that package.

We will need to move beyond product release decisions based on a few analytical pass/fail tests, to manufacturing based on detailed knowledge of in-process parameters and a sophisticated process control strategy. We will have continuous manufacturing data available upon which to make real time release decisions. Costs will come down and quality will go up.

What specific strategies, tactics, and techniques might we use to achieve our facility of the future?

What do we need to do to achieve FoF?

First, which "facility of the future" is right for our situation? Are we a multinational company with a global supply chain? Are we a boutique niche player with a single plant and novel product technology? Are we acquiring new network capacity through mergers or acquisitions? Do we transfer product manufacturing technology across the globe, or across the campus?

From the C-suites and the offices of global management consultants come the top-down manufacturing supply chain strategies, based on some analysis of market demands, cost, and other factors that generally drive capital project budget realities and location decisions. From our understanding of the external forces at play and the desired attributes of our facility, available technologies, supplier capabilities, and many other considerations become the bottom up opportunities, challenges, and limitations on what we can achieve. We must integrate these top-down and bottom-up mandates and realities to forge our specific facility of the future.

What specific strategies, tactics, and techniques might we use to achieve our facility of the future? We must successfully integrate process knowledge, equipment and automation design, delivery and operation, personnel training and qualification within the constraints of a project schedule, budget, and quality/ regulatory requirements. Key elements to be integrated include:

- Understanding our processes and listen to the voice of the product: What does the product require from the equipment, systems, and process control strategy in order to be manufactured consistently and of high quality?
- Having a disciplined process to establish the requirements, design to those requirements, invest in design reviews, and then follow through with a well-planned and managed delivery, commissioning, and initial operations process.
- Designing for life cycle operating cost: This is required even before one commences design of FoF. Along with what the product requires, we need to move away from the "old way of engineering and designing manufacturing facilities."
- Designing for reliability.
- Optimizing maintenance strategies.
- Improving use of automation and information management.
- Rethinking how operators are trained and qualified.
- Being passionate about risk management—not just quality risks, but business risks. Focusing on risk management and risk reduction, not just risk understanding and hazard detection.
- Be willing to challenge sacred cows of compliance practices: We must do nothing just for the sake of compliance.

Summary and conclusion

There can be many challenges and barriers to achieving our vision for a facility of the future. The obvious ones include compliance fears (doing something because we think regulators want to see it done that way), project delivery timelines, project budget limitations, and lack of sufficient talent/ skills/ experience in our workforce. How do we overcome these challenges?

How do we bridge the "canyon" of technological differences between basic sciences that are light years ahead of applied sciences? Applied science—how we manufacture product, has remained stagnate over the last 15–20 years with the exception of "spurts" of change such as some current continuous oral solid dosage manufacturing operations. For most of the changes, the only real change is the ability to collect real time data in a process analytical technology format. Little has changed in the actual operating principles of the equipment, systems, maintenance reliability, etc.

How do we bridge the "canyon" of technological differences between basic sciences that are light years ahead of applied sciences?

Regulators have been pushing industry towards quality risk management as a more sophisticated, nuanced approach to GMP compliance. That being said, we are on a long journey to implement more significant change, and we must constantly adjust our compass as new paths emerge. Fundamentally, though, both regulators and industry need to seriously accelerate the adoption of new technologies, new methods of process and quality control, and other methods that promote flexibility, lower cost, and higher quality.

We must continue to explore new technologies, educate ourselves, our industry, and the regulators. We must achieve greater industry standardization in terms of project delivery methods, regulatory expectations, and human performance goals. We should look to other industries for benchmarks, novel technologies, and world-class manufacturing methodologies. We must accommodate and embrace change and improvement.

We are given a limited amount of time, money, and talent—never enough. We must understand the principles needed to minimize our cost of goods sold, we must identify the opportunities available to us in our project scenario, must work within an efficient project delivery system, and we must successfully integrate a program for the process, the staff, and the plant/equipment. If we do these things well—from concept design to full-scale operation, we can achieve that facility of the future, delivering better quality, significant therapeutic value, and greater quantities of product to our customer-patients, and providing our shareholders with a solid return on their investment. ■

Robert E. Chew

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FACILITIES AND EQUIPMENT

Evaluating the Benefits of Prefabricated Cleanroom Infrastructure Designs and Costs

Maik Jornitz and Sidney Backstrom

In the last 10 years, biopharmaceutical processing platforms have moved from rigid stainless steel to flexible single use, which are more agile and run more efficiently. Single-use process technology also accommodates multiple products within the same process.[1–2] This flexibility is a tremendous advantage in optimizing the capacity of the equipment and process.

The need for flexibility is now shifting to cleanroom infrastructures, manufacturing sites and facility designs. Traditional single-product facilities built for maximum forecasted sales required costly and lengthy planning – especially in capacity planning, since the structure's inflexibility did not allow for easy scaling of the required cleanroom space.

Overall, this type of manufacturing system did not accommodate flexibility of scale or multiproduct needs, nor did it accommodate the benefits of single-use technology. What has become clear since the advent of single-use systems is that while single-use technology processes are much more mobile than stainless steel processes, they can only provide as much flexibility as the cleanroom infrastructure around them. Often single-use hold bags are moved around, potentially from room to room. To achieve single-use technology's full utilization and flexibility, new facility designs had to be developed.

Such new cleanroom infrastructures are now available. The cleanroom is not constructed at the site, but prefabricated offsite and shipped as an outfitted unit, also known as a POD. These units can be scaled to meet demand and are easily moved (see Figure 1).

Prefabricated cleanroom units replace so-called flexible modular structures, which, once built, offer no flexibility at all. These prefabricated units are built off-site in weeks. Upon completion, they are moved into a simple shell building, either an existing structure or one erected in parallel to the manufacture of the cleanroom units. This not only provides flexibility and scalability, but, perhaps more importantly, "repurpose-ability." These flexible, repurposable, multiproduct cleanroom structures can replace single-use, single-process, single-product facilities.

Costs affect design

Historically, the pharmaceutical industry built large centralized product-dedicated manufacturing sites for global product distribution instead of constructing multiple regional centers. Recent events have changed this mindset. As patents expire, for example, the resulting loss of market share and lack of production capacity have forced the closing of some large-scale sites, which often become more of a burden than an asset. It is now fairly common to hear of "abandoned assets" in facility discussions with pharmaceutical companies.

Why? Costs for insurance, utilities, security, and the like persist well after the facility is decommissioned. In addition, rising operation and transportation costs are a factor, as are supply chain concerns about distributing drug products to multiple locations. Perhaps most significantly, import taxes by countries that seek to build more industry and infrastructure have generated more need for "in-country/for-country" production. Moreover, increased cell-expression rates and advances in continuous processing allow smaller bioprocessing volumes. These can be served by single-use bioreactors, which are shorter and have a much smaller footprint, which means they can be used in smaller cleanrooms.[3–5]

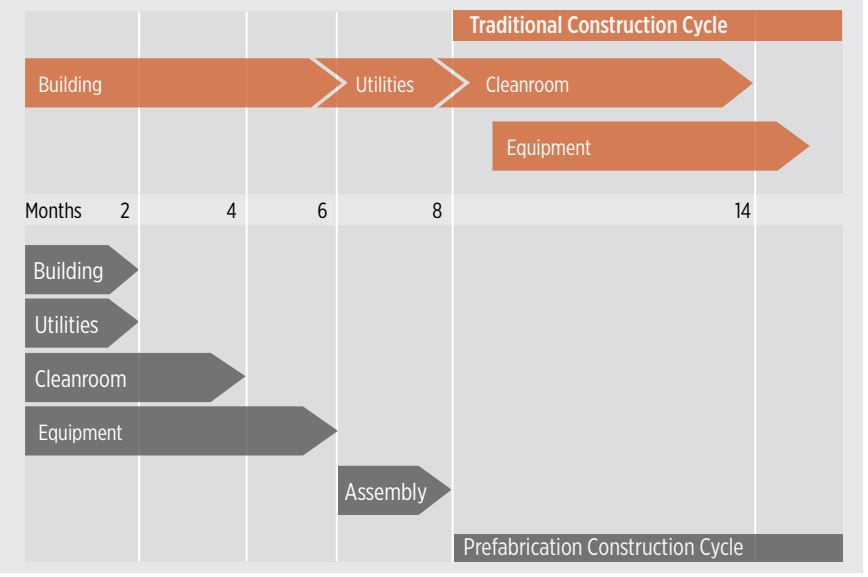
Direct and indirect costs for large aging facilities have also influenced this shift. Direct costs, such as operating and maintenance expenses, only increase with each year of service. Indirect costs include manufacturing products to meet forecast demand. Product shortages, overproduction, and expiration of products also have significant effects on profitability. A classic example is the expiration of vaccine doses stockpiled to supply

Figure 1: Prefabricated cleanroom unit (POD) with integrated air handling system in shell building

To achieve single-use technology's full utilization and flexibility, new facility designs had to be developed

an estimated patient base. Smaller volume sites, which have a lower raw material demand, would be able to convert traditional large-scale processes to small-scale, flexible or multi-product processes and assure the ability to supply product on demand. Losses from cold chain shipments could be avoided by creating in-country/for-country small-volume sites to supply local markets with shorter distribution distances.

Figure 2: Depiction of construction timelines of traditional or stick-built approach versus off-site built modular



For those who focus only on cost per square foot, the costs of switching to an autonomous modular POD (versus "stick-built") approach can be a stumbling block. Such a myopic focus, though, is not appropriate in light of all of the benefits provided by offsite, prefabricated modular-built facilities (Figure 2), including:

- Design costs (conceptual, basic, detailed) are significantly lower because all units use the same basic architecture. Costs are reduced even further as modular sites are cloned.
- Personnel, engineering, and supervision requirements are much shorter. Would you rather have the contractor for at the site for 6–8 months or for 14 days?
- Prefabricated cleanroom units, also called PODs, do not need the extensive laydown areas seen in traditional cleanroom constructions.
- Insurance costs and safety concerns typical in lengthy on-site construction are minimized.
- No detailed and complex infrastructure on top of the actual stick-built cleanroom space is required; instead, all ductwork and piping is run within the module structure. these runs are much more compact, efficient and are not exposed to potential hazards
- Operating expenses are lower, because modular units lose less energy in long pipe runs and leaks.[6]
- The cleanroom structure can be repurposed for more than one product. Off-site built modular systems can be readily disconnected from the host facility and moved in a matter of hours.
- Moveable cleanrooms can be depreciated as equipment (8 years); in-place construction is depreciated on the same terms as real estate (30 years).
- Scalability: It's not necessary to shut down existing cleanroom infrastructures when new space is added. Additional units can be added without affecting the existing operation.
- Cleaning and sanitization: If an excursion occurs, the production floor need not be shut down for an extended period of time. All surfaces are suitable for vaporized hydrogen peroxide (VHP) cleaning.
- Time to first product run can be cut to at least half of the time for traditional structures. This also means capital investment decision can be delayed, if necessary
- Qualification and validation costs are reduced because each unit has the same basic characteristics, architecture, and bill of materials.
- No additional costs or add-ons required. Stick-built approaches generally require the owner to contract for a cleanroom floor as well as the design and construction of an automated heating, ventilation, and air conditioning (HVAC) system.

These are only some of the relevant costs that should be considered in determining which cleanroom system to employ. But it should be clear that comparing the price of an offsite modular-built system to a stick-built system on a cost per square foot basis not appropriate.

Regulatory considerations

Both industry and regulatory authorities seem to see the need for change in the manufacturing paradigm. The Food and Drug Administration's 21st Century Initiative declared the need for

> *A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.*

Certainly, there is some idealism in that statement. But it also shows that failing to change to a more flexible and agile system may lead to being seen as old, aging, or obsolete, which is something that industry certainly would not welcome.

The terms "maximally efficient," "agile," and "flexible" also suggest that yesterday's facilities will not fare well tomorrow. Single-product behemoths built in the latter part of the twentieth century do not meet any of those goals. As regulatory pressure increases on these facilities, decision makers will probably become more willing to embrace the new facility approaches.

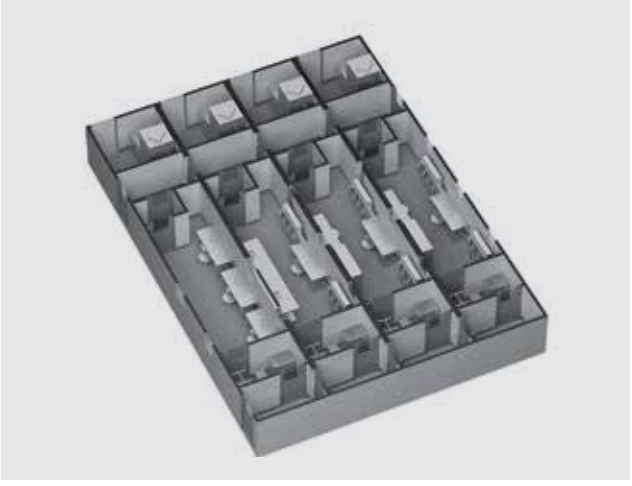
If regulators support these new paradigms, preapproval inspections could be abbreviated when a facility has been cloned and the originator facility already been inspected. In the same way, oversight might be reduced or abbreviated when a flexible site produces reliably high-quality drug products.

Agility and flexibility

Since industry, trade organizations, and regulatory authorities all use the terms "agility" and "flexibility," it is important to consider their definitions. For the pharmaceutical and biopharmaceutical industries they mean:

- Capacity scalability (up and down)
- Multiproduct production
- Rapid deployment, or short time to product run
- Rapid changeover or layout changes
- Repurposability
- Mobility

Figure 3: Example of a cluster of four prefabricated cleanroom structures (PODs)



Putting all these attributes together, what manufacturers need are small-footprint, high-quality manufacturing facilities that can scale up or down to meet demand, be moved, and be delivered in months, not years, at a much lower total cost than usually seen to date. Such an approach would make "mothballing" or abandoning a facility a thing of the past.[7–9] It would allow single-use equipment to be used for multiple purposes, spreading the cost

Current trends strongly suggest that smaller, more agile platforms are the future

over many products and reducing the cost per dose for each. It would also reduce the need to manufacture to forecast and lower costs inherent drug expiration and/or shortage.

In addition, when a cleanroom asset can be repurposed it becomes a lower investment risk because a secondary market for that asset exists. Repurposing has been used for decades in the airplane industry, where outer structures have been used for as many as 50 years. Prefabricated autonomous cleanroom systems with equally robust outer aluminum structures may fulfill the same purpose in the pharmaceutical and biopharmaceutical industry.

Scalability and flexibility also play a major role in new and rapidly rising therapeutic treatment segments like cell therapy and personalized medicines. These processes are patient-based, meaning that tissue from the patient is needed to make the end product. Moreover, they must be formulated and filled at the highest level of aseptic processing, which requires not only strict containment, but also rapid cleaning and sanitization options, preferably with VHP.

Because these products will not be instant blockbusters, given their manufacturing protocols, the ability to add capacity is important. These additions should not interrupt facilities that are already online, and new structures must come online in a plug-and-play fashion (see Figure 3). In addition, the processing facility may be located regionally at hospital level, since the needle-to-needle quality assurance level must be maintained. These requirements cannot be met by large purpose-built facilities or onsite-built modular systems (Table A). Expense and logistics take away the viability of the former. Business interruption, HVAC rebalancing, permitting problems, and a host of other issues condemn the latter.

Conclusion

Multiple facility options exist. Brick-and-mortar facilities built to meet maximum forecasted demand for a single product are becoming an inefficient manufacturing platform, and are increasingly mothballed after the product life cycle ends. Asset minimization or at least redeployment is a more favorable outcome. Modular facilities are cheaper but suffer from

Table A: Strength and weakness analysis of the different facility designs available

Facility Design	Strengths	Weaknesses
Bricks and mortar	■ Extensive experience with such facilities ■ Dedicated product segregation ■ Large areas	■ Difficult to repurpose ■ One product life cycle ■ High capital expenditure (CapEx) ■ Time to run: Up to 4 years ■ Complex, tremendous resource needs ■ Inflexible ■ Large HVAC superstructure ■ Difficult to decontaminate
Modular container	■ CapEx 70%–90% of traditional built ■ Time to run 18–24 months ■ Off-site buildup ■ Lower amount of personnel needs to build site	■ Large, interconnected, inflexible facility ■ Large HVAC superstructure ■ Shipping costs ■ Not scalable
Stick-built modular	■ CapEx 50% lower than traditional built ■ Time to run 6–24 months ■ Build into a shell building ■ Potentially scalable	■ Large, interconnected, inflexible layout ■ Large HVAC superstructure ■ Needs on-site buildup with large lay-down ■ Construction personnel on site for months
Isolator or controlled environment module	■ CapEx 50% lower than traditional built ■ Time to run 12–18 months ■ Repurposable ■ Can be decontaminated ■ Scalable	■ Size limitations make using large equipment difficult ■ Biosafety level containment limitations ■ Centralized HVAC
Autonomous cleanroom POD	■ CapEx 40–50% of traditional built ■ Time to run 6–12 months ■ Moved into a shell building ■ PODs are repurposable ■ Easy to decontaminate with VHP ■ Factory acceptance test and prequalification off-site ■ Scalable ■ Personnel required on site for days, not months	■ Shipping costs ■ Equipment size excursions require project POD

Failing to change to a more flexible and agile system may lead to being seen as old, aging, or obsolete

the same principal defect: inflexibility. Once built, they are also product-dedicated, fixed installations that cannot be repurposed or moved.[8] The need for flexibility and agility in pharmaceutical and biopharmaceutical manufacturing systems is clear.[3,5]

Process technologies have gone from stainless steel to flexible, agile, single-use process technologies. If facilities follow with the same type of innovation,[10] the flexibility of single-use equipment would be even more apparent. The cost of drugs would be less affected by overproduction, underproduction, expiration, transportation costs, import taxes, and other negative factors.

Flexible-facility platforms are emerging and available, but the industry's customary hesitancy is as prevalent as it once was with single-use technologies. A total cost comparison may be needed to convince those wary of making the change. Or perhaps a small minority with a true vision will lead the way. There are already "green shoots" evidencing this: See, for example, the press release introducing the concept of multiple small-footprint facilities for the production of oral solid dosage forms.[11] How far that will go and whether others will follow remains to be seen. But if industry heavyweights begin to change, expect to see many others follow suit. One solution will not be ideal for every application, but ultimately, current trends strongly suggest that smaller, more agile platforms are the future. ■

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Biopharmaceutical Manufacturing Process Validation and Quality Risk Management

Francisco C. Castillo, Brendan Cooney, and Howard L. Levine

Process validation today is a continual, risk-based, quality-focused exercise that encompasses the entire product life cycle.

Manufacturing processes for biopharmaceuticals must be designed to produce products that have consistent quality attributes. This entails removing impurities and contaminants that include endotoxins, viruses, cell membranes, nucleic acids, proteins, culture media components, process chemicals, and ligands leached from chromatography media, as well as product modifications, aggregates, and inactive forms.

Manufacturing processes should be validated by applying a scientifically rigorous and well-documented exercise demonstrating that the process, and every piece of equipment used in it, consistently performs as intended, and that the process, when operated within established limits, generates a product that routinely and reliably meets its required quality standards.

The principles of process validation were initially established in the 1987 US Food and Drug Administration (FDA) document "Guideline on General Principles of Process Validation," which defined process validation as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."[1] This definition has since been adopted in guidance documents worldwide, including the current good manufacturing practices (cGMP) regulations promulgated by European regulatory agencies and the International Conference on Harmonisation (ICH).

When the 1987 FDA guidance was published, validation during early stages of product development (before Phase 1 clinical trials) was minimal:

- Qualifying master and working cell banks
- Demonstrating adequate virus clearance (removal and inactivation) by the manufacturing process
- Validating sterilization and aseptic processes used to manufacture the drug product

At that time, most process validation activities were conducted in the later stages of product development, primarily during Phase 3 clinical trials, in preparation for filing a biologics license application (BLA) and eventual commercialization of the product. These activities included:

- Identifying critical process parameters (CPPs): those independent process inputs or variables related to each individual unit operation in a manufacturing process that directly affected product quality
- Conducting range studies on these parameters to determine the points at which the process fails to yield acceptable product
- Producing a series (three to five) of consecutive full-scale conformance lots in qualified equipment under cGMP conditions

Equipment qualification involved confirming and documenting that the design, installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ) of the manufacturing equipment were capable of satisfying the process requirements.

Analytical methods used for in-process testing and final product release were validated prior to initiation of full-scale conformance lots. After conformance lot approval, the validated process could not be materially modified without revalidation to confirm that the process was still under control and still resulted in a product of acceptable (comparable) quality.

Evolution

Since 1987 the concepts of validation in general, and process validation in particular, have evolved. Process validation is now viewed as a continuum of activities rather than a series of discrete actions that are performed once and rarely repeated. Regulatory authorities also now consider process validation as encompassing not only a full demonstration of process consistency and understanding, but also ongoing verification to ensure the process remains within its qualified design space and product consistently meets all specifications.

In addition, regulatory authorities expect companies to develop unique validation protocols suited to their individual organizations. These protocols are no longer based on conformance to a fixed set of guidelines, but are designed using a risk-based approach that identifies and controls potential risks within the manufacturing process. This approach to overall product development and validation was outlined in 2004 by FDA in "Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach,"[2] and reinforced in 2005 with the approval of ICH Q9,[3] which formalized the requirements of quality risk management for the pharmaceutical industry.

This was further defined in FDA's 2011 guidance on process validation[4] and the European Medicines Agency (EMA) 2012 draft process validation guideline.[5]

As a result, validation must now take a continual life cycle approach. This shift acknowledges the need for improvement in manufacturing processes, in alignment with the quality by design (QbD) approach.[6] In addition, both FDA and EMA guidelines are now in line with ICH Q8(R2), Q9, and Q10, and Q11; both also require adherence to cGMP regulations. But there are subtle differences between the two.

FDA's 2011 guidance divides the validation of a manufacturing process across the life cycle of the product into three stages: process design, process performance qualification, and continued process verification.

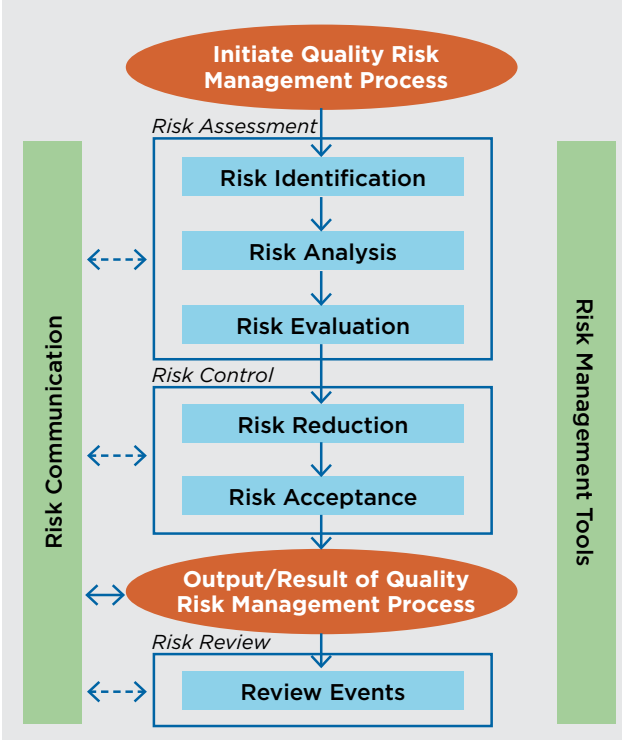
The EMA guideline does not divide process validation into stages. It also allows for a hybrid approach that combines the new process validation guidance with the traditional approach; FDA requires that the new guidelines supersede the traditional practice.

Quality risk management

To meet the regulatory requirement that commercial pharmaceutical manufacturing processes be "validated with a high degree of assurance,"[7] regulatory authorities now consider a systematic risk analysis and management program to be a critical component of validation.[8] A quality risk management program (see Figure 1) will encompass risk control, risk review, and, most importantly, risk assessment, which is the most critical aspect for process validation.

Process validation is now viewed as a continuum of activities rather than a series of discrete actions

Figure 1: Overview of quality risk management



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

Risk assessments should be based on sound science, process characterization information, and data collected from both scaled-down models of the manufacturing process and actual product batches produced during clinical development and scale-up. The data should include information about the source and quality of all materials used in the manufacturing process, as well as the effect of each material or procedure used in the process on the quality, efficacy, and safety of the final product. Risk assessments should be conducted throughout the product life cycle, starting with process design and continuing through ongoing assessment of commercial manufacturing operations.

Risk assessment approaches used initially to determine product critical quality attributes (CQAs) include risk ranking and preliminary hazard analysis (PHA). These are illustrated in a 2009 case study for a monoclonal antibody bioprocess development, which is a practical guide on how to use both QbD and life cycle approach to validation.[9] Later risk assessments include process risk assessment (PRA), which is conducted using failure modes effects analysis (FMEA); failure modes effects criticality analysis (FMECA); or the hazard analysis and critical control point (HACCP) methodology.

Risk assessments should be conducted at phase-appropriate intervals, and any time that changes are made to the manufacturing process. Depending on situation and need, they can, and should be, both formal and informal. As the product matures and additional process knowledge accrues, risk assessment and analysis will become more comprehensive, helping to determine the potential effects of even subtle manufacturing process changes on product quality.

The glycosylation of recombinant proteins, for example, can be altered by a range of factors associated with cellular metabolism and metabolic flux as well as the efficiency of the glycosylation process. Since changes in glycosylation can have a significant effect on biopharmaceutical product pharmacokinetics, efficacy, and immunogenicity, it's important to assess the risk of variations in the production bioreactor operating parameters and any possible effects on product glycosylation.[10] This is especially important since subtle variations of nominally identical bioreactor operating parameters can alter glycosylation.[11] It may be difficult to determine the effect of certain manufacturing parameters on glycosylation early in the product life cycle, however, due to the limited number of batches produced during clinical development and the limited clinical data available at that time.

The potential risks associated with raw materials, process equipment, and manufacturing processes on biopharmaceutical product quality should also be part of the evaluation. The criticality of these risks should be determined, as should methods or policies designed to eliminate, mitigate, or control them. A quality risk management program will define and prioritize the operating parameters that must be controlled during a manufacturing process.

In alignment with QbD, quality risk management acknowledges that it is not possible to achieve control of product quality by final product testing alone. Product's CQAs should also be identified using appropriate risk assessments, and confirmed during process development and early-stage manufacturing. These CQAs should then be maintained throughout the product life cycle by carefully controlling and monitoring those CPPs that may affect them.

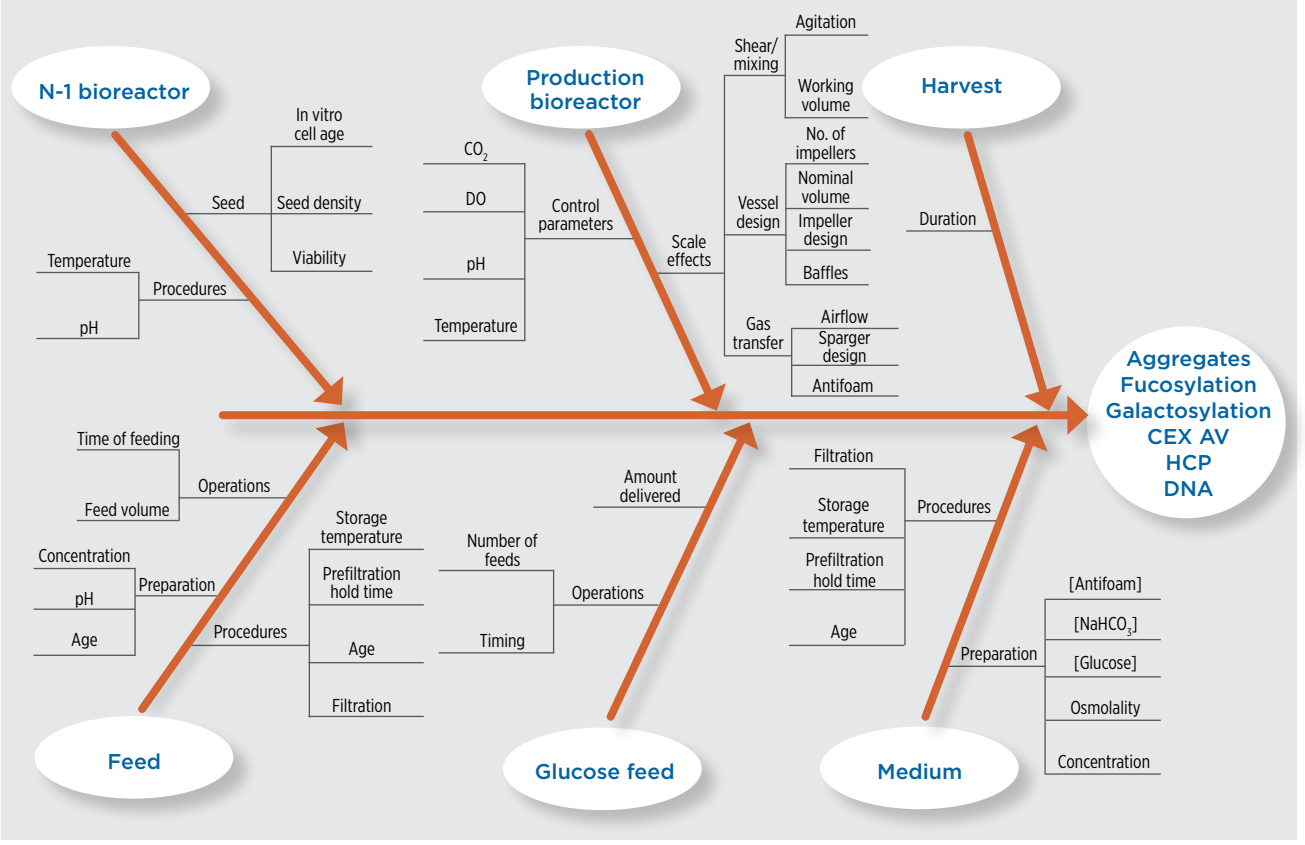
By establishing the CQAs for a product, defining the acceptable ranges for each CPP to achieve these CQAs, and controlling those CPPs during manufacturing, it's possible to define a design space for each process step that incorporates the acceptable operating ranges of all CPPs. This approach allows a manufacturing process to be optimized or changed as long as design space parameters are maintained. Staying within the process design space will eliminate the requirement for revalidation of the manufacturing process, encourage innovation, and allow process changes to be implemented with minimum regulatory delay and expense.

An additional useful tool in conducting an initial risk assessment is the Ishikawa or fishbone diagram, which can be used to identify all possible causes for a given effect. Such an analysis is helpful, for example, in evaluating how different process parameters might affect certain process attributes. In the A-Mab case study mentioned earlier,[9] a fishbone diagram was used to identify equipment design, control parameters, processing conditions, and starting materials for a production bioreactor and its seed reactor that might have posed a significant risk to the quality attributes of a monoclonal antibody product. This analysis, shown in Figure 2, helped assess the potential effect of each process parameter on product yield and cell viability of the culture. It also identified soluble aggregates, variability in glycosylation, deamidation, and levels of host cell protein or DNA at harvest.

Risk assessment tools

ICH Q9 recommends the use of such standard risk analysis tools as FMEA/FMECA and HACCP to quantify the risk associated with each step in a manufacturing process and determine CPPs.[3] Additionally, risk ranking and PHA can be used to determine the CQAs.[9] Individual risk assessment techniques are best used in a complementary manner to eliminate knowledge gaps.

Figure 2: Quality risk management overview



Source: CMC-Biotech Working Group. "A-Mab: A Case Study in Bioprocess Development." Version 2.1. 30 October 2009.

Before initiating any risk assessment the scope must be defined, the risk assessment tool chosen, an appropriate team selected, and any potential decisions that will be based on the assessment clearly stated. Defining the scope of the risk assessment will also help determine the proper team composition. Risk assessment teams should include all individuals required to bring the necessary expertise to the assessment; they may include representatives from validation, process development, quality, and manufacturing.[8]

A simple but effective approach to risk analysis is provided by Katz and Campbell:[12] A manufacturing process is broken down to its constituent unit operations and the specific parameters of each operation are analyzed to determine whether that parameter poses a risk to product identity, strength, quality, purity, or potency. Since each unit operation intended is to meet or maintain some section(s) of the quality target product profile, identifying and managing those process parameters that affect the product's CQAs constitutes the control strategy for that particular unit operation.

PHA

This risk assessment tool can be used to rank quality attributes based on the probability and severity of failure by leveraging prior knowledge to identify future risks to the patient.[3] PHA produces a severity score, which considers risks to safety and/or efficacy based on prior knowledge elements. PHA also calculates a probability score based on the chances of a quality attribute affecting safety and/or efficacy by going outside of the currently established ranges.[9] The probability and severity scores are multiplied to calculate the risk priority number (RPN), which allows the quality attributes to be ranked.

FMEA

FMEA is a methodology for identifying potential failure modes for a product or process; it is designed to assess the risk associated with those failure modes and to classify the severity of failures on the product or process. FMEA analysis ranks potential failure modes and identifies corrective actions to address the most serious concerns. Failure modes are defined as any errors or defects in a process or product, especially those that affect the product's safety or efficacy.

FMEA considers three factors in evaluating the effect of a failure:[13]

- Severity: the impact of failure
- Probability: the likelihood of failure
- Detection: the detectability of failure

These factors are assigned scores determined by the scale assigned for each one. The scores are multiplied to calculate the RPN, which ranks the failure mode, prioritizes risks, and evaluates risk mitigation.[3] FMEA is best suited for the evaluation of equipment and manufacturing processes. FMEA/FMECA may be used in the PRA to identify parameters for screening in-process characterization studies.

Incorporating science-driven risk-based process development and validation will result in more reliable processes that can be readily adapted to new process information

HACCP

This systematic preventive approach to product safety addresses hazard identification, evaluation, and control rather than finished product inspection. Used for years in the food industry,[14] HACCP can be applied to biopharmaceutical product development and manufacturing as a means of identifying the points in a process at which specified critical control points may be controlled, the limits of control available, monitoring requirements, and required corrective actions.

For most biopharmaceutical product manufacturing processes, FMEA is generally used to determine risks associated with the manufacturing process. For those manufacturing processes where controlling hazards is a critical issue, however, HACCP may be more appropriate. This is because HACCP focuses on critical control points to prevent or eliminate hazards and risk, while FMEA focuses on the potential effects of any identified failure mode. An HACCP analysis, for example, may be better suited than an FMEA analysis for determining risks when a filling process for a biopharmaceutical molecule conjugated to a toxic compound relies heavily on environmental and manufacturing controls to ensure not just product quality, but patient and operator safety.

Risk ranking

Risk ranking is used to assess product quality attributes and determine which must be controlled as CQAs. Risk ranking evaluates quality attributes based on their potential to affect the patient adversely multiplied by the level of confidence in the knowledge used to determine that effect. This is scored by evaluating known or potential effects on safety and/or efficacy.[9] The uncertainty is scored by leveraging prior knowledge elements as recommended by ICH Q9. Scoring for each category should be established using a numerical system commensurate with the criteria for each category. The numerical scale used is considered arbitrary, provided it gives appropriate to the impact score.

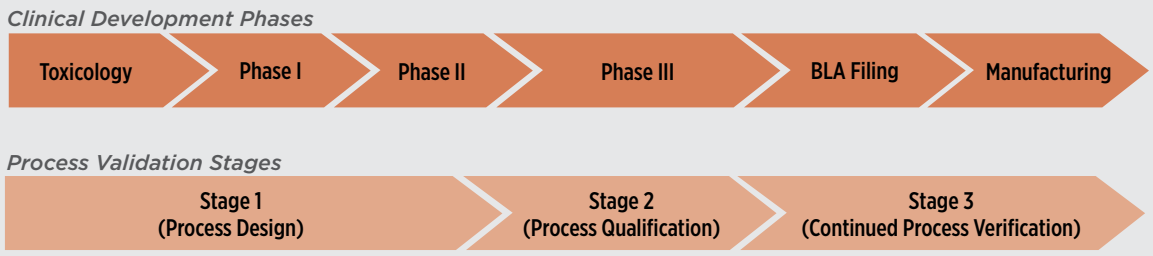
Risk ranking does not take into consideration the detectability or controllability of a failure; as a result, the criticality score will not change as product and process knowledge evolve. It will change, however, as understanding of the product increases. Risk ranking should be used during the initial assessment of product quality attributes and reevaluated over the course of the product life cycle at phase-appropriate intervals.

An example of the type of risk analysis and ranking that can be used to assess the impact of raw materials or process parameters on product quality attributes and the assignment of CQAs is provided by Boychyn and Hart, who applied this approach in assessing the risk of adventitious agent contamination of raw materials used in cell culture media.[15] Their assessment concluded that the highest risk for viral contamination in media was associated with use of raw materials containing animal-derived ingredients, materials that are a potential food for rodents, materials that are not highly purified, or when raw materials represented greater than 10% of the volume of the media. These factors had a risk potential several orders of magnitude greater than the next-highest set of raw material risks evaluated. As a result of this analysis, cell culture media containing the highest-risk raw materials should be subjected to viral inactivation processes before they are used in product manufacturing. A similar analysis by Kiss concluded that the highest-impact risk mitigation strategy was to provide an efficacious virus barrier at the point of use in the manufacturing facility.[16]

"Life cycle" process validation

With the introduction of QbD and quality risk management, process validation has evolved from a traditional "fixed-point" manufacturing process following process validation to a "life cycle" methodology that enables more continuous improvement of manufacturing processes. In this modernized approach, manufacturing processes are continually reviewed during routine manufacture to ensure that adverse trends are identified and corrected before the product fails to meet its final specifications. These new process validation guidelines promote designing quality into the product rather than simply testing for quality in the finished product. As defined in the FDA January 2011 guidance, the life cycle approach specifies that traditional process validation,

Figure 3: Relationship between the phases of product development and the process validation life cycle



which typically relies on three consecutive successful full-scale conformance runs, should be replaced by a deliberate design process, commercial process qualification, and ongoing review of processes with increased use of continuous process monitoring.[4]

The relationship between the various phases of clinical development and commercialization of a biopharmaceutical product and the three stages of process validation (process design, process qualification, and process verification) is shown in Figure 3. As knowledge about the safety and efficacy of a product increases during its clinical development, so too does the knowledge of its manufacturing process. Now the CQAs of the product and CPPs of the manufacturing process, initially defined during process validation Stages 1 and 2, are continuously monitored and verified during Stage 3. This requirement for continued process verification remains throughout the commercial life of the product.

Stage 1: process design

During process design, the manufacturing process is developed, characterized, and then scaled up to commercial levels as outlined earlier in this paper. During Stage 1, product CQAs should be identified and the critical and key process parameters for the manufacturing process defined.[17]

Since CPPs must be maintained or controlled within their specified ranges to demonstrate process robustness and suitability, acceptable operating ranges for these parameters should be established during this stage. As described below, much process design and process development work can be done using scaled-down process models and high-throughput development techniques. FDA guidance recommends using statistical design of experiments to study the interaction of different process parameters using multivariate experiments.[4]

Process design during Stage 1 encompasses laboratory activities for process development and process characterization, as well as establishment of a commercial process control strategy. Key prerequisites include sufficient product characterization data to establish product CQAs, and sufficient scale-up/scale-down data to ensure that the laboratory models used in process characterization represent full-scale manufacturing performance.

During Stage 1, a standardized approach such as that outlined in Figure 4 allows all unit operations, analytical methods, and product specifications to be scrutinized carefully and developed properly. Each CPP in the manufacturing process should also be classified.

A CPP is "a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired product quality."[18] Process parameters are classified as either critical or non-critical through risk assessment, as discussed above.

These additional classifications, while not an absolute regulatory requirement, can be helpful during routine manufacturing to determine acceptable responses to process deviations or excursions. Non-CPPs may be divided into two discrete categories, key and non-key process parameters, in accordance with the definitions established by the Parenteral Drug Association. Non-CPPs that do not affect product quality, but may affect process performance such as yield, are classified as key process parameters (KPPs). Non-key process parameters (non-KPPs) are those that have no effect on process performance or product quality.

CPPs, KPPs, and non-KPPs do not represent a continuum of criticality. While designation of a process parameter as CPP or non-CPP is based on a continuum of risk, the decision to classify parameters as KPP or non-KPP is binary.[19] There is no universal definition for categorization of process parameters as CPP or non-CPP, and as such these categorizations are not necessarily recognized by global regulatory authorities.[19–20] Regulatory authorities generally discourage the use of key and non-key parameters in regulatory submissions. However, it is possible to define categories of process parameter criticality to meet individual program requirements.

The A-Mab case study provides an example of how criticality rankings can be customized. In this study, critical process parameters were classified as either CPP or well-controlled CPP (WC-CPP). Non-critical process parameters were designated non-CPP or general process parameter (GPP). This process acknowledges that although criticality assignment is binary, the potential effect of a process parameter can depend on a variety of factors, including the controllability of an individual process parameter.[9] A criticality assignment process with greater granularity can facilitate better decisions regarding controls for process parameters.

A list of activities typically performed during process design is provided in Table A along with the deliverable used to document completion of the activity and its outcome.

Careful planning and forward thinking during Stage 1 are essential to a successful validation program. The life cycle validation approach requires a

Table A: Typical stage 1 process design activities

Activity	Deliverable
Characterize the process and define control ranges: ■ Define process control ranges ■ Define parameter criticality ■ Establish scaled-down models of the manufacturing process	■ Critical controlled parameters report or process control parameters report. ■ Process development (unit operations) report. ■ Scale down model report
Establish in-process and release specifications: ■ Define CQAs ■ Structure – Function elucidation	■ Product specification ■ Justify specifications report and/or CQA report
Scale-up manufacturing process and gain manufacturing experience: ■ Engineering/scale-up batches ■ GMP manufacturing ■ Shipping qualification	■ Tech transfer report ■ Master batch record ■ Evaluate shipping impact (temperature control, shipping hazards) on drug substance, drug product, and finished goods

strong foundation as quality must be built in from the start. Good studies in Stage 1 strongly contribute to Stage 2, process qualifications.

Stage 2: process qualification

Process qualification, as defined by FDA guidance, shares many of the same features as the traditional fixed-point approach. The main difference is in how the acceptance criteria that define suitability for market registration are set.

Process qualification includes an evaluation of the process design defined in Stage 1 to ensure that the manufacturing process is capable of reliably producing a product that meets all release criteria during routine commercial manufacturing. During Stage 2, the defined scaled-up manufacturing process is run at commercial scale by trained staff under full cGMP conditions using prequalified equipment in the proposed commercial manufacturing plant. Complete process qualification will include the validation of the performance of process chemicals and raw materials used in each unit operation, qualification of all supporting facilities and utilities necessary for the manufacturing process, qualification of all process equipment, validation of each individual unit operation, and validation of the entire process as it is intended to be operated at commercial scale.

Before process qualification can be performed, a series of related activities outlined in Table B must be completed to ensure the success of the process qualification. These activities include the validation of in-process and release-testing methods, scale-up of the manufacturing process, and validation of related equipment and processes.

Each batch of biopharmaceutical product produced during process qualification is tested using validated in-process and final product test methods to confirm that the product meets preset specifications and in-process acceptance criteria. Additional process characterization methods and analyses are also expected during this stage to fully characterize and qualify the process. Process controls, including the analytical test methods used for both in-process testing and final product release must be sufficient to confirm that each CPP is held within its preapproved range and that the final product meets all release specifications. The combination of process design studies performed during Stage 1 and process qualification performed during Stage 2 should confirm that the various manufacturing processes are reliable, reproducible and that they adequately control all of the product's CQAs. Assuming this is the case, the process is considered to be "validated" and the product may be released for commercial use.

Table B: Typical Stage 2 Process Qualification Activities

Activity	Deliverable
Completed before performance qualification runs	
Implement process control strategy	■ Master batch record ■ In-process and release specifications ■ Raw material specifications
Complete utilities and equipment qualification	■ Equipment IQ/OQ/PQ that meets process requirements
Full-scale manufacturing runs	■ Completed manufacturing batch records
Validate commercial testing methods	■ Validation reports for all noncompendial methods used for in-process testing and product release ■ Qualified assays can be used for characterization testing during PPQ
Sterile filtration membrane validation	■ Required for any step claiming sterility – report validating compatibility of membranes with the process solution
Container closure validation	■ Required for any container/closure claiming sterility
Facility GMP review	■ Review facility and equipment design/qualification for commercial manufacturing
Performance qualification	
Execute performance qualification runs	■ PPQ protocol and report
Completed before or concurrent with performance qualification runs	
Leachable extractable characterization	■ Process leachable/extractables report ■ Toxicology assessment may need to be performed for compounds identified
Cleaning validation	■ Cleaning validation protocol and report
Membrane and resin reuse lifetime study	■ Column and membrane lifetime study protocols and reports
Completed after performance qualification runs	
Stability assessment	■ GMP stability study for drug substance and drug product

Table C: Sample VMP table of contents

1. Introduction
2. Scope of plan
3. Acceptance criteria for all protocols
4. Project schedule and budget
5. Resource requirements
   a. Documentation
   b. Facilities
   c. Personnel
6. Document format
7. List of individual protocols
8. Standard operating procedures

Stage 3: process verification

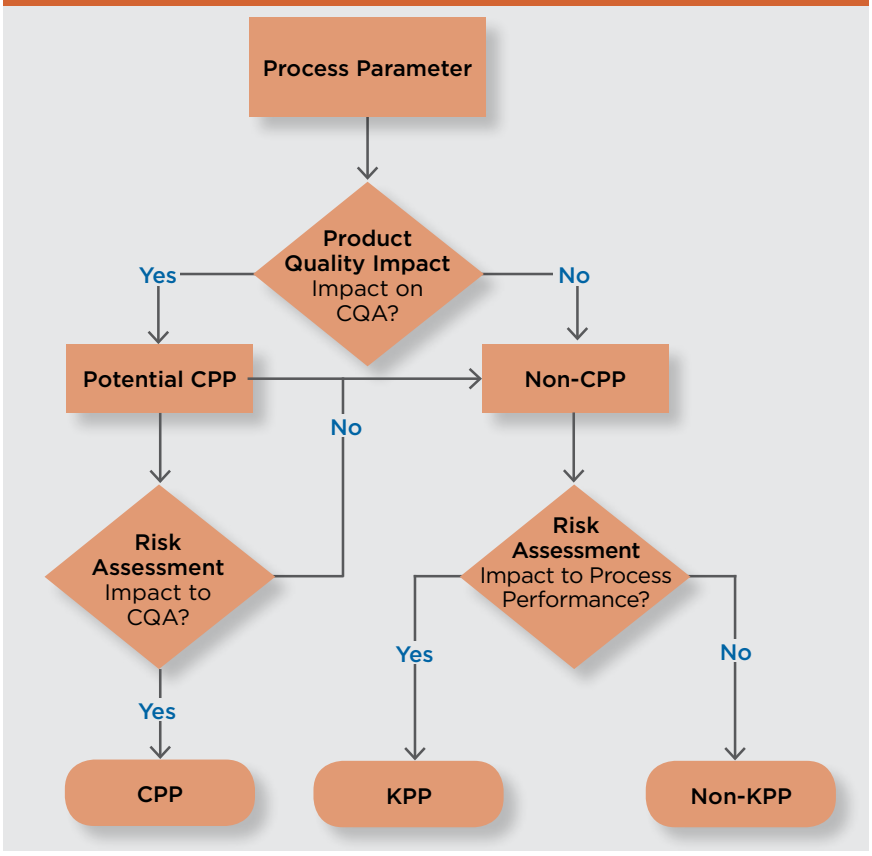
Following completion of Stages 1 and 2, routine product manufacturing should be monitored using the validated in-process and final product test methods to ensure that the manufacturing process remains in control and that the product continues to meet all CQAs. The particular strategy for continuous process verification in Stage 3 should be dictated by information gathered during Stage 2.[21] The intent of this continued process verification is to monitor the process throughout the product life cycle, demonstrating continued control of the manufacturing process. Since changes may occur in the testing protocols or the analytical methods used during the product life cycle, it is important that these revised test methods be appropriately validated and that results of these new methods correlate with those obtained previously.

While the FDA guidance does not specify the extent of sampling and testing necessary to ensure adequate process control, it does recommend that monitoring and sampling of process parameters and quality attributes be continued until sufficient data are available to estimate the extent of variability of the manufacturing process. FDA recommends that testing programs be designed by someone with sufficient training and knowledge in statistics to ensure that the monitoring plan meets regulatory expectations and that the overall monitoring plan—including a description of how data trending and all other calculations will be performed—be fully described in the Stage 3 validation protocol.[22]

The purpose of continued process verification is to establish the appropriate levels and frequency of routine sampling and monitoring for a particular product and process to meet the cGMP requirement of "statistically appropriate and representative levels."[22] During Stage 3, production data should be collected on an ongoing basis and appropriate alert and action limits set. Since the number of batches of biopharmaceutical product produced prior to completion of process qualification (Stage 2) is likely to be small, the amount of sampling and in-process testing required during routine commercial manufacturing may be greater in the early years of commercialization than later in the product life cycle. The data collected should be sufficient to provide strong statistical evidence that all CPPs are being held within their acceptable ranges and that there are no trends among any of the CQAs towards out-of-specification results. As commercial manufacturing progresses, the extent of testing may decrease as increased confidence in process capability and reproducibility is confirmed. Once sufficient data are available to establish the statistically meaningful extent of process variability, the monitoring program can be adjusted accordingly.

Continuous process verification strategies will vary from process to process, but typically involves additional process sampling and monitoring outside of parameters routinely recorded in the master batch record. Based on testing results, control ranges for certain operating parameters may be adjusted over time and some routine testing may be eliminated after sufficient manufacturing experience is obtained. The requirements for extensive in-process testing and process monitoring during Stage 3 is more stringent than the simple trending review of routine annual production performance required by regulatory authorities in the past. Once process robustness has been established, some of the extra in-process testing and process monitoring conducted during validation may be discontinued, with appropriate justification.

Figure 4: Process parameter classification



Defining CPPs

The CQAs of a biopharmaceutical product are those physical, chemical, biological, and microbiological properties and characteristics that must be controlled within an appropriate range to ensure the desired product quality. CQAs are also factors that affect product purity, strength, or stability, particularly post-translational modifications such as glycosylation and heterogeneity resulting from the presence of various glycoforms. The CQAs of a biopharmaceutical product will always include product potency and immunogenicity. Because product-related impurity levels (e.g., aggregated or clipped forms) and other process-related impurities can affect product safety or efficacy, they may also be included in the CQAs for a biopharmaceutical product.

A key element of QbD and the new process validation standards is that these CQAs can be linked to certain CPPs in the manufacturing process. These can be identified during the earlier stages of process design by an initial risk analysis, but additional CPPs may be identified at any time during the product life cycle as a result of continuous process monitoring. Besides affecting the CQAs, the ability to control a process parameter within its intended range is a significant factor in defining its criticality, especially in the manufacture of biopharmaceutical products.

To control the CPPs for a manufacturing process, it is important to have a clear understanding of the desired settings and ranges for each parameter. During process development, three nested ranges of relevance may be established for each process parameter:

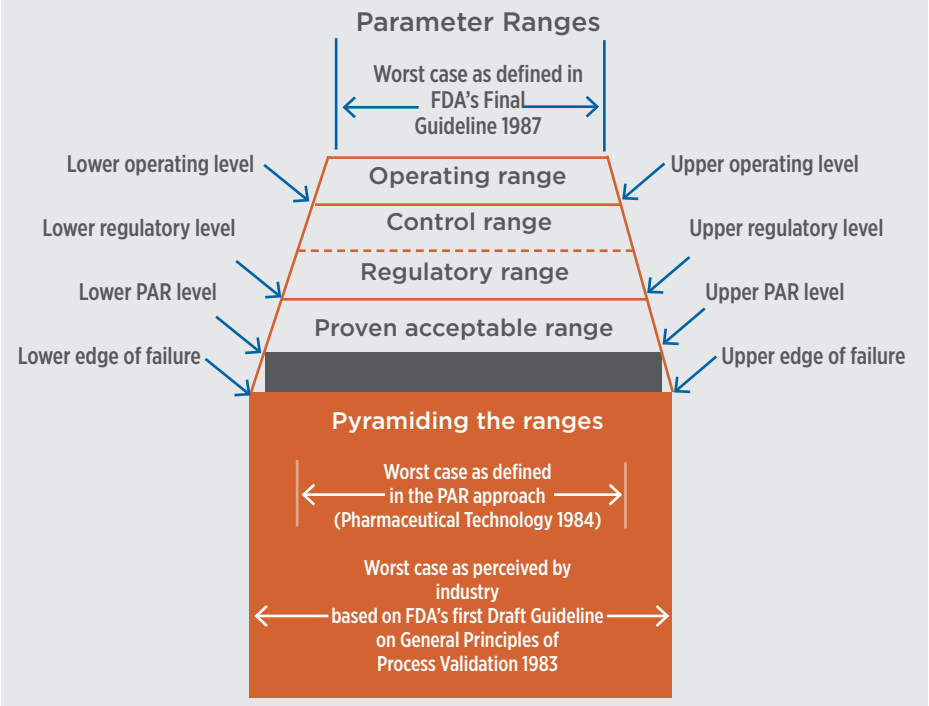
- The widest range is the proven acceptable range (PAR) within which the product produced always meets its desired release specifications and CQAs. Outside the PAR, the process will fail and the product may not meet its desired CQAs. Establishing the PAR is sometimes referred to as "testing to the edge of failure" and is normally done during process development.
- Embedded within the PAR is the regulatory or validated range, which is the range for the parameter that is tested during validation studies and represents those ranges included in a product registration application (e.g., BLA).
- Embedded within the regulatory range is the normal operating range, which is the range for the parameter specified in the master batch record that is expected to be used for routine commercial production of the monoclonal antibody product.

"Pyramiding" ranges for operating parameters (Figure 5) was originally proposed by Chapman in 1984 when he introduced the "proven acceptable range" (PAR) approach to process validation.[23] As defined by ISPE, the PAR for a critical parameter is the range determined to be achievable and appropriate for the process or processes with which it is associated.[30–31] By using knowledge gathered during development, the PAR approach helps ensure that the regulatory range for each parameter is wider than the routine operating range and further ensures that the process is not operating at the edge of failure.[24] Such an approach allows for minor process variations beyond the operating range, prevents failure of the unit operation or overall process, and results in a more robust process that is less likely to fail.

A risk analysis of each unit operation based on data collected during development and the potential result of failure to control a specific parameter within its acceptable product CQA range should be conducted to establish which of the many process parameters in a biopharmaceutical manufacturing process are critical. This will help refine the acceptable ranges of each parameter and minimize the potential for process variability and failure.

Many process parameters in a biopharmaceutical manufacturing process will have wide acceptable ranges, so that it is not necessary to establish what the acceptable range truly is, as long as an operating range is defined within this broad range. These parameters are not likely to be critical. On the other hand, if the PAR for a specific process parameter is narrow, it is likely that parameter is critical to meeting the product CQAs. In such a case, the validated range should be established so that it approaches the boundaries of the acceptable range, but remains safely away from the edge

Figure 5: Defining operating parameter ranges



Source: Reproduced with permission from Chapman, Kenneth G., Gamal Amer, Cheryl Boyce, George Brower, Cindy Green, William E. Hall, Dan Harpaz, and Barbara Mullendore. "Proposed Validation Standard VS-1." *Journal of Validation Technology* 6, no. 2 (February 2000): 502–521.

of failure. Both the temperature and pH of the cell culture medium in a bioreactor may have the potential to affect product quality, for example, but the acceptable range for temperature may be relatively broad while the acceptable pH range may be much tighter and represent a much higher risk for product failure resulting from a process excursion outside this range.

Process validation planning and execution

Although it is not mandatory, regulatory agencies have come to expect that a sponsor's approach to process validation will be described in a validation master plan (VMP). This documents a company's approach to process validation and also clarifies or defines responsibilities, general objectives, and procedures to be followed for validation. It may reference several protocols, procedures, and processes to qualify different pieces of equipment, and may also specify validation schedules and resource allocations needed to perform each validation study. A typical VMP for the manufacture of biopharmaceutical bulk drug substance should contain, at a minimum, the information listed in Table C.

Individual process validation protocols should:

- Describe the procedures to be followed in detail
- Specify critical and key operational parameters and their respective ranges, as well as data acceptance criteria
- Detail the procedures required to perform the validation, including the sampling plan and the responsibilities of various team members participating in the validation study
- Specify a sufficient number of replicate process runs to demonstrate process reproducibility and provide an accurate measure of variability among successive runs

Test conditions for each process validation run should encompass the upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure compared to ideal conditions. Such conditions have become widely known as "worst case" conditions (sometimes referred to as "most appropriate challenge" conditions).

The new process validation guidance specifies that it is not necessary to employ the "test-to-failure" approach, but only to ensure that those conditions posing the greatest risk of variation beyond acceptable limits or the greatest risk to the quality of the product should be studied adequately.[1] It is anticipated that in the future a design space will be generated for each critical process that encompasses all acceptable operating conditions.

At the conclusion of each process validation study, a final validation report should be prepared to documents the results. This report should include data from any qualification or production batch run as part of the protocol, a summary of protocol or batch nonconformances—along with the investigation of the nonconformance and any conclusions or recommendations resulting from the investigations—and a summary of whether the acceptance criteria of the protocol have been met. Aside from meeting the regulatory requirements for process validation, the VMP, validation protocols, and final reports will serve as a repository of key development and process information. These can support future process changes and improvements, as well as further development of the design space for the manufacturing process.

Future perspective

The increasing adoption and use of manufacturing technology platforms, especially in the production of monoclonal antibodies, and advances in high-throughput automation will continue to strengthen process design and optimization. These advances will expedite the development of high-yielding, reliable, and robust processes.[25–29] Likewise, continued advances in analytical methods for characterizing biopharmaceutical products and processes, including the development and implementation of process analytical technologies for inline monitoring and control, will provide better and more sophisticated tools to enhance and facilitate process qualification and continuous process verification.

In the near term, as industry moves from the traditional fixed-point validation to a life cycle approach, the incorporation of QbD and new concepts of process verification and validation are expected to be flexible as regulatory authorities define the requirements and expectations of these new initiatives. During this transition, regulatory filings are expected to incorporate blended elements of both approaches.

In the long run, however, incorporating science-driven risk-based process development and validation will result in more reliable processes that can be readily adapted to new process information. This will ensure continued viability of these processes and minimize the risks of process failures and potential shortages of critical medicines. By conforming to best industrial practices and embracing the new process validation guidelines and initiatives, biopharmaceutical manufacturing will continue to improve for the betterment of our industry and patients worldwide. ■

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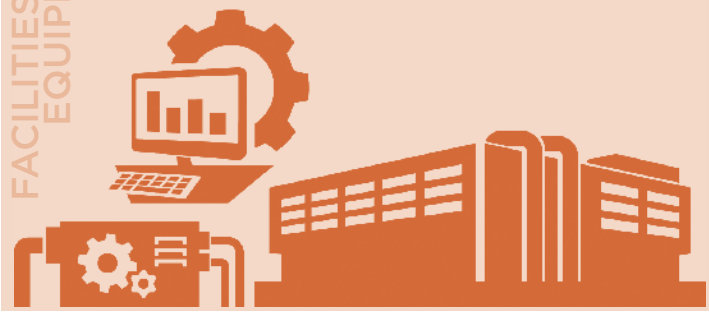
FACILITIES AND EQUIPMENT



Energy Optimization of an Existing HVAC System in a Bulk Pharmaceutical Facility

James Heemer, Duane Mowrey, and Joel Martinez

Energy optimization opportunities can be overlooked when focusing on product quality in pharmaceutical manufacturing facilities. An HVAC energy audit during a facility renovation identified low-capital-cost changes that realized over $1 million in energy savings.

When Eli Lilly and Company commissioned a new bulk active pharmaceutical ingredient (API) facility in 2005 at their Carolina, Puerto Rico, site, the air turnover rate was a minimum 20 air changes per hour in most of the facility. It was determined that based on area classification, the air changes could be adjusted and still meet the requirements for air cleanliness (particle levels).

As part of a capital project to revise the facility, an energy audit was conducted in 2013 on the existing HVAC systems, with data collected from certified testing, adjusting, and balancing (TAB) reports and the building management system (BMS).

At the time of the audit, some utilities rates that were needed for the savings calculations were:

- Electricity = $0.246 per kilowatt-hour (kWh) [$0.0683 per megajoule (MJ)]
- Chilled water = $0.22 per ton-hour [$0.063 per kilojoule per second (kJ/s), which includes electric and water cost
- Heating hot water = $3.23 per therm [$30.62 per kilojoule (kJ)]

The following actions were identified for energy savings:

- Air turnover rate reduction
- Outdoor airflow reduction
- Air filtration efficiency reduction
- Increase terminal reheat coil ΔT

Air turnover rate reduction

By designing for space cooling requirements only, the average air turnover rate could be reduced from 20 air changes per hour to 14, and the total supply airflow could be reduced 21,400 cubic feet per minute (cfm) in six air handling units (AHUs); this reduces supply fan power, cooling load, and terminal reheat load.

Supply fan power savings

Current airflow and power consumption were obtained from existing TAB reports. HVAC modeling was performed to determine the revised room design airflow for rooms where airflows could be reduced. Fan affinity law[1] (Equation 1) was used to determine the supply fan power reduction as indicated in the airflow reduction summary (Table A).

Equation 1

$$\text{Power}_{\text{Revised}} = \left(\frac{\text{Airflow}_{\text{Revised}}}{\text{Airflow}_{\text{Current}}}\right)^3$$

Where:

Power is in brake horsepower (bhp)
Airflow is in cfm/s or cubic meters per second (cms)

The power reduction is estimated to be:

Horsepower at higher airflow – horsepower at lower airflow = Horsepower savings

87.38 bhp (65.1591 kJ/s) – 49.60 bhp (37.0407 kJ/s) = 37.78 bhp (28.172555 kJ/s)

Assuming the HVAC system has a 95% run rate:

Annual motor energy savings = (37.78 bhp)(0.745699872 kW/bhp)(8,760 hrs/yr)(95% run rate)

= 234,452 kWh

= (234,452 kWh)($0.246/kWh) = $57,675

Or in SI units:

(28.172555 kJ/sec)(1kJ/s)(1kW/kJ)(8,760 hrs/yr) 95% run rate) = 234,452 kWh

(234,452 kWh)($0.246/kWh) = $57,675 annual motor energy savings

Table A: Bhp reduction due to reduced airflow

System	Current cfm (m^3/s)*	Current bhp (kJ/s)	Revised cfm (m^3/s)	Revised bhp (kJ/s)
AHU-216	7,857 (3.708)	7.30 (5.44361)	6,914 (3.263)	4.97 (3.7061)
AHU-225	14,345 (6.769)	10.17 (7.58377)	0†	0
AHU-232	11,990 (5.658)	16.34 (12.18474)	9,765 (4.608)	8.83 (6.5845)
AHU-233	10,586 (4.996)	22.34 (16.65894)	9,066 (4.278)	14.03 (10.462)
AHU-234	12,280 (5.795)	20.88 (15.57021)	10,648 (5.025)	13.61 (10.14622)
AHU-236	9,817 (4.633)	10.35 (7.71799)	9,070 (4.280)	8.16 (6.0849)
Total	**66,875 (31.558)**	**87.38 (65.1591)**	**45,463 (21.454)**	**49.60 (37.0407)**

* TAB report data reduction

† Space served by AHU-225 now served by AHU-216 with 700 cfm. This has been added to AHU-216 air flow.

Energy optimization opportunities can be overlooked when focusing on product quality in pharmaceutical manufacturing facilities

Cooling load savings

Chilled water is used for cooling and dehumidification. Separate AHUs cool and dehumidify outdoor air, which is supplied to recirculating AHUs that serve different types of zones. The recirculating AHU supply air temperature should be low enough to maintain acceptable humidity levels in the rooms served.

According to BMS data, the average weighted temperature of the AHU discharge is 62.3°F (16.8°C). The average air change rate was reduced from 20 air changes per hour to 14. An HVAC energy modeling program was used to calculate the cooling load savings of 16.8 tons (59.08 kJ/s) on average, based on typical yearly outdoor temperatures.

On this basis the energy savings is:

(16.8 tons)(8,760 hrs/yr)(0.95 run rate)($0.22/ton-hour) = $30,758 annual savings

Or in SI units:

(59.08 kJ/s)(8,760 hrs/yr)(0.95 run rate)($0.063/kJ/s) = $30,778 annual savings

Terminal reheat load savings

Heating hot water is used for terminal reheat. Terminal reheat load savings is based on two factors:

- The reduced airflow requires less terminal reheat to achieve acceptable room temperature.
- With reduced airflow, the air should be delivered to the room at a lower temperature to meet the cooling load, further reducing terminal reheat load.

Terminal reheat energy savings were calculated by the HVAC modeling software to be $4,715 per year; this includes both steam to heat the water and electricity for pumping water.

Total savings from air change rate reduction

Total annual savings for air change reduction is $57,620 + $30,760 + $4,715 = $93,095.

Capital expenditure is required for HVAC rebalancing. An estimate of $5,000 was made per air handling system for a total cost of $30,000.

Outdoor airflow reduction

TAB report data indicated outdoor airflow rates exceeded code minimum and design, to achieve room differential pressure relationships. In addition, current exhaust airflow was reported to exceed requirements. Exhaust and outdoor airflow rates were evaluated and reduced where permitted for process requirements and code, resulting in 2,550 cfm total outdoor airflow reduction. The AHUs that were found to have high excess outdoor airflow are indicated in Table B. The outdoor airflow rates were compared to; 1) code minimum outdoor airflow rates and 2) make-up air needed to

Table B: Outdoor airflow reduction

System	Outdoor airflow		Exhaust airflow		Revised exhaust airflow, cfm (cms)	Revised outdoor airflow, cfm (cms)	Reduction in outdoor airflow, cfm (cms)
	Design, cfm (cms)	Current, cfm (cms)	Design, cfm (cms)	Current, cfm (cms)			
AHU-211	252 (0.119)	1,026 (0.484)	420 (0.198)	209 (0.0986)	0	817 (0.386)	209 (0.099)
AHU-216	1,596 (0.753)	2,610 (1,232)	3,346 (1.579)	4,791 (2.261)	3,777 (1.782)	1,596 (0.753)	1,014 (0.478)
AHU-219	1,006 (0.474)	2,620 (1.236)	445 (0.210)	227 (0.107)	0	2,393 (1.129)	227 (0.107)
AHU-232	2,390 (1.128)	2,823 (1.332)	3208 (1.514)	3,183 (1.502)	2,750 (1.298)	2,390 (1.128)	433 (0.204)
AHU-233	2,119 (1.00)	3,931 (1.855)	1,045 (0.493)	303 (0.143)	0	3,628 (1.712)	303 (0.143)
AHU-234	2,516 (1.187)	2,880 (1.359)	3,369 (1.590)	1,820 (0.859)	1,456 (0.687)	2,516 (1.187)	364 (0.172)
Total outdoor airflow reduction, cfm (cms)							**2,550 (1.204)**

maintain space pressurization. The outdoor and exhaust air were reduced to provide a 10% margin on the higher of the two requirements.

The facility has outdoor air preconditioning AHUs that reduce the temperature of the outdoor air to 55°F dry bulb (DB)/55.2 wet bulb (WB). The mean outdoor air temperature in Puerto Rico is 80°F DB/70°F WB. Cooling this high-temperature, high-humidity air with high-cost electricity affects the plant's operating cost. The annual chilled water savings is calculated at $29,100 and the associated reduction in exhaust fan power is calculated at $8,950, for a total annual savings of $38,050. The basis for the savings was calculated from the Trane Trace 700 load program.[2] Capital expenditure is required for HVAC rebalancing. An estimate of $5,000 was made per air-handling system for a total cost of $10,000 (rebalancing for four systems included in air-change rate reduction savings).

Air-filtration efficiency reduction

The original HVAC design for the site required the use high-efficiency particle air (HEPA) filtration in several rooms. Based on room classifications, HEPA filters were not required in all areas. The energy savings analysis was performed to account for the lower airflow and lower HEPA pressure-drop reduction. Design airflow data through each HEPA filter was used along with the filter manufacturer's data to estimate pressure drops across the filters. Total system pressure drop and associated fan horsepower was determined from TAB report data, and overall fan power and energy savings was calculated. The fan bhp equation[1] (Equation 2) shows estimated bhp savings:

Equation 2

$$\text{bhp savings} = \frac{[(\text{Airflow})(\text{HEPA static})(\text{SG})]}{[(6{,}356)\ (\text{Fan efficiency})]}$$

Where:

bhp savings = fan reduction in fan hp due to HEPA removal

Airflow = Supply fan airflow in cfm

HEPA static = Average HEPA filter pressure drop in inches water column (inch WC)

SG = specific gravity of air = 0.977 @ 60°F, 50 feet above sea level

Fan efficiency = 70% = 0.7

See Table C for a summary of horsepower savings.

Annual energy savings = (11.44 kWh)(365 days)(24 hrs)(95% run rate) ($0.246 per kWh)

= $23,420 energy savings per year

Fifty terminal HEPA filters were removed from seven air handling systems. Maintenance savings was estimated at 4 hours of inspection per terminal HEPA every 6 months at a labor rate of $75 per hour for an annual savings of $30,000.

HEPA filters were removed from 12 AHU banks; no maintenance savings was assumed for these filters. The capital expenditure to remove the filters was estimated at $500 per terminal HEPA and $500 per AHU HEPA bank, for a total of $31,000.

Annual savings includes reduced energy consumption at $23,420 per year plus the maintenance savings of $30,000 per year for a total annual savings of $54,420.

Increase terminal reheat coil ΔT

The facility expansion includes 15 new reheat coils, in addition to multiple coils in the existing facility that need to be replaced due to increased loads. Existing coils are designed to run at a 20°F (11.1°C) ΔT. Keeping this same ΔT for the facility expansion would have required the existing 2-inch pipe to be replaced with 3-inch pipe to serve the new load. As a result, an alternative approach was taken: The new terminal reheat coils were designed for 50°F ΔT instead of 20°F ΔT to reduce heating hot water (HHW) flow by 60%.

The question "How does this affect the capacity of the existing steam to hot water heat exchanger?" was posed. Equation 3 shows heat-transfer calculation[3] for a heat exchanger:

Table C: HEPA filter removal summary

System	Airflow cfm (cms)	Filter ΔP Inches WC (pascals)	Fan efficiency, %	Horsepower savings
AHU-215	9,321 (4.399)	0.42 (104)	70.9	0.85
AHU-216	7,589 (3.581)	1.08 (269)	69.0	1.83
AHU-217	10,387 (4.902)	0.52 (129)	71.5	0.12
AHU-218	10,266 (4.845)	0.52 (129)	70.9	1.16
AHU-219	10,323 (1.209)	0.98 (244)	71.6	2.17
AHU-220	2,561 (1.209)	0.31 (77)	60.0	0.20
AHU-231	4,535 (2.140)	0.29 (72)	61.6	0.33
AHU-232	11,635 (5.491)	0.35 (87)	72.7	0.86
AHU-233	8,290 (3.912)	0.35 (87)	71.5	0.62
AHU-234	11,118 (5.247)	1.02 (254)	71.8	2.43
AHU-235	11,591 (5.470)	0.31 (77)	72.7	0.76
AHU-240	4,534 (2.140)	0.35 (87)	66.2	0.37
AHU-241	3,496 (1.650)	0.21 (52)	64.7	0.10
AHU-242	2,800 (1.324)	1.0 (249)	59.6	0.72
AHU-243	4,916 (2.320)	0.34 (84)	65.9	0.39
AHU-251	10,530 (4.970	0.33 (82)	72.7	0.74
AHU-252	4,411 (2.082)	1.54 (383)	61.2	1.70
Total BHP				**15.35**
Total kW = 15.35 bhp × 0.745 kW/bhp =				**11.44**

When reviewing the quotation for the 50°F ΔT reheat coils against the 20°F ΔT coils, the following was found:

- Average air pressured drop across the coil increased 0.028 inch WC [69 kilopascals (kPa)]
- Water side pressure drop decreased 1 foot WC (251 kPa) from 90- to 89-foot WC drop
- Flow on the water side dropped 60% from 70.4 to 30.6 gallons per minute (gpm) at peak flow, for a drop in flow of 39.8 gpm at design

Additional fan energy with higher air side pressure drop:

= (cfm)(added static)(SG)/[(6,356)(fan efficiency)]

= (25,030CFM)(0.028 inches water column)(0.977)/[(6,356)(0.7)]

= 0.15 bhp

Or in SI units

(CMS)(added static)(SG)/[(746.9)(Fan efficiency)

= (11.812 CMS)(6.97 pascals)(0.977)/[(746.9)(0.7)] = 0.15 bhp

Equation 4 shows reduced pump power factoring in pump head change associated with the added pressure drop and reduction in flow[4] (assuming average flow one-half of design or 19.9 gpm):

Equation 3

"Q = U × A × LMTD"

Q = overall heat transfer (Btu/hr)(kJ/s)

U = overall heat transfer coefficient (Btu/sq ft)/(hr)(°F)(sq ft)] or [(kJ/m^2)(s)(°C)(m^2)

A = area (sq ft)(m^2)

LMTD = log mean temperature difference (°F)(°C)

The existing heat exchanger was operating at approximately 1/3 capacity at peak load. The heat-transfer coefficient will be affected by the change in velocity of the HHW through the heat exchanger and the change to LMTD. With increased loads, water flow through the heat exchanger will increase the heat-transfer rate. With a portion of the HHW flow returning at a lower temperature, LMTD will increase, resulting in increased steam-to-HHW heat exchanger capacity. On this basis, there was no issue with increasing the ΔT across the new terminal reheat coils in the new facility expansion.

There are three results from energy spent at each higher ΔT coil:

- Additional air side pressure drop
- Change in water side pressure drop
- Reduced water side flow

Equation 4

= (gpm reduction)(system static + coil static increase)(SG)/[(3596)(pump efficiency)]

= (19.9 gpm)(37)(0.986)/[(3,596)(.75)] = 0.27 bhp

Specific gravity (SG) based on water at pump at 130°F.

Static head is estimated at 37 feet based on piping configuration, 50% design flow. Since coil water side pressure drop for the new coils was less it did not add to the pressure drop of the system.

Or in SI units:

= (4.52 centimeters/hr)(9,213 kPa)(0.986)/[(202,706)(0.75)] = 0.27 bhp

Total power reduction = pump power savings – added fan power = 0.27 hp – 0.15 hp = 0.12 hp

Annual electrical power savings:

= (0.12 hp)(0.7545 kWh/hp)(365)(24)(95% run rate)

= 753 kWh savings per year

Annual cost savings = (753)($0.246/kWh) = $185

Table D: Annual operating savings

Action	Capital cost	Annual savings	NPV 15% ROI/15 yr	Carbon reduction, tonnes/15-yr life
Air change rate reduction	$30,000	$93,106	$514,425	3,806
Outdoor airflow rate reduction	N/A	$38,050	$222,492	1,211
Air filtration efficiency reduction	$31,000	$53,420	$340,681	131
Increase terminal reheat ΔT	–$2,250	$185	$3,322	7.5
Totals	**$58,750**	**$185,487**	**$1,012,328**	**5,156**

Results

The four energy saving actions provide an annual operating savings of approximately $163,000. The carbon footprint savings is also significant (see Table D).

Summary

Energy savings were found that provided significant value without a detriment to the project scope; this benefitted the facility and society by using fewer resources and reducing our carbon footprint with no loss in production. Being alert to potential energy savings opportunities is key, along with the ability to identify pitfalls and develop an analysis to allow for life cycle cost evaluation. What this also shows is that quite a bit of analysis can be done with minimal time spent in the facility. This energy optimization was part of a facility expansion that required team work with the owners and quality control unit, using f design documentation, TAB reports, and BMS data to identify potential actions that resulted in high energy savings. ■

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The Role of Generics in Drug Shortages

Shortages of generic drugs occur worldwide, with examples ranging from a critical shortage of the anticonvulsant medication valproic acid in Canada[1] to injectable cancer drugs and some antibiotics in many jurisdictions.[2] In the United States, most drug shortages involve generic drugs.[12] Beyond the health care implications, these shortages are of economic concern. Generics enhance competition and can mitigate against high prices, accounting for 88% of US prescriptions and saving the American health system well over $200 billion each year.[3]

The Hatch–Waxman Act of 1984 streamlined the development and US Food and Drug Administration (FDA) approval of generic drugs to encourage competition. Manufacturers are permitted to create a duplicate of a patented drug without expensive and time-consuming clinical trials, provided that the generic is biosimilar to the innovator product.[4] The act significantly reduced the price of generics, especially when there were multiple competing versions.[5] So what led to the current shortages?

Supply: Supply chain interruptions, manufacturing safety and quality problems, or unavailability of raw ingredients can reduce the number of suppliers.

Cost: Large price reductions had the unintended consequence of removing the incentive to enter the market. Development can cost $50–$500 million, with the higher figures for the newer biologics, combo products, and new dosage entities. For a drug like Daraprim, which was prescribed fewer than 9,000 times and had revenues of only about $10 million in 2014, the return wasn't worth the investment.[6] Consolidation through acquisition by the few big players that remain has shrunk the pool of generic makers further. The absence of competitors has reduced supply and increased prices.

Given that most pipeline dollars are going to be in biologics for the next 20 years, it is worth considering what all this mean for generics' big cousins.

Backlog: A further cause of shortages has been the backlog of thousands of generic applications at the FDA, due, in part, to a lack of funding for its Office of Generic Drugs.[5]

Solutions

The Generic Drug User Fee Act was enacted in 2012 to help speed up approvals. It appears to be working, according to Senate testimony given by Janet Woodcock, the director of FDA's Center for Drug Evaluation and Research.[7] There were 63 full Abbreviated New Drug Application approvals and 16 tentative approvals for March 2016, while receipts and approvals look like they will be closely aligned for the fiscal year.[8]

The FDA recently approved—for the first time—a company's switch from batch processing of a drug to continuous manufacturing, making the connection between streamlining production, improving quality, and reducing the potential for drug shortages.[9]

Others have suggested that US drug shortages could be alleviated by allowing generics from other jurisdictions with regulatory standards comparable to the FDA to be sold in the US.5 They cite the examples of $1 pyrimethamine (Daraprim) in Canada, Australia, and the UK. Many American patients already purchase cheaper versions of prescription medicines online.[10]

Given that most pipeline dollars are going to be in biologics for the next 20 years, it is worth considering what all this mean for generics' big cousins. Since the first biosimilar received FDA approval—Sandoz's Zarxio, in 2015—many more have come to market. Biosimilars are estimated to cost 30%–40% less than innovator biologics.[11]

It might well be that ch anges at the FDA, the boom in biologics, and the surge in the implementation of continuous manufacturing will help mitigate shortages of generic drugs. ■

Scott Fotheringham, PhD

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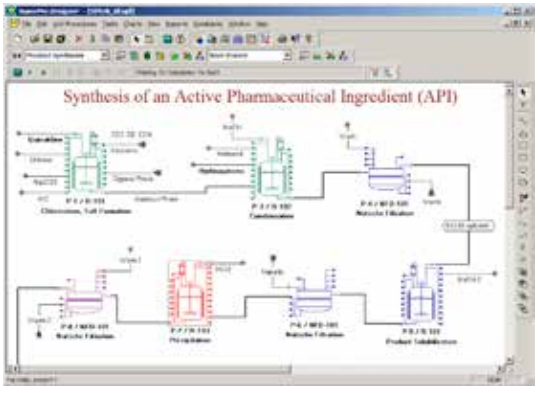

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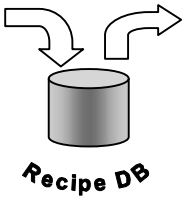

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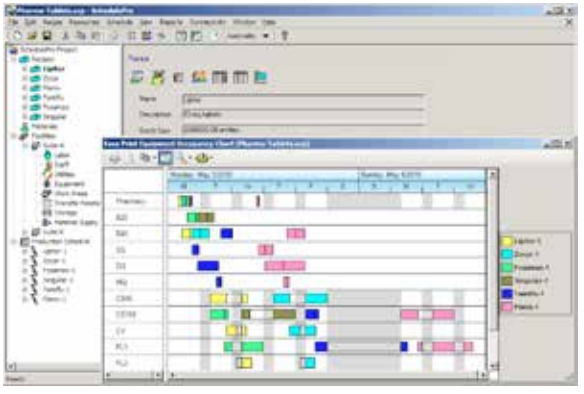

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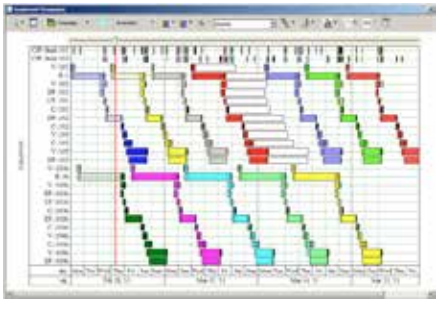

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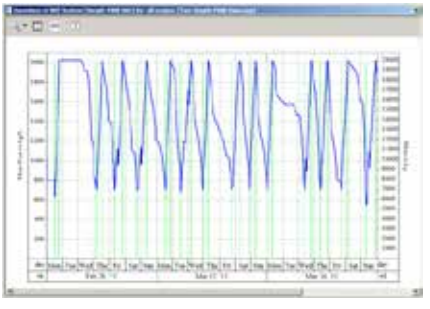

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