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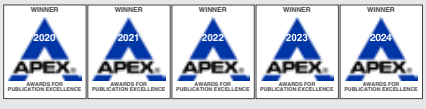

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ARE YOU READY?

By Scott W. Billman


Scott W. Billman

ISPE 2024: Reflecting on Another Great Year

As we come out of the 2024 ISPE Annual Meeting & Expo and move toward the end of the year, I find myself looking back and reflecting on what the ISPE community has accomplished over the past year.

We launched two new Communities of Practice (CoPs), with Sustainability and Artificial Intelligence joining the other active communities. There are now 22 CoPs comprising approximately 700 members who develop content for webinars, conferences, *Pharmaceutical Engineering®*, and guidance documents and lead discussions and collaborations on Engage.

This year, more than 300 ISPE members helped write and review guidance documents on validation and compliance of computerized GCP systems and data; unique identification of glass primary containers; 503A compounding; SMEPAC (Standardized Methodology for the Evaluation of Pharmaceutical Airborne particle emissions from Containment systems); heating, ventilation, and air conditioning; and ozone sanitization of pharmaceutical water systems.

CONFERENCES

Our membership came together to organize and present at six conferences throughout the year. The content and subject matter is driven by you, the membership, to share knowledge and support the continuous learning and advancements that we need as an industry. In 2024, we hosted three conferences in North America and three conferences in Europe, bringing together over 5,500 conference attendees to expand their knowledge and enhance their connections. Approximately 85 volunteers across six program committees worked all year to accomplish this.

CHAPTERS AND AFFILIATES

The local Chapters and Affiliates did even more! Our local Chapter and Affiliate membership continues to thrive and be active. Technical sessions, cultural events, training, exhibitor events (and maybe just a few golf outings) only begin the list of activities that members organize and attend across the globe. As a professional society of over 22,000 active members, we continue to come together to innovate and share knowledge to advance the pharmaceutical and biotechnology industries.

Our global Affiliates and Chapters are committed to fostering innovation, cultural awareness, and the professional growth of future industry leaders. Here are a few 2024 highlights:

- ISPE Germany/Australia/Switzerland (D/A/CH) Affiliate hosted the inaugural Robotics Applications of the Year Awards, celebrating groundbreaking robotics technologies in laboratories and production sites, fostering industry advancement.
- ISPE Boston held its second annual Juneteenth Celebration, an enriching evening of culture, education, and networking, featuring a historian's insights into Black history.
- ISPE Malaysia and ISPE Thailand conducted a student networking activity in Bangkok, where 30 Malaysian students toured a plant and exchanged experiences with their Thai counterparts, supported by a grant from the 2024 ISPE Affiliate/Chapter Growth Fund.

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- ISPE Philippines held "Gear Up 6.0 C2C: Classroom to Career," a pivotal career development seminar designed to bridge the gap between academia and the professional world, also made possible by a grant from the 2024 ISPE Affiliate/Chapter Growth Fund.

GRANTS

This year, the ISPE Foundation's Professional Development Grants program, supported by the Moderna Foundation, enabled over 44 STEM students and Emerging Leaders to attend the 2024 ISPE Annual Meeting & Expo and the 2024 ISPE Europe Annual Conference. The program fosters professional development and promotes global health equity by providing access to knowledge and nurturing diverse talent.

VOLUNTEERS AND STAFF

I want to thank all the volunteers who have fulfilled leadership roles at the International, Chapter, and Affiliate levels. It has been an honor serving the past year as Chair of the International Board alongside all these dedicated leaders. I appreciate the work the Board members have done throughout the year, including being liaisons to conferences, attending local events, and leading initiatives that continue the mission and vision of ISPE. I also want to thank the dedicated and talented ISPE staff. Their tireless attention to detail in executing the plans for the year have made 2024 another successful year for ISPE.

This year, our CEO and President, Tom Hartman, made the decision to retire. The Board and staff are thankful for his efforts and leadership to advance the organization in a post-pandemic world of conferences and travel. The Board of Directors has selected an Interim President and CEO of ISPE and the ISPE Foundation, Michael L. Rutherford. Michael is thoroughly knowledgeable about ISPE, having served on the ISPE International Board of Directors since 2017 and as an ISPE member involved with GAMP® for more than 20 years. Michael has more than 36 years of experience as a pharmaceutical industry quality professional. Prior to accepting the Interim President and CEO position, he was the Immediate Past Chair of the ISPE International Board Executive Committee and Board of Directors after serving as Board Chairman 2022–2023. He has also served as a Director and Executive Committee member on the ISPE Foundation Board.

With the addition of Michael, we look forward to building upon Tom's legacy as well as supporting the continued growth and success of ISPE and the ISPE Foundation. We now look forward to the next phase of growth and development with a new CEO and President to advance the next three-year strategic plan that will be developed by the International Board of Directors in 2025.

Scott W. Billman is Corporate Vice President of Global Engineering, Real Estate, and Facilities Services at Solventum and the 2023–2024 ISPE International Board Chair. He has been an ISPE member since 1996.

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By Vivien Santillan


Vivien Santillan

WOMEN IN PHARMA®: A YEAR OF REMARKABLE ACHIEVEMENTS

As we approach the end of another impactful year, it is a pleasure to reflect on the outstanding achievements and contributions of ISPE's Women in Pharma community, both regionally and internationally.

This year has been marked by significant milestones, collaborative efforts, and enriching events that have collectively propelled our mission forward. Here's a recap of the key successes:

WEBINARS AND SPECIAL SESSIONS

Empowering Voices: Creating a More Inclusive Pharmaceutical Industry & Patient Experience

In this impactful webinar, industry leaders and influencers discussed the critical need for diversity and inclusion in pharmaceutical development and healthcare delivery. They explored the root causes of disparities in healthcare access and outcomes, emphasizing the importance of ensuring that drug products reflect the diversity of the populations they serve. The session also highlighted the significance of representation in pharmaceutical leadership and the creation of inclusive work environments to drive innovation and equity in the industry.

Women in GAMP®

I had the honor of moderating an insightful webinar, "Women in GAMP: Empowering Women in Pharmaceutical Compliance." This webinar showcased the significant contributions of women in fields related to GAMP and explored the unique challenges and opportunities they faced. Attendees gained insights into best practices, career development, and the importance of diversity and inclusion in fostering innovation and excellence in pharmaceutical compliance.

Collaboration with Women for Advanced Therapies

Our collaboration with Women for Advanced Therapies resulted in a virtual panel discussion that highlighted the intersection of gender and racial diversity within the pharmaceutical industry, and how the emphasis on gender and racial diversity allows for improved healthcare across the globe. This partnership brought together thought leaders and professionals of various backgrounds and ages and sparked a meaningful discussion and exchange of knowledge.

ENHANCED COLLABORATION

Connecting Affiliates and Chapters

We strengthened the ties between our Affiliates and Chapters by facilitating direct connections with the Women in Pharma Steering Committee. This initiative aimed to enhance local collaboration and ensure that regional activities are aligned with our global vision. Through these monthly meetings, we've had the opportunity to exchange ideas, answer key questions, share successes, and develop resources to better support the efforts of Women in Pharma on the local level.

Mentor ISPE

The Mentor ISPE program continues to thrive, providing mentorship opportunities that empower all members within the pharmaceutical industry. This program has been instrumental in fostering professional growth and development through guidance and support and continues to evolve to better meet the needs of our members.

CONFERENCE EVENTS

Facilities of the Future

Women in Pharma started the year strong at the Facilities of the Future conference in January with an all-female executive forum panel. The discussion featured powerful women who shared insights on industry trends, balancing professional and societal pressures, and advancing women's roles across industry sectors.

Aseptic Conference

The session titled "Winding Path to Success where Titles, Salaries, and Culture Intersect" offered valuable perspectives on career growth and workplace culture.

Europe Annual Conference

The "Leveraging Digitalization on the Path to Healthcare Equality" panel, led by Women in Pharma, focused on evaluating how digitalization can drive healthcare equality. The discussion stressed

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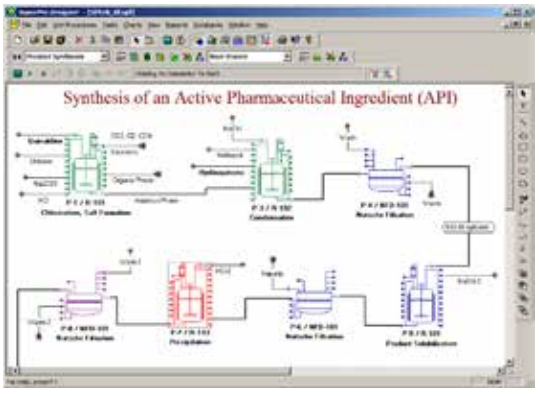

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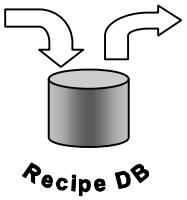

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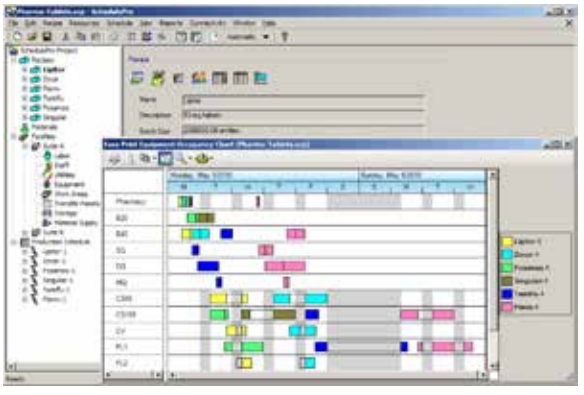
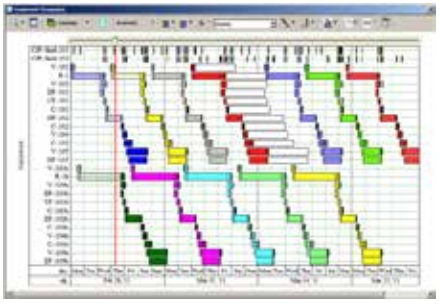
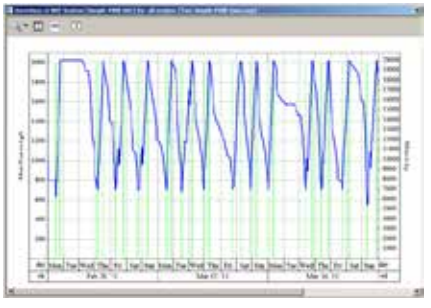


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling

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



Managing inventories for input, intermediate, and output materials

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

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

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Biotechnology Conference

The "Beyond Boundaries: AI-Driven Efficiency in Modern Workspaces" session encouraged professionals to embrace artificial intelligence (AI) in their daily business and explored how AI could enhance efficiency and work-life balance in dynamic work environments.

Annual Meeting & Expo

"Masked Connections" was a unique networking event sponsored by AstraZeneca. Attendees enjoyed dinner and drinks while wearing Venetian masks, fostering deeper connections in a memorable setting. The Sunday Workshop focused on professional development and included a regulatory panel with experts from across the globe.

Pharma 4.0™ & Annex 1 Conference

The "Pioneering Change: Innovation Across Life Science Sustainability & ESG Excellence" panel will explore strategies for integrating environmental, social, and governance (ESG) criteria into life sciences. The discussion will also address the upcoming EU Legislation Corporate Sustainability Reporting Directive, which will require detailed disclosure of sustainability practices. It will also highlight the importance of gender equity policies, sustainable procurement, and decarbonization strategies.

Acknowledgements

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As we celebrate these accomplishments, we remain committed to our mission of promoting gender diversity and empowering women in the pharmaceutical industry. The successes of this year are a testament to the collective effort and dedication of our members, volunteers, Affiliate and Chapter Leaders, and our International Steering Committee. We look forward to continuing this momentum into the new year, driving positive change, and inspiring the next generation of women leaders in pharma.

Vivien E. Santillan is Regional Director for Asia at Novatek International and the 2023–2024 Chair of the Women in Pharma International Steering Committee. She has been a member of ISPE since 2012.

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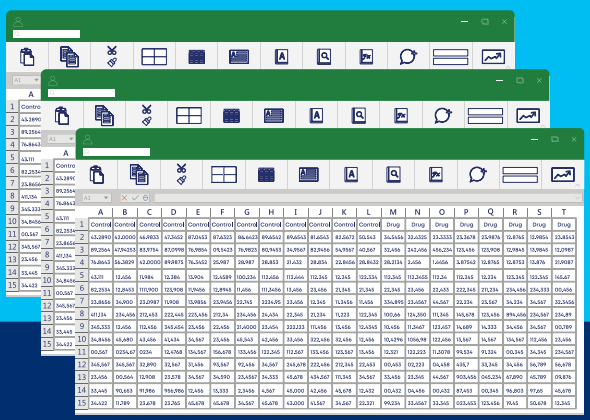

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By Monique L. Sprueill


Monique L. Sprueill

SUSTAINABILITY AND OPPORTUNITIES FOR EMERGING LEADERS

The pharmaceutical, biotechnology, and medical device industries continue to grow as patients require more access to medicine, data that allows them to make informed decisions, and personalized care. Achieving sustainability across the supply chain while adhering to quality compliance requirements presents a challenge.

Ways of working are evolving, and role requirements are being refined. Years ago, there was a strong focus on production and release per specifications. This evolved into incorporating quality throughout the end-to-end process. Now quality remains a driving force, but environment and social responsibilities are also high on the list for companies across the globe.

We are constantly searching for opportunities to reduce waste, engage with responsible suppliers, and increase effectiveness in business and operational processes. This leads to projects that promote minimum energy consumption, review recycling efforts, and increase the reliability of equipment and instruments as appropriate.

These projects provide unique opportunities for Emerging Leaders to contribute to organizations with fresh ideas and perspectives. Completing assessments and value stream mapping helps identify areas where increased efficiency would enable increased product yield, decrease non-value-added activities, and improve the lives of more patients by providing affordable medicine.

When considering a role, research the company's position on sustainability. Demonstrate an interest in ongoing efforts. Ask about raw material and packaging material sources, energy consumption, and community programs. If you have some experience in this area, be prepared to discuss it during an interview.

As an ISPE member, you have access to industry professionals, potential mentors, *Pharmaceutical Engineering®*, and networking events. These, as well as guidance documents, webinars, and blogs, are tools that can inspire you and assist in professional development. You can contribute by providing content to share your experience with our members. This may lead to network expansion or interest from potential employers. Full-time, internship, and co-op open roles may be viewed at jobs.ispe.org

We are constantly searching for opportunities to reduce waste, engage with responsible suppliers, and increase effectiveness in business and operational processes.

Are you interested in being a member of a group that supports your career advancement? Join ISPE at www.ispe.org as a student member or Emerging Leader. Build your network, develop skills, and take your career to the next level.

Keep track of what is going on at your local Chapter or Affiliate. Find out which committees are in search of new members. Volunteer to share your talents, meet others who have similar interests, and gain more exposure. Actively participate in program planning to ensure that relevant topics are offered.

Key advantages of joining ISPE as an Emerging Leader or student are:

- Professional development
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- Exposure to thought leadership events
- Participation in Hackathons
- Career solutions that promote advancement

We invite members to:

- Actively participate in Emerging Leader and student activities in your local Affiliate or Chapter
- Join Communities of Practice and connect with other industry professionals
- Add content, ask questions, and post your ideas on Engage
- Write a blog or article
- Talk with your manager and colleagues about presenting your project at a conference or local program

Visit ispe.org/membership to learn more.

Monique L. Sprueill, CQA, CMQ/OE, PMP, is a Quality Risk Management Leader and the 2023–2024 International Emerging Leaders Chair. She has been an ISPE member since 2002.

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Lou Schmukler

LEADERSHIP AS ART AND SCIENCE

I am enthusiastic and humbled to have the opportunity to author a column on leadership for the ISPE membership. The subject of leadership has been a passion of mine since the very start of my career, 45 years ago. From the shop floor to the C-suite, I have been an ardent student of the subject.

There are currently over 50,000 leadership titles listed on Amazon. In a recent survey, 77% of organizations reported gaps in leadership, with 83% saying developing leaders at every level was critical [1]. It's a topic that continues to attract great interest from experienced practitioners and new and aspiring leaders. There is no single factor determinant of an organization's success; however, leadership is certainly on the short list.

Three highly respected leadership experts define leadership as follows:

- Warren Bennis: "Leadership is the ability to translate vision into reality."
- John Maxwell: "Leadership is influence—nothing more, nothing less."
- Marissa Mayer: "Leadership is helping believe in a better tomorrow or a better outcome than you have today."

These are good definitions. They are rudimentary, but they open the door for a deeper understanding. In this column, I will attempt to dissect the expansive topic of leadership into its various elements. I will blend the theoretical with the practical. I will reference key thought leaders in the field for their important insights. Because there is value in history—how views on leadership have evolved over time, lessons from the past, and their application to our current day—I may also include some of my own experiences if useful to further drive home a point.

There are a number of excellent leadership models that can be considered, and something can be learned from each. You'll find a lot of similarities when comparing them. I developed my own over a period of years by studying other models and then selecting, modifying, and combining the respective principles I found most valuable. The example of other effective leaders was also an influence on my own model.

I'm a big believer in the concept of simplicity. Simple is usually better, and, as Leonardo da Vinci said, "Simplicity is the ultimate sophistication." If you're asked to share your leadership principles and can't do it in a few minutes or less, chances are they are either too complicated or you've yet to crystalize them for yourself. Accordingly, I aimed for my framework to be relevant and straightforward. I'll be painting with a broad brush in this introduction, as the following high-level framework will serve as an outline for future column topics. The ideas shared may not be new, but it's my goal and hope that you'll find them useful wherever you are on your personal leadership journey.

LEADERSHIP PRINCIPLES

Let me begin with what I believe great leadership is. My leadership model is composed of five key principles or practices, and each is substantial in and of itself. I believe, when viewed collectively, they cover the essential aspects of effective leadership.

Having the Highest Ethics and Integrity

Having the highest ethics and integrity is intentionally listed first. Peter Drucker said, "Although followers will forgive a leader much, they will never forgive a lack of integrity." Personal integrity must be a part of everything that a leader does, and without it, a leader has no legitimacy to lead and will not be trusted. Leaders must model the way. Say what you're going to do and then ensure you follow through and do it. The familiar phrase "she walks the talk" comes to mind here. Personal integrity plays a major role in a professional becoming a leader.

Being Future Focused

Being future focused is about vision, mission, and strategy. This is a vital principle of effective leadership. Providing clarity of direction, structure, measurement, and a shared sense of purpose is paramount to an organization's overall success. When a leader can paint a compelling picture of the future, and articulate the "why" behind it, the "how" becomes easy. If this is done well, it can serve as an incredible inspiration and motivation for people.

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Enabling Others to Act

Enabling others to act refers to empowerment. This entails job enlargement and enrichment. Giving employees more control and autonomy over their work leads to enhanced engagement, productivity, and creativity. It requires a management mindset that facilitates sharing information, increasing responsibility, and yielding power. I think about this process as inverting the traditional pyramidal hierarchy of organizations. Servant leadership is very much emblematic of these concepts.

Fostering the Right Environment

Fostering the right environment is about building culture. The culture of any social unit includes group norms, shared perceptions, espoused values, and consensus around goals and objectives. Culture includes the way people interact with each other, how they solve problems, and how they justify themselves. Culture is the glue that holds the organization together and can be described as "the way we get stuff done around here." A healthy vs. toxic culture is the difference between success and failure, and leaders play the pivotal role in shaping culture.

Nurturing Growth and Development

The fifth and final principle is nurturing growth and development. This principle is multidimensional. Most organizations never realize their full potential, and it is often due to a lack of emphasis on this area. This principle can truly be a force multiplier. It includes the benefits of increased engagement, retention, organizational capability, and capacity all driving better business performance. Investing in the organization's most valuable asset is good business.

LEADERSHIP SUCCESS

With this brief introduction, I'm looking forward to taking a deeper dive into the topic of leadership. Leadership is a combination of both innate traits and learned skills. Some people may be born with natural leadership traits, but their success often depends on how they develop and refine those qualities through learning and experience. The study of leadership can, and should, be educational, fascinating, stimulating, and rewarding. It's my expectation that, in some small way, this column accomplishes this.

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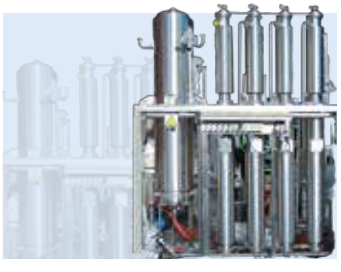


eMES (Multi-effect Still)

eVCS (Vapor Compressor)

Membrane WFI

PLASTIC PROCESS WASTE in Biopharmaceutical Manufacturing

By Andrew Sinclair, CEng, FIChemE, FREng, Cristina Van Loy, PhD, Adam Goldstein, and Pietro Perrone, PhD, PE

This article presents a comprehensive analysis of plastic waste generation in the biopharmaceutical industry, focusing on using single-use technologies (SUT) in bioprocessing for monoclonal antibody (mAb) production. It aims to inform sustainable practices within the biopharmaceutical industry and to encourage the development of more sustainable disposable technologies.

Since the 1990s, the biopharmaceutical sector has increasingly adopted single-use systems in manufacturing, raising concerns about the sustainability of these practices due to the resulting plastic waste streams. A commercial bioprocess modeling package estimates the plastic usage for typical mAb production at varying scales, offering a detailed exploration of waste composition, including fluid handling components, filters, and resins.

This batch-related plastics usage is linked to the forecast of worldwide mAb requirements to estimate the total annual metric tons per year of bioprocess-related plastic waste generated by the industry. The findings highlight the relative volume of bioprocessing waste compared to medical waste from healthcare facilities, discussing possible synergies to identify recycling and waste treatment options. Through quantitative assessments, this study explores the scale of plastic waste produced, comparing it with the healthcare sector.

BACKGROUND

Since adopting SUT in biopharmaceutical manufacturing in the 1990s, there has been concern about the generated plastic waste streams. Estimates for plastic waste based on production quantities provide the biopharmaceutical industry with methods to predict the waste produced and to establish disposal methods as SUT products expand into the mainstream production of biologics.

THE CHALLENGE

This concern over plastic waste is not new and has grown as the implementation of single-use technologies has expanded [1]. Over the years, several assessments have evaluated the comparative environmental benefit of single-use (SU)-based vs. stainless steel (SS)-based manufacturing [2–4]. Despite the evidence that SUT in bioprocessing have an overall advantage over SS-based manufacturing in regard to utilities, clean water, steam, and clean-in-place solutions at more minor scales, the concern over the amount of generated plastic waste persists.

To assess the significance of plastic waste generated by bioprocessing, the scale of the plastic waste stream must be determined, allowing its relevance relative to other sectors to be estimated. This article addresses this challenge. In addition, it will classify the waste into broad categories: fluid handling, filters, and resins.

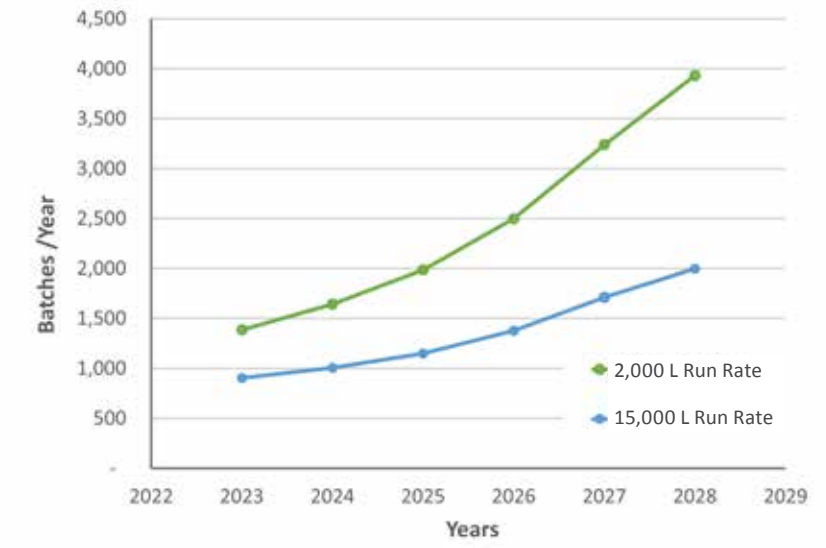
The potential total volume of bioprocessing waste and its relative scale compared to healthcare plastic waste informs the value to recyclers and opportunities to integrate with existing treatment options. It could also provide input for the development of new treatment options.

The approach used to assess the plastic stream is to estimate the plastics used to manufacture a batch of products using a commercial bioprocess modeling package [5]. The bioprocess modeling package was used to model the typical mAb manufacturing processes—at 2,000-liter (L) SU and 15,000-L SS scales, described in more detail later. The amount of product manufactured each year by scale and technology was estimated. From an understanding of the market for mAb manufacturing, an estimate of the number of batches and the amount of plastic per batch was made, thus generating the annual total plastic usage.

PRODUCT BASIS

Referring to data published in late 2023, the analysis by Ecker [6], identified that 85% of the products in development and commercial manufacture are in mammalian cell–culture systems and that mAbs account for 98% of the kilograms of mammalian marketed

Figure 1: Model estimate of batches required to meet demand at two scales.



products. Antibody dose requirements are significantly higher than those for many other product classes, such as enzymes, hormones, or cytokines. Therefore, it is reasonable to assume that mAbs account for the bulk of the manufacturing capacity requirements and, as such, would be a good baseline product class to estimate the plastic waste stream and would be a realistic indication of the scale of biopharmaceutical waste streams.

MARKET SIZE AND MANUFACTURING CONFIGURATION

This study focuses on commercial manufacturing of mAbs. The first step is to determine the number and size of batches now and in the future, which requires an estimate of current and future demand expressed in kilograms per year (kg/yr). The second step is to estimate the different manufacturing scales and bioreactor types. The last step is to get an idea of the bioreactor titers used in commercial manufacturing.

For this analysis, the demand for all cell-culture products is based on information supplied by Ecker [6]. The estimate is that the total mass of mammalian-derived products in 2023 was 41 metric tons, rising to 94 in 2028. Products related to mAb account for 98% of this tonnage.

Outputs from a manufacturing capacity database [7] provided records of historical cell culture installed capacity. This data estimates the proportion of stainless-steel bioreactors' (SSB) capacity vs. single-use bioreactors' (SUB) capacity. The proportion of SUBs in 2016 was 7.6%, rising to 12.1% in 2024, and is predicted to increase to 21.3% by 2028.

This analysis used the year-by-year distribution bioreactor capacity between SUBs and SSBs [7]. To identify the number of batches manufactured, it was assumed that the typical size of an SUB was 2,000 L, which is historically the average size of SUBs available. Larger sizes are now available and will be adopted over the coming years, reducing the amount of plastics used in scaling up manufacturing.

This analysis compared SSBs to SUBs using a 15,000-L working volume bioreactor size. This is considered a typical batch size for an SSB [8]. Assigning a titer to the different products is necessary to approximate the number of batches per year. A simplifying assumption is to use an average titer for all products.

In a paper by Rader [9], the estimate for the average titer of all products on the market in 2020 is 3.5 grams per liter (g/L). This figure is the basis for this analysis. Using typical process parameters for the mAb process, the model calculates the batch size for the purified bulk drug substance at 4.9 kg/batch for the 2000-L bioreactor and 36.9 kg/batch for the 15,000-L bioreactor.

The output of the model is summarized in Figure 1 which shows the distribution of batches per year between the large scale 15,000-L SSB and the smaller scale 2000-L SUB runs. This estimate of manufacturing batches per year when combined with bill of materials data is used to forecast plastics usage. This approach is presented later in this article.

PLASTICS GENERATION

Having determined the number of batches at different manufacturing scales, the next step is determining the amount of process plastics required to manufacture a batch of material. The study used a bioprocess modeling package [5] for biotechnological and related applications used for techno-economic and eco-design analyses. The software package uses process configuration supplied by users that reference a database of commercially relevant resources, including costs and weights for equipment and materials based on averaged supplier data. It was used in this study because it can perform bioprocess modeling and calculate the mass of plastics used to manufacture a product batch. This model has generally

Table 1: Breakdown of plastics used per batch.

	Configuration		
	1	2	3
Type	SU	SS Only	SS Hybrid
Bioreactor Size	2,000 L	15,000 L	15,000 L
Batch Size	4.9 kg	36.9 kg	36.9 kg
Plastic Use (measured in kg per batch)			
Resins	4.2	28.0	28.0
Bags and Tubing	310.0	0.0	140.7
Filters	197.5	140.3	178.9
Packaging	255.8	84.2	173.8
Totals	**767.5**	**252.5**	**521.4**
PMI (measured in gram of material required to manufacture a gram of product)			
Process Water	3,376	2,789	2,788
Process Plastics	156	7	14
Process Materials	22	24	24
Cleaning Water	0	6,768	5,434
Cleaning Materials	0	10	8
Totals	**3,554**	**9,598**	**8,268**

PMI, process mass intensity; SS, stainless steel; SU, single use.

been accepted as the default modeling tool by numerous industry forums, end users, and supporting vendors via publications over the past 25 years.

Three modules are used to determine the data sets:

- Resource database: a proprietary database of all the "typical" commercially supplied components required for bioprocessing, ranging from small to large scale. It includes plastic components such as bags, tubing sets, and filters. Each element will have a scale, cost, and weight of plastic. This data set is updated regularly based on supplier data that is averaged; the last update was in 2023.
- Recipe module: defines the process. It comprises a set of scaling rules and a scaleless recipe, which, when given a scale, calculates the mass balance, process equipment, process material, labor, and consumable requirements that reference the resource database. The processing module drives the estimate for the utilities, solution management, facility, and energy modules.
- Output module: generates a wide range of outputs. This study uses the bill of materials report, which identifies all the consumable components in terms of the size, number, and mass required to manufacture one batch. This information is used to determine the category and mass of plastics used.

The process used as a basis for mAb manufacture is based on a baseline reference process defined as a part of the Biopharm Manufacturing Technology Roadmap in 2017 [10]. Adjustments were made to include tubing and plastic fluid transfer sets often deployed in SU manufacturing setups based on a presentation by Goldstein [11]. Three different configurations were modeled to estimate the plastics used per batch.

- Configuration 1: This SU facility has a bioreactor capacity of around 2,000 L. Although larger-scale bioreactors are available and showing promise in reducing plastic use overall, they are relatively new and only represent a small proportion of the installed SUB base to date. This will change in the future.
- Configuration 2: A fully SS production line with no SU components. This is based on a 15,000-L bioreactor scale. This is representative of the legacy facilities.
- Configuration 3: A hybrid SS production line with SU components used in the seed train and fluid management where the size fits. This is based on a 15,000-L bioreactor scale and is representative of the newer SS facilities.

Each configuration was set up and modeled, and estimates of plastic use were determined. These are detailed in Table 1, together with the process mass intensity (PMI) values [12]. PMI accounts for all materials used within the process, including cleaning and direct materials, as a ratio of input materials to the mass of the product.

The PMI compares the efficiency of processes in converting the input materials to products. In this case, an SU process uses considerably more plastics per output unit than the two larger-scale SS-based processes. This contrasts with the use of water, where SS-based manufacturing uses significantly more water for cleaning.

There is little published data on plastic use by processes that can be used to confirm the validity of the model predictions. Budzinski [13] published a paper on streamlined life cycle assessment of SUT. A comparison was made between the plastics used in the paper and the model's predicted value. The basis of comparison was PMI for the plastics category, which measures the gram of plastics required to manufacture a gram of product.

The Budzinski paper [13] references a 2,000-L SU process using prepacked columns; the PMI for SU components is 513. When the same workflow is modeled in the BioSolve Process [5], the PMI for the plastics is calculated as 507. There is good alignment between the published paper and the BioSolve Process model.

The Budzinski paper [13] used a titer of 1.07 g/L, which is low compared to commercial titers. The model used for this paper used the same process with an increased titer of 3.5 g/L and reusable chromatography columns. With these changes, the PMI for plastics dropped to 156. This aligns with expectations given that PMI upstream is directly influenced by titer and downstream processing PMI for bags and tubing decreases with increasing scale.

PLASTICS USE BY CATEGORY

In this study, by estimating the number of batches for each configuration and knowing the mass of plastic waste generated per batch, the total quantity of plastic waste generated yearly can be calculated for mAb manufacturing. The critical assumption is that the amount of plastic packaging associated with the consumables is estimated

to be 50% of the consumable mass. The second assumption is that the proportion of products manufactured in the hybrid SS vs. all SS is again assumed to be 50%.

Figure 2 gives the total estimate of annual process plastics use for the next five years. The figures are based on the actual plastic mass of materials going into the process; the waste streams will be heavier than just the calculated plastic waste, as they will also contain process water and solids. The compounded annual growth rate over these five years is 22%.

The plastics are broken into three categories: packaging plastic, contaminated process plastic, and noncontaminated process plastic. Packaging comprises 33% of total plastic waste and can be directly processed from the receiving warehouse, where materials are removed from their primary packaging such as cardboard and bubble wrap. This material avoids contamination, as it is away from the manufacturing and laboratory spaces.

Waste is deemed to be contaminated if it is potentially exposed to cell-culture microorganisms. Of the total plastic waste, 14% is contaminated process plastics, which may need specific decontamination measures before onward processing. Noncontaminated process plastic waste represents 53% of the total plastic waste.

The plastics consumption data can be analyzed in terms of its application in the process. Figure 3 is broken out into four categories, as these categories will influence the onward processing of the waste streams. Ignoring packaging (33%) and resins/membrane adsorbers (MA), the bulk of the plastics used by the process fall into two categories: fluid management, represented by bags and tubing (34%), and filters (29%). The processing of filtration waste (including depth filters, tangential flow filtration, and sterile filters) would be different from fluid management (hold bags, mixer bags, bioreactors, tubing, and connectors). These two main categories would be further segregated into contaminated (biologically) and non-contaminated, with the contaminated waste stream typically requiring pre-treatment at the manufacturing site before onward processing.

Although the exact composition of the plastic products is not readily available, the component weights used are based on averages across different suppliers' products. On that basis, resins mostly contain silica or cross-linked agarose. Bioprocess container films usually contain polyethylene, polyester, nylon, ethylene vinyl acetate, and ethyl vinyl alcohol layers. Tubing contains silicone, thermoplastic elastomer, and polyvinyl chloride. Filters contain polyethersulfone and polyvinylidene fluoride membranes and a polyethylene housing.

Though not representative of the whole biopharmaceutical sector, mAbs are dominant in terms of manufacturing scale. So, how much more must be added to account for all the other products and drug products? The total amount of plastics will likely be at most two to three times the mAb quantities. On that basis, total consumptions of between 1,500–4,500 metric tons/year (mt/yr) for 2023 and 3,900–11,700 mt/yr by 2028 is a reasonable estimate. By any measure, there is a significant growth in the waste streams. As the industry is focusing on waste reduction and net-zero

Figure 2: Estimate of annual plastic use by waste stream allocation.

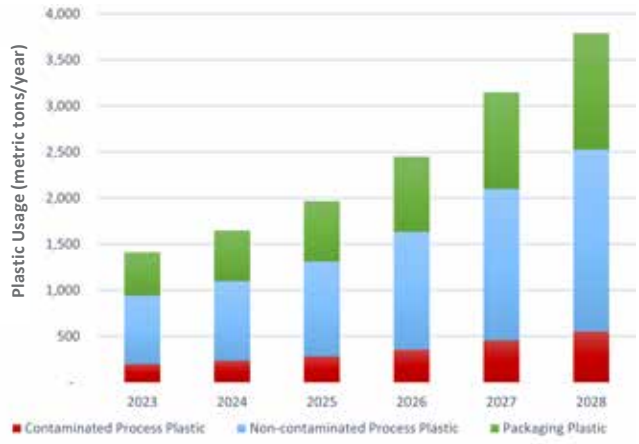
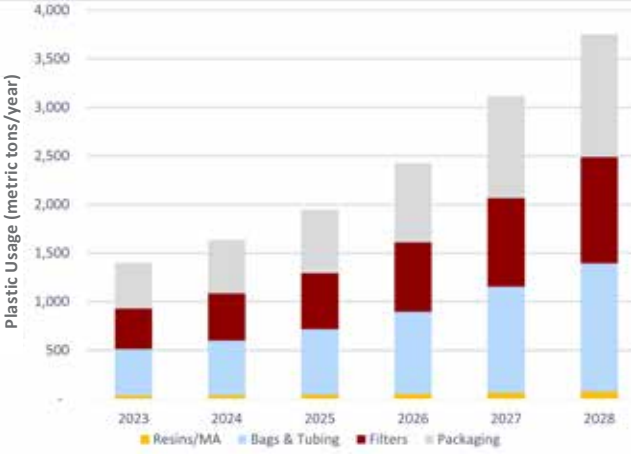


Figure 3: Estimate of annual plastic consumption by application.



greenhouse gas emission strategies, this is an issue that needs to be addressed now.

One question is how significant a waste stream is relative to other elements of the supply chain that may share the same challenges and could work together for solutions. It's an important question because it will influence third-party interest in managing the waste stream vs. suppliers taking on the responsibility of managing waste streams associated with their products.

PLASTIC HANDLING IN HEALTHCARE

This article has discussed the scale of plastics generated by the biopharmaceutical manufacturing industry, and the economic sector downstream in the supply chain is the healthcare sector. Although different in scale, healthcare facilities use large quantities of SU plastics and have similar challenges in managing these waste

streams. As a mature sector, healthcare facilities have established third-party companies that handle their waste streams. In terms of volume, how does the biopharmaceutical industry compare?

Here are two cases: the UK and the US. The UK National Health Service (NHS) has a strategy to reduce clinical waste and collects figures for all the healthcare in the UK in its NHS clinical waste strategy document [14]. The NHS healthcare providers produce approximately 156,000 mt/yr (2023) of clinical waste that is either sent to high-temperature incineration or for alternative treatment. It is estimated that 12,700 metric tons of waste are generated daily in US healthcare facilities; about 20%–25% of the waste is plastic [15]. This represents about 930,000–1,160,000 mt/yr of plastic waste.

Healthcare facilities have similar challenges in identifying solutions for their plastic waste. These facilities also have a mix of contaminated and noncontaminated materials of various plastic types and logistical hurdles for sorting the waste and identifying recycling solutions [16]. Healthcare plastic materials include rigid trays, bottles, flexible packaging, sterilization wraps, and multi-layer bags for solution delivery.

There are many parallels between these challenges and the plastic waste that results from the biopharmaceutical industry. Solutions that may improve the healthcare industry's plastics waste could also be applied to biopharmaceutical waste. This is also an opportunity to combine bioprocessing waste with healthcare waste to increase the total volume that recyclers should consider as feedstock for their processes.

Working more closely with recyclers to identify or develop solutions for this high-quality plastic waste is critical. Recyclers are continually looking for large-volume streams of plastic to use as feedstock in their processes. They must continuously flow into their facilities to maintain efficient processing and manage costs. Mechanical recycling requires a mono-material or minimal-complexity plastic stream, whereas some advanced recycling technologies being developed can handle more complex material mixes. Sorting technologies continue to evolve to simplify managing incoming material for recycling. Significant variations in the local recycling infrastructure are also available depending on the city, state, or country in question. These considerations also factor into the options available for recycling biopharmaceutical waste.

CONCLUSION

The results of this study provide an initial estimate of the volume of biopharmaceutical manufacturing plastic waste that may be available for recyclers to consider as feedstock. The study used market information about mAb production and the BioSolve Process [5] with its embedded SU bioprocessing database of materials for various production scales. This resulted in a conservative estimate of 1,500–4,500 mt/yr and is poised to continue increasing over the next five years to as much as 3,900–11,700 mt/yr. The total volume would be greater when considering other materials made using SU bioprocessing technologies, but likely not many orders of magnitude.

For comparison, healthcare plastic waste examples were examined. Two other reports for healthcare plastic waste indicate the scale observed there:

- It has been indicated that the UK NHS disposes of 156,000 mt/yr, with only about 5% of that plastic waste being recovered [14].
- In the US, 12,700 metric tons of waste are generated daily in healthcare facilities, and 20%–25% is estimated to be plastic waste, approximately 1,000,000 mt/yr [15].

The estimated bioprocessing waste, although not at the scale of healthcare waste, also represents a significant volume of plastic that is mainly going to incineration, waste-to-energy recovery, and landfills [17]. There is an opportunity to continue working with recyclers to identify alternative solutions at end of use. Given some common challenges with healthcare plastic waste, the biopharmaceutical manufacturing industry could consider collaborating or learning from the healthcare industry to identify recycling solutions.

There are also opportunities for co-located companies to identify solutions to combine their waste volumes to encourage a local recycler to take this material. A single company may need more volume but combining it with others to generate a routine feedstock stream could drive better recycling options.

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3R INITIATIVE
Within Roche's Global QC Network

By Sven M. Deutschmann, PhD

This article describes the numerous activities in the commercial quality control (QC) network that aim to replace in vivo assays with alternative methods in the course of production and release. Specifically, three areas are considered: cell bank testing, pyrogen testing, and potency testing. For each area, examples are provided for alternative assays or control concepts with which in vivo–based assays in QC could be successfully replaced. The successfully completed and implemented 3R projects described in this article are intended to highlight alternative testing concepts to biopharmaceutical quality managers, so they can evaluate which in vivo assays in their QC network could be replaced by alternative assays.

In 1959, British scientists William Russel and Rex Burch published the book "The Principles of Human Experimental Technique" [1], in which they defined the 3R principles. These principles are aimed at completely avoiding (replacement) or reducing (reduction) the number of animals used for testing and improving animals' living conditions (refine improvement). In Europe, the objectives of the 3R principles were established more than 35 years ago in a convention for the protection of vertebrates used for experimental and other scientific purposes [2].

This agreement was ultimately the basis for the European Union (EU) Directive 2010/63/EU on the protection of animals used for scientific purposes [3]. This directive embedded the internationally recognized 3R principles into European law for the first time. Hence, all national and European authorities (e.g., the European Pharmacopoeia, a council of the EU) are bound by these requirements, and an annual reporting has been established to monitor the progress of the implementation of the 3R principles in the EU.

The ALURES Statistical EU Database contains data on the use of animals for scientific purposes collected by the member states [4]. Data extracted from the statistical reports uploaded to ALURES Statistical EU Database (see Table 1) indicate that between 1991 (the first report available on the database) and 2020, the number of in vivo assays decreased from almost 11.5 million to ~10.5 million per year. It should be noted that the number of EU member states reporting their annual data has steadily increased from 11 (in 1991) to 29 (28 member states and Norway) in 2020. It must therefore be assumed that in the years 1991–2008, when there were fewer member states reporting their data, the number of in vivo assays performed in the EU was higher than indicated in the annual reports.

Table 1: Number of in vivo assays in the EU.

Report No.	Year	Approximate Number of In Vivo Assays per Year (Million)	Number of Reporting Countries
1	1991	11.5	11 member states
2	1996	11.6	15 member states
3	1999	9.8	14 member states
4	2002	10.7	15 member states
5	2005	12.1	15 member states
6	2008	12	27 member states
7	2011	11.5	27 member states
8	2015	9.59	28 member states
	2016	9.82	28 member states
	2017	9.39	28 member states
9	2018	10.57	28 member states and Norway
10	2019	10.40	28 member states and Norway
11	2020	10.25	28 member states and Norway

In the EU, basic research and development in human and veterinary medicine are the areas that use the highest number of animals for scientific purposes. The percentage of animal experiments for regulatory use to satisfy regulatory requirements (~15%) and for routine production (~5%) has remained relatively constant.

Many pharmaceutical companies are globally active and market their products internationally. This means that approval of alternative methods to in vivo assays by regulatory authorities would be required internationally to achieve a reduction in animal consumption. As part of the harmonization of the requirements for the validation and implementation of alternative methods, alternative approaches are discussed in international forums and harmonized internationally.

These forums include groups like the Organization for Economic Co-operation and Development (OECD), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), and the International Cooperation on Alternative Test Methods (ICATM). The overarching aim of these groups is to promote increased international cooperation and coordination in the scientific development, validation, implementation, and regulatory use of alternative approaches.

IN VIVO ASSAYS IN QC

Animal-based in vivo QC assays are typically used for the development and manufacturing of biopharmaceutical products. These include the qualification of eukaryotic cell lines, specific testing for viral clearance of products, demonstration of the absence of pyrogens to ensure patient safety, and the determination of potency of the manufactured biopharmaceuticals.

The majority of in vivo assays used in QC can be avoided without losing the appropriateness of the quality assessments. Following the 3R principles, all in vivo assays should be assessed and replaced or reduced. This would also help meet increasing regional and global sustainability goals. Novel analytical/QC technologies enable the replacement of existing in vivo assays while ensuring the efficacy of the active pharmaceutical ingredient and the absence of contamination that poses a risk to patients.

CELL BANK TESTING

In most cases, complex biopharmaceutical molecules are manufactured using eukaryotic expression systems (typically using recombinant Chinese hamster ovary [CHO] cells). To guarantee a robust manufacturing process and a constant product quality over a long period of time, so-called cell banks are used.

Cell banking is the process of preserving and storing cells for future manufacturing purposes. It typically involves a two-tier system, establishing a master cell bank first and a working cell bank from a single cell source second, expanding the cells, and cryopreserving them for long-term storage. It is crucial to comprehensively characterize and test these cell banks of the recombinant cell lines to ensure identity, stability, performance, quality, and safety.

To guarantee the quality and safety of the cell banks, various tests must be carried out to demonstrate the absence of a contamination caused by "adventitious agents" in the cell bank(s). Traditionally, in vivo assays have been used to detect viral contamination in cell banks.

In Vivo Virus Detection Assay

The in vivo virus detection assay [5] is used to detect viral contamination that could contaminate mammals—the CHO host cells but also patients. For this purpose, the cell bank cell culture fluid is injected into adult and suckling mice, as well as embryonated eggs. Depending on the source and nature of the manufacturing cell lines, additional animal species, (e.g., hamsters) may need to be tested. After injection, the health of the animals is monitored, and any abnormality is investigated to determine the cause. For the assessment of one cell bank using the in vivo virus detection assay, 75 mice (15 adult/60 suckling) and 80 embryonated eggs are required.

In Vivo Antibody Production Test

These in vivo assays should be used when the potential exists for exposure to viruses of a specific animal species. For example, murine viruses that are specific to certain rodent mammals can be detected using an immunologically based in vivo assay, the antibody production test. For this purpose, the test article is injected into virus-free, highly susceptible natural hosts (i.e., mice or hamsters) and the antibody level in the serum of the animals is assessed after a specified time using sensitive and specific serological assays. Examples of such tests that are carried out for the cell bank control are the mouse antibody production (MAP) test and the hamster antibody production (HAP) test.

Specific molecular biological assays—for example, nucleic acid amplification techniques (such as the polymerase chain reaction [PCR]) or next-generation sequencing (NGS, or massively parallel sequencing [MPS] or high-throughput sequencing [HTS])—can replace the in vivo assays described previously. The revised version of the ICH Guideline Q5A(R2) on viral safety evaluation of biotechnology products derived from cell lines of human or animal origin [5] encourages applicants to use these alternative assays.

Roche has recently implemented a multiplexed degenerated PCR [6] into their control concept that combines the advantages of PCR, speed and sensitivity, with a broad specificity to detect a large number of virus variants. As a result, the species-specific viruses that can be detected by the in vivo MAP and HAP tests can be detected by a PCR-based in vitro assay. In recent years, the introduction of the PCR-based virus detection method reduced the need for animals by up to 90 mice and almost 45 hamsters per year.

PYROGEN TESTING

Pyrogens are fever-inducing substances of various origins, like bacteria (dead or viable), fungi, viruses, or even chemicals. The

innate human immune system reacts to pyrogens by releasing cytokines, which lead to an increase in body temperature (fever) and inflammation. Severe (over)reaction of the innate immune system (adverse reaction) can lead to an unregulated release of cytokines and ultimately to shock, multiple organ failure, and even death. For this reason, only therapeutics that are free of pyrogens may be marketed and health authorities require testing for pyrogens at various points in the production process. Three different tests are carried out for this purpose:

Rabbit Pyrogen Test

Owing to a comparable pyrogen sensitivity in humans and rabbits, the implementation of the in vivo rabbit pyrogen test (RPT) in the 1940s was able to significantly increase the safety of pharmaceutical products. The test is based on the reaction of a rabbit's innate immune system, which, like humans, reacts to pyrogenic substances by increasing body temperature and can therefore detect the majority of pyrogens. This includes endotoxin derived from gram-negative bacteria as well as non-endotoxin pyrogens derived from gram-positive bacteria, fungi, virus, or chemicals.

In the RPT, the product being tested is injected intravenously into the ear vein of rabbits. The temperature of the rabbits is monitored over a defined period of time. Finally, either the sum of the body temperature increase is calculated [7] or the increase of the body temperature of individual rabbits [8] is assessed. If the summed response does not exceed a threshold value (European Pharmacopeia acceptance criterion) or no rabbit shows an individual rise in temperature of 0.5°C or more above its respective control temperature (US Pharmacopeia acceptance criterion), the product meets the requirements for the absence of pyrogens.

The RPT currently consumes a significant number of animals. In the EU, ~50,000 animals were used for this test in 2015 and ~25,000 in 2021 [4]. The assumption for worldwide use is ~400,000 rabbits per year. In response to animal welfare objectives, multinational measures have been initiated in the EU to avoid the RPT. One notable initiative is led by the European Directorate for the Quality of Medicines & HealthCare, which aims to remove the RPT from the European Pharmacopeia [9–12]. This objective involves creating new or revising existing European Pharmacopeia General Chapters and the revision of around 60 monographs to replace the RPT with either the monocyte activation test (MAT) or the bacterial endotoxins test (BET) (described as follows).

Monocyte Activation Test

The monocyte activation test (MAT) [13] is an in vitro assay that mimics the reaction of the human innate immune system to pyrogens. A cell suspension containing monocytic cells (either peripheral blood mononuclear cells [PBMCs] or whole blood) produces cytokines (e.g., interleukins such as IL-1β or IL 6) by activation with pyrogens, and the released cytokines can be detected by an immunological assay (e.g., enzyme-linked immunosorbent assay [ELISA]).

Bacterial Endotoxins Test

Bacterial endotoxins, a subset of pyrogens, are lipopolysaccharides (LPS), a component of the outer cell wall of gram-negative bacteria. Endotoxin is a heat-stable substance and is known to be the most potent pyrogen. Because of these properties and their ubiquitous occurrence, the absence of endotoxin in the final product is of particular importance for pharmaceutical production.

In contrast to the MAT or the RPT, the BET is highly specific for endotoxins. Non-endotoxin pyrogens such as components of gram-positive bacteria, nucleic acids, proteins, or chemical components cannot be detected by the BET. Two different versions of the BET are accepted by the health authorities: the Limulus amoebocyte lysate–based BET (LAL assay) and the recombinant Factor C-based BET (rFC assay).

LAL assay

For almost 50 years, the LAL-based BET [14, 15] has been used for the determination of endotoxins, which rely on the blood from ancient and endangered horseshoe crabs (*Limulus polyphemus* or *Tachypleus tridentatus*). This test is based on the amoebocytes in the horseshoe crab's "blood," which provide the animals' natural defense mechanism against bacterial endotoxins and other pathogens. When the amoebocytes come into contact with bacterial endotoxins, an enzyme cascade is activated, which finally leads to clot formation of the LAL. Different variants of the LAL-based BET were developed: the gel clot assay and end-point or kinetic versions of a turbidimetric and a chromogenic assay.

rFC assay

The basis for this BET [16] is a synthetic rFC, the first enzyme in the LAL enzyme cascade. The activation of rFC by endotoxins leads to cleavage of a synthetic fluorogenic substrate present in the test system and thus to a fluorescent end product that can be quantified. The advantage of the rFC-based BET is that no animal-sourced reagent of an endangered species, such as the horseshoe crab, is required.

Avoiding In Vivo Pyrogen Tests

To avoid in vivo assays or the use of animal-sourced reagents for pyrogen testing, we have initiated several projects, which are discussed in the following sections.

Replacing the in vivo RPT with the BET

An analytical variation was submitted to replace the in vivo RPT assay with the LAL-based BET. It is one of our legacy products for which the RPT was originally filed many years ago as the pyrogen test method to release produced batches. The rationales for replacing the in vivo RPT were a) improved microbial control of the manufacturing process to prevent any unintentional introduction of pyrogens into the manufacturing process and b) prior knowledge based on hundreds of batches produced and released that demonstrated that the product itself was not pyrogenic. The analytical variation for lot release testing was accepted by the

US Food and Drug Administration (FDA) [17]. This update to the control system means that beginning in 2023 (the year of approval of the analytical variation) approximately 40 rabbits per year no longer need to be used for the release-relevant in vivo RPT.

Replacing the in vivo RPT with the MAT

During the development of a new manufacturing process for biologics, it must be shown that the manufactured biotherapeutics are free of pyrogens. In Europe, the MAT [13] can be used to demonstrate the absence of pyrogens. Unfortunately, in most counties outside of the EU, the MAT is still considered as an "alternative method" and in this respect the absence of non-endotoxin pyrogens must be demonstrated using the in vivo RPT.

For the US, this requirement is described in a federal law, 21 CFR 610.13(b) [18]. However, according to 21 CFR 610.9 [19], it is acceptable for the in vivo RPT to be waived if an alternative method is used that is equivalent to the in vivo RPT. The equivalence is usually demonstrated by analyzing a few representative batches in parallel with the in vivo RPT and the alternative method—typically the LAL-based BET. If the LAL-based BET is negative (demonstration that no endotoxins are present in the product) and the in vivo RPT is negative for the same batches (demonstration that neither endotoxins nor non-endotoxin pyrogens are present in the product), this is considered proof of equivalency. This means batches produced in the future may be released on the result of the LAL-based BET.

Following the described approach, it is required that some manufactured lots must be tested in parallel with the BET and the in vivo RPT. This concept is therefore still based on in vivo assays. Roche recently submitted a dossier for a pilot product, firstly describing a validated MAT and secondly demonstrating the absence of pyrogens using the in vitro MAT. This revised validation strategy, which makes the in vivo RPT superfluous, was recently approved by the US FDA [20] and is to be used in the future for all product and process developments. With the revised validation concept, at least 9–24 rabbits can be saved for each product under development.

Replacing the LAL-based BET with the rFC-based BET

Pharmaceutical products for parenteral administration must not be contaminated with endotoxins during the production process. As previously described, for almost 50 years, the LAL-based BET has been used for the determination of endotoxins, which rely on the blood from ancient and endangered horseshoe crabs (*Limulus polyphemus* or *Tachypleus tridentatus*).

Only a component of the "blood" of the horseshoe crabs is used to produce the LAL, so the LAL-based BET is by definition not an in vivo assay. However, a replacement of the LAL-based BET is desirable for ethical reasons. This is because the horseshoe crabs must be removed from their natural habitat for blood collection, and not all horseshoe crabs survive when the "blood" is taken from them. The solution to reduce the impact of horseshoe crab dependency is the use of the rFC-based BET [16].

As part of our 3R initiative, the LAL-based BET is currently being replaced by the rFC-based BET for testing water samples and product samples. For more than a year, water testing using the rFC-based BET has been successfully carried out at a pilot site in our QC network. At this site alone, more than 11,000 LAL-based BETs can be replaced with the recombinant alternative. The rFC-based testing of water samples is currently being transferred to other internal QC sites.

> The majority of in vivo assays used in QC can be avoided without losing the appropriateness of the quality assessments.

In a parallel project, the testing of product samples using the rFC-based BET is also being evaluated. Recently, the dossier of a pilot product was submitted worldwide, in which both the in-process control samples and the release-relevant samples are tested using the rFC-based BET. This analytical variation has already been accepted by some health authorities (e.g., FDA [21] and European Medicines Agencies/Committee for Medicinal Products for Human Use [EMA/CHMP]). In the next step, the method will be implemented worldwide in our QC network and will be used for future products.

POTENCY TESTING

Potency testing is crucial for assessing therapeutic effectiveness and biological activity as well as ensuring consistent batch-to-batch quality of pharmaceutical products. Common approaches include various product-specific types of bioassays, such as cell-based, receptor-binding, and neutralization assays, which directly assess the product's potency to stimulate or inhibit specific cell growth. In addition, in vivo assays are still used for longer marketed products. To meet 3R requirements, replacing the in vivo potency assays should be considered, if possible, with in vitro cell-based assays.

For one recombinant biopharmaceutical product, thousands of mice are used per year to demonstrate the biological activity of the produced batches via an in vivo potency assay. To avoid these in vivo assays in the future, we developed an in vitro reporter gene assay to determine the bioactivity. For this purpose, a genetically modified cell line is used to mimic the mode of action in vitro. The cell line enables the assessment of the pathway from the binding of the ligand to its specific receptor until the activation of gene expression.

In the in vitro reporter gene assay, the gene that is finally activated is modified. In the new in vitro reporter gene potency assay, it is not the formation of new cells that is achieved, but the expression of an enzyme. Ultimately, the activity of the enzyme can be used for an alternative readout, e.g., bioluminescence, ELISA, or another suitable readout system.

We recently obtained approval from the US FDA [22] to use the in vitro reporter gene assay for the determination of the biological

potency of the produced biopharmaceutical product. With the implementation of this analytical variation, the use of several thousand mice per year that are currently required for the in vivo potency assay can be avoided.

CONCLUSION

The sustainability goals of numerous regulatory authorities worldwide have initiated the development of alternative methods as a replacement for in vivo assays. A thorough method validation was performed for each of the alternative methods. As part of the validation, the relevant parameters [23] of the alternative methods were investigated. In addition, the method validations demonstrated that the alternative methods are comparable (non-inferior) to the traditional in vivo assays used to date and provide equivalent results. They also ultimately "provide assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the assurances provided by the method or process specified in the general standards or additional standards for the biological product" [19].

The submitted results of the method validations of the alternative methods were reviewed by the competent authorities and as an outcome of this review, the use of the alternative methods were approved as a replacement for the traditionally used in vivo assays.

The projects described demonstrate the potential that 3R initiatives have in the strongly regulated quality and manufacturing environment and show that it is possible to reduce dependence on in vivo assays. By using alternative methods and considering the 3R principles in the control concepts of biopharmaceutical products, the industry can contribute to significantly improving animal welfare.

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DECARBONIZING
Pharmaceutical Manufacturing Facilities

By Koichi Goto, Hideki Hasunama, PhD, Yoshiyuki Inoue, and Shigehiro Tahara

Reducing the pharmaceutical industry's carbon footprint has become a management responsibility. This article introduces some of the key points, actual methods, and practical examples of our implementation to reduce carbon emissions from pharmaceutical manufacturing facilities in Southeast Asia.

In general drug production facilities, a hazard identification and risk assessment from a GMP perspective should always be performed on the proposed energy efficiency improvements identified from an engineering perspective, and the necessary actions should be considered. Sometimes, it is possible that a proposed improvement may not be effective or feasible. Therefore, there are considerable hurdles to reduce carbon emission from drug manufacturing plants compared to general facilities. As an example, we will describe our approach for the decarbonization at an operational pharmaceutical manufacturing facility in Southeast Asia, highlighting key steps along the way. The article also includes a note on the sustainability aspects of the sustainable development goals (SDGs).

REDUCING CARBON EMISSIONS

In recent years, reducing the carbon emissions produced by products and services has become a management task in corporate responses to climate change. Without exception, the pharmaceutical industry needs to decarbonize its manufacturing facilities and equipment. This might include a broad range of actions, including purchasing carbon credits, installing renewable energy solutions, and lowering the carbon footprint of its supply chain. In short, emissions reduction planning requires consideration of a manufacturing facility's entire life cycle. We hope this article will provide key insights to help facilities further reduce the carbon footprint of pharmaceutical manufacturing processes.

Several approaches to low-carbon emission manufacturing facilities have been described in *Pharmaceutical Engineering*® articles. This article presents some key considerations, practical approaches, and examples of the reduction of greenhouse gas (GHG) emissions from pharmaceutical manufacturing facilities in Southeast Asia. The area is expected to be one of the fastest growing regions in the world regarding gross domestic product growth. The impact of GHG-related natural disasters in Southeast Asia is increasing, and international cooperation to reduce GHG emissions is expected.

CARBON NEUTRALITY IN SOUTHEAST ASIA

The Association of Southeast Asian Nations (ASEAN) [1] region is simultaneously exposed to many changes. It is expected to be the region most affected by future economic growth [2], increased energy consumption [3], and climate change worldwide [4].

Each government in ASEAN sets a GHG reduction target (Nationally Determined Contribution [NDC]) based on the Paris Agreement framework. Table 1 describes the GHG emissions with the baseline scenario and policy scenario for ASEAN's 10 countries [5]. The baseline scenario shows the expected emissions if no emission reduction activities are implemented. The emission scenario has two cases: unconditional and conditional. The unconditional target is the country's national policy without other countries' actions. In contrast, the conditional target is the unconditional target subject to achieving international support relating to finance resources, technology transfer, and technical cooperation.

Furthermore, given the global trend of environmental, social, and governance (ESG) investment in the world, decarbonization actions can be evaluated and thus help secure growth resources such as capital investment [6]. Based on actions consistent with these policy goals within the region and the availability of ESG investment funds, an increase in GHG-reducing actions in drug manufacturing plants in Southeast Asia is expected.

PROMOTE DECARBONIZATION

One way to reduce the carbon footprint of pharmaceutical products is to promote the decarbonization of manufacturing facilities. This approach to reduce GHG emissions from medical drug manufacturing facilities helps reduce the carbon footprint of pharmaceuticals and has been described in several *Pharmaceutical Engineering*® articles [7–10]. The methods for decarbonizing manufacturing facilities can be broadly divided into hard and soft measures, as described in Table 2 [11].

In addition, compliance with GMP is required for manufacturing conditions and operational aspects to maintain pharmaceutical quality and regulatory compliance. The location and environmental conditions of the manufacturing facility must also be considered. Therefore, the key items to understand and the required information to be gathered regarding the decarbonization of pharmaceutical manufacturing facilities are shown in Table 3. There are a wide variety of issues and considerable hurdles to achieving lowering of GHG emissions from facilities compared to less specialized general commercial and industrial facilities.

Table 1: ASEAN countries' baseline emissions and NDC pledges in 2030 [5].

Country	Baseline Emissions (MtCO2e)	Target Type	Target Emissions in 2030 (MtCO2e)	Gap from Policy Scenario (MtCO2e)
Brunei Darussalam	13.9	UC	10.3	4
		C	10.3	4
Cambodia	15.3	UC	15.3	-
		C	11.2	4
Indonesia	1,450.3	UC	1,218.2	232
		C	1,160.2	290
Lao PDR	22.5	UC	22.5	-
		C	21.4	1
Malaysia	544.4	UC	539.8	5
		C	456.8	88
Myanmar	72.8	UC	72.8	-
		C	69.6	3
Philippines	293.1	UC	293.1	-
		C	87.9	205
Singapore	51.4	UC	65.0	-14
		C	65.0	-14
Thailand	645.0	UC	516.0	129
		C	483.7	161
Vietnam	570.9	UC	525.3	46
		C	428.2	143
ASEAN	**3.679.6**	**UC**	**3264.7**	**415**
		C	**2780.7**	**899**

UC: unconditional, C: conditional

Note: Estimates exclude LULUCF-related emissions. Country emissions may not sum to the ASEAN totals due to rounding.

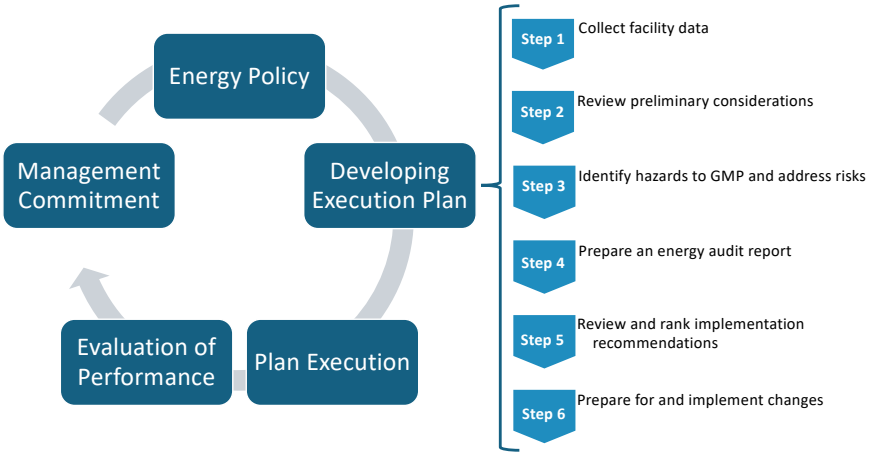
Table 2: Methods for decarbonization of pharmaceutical manufacturing facilities (examples).

	Category	Methods
H1	Hard measure	Shifting to the low-carbon energy source (solar, hydro, wind, geothermal, nuclear, etc.)
H2	Hard measure	Installing new or renovating existing equipment to improve energy efficiency
S1	Soft measure	Bridging the gap between required and actual operating conditions in response to increased or decreased production, and/or assessing the utility requirements out of the utility capacity to optimize system operation
S2	Soft measure	Setting lower operating conditions during nonworking hours, including nighttime or nonoperation hours for production lines

Table 3: Key factors regarding pharmaceutical manufacturing facility decarbonization (examples).

	Category	Essential Subjects and Information
1	Regulations related to GMP	• GMP in the region and regions the facility supplies • Pharmaceutical quality system and validation practices at the subject facility
2	Regulations related to decarbonization and environmental protection	The latest regulations related to GHG reduction and environmental protection in the area where the subject facility is located
3	Building design	Optimal layout design and thermal performance
4	Heating, ventilation, and air conditioning (HVAC); electricity; and utility design	Optimal system design and operational control
5	Production equipment/ processes	• Pharmaceutical quality management and manufacturing conditions • Production procedures and operating methods during manufacturing at the facility
6	Decarbonization and energy-saving technologies	The latest technologies and trends in GHG-reducing products and services
7	Pharmaceutical manufacturing technologies	The latest technologies and trends in production/ utility facilities
8	Other environmental conditions	Environmental conditions (including costs) in the area of the facility

Figure 1: Approaches to realization and examples of decarbonization [12].



APPROACHES AND DECARBONIZATION EXAMPLES

In this section, we consider the entire manufacturing facility and present a systematic approach to decarbonize pharmaceutical manufacturing plants in Southeast Asia. Pharmaceutical manufacturing facilities, being business organizations, should follow a management system. The main stages are presented next, based on ISO 50001 [12]: Management commitment, energy policy, developing execution plan, plan execution, and evaluation of performance (see Figure 1).

Management Commitment and Energy Policy

A facility's management organizes the person and/or team responsible for carrying out energy management activities and establishes an energy policy that articulates its commitment to achieving improvements in energy performance. Based on the energy policy, energy management activities are planned and implemented. The management also provides financial and human resources to realize its commitments.

Develop a Plan

An energy audit should be conducted to determine the entire manufacturing facility's energy supply and consumption status. This process will include proposals for specific measures to improve energy efficiency and reduce costs based on energy usage status. It consists of the following steps.

Step 1: Collect facility data

Collect ongoing facility and energy-related data from the facility's engineering department. Multiple years of data are preferred to account for seasonality and longer-term trends. It may be necessary to take supplementary measurements or even add instrumentation to assess specific leads.

The data items should include product items and their specifics, manufacturing process information, an overview of the facility and equipment, cost data for energy sources to be procured, types of energy consumed, and energy consumption data for each facility (production machinery, utilities, HVAC equipment, etc.).

Step 2: Review preliminary considerations

Based on the data collected, a desk-based energy consumption analysis should be conducted to examine options from a comprehensive perspective of efficient use and waste reduction. Using Sankey diagrams can be very helpful when sharing or reporting energy-related information. Examples of basic options follow.

- Change to a more energy-efficient utility system if the plant is equipped with its own power generation or steam generator
- Change the energy source to a lower- or zero-carbon option
- Retrofit or upgrade to higher-efficiency equipment or equipment components
- Minimize water consumption by reducing use or reuse
- Review operational states and consider intermittent use (turning off), silent hour setback, and campaign working

Based on the preliminary study results from step 2, conduct field inspections. The following are examples of items to be checked in the field: verification of preliminary considered options; age of the facility, maintenance records, and history of facility modifications and changes; up-to-date facility, systems engineering drawings, and documentation; verification of the environmental conditions of the manufacturing environment, especially the performance of the HVAC system; and identification of waste and inefficient areas and operations of the facility from an energy consumption perspective.

Step 3: Identify hazards to GMP and address risks

Two key activities are defined by ISO 50001 [12]: the plan-do-check-act (PDCA) cycle to achieve efficiency in energy use, and the PDCA cycle to ensure compliance with energy-related regulatory

requirements. In pharmaceutical production facilities, the environmental conditions under which products are manufactured and maintained in pharmaceutical production facilities are strictly regulated by law and GMP, and compliance is mandatory.

For every energy efficiency improvement idea identified from an engineering perspective, a hazard identification and risk assessment must be performed. This should be done from a GMP perspective, and the necessary actions must be considered. It is not unusual to conclude that the improvement proposal may not be feasible, effective, or practical, or that it presents too great a risk. In addition, a change of control must be prepared for all planned changes. The necessity and scope of requalification and revalidation must be discussed and approved by a quality assurance (QA) manager, and appropriate qualification and/or validation must be performed.

A characteristic of drug production plants is that they are often overdesigned initially to allow for factors such as performance safety margin, reserve capacity for changes in use or occupancy, and expansion. Additionally, production changes, increases, and decreases from the originally anticipated manufacturing plan lead to a high probability of a significant discrepancy between the design intent and the current facility utilization. By understanding the divergence between these, it is possible to identify opportunities to remove excess equipment or adjust and regulate systems to reduce excess capacity specifications. There are two different perspectives for reviewing these matters: a review of production environmental parameters and a review of operational management.

Review of production environment parameters

Review the latest production environmental control performance parameters, including clean room ventilation air changes, air supply/exhaust volume, room temperature, relative humidity, and room pressure differential settings. Adjustments should be made to the extent that the changes do not affect quality, thereby improving productivity and reducing energy consumption and carbon emissions.

Review of operational management

Encourage energy conservation by reviewing facility operation and management during nonoperating periods. Significant energy savings can be achieved by shutting down systems during nonproduction periods, setting back performance during production idling mode, closing steam lines when they are not required due to seasonal needs, etc.

Step 4: Prepare an energy audit report

The energy audit report is prepared by analyzing the results to date. Its structure is as follows. First, energy consumption is analyzed, including for the entire manufacturing facility, all processes and staff, and each system within the facility. Second, comprehensive engineering proposals are created to improve the efficiency of the energy used. Third, inefficient energy use is identified and ways to address it are developed. Fourth, the magnitude of capital investment required and the resulting energy conservation reduction effects are considered. If appropriate, the investment payback period and return on investment (ROI) should be defined and considered. It should be noted that carbon reduction measures, such as changing the energy source from gas or oil to electricity, may not save money and may cost more to operate.

For every energy efficiency improvement idea identified from an engineering perspective, a hazard identification and risk assessment must be performed. This should be done from a GMP perspective, and the necessary actions must be considered.

Typical project categories include proposals with:

- Small or no additional investment and an energy reduction target of about 5%, e.g., equipment optimization tuning
- Moderate investment and an energy reduction target of 5%–15%, e.g., introduction of new technology and high-efficiency equipment
- Large investment and an energy reduction target of 15%–30%, e.g., introduction of new technology and high-efficiency equipment renewal of aging facilities

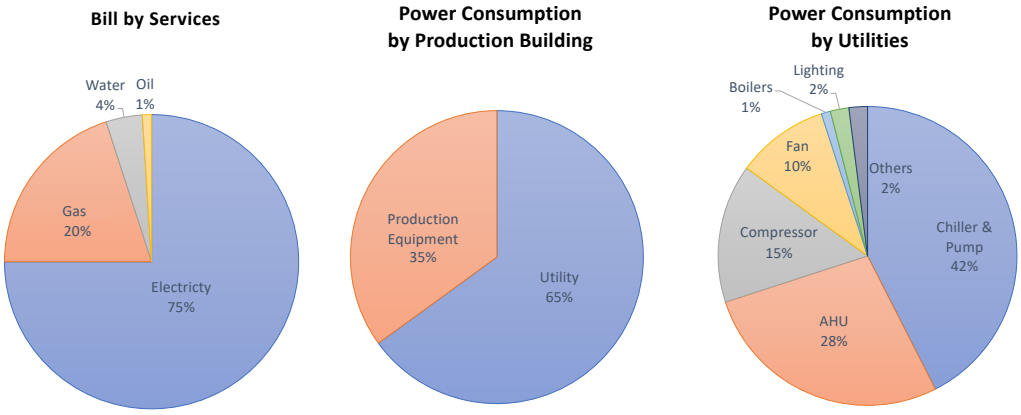
An energy audit usually takes about two months from the start to the submission of the report. Analysis and consideration of options are difficult when insufficient materials for analysis are available or when energy use and consumption are not visible. An estimation based on decarbonization and energy-saving technologies given in Table 3 may also be useful in this situation.

The report should provide a status report and a future vision of carbon neutrality in manufacturing facilities for the management of the company owning the facility and the facility's management. The process of preparing the energy audit and report, which is a collaborative effort with the employees of the manufacturing facility, can be seen as an introduction to a series of hypotheses, considerations, and implementation of solutions for continued energy efficiency and carbon reduction over time.

Step 5: Review and rank implementation recommendations

The faculty management personnel should review the current

Figure 2: Visualization of energy consumption categories.



AHU: air handling unit

situation at the target facility and proposals for improving energy efficiency internally to determine whether they should be implemented. Management will select the proposals for implementation based on each proposal's ROI or carbon savings in a manner linked to the production, capital investment, and maintenance plans.

In addition, as indicated in the report, the effort to go carbon neutral for a manufacturing facility will be long term, so the capability of energy consumption visualization will be essential (see Figure 2). The factory energy management system is a useful numerical dashboard for considering and implementing carbon neutrality measures, as both a building management system and an environment monitoring system become essential systems in the facilities.

Step 6: Prepare for and implement changes

After the management team reviews and ranks the proposals, they should be organized and implemented as a project. Capital investment should then be made based on the payback period, if applicable. This includes life cycle costs, energy-saving measures, and production efficiency improvements. In doing so, financing methods such as leases, rentals, and subsidies should be considered.

Plan Execution, Monitoring, and Follow-Up

The project is executed in accordance with the PDCA cycle, which includes the process evaluation based on the measured results. This article focuses on the planning process, which is the most essential aspect to consider in terms of numbers. Efforts to become carbon neutral in the plants require a long time. Therefore, achieving incremental CO_2 emissions reductions will require continuous reductions in inefficient energy consumption in equipment and operations throughout the facility. The series of tasks outlined previously should be repeated to achieve this reduction. In addition, the information on the decarbonization of pharmaceutical manufacturing facilities listed in Table 3 requires continuous follow-up activities because they change with technological advancements, regulations, etc.

DECARBONIZATION AND GMP COMPLIANCE

We will now consider the decarbonization of two specific systems. These are HVAC and pharmaceutical water systems that are critical from a GMP perspective. Both systems have significant energy and GHG impact.

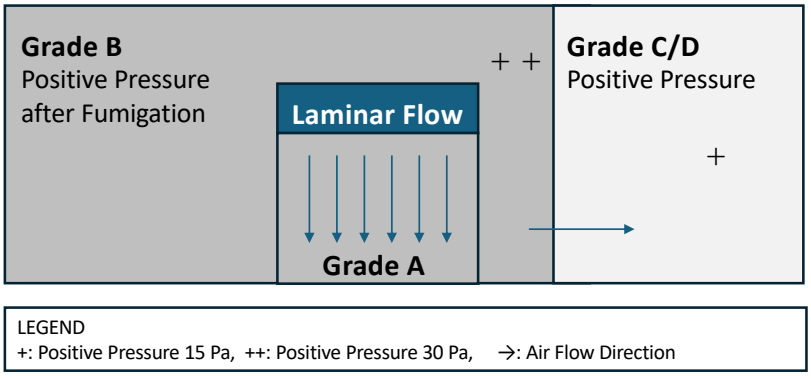
HVAC System

While the HVAC system in pharmaceutical plants is an important system for maintaining a high level of manufacturing environment control, the energy savings associated with changes in equipment and operating conditions can be significant. Therefore, conducting a risk assessment for each feasible energy-saving item is important to see if GMP-like problems arise. For example, will the differential pressure between rooms be maintained if the ventilation rate is reduced? Can the cleanliness level be maintained? Will it affect temperature and humidity control? During the evaluation and assessment, it is important to review the HVAC and system control diagrams with the engineer, identify risks jointly, and determine avoidance measures and recommissioning or requalification requirements.

First, it is important to establish the required air volume supply requirements. That may be expressed as numerical air changes–rate per hour based on airborne cleanliness level and contamination source strength load, heat gains in the occupied space, and recovery times specified in GMP guidance documents such as Annex 1 of the PIC/S GMP. ISO 14644-16 [13] highlights that the airflow contributes significantly to the cleanroom's energy consumption. Therefore, reducing airflow rate leads to significant energy savings. Theoretically, the ventilation power by fans depends on the cube of the airflow rate [7], so if the airflow is reduced by half, electrical consumption by fans is reduced by one-eighth (see S1, S2 from Table 2). Therefore, introducing nighttime and holiday modes, which reduce the air flow rate during nonoperating hours such as nighttime and holidays, has a significant energy-saving effect.

When considering aseptic drug product manufacturing facilities, the reality is that sterility assurance is the most critical

Figure 3: Assurance of a sterile environment and air conditioning environmental conditions.



issue, and reducing the risk of loss of aseptic processing conditions is achieved by ensuring robust conditions. To save energy, it is advisable first to consider whether it is feasible to shut down the air conditioning during nonoperating periods in Grade C/D, which occupy the least amount of cleanliness in the largest area (see S2 in Table 2). Consideration could be given to whether it is possible to reduce the air change rate during nonworking hours in Grade B while maintaining room pressure. It may also be necessary to consider whether it is feasible to shut down unidirectional Grade A airflow during nonoperating periods to achieve further energy savings (see S2 in Table 2).

In many cases in Southeast Asia, aseptic operations are still conducted under conventional Grade A unidirectional airflow, and aseptic assurance in conventional Grade A and Grade B facilities usually employs periodic bio-decontamination based on sterilization. This means stopping the airflow is unlikely to be acceptable due to the significant time required to re-establish aseptic conditions. A more practical approach would be reducing velocity during silent hours, ensuring that the Grade A cleanliness is maintained in a rest state.

Many QAs consider a sterile break as soon as the laminar flow is stopped during nonoperating hours. This is because it is almost impossible to validate the reproduction of an aseptic environment when the laminar flow is restarted by any method other than sterilization (see Figure 3). In this case, it is a balance between the energy-saving effect, the labor required for verification, and the risk of aseptic assurance. Thus, although the operation of air conditioning equipment during nonoperation is a huge energy-saving target item, some issues need to be resolved to apply soft measures to a sterile environment.

Pharmaceutical Water Utilities

Water used for the manufacture of sterile products, water for injection (WFI), is required to be highly controlled for microbial levels, endotoxins, total organic carbon, and conductivity. The water, frequently produced by high-temperature distillation, is maintained over 80°C/176°F [14] within the storage and distribution system to inhibit microbial growth and then cooled for use during processing. Therefore, energy consumption for heating and cooling is significant, and alternative approaches should be considered to save energy and associated CO_2.

Figure 4: Example of WFI facility configuration.

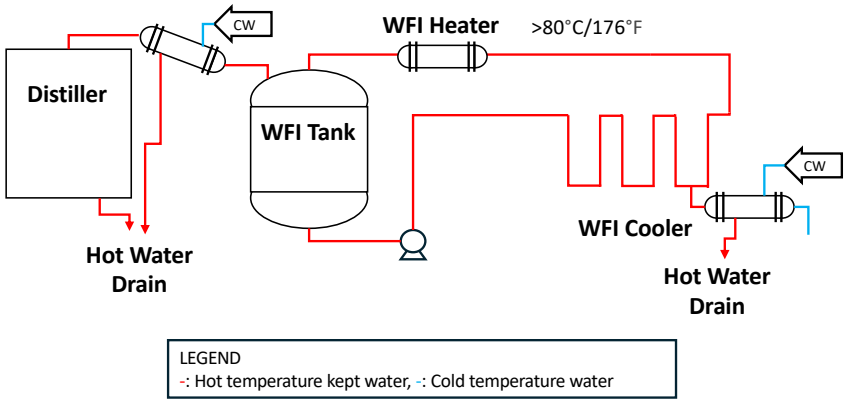
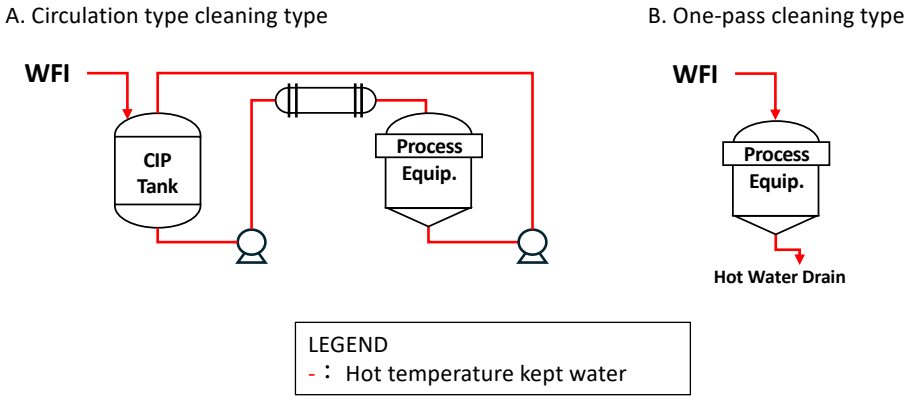


Figure 5: Example of clean-in-place system.



Pharmaceutical water systems consume energy to maintain pharmaceutical water quality. Therefore, the energy conservation policy is to build a system that uses as little heat source as possible, and to reduce the amount of WFI used as much as possible and reduce the capacity of the system.

Now that the major pharmacopeias (US, Europe, and Japan) have been revised to accept the technology of room temperature membrane-based systems, there is an opportunity to adopt this system. We have the opportunity to change to ambient temperature membrane-based systems because most pharmacopeias have been revised to accept this technology. These systems operate in conjunction with the ozonation of the storage and distribution system to inhibit microbial growth. Such systems obviate the need to provide steam heating and high-capacity cooling utilities.

When WFI is produced by distillation, heat source steam is used, and a large amount of cooling water is used in the distiller's condenser. The produced WFI is kept hot (> 80°C/176°F) in the WFI tank and circulation loop and cooled by a local cooler at the time of use (see Figure 4). The wastewater from each process is mixed with high and low temperatures and discarded as medium-temperature wastewater, making heat recovery difficult. However, this can be designed in advance to recover heat from wastewater, although additional equipment for heat recovery and the cost-effectiveness of heat recovery must be considered.

When distillation-based WFI systems are employed, it is possible to design a system that uses heat recovery in a manner that does not conflict with GMP. However, additional equipment for heat recovery and the cost-effectiveness of heat recovery should be considered. Reducing the consumption of WFI is also a mechanism for energy reduction. Experience tells us that the amount of WFI used for cleaning is often greater than the aqueous component of the product.

In this case, the following examples can be considered.

- Reducing washing water by switching from one-pass washing (see Figure 5B) to circulating washing is possible but involves large-scale production facility changes (see Figure 5A).
- It is possible to reduce cleaning water by reducing unnecessary cleaning time with regard to the construction of changes to pro-

duction facilities. Reducing wastage due to excessive cleaning time from the safety side approach during validation is proposed as one of the methods.

Therefore, reducing usage by a reduction in cleaning time entails reconfirming cleaning effectiveness (cleaning validation).

BECOMING A SUSTAINABLE FACILITY

We recommend, and emphasize, three perspectives when realizing the approaches we have discussed for promoting the GHG reduction from drug manufacturing facilities and examining risks from a GMP perspective.

Long-Term Commitment

Achieving decarbonization of a drug production facility requires optimization of CO_2 emissions, energy consumption, and product output throughout the facility's life cycle period. The facility's life cycle cost includes energy consumption but also maintenance, renewal of facilities, and more. Therefore, it is essential to understand the effects and costs during the long-term life cycle period.

The Human Factor

Because this is a companywide initiative and must be based on a long-term plan, the top management leadership of the manufacturing facility is paramount. Disclosure of the initiative to all staff, progress based on consensus, and reflection as a management indicator are desirable. The hurdles to optimizing operations and higher quality from the perspective of quality first and GMP validation are high.

Communication between quality control, production, and facility management departments is essential, and management commitment is critical. The optimization of energy usage will be encouraged based on the optimization of the production system. Proposals for the renewal of aging facilities by the facility management department will be more effective if the payback on investment based on optimized energy usage is considered.

Master Plans Through the Life Cycle

Master planning through the life cycle period and forecasting can be used to promote ongoing optimization. The master plan includes annual production targets, CO_2 reduction measures and targets, energy consumption targets, payback (if applicable), replacement plans for aging equipment, and maintenance (including overhauls). Optimization needs to be reviewed each time because production status and items change. The master plan is vital as a basic guideline in such cases.

However, to pass on manufacturing facilities to the next generation, we must not forget the sustainability perspective of the SDGs as we work to reduce GHG emissions. Manufacturing facilities undergo numerous upgrades over the decades, and their carbon footprint must be reduced over their life cycle.

If the plant is in a country that is on track to achieve carbon neutrality by 2050, synchronize the plant's long-term roadmap to decarbonization with the policy goal.

ADAPTING LOCAL CIRCUMSTANCES

If the plant is in a country that is on track to achieve carbon neutrality by 2050, synchronize the plant's long-term roadmap to decarbonization with the policy goal. Product items and other factors manufactured in factories tend to change more frequently in response to recent technological innovations, economic growth, and geopolitical balances. Therefore, long-term efforts will need to be reviewed throughout the life cycle, and the methods that are appropriate to the production situation should be continually sought.

Southeast Asian plants have an annual cooling load with no winter heating due to high year-round temperatures. Based on these related temperature characteristics, the key points are to reduce the amount of outdoor air treated (with high enthalpy throughout the year) and to reduce the cooling load. In the future, climate change will likely require consideration of load increase in response to temperature and pressure changes in extreme weather.

CONCLUSION

In addition to achieving carbon neutrality, reducing the carbon footprint of pharmaceuticals is a management issue of increasing importance. This article presents some of the considerations, practical methods, and examples of practices we have implemented to decarbonize pharmaceutical manufacturing facilities in Southeast Asia, an area expected to be one of the fastest growing regions in the world regarding gross domestic product growth.

In similar facilities, it is always necessary to conduct risk analysis from a GMP perspective and consider necessary measures for the energy efficiency improvement proposals identified from an engineering perspective. Depending on the circumstances, it is possible that declining a proposed improvement may not be effective or feasible. Therefore, there are considerable hurdles in achieving GHG reduction from drug production plants compared to general facilities.

Our team presented an approach and examples study of decreasing GHG emissions at an operating pharmaceutical manufacturing plant in Southeast Asia. The main steps involved assessing the current situation, listing and prioritizing measures, installing equipment, changing operating conditions and validation, and following up with ongoing monitoring.

In promoting decarbonization, the sustainability perspective of the SDGs for carbon footprint reduction from a manufacturing facility must also be considered. The carbon footprint reduction also requires a long-term incremental reduction plan considering the manufacturing facility's life cycle. Implementing a carbon reduction plan will be a long and arduous journey, but we would like to offer encouragement for those working to implement similar measures in their facilities: It can be done!

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FOYA Projects Embrace Innovative Sustainability Solutions

By Marcy Sanford

Established in 2004, the Facility of the Year Awards (FOYA) recognize state-of-the-art projects utilizing new, innovative technologies to improve the quality of products, reduce the cost of producing high-quality medicines, and demonstrate advances in project delivery.

The FOYA program provides a platform for the pharmaceutical science and manufacturing industry to showcase its accomplishments in facility design, construction, and operations while sharing the development of new applications of technology and cutting-edge approaches. In 2019, Celgene International was awarded a FOYA in Sustainability for its project La Fée Verte in Switzerland. But, as the industry became more aware of the need to design with the environment in mind, sustainability became a must-have to be considered for a FOYA. This year's category winners are no different. Each winner incorporated sustainability design into their project and has ambitious goals to help protect our environment for the future.

INNOVATION: IE2B

Sustainability responsibility has always been important to Lilly. Making medicines requires the use of valuable resources including energy, water, and raw materials, and Lilly has an ambitious goal to become net zero by 2030. Innovative engineering design plays a significant part in Lilly's sustainability journey. Decarbonization needs capital investment to replace established high carbon footprint manufacturing platforms and technology with low carbon footprint technologies and efficient unit operation design. Having a sustainability focus in the early design phase of a new facility or project can yield significant benefits—equipment and technology choice is correct from the beginning versus an expensive retrofit of equipment in an already operating plant. Deliberate forward thinking decisions can ensure smart design to optimize energy usage, water usage, and raw material usage. This approach can yield significant sustainability advantages but also may yield lower operational costs and efficiency for manufacturing plants, creating a potential win-win.

Sustainability was a significant consideration when Eli Lilly Kinsale Limited was designing its new synthetic peptide manufacturing facility (IE2b) located in Kinsale, Ireland. The new IE2b facility uses a hybrid manufacturing platform—liquid-phase peptide synthesis/solid-phase peptide synthesis (LPPS/SPPS). This combines the traditional approaches to synthetic peptide production using SPPS to manufacture high-purity preassembled peptide fragments. This is combined with coupling the fragments via LPPS using continuous processing technology.

The process is designed to be efficient with many of the continuous processing steps, producing conversion yields of over 98%. This ensures minimal waste of input raw materials. The telescoped nature (running steps one to three as one continuous process) of the design eliminates the need for multiple setups and cleanups between each process step, which reduces the need for additional cleaning solvents and cleaning materials.

Other highlights include:

- The integrated modular cleaning and maintenance strategy has reduced cleaning timelines by approximately 25%.

- The IE2b peptide hybrid manufacturing process produces 20% less solvent waste per month compared to a typical batch-based small-molecule process.
- The telescoped design of the process eliminates the need for individual step cleanups, which equates to an annual reduction of over 100 metric tons of solvent needed for cleaning activities when compared with a traditional three-step batch-based equivalent process.

Lilly Kinsale also installed a 5.6-megawatt (MW) commercial solar farm adjacent to the Kinsale manufacturing site. This solar farm contributes to approximately 15% of the IE2b facility power needs and supplements the power needs of the rest of the Kinsale site.

PROJECT EXECUTION: TUAS 2

Pfizer Asia Pacific Manufacturing Ltd.'s Tuas 2 facility in Tuas, Singapore, will produce active pharmaceutical ingredients (APIs) for a portfolio of medicines across a range of therapeutic areas such as oncology, autoimmune disease, cardiology, and antibiotics. Pfizer identified and implemented over 184 sustainability improvement opportunities at the site, including:

- Installing a roof-mounted photovoltaic panel system capable of meeting all the site's nonprocessing electricity needs
- Replacing cabled street lighting with LED solar-powered street lighting and maximizing natural lighting inside
- Providing better bus, bicycle, and electric car facilities
- Using native and drought-resistant plants in landscaping
- Improving heating, ventilation, and air conditioning (HVAC) systems by using recirculation and heat recovery systems
- Improving the endotoxin water system by challenging end user loads and equipment and system needs
- Reducing the piping requirement, equipment sizes, and loop sizes of the water system, and specifying a reverse osmosis system with very low reject water over variable frequency drive and demand control

As the industry became more aware of the need to design with the environment in mind, sustainability became a must-have to be considered for a FOYA. Each category winner incorporated sustainability design into their project and has ambitious goals to help protect our environment for the future.

- Installing electronically commutated fan walls where atmosphere explosible requirements and duct pressures allowed: this space-saving solution improved specific fan power with a greater level of redundancy

It is anticipated that all the sustainability improvements could lead to an annual energy savings of 80.5 terajoules, which is an incredible 31% improvement from the initial concept design.

OPERATIONS — FACILITY FIT: TAKEDA'S MANUFACTURING SITE LINZ, AUSTRIA

The focus of Takeda's Manufacturing Site in Linz, Austria, is the production of biologics for the treatment of chronic inflammatory bowel diseases in various forms. Takeda managed to reduce the

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process performance qualification time by 50% for the new prefilled syringe filling line. Once fully operational, the Linz site will fill and finish 70% of the global demand for this product.

With a strong focus on sustainability, Takeda installed about 20 new freezers to store the active ingredient, shortening global supply chains. The team made a notable transition to non-multipack packaging and up to 70% of cartons and 50% of leaflets are anticipated to be saved with this change. In addition to reducing waste, these steps also reduce Takeda's carbon footprint, aligning with their sustainability goals. Takeda continues to evaluate and implement innovative sustainable solutions, such as a renewable energy supply, along the entire value chain.

SOCIAL IMPACT: UK4

As part of its business strategy, Chugai Pharma Manufacturing Co., Ltd. has placed sustainability at the heart of its business activities and aims to be a global role model. UK4, their new 40,000-square-foot biological drug substance manufacturing facility in Tokyo, Japan, was specifically designed and built for the manufacture of early-stage investigational medicinal products under a "Three Zeros for Sustainable Development" concept. UK4 employed innovative solutions to achieve the Three Zeros goal.

- Zero halogenated hydrocarbons: They used naturally occurring coolants like NH_3 and CO_2 instead of the traditional halogenated hydrocarbons to achieve the goal of zero halogenated hydrocarbons. The cooling source is provided by ammonia chillers, whereas the heating source is provided by CO_2 heat pumps.
- Zero natural gas: To avoid using natural gas, they installed electric boilers to supply the needed steam. This was possible, in great part, due to several design decisions that resulted in reduced steam demand. These included using CO_2 pumps as heat sources, increasing the use of single-use equipment, eliminating the need for cleaning, and adopting a membrane-based process water system (cold water for injection system) instead of distillation-based equipment.
- Zero CO_2 in non-GMP areas: To achieve the last goal of zero CO_2 in non-GMP areas, UK4 implemented several solutions to reduce energy consumption and to generate what was needed using renewable sources. Solar panels were installed on the roof and integrated into the facade of the building. The northern facade featured louvers to block direct sunlight and redirect natural light into the clean rooms. Several additional energy management solutions were implemented across the site, including adjustments to room air changes based on load and lighting control based on occupancy.

Finally, a water reuse strategy was implemented that included recovering rainwater and HVAC condensate to reduce water consumption and the energy needed to produce it. All of this is monitored by a centralized energy and environmental monitoring system to ensure proper operation and to validate efficiency.

FOYA HONORABLE MENTION: UNITED THERAPEUTICS' RESEARCH TRIANGLE PARK SITE

United Therapeutics needed to expand their warehousing and logistics capabilities to support their growing operations due to the anticipated FDA approval of Tyvaso DPI, a new formulation

and inhalation device for inhaled treprostinil and the only dry powder inhaler approved by the FDA for use in pulmonary arterial hypertension and pulmonary arterial hypertension with interstitial lung disease (PH-ILD).

They identified site carbon and net zero as two sustainability requirements for the project and adopted the mindset that they could develop life-saving medicines for patients without harming the planet. The new facility is unmatched when it comes to environmental responsibility for a current GMP warehouse and operations center and is designed to be able to maintain operation even during electrical grid outages.

The facility incorporates several technological innovations that contribute to its site net- and carbon-zero goals, such as passive and active energy reduction strategies, rooftop photovoltaic arrays, a geothermal exchange system, microgrid technology, and a battery backup system (Tesla Megapacks). These systems allow the facility to use renewable energy, push excess energy back to the grid, and maintain a stable current GMP environment for the ambient and cold storage areas. The project is expected to receive LEED Gold, LEED Zero Energy, LEED Zero Carbon, and Energy Star certifications.

To minimize the ecological impact of the project, United Therapeutics built the new facility on an existing underutilized soccer field on their Research Triangle Park campus in Raleigh, North Carolina. Locating the facility on the corner of their campus adjacent to their new site net-zero childcare center enabled them to avoid clear-cutting the remaining wooded area on campus and provided for the adaptive reuse of the existing fieldhouse.

Sustainability achievements included:

- All-electric system design to facilitate on-site energy offset with renewables
- Low-energy design without impact on the program needs of the current GMP facility
- A ground-coupled geothermal heating and cooling system generating chilled water and heating water for the current GMP warehouse
- On-site zero energy, producing as much or more energy from renewables as is consumed
- On-site zero carbon, offsetting all carbon emissions associated with energy for typical building operations with on-site renewables
- Two Tesla Megapacks of battery energy storage systems with a total of 6.2 megawatt-hour (MWH) of backup power. This supports 8, 24, and 48 hours of code-required loads, ambient storage, and cold storage without any recharging

United Therapeutics' facility is the first of its kind in the world to deliver this performance to a current GMP operations and logistics facility. With the completion of the new warehouse, United Therapeutics has completed four site net-zero energy projects and has numerous LEED-certified projects including the Unisphere, their award-winning headquarters in Silver Spring, Maryland, which is the US's largest site net-zero urban office building.

FOYA HONORABLE MENTION: ZYDUS PHARMACEUTICALS' GUJARAT SITE

Zydus Pharmaceuticals' new greenfield cutting-edge oral solid dosage (OSD) manufacturing facility located in Gujarat, India, is dedicated to manufacturing OSD products. Zydus as an organization believes in sustainable inclusive growth where not only the organization but also the stakeholders' interests and well-being are prioritized. To that end, the following are a few of the measures they took with the new facility:

- Initiated a watershed development project in water-stressed areas of Gujarat including several interventions such as developing village ponds, farm ponds, rainwater injection bore wells, and check dams through which runoff rainwater is stored and harvested in aquifers. The organization is trying to harvest about 2 billion liters of water in three years through these interventions.
- Extensive planting through a seedball campaign
- Focused water and energy conservation activities including recycling wastewater through robust treatment using energy-efficient motors, motion sensors, LED lights, and green fuel for boilers
- Recycling 420 metric tons of plastic waste generated from its operations as extended producer responsibility
- Sending more than 2,700 metric tons of hazardous waste with high-calorific value to the cement industry for co-processing during the 2022–2023 financial year

Additionally, the site environmental management system includes infrastructure like a wastewater treatment plant, dedicated stormwater drains, hazardous waste storage facility, and emission control equipment. Process vents are equipped with HEPA filters and the performance of the pollution control equipment is monitored on a regular basis.

To learn more about the 2024 FOYA category winners, including the 2024 FOYA winner, visit ispe.org/facility-year-awards

Be Inspired at the ISPE Pharma 4.0™ and Annex 1 Conference

By Richard Denk and Line Lundsberg-Nielsen, PhD

The 2024 ISPE Pharma 4.0™ and Annex 1 Conference will be held 10–11 December in Rome, Italy, and virtually. Richard Denk and Line Lundsberg-Nielsen, the conference's Executive Chairs, offer advice and share what attendees can expect at the upcoming conference.

What are the top three reasons you would tell someone they should attend this conference?

Denk

The first reason for me would be that there is no better combination of topics. I believe Annex 1 is an enabler for Pharma 4.0™. The second reason would be the network that you can only have at such international conferences: during breaks, in the corridors, and after the first day of the conference in and around the conference hotel. During conversations you can not only get to know new people, but also deepen what you have heard, or also get in direct contact with the speakers.

The third reason is certainly the lectures, especially this year's presentation by Christina Meissner and Ronald Bauer from the Austrian Agency for Health and Food Safety (AGES), the regulatory authority in Austria. Both are experts in their fields—Christina in requirements from an inspector's perspective and Roland in Pharma 4.0™ and digital transformation.

Lundsberg-Nielsen

I agree the networking opportunities at the conference and the speakers we have lined up are wonderful. I am really looking forward to our keynote speakers, Flemming Dahl, who will be exploring the strategies and considerations involved in building fill and finish facilities across a global manufacturing network, and Malcolm Jeffers, whose presentation will focus on equipping people to accelerate Pharma 4.0™ transformations and lead the life sciences industry forward through innovative manufacturing to ensure better medicines, devices, and diagnostics for patients.

What are you most looking forward to?

Denk

The mixture of Annex 1 and Pharma 4.0™ offers so many opportunities to shape the future in pharmaceutical manufacturing. Of course, I'm looking forward to my Annex 1 track, which I'm leading together with Pol Bonet. We have put together a variety of very innovative and informative lectures. These range from the areas of assessing and ensuring Annex 1 compliance during GMP internal and external audits to robot telemanipulation, removing direct human contact.

Lundsberg-Nielsen

I'm looking forward to being inspired by what other end users are doing and hearing about how the end users' partners are helping them, understanding the challenges other companies have had in implementing digital solutions and how they've overcome them, and engaging with the regulators. I always get very inspired at these conferences and bring back a lot of ideas.

Any advice for someone to make the most out of the conference?

Denk

Prepare well for the conference. Download the ISPE app, where you can network with participants and get in touch weeks before the event. If you are coming to an ISPE conference for the first time and are not sure how to get in touch with others, this is an ideal opportunity to choose a professional and contact them to see if you can meet them at the conference.

Lundsberg-Nielsen

I agree with Richard , be prepared. Prepare questions and don't be shy to ask them during sessions, breaks, and afterward. Share the conference program with your work team and ask if they would like you to focus on anything particular or if they have any questions they would like you to ask. After each session, make a few notes: What was the outcome? What will you take back? You will get so many ideas and so much inspiration. Prepare for the conference, but also prepare for what you're going to do with the knowledge you gained when you return.

About the authors

Richard Denk is the Senior Consultant for Aseptic Processing and Containment at SKAN AG, headquartered in Allschwil, Switzerland. More than 15 years ago, he helped form the expert ISPE Germany, Austria, and Switzerland (D/A/CH) Containment Community of Practice. Richard has spent more than 30 years with the subject of production of aseptic processing and highly active/highly hazardous substances. He developed the containment pyramid and was a co-author and chair of the *ISPE Good Practice Guide: Containment for Potent Compounds*. He joined ISPE in 2003.

Line Lundsberg-Nielsen, PhD, works as a Managing Consultant at NNE, providing services based on science and risk principles for quality by design, process analytic technology (PAT), control strategy, real-time release testing, process validation, science- and risk-based qualification, and technology transfer. She is a physicist with a background in pharmaceutical manufacturing and development, and she is passionate about control strategy. Line holds a PhD in PAT. She joined ISPE in 2001 and has been active with Pharma 4.0™ from its beginning.

At a Glance: Foundation News

By Isabella Stroup

This year, the ISPE Foundation's Professional Development Grants program, supported by the Moderna Foundation, enabled 24 STEM students and Emerging Leaders to attend the 2024 ISPE Annual Meeting & Expo with all expenses covered.

The ISPE Foundation's Professional Development Grants program fosters professional development and promotes global health equity by providing access to knowledge and nurturing diverse talent. Participants in the program gained invaluable knowledge, attended educational sessions, networked with industry leaders, and received a two-year ISPE membership. Additionally, over 20 recipients attended the 2024 ISPE Europe Annual Conference.

A past grant recipient, Silas Tamufor, shared, "The ISPE Foundation not only improves the lives of individuals but also fosters a stronger, more resilient community. The impact extends far beyond immediate assistance. ISPE Foundation equips individuals with the skills, knowledge, and resources to break free from the generational cycle of adversity. It is a lifeline for individuals like me and a testament to the power of compassion and collective action. Your support has the potential to change lives, inspire confidence, uplift communities, and create a brighter future with a lasting impact. It is essential to recognize that it would not be possible without the generosity and dedication of individuals like you."

To learn more about how you can make a difference in the lives of students and recent graduates, please visit ispefoundation.org/scholarships-grants

Isabella Stroup, ISPE Foundation Development Coordinator

Meet the ISPE STAFF

NADA ELSAYED

Hometown: Tampa, Florida

In each issue of *Pharmaceutical Engineering*®, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Nada Elsayed, Content Development Manager on the Publications Team.

Tell us about your role at ISPE: What do you do each day?

My role is very dynamic. I interact daily with our fabulous volunteers in our Communities of Practice. I also support our volunteers with any technical content they would like to develop. This includes the early stages of writing guides along with proactively identifying topic areas that would benefit from new content for a variety of reasons, such as new updates, regulatory requirements, processes, technologies, and so on. I also leverage my industry experience and technical background to support evaluating our content for technical accuracy.

What do you love about your job?

I love being able to support our volunteers with all their ISPE needs related to technical content, whether it be a guide, webinar, roundtable discussion, blog post, or something else. I'm fascinated by the amazing energy that all our volunteers have. It keeps me going every day. I get to learn about all the incredible work that they do in their day jobs and get exposure to all the happenings in the pharma industry through their lenses.

What do you like to do when you are not at work?

I love spending time with my family. I'm usually super busy with my kids' competitive soccer and gymnastics schedules. When I'm not at work, you will find me cheering (or screaming) on the sidelines at games.

2024 ISPE PHARMA 4.0™ AND ANNEX 1 CONFERENCE

ISPE®

10-11 December 2024 | Rome, Italy and Virtual

ISPE®

Hear from top industry thought leaders as they dive into the challenges and solutions impacting the pharmaceutical industry, including:

- **Pharma 4.0 Interconnected Facility Design and Construction:** Gain insight into how 'plug and produce' principles offer opportunities for creating an integrated and interconnected facility, but they also come with challenges
- **Annex 1 Implementation and Pharma 4.0:** Learn strategies for implementing the latest Annex 1 version through real-world case studies, ensuring smooth operational changes and hardware integration
- **How ATMPs Manufacturing can be Supported by Annex 1 and Digital Transformation:** Discover how the pharmaceutical industry can ensure the delivery of safe products to patients by improving their processes, implementing Annex 1, and utilizing enhanced data management for faster product release

Featured Industry Thought Leaders

BAYER · Boehringer Ingelheim · EMD Serono · novo nordisk® · Roche · Takeda

LEARN MORE AND REGISTER AT ISPE.org/2024-Pharma-40

VOLUNTEER PROFILE

SUSTAINABILITY COMMUNITY OF PRACTICE CHAIR

ESTER LOVSIN BARLE, DVM, MSC, PHD, MSCTOX

Ester Lovsin Barle's journey from veterinary lecturer in Slovenia to the Global Head of Product Sustainability and Stewardship at Takeda Pharmaceuticals in Switzerland was fueled by her curiosity and passion for continual learning and a desire to help others do the same. "We are never at the end of our learning curve, and it's so important to continue to learn and be open-minded about new solutions, new areas, and new connections because when you do, you never know what solutions you'll find."

"My original education was as a veterinarian, but one of my mentors worked with the pharmaceutical industry and encouraged me to take on a role as an occupational toxicologist." Ester earned a master's degree in toxicology and risk assessment and then established processes to protect worker safety at Lonza and Novartis before joining Takeda.

During the COVID-19 pandemic, she began to contemplate how the pharmaceutical industry was going to look after the global crisis and started trying to determine ways to bring about a more environmentally sustainable future.

"I was trying to understand where the world would be after the pandemic. I saw an opportunity to partner my knowledge of toxicology, chemical compliance, and the regulations that were starting to come out in Europe. I wanted to make sure we did not just focus on one side of the story. Pollution is a big issue, but we also have to be careful about biodiversity and climate change."

"I did an environmental study and used the knowledge I had in this area to create a sustainability by design program for Takeda and then partnered with coworkers to determine how to break the overall program into tangible actions. The sustainability by design program integrates sustainability into the life cycle of the products that we manufacture or develop. Helping build a company culture based on sustainability is very exciting. You see people get excited about their work and being champions of the environment."

"In my role, I also focus on regulatory aspects. My team and I monitor global regulations related to chemical and material compliance, assessing their potential impacts. We proactively integrate these insights and exclude certain chemicals from development to avoid future regulatory issues."

Throughout her career, Ester has relied on ISPE for information and inspiration and is excited to help kick start the new Sustainability Community of Practice (CoP). "When I was working on occupational toxicology, I used ISPE Guidance Documents and information as my north star. They were always very useful and extremely well written. I hoped that one day I would have an opportunity to be able to work with ISPE and generate something meaningful. I'm really happy to have this opportunity as Chair of the new Sustainability CoP. The idea is to provide a venue for professional growth in the sustainability area because it is a part of our future. I'm hoping we'll discuss challenges, discover ways to collaborate, and work to find innovative solutions."

— Marcy Sanford, ISPE Publications Coordinator

Learn more about all of ISPE's CoPs and join one at

ispe.org/Communities-Practice

VOLUNTEER
PROFILE

COMBINATION PRODUCTS COMMUNITY OF PRACTICE CHAIR

JAMES P. WABBY, MHMS

For more than 22 years, James P. Wabby has dedicated his career to quality operations, regulatory compliance, and regulatory affairs pertaining to medical device technology, medicinal delivery platforms, complex generics, companion diagnostics, digital medicine, and combination product areas. In 2017, during one of the biggest regulatory changes within the European Union in over 20 years, James led the EU Medical Device Regulation/In Vitro Diagnostic Regulation project to incorporate the new regulatory requirements. This was done while maintaining the supply of existing products to market and developing new work streams to optimize the global quality management systems for sustainability.

Although he initially thought he would go to medical school to become a cardiovascular surgeon, James became interested in the pharmaceutical industry while working on a master's degree in healthcare law and policy. "I was very interested in product development, clinical research, and the usability of products for patients. Part of the program focused on challenges and opportunities within the healthcare industry from developing products to ensuring treatments are available to the patients in need."

Now as the Head of Global Regulatory Affairs for Combination Products, Devices, and Emerging Technologies at AbbVie, James oversees a department that has grown from five people to 25 people in six years. That department is working to bring products from development into commercialization and then sustain those products in the commercial space for years to come. "Years ago, you had stand-alone devices and stand-alone medicinal products, but now with the growth of precision medicine and the next generation of medicine, the industry has to become more focused on advanced technologies for medicinal delivery which are user-centric."

"The biopharmaceutical industry continues to increase its focus on precision medicine; to match the right medicine to the right patient at the right time. In addition, there will be a focus on developing products that are more user-centric to deliver medicines to address areas of unmet medical needs. One of the challenges we need to focus on is development of a range of user-centric delivery systems to ensure we address the user requirements from the pediatric population to the adult population."

James is also an Adjunct Assistant Professor at University of Southern California School of Pharmacy –Regulatory and Quality Sciences, an international speaker, chair for various symposia, council member of the Drug Information Association (DIA)'s Americas Regional Advisory Council (RAC), a moderator for various global regulatory panel discussions, and an active member of ISPE.

"I am honored to be the Chair for the Combination Products Community of Practice (CoP). We are currently working on providing feedback pertaining to the US Food and Drug Administration draft guidance for essential drug delivery outputs (EDDO) pertaining to devices, platform technologies, and use-related risk analysis (URRA) for drug- and biologic-led combination products. New draft guidance has come out in the past few months, and we are working within the industry cross-functionally to identify areas for clarification."

"ISPE leadership understands the global regulatory landscape within the industry and has given our CoP the ability to collaborate with other CoPs such as the ATMP [advanced therapy medicinal product] CoP to present on a cross-functional panel at the ISPE Annual Meeting & Expo where we explored innovative medical device concepts and products to address unmet medical needs."

— Marcy Sanford, ISPE Publications Coordinator

ISPE Releases New GAMP® Good Practice Guide

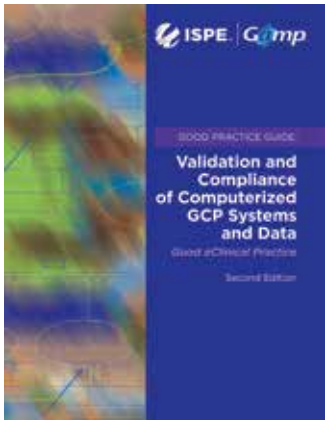
By Marcy Sanford

This summer ISPE released the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data – Good eClinical Practice (Second Edition).*

THE NEED FOR AN UPDATE

Since its publication in 2017, the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data – Good eClinical Practice* has provided users with a robust validation framework to help support the integrity and efficiency of clinical trials. However, advancement and changes in technology, the volume of data collected, and new regulations necessitated an update.

"The first edition provided solid guidance for applying the GAMP principles to clinical systems," said Guide Co-Lead Frank Henrichmann, Senior Executive Consultant, QFINITY. "But GCP is a very dynamic area and is always changing due to technology and what is possible. Then the pandemic blew everything apart because companies that were executing clinical trials had to figure out how to do a clinical trial if patients could no longer come to the clinical site, and there was a need for different technologies and approaches that are now well-established, but these come with new challenges and opportunities."



WHAT'S IN THE NEW EDITION?

"The second edition has been significantly expanded to address these challenges and opportunities," said Guide Co-Lead Maximilian Stroebe, PhD, Senior Manager, Janssen Vaccines and Prevention. "The Guide discusses the increased complexity of hybrid or participant-centric decentralized trials and offers best practices for managing this complexity, which is caused by various factors such as a greater reliance on contractor/subcontractor processes and the use of participant-owned digital health technologies and devices, for example, a smartphone."

Written by subject matter experts in the field and members of the GAMP Community of Practice, the Guide discusses the processes involved in clinical studies. It highlights the unique challenges of collecting data by investigators that is later processed and analyzed by sponsors and/or suppliers. The Guide then provides validation approaches for the varied systems used in each process. Additionally, it offers suggestions for developing common systems applicable to multiple studies to minimize customization while meeting the unique needs of the individual project that is a clinical study.

"Although it has been extensively updated and aligned with current regulatory guidelines and the second edition of the *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems,* the goal of the Guide remains the same: to provide a comprehensive framework that supports effective and efficient quality assurance of computerized systems and electronic data used in GCP environments, thereby safeguarding the rights, safety, and well-being of trial participants while ensuring the credibility and reliability of clinical data," said Guide Co-Lead Oliver Herrmann, Managing Director, QFINITY.

For more information on this and other ISPE Guidance Documents, visit ispe.org/publications/guidance-documents

ISPE Announces ISPE AI®

By Katie LeChase

ISPE recently announced ISPE AI®, an initiative aimed at aiding the pharmaceutical industry in realizing the potential of artificial intelligence (AI). The initiative will include a multifaceted approach to supporting the industry in AI readiness, beginning with the launch of the ISPE Community of Practice (CoP) on AI.

Over time, ISPE will also provide new ISPE Guidance Documents, additional conference sessions, new training courses, and more resources that focus on AI-related planning and implementation.

"Recent advances in AI have brought attention to this rapidly accelerating technological innovation. The launch of this AI CoP is a testament to ISPE's commitment to shaping the future of the pharmaceutical industry," said Thomas Hartman, Past President and CEO of ISPE. "We are acutely aware of the needs and interest areas of our members and recognize the importance of supporting the pharmaceutical industry in the responsible advancement of AI."

ISPE's AI CoP is available for ISPE members to join effective immediately. The new CoP joins ISPE's existing global technical CoPs. Each ISPE Global CoP has a Steering Committee composed of subject matter experts who specialize in each respective CoP topic area. CoP Steering Committees collaborate on ISPE content generation plans, which may include ISPE Guidance Documents, *Pharmaceutical Engineering*® articles, webinars, educational materials, and conference content.

The new AI CoP Steering Committee will address essential areas such as the regulatory aspects of AI, guidance on applications of AI throughout the pharmaceutical life cycle, organizational preparedness for implementation of AI, benchmarking, workforce education and skills development, and organizational impacts. The new CoP will also build upon the endeavors of the ISPE GAMP® Artificial Intelligence/Machine Learning Special Interest Group, and ISPE's Pharma 4.0™ initiatives. These have been actively contributing to the industry's adoption of digitalization strategies and AI/machine learning (ML) technologies.

"As a trusted leader in the pharmaceutical industry, ISPE is uniquely positioned to support this increased focus into the critical area of AI/ML. As with all ISPE CoPs, our AI CoP will aim to identify and provide best practices, interface with regulatory authorities, and share lessons learned as well as emerging case studies to inform effective AI/ML strategy and implementation," said Ben Stevens, Director of CMC Policy and Advocacy with GSK and the ISPE AI CoP Chair.

Existing ISPE members are invited to join the the ISPE AI CoP by selecting "Artificial Intelligence" in the Communities tab in their ISPE profiles. To view the list of existing CoPs, visit ISPE.org/CoP

Katie LeChase, ISPE Director of Communications

Pharmaceutical Engineering® Article Wins 2024 APEX Award

ISPE has been honored with a 2024 APEX Award of Excellence in Writing for "ChatGPT, BARD, and Other Large Language Models Meet Regulated Pharma" by Frederick Blumenthal, Martin Heitmann, Stefan Münch, and Brandi Stockton published in the July/August 2023 issue of *Pharmaceutical Engineering*®.

This marks the fifth consecutive year that *Pharmaceutical Engineering*® has received an APEX Award. The APEX Awards commend excellence in writing, editing, and graphics across a wide range of communications in nonprofit and for-profit publishing and communications organizations. Awards of Excellence recognize exceptional entries in 100 subcategories. ISPE's article was recognized in the Writing/Topics – Artificial Intelligence (AI)/Robotics subcategory.

"ChatGPT, BARD, and Other Large Language Models Meet Regulated Pharma" explores the possibility of applying artificial intelligence large language model tools in a safety-critical, product-related environment and whether the technology could be helpful in regulated areas of the pharmaceutical industry. The authors examine the issue from quality, risk, and efficiency perspectives and present ways these tools can shift thinking around validation and quality assurance.

ISPE Announces Sustainability Community of Practice

By Katie LeChase

Governments around the world have made international commitments to reduce their environmental impact and protect nature. Policy frameworks have been established to facilitate and drive progress against agreed-upon targets. These directly impact end-to-end activities for the biopharmaceutical, pharmaceutical, and medical device sectors, including research and development, manufacturing, commercial activities, and extended supply chains and logistics.

The supplier base and contract development and manufacturing landscape are also heavily impacted, as both significantly affect the product footprint on environmental, social, and governance.

ISPE recently launched a Community of Practice (CoP) on Sustainability. The new Sustainability CoP will provide ISPE members with:

- A community focused on the topic of sustainability in the pharmaceutical industry and its end-to-end value chains
- A forum to help members problem solve and engage in networking, through ISPE Engage sites and other communication methods
- The ability to innovate and create breakthrough ideas, knowledge, and practices to improve the practice of sustainability
- ISPE content on sustainability topics and best practices
- A way for regulators and legislative bodies to provide guidance, harmonization, and industry comment, when applicable
- Alignment with the Science Based Targets initiative (SBTi) and Sustainable Market initiative to bring together stakeholders

The Sustainability CoP will be holistic, focusing on sustainability and responsibility in all facets across the product life cycle. These include:

- Energy and carbon reduction
- Waste and packaging reduction
- Green chemistry
- Process efficiency
- Research and development efficiency
- Water usage and impacts
- Product stewardship, including sustainability and relevant legislative aspects
- Impacts on organization and culture
- Considerations for future states enabled by digital transformation and Pharma 4.0™ concepts that impact sustainability goals

Members of the Sustainability CoP will aim to bring forward solutions for the industry's unique challenges related to sustainability, gathering insights and engaging in data as well as knowledge-sharing with the pharmaceutical community.

"Environmental sustainability is vital for protecting the well-being of both people and the planet, ensuring a healthier future for generations to come. We believe that as a nonprofit and given the scope and caliber of its robust network of 22,000 members, which includes pharmaceutical companies and their suppliers, ISPE is uniquely positioned to facilitate one unified and aligned approach to help fulfill our industrywide commitments to sustainability," said Ester Lovsin Barle, Takeda, Head of Product Sustainability and Stewardship and the ISPE Sustainability CoP Chair. "With the addition of this new CoP, we plan to identify and bring forth best practices, define maturity levels, liaise with regulatory and law-making bodies, and communicate valuable lessons learned and case studies with relevant stakeholders—all while maintaining focus on quality and safety."

Members of the Sustainability CoP will aim to bring forward solutions for the industry's unique challenges related to sustainability, gathering insights and engaging in data as well as knowledge-sharing with the pharmaceutical community. The new CoP offers members the opportunity to collaborate with existing CoPs in the ISPE community to deliver solutions around sustainability, leveraging existing resources such as the *ISPE Baseline Guide Volume 6: Biomanufacturing Facilities (3rd Edition)* and exploring pertinent topics like the influence on the reduction of energy consumption in facility design.

Existing ISPE members are invited to join the Sustainability CoP by selecting the Sustainability CoP in their ISPE profiles. To view the list of existing CoPs, visit ISPE.org/CoP

Japan Affiliate Emerging Leaders Activities

By Hiroyuki Miyazaki

The ISPE Japan Affiliate held the "Young Professionals Seminar" to support the growth of recent graduates. Starting on 14 July 2023, this seminar spanned four sessions and took place at the Nihonbashi Life Science Building and Taiyo Pharma Tech Takatsuki Plant. Led by ISPE Emerging Leaders, the seminar aimed to cultivate the next generation of leaders in the pharmaceutical industry.

KEY FEATURES OF THE SEMINAR

This seminar offered a comprehensive educational program specifically designed for students and recent graduates. Each session covered essential topics, such as the basics of commissioning and qualification, aseptic isolators, and single-use bioreactor systems. Through practical group work and homework assignments, students and recent graduates engaged in creating user requirement specifications and conducting risk assessments.

OBJECTIVES AND OUTCOMES

This seminar, planned and operated by Emerging Leaders, is dedicated to nurturing future leaders in the pharmaceutical industry. Students and recent graduates not only acquire theoretical knowledge, but also develop practical skills through group work and homework, resulting in tangible deliverables. This approach ensures all participants become immediate assets in the workplace, equipped with deep understanding and hands-on experience.

Guest speakers from various system companies were invited to each session to lecture on the latest technological trends and practical case studies. This enabled attendees to learn directly from industry experts at the forefront of their fields, greatly benefiting their career development.

Throughout the event, students and recent graduates presented their cumulative learning; this was especially true in the fourth session's Hackathon. This presentation session allowed the participants to reflect on their growth and share insights with peers and instructors. Additionally, the visit to the Taiyo Pharma Tech Takatsuki Plant offered a valuable opportunity to experience the actual manufacturing environment, bridging theory and practice.

The Japan Hackathon 2023 Emerging Leaders Executive Committee

The Japan Hackathon 2023 Emerging Leaders Executive Committee included the following individuals:

- Tetsuro Hatsuoka, Kajima Corporation
- Nobumitsu Kobayashi, Dalton Corporation
- Hiroyuki Miyazaki, Takeda Pharmaceutical Company Limited
- Mayuko Shimokawa, Taiyo Pharmatech Co., LTD
- Takanori Tatezawa, Daiichi Jitsugyo Co., LTD
- Emiko Yamada, Mitsubishi Chemical Engineering Corporation

SEMINAR PURPOSE, IMPLEMENTATION, AND EVALUATION

From the Emerging Leader perspective, this seminar not only aimed to educate students and recent graduates, but also to foster leadership within the Emerging Leader community. By taking the initiative to plan and execute this seminar, Emerging Leader members cultivated essential leadership skills and expanded their professional networks through collaboration with the Board of Directors and Communities of Practice. This collaborative approach strengthened interpersonal relationships within ISPE and positioned Emerging Leaders as proactive leaders ready to tackle future challenges.

The planning and execution process itself will serve as a learning platform for Emerging Leaders, enhancing their project management and organizational skills. The interaction with industry experts and peers during the seminar will contribute to their professional growth and leadership development.

A PLATFORM FOR FUTURE LEADERS

The ISPE Japan Affiliate's seminar, led by Emerging Leaders, provides a valuable platform for the personal and professional growth of ISPE students and recent graduates. As young professionals strive to become future leaders in the pharmaceutical industry, their journey of merging theory with practice is an inspiring vision for the entire industry. This seminar is expected to play a crucial role in shaping the careers of students and recent graduates and fostering the next generation of industry leaders.

Hiroyuki Miyazaki is the Engineering Services Manager at the Engineering Osaka Plant GMS Japan for Takeda Pharmaceuticals Company Limited. He joined ISPE in 2023.

In Memoriam: Antonio (Tony) R. Moreira, PhD, and James (Jim) O'Brien

We lost two members of the ISPE family this year, both of whom played instrumental roles in shaping the pharmaceutical industry and ISPE.

TONY R. MOREIRA, PhD

Tony R. Moreira was an instrumental force for ISPE for over 20 years. He served as a member of the ISPE International Board of Directors and was the founding President of the ISPE Chesapeake Bay Area Chapter. He was also Board Chair of the ISPE Foundation. His tenure spanned from 2020 until his passing.

Tony dedicated his career to educating and helping others. He worked for over 30 years in the biopharmaceutical sector and nearly 10 years in management positions in the private sector. He served as a mentor to many through his roles in academia and the pharmaceutical industry. He regularly met with ISPE Foundation Professional Development Grant recipients at conferences and events, providing them with guidance, expert counsel, and support.

Tony was the co-editor of several books and a frequent speaker at national and international conferences. He also presented short courses in biotechnology topics for industry and regulatory agencies. Tony was published in many peer-reviewed publications and was an author of many articles for *Pharmaceutical Engineering®* and the iSpeak blog.

Before his passing, Tony served as the Vice Provost for Academic Affairs at the University of Maryland, Baltimore County. He was responsible for academic-affairs-related matters within the Office of the Provost and maintained an active teaching and research program in bioprocessing, regulatory science, and engineering.

Tony graduated with a BS in chemical engineering from the University of Oporto in his native Portugal and an MS and PhD in chemical and biochemical engineering from the University of Pennsylvania.

"We would like to express our sincere gratitude for Tony's contributions to ISPE, the ISPE Foundation, the pharmaceutical industry, academia, and the many lives he has positively impacted. We would also like to share our condolences to all who have been honored with the great privilege of knowing Tony," said Thomas Hartman, Past President and CEO of ISPE.

JIM O'BRIEN

Jim O'Brien was a founding member of ISPE and a luminary in the field of pharmaceutical engineering. Jim was a recognized expert in the design and engineering of pharmaceutical facilities. His profound influence has shaped our industry.

As an accomplished leader, Jim managed multimillion-dollar projects, consistently delivering state-of-the-art research facilities on time and within budget. His expertise in applying engineering concepts to laboratories was unparalleled, with extensive project management experience in both manufacturing and research facilities for the pharmaceutical and cosmetic industries. His global experience, serving Fortune 500 companies across the US, South America, Canada, Europe, and Asia, was a testament to his vast knowledge and impact.

Since joining Merck & Co., Inc. in the mid-1980s, Jim held several key positions, including Senior Facilities Project Engineer, Manager of Laboratory and Operational Projects, and Senior Project Engineer. At Merck, he led cross-functional teams in the Research and Manufacturing Division, overseeing projects from concept to commissioning and validation. His meticulous approach to project documentation, execution plans, funding requests, and design development ensured the successful completion of numerous facilities.

Jim earned his BS in mechanical engineering from the New Jersey Institute of Technology. His leadership within ISPE was exemplary; he served as Vice President, Executive Vice President, and President of the ISPE New Jersey Chapter. He then remained an influential figure as Chair of ISPE's International Task Team for the development of the worldwide laboratory guide. Jim also served as the ISPE International Board of Director Chair from 1982–1983.

"Jim's legacy is one of dedication, innovation, and excellence. He was not only a mentor and leader but also an inspiration to many in our community. As we remember Jim, we celebrate his remarkable contributions to the field and his lasting impact on ISPE," said Hartman.

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NET-ZERO MANUFACTURING FACILITIES:
Obstacles and Benefits

By Matt White, PE

The decision to pursue net-zero facility design in manufacturing is complicated. There are significant challenges related to initial project costs, physical space constraints, and project site considerations—but also substantive benefits from operational savings, environmental impact, building brand trust, and working toward a more sustainable future.

Projects can implore creative strategies to navigate challenges, and the people involved in projects can take steps to break free of a traditional project management approach. This approach focuses solely on schedule and costs to adapt a more collaborative process that places environmental impact above other factors. Though net zero is an objective and quantifiable metric, organizations should still strive to adapt as many of these practices as possible into their project delivery model, even if reaching net zero may not be feasible for a given project. With manufacturing in the US continuing to grow at an astounding rate, every project where we can ask the hard questions early and integrate some of these approaches makes critical progress toward a more sustainable future for the manufacturing industry at large.

BACKGROUND

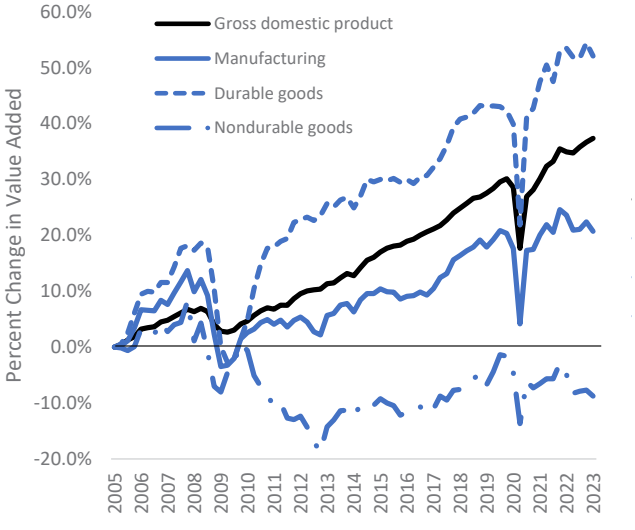
The current social and industrial landscape is dominated by trends that inform organizational policies and strategic planning. "Net-zero energy" has become a trendy phase, but is it truly feasible for large-scale pharmaceutical manufacturing facilities? As illustrated in Figure 1, construction spend on manufacturing facilities has nearly doubled in the United States since June 2021, according to the Department of the Treasury [1]. The two primary drivers of that surge domestically are semiconductors and pharmaceuticals.

The US has an estimated 14.8 billion square feet (sq. ft.) of industrial and manufacturing space [2], roughly 15.4% of the total square footage of commercial real estate. Furthermore, the total commercial square footage in the US is expected to grow to 124.6 billion by 2050 [3], which, if the ratio of industrial square footage continues to hold, implies we will build 4.4 billion sq. ft. of new industrial and manufacturing space in the next 25 years. If those new manufacturing facilities use our current power grid with no significant changes or considerations for sustainable or on-site energy generation, we will have to plant a forest the size of the state of Vermont every year to offset carbon emissions for the new manufacturing buildings alone [4–7].

Constructing facilities to use net-zero energy is one solution to this issue. Net-zero energy usage, in the simplest terms, is creating a facility or campus that generates at least as much energy as it consumes. Although the concept can be great in theory, it becomes more difficult when you focus on manufacturing environments, as well as other sectors with high power usage densities.

This article features a case study examining the design of a fictional 200,000 sq. ft. manufacturing facility with a baseline

Figure 1: US manufacturing value-added change [8].



energy use intensity of 150 kilo British thermal units (kBTU) per square foot per year. We are going to consider cost, space, geotechnical, and other considerations of pursuing net-zero usage for the facility, as well as energy savings, cost savings, and environmental impact of the decision throughout the first 15 years of operation.

NET-ZERO DESIGN CHALLENGES

Cost

The largest challenge for building a net-zero facility is cost. For manufacturing projects, you should assume that targeting net-zero energy usage is going to result in 15%–25% higher initial projects costs than a similar project not pursuing that goal. The additional cost comes from design and procurement of energy generation equipment. This includes solar panels or wind turbines, as well as upgrading building systems like heating, ventilation, and air conditioning (HVAC); plumbing; electrical; and even process equipment to higher efficiency models to minimize energy usage.

One of the most difficult cost-related obstacles to overcome is adapting your criteria for procurement to treat cost as secondary to efficiency, performance, and the environmental impact of the equipment. Because this shift in approach is nontraditional and requires organizational buy-in at every level of a team, communicating the approach and the goal for net zero early is key.

There are also several other avenues to consider that can help mitigate the higher project costs. First, involve site utility providers in the design process as early as possible and communicate the net-zero goal with them. Utility providers have a vested interest in making efficient projects, and they can often work with the design team to create custom grants for things like detailed energy modeling or covering the cost difference between a certain piece of building or process equipment and a more efficient model. Although this does add complexity and another stakeholder in the design process, it typically adds another valuable perspective to the table while helping reduce costs significantly.

Second, if the project and operational budget for the facility are structured such that initial project costs place net zero out of reach, but monthly energy cost is considered (which would be approximately zero if net zero was achieved), a project could choose to go into operation without the power generation equipment installed day one, and partner with an energy services company (ESCO) to install power generation equipment over the course of the first few years of operation.

This doesn't necessarily save costs, but it does shift the cost from the capital project into the operational budget for the facility and splits up the cost over several years. Lastly, it could also be beneficial to engage an engineering and accounting firm to support the project. Although these hybrid firms are a rather recent addition to project landscapes, they can help identify tax credits and other government incentive programs that help put the project within reach.

Space

The next hurdle net-zero projects face, especially for high power density uses like manufacturing, is having the physical space for power-generating equipment. In the given example, the 200,000 sq. ft. building would need roughly 244,000 sq. ft. of solar panels to offset that energy usage, meaning the solar array couldn't physically be housed on a traditional rooftop. Instead, this may require solar panel–covered entryways for the building, or to have a solar field elsewhere on the site for additional space. Obviously, having that many solar panels on the roof adds a significant structural load for the building as well, which can be another factor to consider that can add cost. If the project pursues wind turbines or a solar field, the space requirements should be considered, as well as how that will interface with parking and other logistical use requirements. It may impact the lot size needed for the project, even if the footprint of the building itself is already known.

Site Restrictions

One key method to save massive energy in new facilities is to use ground loop heating and cooling systems, both for HVAC and process loads, where applicable. However, not every project site is a good fit for these systems. Some sites have combinations of rock and soil types that would not be feasible to install a ground loop system in, and other sites might have soil compositions with poor thermal properties, where the full benefits of a ground loop system cannot be realized. Geotechnical testing and inspections on prospective project sites can confirm if the site will utilize a ground loop system effectively before moving forward with the land procurement and project delivery process.

Conviction and Accountability

As a net-zero project progresses, there will be a series of key decisions that could throw the sustainability goal off course. Perhaps an equipment vendor comes back with a significant lead time difference for a more efficient piece of equipment that may impact the project schedule, or the solar array size must get larger because the solar irradiance values for the project site are not as good as the team thought they would be. When these key decisions present themselves, it can be easy to revert to the traditional project management mindset and make decisions based on schedule and cost that jeopardize the net-zero goal. One effective method to combat this is to make the net-zero goal public once the organization and the project team agree on the direction. This adds a layer of environmental and societal accountability to the decision-making process.

NET-ZERO DESIGN BENEFITS

Energy Cost Savings

Once we navigate all the challenges, our example project will be set up to generate at least 8.8 million kilowatts (kW) of power every year. At the average US electricity rate [9], we will save just shy of US $1.1 million in energy costs every calendar year. Over the course

Any amount of equipment efficiencies or on-site power generation goes a long way to reducing the environmental impact.

of the first 15 years of facility operation, this building would save about US $16.3 million in grid energy costs.

Environmental Impact

By designing this one building as net zero, we offset carbon emissions over the first 15 years of operation equivalent to planting a 700-acre forest. Every decision and every project where we prioritize net-zero thinking and have a bias for action works toward a more sustainable future.

Impact on Corporate Identity and Brand Trust

Over 70% of Americans say that sustainability is more important to them than ever before and it is a key consideration factor when selecting products or services [10]. Designing net-zero facilities works toward making climate action pledges and corporate goals into realities and builds trust with current employees and clients. Investing in a sustainable world-class facility can have a measurable return on investment in sales.

Energy Independence

Energy costs have continued to rise across the US and globally over the last decade, and in recent years has even approached 10%–15% increases year over year, surpassing typical market inflation and consumer cost index increases [11]. Rising energy costs and dependence on an aging energy grid are legitimate risks for businesses—especially in manufacturing, where process uptime is a critical success metric.

CONCLUSION

Designing and building net-zero manufacturing facilities may not always be possible; there are real challenges with initial cost and site limitations on space or geotechnical properties. However, as grid energy costs rise and sustainability contributes more to employment or product choices, the return on investment for pursuing net-zero facilities is going to become more attractive. Focusing on net-zero design can also set projects up to more easily pursue and achieve other key sustainability processes, like US Green Building Council LEED or the Living Building Challenge.

One other key shortcoming with how we think about net-zero design is that it is an all-or-nothing pursuit. This typically happens after the results of a feasibility study come in. If those results look like achieving net zero won't be possible, it is easy to cast the idea and those design principles aside. Any amount of equipment efficiencies or on-site power generation we can add to projects goes a long way to reducing the environmental impact of the project and setting the stage for a more sustainable future. The following analogy comes to mind. If someone was considering becoming a runner and a feasibility analysis on "could I run a marathon?" came back negatively, the logical response wouldn't be to not run at all. The better response would be to start making a training program, beginning with running as far as it is safe and productive to do so.

When we move past the challenges, there are also very substantive, intrinsic organizational and environmental benefits. Looking ahead to building 4.4 billion sq. ft. of new manufacturing space by 2050, it is our social responsibility to ask hard questions about what we can do to work toward net zero in those facilities. At the same time, we should ask how we can continue to adopt project delivery processes to place a larger focus on environmental impact.

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About the author

Matt White, PE, is Regional Director for the Washington team at Performance Validation and a highly accomplished facilities professional. As Regional Director, Matt leads the facilities team, which focuses on driving successful outcomes for sustainability initiatives in new construction projects and major remodels. His passion is coaching his team on the importance of understanding sustainability initiatives from ideation to execution to understand their role in projects and provide practical advice to clients. Matt has worked on the design and commissioning scopes of over 30 projects that have pursued net-zero operation, LEED certification, and other key sustainability initiatives. He has a degree in mechanical engineering from Ohio Northern University and is a registered professional engineer.

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SINGLE-USE TECHNOLOGY WASTE in Manufacturing Operations

By Cristina Van Loy, PhD, Pietro Perrone, PhD, PE, Adam Goldstein, Andrew Sinclair, CEng, FIChemE, FREng, Eric Langer, Treasa Rohrer, Katell Mignot, and Javier Lozano

Single-use products used in the production of biologics provide flexibility that was unimaginable a few years ago. The implementation of single-use technology (SUT) in manufacturing operations has accelerated due to reduced risk, flexible process equipment adjustments, and lower capital cost. The widespread use of this technology has raised questions about its impact on the environment due to the shift from traditional operational utilities (heat, water, chemicals) to single-use plastic products.

The introduction of SUT in biologics production has raised questions concerning the proper handling of SUT consumables once they have been used to create valuable therapeutics [1]. This topic has been researched from various perspectives; research shows that SUT systems can have a lower environmental impact when compared to traditional systems, which require high-purity water and heat to clean and sterilize reusable materials [1].

However, although SUT systems reduce the carbon footprint from energy use, they increase the quantity of plastic materials used. To address the plastic use, we can look at ways to minimize utilization, but ultimately there will be waste that requires disposal.

There are significant challenges for waste disposal and handling at the manufacturing plant level:

- Separation of different types of plastics (recyclable and noncompliant materials)
- Management and waste of cardboard and associated dunnage
- Development of an inactivation procedure if considered regulated medical waste (chemical or heat)
- Staging of materials as process waste in the suites and in holding areas outside of manufacturing
- Limited options for local waste collection or hauling to potential recycling facilities

Even though the handling of plastic waste is already incorporated into the typical manufacturing process, the quantity increases significantly in a manufacturing operation when SUT is implemented. What is the industry currently doing to handle this increased plastic waste and is there potential for improvement? These are the main topics that initiated this investigation by the ISPE Disposables/Single-Use Community of Practice (CoP).

A focus team in the ISPE Disposables/Single-Use CoP conducted in-depth surveys of biopharmaceutical manufacturers to assess the importance of dealing with SUT waste materials and the respondents' sensitivity to reducing the waste's impact on the environment. Although over 40 people responded, not all of them replied to every question. The purpose was to obtain feedback, in an area where there is none, from users to help inform others in the industry and guide future work.

SURVEY DETAILS

Size of Participating Organizations

The participants in the survey included organizations of various sizes. These organizations ranged from small firms (up to 100 employees) to larger companies (> 1,000 employees). The results were categorized in these four size segments: companies with < 100 employee, 101–300 employees, 301–1,000 employees, and > 1,000 employees.

Regions of Participating Organizations

The respondents represented companies across the globe. Although many companies operate in more than one region, respondents that identified a specific area included companies in the regions classified in Figure 1.

TOPICS DISCUSSED

The survey covered two broad areas. The first area dealt with current practices for the disposal of plastic waste. The second dealt with options for improving the outcome with the disposal of the SUT assemblies. The results shown are presented accordingly in this article.

SURVEY RESULTS

Quantity of Waste Produced

Participants were asked to estimate the total weight of the single-use assembly waste being generated at their facility. The total weight indicated greatly varied, with one-third of respondents estimating roughly 200 kilograms (kg)/month, one-third of respondents

estimating up to 1,000 kg/month, and one-third of respondents representing larger users and estimating > 1,000 kg/month. The large variations seen are impacted by the size of the plant, the level of integration of single-use products, and the throughput of the single-use assembly materials.

Disassembly of Single-Use Assemblies

Approximately one-third of the respondents required the disassembly of SUT items. If a facility is employing SUT recycling, it may be necessary to separate out resin materials to facilitate the sorting of different materials of construction. For those that send their single-use waste out for incineration, environmental policies can restrict the burning of some types of plastics. For 60% of respondents, laboratory and operations staff accomplish disassembly, but 40% of respondents noted their janitorial staff handle these activities.

The removal of accessory parts before disposal involves significant time and manual effort. It can also lead to environmental health and safety risks to the operators. The additional work and risk that result from disassembly, with only minimal benefits, may account for the significant percentage of respondents (63%) that simply dispose without disassembly.

The majority of what is removed from single-use assemblies appears to be metallic, including clamps and metal components. Of the respondents, 23% mention both categories (plastics and metals; multiple responses were permitted). The study did not indicate whether plastic or metal clamps were being removed before disposing of the SUT items. Clamps may be removed to facilitate the breakdown of assemblies or allow incineration/energy co-generation. Other components removed include PVC, various types of tubing (making up 17% of mentions each), and filters (12% of mentions). Additional components removed from the assemblies include sensors, pumps, and rigid plastic parts.

Current Disposal Practices

Over 60% of participants currently use incineration (some with energy capture) as the major disposal method for single-use assemblies. Nearly 30% of the end users dispose of SUT via traditional landfilling, and less than 15% use any form of chemical or mechanical recycling (note that multiple responses were permitted) (see Figure 2). These responses suggest that there is a large opportunity (> 45%) for alternative recycling or sustainable actions by the end users.

Handling of Biological and Regulated Medical Waste

A common challenge that end users face with biopharmaceutical waste is the mix of applications that result in both biological and regulated medical waste and nonhazardous waste. This can partially dictate some of the options for the potential recycling of plastic waste. Some organizations have established processes to handle and decontaminate waste, whereas others may not want to spend the extra time and resources to do so and dispose of the waste through regulated waste channels.

Figure 1: Regions of survey respondents.

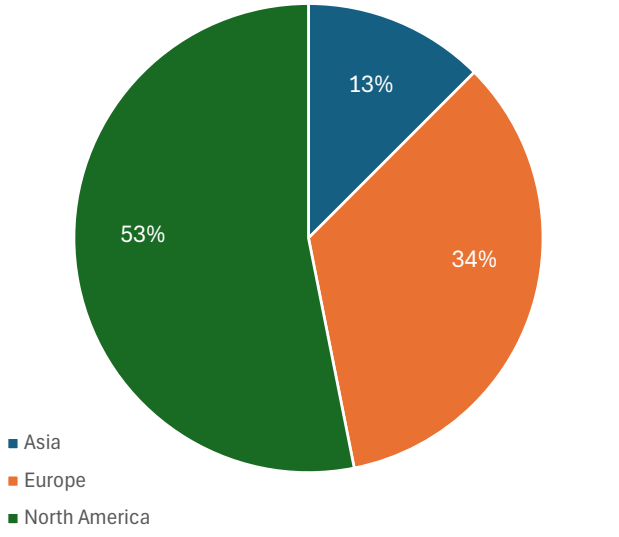
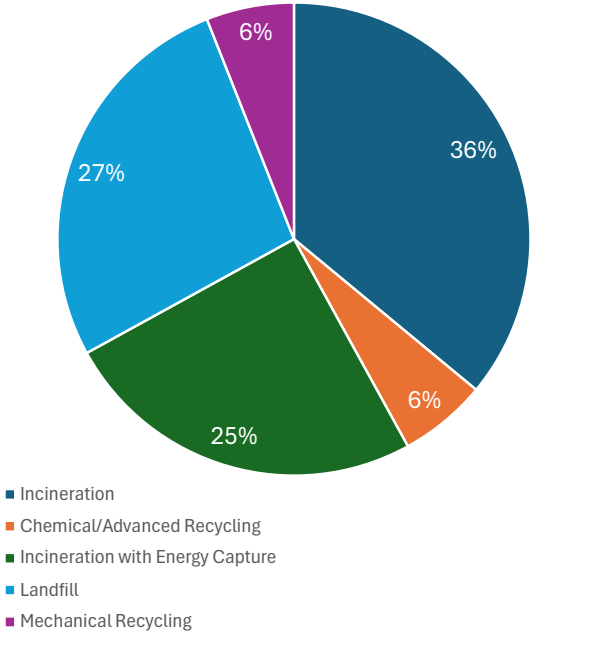


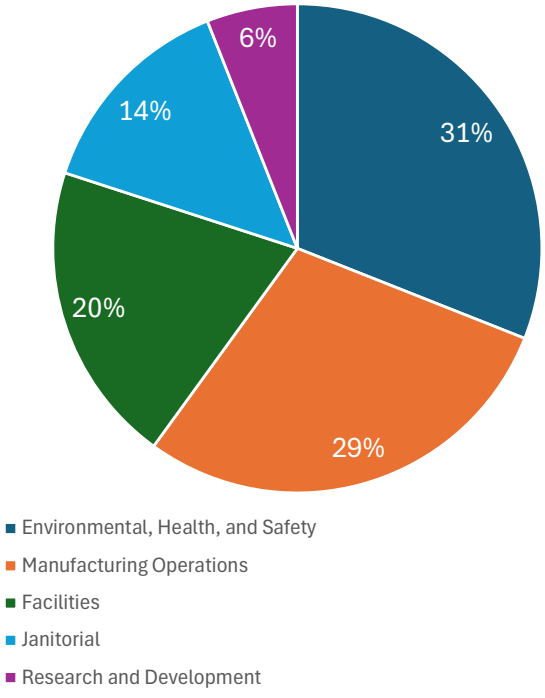
Figure 2: Current methods of disposal of plastic waste.



We asked survey participants if the single-use assembly waste at their facilities is considered nonhazardous or biological and regulated medical waste after use. Approximately 38% of respondents indicated that all single-use assembly waste is considered biological or regulated medical waste, 23% indicated it is all nonhazardous waste, and approximately 38% indicated they have a mix of both. For those that indicated both, nearly 50% of the waste is estimated to be nonhazardous.

For the biological and regulated medical waste created, 41% of respondents sterilize the single-use assemblies after

Figure 3: Function responsible for managing waste.



use. Various methods are used for decontamination, including the use of on-site heat decontamination equipment (53% of mentions), on-site chemical decontamination (33% of mentions), and third-party removal or decontamination (14% of mentions). Decontamination prior to disposal can decrease the costs to dispose the waste by reducing the need to handle it as biological or regulated medical waste. Decontamination may also offer more opportunities to recycle.

The methods used for decontamination are varied and the impact needs to be assessed on a case-by-case basis. For example, steam-based techniques are routinely used to treat single-use materials. Although additional costs are required to purchase and operate the machines, these costs are offset by the large reduction in the volume of biological and regulated medical waste. This reduces subsequent transport and processing costs and creates potential opportunities for recycling. This is an area that needs further investigation and analysis.

Function Responsible for Managing Waste

Managing waste at the site level can be complex, time intensive, and a challenge with regard to storage space, logistics flows, and safety considerations.

Waste from single-use assemblies results from at least three different areas:

- Packaging waste (polystyrene; plastic bubble wrap and film; cardboard; miscellaneous straps; and adhesive tape)
- The consumable bioprocess container or tubing set being used in the process
- Inactivated waste from decontamination, including the melted single-use assembly from heat inactivation (autoclaving), bleach use, base, or other inactivation solutions

The specific function within an organization that handles each of the previously mentioned waste streams at a typical manufacturing site can vary greatly depending on the waste stream and how the facilities' duties are divided (see Figure 3). The survey results indicated that approximately 60% of the handling is performed by manufacturing operations and environmental, health, and safety roles—accounting for the highest level of waste management. Only 20% of the handling was performed by facilities teams, with another 20% of the handling being performed by janitorial and research and development functions.

A total of 42% of the respondents selected more than one function, showing that there is a large discrepancy on how, and by whom, waste is handled, and that there are opportunities to streamline the processes.

Increasing Process Efficiency

Many single-use advocates and end user decision-makers consider the current methods for the disposal of biological single-use assemblies to be unsustainable and less than desirable. Research has shown that most end users feel something better can and should be done [2–3]. More ecological ways exist to transfer the used products out of the production line and into a process that minimizes costs and environmental impact. The survey results confirm the generally held view that current methods are inadequate and that there is a lack of more acceptable options.

Many of the respondents, comprising organizations in all regions and of a variety of sizes, indicated that their organizations have established goals for environmental sustainability and are committed to improving their practices. (Note that more than one option could be selected.)

- Almost half (49%) have a corporate sustainability waste goal
- Nearly half (46%) have initiatives focused on reducing single-use assembly waste
- Over half (52%) have initiatives for recycling or better end-of-life management of single-use assemblies
- Approximately one-third (27%) have goals or initiatives for all three of the previously listed objectives

Improving Disposal of SUT Assemblies

The great news for the industry is that most survey respondents support becoming more actively engaged in effective end-of-life management solutions. From survey responses, the preferred methods of disposal for single-use assemblies were incineration with energy capture, mechanical recycling, and chemical recycling. (Note that more than one option could be selected.)

- 74% selected recycling, chemical, and/or mechanical
- 42% selected incineration with energy capture
- 18% selected incineration without energy capture
- 5% selected landfill

Overall, most respondents are looking to dispose of single-use assembly waste more sustainably, with chemical and mechanical recycling being top choices. There are currently limited options for recycling SUT materials, but increased use of SUT products in the industry can increase the available options.

There are potential opportunities for landfill avoidance through waste to energy (incineration), mechanical recycling (e.g., conversion to plastic lumber) [4], and chemical recycling (chemical breakdown of molecules to create inputs for plastic resin manufacturing).

Recycling requires one or more steps to support rerouting waste compared to landfill disposal. However, 92% (35 of 38) of respondents indicated they are willing to take additional actions in handling single-use materials to allow for better end-of-life management. If better end-of-life management were available, approximately half of the respondents would be willing to sort packaging separately (55% of mentions), remove metal components (50% of mentions), and/or decontaminate single-use assemblies (47% of mentions).

Additionally, 42% of respondents would be willing to remove tubing from single-use assemblies. Eight percent of respondents suggested they would be willing to take the extra step to sort plastic types separately. A low percentage of respondents (8%) indicated they would not be willing to carry out any of the actions listed. Note that more than one option could be selected and 53% of respondents selected two or more options.

Most respondents would be willing to take action to handle the single-use assembly waste to enable more sustainable disposal options. Sorting of packaging materials is one of the simpler actions that could be easily adopted. Removal of specific components within the single-use assemblies requires more labor and could be more feasible if changes in product design allowed for the easy removal of specific components. Decontamination also requires more labor, but has benefits in reducing the volume of biological and regulated medical waste.

Partnering with Suppliers

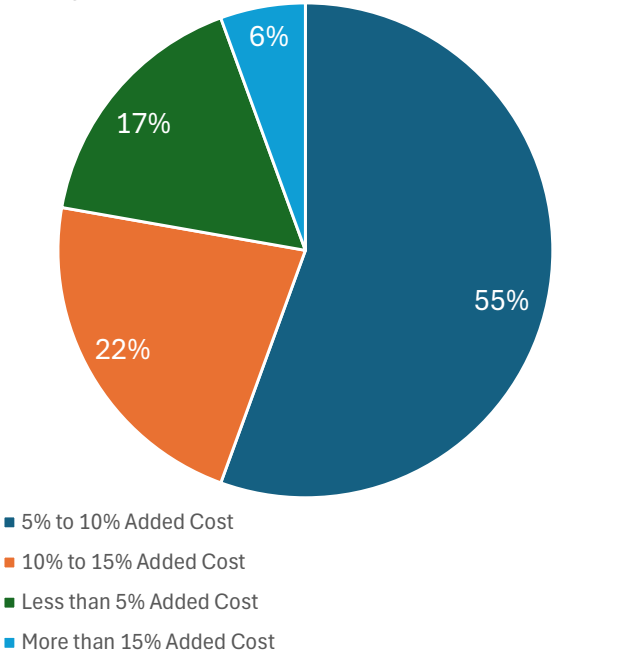
Survey results suggest that product suppliers could impact end-of-life outcomes, with 64% of respondents indicating they would pay them a premium price for better end-of-life management. Figure 4 shows how much added cost the respondents that indicated they would pay a premium price would consider acceptable:

The data shows that over half of the respondents would be willing to pay a small premium for the products they purchase for more sustainable disposal options. Purchasing cost sensitivities can impact the decision to choose a more sustainable product, but looking more holistically at the total product life cycle cost may show a cost benefit if disposal impacts are reduced.

Survey participants were asked to rank various potential supplier offerings for better end-of-life management of single-use assemblies. The top three ranked options were:

1. Provide a third-party recycling company that can offer recycling and transport at the same or lower cost than current disposal method
2. Optimize packaging to reduce packaging waste
3. Add to product cost for end-of-life management but with a more environmentally sustainable solution for disposal

Figure 4: Acceptable upcharge for plastic waste that is easier to manage.



If suppliers improved the single-use assembly design for better end-of-life management, most users would consider them for their processes. Eighty-five percent of respondents would consider purchasing the improved designs for new and existing processes. Of these, 59% would consider replacing assemblies for existing processes.

A majority of respondents (81%) also indicated that their organizations would dedicate additional resources to support improved end-of-life management. An additional 10 hours a week was considered acceptable for 78% of respondents. Survey respondents provided the following suggestions for how suppliers can help improve end-of-life management of single-use materials:

- Provide more information on options and approaches
- Design the assemblies to be easily disassembled
- Reduce the extent of single-use assemblies by using reusable systems
- Take back used components and systems

Other comments are aligned to approaches for recycling. This includes an increase in thermoplastics for melting and reuse and chemical and biological approaches to recycling. It is likely that the survey is self-selecting, or that those that have a strong interest in this area have responded. It is encouraging that those that did respond are keen to actively take part in improving end-of-life management.

The survey respondents all have a strong commitment to recycling using internal resources. Further, users are open to incorporating innovative designs for components and systems that ease end-of-life management.

CONCLUSION

The survey research shows that collaboration and partnerships are essential factors to improve the management of SUT waste:

- For manufacturers: Change designs to facilitate easier recycling and disassembly at end of life, optimize and reduce packaging waste, and provide end-of-life solutions.
- For end users: Dedicate resource time to decontaminate and remove parts of the single-use assemblies for recycling.
- For recyclers: Partner with suppliers to provide design recommendations for recyclable products and to conduct feasibility for current design recyclability.

Organizations aim to make their operations sustainable. However, with increased SUT use, the bioprocessing industry is worried about the management of waste and the environmental impact of single-use products. It is evident from the responses in this survey that end users feel that the current waste treatment methods are insufficient and require improvement.

The survey results provide direction that requires industry collaboration. There is a need to evaluate which of the identified solutions offers the greatest potential for improvements. In addition, we may gain insights to further solutions by observing how other industries approach the issue of SUT waste and evaluate whether there are any viable options for the biopharmaceutical industry.

Acknowledgments

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Additional resources

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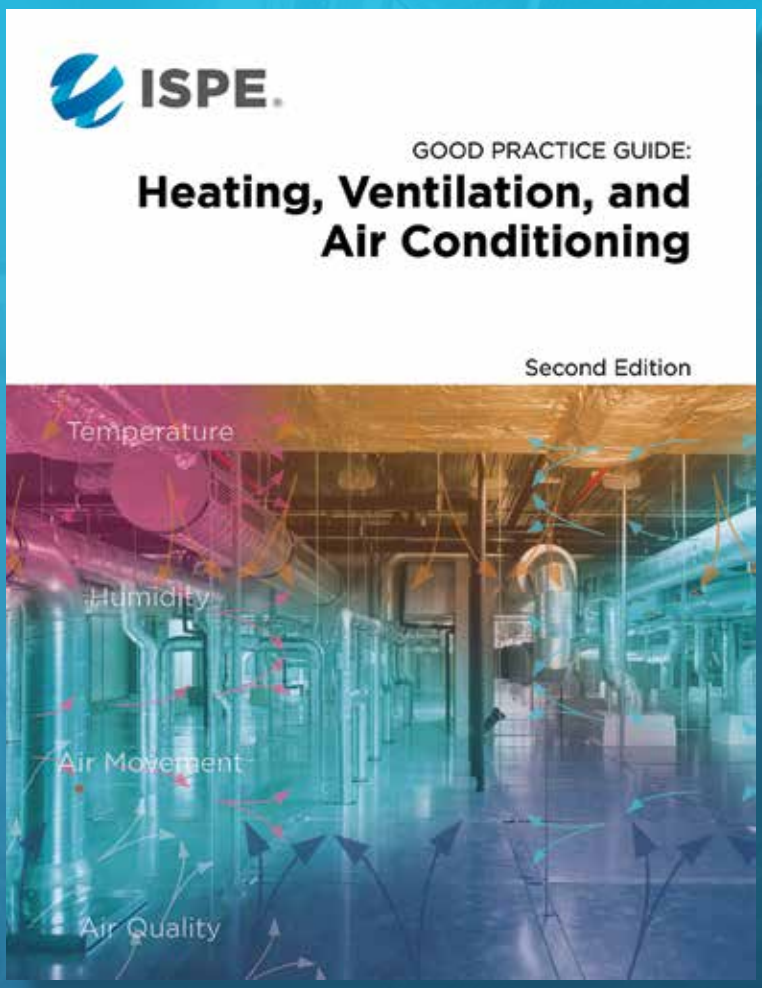
OPTIMIZE YOUR FACILITY'S PERFORMANCE

KEY HIGHLIGHTS:

- Improved HVAC design strategies to enhance system performance, maintain compliance, and protect product quality
- Energy efficiency optimization with strategies that reduce consumption and support sustainability initiatives
- Tailored system solutions to meet specific facility needs and safeguard product safety through precise environmental controls



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SETTING NET-ZERO TARGETS:
Tangible Benefits of Sustainability

By Aoife Kelly, Brian Frymyer, PhD, and Ankur K. Shah

Many organizations are on the right path to sustainability, but more can still be done—especially for setting and meeting net-zero targets. Although a commitment to net-zero operations is important for all industries, it's particularly necessary for the pharmaceutical industry, with its high energy consumption, high water demands, and the use of solvents for manufacturing.

According to the United Nations, most scientific estimates indicate that the Earth is already about 1.1 degrees Celsius (°C) warmer than it was in the late 1800s, and emissions continue to rise. To keep global warming to no more than 1.5°C (a limit established in the Paris Agreement), emissions need to be reduced by 45% by 2030, with a goal of reaching net zero by 2050 [1].

As a reminder, net zero is the point at which global greenhouse gases (GHGs) are balanced by real emissions reductions and carbon removal projects. It is an ambitious undertaking. When evaluating what's being done by businesses on a global scale, there's good and bad news. Figure 1 shows a comparison of global GHG emissions across sectors.

Net Zero Tracker, an independent group that follows corporate pledges, recently studied 2,000 of the world's largest publicly traded companies. They determined that half of those companies already have a net-zero target. That's a 40% increase over 18 months, from 702 in June 2022 to 1,003 in October 2023. Many of these corporations are in a "substantive transitional phase," meaning they've accepted the climate issue and are working to make good on their sustainability goals [3].

On the other hand, the pharmaceutical industry still has a lot of work to do regarding the scale of its emissions. A recent study of the biotech and pharma industries by My Green Lab shows that "90% of the 91 public companies analyzed in the sector still do not have targets in the short term (2021-2025) that are aligned with a 1.5 degree Centigrade increase worldwide." Figure 2 shows the breakdown of GHG emissions for the pharmaceutical sector under scope 1, 2, and 3.

Even when an organization sets a sustainability target that does not necessarily mean its efforts are meeting expectations for that target. Last year, a research highlight in *MIT Sloan Management Review* determined that sustainability progress is stalled at many US companies. Less than one-third of US employees surveyed said their organizations have practices to ensure sustainability goals in business models and employee roles [4].

Figure 1: Comparison of GHG emissions across sectors [2].

- The pharmaceuticals industry represents >5% of global GHG emissions.
- Aviation is approximately 3.5%.

Emissions are forecasted to triple by 2050 if left unchecked.

- Pharmaceuticals generate 55% more GHG emissions (globally) per $1M generated than the automotive industry.

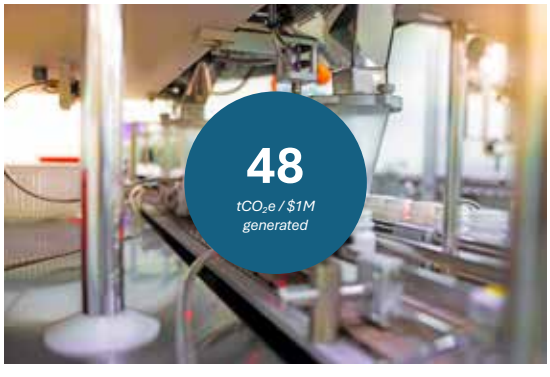
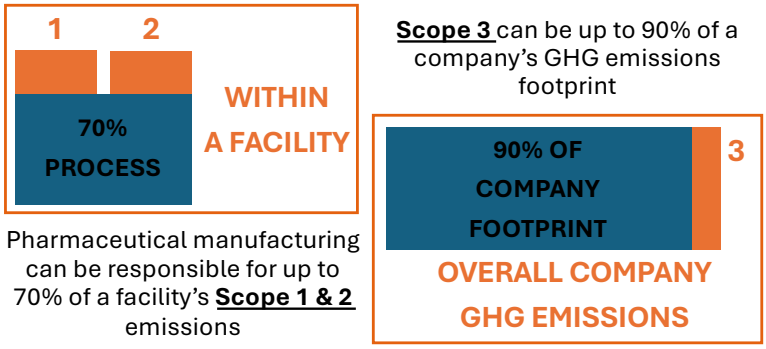


Figure 2: GHG emissions of pharmaceutical sector by scope.



To be successful in achieving a net-zero target, according to the MIT research highlight, a company must have "embedded sustainability into their corporate DNA. This means that they have endowed their employees with a sense of sustainable ownership, spurring them to engage in more sustainability-supporting behaviors. When every employee integrates environmental and social concerns into every business decision, sustainability progress is accelerated" [4].

In many cases, that's easier said than done because of established business best practices. Projects can start out with ambitious sustainability targets, but once capital costs are calculated, many sustainable features are stripped out because benefits to the bottom line are unclear. If the focus can shift toward the whole life cycle cost analysis of a project, the benefits become clearer, such as reduced costs and more efficient operations.

However, environmental experts are urging business to think differently [5]: We can and must change behaviors, processes, and equipment (and we should do it in that order). We must find ways to reduce consumption, and then find ways to replace systems and optimize existing processes. Even small incremental changes can add up when considered across the scale of a manufacturing company.

One of the most persuasive ways to change existing attitudes and behavior—and to create a culture of sustainability in manufacturing organizations—is to show that we can move toward a net-zero target while also achieving operational efficiencies. These efficiencies then translate directly to corporate savings. After that, successes in one area of operations can prompt others to make incremental changes in their own areas. Taken together, these small successes can lead to a culture that will more fully embrace sustainability and lead to achievement of net-zero targets.

In this article, we look at several case studies that have yielded not only more sustainable operations for pharmaceutical companies, but that have also contributed to a healthier bottom line. We'll address progress being made in the pharmaceutical industry in architectural design, process design, and heating, ventilation, and air conditioning (HVAC) systems. Then we'll examine how an organization can establish its own net-zero targets and move toward companywide integration of sustainability.

ARCHITECTURAL DESIGN

A noteworthy example of how architectural design can embrace sustainability goals is a warehouse designed for a company that manufactures and packages an immunosuppressant product. This project comprised a 7,358-square meter, state-of-the-art warehouse, production and quality control space, including offices and plant rooms supporting an existing pharmaceutical facility.

The purpose of this warehouse structure is to store finished pharmaceutical products in a controlled environment. The goal of its design was to accommodate the future needs of this and a companion site, reducing transport emissions by 680 metric tons per year. To that end, the project was designed to conform to ISPE guidelines, the Leadership in Energy and Environmental Design (LEED) certification program, and energy-efficient design principles.

Energy-efficient design protocol highlighted the need for high-energy performance building fabric, advanced lighting technology and controls, renewable generation, application of clean technology, and energy considerations on all significant energy users. During construction, every effort was made to reduce environmental impact. A construction environmental management plan provided project-specific measures, with procedures for the scope of both permanent and temporary construction work.

Integrating sustainability into the design had both environmental and financial benefits. To maximize energy generation, the roof was designed with a parapet edge to protect photovoltaic panels from wind uplift, which removed the requirement for additional steel. To introduce natural light deep into the building, the south and east elevations featured large-scale glazing, and the personnel and material corridors had glazed walls. With this design, more daylight reached into labs, offices, and corridors, reducing artificial lighting and subsequent cooling load (which reduced the energy use of the building) while increasing indoor environmental quality.

Figure 3: Example of sustainable design measures at a facility.

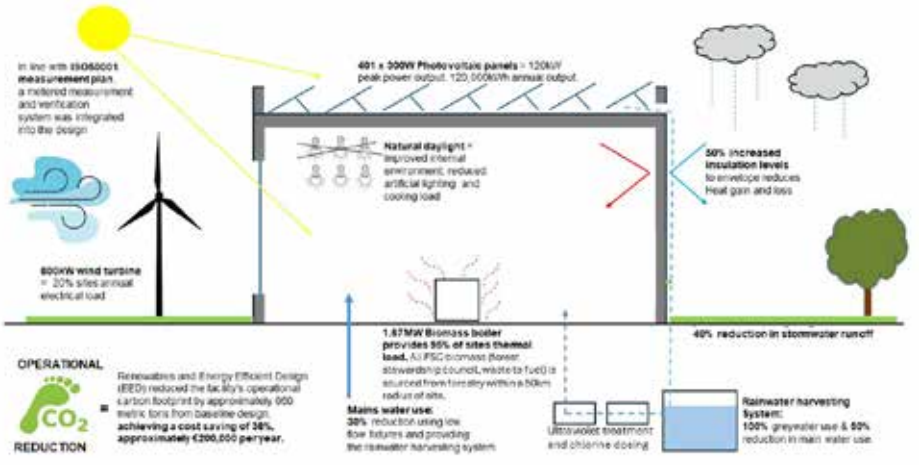


Figure 4: Strategy and implementation steps for existing facilities.

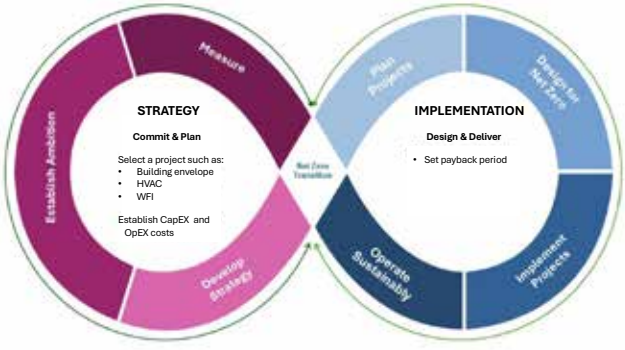


Figure 5: Opportunities for sustainability in the design of processing facilities.

The supply chain was limited during and after the project's construction. Approximately 33% of materials by cost were to be sourced from within 800 km of the site, including steel, glazing, and insulation panels. This supported the use of indigenous resources, involving local communities and thereby reducing the environmental impacts resulting from transportation.

Energy

A key objective for the design team was to reduce the carbon dioxide (CO_2) impact of the facility. Energy-efficient design protocol and best practices were put in place. These practices highlight the need for high energy performance, advanced lighting technology and controls, renewable generation, application of clean technology, and energy considerations on all significant energy users. Figure 3 describes the measures incorporated into the design.

As a result of these efforts, although the site area increased by 50%, the overall site continued to receive 98% of power from renewables (40% from on-site generated renewables and 58% from certified renewable grid import). This effectively created a 98% reduction in CO_2 emissions. The operational carbon footprint of the facility reduced by approximately 950 metric tons from the baseline design or €200,000 a year.

This project demonstrates the benefit of integrating sustainability into the design from the project's outset. It also shows how a business can grow and expand in a sustainable manner when the building and its function, site, and geographical location are viewed as one linked system. When existing facilities are retrofitted, the approach is a little different. It is recommended to perform an audit of the building(s), utilities, and all current and planned activities where the most obvious or biggest energy users can be identified (see Figure 4).

PROCESS DESIGN

Figure 5 provides a high-level summary of opportunities for sustainability in the design of processing facilities. Theoretically

speaking, many of these opportunities rely on early implementation for long-term environmental benefit. However, a balance is sought between sustainable chemistry practices and expediting delivery of a medication to a patient. There are many opportunities for introducing sustainability into the design of processing facilities.

This article focuses on two aspects of the opportunities shown in Figure 5: solvent recovery as an element of waste segregation and recovery, and water for injection (WFI) as a part of process utilities. In both cases, the financial impact on an organization, and the industry in general, may be considerable.

A March 2024 report update from the analyst firm Markets and Markets shows that the worldwide market for solvent recovery and recycling was valued at $1.085 billion in 2023 [6]. This market is projected to reach $1.38 billion in 2028, growing at 5% compound annual growth rate (CAGR) from 2023 to 2028. The pharmaceutical industry is one of the chief markets for solvent recovery; others include the chemical, automotive, printing, and paint and coating industries [6].

According to a December 2023 report from Coherent Market Insights, the overall pharmaceutical water market "is expected to reach $10.66 billion by 2030, from $6.2 billion in 2023, growing at a CAGR of 7.9% during the forecast period" [7].

Solvent Recovery

Solvent recovery can be expensive and greatly impacts the environment when processing waste material without using sustainable design and methods. Typically, waste solvents are treated as hazardous waste and sent to an off-site waste handling company. Off-site, the solvents face three fates: be separated; be chemically broken down to smaller, less harmful components; or, more frequently, be incinerated.

One sustainable solution to handling organic wastes incorporates "downcycling." This involves recovering solvents from a waste stream and reusing them in the facility for an alternative (typically less critical) use. Alternatively, if the recovered solvent meets a particular market need, it may be sold off as a byproduct. In this case, the pursuit of sustainability can result in a company being able to generate income through the sale of the organic solvent resulting from the solvent recovery system. Additionally, any water recovered from solvent recovery can supply the facility's gray water requirements.

To understand how solvent recovery was addressed in process design, consider the case of a major diagnostics testing supplier. The company had an aqueous-organic blended hazardous waste stream, comprising 65% water and 35% organics with toluene and methanol as primary organic components. This hazardous waste stream was shipped off-site and then incinerated to recover the energy from the organics. As a sustainable design solution, the manufacturer recovered a part of the waste stream and sent it to a recovery process.

The waste solvent flow rate here was approximately 10 gallons per minute, and distillation was used to recover the solvent. The blended waste stream was heated from ambient conditions to distillation operation temperature by heating it with a hot glycol system. By incorporating preheaters into the design, less hot glycol was used in the process, which reduced the amount of energy required for heating and cooling.

The distillation process for this facility resulted in a recovery rate of 95% for organic solvents and more than 99% for water. The organic solvents were sold to a cleaning chemicals supplier, and the recovered water was used to support water usage in the office building. Hence the solvent and water, once spent from the process operations, were both downcycled and used for subsequent applications.

This system has been in operation for two years. The return on investment is anticipated to be reached in four years, which considers the value of the recovered solvents and reduced water demand. The key elements in the process design were waste collection and segregation, as well as how the products were to be distributed. For some sustainability-focused initiatives, longer payback periods (even upward of eight years) are frequently acceptable based on positive environmental impact and the scale of the investment being made.

WFI

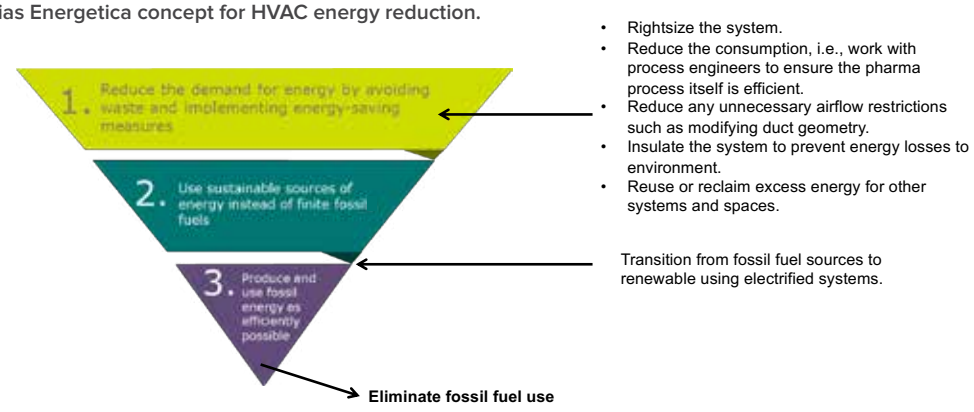
Because water is one of the most expensive utilities for pharmaceutical facilities, any improvement in an organization's WFI process efficiency can have significant financial and operational benefit. Improved energy efficiency in WFI systems reduces the direct utility requirements of the systems and the size of supporting utility equipment, such as boilers and chillers. This reduces the overall energy consumption footprint required and simplifies operations.

Another diagnostics supplier wanted to approach its WFI generation more sustainably. Their existing system used a multiple effect still (MES) system, generating two gallons per minute. The current volume of WFI generation produced using this system has been at capacity for nearly 16 years. The facility, now undergoing an expansion, required generating four gallons per minute. This is why they undertook a design process in which every sustainable option was to be evaluated to address efficiency while also reducing energy consumption.

MES is among the most energy-intensive ways to make WFI. Potable water is fed into the system and must be boiled using low-pressure steam. The system in this particular facility used both a hot loop (operating at 80°C) and an ambient loop (operating at 20°C) that is cooled by a chiller.

A number of options were explored to meet the organization's goals of doubling the WFI output capacity while reducing energy consumption. One option considered was a membrane-based reverse osmosis system, which typically requires less energy than an MES system. Ozonation for sanitization also reduces the energy consumption, as compared to a conventional heat-based sanitization approach. Because generation rates were to be doubled, other parameters such as line sizing were also evaluated. Further, the facility's chilled water supply and return temperatures were found to be working at nonoptimal operating points.

Figure 6: The Trias Energetica concept for HVAC energy reduction.



Another consideration was that membrane-based WFI generation systems produce ambient WFI. A new design concept introduced point-of-use electric heaters to heat only the limited users of hot WFI. This, in turn, would allow the entire hot loop to be eliminated, with all users fed off the ambient WFI loop. The return on investment in this larger WFI system was projected to fall within two to six years, depending on how many of the suggested options were implemented.

From a process facility design perspective, the best approach to sustainability is to start small. Evaluate what can be done to make existing systems more sustainable. Starting small and realizing the benefits through practical use of the system helps set up a culture of sustainability that will lead to easier implementation of more sophisticated or involved design changes down the road.

Once that culture and entrepreneurial spirit is established, people in the organization will suggest other ways to address sustainability and reduce energy consumption. At a Parenteral Drug Administration Annual Conference in March 2024, one of the speakers noted that their organization was operating freezers at -70°C (as compared to -80°C). Changing the operating temperature to a higher but still acceptable level reduced their freezer energy consumption by 20%.

Although this example merits further detailed investigation from a risk and quality perspective, and the organization is continuing long-term studies to ensure there are no adverse effects on samples, it shows that small changes in thinking can yield substantial benefits and enhance a sustainability mindset internally. These small changes might also yield a faster return on investment than broader process designs with more ambitious goals. There's no idea that is too small in a sustainable culture.

HVAC AND MECHANICAL SYSTEMS

HVAC systems, both wet and dry, can account for approximately 70% of energy use in a pharmaceutical facility. Moving toward net-zero design for HVAC could be summarized as shown in Figure 6. When it comes to HVAC and mechanical systems, chilled water and hot water systems are the energy backbone of the building and are related through heat pumps. In pharmaceutical applications, subcooling is typically used to remove moisture and dehumidify air during the summer, which is then reheated to maintain space temperatures. This is due to the high air changes required in the production process.

Although sustainable principles first call for reduced consumption, this can be challenging depending on the type of pharmaceutical process. An example of reducing consumption is to use a closed, rather than an open, processing unit. The overall cleanroom grade can be reduced, which reduces the size of the HVAC and its subsequent energy use. Where this is not possible, the next approach is to consider ways to improve the efficiency of the system and reuse materials and energy.

Reuse

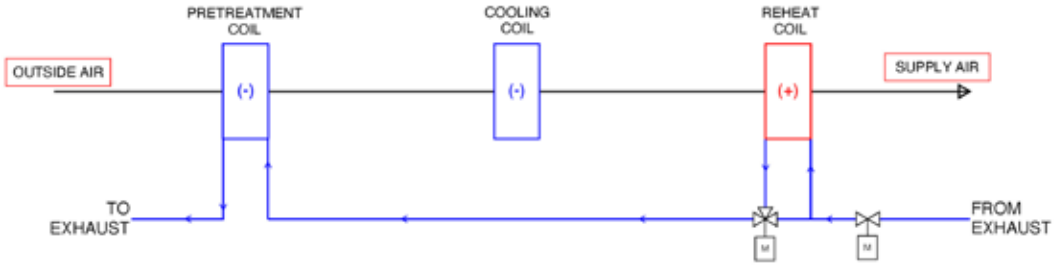
Reuse was done particularly well on a greenfield project for a pharmaceutical company specializing in ribonucleic acid therapies. This company uses a considerable amount of flammable material, with a high demand for outside air. Twenty-five air changes per hour of outside air in the production space were required to maintain the spaces below 25% of the lower explosion limit. This organization's goals were met by installing an intelligent runaround loop, with a process chilled water system on its own dedicated heat pump system, to generate hot water for the HVAC system.

Most facilities that require energy to be recovered from exhaust air make use of a standard runaround loop, comprised of a coil in the exhaust system, a coil in the supply system, and a pump running either water or water with glycol between the two. At peak conditions, that type of system produces about 10% energy recovery.

By contrast, an intelligent runaround loop uses temperature monitoring on both sides of the system and integrates multiple air handling units and exhaust streams into a single system (provided they're operating at generally the same temperature). The pump flow will vary, with control valves allowing the system to adjust the flow rate to each coil.

This facility required six large air handlers—approximately 170,000 cubic feet per minute, divided among the handlers, all connected via the intelligent runaround loop system. The system

Figure 7: Intelligent runaround loop system AHU configuration that provides free reheat.



achieves over 25% energy recovery during peak cooling conditions and over 30% heat recovery at peak heating conditions. The system can also provide about 90 refrigeration tons of cooling to electrical and information technology (IT) rooms during the winter and redistribute that heat to other rooms. The free cooling system allows for the shutdown of the cooling towers during the winter.

When designing more sustainable HVAC systems, it's important to look for any simultaneous loads that will enable systems to transfer energy. In this case, the facility transferred energy between the process chilled water system and building heating hot water systems using heat pumps.

During the summer, water comes from exhaust air in the system and provides the primary source of reheat via the reheat coil in the air handling units (AHU), which allows the system to recover additional cooling capacity. The energy recovery fluid is then run through the pretreatment coil. This configuration provides free reheat and maximizes the amount of cooling recovered (see Figure 7).

Heat recovery from the exhaust air can also be improved by using an intelligent runaround loop system during the winter. The system design is capable of over 35% energy recovery from exhaust air during peak heating demand. In practical use, however, the result was closer to 30% because the spaces are humidified to 30% relative humidity. This limits the heat recovery because of frosting on the heat recovery coils in the exhaust air. Consequently, although greater recovery is theoretically possible, strict humidity requirements in processing limit the energy that may be recovered. High humidity may lead to icing on the coils.

With its intelligent runaround loop system, the company was able to realize nearly 30% energy recovery, as opposed to the 10% that is typical of a standard runaround loop. The intelligent runaround loop system paid for itself in approximately four years with the associated energy savings. Chilled and hot water systems typically have an operational lifespan of about 25 years, which results in significant net savings over the life of the system.

There are specific sustainability challenges to HVAC design for pharmaceutical and hazardous exhaust facilities. Organizations need to make certain they are not cross-contaminating their supply with exhaust. In the runaround loop case detailed here, the supply and exhaust are separated. In other cases, a company must know how tolerant the facility is to cross-contamination as a risk associated with energy recovery that may allow the use of other energy recovery technologies.

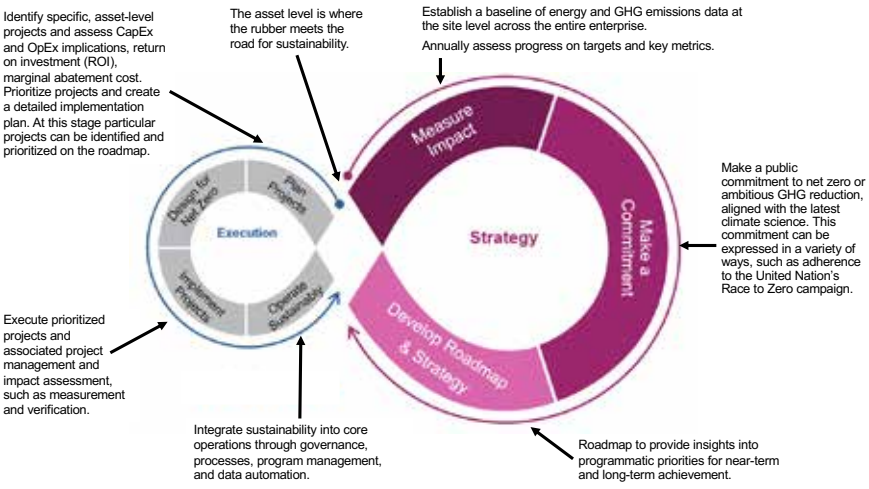
Figure 8: Net-zero design approach.

The development of energy-efficient systems to reuse the energy available is the first step in achieving net-zero HVAC systems. The concepts presented here are the first steps in the electrification of HVAC systems to achieve net zero.

THE NET-ZERO LIFE CYCLE

As seen in the preceding examples, sustainability in operations should not only be considered "nice to have." In practical and measurable ways, sustainability can create improvements that lower operational costs or even allow some processes to essentially pay for themselves. Reviewing the facility as one linked system (as shown in Figure 8) from the project outset, be it a new facility or retrofit, creates the opportunity to make the most impactful and cost-efficient solutions. One decision will impact another.

Figure 9: Net-zero transition diagram.



At the same time, forward-looking organizations are even implementing sustainability initiatives that have no return on investment—that is, they are implementing sustainable design elements because they are good for the environment while recognizing that they are expensive to implement. Capital expenditures (CapEx) can increase while operating expenditures (OpEx) decrease.

The net-zero life cycle is a journey undertaken by an organization to embrace improvements to its operations to slow the effects of climate change. It includes both enterprise- and asset-level considerations. Starting at the company level and moving to each site allows organizations to prioritize the most appropriate projects on the roadmap. This process is summarized in Figure 9.

CONCLUSION

Designing future assets with net zero and company commitments in mind should consider circularity, designing out waste, remediation, and land use changes. Planning for net zero can be a challenging undertaking. But as the saying goes, the longest journey begins with a single step. Grants and private and state funding are available globally for decarbonization projects that can support a company's net-zero journey. Small changes, even at an individual level, can contribute to an organizational culture that understands the value of sustainability in dollars and cents and that provides a vital and lasting legacy to future generations.

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A CLOUD SERVICE PROVIDER EXIT STRATEGY

By Anders Vidstrup and Anette Westphal

Traditionally, a regulated company is accountable for all aspects of their infrastructure qualification and application validation. With the introduction of public cloud service providers (CSPs), part of that technical responsibility has shifted to a cloud supplier, making supplier assessment and supplier management more important than ever—even though the regulated company is still accountable for compliance to existing legislations and regulations.

The mergers and acquisitions of CSPs also lead to the potential need to move data from the cloud. The risk of financial instability for the provider should also be taken into consideration. Consequently, it is essential to consider the risk of supplier termination and how it could be formalized in an exit strategy to mitigate that risk. The following article will explore this topic. The article is divided into two parts: cloud solutions and what to be aware of in relation to software-as-a-service (SaaS) solutions.

REGULATORY BACKGROUND

Several regulations include content around the handling of suppliers and specifically the handling of data.

OECD

The Organisation for Economic Co-operation and Development (OECD) "Advisory Document on GLP & Cloud Computing – Supplement 1 to Document Number 17 on Application of GLP Principles to Computerised Systems" [1] contains the following text under section 5.3.3., Service Level Agreement (SLA): "Exit strategy: The SLA should clearly describe the test facility's right to obtain all data and meta-data (including audit trails) in a readable and convertible format, in case the contract with the cloud service provider is terminated."

US FDA and ISO

The US FDA's 21 CFR part 11 [2] focuses heavily on the integrity of cGMP data throughout its entire life cycle, which means a plan should be in place to repatriate data if there's a possibility of the contract with a CSP terminating for whatever reason. Part 211.180(a)(b) of 21 CFR [3] requires that records be maintained for all components, drug product containers, closures, and labeling for at least one year after the expiration date. It is essential that data can be exported into a readable format under the appropriate controls to ensure data integrity. Similarly, 21 CFR part 820 [4] and ISO 13485 [5] require ongoing risk management where contract termination is a risk.

European Commission

The European Commission's Annex 11 [6] does not explicitly call out the need for an exit strategy in its guidance around suppliers and service providers. However, it does state that risk management should be applied throughout the life cycle of the computerized system, and this should consider patient safety, data integrity, and product quality. The termination of the contract with a service provider is a risk that should be considered.

Annex 11 Section 3.1

Section 3.1 states that a formal agreement must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. As one of the possible formal agreements, a quality agreement should cover all topics in accordance with a defined and established life cycle, such as how to export data when exiting the CSP.

Annex 11 Sections 7.1 and 17

Sections 7.1 and 17 cover requirements for data storage and archiving and require that access to data be ensured throughout the retention period. This will indirectly force the regulated company to be able to extract data as a part of the exit strategy.

Annex 11 Section 16

Section 16, Business Continuity, covers the availability of computerized systems that support critical processes. It states that provisions should be made to ensure continuity of support for those processes in the event of a system breakdown. Those provisions could include reverting to manual processes or making an alternative system available, or the same system available in an alternative location. The technical provision would be detailed in the application's disaster recovery plan. The termination of the contract with a CSP

would make the current solution unavailable and would trigger business continuity and disaster recovery plans.

SUPPLIER MANAGEMENT

At the start of a supplier relationship, an exit strategy should be defined to ensure any needs will be included in the final contract, including addressing access to documentation after the exit has taken place. This ensures minimum business and customer disruption if the relationship is terminated and the ability to demonstrate compliance in inspections. The exit strategy should then be reviewed as part of the regulated company's annual supplier reviews, or if there's any other significant change in circumstances.

Where possible, an assessment or audit of the CSP and its quality and information management system should be conducted. This is to ensure that processes to provide support during an exit activity are in place and well implemented.

CONTRACT

As with any contract, there are situations where either party may want to terminate the contract. From a CSP perspective, the only logical reason to terminate a contract is due to a breach of the customer agreement. For a customer, there are several reasons why you might want to end a relationship with a CSP. It could be some external influence that necessitates an exit, such as legal or regulatory changes. This decision could be related to the service, SLA, or finances.

Whatever the reason, the regulated company will usually have a period of time (stipulated in the clauses of the contract) to recover the content from the CSP before contract termination. The regulated company should assess the standard terms to determine if it includes sufficient time for them to recover their content and negotiate a change if required; for example, 30 days until all assets have been transferred.

EXIT STRATEGY COMPONENTS

As previously mentioned, the focus of exit strategies is ensuring that data can be retrieved from the CSP. Although the regulated company should certainly have business continuity plans and disaster recovery plans, from a regulatory perspective, the exit strategy should focus on the data. It should complement, but not duplicate, the business continuity and disaster recovery plans.

However, it is important to also note that the data must be readable. This may mean ensuring the application can be transferred so proprietary data can be read. The alternative solution is a validated migration of the data to an archive if that data is no longer actively used.

It should be highlighted that data includes all relevant metadata and audit trail information associated with the electronic records contained within the system. Special consideration may be required to ensure metadata and audit trail information remain readable and linked to the associated electronic record.

Furthermore, the CSP may have created records related to the installation of computer systems of qualification of the underlying infrastructure. The records must be accessible in a timely manner in case of an inspection.

When defining an exit strategy, it is important to apply a risk-based approach and critical thinking and to not overreact and overengineer a solution.

Risk Assessment

From a risk management perspective, the sudden termination of a contract with only 30 days to respond is unlikely but should still be considered in the exit strategy. The more likely trigger is a simple decision to change providers, in which case, the regulated company controls the timeline and the contract termination date.

When defining an exit strategy, it is important to apply a risk-based approach and critical thinking and to not overreact and overengineer a solution. For example, some interpret the need for an exit strategy as having another cloud provider waiting or having workloads spread across multiple providers, i.e., adopting a multicloud strategy. There are various reasons why a company may want to adopt a multicloud strategy, but the need for an exit strategy should not be one of them. However, if the regulated company already uses multiple CSPs, it can certainly leverage that as part of the strategy.

Trigger Scenarios

As mentioned, the trigger is either the CSP or the regulated company terminating the relationship, which results in either a short-term or long-term response. The following are some potential scenarios.

Long- or mid-term exit (more than six months of lead time):

- Exit CSP for strategic reasons (e.g., costs, performance, etc.)
- Exit CSP due to compliance or legal requirements (e.g., controls cannot be fulfilled)
- CSP terminates functionalities of individual cloud services (notice of deprecation)

Short-term exit (less than six months of lead time):

- Exit CSP due to infrastructure problems with the CSP (e.g., instability or network issues)
- Service termination initiated by CSP (proclamation)

Table 1: Steps for an exit strategy.

Step	Suggested Place Where Activity Could Be Anchored	Activity
1	Supplier Assessment	Assessment of risk that the supplier cannot deliver as agreed.
2	Contract	Termination considerations to be included in the contract.
3	IT Risk Assessment	For each application, assess the criticality of data.
4	Exit Planning	Anchor the exit strategy within existing documentation.

Scenarios for long- or mid-term exits can be planned for ahead of time, and projected migrations of data and applications can be arranged on an individual basis. Data backup and configuration can be transferred at a specified time during the migration process. A data migration process should be managed and controlled within the quality management system (QMS) of the regulated company.

However, scenarios for a short-term exit might lead to sudden inaccessibility of the cloud services at a certain point of time, which is not under control of the regulated company. For these cases, it is essential to have a disaster recovery plan in place that employs techniques like frequent backups of relevant data. The topic of backup and restore is covered in other guidance, such as *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*, Appendix O9 [7].

Another scenario potentially exists: the possibility of supplier liquidation or insolvency. This scenario is not discussed here because it is a part of the basic supplier assessment to evaluate the supplier business. It is covered in other guidance, such as *GAMP® 5 (Second Edition)*, Appendix M2 [7]. If the regulated company decides to go with a high-risk supplier for that scenario, operational work instructions for handling that scenario should be implemented.

Data Repatriation and Workload Migration

The business continuity and disaster recovery plans should consider data and application backups and the ability to restore to a disaster recovery site. However, this may simply be another region of the same CSP. Extend the disaster recovery plan to include a contingency of restoring data to another CSP or on-premises. It is not necessary to always retain backups on another CSP or on-premises. However, have a plan in place to do so if required.

Similarly, restoration of system functionality in case of a disaster should already be in the disaster recovery plan. Workload migration is more complex than recovering the data, so any experience gained through an initial migration from on-premises to cloud should be leveraged to move workloads again.

HOW TO IMPLEMENT AN EXIT STRATEGY

The exit strategy should be anchored within the contract and existing documentation for the specific application. The general process consists of the following four steps (see Table 1).

Step 1

As part of the supplier assessment, the risk of the supplier not being able to reliably provide the service as agreed upon for the duration required should be assessed. A supplier must be approved to host workloads that process or store critical data. A supplier may be approved with residual risk, to be addressed in the next steps. The topic of supplier assessment is covered in other guidance, such as *GAMP 5® (Second Edition)*, Appendix M2 [7].

Step 2

If a supplier is approved, as much residual risk as possible should be addressed in the contract. The following points should be included in the contract.

Termination assistance

Explore including a clause confirming help from the CSP until the transfer to a replacement provider is complete. Or, more typically, a part of the engagement of a new CSP could be to help with the migration.

No withholding of data

Contracts tend to state the customer always retains ownership of their content. The contract should address the retention of access until the data can be moved.

Relief of data retention obligation

The CSP does not have an obligation for data retention. As such, it is always the responsibility of the regulated company, and therefore it is recommended to assess whether a clause should be added to the contract giving the regulated company extra days to recover data.

Destruction of customer data

The regulated company is responsible for the deletion of their data. Assurance for the effective deletion of customer data should be clarified and potentially included in the contract.

Provisioning of validation and qualification records

The regulated company must be able to demonstrate compliance of the services provided by the CSP via information from the CSP and how they meet the requirements of the technical and quality agreements. The contract should address the availability and provisioning of the records concerning the retention periods.

Step 3

With a contract in place, the portfolio of current or planned applications should be analyzed to identify those that process critical data stored at the CSP.

Step 4

For each identified application, an exit plan should be defined. This should be done by looking into the following details of the data and application:

- Amount of data (which potentially could lead to high migration times and related cost)
- Required validation and qualification records
- Necessity of migrating the application to maintain data readability
- The build time of the application, if required
- Country data boundaries
- Appropriate alternative CSP or data location
- An updated application documentation, such as a disaster recovery plan
- Test (continuously)

It may be worth considering performing this step early for a large or complex workload as an input to contracting.

SPECIAL CONSIDERATIONS FOR SAAS SOLUTIONS

A pharma company co-engaging with a SaaS provider must understand the platform model ("stack") that supports the SaaS offering to fully understand the risks, mitigate them, and develop the associated exit strategy. When planning an exit strategy for a SaaS solution hosted in the cloud, it is important to consider the following key elements.

Data Backup and Export

Ensure that the regulated company has a mechanism in place to regularly back up data stored in the cloud. Additionally, make sure there are options to easily export data in a usable format that can be migrated to another system. Considerations should be given to what happens with the backup at the CSP after the regulated company has left the SaaS service: Will the old backup be removed?

Vendor Contract and Agreement Review

A thorough review of the contract and SLA with the cloud SaaS provider should be conducted to understand the terms and conditions related to termination and data retrieval. Any obligations, restrictions, or costs associated with the termination process should be identified.

Application Dependency Analysis

Assess the dependencies of the SaaS application, such as integration with other systems, customizations, or extensions. Identify potential challenges that may arise during the migration process and plan for how these dependencies will be handled or replaced in the new environment.

Alternative Provider Evaluation

Research and evaluate alternative cloud SaaS providers or on-premises solutions that could meet the business needs. Consider factors such as cost, functionality, scalability, security, and data management capabilities. Also consider regulatory requirements and policies in the QMS. Generally, all aspects that apply to "normal" software suppliers should be considered.

Migration Plan

Develop a detailed migration plan that outlines the steps required to transition from the existing cloud SaaS solution to the new environment. This plan should include timelines, resource allocation, data migration strategies, testing procedures, and contingency plans to mitigate potential risks. Special awareness should be given to the full stack. This is because SaaS requires a setup of infrastructure-as-a-service (IaaS), platform-as-a-service (PaaS), and related parameters.

Communication with Stakeholders

Clearly communicate intentions and plans to stakeholders, including employees, customers, and any other parties affected by the transition. Provide regular updates throughout the process to manage expectations and address concerns.

Legal and Regulatory Compliance

Consider any legal and regulatory requirements that may impact the migration process. Ensure compliance with data protection and privacy laws, contractual obligations, and any industry-specific regulations applicable to your organization. Aspects like the ability to reprocess data might be tricky as well. If possible, standard export data formats like the Clinical Data Interchange Standards Consortium (CDISC) [8] (for Google cloud platform data) or E2B for safety data should be considered. Typically, a SaaS creates a higher amount of validation and qualification records, as it is installing and maintaining the computer system. These records are critical for demonstrating compliance and need to remain available.

Training and Support

Plan for training and support to enable a smooth transition for end users. This may include training sessions, documentation, or access to support resources to help users adapt to the new system.

Contingency Planning

Identify potential risks and develop contingency plans to address unforeseen circumstances during the migration process. Consider backup solutions, failover mechanisms, and fallback options to minimize any disruptions to business operations.

Metadata and Audit Trail

To ensure data integrity, compliance, and continuity, it is important to pay attention to metadata and audit trails when exiting a SaaS solution. The following elements should be considered.

Metadata documentation

Review and document the metadata associated with the SaaS solution. This includes information about data fields, data types, relationships, and any customizations or extensions.

Understanding the metadata will help the regulated company ensure data integrity during the migration process and facilitate the mapping of data to a new system, if necessary. This is especially true if there is a legal need for maintaining the link between signatures and records.

Data retention and archival

Determine the duration for which the regulated company needs to retain audit logs and other relevant metadata. Ensure that the SaaS provider offers a mechanism to export and retain this data in a format that is usable and complies with any legal or regulatory requirements.

Audit trail export

Confirm that the SaaS solution provides an option to export comprehensive audit trails. These audit trails should capture critical events such as user activity, system changes, data access, and modifications. Exporting this data will be crucial for future compliance purposes, historical analysis, and potential audits.

Data ownership and access

Clarify the ownership and accessibility of metadata and audit trails after termination. Ensure that the regulated company has the necessary rights and permissions to access and retrieve this information, even after your subscription with the SaaS provider has ended (if possible).

Data encryption and security

Evaluate the security measures implemented by the SaaS provider to protect metadata and audit trails. Assess their data encryption practices, access controls, and data protection mechanisms to ensure the confidentiality and integrity of information during the exit process.

Data validation and verification

Perform a thorough validation and verification process when exporting metadata and audit trails from the SaaS solution. Check for data completeness, accuracy, and integrity to ensure that all necessary information is captured and transferred correctly.

Documentation and evidence

Maintain detailed documentation of the metadata and audit trails throughout the exit process. This documentation will serve as evidence of compliance, data integrity, and continuity if required in the future—and also fulfill GxP requirements for good documentation practice.

Third-integration

If the SaaS solution integrates with other systems or services, it must be ensured that the metadata and audit trails associated with those integrations are appropriately managed and migrated. Consider the impact on data flow and reporting capabilities when transitioning to a new solution.

Transition testing and verification

Before fully discontinuing the use of the SaaS solution, conduct thorough testing and verification of the migrated metadata and audit trails in the new environment. This step helps ensure that all data has been successfully migrated and is functioning as expected.

CONCLUSION

As this article discusses, the need for an exit strategy does not mean the need for overly complex and costly multicloud architectures. An exit strategy is a plan for taking care of data and business continuity. Its purpose is to comply with regulation and to support patient safety, product quality, and data integrity. Fundamentally, the strategy is to plan, mitigate the risk of contract termination as much as possible through contract clauses, and include contract termination as a trigger in business continuity and disaster recovery planning.

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