PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

March-April 2023 | Volume 43, Number 2

SUSTAINABILITY

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SUSTAINABILITY

ON THE COVER The EKG and leaves symbolize the importance of sustainability to the life of the earth, an importance that is increasingly being explored and implemented in the pharmaceutical industry.

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37 A NEW REGULATORY APPROACH TO DRIVE SUSTAINABLE MEDICINES

To enable changes across the pharmaceutical industry, sustainability should be included alongside quality, efficacy, and safety when assessing medicines. This article reviews two case studies that cover sustainable pack types and extension of shelf life. With the drive to manage unmet medical need through acceleration of drug development programs, postapproval sustainability variations will always be required. Here we discuss if current regulations will be fit for a sustainable future.

43 CASE STUDY: MEETING MANUFACTURING NEEDS WITH A NET ZERO ENERGY FACILITY

The expected FDA approval for a Treprostinil dry powder inhaler revealed a need for the manufacturer to expand its warehousing and logistics capabilities to support its growing operations. The company's senior leadership wanted to ensure this expansion came with as minimal an impact on the environment as possible, so a key priority was to provide a net zero energy facility. With a vision for what the project could be, the team named the upcoming endeavor Project Lightyear. To infinity and beyond, indeed.

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PHARMACEUTICAL ENGINEERING

Volume 43, Number 2

ISSN 0273-8139
Pharmaceutical Engineering is published six times a year by ISPE and is online at ISPE.org/Pharmaceutical-Engineering

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THOR Design, Inc., www.thor.design

Printing
Sheridan NH

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By Michael L. Rutherford


Michael L. Rutherford

Moving to One ISPE

2023 continues to move right along—the first quarter is almost over. I remain very optimistic about this year as ISPE International, with support from the International Board, continues to make progress on our 2023 objectives and the 2023—2025 ISPE Strategic Plan.

ISPE has already held two conferences in 2023: the 2023 ISPE Facilities of the Future Conference on 31 January–1 February and the 2023 ISPE Aseptic Conference on 6–7 March. The 2023 ISPE Europe Annual Conference in Amsterdam, The Netherlands, is fast approaching on 8–10 May. (Please register quickly as we expect this conference to be highly attended.)

SUSTAINABILITY

International initiatives like the Paris Agreement on climate change and the United Nations Climate Change Reports on Impacts, Adaptation, and Vulnerability continue to emphasize the importance of sustainability for the world and our pharmaceutical industry. Increased concerns around sustainability in our industry have driven the need for and adoption of better design, development, and manufacturing of biotech and pharma products using more efficient processes that reduce resource requirements, minimize waste, and reduce or eliminate the use or generation of hazardous substances.

Large biotechnology and pharmaceutical companies and their suppliers have outlined their key sustainability targets to meet the goals of reducing direct and indirect greenhouse gas emissions in their own operations, as well as sources of greenhouse emissions that they control. They are also focused on their supply chains, including emissions from their logistics, transportation, and suppliers. These practices have resulted in more environmentally sustainable practices and technology throughout the drug development process. The importance of sustainability practices in our industry has never been greater, and the opportunity for us to learn, share, and drive best practices knowledge through ISPE publications, conferences, and forums is what our membership wants and needs. I hope you enjoy this issue of *Pharmaceutical Engineering*® and its focus on sustainability.

ONE ISPE

I'd like to focus on another objective in the 2023–2025 ISPE Strategic Plan: One ISPE. ISPE is a global organization and, as such, needs to function as one and support the One ISPE Program and Network of Affiliates and Chapters to enable content delivery to meet regional and demographic needs. One ISPE provides all Affiliates and Chapters with the support and ability to grow and better serve their local ISPE members while globally expanding the ISPE brand and benefits. The ISPE International Board and I remain committed to supporting the Affiliates and Chapters through the assignment

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of Board Liaisons and participation in local and regional events whenever possible. Supporting each other and growing ISPE is the common goal for all of us.

A key element of One ISPE is to put in place a new updated charter for all Affiliates and Chapters that provides a consistent framework and operating model. Affiliates and Chapters that are part of One ISPE receive benefits that support the local level, including membership growth incentives, digitally packaged ISPE International session videos from select events, and the selection of the one official ISPE Training. Also, all Affiliates and Chapters as part of One ISPE benefit from having an ISPE International Board liaison and annual local board orientation and onboarding.

Another key element is the ISPE Affiliate/Chapter Growth Fund, which allows Affiliates and Chapters that are part of One ISPE to apply for potential funding to support local efforts. Financial contributions to this fund are made by Affiliates and Chapters with gross revenues over $50,000 and matched by ISPE International annually to provide funds for grant requests by Chapters and Affiliates to support initiatives. A member-led Affiliate/Chapter Growth Fund Committee has been established with representation from the Affiliates and Chapters and the International Board of Directors to oversee these grants. (Affiliates and Chapters are strongly encouraged to identify projects and submit grants in 2023.)

With input from the Affiliates and Chapters, and per the Charter Amendment Policy, a revised 2023 Charter was created and approved by the ISPE International Board in January and sent for signature by Affiliate and Chapter leaders during Q1 2023. With the 2023 revision of the Affiliate/Chapter Charter, One ISPE moves even closer to expanding our global organization while enabling synergistic value and encouraging coordination between Affiliates and Chapters and ISPE International.

I would like to especially thank Jessica Hardy, ISPE Senior Director, Membership & Chapter Relations, and her ISPE team; Thomas Hartman, ISPE President and CEO; Mark Hernick, ISPE Chief Operating Officer; the Affiliate and Chapter Leadership and Regional Leadership Committees; and the International Board Liaisons for all of their efforts to put in place the new Affiliate/Chapter Charter process.

Michael L. Rutherford is Executive Director, Computer Systems Quality and Data Integrity, at Syneos Health, and the 2022–2023 ISPE International Board Chair. He has been an ISPE member since 2003.

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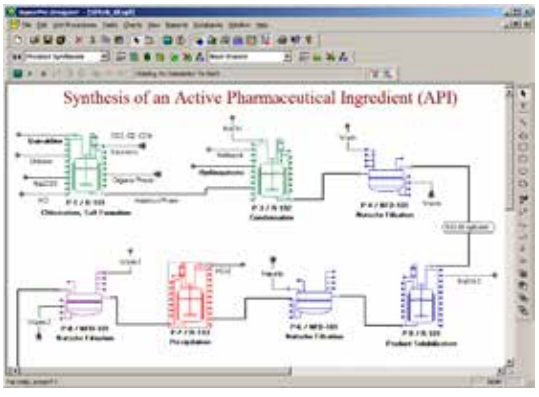

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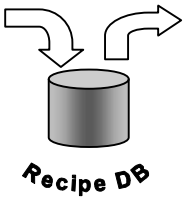

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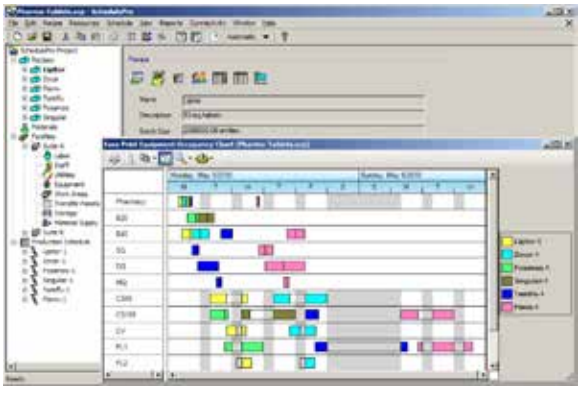

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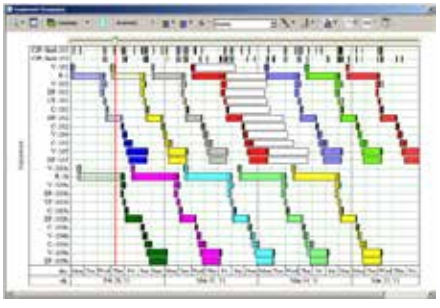

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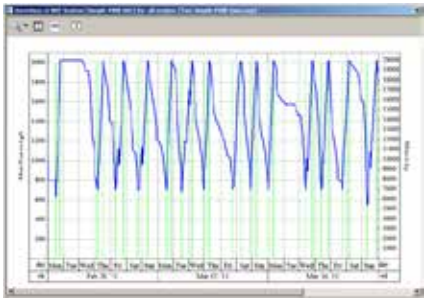

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, 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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By Carolina I. Serrano Martinez


Carolina I. Serrano Martinez

MENTOR ISPE LAUNCHES FOR ALL GENDERS

Arriving in the United States at the age of 17 to pursue my dreams was one of the greatest challenges of my life. It it was through this experience that I learned the importance of challenging my perspective. This was made possible through my involvement with ISPE, and four years later, I'm proud to announce the launch of Mentor ISPE.

This innovative approach to mentorship redefines the traditional relationship between mentor and mentee with an all-inclusive approach to growth, regardless of gender, age, or industry experience.

Finding ISPE helped me to find my way when I immigrated to the United States from Colombia in pursuit of my dreams. I was alone and trying to navigate a new country and a foreign education system.

I first got involved with ISPE when I was a sophomore chemical engineering student at Texas A&M University working as a Technical Operations Antibiotic Filling Co-Op for Merck. I saw a bulletin board flyer promoting ISPE and its member benefits, and it sparked an idea: we needed an ISPE Student Chapter at Texas A&M University.

SEEKING GUIDANCE AND CONNECTION

I barely understood what ISPE could do for my career or my peers', but I knew we needed guidance and connections to move forward. I'm glad I trusted my instinct. After launching the Student Chapter with the support of ISPE's South Central Chapter and ISPE International, I gained access to resources I never thought possible, including mentors. These key relationships helped pave the path that led me to my current role at Eli Lily as Operations Improvement Engineer and Top Talent Engineering Recruiter for Texas A&M.

Since graduating, I've stayed a part of ISPE, and was proud to not only get involved as an Emerging Leader, but also to join Women in Pharma®. As a woman of color pursuing a career in a male-dominated industry, I recognize the importance of Women in Pharma, its emphasis on diversifying the pharmaceutical workforce, and the untapped potential that lies within underrepresented groups. As a result, I was glad to be part of developing Mentor ISPE.

Having mentors, especially those you don't necessarily identify with, plays a critical role.

Being a part of one of those underrepresented groups, I have experienced first-hand the lengths we must go to prove that we are capable of achieving great results. Having mentors, especially those you don't necessarily identify with, plays a critical role.

MENTOR ISPE'S DEBUT

In collaboration with Sara Brothers, Women in Pharma's Mentorship Committee Co-Chair, and the Women in Pharma Mentorship Committee, Mentor ISPE sets out to connect participants from all corners of the world, of all ages and experience. Each group will consist of one student, Emerging Leader (EL), mid-level professional, and senior executive. This differs from the Mentor Circles because those are regional, while Mentor ISPE is international. Each participant will have the opportunity to teach and learn from each another regarding the industry, emerging technologies, and the future workforce. This program is designed to provide emerging professionals access to key relationships to move their careers forward, provide insight on technologies for a remote work environment, and help senior professionals prepare their organizations for the future.

Carolina I. Serrano Martinez is a Process Engineer at Eli Lily, Women in Pharma Mentor Committee Chair, and Women in Pharma Extended International Committee–Emerging Leader ISPE Great Lakes Chapter Emerging Leaders Chair. She has been in ISPE member since 2019.

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By Zen-Zen Yen


Zen-Zen Yen

SUSTAINABILITY: A Priority for Emerging Leaders

Sustainability is a buzzword that has been tossed back and forth across industries for decades. For a while, it was seen as something that consumers didn't really care about, but now the reality is different. According to a 2022 study [1], nearly 80% of consumers think about sustainability when purchasing products. Sustainability efforts can range from a specific product to an entire brand, or even an industry as a whole. In the pharmaceutical industry, there is a lot of work to be done when it comes to sustainability, but the time is now.

When considering the younger generations such as millennials and Generation Z, sustainability becomes even more critical. As these generations gain more buying power and become more influential, this trend will only continue to rise, but it doesn't stop there. During our last ISPE Germany/Austria/Switzerland (D/A/CH) Affiliate Board meeting, our Emerging Leaders (EL) representatives decided to take the train rather than fly despite the difference in the trip's duration because they saw it as a sustainable action.

SUSTAINABLE VALUES

For companies to be competitive in the most demanding hiring markets, they have to feature values in alignment with the best candidates. Strong future leaders are often willing to sacrifice pay to work at a company that aligns with their sustainable values. While only 17% of baby boomers have taken a job because the company championed sustainability, nearly 40% of millennials have chosen a job for that very reason [2]. To stay competitive and attract top talent, organizations of all types have to put sustainability at the forefront of their business.

Takeda is taking sustainability to heart; it is building its first zero-energy facility in Singapore [3]. The building, which will greatly expand Takeda's manufacturing capabilities, is the first net zero carbon emissions structure of its kind in the biotech industry in Singapore. Having already achieved carbon neutrality in 2020, Takeda is a model organization to look to for inspiration and practical implementation ideas when it comes to sustainable business practices. While big changes can have a big impact, operating with sustainability in mind does not have to mean constructing a new set of manufacturing buildings; instead, organizations of any size can incorporate small daily practices that, when combined, can make a massive difference. Opportunities to reduce the impact on our planet can be found in all technical areas.

A DIFFERENTIATING FACTOR

In addition to the idea of planet preservation, sustainability is a differentiating factor for companies nowadays. Today, consumers notice when an organization aligns with their values. It's not just about having the best product anymore; it's about having the best product and making it in a way that people can feel good about supporting, or joining as an employee.

As ELs are increasingly conscious about sustainability, I want to drive our engagement in the technical communities to increase awareness. Because I believe that collaboration and different perspectives are key for providing the best solutions for our patients, our engagement as ELs with ISPE's Communities of Practice (CoPs) is one of my key priorities for this year. We will bring those groups together on 23 March 2023 in our first Emerging Leaders CoP Day–Meet the Leaders of the ISPE Technical Communities to kick-start and increase our visibility and engagement.

Our industry serves the health and safety of patients around the globe, and we can't do that without factoring sustainability into the very fabric of our operations.

References

1. Ashkin Group. "Survey: Do Consumers Value Sustainability-Based Products?" Cleanlink.com (2 June 2022). https://www.cleanlink.com/news/article/Survey-Do-Consumers-Value-Sustainability-Based-Products--28560#:~:text=Nearly%2080%20percent%20of%20U.S.,off%20in%20increased%20customer%20loyalty.
2. Peters, A. "Most Millennials Would Take a Pay Cut to Work at a Environmentally Responsible Company." Fastcompany.com (2 April 2019). https://www.fastcompany.com/90306556/most-millennials-would-take-a-pay-cut-to-work-at-a-sustainable-company
3. "Takeda Breaks Ground on its First Zero Energy Building in Singapore." Press release, 23 September 2021. https://www.takeda.com/newsroom/newsreleases/2021/takeda-breaks-ground-on-its-first-zero-energy-building-in-singapore/#:~:text=The%20building%2C%20a%20%2414%20million,the%20biotechnology%20industry%20in%20Singapore.

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SUSTAINABILITY BY DESIGN
for Pharmaceutical Products

By Ester Lovsin Barle, Patricia (Trish) Melton, PhD, and Eamon Judge

As the pharmaceutical industry faces ever-changing global challenges and market forces, it must review and revise product design to ensure that quality products remain available in the marketplace while moving toward zero pollution for air, water, and soil. This article provides an introduction on how quality products can integrate sustainability by design.

Sustainability by design (SbD) is a framework that aims to minimize impact on the environment along the entire product life cycle. To use the SbD method, two concepts of "life cycle" need to be simultaneously considered:

1. Product sustainability-associated life cycle (Figure 1): raw materials → manufacturing → packaging → distribution → use → end of life
2. Drug development life cycle (Figure 2): early development → late development → commercial phase

SbD uses life-cycle assessment (LCA) data and eco-design principles [1] to inform and direct product decisions that minimize the environmental impact of products by reducing greenhouse gas emissions, reducing use of energy and materials, avoiding hazardous materials, generating less waste, and improving sustainability potential.

WHY IS SbD NEEDED?

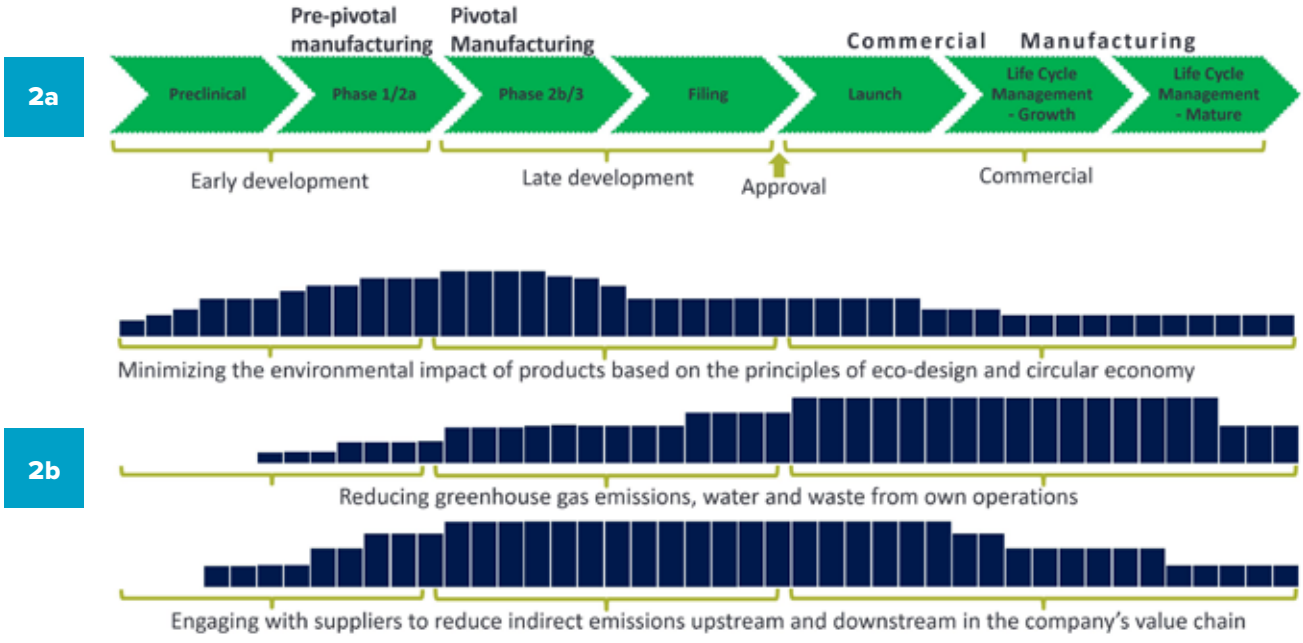
Previous research analysis has shown that the emission intensity of the pharmaceutical industry is significantly higher than that of the automotive industry [2], although the figures are challenging to compare. Pharmaceutical companies want manufacturing, products, and supply chain to be sustainable to drive the high quality of products while minimizing impact to the environment. To address the environmental challenges, we need a transformational change from the way we have been operating to create a sustainable future.

Figure 1: Product life-cycle stages as used for life-cycle thinking and assessment.

For that reason, pharmaceutical companies are rethinking how drug products are designed, manufactured, transported, administered, and disposed of across the full life cycle, including their own operations and across the value chain in healthcare systems.

The focus on the whole product life cycle aims to build in sustainability and in that regard, it is analogous to the approach taken in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline Q8 (R2): Pharmaceutical Development, which describes quality by design (QbD) for the development of pharmaceutical products [3]. QbD aims to develop quality products and processes through active management of the development knowledge to build a "design space" that uses scientific data to establish both normal operating ranges and a "control space" that supports scale-up and operation. In this way, quality is "built-in" to the product and process.

Figure 2: Pharmaceutical drug product life cycle from development through life-cycle management (Figure 2a) and relative efforts for three workstreams that deliver sustainability improvements during development stages (Figure 2b).



ICH Q8 recognizes that "quality cannot be tested into products" [3]; it needs to be a part of the development process and therefore considered at the very start of the product life cycle. To be successful, QbD requires scientific data to support knowledge of what is quality-critical and how that may change as a process is scaled up commercially. The more knowledge, the broader the design space and the more scope for operating within different parts of the design space while remaining compliant. Quality risk assessment is a vital part of this process.

It would therefore seem appropriate to take the same approach for SbD: Develop a design space that identifies those aspects of the product or process that drive environmental impacts. Conducting this evaluation during the early development phase has the potential to support "built-in" sustainability. Fundamental to this process is a strategy, integration of environmental requirements into drug development, and knowledge development management [4].

INCORPORATING SbD INTO PHARMACEUTICAL PRODUCTS

There are three synergistic workstreams that will deliver efficiency and quality requirements as intended without exceeding environmental and ecological boundaries throughout the entire life cycle.

1. Minimizing the environmental impact of products based on the principles of eco-design and circular economy
2. Reducing greenhouse gas emissions, water, and waste from the company's own operations

> We need a transformational change from the way we have been operating to create a sustainable future.

3. Engaging with suppliers to reduce indirect emissions upstream and downstream in the company's value chain

The efforts required by these three workstreams are not equal and they are not equally used in all stages of the drug product life cycle. All three workstreams, however, need to be considered in the context of the materials, energy, and overall resources that are needed to bring a product to market, and through them influence resource reduction.

It has been postulated that up to 80% of a product's environmental impacts are determined at the development phase. Development is the most powerful and cost-effective point to address the resource footprint of future products [5], with early development (from preclinical to phase 2) having the most impact on possible changes, followed by late development (phase 2b to approval) [4], as seen in Figure 2. This highlights the importance of embedding sustainability in pharmaceutical research and development in line with the chemistry, manufacturing, and controls (CMC) timelines.

Table 1: Sustainability opportunities before and after regulatory approval and launch for each life-cycle stage of products. Bold = indicated activities in the stage when they are easier to influence or adopt.

Life-cycle stage	Pre-approval and launch	Post-approval and launch	Examples
Raw materials	• **Material vendor selection** • **Material use** • **Restricted substances lists**	• Material vendor selection • Material use • **Material reuse, recycling** • Updates to restricted substances lists	• Water-based synthesis instead of organic solvent [9]. • Green chemistry principles [8]. • Amendment of REACH regulation adding Triton X-100 (octyl phenol ethoxylate) to authorization list [10, 11].
Manufacturing	• **Process innovation** • **Process improvement** • **CDMO vendor selection** • **CMO vendor selection**	• CMO vendor selection • **Process optimization** • **Waste-to-energy** • **Secondary energy use** • **Renewable energy options**	• Kilogram-scale GMP manufacture of Tirzepatide using a hybrid SPPS/LPPS approach with continuous manufacturing [12]. • By closing the loop and recirculating materials, companies reduce new material demand and waste. • Use of solar farm to reduce site's carbon footprint, consequently reducing the footprint of the products manufactured at the site. • Green engineering principles [13].
Packaging and device	• **Material vendor selection** • **Material type selection** • **Packaging design** • **Reduction of packaging weight (primary, secondary, tertiary)** • **Drug delivery device design** • **Restricted substances lists** • **Recyclability and recycled content**	• Material vendor selection • Material type selection • Reduction of packaging weight (secondary, tertiary) • Updates to restricted substances lists • Recyclability and recycled content	• Thousands of the most notorious chemicals will be rapidly banned in Europe, as part of the zero-pollution goal in the EU Green Deal [14].
Distribution	• Renewable energy options • Vendor selection • **Storage conditions** • **Forecast planning**	• **Maximizing distribution routes** • **Renewable energy options** • Vendor selection	• The Science Based Targets initiative provides guidance on setting greenhouse gas reduction goals in the value chain in line with climate science. Companies are working to implement supplier engagement strategy to reach scope 3 reduction targets, which influences vendor selection [15].
Use	• **Clinical trial planning** • **Right the first time** • **Responsible use (preclinical, clinical)**	• Right the first time • **Responsible use (commercial)**	• Right-the-first-time manufacturing minimizes waste by ensuring procedures are consistently executed according to standard operating procedures [16].
End of life	• **Maximizing product lifetime (shelf-life)**	• **Packaging waste management** • **Packaging recycling** • **Pharmaceutical waste reduction (PIE)** • **Drug take-back** • **Device take-back**	• Ongoing revision of the Packaging and Packaging Waste Directive (PPWD) will seek to make all packaging recyclable by 2030 with reuse targets [17].

However, it is noteworthy to mention that while major sustainability improvements can be influences after a lead compound is identified through drug discovery and continues through all remaining stages of the drug development life cycle, the product also benefits from improvements to the facility where its manufacturing occurs. That is why synergistic efforts are needed from the manufacturing sites to reduce the energy consumption and use renewables at manufacturing facilities), as well as engage all stakeholders in the value chain.

To design a safe and environmentally sustainable chemical, material, or pharmaceutical product, principles such as green chemistry, green engineering, sustainable chemistry, circular chemistry, and safe by design have been used [6]. Recently, comprehensive sustainability improvements for newer modality have

Sustainability Definitions for the Pharmaceutical Industry

By William Whitford and Ester Lovsin Barle

While financial investment in novel therapies provides patients with new treatment options and improved quality of care, the pharmaceutical industry also recognizes its responsibility to transition toward more sustainable development, manufacturing, and stewardship of medicines throughout their life cycle.

The pharmaceutical industry commits substantial resources in new medicines and treatment options to combat a variety of illnesses and diseases affecting communities globally. This initiative's goal has always been to improve patient care and lives, but now it aims to also transition to more sustainable options, particularly the principles of a circular economy. For example, currently, every 1 kg of small molecule active ingredient can take more than 100 kg of materials to produce, requiring huge facilities for production and waste disposal, as well as long lead times [1]. Therefore, sustainability activities focus on identifying and testing alternatives to existing pharmaceutical manufacturing processes in terms of technology, ingredients, materials used, etc., while meeting patient needs as a primary goal.

Sustainability Definitions

The term *sustainability* has several distinct meanings in various contexts. The most inclusive comes from the United Nation's 2015 Sustainable Development Goal, in which 17 categories and 169 targets promote human rights and gender equality in a balance of economic, social, and environmental concerns [2]. Many have a narrower, focused view of the topic—simply envisioning the reduction of environmental impacts through use of "greener" technology.

Others adopt a more holistic view, and allow that sustainable product, process, and facility design more properly refer to creating product economies that are responsible, healthy, just, and profitable [3]. As such, the general UN definition of sustainability—"meeting the needs of the present without compromising the ability of future generations to meet their own needs"—is also the basis of approaches used in pharmaceutical applications.

In greening the arena of pharmaceuticals, we therefore look holistically at natural, human, and economic systems and seek solutions that support quality of life for all. Design decisions are evaluated against a triple-bottom-line concept that incorporates a long-term view of assessing potential effects and best practices for people (social capital), planet (natural capital), and profit (economic capital) [4]. In establishing a scope for the most important factors to consider in the corporate arena, some are defining a company's environmental, social, and governance (ESG) performance [5].

Sustainability Criteria

Environmental sustainability can be defined as responsible interaction with the environment to avoid depletion or degradation of natural resources and ecosystems and allow for long-term environmental prosperity. Organizations attribute various weight or priority to

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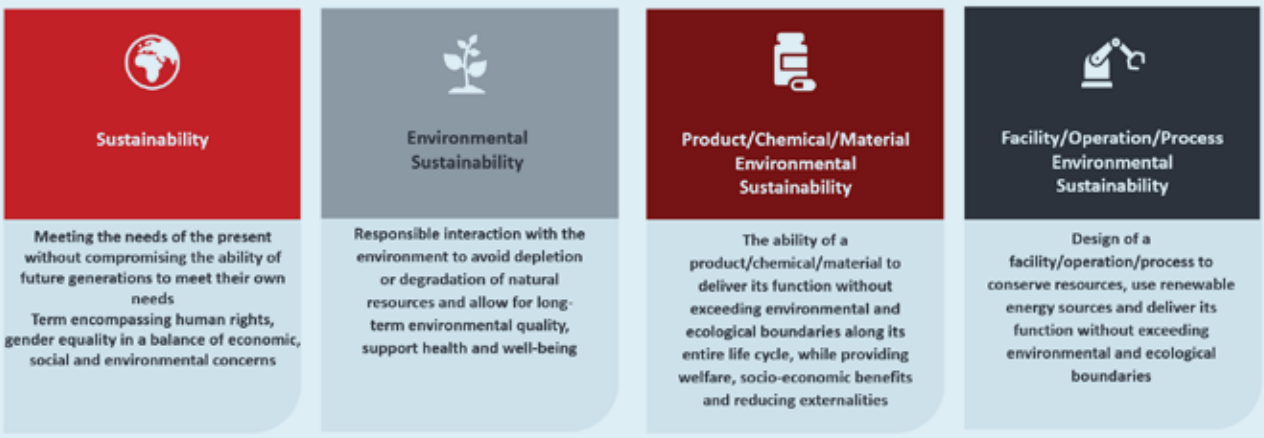
Figure 1: Definitions for sustainability concepts relevant to pharmaceuticals as integrated in the wide context of overall sustainability.



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individual environmental burden types for different, often individual, reasons. Some can maintain a differential sensitivity to particular burdens per se and impart additional weight to the consideration of those burdens.

For example, not everyone regards, a priori, the relative damage to our land, water, or air in the same way. Others can emphasize individual burdens due to local (regional setting) factors, such as water use in dry regions, or to the particular type of products, such as organic solvents in oligonucleotide production. Such ranking can also be due to special interest goals influenced by customers, regulations, or bylaws.

Consistent with the preceding general considerations, environmental sustainability in the pharmaceutical industry can be perceived from two directions: from the side of the product or operations, processes and/or facilities, both of which are required to achieve a comprehensive sustainability program. Sustainability of pharmaceutical products can be defined considering the recent JRC Technical Report (2022) [6], which has provided the following definitions for sustainable chemicals and materials:

"Sustainability could be formulated as the ability of a chemical/material to deliver its function without exceeding environmental and ecological boundaries along its entire life cycle, while providing welfare, socio-economic benefits and reducing externalities. Overall sustainability should be ensured by minimizing the environmental footprint of chemicals on climate change, resource use, ecosystems and biodiversity from a life cycle perspective."

This definition is based on criteria from the Organisation for Economic Co-operation and Development (OECD) (2004) [7] involving reducing the consumption of resources and energy and avoiding the use of dangerous substances. Additional principles refer to the following:

- Use of harmless substances or, where this is impossible, substances involving a low risk for humans and the environment, and manufacturing of products in a resource-saving manner.
- Reduction of the consumption of natural resources, which should be renewable wherever possible, and avoidance or minimization of emission and introduction of chemicals or pollutants into the environment.
- Avoidance, already at the stage of development and prior to marketing, of materials that endanger the environment and human health during their life cycle and make excessive use of the environment as a source or sink.

Sustainability in Application

The preceding sustainability criteria can also be applied to facilities, operations, and processes, prompting design that conserves natural resources, such as energy and water, and utilization of renewable energy sources within the ecological boundaries. Sustainable process or facility design requires a new way of thinking and approaches to a project: be it a new build, renovation, or operations development and maintenance.

This now includes employing critical thinking and a science-based approach to innovations and solutions. More specifically, this involves such design factors as the site, surrounding environment and community, the buildings (existing or proposed), their interiors, operations, and any ongoing maintenance processes, until the project reaches the end of its life and its parts are recycled or reused. This approach encourages an early engagement and harmonization of all stakeholders, including designers and building users in the building/process owner's purview, while establishing formalized project needs and performance targets.

Finally, the approach taken to facilities and their operation should form part of a wider program of attaining holistic sustainability goals that span across the value chain: all business operations (R&D, manufacturing and supply logistics, sales and marketing), the role of various tiers of suppliers of goods and services in the supply chain, and the end-to-end impact of medicines on the environment (covering both used and unused medicines).

The various program elements within the framework presented in Figure 1 will need collective reporting that is accurate and auditable to ensure there is no suggestion of greenwashing. Some of the many themes relevant to the general concept of sustainability will be developed elsewhere in this issue of *Pharmaceutical Engineering®*.

References

1. European Commission. "Green Manufacturing for the Pharmaceutical Industry." 7 December 2017. https://ec.europa.eu/research-and-innovation/en/projects/success-stories/all/green-manufacturing-pharmaceutical-industry
2. United Nations. Department of Economic and Social Affairs: Sustainable Development. "Transforming Our World: The 2030 Agenda for Sustainable Development." October 2015. https://sdgs.un.org/2030agenda
3. AstraZeneca. "Sustainability Report 2021." www.astrazeneca.com/content/dam/az/Sustainability/2022/pdf/Sustainability_Report_2021.pdf
4. US Green Building Council. LEED Core Concepts Guide. An Introduction to LEED and Green Building, 3rd edition. Washington D.C.: US Green Building Council, 2014.
5. Peasoup. "ESG and Sustainability–What's the Difference?" https://peasoup.cloud/eco/esg-and-sustainability-whats-the-difference/
6. European Commission. Safe and Sustainable by Design—Chemicals and Materials. JRC Technical Report. 17 March 2022. doi:10.2760/879069
7. International Workshop on Sustainable Chemistry–Integrated Management of Chemicals, 572 Products and Processes. 27–29 January 2004. doi:10.1039/B404170B

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been described [7] showing that assessment against the 12 principles of green chemistry [8] are relevant also for oligonucleotides, especially in the areas of waste prevention, atom efficiency, renewable feedstocks, derivatives reduction, and real-time analysis for pollution prevention.

Due to the high importance of bringing new medicines to the market while accelerating product development and lowering operational costs, many of the potential sustainability improvements identified in drug development may not be able to be implemented. Therefore, the progress of product sustainability needs to also be embedded in the product's life-cycle management from the product's first launch into the market until its final withdrawal (Figure 2).

In parallel, streamlined LCA should be applied in development phases together with qualitative measures providing products' life-cycle emissions that generate comparisons of processes and materials that help identify targeted greenhouse gas emission reduction opportunities (e.g., preferred solvents, toxic substance evaluation). Although much more complex due to regulatory restrictions, some retrofitting of existing commercial drug products with the same method will be necessary to reach ambitious environmental goals. The decision to engage in retrofitting will need to include volume of product produced, process/energy intensity, and stage of the product in life-cycle management. Inclusion of sustainability attributes and metrics in the development of stage-gating processes will assure that suitability improvements done previously are not lost.

With patient centricity and quality attributes in central focus during drug development and commercialization, distinct opportunities before and after the regulatory approval and launch of the product (Table 1) are feasible, leading to improved sustainability performance. SbD starts by intentionally designing a more sustainable process in early development. Sustainability metrics are established for each step—from scale-up and validation through to the commercialization of the final approved product—to avoid any decisions that would hinder efforts to maximize sustainability gains.

However, these decisions are always in the context of the primary goal of getting new medicines to market, particularly in considering new life-saving therapies. This undertaking demands collaborative efforts from the entire organization because many decisions—such as material use, process design, and selection of the manufacturing sites—are locked in place before launch of the product. In addition, SbD requires cross-organizational adaptation of digital tools and databases, upgrading of capabilities in the drug development and technical functions, and sustainability acumen in the entire organization. In the end, everyone in the organization can and will contribute to a particular aspect of the product life-cycle with sustainability as one of the key criteria in mind.

Another important point to achieving SbD gains is agreeing on the type of metrics to use to track the sustainability impacts. Environmental metrics (e.g., process mass intensity, atom efficiency) have been developed over the past two decades to evaluate the environmental sustainability of chemical synthesis routes of active pharmaceutical ingredients (APIs) (primary manufacturing); dosage form production (secondary manufacturing); and packaging, distribution, and logistics (end-of-life phase) [18]. Recently, within the European Green Deal, the Chemicals Strategy for Sustainability (CSS) [14] identified several interventions to reduce impacts on human health and the environment associated with chemicals and materials (including medicines), which can be applied to existing and new medicines. The European Commission (EC) thinking emphasizes framework and principles assessing environmental and ecological boundaries [6]. This puts safety and sustainability performance in combined focus,

In the global pharmaceutical industry, there is clearly a drive to minimize the environmental impact of products and processes.

evaluating metrics related to chemical hazards alongside greenhouse gas, water, and waste reduction.

In the global pharmaceutical industry, there is clearly a drive to minimize the environmental impact of products and processes. SbD is a methodical, data-driven process that aligns with the principles of QbD: obtain knowledge early and robustly through consideration of how the environmental impact can be minimized, defining those parameters that are critical to sustainability and quality. To reach ambitious environmental goals, combining product and facility sustainability design internally and in the value chain is required.

References

1. Jugend, D., M. A. P. Pinheiro, J. V. R. Luiz, A. Varandas, and P. A. Cauchick-Miguel. "Chapter 6– Achieving Environmental Sustainability with Ecodesign Practices and Tools for New Product Development." C. M. Galanakis, ed. *Innovation Strategies in Environmental Science.* Elsevier (2020): 179–207. doi:10.1016/B978-0-12-817382-4.00006-X
2. Belkhir, L., and A. Elmeligi. "Carbon Footprint of the Global Pharmaceutical Industry and Relative Impact of its Major Players." *Journal of Cleaner Production* 214 (2019): 185–194. doi:10.1016/j.jclepro.2018.11.204
3. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q8 (R2): Pharmaceutical Development." Published August 2009. https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf
4. Luu, D. N., H. Gachet, C. J. Maier, N. Maranzana, and A. Aoussat. "Eco-Design and Medicine: Opportunities to Implement Eco-Design in the Pharmaceutical R&D Process." *Journal of Cleaner Production* 365 (2022): 132785. doi:10.1016/j.jclepro.2022.132785
5. Fuchs, S., S. Mohr, M. Orebäck, and J. Rys. "Product Sustainability: Back to the Drawing Board." McKinsey & Company. (2022) Accessed 2 January 2023. https://www.mckinsey.com/capabilities/operations/our-insights/product-sustainability-back-to-the-drawing-board
6. Caldeira, C., R. Farcal, I. Garmendia Aguirre, L. Mancini, D. Tosches, et al. "Safe and Sustainable by Design Chemicals and Materials—Framework for the Definition of Criteria and Evaluation Procedure for Chemicals and Materials." Publications Office of the European Union: Luxembourg (2022). doi:10.2760/487955, JRC128591
7. Andrews, B. I., F. D. Antia, S. B. Brueggemeier, L. J. Diorazio, S. G. Koenig, M. E. Kopach, et al. "Sustainability Challenges and Opportunities in Oligonucleotide Manufacturing." *The Journal of Organic Chemistry* 86 no. 1 (2021): 49–61. doi:10.1021/acs.joc.0c02291
8. Anastas, P. T., and J. C. Warner. "Green Chemistry: Theory and Practice." Oxford University Press: New York (1998): 30. Accessed 2 January 2023. https://www.acs.org/content/acs/en/greenchemistry/principles/12-principles-of-green-chemistry.html
9. Bailey, J. D., E. Helbling, A. Mankar, M. Stirling, F. Hicks, and D. K. Leahy. "Beyond Organic Solvents: Synthesis of a 5-HT4 Receptor Agonist in Water." *Green Chemistry* 23 (2021): 788–795. Accessed 2 January 2023. https://pubs.rsc.org/en/content/articlelanding/2021/GC/D0GC03316B
10. European Commission. Commission Regulation (EU) 2017/999 of 13 June 2017 Amending Annex XIV to Regulation (EC) No 1907/2006 of the European Parliament and of the Council Concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). (2017) Accessed 2 January 2023. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2017.150.01.0007.01.ENG&toc=OJ:L:2017:150:TOC
11. Ujaczki, É., V. Stark-Rogel, M. Olbrich, M. Fuetsch, and J. Backmann. "Experiences and Consequences of Phasing Out Substances of Concern in a Multinational Healthcare Company." *Environmental Sciences Europe* 34 (2022): 101. doi:10.1186/s12302-022-00678-0
12. Frederick, M. O., R. A. Boyse, T. M. Braden, J. R. Calvin, B. M. Campbell, et al. "Kilogram-Scale GMP Manufacture of Tirzepatide Using a Hybrid SPPS/LPPS Approach with Continuous Manufacturing." *Organic Process Research & Development* 25 no. 7 (2021): 1628–1636. doi:10.1021/acs.oprd.1c00108
13. Anastas, P. T., and J. B. Zimmerman. "Design Through the Twelve Principles of Green Engineering." *Environmental Science & Technology* 37 no. 5 (2003): 94A–101A. Accessed 2 January 2023. https://www.acs.org/content/acs/en/greenchemistry/principles/12-design-principles-of-green-engineering.html
14. European Commission. Commission Staff Working Document, Restrictions Roadmap Under the Chemicals Strategy for Sustainability. 25 April 2022. https://ec.europa.eu/docsroom/documents/49734
15. "Value Change in the Value Chain: Best Practices in Scope 3 Greenhouse Gas Management." Science Based Targets. November 2018. https://sciencebasedtargets.org/resources/files/SBT_Value_Chain_Report-1.pdf
16. Pham T. N. "How Pharma Can Optimize for Right-the-First-Time Drug Manufacturing and Sustainability." Pharmaceutical Processing World. 19 May 2022. https://www.pharmaceuticalprocessingworld.com/how-pharma-can-optimize-for-right-the-first-time-drug-manufacturing-and-sustainability/
17. European Commission. Implementation of the Packaging Directive. https://environment.ec.europa.eu/topics/waste-and-recycling/packaging-waste/implementation-packaging-directive_en
18. De Soete, W., C. Jiménez-González, P. Dahlin, and J. Dewulf. "Challenges and Recommendations for Environmental Sustainability Assessments of Pharmaceutical Products in the Healthcare Sector." *Green Chemistry* 15 (2017): 3493–3509. Accessed 2 January 2023. https://pubs.rsc.org/en/content/articlelanding/2017/gc/c7gc00833c

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CHALLENGES FOR Net Zero Carbon Pharmaceutical Manufacturing

By Keith Beattie, Michael Hell, PhD, Sarah Mandlebaum, and Ester Lovsin Barle

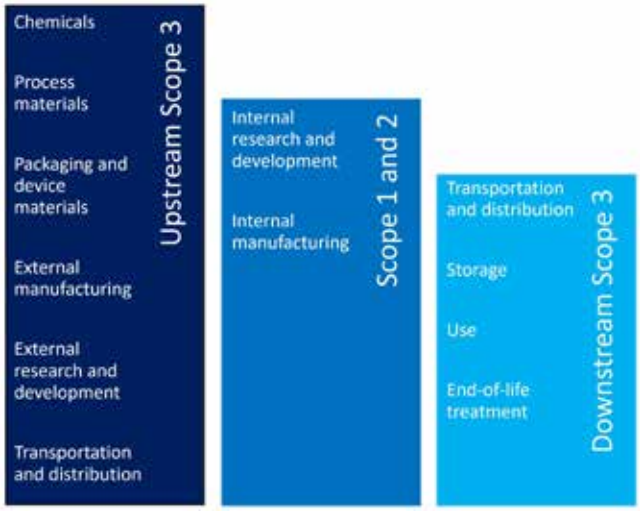
The scientific community accepts that greenhouse gas (GHG) emissions cause global warming and climate change [1]. Many organizations in the pharmaceutical industry have set net zero carbon goals and targets; they participate in the science-based targets initiative or sustainable markets initiative and disclose carbon emissions in databases like the Carbon Disclosure Project (CDP; https://www.cdp.net/). The vast majority of those in the pharmaceutical industry have shared partial decarbonization plans, but do not yet have concrete plans to achieve these decarbonization goals in the next 10–15 years, often citing a highly regulated environment as a hurdle. Growing public awareness and pressure, as well as technological advances coupled with CO_2 prices, are slowly changing the focus, putting the needs of our planet on the agenda.

A recent study published by My Green Lab [2] presented data from 74 biotechnology and pharmaceutical companies tracking the change in scope 1, 2, and 3 carbon intensity (measured in tons of CO_2 emitted vs. the company's revenue in USD) since 2015. This study showed that only 9% of the companies currently have targets aligned with a 1.5°C global warming scenario by 2030, which is widely acknowledged to be necessary to avoid the worst impacts of climate change. However, the target dashboard on the Science Based Targets website [3] shows a more encouraging status: 42 of 79 companies in the pharmaceutical, biotechnology, and life science sector have approved near-term targets aligned with a 1.5°C global warming scenario. Thirty-seven companies have committed to net zero, yet only four companies have long-term targets.

While commitment to carbon emissions reductions have been evolving over the last decade or more, what really counts is the progress being made on delivering tangible results. The My Green Lab study [2] found that the top 15 best-performing companies have reduced scope 1 and 2 carbon intensity by an average of 9.02% year-over-year. Yet if we consider these 74 companies to be representative of the entire biotechnology and pharmaceutical industry, the carbon intensity has increased by over 40% since 2015, with a marked increase over the last 2 years (2020 and 2021). As a whole, the industry is far from performing well in delivering carbon emissions reductions. The global healthcare industry is responsible for 4–5% of global emissions; in industrial nations, this rises to 10% of national emissions, with the pharmaceutical industry making up around 20% of healthcare industry emissions [4].

It is becoming clear that there is a large gap between the stated emissions reduction targets and the measurable results being achieved. A handful of companies have a clear vision and long-term strategies for delivering their stated commitments. But most companies do not. If they did, we would see much more progress on embedding fundamental prerequisites, such as energy

Figure 1: **Product level scope 1, 2, and 3 impact categories.**



efficiency, and deploying these at pace within the industry. There is a risk that ambitious and achievable industry targets will regress into "greenwashing" and not solve the problems at hand.

This article aims to provide some insights to help with building organization strategies and action plans for decarbonization and to provide confidence that no-regrets actions can be taken now. The science of climate change is clear, and the sense of urgency is building. Much of what the industry needs to do is very well-understood, very affordable, supports or improves GMP compliance, and relies on proven technologies. It is time to move from target setting to taking meaningful action, at a pace and scale that the industry has not seen previously.

To better understand what decarbonization strategies can be applied in the pharmaceutical industry, one needs to differentiate the emissions by source of origin.

GREENHOUSE GAS EMISSIONS

The scopes of GHG emissions are differentiated by what stage in the value chain the GHG are emitted (see Figure 1).

Scope 1 or direct GHG emissions are emitted on premises of a particular company, or by company vehicles and mobile equipment. These could be process-related (e.g., using CO_2 as inerting gas) or not (e.g., providing building heating). Emissions are not limited to CO_2 as the best-known emitter, but also other gases that have a global warming potential (GWP), often significantly larger than CO_2. These include, for example, refrigerant gases like hydrofluorinated carbons. Typically, emissions of all GHG are converted and expressed as tons, kilotons, or even megatons of CO_2 equivalents (CO_2eq) based on their GWP [5].

Scope 2 or indirect (owned) GHG emissions are emissions related to energy (most typically electricity, but also heat, steam, or cooling) consumed on company premises but generated externally.

Scope 3 or indirect (not owned) GHG emissions are emissions generated by the upstream and downstream value chain needed to ensure proper operations. In other words, scope 3 emissions are scope 1 and 2 emissions of that company's partners in the value chain. These are a heterogenous class of GHG emissions associated with purchased goods and services to manufacture and distribute a given product. For pharmaceutical companies, purchased goods (e.g., raw materials), use of sold products, and distribution typically compose a significant share of scope 3 GHG emissions; however, depending on the circumstances and products, other categories can also make a sizeable contribution. In the pharmaceutical industry, scope 1 and 2 GHG emissions are usually significantly smaller in proportion to scope 3 emissions. While scope 1 and 2 emissions are typically captured well and under the full control of a given company, scope 3 emissions are significantly less well-understood and not under full control of a company.

GHG emissions associated with a given reporting company are differentiated by scope 1 (by company-owned facilities and equipment), scope 2 (from purchased electricity, steam, heating, or cooling), and scope 3 (emissions in the upstream and downstream value chain) [5].

NET ZERO AMBITION IN BIOPHARMACEUTICAL INDUSTRY

Scope 1

Carbon emissions classed as scope 1 are firmly within the organization's control to mitigate but are often the most challenging to decarbonize. The most significant source of scope 1 emissions is associated with on-site combustion to generate heat and power using fossil fuels such as natural gas and diesel/fuel oil. There are other scope 1 emissions to be considered, including volatile organic compounds (solvents) and high-GWP refrigerant gas leakage, which can be very difficult to abate in a practical and economic way in the short term and will most likely be addressed in the longer term through process and technology advancements and sustainability by design principles.

As most manufacturing sites currently require high temperature heat for process, sterilization, and/or quality water generation, the provision of heat can be a major emissions source. Historically, many manufacturing organizations have invested in cogeneration (combined heat and power) to generate electricity as a byproduct of heat generation.

Cogeneration was originally seen as an economic way to provide energy, as it created a level of energy security and provided a carbon reduction benefit. This is no longer the case in most instances. The carbon reduction benefit has been negated by national electricity grid decarbonization, and fossil fuel energy security cannot be guaranteed as seen with the current global energy crisis. While there may be economic benefits, these are rapidly being eroded with fossil fuel price increases and ratcheting local and national government policy leading to increased carbon taxation.

Fortunately, there are alternative, more sustainable solutions for heat provision, although not all of these are low- or zero-carbon

Table 1: Alternative technologies being evaluated in the pharmaceutical industry.

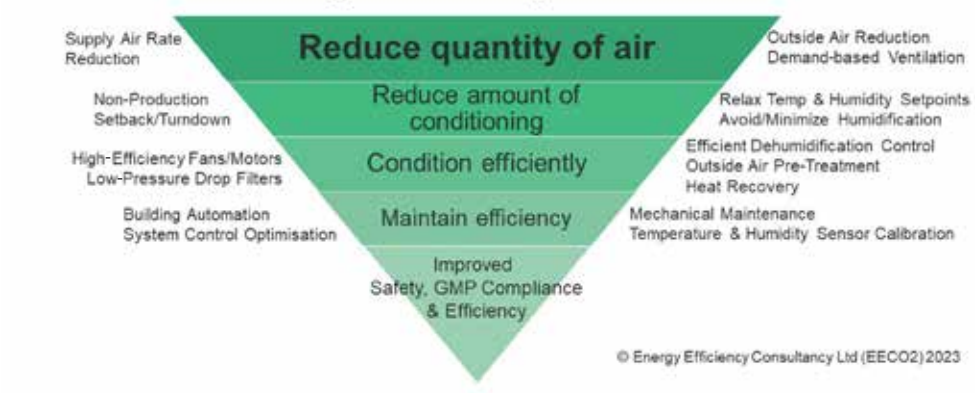
Heat Source	Zero GHG Emissions?	Description	Upsides	Downsides
Electric Boiler	Yes, if power is generated from renewable sources	Steam/hot water boiler produced by electric boiler	More efficient (close to 100%) than fossil fuel boilers (no combustion losses)	Electricity is often more expensive than fossil fuel (per unit) Requires additional electricity to be available, which requires suitable infrastructure
Electric Heat Pump	Yes, if power is generated from renewable sources and low-GWP refrigerant	Hot water generated by heat pump from a consistent low-grade heat source, normally air or water	Generally, 3–6 times heat output per unit of input energy Can use waste low-grade heat to boost efficiency and deliver more useful temperatures	High temperature is limited by technology and efficiency Refrigerant can have high GWP (mitigated by use of natural refrigerant)
Geothermal	Yes	Water pumped deep underground is heated by the earth through seismic and other geological phenomena Combined with heat pump to boost to higher temperature or reversed to provide cooling	Almost completely emissions-free and renewable heat source Low operational cost	The temperature accessible depends on local geological conditions: >150°C/300°F required for electricity generation and only economically viable in regions which are geologically active near the earth's surface (e.g., Iceland, Hawaii, New Zealand), but lower temperatures can be attained more widely at varying depths and can be used directly or boosted by heat pumps for space heating Deep geothermal yields higher temperatures but is more costly to install Local permitting may be required
Biomass	No, it is a combustion process	Pelletized plant material (woodchip or rice husk is common) that can be burnt in a boiler to generate heat	Biomass material from a renewable source Avoids use of fossil fuel Can use material that would otherwise be wasted	Biomass source availability can be a major constraint Remains a combustion process, so does emit CO_2 and other GHGs to environment Can increase scope 3 emissions because it requires delivery to site Concern over land use for biomass vs. food production and subsequent deforestation
Biogas (methane)	No, it is a combustion process	Methane is created and captured when anaerobic digestion (AD) breaks down organic matter	Existing gas boilers can use AD-generated methane with little impact Can be considered a transition fuel en route to completely carbon-free supply Power purchase agreements can fund generation capacity increase	Availability of feedstock for AD plant Remains a combustion process, so does emit CO_2 and other GHGs to environment Can increase scope 3 emissions because feedstock has to be transported
Green Hydrogen	Yes, if hydrogen is generated from renewable sources	Electrolysis of water to generate H_2 Evolving technology (immature) not currently widely deployed	Completely clean and high-temperature combustion process	Small gas molecule prone to leakage: safety considerations are a major factor Requires existing boilers to be converted Supply and cryogenic storage is expensive and complex

solutions. Some of these technologies are mature; others are evolving and developing. Table 1 summarizes the main technologies that are currently being evaluated for application in the pharmaceutical industry.

ENERGY EFFICIENCY

Before considering fuel switching to a renewable/more sustainable source, energy efficiency must be improved. Energy efficiency is often cited as the first renewable fuel and is widely under-exploited. Using fewer resources to deliver the same or more output is inherent in pharmaceutical business practices. The International Energy Agency (IEA) net zero by 2050 roadmap [6] recognizes energy efficiency as a key enabler to deliver net zero targets. With rising global demand for energy, doing more with fewer resources is good for the planet, business, and consumers. While fuel switching is a cost to be borne over the long term,

Figure 2: HVAC energy reduction hierarchy.



energy efficiency delivers immediate benefits with existing, well-proven technologies and will provide lower utility costs.

Detailed studies conducted by Energy Efficiency Consultancy (EECO2) over recent years have shown that almost all biotechnology and pharmaceutical plants can reduce energy use by 20%–50% by applying well-proven existing technologies [7]. Energy efficiency can affect both scope 1 and 2 emissions, often concurrently. The general philosophy for scope 1 reduction is to minimize the high-grade (high-temperature) heat demand as much as possible. This involves removing steam use and replacing it with low-temperature hot water.

Major areas for opportunities in existing facilities are discussed in the following sections. This is not a comprehensive list, but gives some examples for consideration that will be important for the low-carbon future. Non-technical measures of energy efficiency can also be considered, e.g., producing batches that require a lot of cooling during cooler periods of the year.

Heating, Ventilation, and Air Conditioning

Heating, ventilation, and air conditioning (HVAC) is often the single largest user of energy, so it deserves careful attention. When considering new systems, designers need to account for the impact of climate change on design conditions. More extreme ambient conditions will be more likely in the future. Indeed, many existing systems may struggle to meet internal room requirements due to ambient conditions exceeding the design limits.

There are many well-proven energy reduction actions that can be applied to existing systems and incorporated in the design of new systems (see Figure 2). HVAC used in cleanrooms is particularly demanding and ISO 14644-16 [8] contains useful guidance on actions that can be taken. Avoiding over-conditioning of spaces leads directly to scope 1 reductions. Controlling very precise temperature and humidity setpoints is hugely energy intensive and rarely necessary for product quality. Minimizing outside (fresh) air to the lowest level necessary for pressurization can also limit heating (and cooling) demands. Where dehumidification is a major factor, pre-conditioning the outside air to remove moisture prior to mixing can lead to huge reductions in both cooling and reheat demands. Maximizing recirculation of air and avoiding 100% outside air systems where possible should be a goal. Where recirculation is not possible, for example, where safety or cross-contamination concerns exist, then heat recovery solutions can be fitted as a last-resort, mitigating solution.

When HVAC demand has been fully optimized, there is then the possibility to use low-grade heat for conditioning. Progressive and forward-thinking design teams are routinely designing new HVAC systems to use 40°C–55°C/100°C–130°F or lower water temperature for heating needs. This is by no means the predominant design practice—but why not? HVAC is an ideal sink for low-grade heat recovery, and heat pump efficiency is particularly good within this temperature range. Retrofitting low-temperature heating is not easy but is possible with creative design and engineering.

Water for Injection

All national pharmacopoeia, with the exception of China, allow the generation of water for injection (WFI) compendial water using distillation or any other purification process that is equivalent to distillation methods [9]. In November 2022, the Chinese Pharmacopoeia announced the intention to include a chapter on ambient WFI in the 2025 edition. This opens the possibility for high-quality water generation by ambient processes that avoid the need for high-temperature steam. Historically, ambient WFI generation has not been favored by the industry, preferring to stick with the tried and tested methods of multi-effect stills and vapor compression [10]. There is some logic in this, but even these trusted methods can experience problems when not designed, managed, or maintained with sufficient care and expertise.

Facilities of the future should consider adopting ambient WFI generation in their designs [10]. There is no mandated temperature requirement in any pharmacopoeia [9] and therefore no requirement for maintaining compendial water at elevated temperatures. Regular sanitization with dissolved ozone is highly effective at

bioburden control and can provide superior results when compared with heat sanitization. The technology is proven to deliver the required quality and reliability at a lower environmental and cost impact.

Process Heating (Steam)

Where there is a process demand for steam, this will be the most difficult area to mitigate, due to the capital investment already made in vessels and equipment and the burden of revalidating production processes when a change is made, for example, to process at lower temperatures. Sustainable product/production process design will make an impact in the future, but for the immediate challenge the options are limited to:

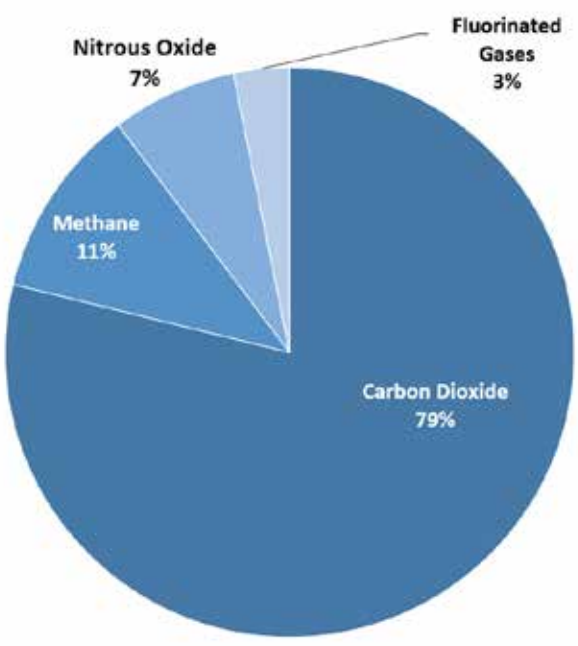
1. Maximize the efficiency of steam generation, avoid waste, and maximize heat recovery.
   - Insulate pipework, valves, and steam trap sets to reduce losses. This obvious action remains an area for continuous improvement and easy wins.
   - Maintain steam traps/improve recovery of steam condensate.
   - Retrofit condensing heat recovery systems to combustion/high-temperature exhausts.
   - Preheat boiler feed water with recovered heat.
2. Replace process heating loads with electric steam boiler. Having first reduced waste/improved efficiency and removed steam demand from unnecessary HVAC users, then the remaining steam load could be 50% smaller, which makes the transition to electrified steam generation much easier.

With creative and considered design, many of the solutions provided can be retrofitted successfully to existing facilities. Many already have been implemented successfully, and there are plenty of examples in the industry to support this fact. Nevertheless, it remains that transition to a net zero future requires much greater deployment at scale of energy efficiency improvements. Some organizations already know they have 20%–50% or more energy waste in their systems; many others are completely unaware of the opportunity for savings that exists. If your organization does not have an effective energy efficiency program that is delivering 5%–10% of efficiency gains year-over-year, then you are missing out on the easiest and most effective actions you can take to add to bottom-line profit and make a positive impact towards reaching your net zero carbon goals.

Fugitive Refrigerant Gas and Solvent Vapor Emissions

At most pharmaceutical facilities, the emissions related to the leakage of fluorinated gases (commonly used in refrigeration systems) and fugitive solvent emissions (used in various pharmaceutical processes) is small compared with emissions related to energy generation and use. These substances are also highly regulated and controlled, much more than other emissions sources, with the most GHG impactful substances being phased out over time. Nevertheless, these chemicals can have a very high GWP

Figure 3: Overview of US greenhouse gas emissions in 2020 [11].



U.S. Environmental Protection Agency (2022). Inventory of U.S. Greenhouse Gas Emissions and Sinks: 1990-2020

value, meaning that even a small amount of fugitive emissions can have a large influence on global warming.

Alternative low and close-to-zero GWP refrigerants are now available, with many requiring equipment change-out. This needs to be considered over the mid to long term and may require significant investment. In the short term, a pragmatic approach may be to aggressively reduce leakage rates from equipment, as it is only when gases get into the environment that they have an effect.

For solvents, the possible short-term mitigation actions will depend on the scale and nature of the processes emitting these substances. For the longer term, sustainability by design could help eliminate the need for solvent use entirely.

Scope 2

Scope 2 GHG emissions are related to energy that is purchased externally and consumed on company premises. Besides electricity, emissions associated with heat, steam, or cold purchased externally need to be considered. While the latter are typically the minority of scope 2 emissions and are typically neglected on first-pass decarbonization strategies, non-electricity-associated emissions need to be considered in net-zero approaches.

In public language, "green electricity" is very widely used; however, electrical power sourced from the public grid is neither green nor carbon rich per se, as it is a mix of all sources. Energy mixes and associated CO_2 conversion factors are available from either the local provider or from public databases [12]. In order to source 100% sustainable electricity, either an on- or near-site

renewable electricity source needs to be established or electricity purchased from the market needs to be linked with a renewable electricity/energy certificate (REC). An REC is a tradable, nontangible commodity that represents proof that a defined unit of electricity/energy was generated from an eligible renewable energy resource.

Arguably, sourcing renewable electricity using RECs is considered a low-hanging fruit on the decarbonization journey. This is true for most developed countries, especially where renewable electricity is more available. Care needs to be taken in countries with a less-developed renewable electricity infrastructure, especially where local regulations differ from global carbon accounting standards requirements, (e.g., internationally recognized certificate standards do not apply and no rights due to the certificate are transferred to the electricity consumer).

There are several ways to generate renewable electricity or other forms of energy; some are also eligible to generate on or near company premises. Most common for pharmaceutical facilities, as mid-size consumers, is the installation of photovoltaic panels, but other technologies like photothermic or geothermic can be installed, sometimes in combination with panels. Installing on-site renewable capacity technically transforms a scope 2 into a scope 1 energy source; however, it is a contributor to scope 2 decarbonization as it often replaces a carbon-bearing external electricity mix with a more renewable footprint. On-site or near-site renewables can be "classical" investments, i.e., facilities run and owned by the operations owner, or through leasing from a third party that operates and/or financed it initially. The latter is commonly covered by a power purchase agreement (PPA) between energy generator and its user, but other forms of partnership are possible (e.g., in industrial parks). The choice between a PPA and owner operations depends on several factors, e.g., owner know-how, expected payback timelines, and internal depreciation rules and funding priorities.

As photovoltaics are the most commonly used type of on- or near-site renewables, key considerations for the business case should be discussed. When sizing the appropriate photovoltaic capacity for a given site, a few factors need to be taken into account: peak capacity, energy storage, structural factors, and grid integration. Sunlight and electrical power fluctuate within a day and also within a year. Photovoltaic output is commonly defined in peak capacity (in watts); however, it is not a constant source of electricity, as would be ideal for pharmaceutical operations having a rather stable electricity demand. To compensate, electricity from the grid is typically used.

Second, this question needs to be answered: whether electricity generated should be stored and used at later points in time to flatten out the electricity supply. Batteries or other storage solutions are a nonnegligible cost factor and need to be carefully considered. Especially for installations aimed to cover full demand of operations, storage should be investigated carefully.

Third, structural factors like whether the building can carry the additional load of the panel installation need to be considered, and accessory support structures might be needed. Last, the integration of the photovoltaic system in the overarching energy grid infrastructure on-site (and potentially beyond) needs to be examined. Many examples of photovoltaic installations on or near sites of pharmaceutical sites are evidence of its applicability to the industry [13].

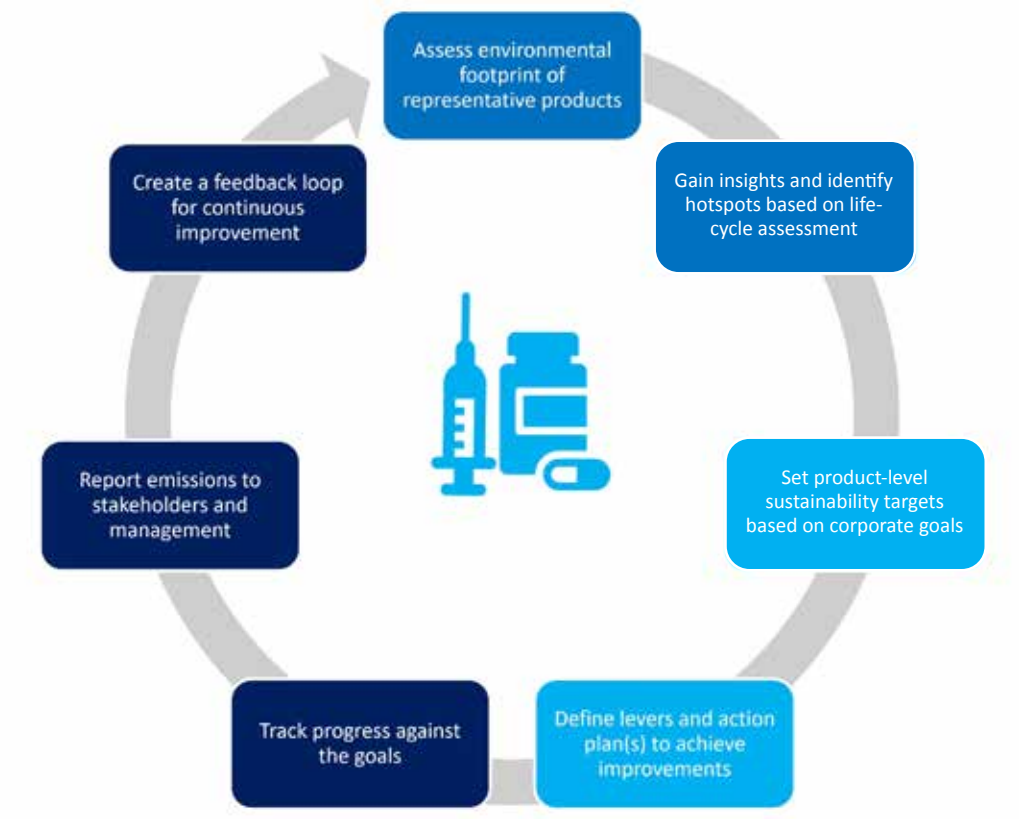
Finally, other sources of purchased energy (e.g., steam, heat, cold) should be highlighted. In principle, the preceding considerations apply to principles of energy generation, GHG accounting mechanism through certificates, and use.

In summary, the scope 2 decarbonization strategy for a typical pharmaceutical operations site or network resides on sourcing renewable energy covered by renewable energy certificates, coupled with on- or near-site renewable generation.

Scope 3

Scope 3 emissions are the result of activities from assets not owned or controlled by the reporting organization, but that the organization indirectly impacts in its value chain [14]. Scope 3 emissions, also referred to as value chain emissions, can represent the largest source of emissions for companies. In the pharmaceutical industry, the biggest impactors are purchased goods (e.g., materials, chemicals), services (e.g., contract manufacturing organizations

Figure 4: Roadmap to net zero through product environmental footprint.



[CMOs] and contract development and manufacturing organizations [CDMOs]). These impactors need to be influenced directly to engage their own GHG reduction, as well as internally though product-level decisions.

Strategies for decarbonization of scope 3 GHG emissions are manifold. Typically, the absolute emissions, but also the complexity, are higher compared to scope 1 and 2. Keeping scope 3 reductions "for later," however, is problematic, as regulations in more and more countries define accountabilities and requirements of the manufacturer/market authorization holder concerning their scope 3 emissions.

There are three relevant scope 3 accounting standards that may be used in pharmaceutical industry:

1. Scope 3 standard accounts for value chain emissions at the corporate level
2. Product standard accounts for life-cycle emissions at the individual product level
3. Corporate standard, a standardized accounting methodology for companies to quantify and report their corporate GHG emissions

These three standards provide a comprehensive approach to value chain GHG measurement and management [5].

Levers for reducing scope 3 emissions can be grouped into two categories: (1) external supply chain levers and (2) internal business and design levers. The first category requires engagement with Tier-1 suppliers as well as suppliers deeper in the supply chain (Tier-2, Tier-3... Tier-n) to incentivize and support them in reducing their own scope 1 and 2 emissions. Depending on the material or service provided by the supplier, the actions for GHG reduction can vary greatly. A contract manufacturer would likely have similar GHG sources and scope 1 and 2 solutions as other biotechnology and pharmaceutical manufacturers compared to a transportation provider or supplier of agricultural raw ingredients and therefore require different mitigating actions.

Levers for how to engage this variety of suppliers as a customer can be mapped on two axes: financial versus nonfinancial and reward versus penalty [14]). For example, a financial reward could be providing beneficial terms while a nonfinancial penalty could be the use of decarbonization criteria in procurement [15]. For suppliers to address their own scope 2 emissions, which are part of customers' scope 3, suppliers can join strategic partnerships for sourcing renewable energy, such as the Energize program via Schneider Electric [16].

The second category covers the internal business choices that have an influence on scope 3 emissions. This could range from

product and process design decisions (e.g., solvent selection, inhaler propellant replacement, and packaging design) to employee travel and commute policy (e.g., limiting air travel, favoring zero/low-emissions modes of transportation on daily commute), and everything in between. To accelerate decarbonization across the value chain, it is also important to push for additional innovative solutions, by funding and piloting new green technology [17].

A product-driven scope 3 perspective aims at making informed choices to reduce GHG emissions from pharmaceutical products. The first step is to understand the carbon footprint of the full life cycle of the product. This assessment helps identify "hot spots" or key drivers of carbon footprint, which in turn helps indicate activities that could have the most impact on scope 3 emissions. Based on the calculations used for product declarations, the emissions baseline can be assessed, and scope 3 reduction planning can be done. In general, these will be done via prioritizing, identifying, and implementing design levers in research and development. In addition, depending on the company climate goal ambitions, additional investigation into design lever opportunities for the commercial portfolio is needed. Decarbonizing commercial products is challenging due to the highly regulated nature of the industry. However, depending on a product's refiling schedule, opportunities will arise to integrate scope 3 reduction opportunities.

When combined with an action plan and performance measurement, product-level sustainability standards form the basis of an effective scope 3 reduction strategy, helping businesses meet evolving net zero requirements and respond to pressures from customers, value chain, and regulators (Figure 4). It is important to note that external manufacturing in CMOs contributes to scope 3 emissions. Outsourcing to CMOs does not eliminate GHG emissions; it just shifts the scope 1 and 2 emissions to the CMO and scope 3, which may have a worse emissions profile than a company-owned manufacturing sites. Therefore, it is important to carefully select CMOs (as well as other suppliers of goods and services), to ensure they have acceptable environmental sustainability credentials, and to verify they apply rigorous GHG emission reduction protocols.

CONCLUSION

Given the urge to address climate action, the pharmaceutical industry must contribute to a global solution of this crisis. Strategies are based on a mix of generic, industry-wide, sector-specific, and company-specific approaches, which need to be embedded in the framework of international guidelines and declaration and control mechanisms. Some elements of the decarbonization journey can be considered quick wins: others require significantly more time, financial resources, and efforts.

Top management needs to be—and remain—engaged in this journey, which will be a task for decades to come. While the pharmaceutical industry has not yet experienced very strong regulatory, public, and customer/patient headwinds when it comes to sustainability, expectations and pressure will rise. For example, environmental, social, and governance (ESG) ratings and sustainability reports have gained enormous importance to financial analysts and investors and will be increasingly scrutinized. Investing in sustainability is no longer seen as nice to have, but as an essential investment in future-proofing any company's foundation. Moreover, being focused and delivering on sustainability is a crucial factor in attracting and retaining the right talent [18, 19], especially among the younger generation.

Last, efforts to achieve decarbonization may also have other benefits, such as reduced resource footprint (e.g., reduction of water and waste), including circularity principles into the operations (e.g., solvent, water recycling) and products (e.g., recycled content in packaging, reduction of packaging weights).

References

1. Intergovernmental Panel on Climate Change (IPCC). "Sixth Assessment Report: Climate Change 2021: The Physical Science Basis." Finalized 9 August 2021. https://www.ipcc.ch/report/sixth-assessment-report-working-group-i/
2. My Green Lab and Urgentem. "The Carbon Impact of Biotech & Pharma: Progress to the UN Race to Zero." My Green Lab website. Revised November 2022. www.mygreenlab.org/carbon-impact-report-resources.html
3. Target Dashboard. Science Based Targets website. Accessed November 2022. https://sciencebasedtargets.org/companies-taking-action#table
4. Hargreaves, B. "Increasing Sustainability in Pharma Requires an Industry-wide Effort." Pharmaphorum website. Published 29 November 2022.https://pharmaphorum.com/views-and-analysis/increasing-sustainability-in-pharma-requires-an-industry-wide-effort/
5. World Resources Institute and World Business Council for Sustainable Development. "Corporate Value Chain (Scope 3) Accounting and Reporting Standard." Greenhouse Gas Protocol website. Published September 2011. https://ghgprotocol.org/sites/default/files/standards/Corporate-Value-Chain-Accounting-Reporing-Standard_041613_2.pdf
6. "Net Zero by 2050–A Roadmap for the Global Energy Sector." IEA website. Published May 2021. https://www.iea.org/reports/net-zero-by-2050
7. Beattie, K. "Two Real-World Experiences in Global Sustainability." *Pharmaceutical Engineering* 40, no. 2 (March/April 2020). https://ispe.org/pharmaceutical-engineering/march-april-2020/two-real-world-experiences-global-sustainability
8. ISO Standard 14644-16. "Cleanrooms and Associated Controlled Environments—Part 16: Energy Efficiency in Cleanrooms and Separative Devices." May 2019. https://www.iso.org/standard/66331.html
9. International Society for Pharmaceutical Engineering. *Good Practice Guide: Membrane-Based WFI Systems.* Table 2.1. North Bethesda, MD: International Society for Pharmaceutical Engineering. 2022.
10. Carlson, C., and J. Wrampe. "Benefits of Membrane Filtration Systems for Ambient WFI Production." CRB Group website. Published November 2022. https://www.crbgroup.com/insights/benefits-membrane-filtration-ambient-wfi
11. US Environmental Protection Agency. "Overview of Greenhouse Gases." Accessed 27 December 2022. https://www.epa.gov/ghgemissions/overview-greenhouse-gases
12. "Emissions Factors 2022: Annual GHG Emission Factors for World Countries from Electricity and Heat Generation." IEA website. Updated September 2022. https://www.iea.org/data-and-statistics/data-product/emissions-factors-2022#emissions-factors
13. Sheehy, P. "Ireland's Biggest Solar Energy Farm Opens in Kinsale." RTE News website. Published 26 July 2021. https://www.rte.ie/news/regional/2021/0726/1237231-solar-farm-kinsale/
14. PSCI. "Scope 3 Greenhouse Gas Emissions Calculation: Guidance for the Pharmaceutical Industry." Pharmaceutical Supply Chain Initiative website. Published October 2020. https://pscinitiative.org/downloadResourceFile?resource=779

15. Sustainable Markets Initiative Health Systems Task Force. "Decarbonizing Healthcare Supply Chains: Recommendations on How to Drive Emissions Reductions Across Healthcare Supply Chains." Published November 2022. https://a.storyblok.com/f/109506/x/c8d17852a1/smi-hstf-supply-chains-whitepaper.pdf

16. "10 Global Pharmaceutical Companies Launch First-of-its-Kind Supplier Program to Advance Climate Action." Schneider Electric website. Published 4 November 2021. https://www.se.com/ww/en/about-us/newsroom/news/press-releases/10-global-pharmaceutical-companies-launch-first-of-its-kind-supplier-program-to-advance-climate-action-6182848cf01af478b619ddd4

17. "Incentives for Scope 3 Supply Chain Decarbonization: Accelerating Implementation." World Business Council for Sustainable Development website. Published 3 November 2022. https://www.wbcsd.org/Programs/Climate-and-Energy/Climate/SOS-1.5/Resources/Incentives-for-Scope-3-supply-chain-decarbonization-accelerating-implementation

18. Pickup, O. "How Sustainability Has Become an Advantage in the Talent War, but Candidates Aren't Fooled by 'Greenwashing' Say Experts." Worklife website. Published 9 November 2021. https://www.worklife.news/talent/how-sustainability-has-become-an-advantage-in-the-talent-war-but-candidates-arent-fooled-by-greenwashing-say-experts/

19. MacPherson, J. "Businesses Lagging on Sustainability, Risk Losing the War for Talent." Mercer website. Published 16 June 2022. https://www.uk.mercer.com/newsroom/businesses-lagging-on-sustainability-risk-losing-the-war-for-talent.html

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Keith Beattie has over 25 years of experience in the pharmaceutical industry. In 2006, he first discovered a passion for sustainability whilst working at Eli Lilly, where he developed sustainability in a complex research and development laboratory campus, resulting in a 30% reduction in energy use and the facility being awarded the Carbon Trust Standard for energy management, a first in the industry. Since 2013, Keith has been leading a global engineered solution provider, specializing in advising and assisting pharmaceutical and life-science sector clients to deliver on their carbon, energy, and water reduction goals as well as compliance and product quality requirements. Keith is member of the ISPE Sustainable Facilities, HVAC and Controlled Environments Community of Practice, and significantly contributed to the creation of ISO 14644-16 (energy efficiency guidelines for cleanrooms). He has been an ISPE member since 2013.

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SUSTAINABILITY:
Corporate Ambition, Governance, and Accelerated Delivery

By Guy Wingate, Ylva Ek, and Patricia (Trish) Melton, PhD

The imperative for global action to tackle climate change is clear and the pharmaceutical industry has a key role to play. Governments have entered into international commitments to reduce climate impact (carbon emissions) and protect nature (water, land, air, and biodiversity) with policy frameworks established to facilitate and drive progress against agreed targets [1, 2]. The effect to the pharmaceutical industry spans its end-to-end activities, including the residual impact of used and unused medicines on the environment. Research and development, manufacturing, commercial (sales and marketing) activities, and their extended supply chains including logistics are all within this scope.

As emphasized at the recent UN Climate Change Conference COP27 (held at the end of 2022 in Sharm el-Sheik, Egypt), international focus is now on implementation. Supporting standards for science-based targets are available and being refined to help organizations measure and manage their environmental impact [3, 4]. Most companies have some existing initiatives underway, but many do not yet have a fully comprehensive and integrated program.

This article explores effective management and oversight processes for accelerated delivery of large-scale programs of work. Practical challenges of working across multiple organizations and countries are discussed together with the growing expectation for independent audit and assurance of claimed benefits delivery. A collaborative mindset must prevail between pharmaceutical companies, suppliers, and regulators and include strategic partnerships that go beyond the pharmaceutical sector so we can move together to a more sustainable future.

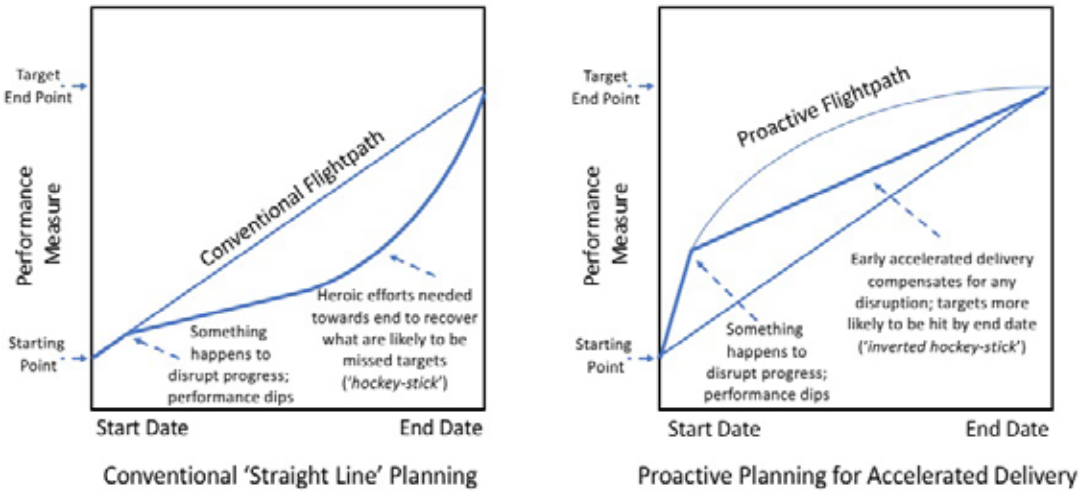
SCOPE AND SCALE OF CORPORATE AMBITION

Company boards have a duty of service to their shareholders to proactively identify and address key risks impacting their organization. These expectations are defined in various national codes [5–7]. Failure to properly address the topic of environmental sustainability not only impedes wider efforts to address climate change, but also could have a material impact on the company's business. For instance, in the future, the company might be unable to supply products and services against new and emerging sustainability requirements, lose sales to competitors who are recognized for their superior sustainability performance, or receive financial penalties or fines for noncompliance.

There are also less tangible, but still very important, reputational risks associated with not taking the topic seriously enough, including damaged reputation—making it harder to attract and retain key talent, especially as potential new recruits become more value driven in their choice of employer—and loss of public goodwill and government discretion, which could adversely impact revenues and investment decisions. The risks are equally applicable to both privately owned and publicly traded companies.

Small- to medium-sized pharmaceutical companies, together with suppliers of goods and services, are not typically held to the same governance standards as larger companies. But they will still need to align with their customer requirements, prioritizing environmental sustainability alongside rather than behind revenue generation. Alternative sources of supply may be sought if suppliers cannot meet their customer expectations. A robust discussion will be required for the company board to agree on the level of ambition for their organization.

Figure 1: Planning for accelerated delivery.



Environmental sustainability goes beyond continuing conventional energy reduction and waste elimination programs to include impacts on water courses (e.g., antimicrobial resistance), effects of pollution on air quality, and a focus on biodiversity, including preserving and restoring ecosystems. The public and investors expect meaningful and stretching goals (e.g., a time horizon of 2030 is much more engaging than 2050). Future market access for medicines will increasingly depend on sustainability prerequisites being satisfied before being able to supply: for example, risk assessments needed for EU product authorization [8], and performance data accompanying commercial tenders for UK National Health Service.

In response, many companies are introducing a new dedicated Environment, Social, and Governance (ESG) scoreboard that will be published as part or alongside the annual shareholder report. Both the company's carbon footprint (CCF) and product carbon footprint (PCF), which describes the total amount of carbon emissions generated by a product or a service over the different stages of its life cycle, for their highest-impact products should be included in the ESG scoreboard. It is key that sustainability goals are confirmed as achievable before they are published. A meaningful method of reporting tangible progress should also be developed that can be consistently applied over the years ahead. Environmental sustainability programs are long-term (ongoing) initiatives and cannot be reported the same way as shorter-term new product developments, factory builds, or major IT deployments.

Company boards should anticipate some tough internal debate when setting goals. Being bold will require business model tradeoffs such as key investments in new facilities or reformulated products, closing facilities that can no longer meet expectations, and changing suppliers and service providers where needed. Companies are expected to take responsibility for ensuring their suppliers and service providers are aligned with their goals. They cannot abdicate corporate accountability for environmental sustainability by handing over responsibilities to a third party. Rather, companies must ensure what they do is appropriate and proportionate.

Company boards should expect growing pressure from the public, shareholders, governments, and employees to do more and go faster. Interim targets for end goals should therefore be set to challenge conventional "straight-line" planning (as shown in Figure 1), which will miss the end goal if some unforeseen event disrupts progress unless a heroic effort is made to recover performance (the so-called "hockey-stick" performance profile). It is recommended that an early step-change in tangible performance is sought to accelerate overall delivery so that if some unforeseen event disrupts progress then it is still relatively easy to achieve the end goal performance (an "inverted hockey stick" performance profile) (see Figure 1).

This change in mindset will increase pressure in the business. Company boards can expect some pushback from leaders and managers who will already be consumed with existing business objectives. It is vital to be clear on priorities to mitigate the squeeze on middle management and ensure creative thinking is employed to seek win-win solutions that collectively address improved sustainability performance, quality, and safety alongside other business objectives. Development of a clear decision-making framework will help establish and maintain consistent and ethical priorities.

It is quite possible that, despite best endeavors, companies will not be able to fully realize absolute goals such as net zero carbon or net positive nature. In this scenario, offsets may be required by which the company invests in external initiatives to improve environmental sustainability. Ideally these initiatives will be in the same geographic region and address the shortfall in a

particular goal (e.g., investment in forestry developments or water preservation).

The use of offsets has come under some criticism owing to it being perceived as an excuse for not doing more within the business. Therefore, before deploying offsets, companies should be able to demonstrate that they did as much as reasonably practical to directly address parameters under their control. Remember, too, that some offset projects will take many years to come to fruition before a company can claim credits for benefits realized: new woodland, meadows, etc., must mature before they can realize their full potential for carbon reduction, and then these ecosystems must be maintained over the long term to secure and preserve these as ongoing benefits.

Once the company's strategic goals and the resulting financial implications are understood and agreed upon, a transformation program with supporting governance and reporting can be put in place. The company board should be given a progress report at least annually, and more frequently if there are decision points or escalation items requiring their attention. A suitable scorecard will need to be developed to show progress against strategic objectives comprising a mix of both lead and lag measures.

Company boards should consider having external verification of progress on their environmental sustainability goals rather than relying on internal reporting to avoid claims of "greenwashing" and the damage that can do to corporate reputation. Independent certifications and statements of assurance can then be used in annual company reports to shareholders. External lobby groups and industry benchmarking organizations such as Dow Jones Sustainability Index and Sustainalytics' ESG ratings will use this and other information released by the company to assess progress. In the future, a common standard comprising a simple set of vital few measures for ESG reporting may emerge. But in the meantime, companies need to align to evolving best practices.

TRANSFORMATION PROGRAM

A transformation program comprising key workstreams and appropriate governance oversight will be needed to deliver on company goals. Consideration should be given to design the workstreams to best fit existing organizational structures, objectives, and priorities. Not all workstreams will trigger new projects; it should be possible to augment existing work.

A central transformation team should be formed that is connected with local business functions and project teams to manage the transformation. The head of that team should have a proven track record of portfolio program management across multiple business units given the potential size of the program. Maintaining strong links with key stakeholders across the business will also be very important. Formal qualifications in program management, such as PRINCE2 [9] or PMI certification [10], and leveraging any previously established working relationships will be advantageous.

Some firms have elected to create a central funding pool to resource all related projects, whereas other firms have asked their business to integrate sustainability into their existing business plans. While each approach has its pros and cons, the most pragmatic approach would seem to be a fusion of both. This would help ensure a good balance is struck between local managers having ownership without overwhelming them with a new central program in which they feel they have little influence. Costs should be monitored and benefits tracked so that ROI projections can be affirmed. The CEO and CFO should be fully engaged and support expenditure plans where the total spend over multiple years on environmental sustainability is very large.

Company standards for various aspects of environmental sustainability should be defined in technical documents and procedures that complement Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), Good Distribution Practice (GDP), etc. that apply to the scope of activities undertaken by their organization. The quality of pharmaceutical products must not be adversely impacted; patient safety must be protected at all times. And of course, standards and operating procedures should be kept up to date under change control. New and emerging nongovernment organization (NGO) guidance, government legislation/regulations, and other recognized reference standards (e.g., national tender requirements) will also be separately monitored to ensure internal standards remain in compliance.

A training curriculum with supporting technical training courses will be essential to build wider organizational capability. Do not assume existing training programs cover what is needed in sufficient detail. Many new graduates will be very familiar with the latest sustainability developments and expectations, whereas other staff may lag behind what is needed without realizing it. It may be necessary to create bespoke training to meet local needs where standard training materials are not available. Further training may also be needed for management engagement and supportive behaviors. Competence-based functionality and assessments can be provided in training where appropriate to help assure a successful capability build. It may be necessary to hire subject matter experts to develop and maintain these standards and provide technical support in this fast-moving topic area.

Timely and accurate progress reporting will be needed: overall company performance for senior executives, workstream level for program management, and at a local business level. A set of operational key performance indicators (KPIs) should be defined for the transformation program to measure tangible performance improvement and not just consist of progress reporting on program activities. Where possible, the KPIs should link to externally defined measures used by external lobby groups and industry benchmarking organizations.

A subset of sustainability metrics should be selected for integration within business dashboards to promote a balanced and considered view on overall business performance and ensure sustainability does not become viewed as a silo. More specific local business performance dashboards can be developed with relevant measures to track and drive the transformation bottom-up.

The central transformation team should be transparent and escalate poor program delivery and poor performance improvement. Calculations behind performance measures need to be clearly defined and controlled. It is important to recognize that small changes in the math used may simplify internal processes but they can also mean those same calculations become out of sync with external benchmarks defined by independent organizations overseeing industry progress. Care must also be taken to ensure no gaps or double accounting exist in the overall calculation of climate and nature impact in the supply chain. This can be particularly challenging when considering the contribution of third parties who do not yet have the methodology or means to provide accurate figures.

GOVERNANCE

Overall governance should be kept as simple as possible. Given the significance of environmental sustainability, it will most likely be appropriate to have a new dedicated top-level forum to provide strategic direction and to oversee implementation and delivery of targets. The seniority of the appointed chair of the top-level forum will indicate how seriously the company is taking environmental sustainability (e.g., having C-suite chair would set a clear tone from the top of an organization).

Representatives from R&D, manufacturing and supply, and commercial should all be included at the top-level forum, along with the main functions needed for delivery such as the sustainability group, engineering, procurement, legal, and corporate communications. The quality function must also be engaged where sustainability changes impact product registrations, analytical testing, manufacturing processes, etc. to ensure that the quality, safety, and efficacy of medicines and devices are not compromised in any way. Of course, care must be taken to ensure quality is not used as a change barrier to avoid sustainability improvements where there is no impact on product quality. Stakeholders will need to be fully informed so that they can have robust conversations and agree on the best solution in what are sometimes difficult and challenging situations.

Responsibilities for members of governance fora should be assigned to named individuals. Decision-making expectations and meeting cadence should be clear. More frequent governance meetings should be considered when initially setting up the transformation program and its supporting activities compared to later routine oversight of established work items.

Existing company governance structures and processes can be used to support this new top-level governance, assuming these meetings can give sufficient priority and agenda time to environmental sustainability. Amendments will be needed to terms of reference and membership of governance meetings. New dedicated oversight will be required where exiting governance cannot be leveraged.

Financial impact assessments that test various business scenarios should be refreshed each year, with their output linked into routine business planning. The first intent should be to avoid environmental impacts (e.g., applying new technology or perhaps simplifying a process to remove a problematic step). Consideration can then be given to reducing the environmental impacts that remain. For instance, a company could consider dramatically improving internal circularity to reuse what might otherwise be waste materials.

> The quality of pharmaceutical products must not be adversely impacted; patient safety must be protected at all times.

Another example might involve developing symbiotic relationships with other companies for them to use what might otherwise be waste (a "circular economy"), e.g., reusing preheated water between neighboring firms or enabling a critical mass of plastic packaging materials to be collected for reprocessing. Firms co-located in a shared building or on a shared campus might also work together to reduce the environmental impact of communal energy streams. An example of this in practice is the Kalundborg Symbiosis, a public-private partnership between pharmaceutical and other companies in Denmark in which they proactively design their businesses operations to exchange material, water, and energy streams to reduce their expenses as well as their collective environmental impact [11].

A repeating cycle of risk scenarios can be spread over several years—for instance, key products followed by internal operations and then external supply chain—to build up a comprehensive picture that can be shared with the company board. Guidance with supporting templates and tools has been issued by both the Task Force on Climate-Related Financial Disclosures (TCFD) and the Task Force on Nature-Related Financial Disclosures (TNFD) [12, 13]. These assessments provide a vital link that aggregates various company risk mitigation activities into a consolidated report.

PROGRAM MANAGEMENT

A holistic and comprehensive program plan needs to be developed to coordinate the various workstreams that span the company. Each workstream may contribute to more than one of the company's sustainability goals. Detailed plans for each workstream need to be developed with critical paths to capture the rate-determining activities that must be successfully completed. Potential bottlenecks between parts of the organization that should work together will need to be addressed. Organizational silos must not be allowed to impede progress. Plans should be aligned with business plans, with interdependencies identified for proactive management. Roles and responsibilities between the central transformation team and local business units need to be clear. There should be a clear handshake between central and business governance.

Waterfall charts are recommended in order to identify a series of improvement opportunities for each end goal (e.g., reduction in carbon, wastewater reduction, improved air quality, increased biodiversity index). The charts can be used to prioritize opportunities to be implemented within the workstreams and to give confidence that goals will be achieved. Implementation glidepaths for each goal can then be developed for conventional project management.

Supporting KPI dashboards should be developed with lag and lead indicators to track current achieved performance and prospective performance improvements, respectively. Care must be taken to avoid the mix of workstream plans and waterfall charts becoming too complex, as this will impact the ability to effectively maintain them. It is important to be able to drive delivery and maintain momentum of the overall program.

The central transformation team should also put into place effective risk management processes that acknowledge and leverage local processes and procedures. Introducing a rigid central standard that overrides local practices can cause confusion and lead to a lack of ownership. Guidance on risk assessment should be provided to promote consistent understanding of the significance of risks. Risk logs should be maintained to track progress with risk mitigation. Risk treatment needs to be timely and proportionate to the characteristics of the risk posed, with local risks managed according to local practices.

Interventions will be needed where warning signals of emerging challenges are identified to avoid them becoming problematic. Realized problems should receive an effective root cause analysis with on-time closure of remedial actions reviewed by appropriate governance. Solutions for thematic issues and problems should be shared across the business, recognizing that global plans will require approval by top-level governance and should be tracked to complete by the central transformation team. Escalation items should only be referred to top-level governance if they cannot be resolved at a local level.

Communicating keynote successes will help encourage engagement and support. It is important to select meaningful news items rather than rely on KPI metrics. Stories that are easily shared are best, describing a tangible achievement: for example, zero to landfill for a region or globally, formulations changed to remove impact on endangered species or habitats, and external awards from accredited authorities such as Carbon Disclosure Project certification.

Companies should ensure transparent reporting against established public standards—such as the Greenhouse Gases (GHG) Protocol Corporate Standard, which categorizes carbon emissions associated with a CCF—and high-visibility metrics such as the product carbon footprint (PCF). Both CCF and PCF targets and achievements, together with progress against any nature goals, should be published for full transparency [14].

Supply Chain and Supplier Partnerships

It can be challenging to assess and track the climate and nature impact in the value chain that is out of the direct control of a pharmaceutical company due to the numerous parties and processes involved. Attention should initially be given to first-tier suppliers to identify the biggest opportunities upon which to focus improvement efforts. After this, second- and third-tier suppliers can be prioritized where they have a particular role to reduce climate impact and improve nature associated with a finished pharmaceutical medicine.

The influence that an individual pharmaceutical company has on a supplier can be very limited when they represent only a small proportion of that supplier's business. In these situations, it is worthwhile to engage in collaborative initiatives with other companies that have aligned interests to increase leverage on that supplier (pending compliance with anticompetition laws and suitable confidentiality agreements).

The Ecovadis' ESG platform—with its standard performance scorecards, benchmarks, and performance improvement tools—is a good example of how many companies are settling on a common approach. The use of such platforms and supporting tools makes processes more cost-efficient for suppliers too, reducing the number and variety of assessments received and progress reports requested from different customers, and for different supplier manufacturing sites related to the same customer.

Strategic partnerships provide another means to help suppliers that might otherwise not be able to access green initiatives. For example, the Energize initiative involving Schneider Electric and 10 pharmaceutical companies is aimed at facilitating access to the green energy market for power purchase agreements for hundreds of small- to medium-sized suppliers that might not otherwise be readily available to them [15]. The program is a first-of-its-kind effort to leverage the scale of a single industry's global supply chain in a precompetitive fashion to drive system-level change.

Environmental sustainability, of course, is just one factor considered when engaging suppliers. Many pharmaceutical companies are integrating sustainability as one of a number of topics—such as human rights and quality, health, and safety—to be evaluated and managed together within an integrated approach. A

single supplier audit may cover multiple topics instead of having a separate audit for each topic, and the results of that audit shared within a customer community with appropriate confidentiality. The procurement department will need to work closely with the business, including the quality department and other relevant functions, to understand the consequences of serious deficiencies and agree on action plans.

Some changes can take a long time to implement, especially if regulatory approvals are needed. Ultimately, if a supplier is unable to meet a customer's sustainability expectations or requirements for another topic, and they cannot address the root cause behind that, then an alternative source might be sought. Care must be taken to ensure selected alternatives do not bring other more pressing problems to the supply chain, such as compromised product quality. Early decisions will therefore be needed on critical supplier relationships so that actions can be completed in a timely manner that does not compromise the pace of overall sustainability transformation.

CULTURE CHANGE

A shift in organizational culture will almost certainly be required to support corporate transformation. It is our experience that there will likely be a strong pull from the broader workforce in support of company efforts toward environmental sustainability. Indeed, many employees will want to be proactively involved in initiatives. While a company will not want to distract employees from their immediate duties, it is also important not to dampen their enthusiasm and commitment for sustainability.

Many companies are engaging their workforce through tangible activities through which employees can feel that they are making a contribution. A good example is the removal of unnecessary single-use plastics in the laboratories and on-site cafeterias. Another example is restoring land in the immediate vicinity of company building to promote biodiversity and to create walking routes for employees to relax in their breaks (with the added benefit of the well-being these spaces can provide).

Middle managers may be more reluctant to fully engage with a corporate transformation program. They may feel squeezed with too many and changing priorities and environmental sustainability can come across as another item on their growing list. The corporate transformation program needs to ensure business priorities are clearly aligned with sustainability goals, rather than trying to make space for separate new targets. An almost seamless integration of objectives will make a big difference to

getting things done. A focus of what really matters each year, and it will change year to year, will be key to success.

Last but not least is the role of senior leaders. They need to lead from the front and not just assign a member of their respective management teams to take accountability for sustainability on their behalf. The corporate transformation office should take time to map out senior stakeholders and consider how to best support them in their company's journey. Some leaders will be natural champions for environmental sustainability, and others less so. Keeping the company's sustainability objectives and transformation program simple and straightforward will help engage leaders while establishing a clear roadmap of projected achievements that can be used to illustrate their commitment and success.

Incentive schemes are worth considering for senior leaders, middle managers, and the broader workforce to foster and reward the good governance and practical execution needed for a successful environmental sustainability transformation. Experience suggests that selecting a couple of current KPIs from the ESG scoreboard works well for shared bonuses and can be supplemented with personal objectives used in annual performance reviews relevant to an individual's role. Pharmaceutical companies can also use recognition events with accompanying publicity to encourage the participation and performance improvements of suppliers. Transparent targets and progress reporting across the supply chain will promote engagement and wider confidence in achieving commitments.

CONCLUSION

Our industry is committed to the patients we serve. This commitment goes beyond the efficacy, safety, and availability of products to address medical needs to include the environmental sustainability of our business operations and products. Comprehensive action by pharmaceutical companies is required to facilitate the necessary transformation for environmental sustainability.

We hope this article inspires the following considerations:

- Has my company set the right level of ambition to help combat climate change?
- Is corporate governance strong enough to drive progress?
- What can be done to do more and go faster?

This article aims to answer these questions with shared insights and experiences on how to establish and manage successful companywide programs for accelerated delivery of environmental sustainability goals. Such programs will be large and complex, presenting a multitude of challenges to manage. Their smooth running and transition to "business as normal" belies the planning and execution effort to make it so.

Further information on project management to help up set up an environmental sustainability program can be found in ISPE's *Good Practice Guide: Project Management for the Pharmaceutical Industry* [16].

References

1. United Nations. Department of Economic and Social Affairs: Sustainable Development. "Transforming Our World: The 2030 Agenda for Sustainable Development." October 2015. https://sdgs.un.org/2030agenda
2. United Nations. Climate Change. "The Paris Agreement." 2015. https://unfccc.int/sites/default/files/english_paris_agreement.pdf
3. Science Based Targets Initiative. www.sciencebasedtargets.org.
4. University of Oxford Department of Biology. Nature-Based Solutions Initiative. www.naturebasedsolutionsinitiative.org/
5. Peter A. Atkins, P. A., M. S. Gerber, and K. J. King. "Directors' Oversight Role Today: Increased Expectations, Responsibility and Accountability—A Macro View, Harvard Law School Forum on Corporate Governance." 10 May 2021. https://corpgov.law.harvard.edu/2021/05/10/directors-oversight-role-today-increased-expectations-responsibility-and-accountability-a-macro-view/
6. Financial Reporting Council. "The UK Corporate Governance Code." April 2016. https://www.frc.org.uk/getattachment/ca7e94c4-b9a9-49e2-a824-ad76a322873c/UK-Corporate-Governance-Code-April-2016.pdf
7. European Commission. "Corporate Sustainability Due Diligence." Proposal for EU Directive. May 2022. www.europarl.europa.eu/RegData/etudes/BRIE/2022/729424/EPRS_BRI(2022)729424_EN.pdf
8. European Medicines Agency. Committee for Medicinal Products for Human Use. "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use." 1 June 2006. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf
9. PRINCE2 (PRojects IN Controlled Environments). www.prince2.com/usa/what-is-prince2
10. Program Management Institute (PMI). https://pmi.org
11. Kalundborg Symbiosis. http://www.symbiosis.dk/en/
12. Task Force on Climate-Related Financial Disclosures. "Annex: Implementing the Recommendations of the Task Force on Climate-related Financial Disclosures." October 2021. https://assets.bbhub.io/company/sites/60/2021/07/2021-TCFD-Implementing_Guidance.pdf
13. Task Force on Nature-Related Financial Disclosures. "The TNFD Nature-Related Risk and Opportunity Management and Disclosure Framework, Version v.03 Beta Release." November 2022. https://framework.tnfd.global/wp-content/uploads/2022/11/TNFD_Management_and_Disclosure_Framework_v0-3_B.pdf
14. World Resources Institute and World Business Council for Sustainable Development. "The Greenhouse Gas Protocol: A Corporate Accounting and Reporting Standard." March 2004. https://ghgprotocol.org/sites/default/files/standards/ghg-protocol-revised.pdf
15. Begley, A. "Energize Initiative to Boost Renewable Energy Access for Pharma Suppliers." *European Pharmaceutical Review* 8 November 2021. https://www.europeanpharmaceuticalreview.com/news/165113/energize-initiative-to-boost-renewable-energy-access-for-pharma-suppliers/
16. International Society for Pharmaceutical Engineering. *Good Practice Guide: Project Management for the Pharmaceutical Industry*. North Bethesda, MD: International Society for Pharmaceutical Engineering. 2011. https://ispe.org/publications/guidance-documents/project-management-pharmaceutical-industry

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A NEW REGULATORY APPROACH to Drive Sustainable Medicines

By Per Niklasson and Greg Carr

To enable changes across the pharmaceutical industry, sustainability should be included alongside quality, efficacy, and safety when assessing medicines. This article reviews two case studies that cover sustainable pack types and extension of shelf life. With the drive to manage unmet medical need through acceleration of drug development programs, postapproval sustainability variations will always be required. Here we discuss if current regulations will be fit for a sustainable future.

For decades, the pharmaceutical industry has worked to transform the lives of patients by researching, developing, and manufacturing medicines for a wide variety of common and rare diseases, something that will continue for many years to come [1]. Now there's an additional focus: sustainability. The implementation of sustainability-driven initiatives associated with the manufacture of medicines faces many challenges from a chemistry, manufacturing, and controls (CMC) regulatory point of view. The regulatory procedures and data requirements make it very complex to improve sustainability for launched products compared to building sustainability into new products during development.

As such there's a growing question of how the industry will improve the sustainability profile of its existing medicines and ensure that sustainability is designed into new medicines, such as products, with a reduced environmental risk, greener manufacturing technologies, and recyclable delivery systems and packaging [2]. With the pharmaceutical industry being such a major contributor to the global economy and impacting the lives of so many [3], the industry finds itself under the spotlight of expectation to give a higher priority to sustainability initiatives.

In order to provide innovative solutions for embedding sustainability into products, industry requires collaborative assistance from global regulators to allow faster implementation of sustainability initiatives by using risk-based scientific approaches as described by ICH Q12 [4] and driving harmonization across regulators globally. Global regulators are assessing drug products for quality, efficacy, and safety. To enable changes across the industry, sustainability should be included alongside these.

This article provide insights from a CMC regulatory perspective into what is required for the pharmaceutical industry to develop and manufacture sustainable medicines which minimize the impact on the environment, utilizing two case studies based on real-world experience.

CASE STUDY ONE: PACKAGING MATERIALS

The first case study looks at developing more sustainable packaging materials and reducing the size of packaging materials. Industry invests significant effort into designing sustainability into the development of new medicines. But what happens when these sustainability-driven options are not developed, or available, to meet the timelines of launching new products for patients, and what about the increasing drive to improve the sustainability profiles of existing medicines that have been, and will continue to be, marketed for many years?

Let's use the example of the packaging for medicines. Modifications to the primary and secondary packaging would be considered for a number of sustainability-driven reasons, such as to:

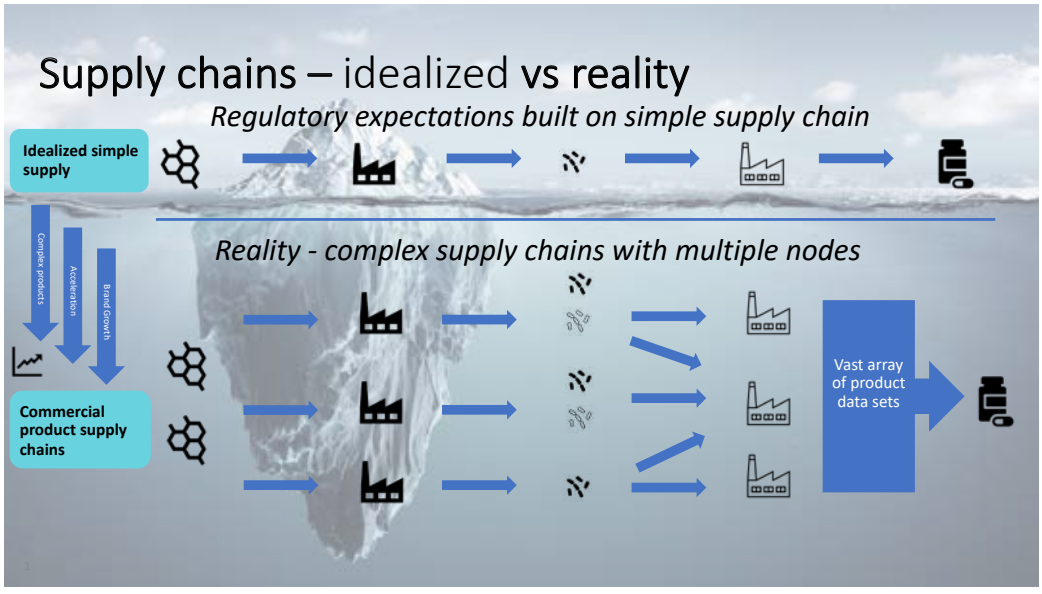
- Decrease material consumption and wastage by reducing the primary packaging dimensions
- Further material savings in the secondary packaging due to reduced primary pack dimensions
- Improve shipping efficiency with reduced secondary packaging dimensions
- Move toward more environmental-friendly or recyclable materials in primary and secondary packaging

As part of the development program for a new medicine, the onus is on the pharmaceutical companies to create sustainable packaging solutions during the development program and have data to

Table 1: Comparison of implementing a sustainable primary pack for new products and established products.

	New Product in Development	Established Product
Product Details	2 strengths for global launch	2 strengths marketed globally
Supply Chain	Simple: • 1 formulation site • 1 packing site	Complex: • 3 formulation sites • 9 global packing sites
Data Requirements	Up to 6 stability studies: • 3 batches per strength	Up to 36 stability studies: • Complex matrix of formulation and packing site • Cost of up to $4.5 million
Implementation Globally	At product launch	Up to 5 years from first stability set down

Figure 1: The reality of commercial supply chains versus regulatory expectations.



support its use available in time for registration. This facilitates launching the new medicine with the desired packaging and meeting the sustainability objectives. The exact data requirements are dependent on the pharmaceutical product. However, this generally equates to a certain amount of real-time stability data in the proposed commercial pack, with the shelf life granted at registration depending on the length of real-time data available, as exemplified in Table 1. It is worth noting that at the time of initial registration, supply chains can often be simpler than those of established commercial products because the new product has yet to undergo brand growth, globalization, and invest in maximizing supply as new indications are introduced.

For commercialized medicines, the equivalent development and switch to a more sustainable packaging material is significantly more challenging. This is largely due to the necessary postapproval regulatory action, lack of harmonized supporting data requirements, and varying approval times observed in different markets. For established medicines supplied globally, the difficulty is further increased by the complexity of supply chains and the impact this has on regulatory data requirements. Figure 1 provides a graphical representation of the situation, where regulatory expectations are built on an idealized simple linear supply chain, i.e., single API site, single formulation, and packing sites.

The reality is that commercial supply chains are becoming increasingly more complex with multiple nodes at every stage, driven by brand growth, the need to accelerate the supply of medicines to patients, and new products becoming more complicated due to the need for specialized equipment for certain unit operations and this being available at specific sites only.

As shown by this sustainable packaging material example, the result of these complex commercial supply chains is that the data requirements to support postapproval changes in the commercial space are vastly increased. Table 1 provides an example of a global product with multiple strengths and packing sites. Due to differing market regulatory requirements—such as packing site-

specific stability studies and registration samples—the volume of data required to support changes such as these is large, demands significant investment to generate the stability data, and takes a considerable amount of time to implement due to both data generation and lengthy regulatory variation procedures.

There is a case for regulatory authorities worldwide to recognize scientific approaches and base their required data package on scientific and technical rationale rather than a request to simply produce data. For example, when introducing an alternative packaging material that is demonstrated to be equivalent or superior, there is no scientific need for additional site-specific stability data to be generated from an established packing site.

The impact of this lack of regulatory harmonization for both regulatory procedural timeframes and data requirements vastly increases the complexity of introducing sustainability-driven improvements to commercial medicines, which creates a barrier for industry. Global harmonization of approval times and requirements, such as a single data package applicable to all markets, would facilitate faster implementation, making changes such as this more achievable for industry to implement.

As stated previously, the onus is on pharmaceutical manufacturers to develop sustainable packaging solutions during product development ready for commercial launch. For commercialized products, however, there is a need for authorities to harmonize regulatory procedures and data requirements to make switching to a more sustainable packaging material a viable and attractive option for pharmaceutical manufacturers. This would reduce the cost and time investment by eradicating unnecessary data requirements based on sound scientific reasoning, which in turn would facilitate faster implementation.

New EU-wide rules were proposed in November 2022 [5] for recyclability requirements for all packaging. According to the proposal, all packaging shall be designed for recycling by 1 January 2030 and be recycled at scale by 1 January 2035. However, exemptions are proposed until 1 January 2035 for immediate packaging (immediately in contact with the medicinal product) for medicinal products for human use. The proposal includes an exclusion from the obligation of a minimum recycled content in plastic packaging for immediate packaging, and for outer packaging in cases where it has to comply with specific requirements to preserve the quality of the medicinal product. The exclusion is justified with human health protection and to avoid any risk to the security of supply and to the safety of medicines.

CASE STUDY TWO: SHELF LIFE EXTENSIONS ACROSS THE LIFE CYCLE

The concept of shelf life extensions is applied differently across the life cycle. Why do submissions require prior approval for commercial products in many markets, but the same markets need no submissions at all for clinical products? Global harmonization with risk-based approaches is required. Does real-time stability data always need to be reviewed by the health authorities or would company internal assessment be appropriate in some situations?

Longer shelf life would be considered for a number of sustainability-driven reasons, such as to:

- Reduce waste and unnecessary product destruction due to short shelf life by increasing the expiry date for new products without health authority prior approval, provided that quality, safety, and efficacy of the drug product can be confirmed by internal company assessment
- Lower carbon dioxide emissions from transportation, made possible by decreasing the number of in-market replenishments as larger quantities of product could be sent to markets in a single shipment; this is especially relevant for the markets that require 75% remaining shelf life for customs clearance

CLINICAL SUPPLY

Development of a Formulation

The drug substance to be investigated in a clinical development program must be administered as a formulation. This formulation will change during the clinical development program. In early clinical phase (phase 1 and 2A), a simple but not patient-friendly formulation is used. An example is an oral solution or suspension that is stored frozen. The formulation must be thawed, diluted, and poured into a dosing cup before being administering to a participant in a clinical trial. Administration is usually performed at a hospital and supported by a pharmacy at the hospital.

For late clinical phase (phase 2B and 3), a patient-friendly but complex formulation is developed. An example is an oral modified release tablet with a functional coating. The tablets are packed in primary and secondary packaging by the sponsor of the clinical trial. Administration is usually performed at home and there is no involvement of a pharmacy.

Shelf Life

For a new formulation—for example, a tablet—the shelf life and storage conditions should be defined based on the stability profile of the drug substance and the available stability data for the drug product. If there is a limited amount of stability data obtained, then the shelf life will be short.

As a development project progresses from early to late clinical phase and switches formulations, the short shelf life for the new formulation becomes problematic. There is insufficient time to generate stability data to ensure a shelf life suitable of meeting the duration of late-phase clinical trials. There are two options to solve this.

- Extend the shelf life for already manufactured supply as more stability data becomes available. This needs to be addressed in the initial clinical trial application and for some countries as amendments to the approved clinical trial application.
- Waste the already manufactured supply and manufacture new supply. This conflicts with sustainability regarding using natural resources in the best way.

Considering sustainability, wasting current supply and manufacturing new product should be avoided as a priority, especially when stability data demonstrates the existing product continues

Table 2: Regulatory procedures for extending the shelf life for clinical supply provided a shelf life extension plan was included in the approved clinical trial submission.

Notification Before Implementation	Notification After Implementation	No Notification	No Shelf Life Defined
Brazil	Canada	Russia	Argentina
	China	Taiwan	Israel
	European Union		Japan
	Norway		Mexico
	UK		South Africa
			US

Table 3: Example of a shelf life extension plan.

	Period (Months)					
Available Stability Data	6	9	12	18	24	36
Proposed Shelf Life	18	21	24	30	36	36

to be safe to use. Opportunities to facilitate this exist, such as provision of a shelf life extension plan as part of the initial clinical trial application, which allows the shelf life to be extended without a prior approval submission in the majority of markets, as shown in Table 2.

In the EU, extrapolation may be used if stability studies are conducted in parallel to and throughout the duration of the clinical studies [6]. Extrapolation is the practice of using a known data set to infer information about future data [7].

Any proposal for a future shelf life extension without a substantial modification submission should be stated in the clinical trial application. A stability protocol covering the maximum planned shelf life, statement to confirm reporting to the competent authority of any significant negative trend in results, and the shelf life extension plan should be provided. An example of a shelf life extension plan is shown in Table 3.

This demonstrates that there are countries that encourage faster implementation of sustainability initiatives for clinical supply (i.e., extending the shelf life for already manufactured supply) by using risk-based scientific approaches (i.e., the shelf life extension plan). If more markets took this approach, sustainability would be improved.

COMMERCIAL SUPPLY

Launch of a New Product

At the point of submission of a new marketing application, the minimum allowable amount of stability data is 12 months at the long-term storage condition and 6 months at accelerated conditions for batches representative of the commercial product [8]. In an ideal situation, the commercial formulation is the same as used in phase 3 clinical trials and it may be possible during the review period to provide additional real-time stability data to justify a longer shelf life upon approval. However, this granted shelf life is not always sufficient to meet the needs of the supply chain to ensure continued supply to patients, and as more real-time data becomes available the shelf life is increased by postapproval regulatory updates.

Packing Sites

For a product launched globally it's not unusual to use several packing sites at different geographical locations. Market differences in regulatory data requirements, such as packing-site-specific stability data, has implications on the data required for the shelf life because stability data is required to be generated for each packing site in the supply chain (as described in case study one), therefore significantly increasing the cost and quantity of data needed to be generated. If markets were to harmonize requirements and recognize scientific and technical rationale, the need to generate additional data could be avoided.

Extending the Shelf Life for Commercial Products

Similar to clinical products, data from stability studies must demonstrate that the approved end-of-shelf-life specifications are still met in order to extend the shelf life for a commercial product. Extrapolation of existing data can also be employed for commercial products, although the majority of markets do not recognize this and insist on the provision of real-time data. The major difference for commercial products is that regulatory submissions are required to be approved prior to implementation of the new shelf life in the vast majority of markets. Egal and Lombardi [9] summarize the current regulatory reporting categories for pharmaceutical products shelf life extension in ICH, PIC/S, and WHO member countries. In only 3 out of 63 countries it is allowable to implement a shelf life extension before informing the health authority.

Similar to case study one, it is observed there is no global regulatory harmonization concerning both data requirements and regulatory procedure type. The need for pack-site-specific stability data shows no global regulatory consistency in recognition of scientific approaches, all of which again demonstrates how this acts as a barrier to industry in implementing sustainability changes such as this.

In this case study, it is also evident there is no harmonization between the clinical and commercial regulatory environments for the same market for what should be a relatively simple change based on real-time stability data. If the commercial regulations were to adopt an approach similar to that used for the clinical products, implementation of sustainability changes such as these would be accelerated.

A pharmaceutical quality system (PQS) is a management system used to direct and control a pharmaceutical company with regard to quality. ICH Q10 [10] describes a model for an effective PQS that is based on International Standards Organization (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP)

regulations and complements ICH Q8 (Pharmaceutical Development) and ICH Q9 (Quality Risk Management) [11, 12]. A PQS can be implemented throughout the product life cycle and should facilitate innovation and continual improvement.

For postapproval changes, such as shelf life extensions, where data is generated to prove suitability of the proposed change, it should be possible for companies to manage the implementation within the PQS and not have to seek prior approval from regulatory agencies. This could be applied to both the clinical and commercial environments and would facilitate a faster implementation of sustainability-driven benefits. Reference is made to the paper by Egal and Lombardi [9] , who raise the question on management of postapproval changes such as this, via PQS only.

CONCLUSION

Will the current regulations be fit for a sustainable future? To enable changes across the industry, sustainability should be included alongside quality, efficacy, and safety when assessing medicines. Two revisions in how postapproval changes are handled could significantly enable sustainability changes, provided that they are combined with an effective PQS:

- For more sustainable pack types, data requirements should be changed to remove the need for packing site-specific data.
- To extend shelf life, regulatory procedures should be changed to allow notification after implementation.

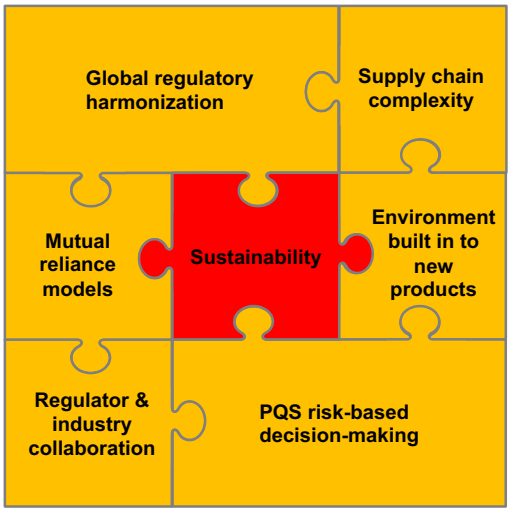
However, inclusion of sustainability as a regulatory requirement would take legislative action and would not be solely determined by regulators in many countries. This could mean that it would take many years to implement.

The two case studies presented provide the general themes that can be applied to the implementation of any sustainability driver within the pharmaceutical industry for which there is regulatory impact. As industry strives to develop novel and sustainable medicines to meet future patient needs and looks to implement as quickly as possible the reduction in environmental impact of the marketed products, help is required from global regulators in two main areas: harmonization and risk.

Regulatory applications are consistently finding divergence in the interpretation of ICH guidelines by regulators from different countries [13]. This divergence becomes a disincentive to improvements and has even caused temporary drug shortages in some markets. When coupled with the differing market data requirements to support regulatory changes, inconsistent approaches to use of scientific rationale, and varying regulatory procedures and timelines, the barriers to industry are high in terms of data generation, cost, time, and complexity of implementation.

Reliance procedures do exist and are used in certain circumstances, but these are not applied consistently or globally. Owing to this global regulatory complexity, individual postapproval changes often take years for full worldwide approval, which reduces the impact of the sustainability improvements they can offer. Current regulatory mechanisms and guidance for these

Figure 2: The sustainability jigsaw.



postapproval changes do not consider the company's latest product and process knowledge when determining the type of filing required to implement the change. The application of ICH Q9 (Quality Risk Management), or the effectiveness of a company's PQS to manage a postapproval change is not considered during the assessment of a change [9, 14].

Application of ICH Q12 [4] could facilitate the introduction of changes to support sustainability. ICH Q12 provides a framework to facilitate the management of postapproval CMC changes in a more predictable and efficient manner. The Post-Approval Change Management Protocol (PACMP) is a regulatory tool that provides predictability regarding the information required to support a CMC change and the type of regulatory submission based on prior agreement between the marketing authorization holder and regulatory authority.

Such a mechanism enables planning and implementation of future changes to established conditions (ECs) in an efficient and predictable manner. The PACMP may be submitted with the original marketing authorization application or subsequently as a standalone submission and can be proposed independent of any prior identification of ECs. The PACMP requires approval by the regulatory authority, and the conditions and acceptance criteria outlined in the protocol must be met and results communicated to the regulatory authority in the manner previously agreed, in order to implement the change(s).

According to the information on the homepage of ICH in January 2023, ICH Q12 has been implemented in the US and Japan but implementation has not been completed in Brazil, Mexico, European Union, Singapore, Canada, Korea, UK, China, Saudi Arabia, Switzerland, Chinese Taipei, or Turkey.

Sustainability is at the heart of a complex regulatory jigsaw (see Figure 2) connected to the themes presented in this article. The current regulatory frameworks for manufacturing changes to

medicines have evolved nationally and regionally and are built on patient safety considerations and safety disasters from the past.

These frameworks are not globally harmonized and do not consider future risks such as the environment. Should authorities be doing more to drive sustainability into medicines by building this into regulatory expectations? Is a modern framework required that includes consideration for the environment, should it be quality, safety, efficacy, and sustainability? Should authorities characterize the carbon footprint and/or environmental impact of an approved product? Should there be an expectation that pharmaceutical manufacturers produce an action plan for reducing the carbon footprint of their medicines?

From the discussions presented previously, one thing remains clear: to drive sustainability forward, industry and regulators require implementation of risk-based approaches as described in ICH Q9, Q10, and Q12. Without the necessary support from global regulators, can industry really deliver on the ICH Q10 expectations of innovation and continual improvement, and utilize this to improve the sustainability profiles of the medical products which impact the lives of so many?

References

1. The IQVIA Institute. "The Global Use of Medicines 2022." 9 December 2021. www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicines-2022/global-use-of-medicines-2022-outlook-to-2026-12-21-forweb.pdf?_=1664783698550
2. Salmenperä, H., S. Kauppi, H. Dahlbo, and P. Fjäder. "Increasing the Circularity of Packaging Along Pharmaceuticals Value Chain." *Sustainability* 14, no. 8 (2022): 4715–4731. doi.org/10.3390/su14084715
3. EFPIA. "The Pharmaceutical Industry in Figures. Key Data 2022." www.efpia.eu/media/637143/the-pharmaceutical-industry-in-figures-2022.pdf
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management." Published November 2019. https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf
5. European Commission. "European Green Deal: Putting an End to Wasteful Packaging, Boosting Reuse and Recycling." Press Release. 30 November 2022. https://ec.europa.eu/commission/presscorner/detail/en/ip_22_7155
6. European Medicines Agency. Committee for Medicinal Products for Human Use. "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials." 27 January 2022. EMA/CHMP/QWP/545525/2017 Rev. 2. www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational_en-1.pdf
7. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q1E: Evaluation for Stability Data." Published 6 February 2003. https://database.ich.org/sites/default/files/Q1E%20Guideline.pdf
8. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q1A(R2): Stability Testing of New Drug Substances and Products." Published 6 February 2003. https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf
9. Egal, N., and K. Lombardi. "Shelf-Life Extensions for Pharmaceutical Products." *Journal of Validation Technology* (26 January 2020). https://bpi.bioprocessintl.com/hubfs/IVT%20-%20GXP%20Archive/1-21-IVT%20Network%20-%20Shelf-Life%20Extensions%20For%20Pharmaceutical%20Products%20-%202021-03-02-1.pdf
10. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q10: Pharmaceutical Quality System." Published June 2008. https://database.ich.org/sites/default/files/Q10%20Guideline.pdf
11. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q8 (R2): Pharmaceutical Development." Published August 2009. https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf
12. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q9: Quality Risk Management." Published November 2005. https://database.ich.org/sites/default/files/Q9%20Guideline.pdf
13. Beierle, J., N. S. Cauchon, T. Graul, Y. Hedberg, M. B. Holm, J. V. Lepore, R. MacKenzie, et al. "Toward a Single Global Control Strategy: Industry Study." *Pharmaceutical Engineering* 42, no. 1 (January-February 2022). www.ispe.org/pharmaceutical-engineering/january-february-2022/toward-single-global-control-strategy-industry
14. Vinther, A., and E. Ramnarine. "Solving the Global Continual Improvement and Innovation Challenge: How an Effective Pharmaceutical Quality System Can Transform Post-Approval Change Management." *PDA Journal of Pharmaceutical Science and Technology* 73, no. 5 (2019): 517–521. doi.org/10.5731/pdajpst.2019.010827

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Case Study: MEETING MANUFACTURING NEEDS WITH A NET ZERO ENERGY FACILITY

By Andy Campbell, PE

The expected FDA approval for a Treprostinil dry powder inhaler revealed a need for the manufacturer to expand its warehousing and logistics capabilities to support its growing operations. The company's senior leadership wanted to ensure this expansion came with as minimal an impact on the environment as possible, so a key priority was to provide a net zero energy facility. With a vision for what the project could be, the team named the upcoming endeavor Project Lightyear. To infinity and beyond, indeed.

In anticipation of the expected FDA approval of our new inhalation device for inhaled Treprostinil—and the only dry powder inhaler approved by the FDA for use in pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease—we identified the urgent need to expand warehousing and logistics capabilities to support growing operations. This new warehouse and logistics center would provide the much-needed space for continued growth and be vitally important in delivering critical resiliency for facility and logistical operations.

It was important to senior leadership that this expansion of treatment options and further fortification of the supply chain came with as minimal an impact on the environment as possible. Given the project's critical nature, it was clear that its success hinged on developing a clear roadmap of project requirements from the onset of conceptual design. The company's CEO laid out that roadmap succinctly during an early project meeting with the corporate real estate, operations, and manufacturing leadership teams.

The primary priority was to provide a site net zero energy facility to support the manufacture, storage, and distribution of the Treprostinil dry powder inhaler and to do so without the use of fossil fuels onsite. This meant no natural gas, diesel, or propane generators for a critical cGMP facility containing an extensive cold room. From there, the cascading priorities laid out the ultimate project framework.

The facility would need to be designed, constructed, commissioned, and validated for occupancy and use by the summer of 2023, when projected growth would test the capacity of existing facilities. It was to be built and assembled using materials made in the United States to the greatest extent possible, without affecting the net zero mission or schedule requirements. This was pursued with the understanding that the first three priorities held precedence and knowledge that this was the kind of executive-led freedom that would allow the project to be a success. From there,

Identifying an experienced architect, engineer, general contractor, and commissioning agent that could work together in a collaborative design-build environment was critical to the success of such a technical and cutting-edge project.

the team was pushed to reduce embodied carbon within the construction of the building, limit ecological impacts within the project's footprint, and pursue LEED and other sustainable certifications.

ASSEMBLING THE TEAM

Identifying an experienced architect, engineer, general contractor, and commissioning agent that could work together in a collaborative design-build environment was critical to the success of such a technical and cutting-edge project. Ultimately, the general contractor was selected based on their extensive experience in developing sustainable projects and history of successfully delivering unique and highly technical projects.

In seeking out a partner architecture and engineering firm, the project benefited from local expertise. An exceptional architecture firm was selected that focused on developing first-in-class facilities for their clients while using creative solutions. A national, industry-leading professional engineering services firm was selected that specialized in consulting, planning, designing, and commissioning dynamic systems for the built environment.

With offices in the Raleigh-Durham, North Carolina, area and around the country, the architecture and engineering firms brought a wide purview on sustainability and extensive portfolios of experience in the life science and biopharmaceutical industry. Their depth of expertise in sustainability and technically complex projects—many of which were the first of their kind and required innovative thinking and persistence—resonated with our team given the task at hand.

Commissioning was procured at the concept design phase to round out a strong team with an integrated design approach. This helped maximize the benefits of having the third-party commissioning provider (CxP) in applying lessons learned from past projects. It also helped ensure that the owner's project requirements were upheld from the beginning for this complex and unique facility. The chosen CxP focused on finding solutions and resolving issues instead of only documenting problems, which proved beneficial in turning over fully functional and highly integrated facilities for critically complicated projects already within the company's portfolio.

Other key stakeholders that played a vital role in the project included the Durham city and county building inspection departments, the Research Triangle Foundation, Duke Energy, FM Global, and numerous departments and teams from within the corporate umbrella itself. All groups brought a unique perspective and bought in on a collaborative environment to ensure that all parties not only achieved positive outcomes, but also gained knowledge and solutions that can be applied to future projects. Together, the assembled team was ready to undertake this ambitious and groundbreaking project.

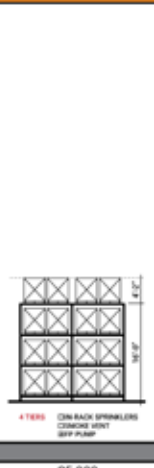
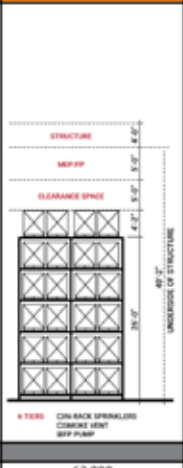
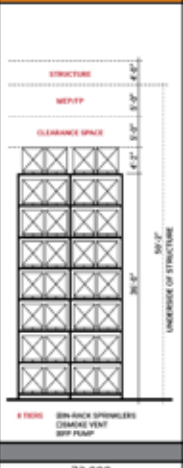
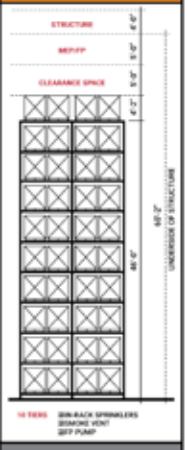
BLOCKING AND TACKLING

To minimize the project's ecological impact, the selected location was an existing underutilized company-owned soccer field and associated field house on our Research Triangle Park campus in Raleigh, North Carolina. The soccer field was adjacent to our new site net zero childcare center. This location provided direct access to TW Alexander, enabled the team to avoid clear-cutting the remaining wooded area on campus, and provided for the adaptive reuse of the existing field house. This adaptive reuse significantly reduced the embodied carbon of the project while creating substantial cost savings due to the overall reduction in newly constructed square footage.

The first step of the building design process was to work with the operations team to determine facility scale, shipping and receiving rates and requirements, and pallet rack position counts required in both ambient and cold room storage. These project requirements were pulled together with the purpose of right-sizing the building to meet capacity needs while optimizing operational efficiencies. The building's shape and scale was critical to informing the overall design because it impacts everything from rack layout to air circulation to the rooftop area available for solar power generation. Ultimately, it was all guided through close coordination with the commercial operations team to anticipate future sales volume and associated storage requirements.

Through these discussions, the team determined that the facility would need to accommodate +/- 2,400 pallet positions within ambient storage and +/- 600 pallet positions within cold room storage. From that base requirement, the building's shape

Figure 1: Pallet rack optimization.

Pallet Rack Vertical Count	4 High	6 High	8 High	10 High
				
Critical Design Considerations				
Total Size (w/ Admin and Mezzanine) (GSF)	85,000	63,000	73,000	70,000
Total Roof Area (SF)	65,000	51,000	54,000	50,000
Acres Disturbed	Slightly More	Baseline	Slightly Less	Slightly Less
Foundation System (pending Geotech and Eng)	Spread Footings	Spread Footings	Spread Footings+Deep Fnd.	Spread Footings+Deep Fnd.
WH Slab on Grade (thickness & reinforcing #/sf)	8"	10"	12"	14"
Structural Steel Frame / Bracing		+20%	+40%	+60%
HVAC Equipment / Volume Increases	Little Less	Baseline	More	Significantly More
In Rack Sprinklers	Not Required	Not Required	Required	Required
Construction Schedule	~ Same	Baseline	Slower - Due to Height	Slower - Due to Height
Building Metrics				
Construction Cost	$$	$	$$	$$$

and footprint was directly informed by a detailed pallet rack height optimization exercise. As illustrated in Figure 1, the design-build team analyzed rack heights ranging from 4 racks high to 10 racks high. The team then analyzed the subsequent impacts on cost, schedule, constructability, technical performance, facility operations, code requirements, and campus integration.

Notably, the differences in building form factor created a delta upward of 15,000 sq. ft. of built area and seven figures of cost implications. These ranges had to be balanced with the needs for a functional net zero energy facility. Ultimately, a six-rack-high ambient storage ratio was determined to provide optimized functionality for the project and would lock in the basis of design. From there, blocking plans ultimately led to a 7,000-sq.-ft. cold room, 27,500 sq. ft. of ambient storage, and facility support spaces that brought the total building to 52,500 sq. ft.

NET ZERO DESIGN

Within the sustainable design community there is much discussion and debate over the practical definition of terms like *net zero energy* and *net zero carbon*. For clarity of purpose, our project team defined *site net zero energy* as a "grid-connected facility for which every watt of energy needed to operate and run the facility over a twelve-month period would be covered by onsite renewable generation." This framing does not allow for offsite production or carbon credits to close the gap. It does allow for the facility to export to the local utility grid or "bank" energy when the facility is operating in a net positive condition (generating more energy than it uses) and to subsequently pull from the local utility grid or "withdraw" the complement of that energy during periods of time when the project is using more electricity than it is generating.

For the design process, it is standard practice to establish an anticipated target goal energy usage intensity (EUI) for the facility. EUI is simply a ratio of energy used by a building divided by its area and provides an important benchmark of energy usage versus its peers. It is generally established through the utilization of baseline expectations from completed and operational projects. From there, the design team's job is to reduce the EUI to the greatest extent possible and provide for the most feasible energy-efficient facility.

Although this is a rather standard starting point for a typical project, there are not published baseline expected EUIs for hybrid ambient/cold room cGMP warehouses and certainly not for similar facilities pursuing such ambitious and innovative sustainable design goals. This is due in large part to the critical nature of these facilities and an overarching design concept provides comprehensive support of belts and suspenders to ensure the building's operation conforms with cGMP requirements. Essentially, energy usage is typically considered secondary to building operations.

Once again, Project Lightyear would be blazing its own path forward, as even attempting to establish a baseline from scratch was often met with blank stares and shrugs from many critical trade partners. However, after discussing the project's goals, those same vendors were excited to get on board and learn with the team. One such example is that energy usage requests to the cold room

Figure 2: Project rendering of design expected to meet the desired net zero energy goals.

vendor were answered with "I don't know" and a litany of follow-up questions digging into the minute details: details such as how often the overhead door into the clean room would be opened in a typical day and how long it would remain open. Such details were vitally important in establishing a meaningful baseline EUI and in turn helping develop a design expected to produce the desired net zero energy goals (Figure 2).

PASSIVE DESIGN STRATEGIES

Once a baseline EUI was fully developed and understood, the design team took their initial step of designing to net zero energy. This first step is typically done by reducing the building's energy demand by implementing passive design strategies. Something as simple as the facility's siting, or cardinal orientation, at a chosen location can be very impactful on its ultimate energy usage and photovoltaic (PV) energy production.

An analysis of the site can help ensure that its chosen orientation provides for optimal PV energy production. This is typically done through solar analysis modeling, which models and tracks the sun's course through the sky at different points in the year. Analyzing that data enables the design team to lay out the site and orient the building to ensure that the planned rooftop PV panels are aligned for peak production values. Beyond that, the project goal of reducing ecological impact was achieved by locating the building to minimize impact to adjacent wetlands, existing tree canopy, and other natural habitats. As noted previously, using the existing soccer field was beneficial in pursuing this goal.

Project Lightyear now had a location and skeleton framework. As was a reoccurring theme, planning for the skin of the building—the façade and roof—would require optimizing often competing priorities. Ensuring the proper level of insulation while providing a cost-effective solution and always with an eye to embodied carbon would prove to be a difficult balancing act. Increasing the insulation values of the roof, walls, and windows was critically important to reducing the facility's energy usage. Building insulation is directly responsible for reducing the facility's heat gain or loss during the various seasons but also comes with significant increases to cost and the facility's embodied carbon. And at a certain point, the amount of insulation hits a level of diminishing returns.

The design team worked hard to balance these issues and right-size the facility's insulation requirements. Ultimately, the roof was insulated to R-42, the façade walls to R-21, and the windows with a U-value of 0.35. These requirements would directly impact and ultimately reduce the sizing of major HVAC equipment and drive down the facility's energy usage by greatly reducing wasted energy.

Further reduction of wasted energy was accomplished through operational design direction. Light occupancy sensors were included to maintain minimum code-mandated lighting levels in unoccupied areas. This allows for lighting to automatically dim and even turn off when not in use. Temperature setbacks and demand control ventilation in administrative spaces ensured that operational noncritical areas were not working hard to heat and cool overnight, over weekends, and generally when not in use.

Energy-Star-certified computer and office equipment would help reduce plug loads and eliminate vampire drain of electronics when not in use. Regenerative charging electric lift trucks would capture the kinetic energy of lift trucks in motion when slowing or stopping to recharge the electric batteries, reducing the energy pull and timing when they are plugged in to recharge. By themselves, these passive design strategies would combine to reduce the expected building EUI by more than 8%—amounting to significant energy savings over the life of the project and would be critical to getting closer to the site net zero project goal.

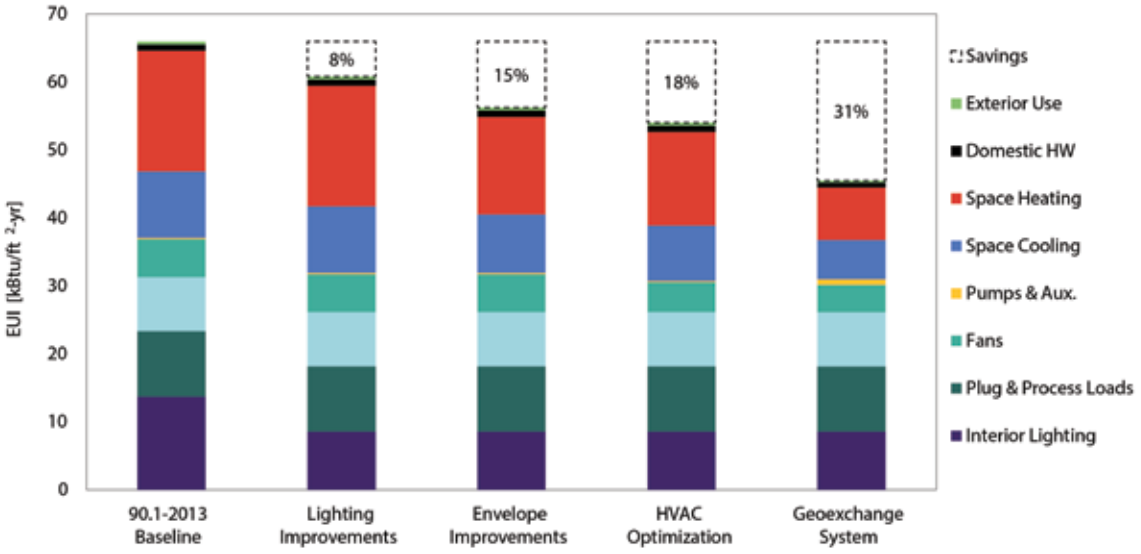
ACTIVE DESIGN STRATEGIES

From there, the designers needed to provide for the optimized implementation of efficient systems and equipment through active design strategies. These design choices typically focus on the major energy draws within a building with a specific focus on HVAC systems, which contribute the most significant driver of building energy use in a cGMP facility.

To provide the most energy-efficient HVAC system for this project, the design team used a closed-loop geothermal exchange system as the basis of design. Geothermal HVAC systems work by using the Earth's temperature as a thermal battery. Fluid is pumped through a series of pipes deep into the Earth and heat is either absorbed or rejected based on current air temperature. Acting as an extremely high-efficiency heat pump, the geothermal HVAC system achieves its efficiency by using the steady-state temperature of the Earth rather than the highly variable outside air temperature to condition the building.

The specific design of a given geothermal HVAC system is dependent on the building requirements and the local subsurface geophysical properties. The building requirements help establish the annual heating and cooling loads as well as the peak heating and cooling loads. The local geophysical properties define how attuned the ground is to accept a geothermal system in a given

Figure 3: EUI design improvement.



location, which informs the design depth and number of vertical geothermal bores required.

Ideally, the annual and peak heating and cooling loads would be well balanced, providing for an equally well-balanced geothermal system. Being too unbalanced in either direction can lead to long-term losses of efficiency in the system. Project Lightyear's design loads led to an annual heating load nearly 10% over cooling and a peak cooling load more than double the peak heating load. This added significant complexity to the system to ensure that the bore field and system was properly sized.

To account for those requirements, the geothermal system was sized with 40 individual bores—each 500 feet deep into the Earth—on a total of three independent loops. This system is coupled with six pipe heat recovery chillers and a 20-ton fluid cooler to balance the loads and optimize the efficiency of the design. A dedicated outdoor air system is used to provide dedicated ventilation to the space and meet the cGMP requirements of the ambient storage area. Recirculating air rotation units then use that ventilation to ensure a consistent steady-state temperature profile throughout the entirety of the ambient storage space.

The cold room itself has dedicated air-cooled direct expansion (DX) condensing units and a desiccant makeup air handler unit sized to the specific expectations on temperature and humidity needs as well as anticipated operational use profiles. The connected field house is optimized through the use of a dedicated air-source variable refrigerant flow (VRF) system.

The design team further utilized LED lighting, variable speed fans and pumps, premium efficiency motors, and high-efficiency cold storage equipment to fully reduce the expected EUI for the building by 31%. This progressive improvement is illustrated in Figure 3.

RENEWABLE ENERGY GENERATION

These sustainable design elements are a feat in and of themselves for a project of this caliber, but they alone do not make for a net zero energy facility. The final element entails a renewable clean energy supply. The team accomplished this by introducing an extensive rooftop PV array. The design of solar PV systems requires careful consideration of the remaining EUI to offset, building massing and orientation, expected PV panel degradation, solar yield variability, future capacity needs, and panel, inverter, and racking system availability.

A probabilistic approach to this design is typically used in concert with the previously mentioned modeling to project theoretical system output over time. In this case, an industry-leading tool called Helioscope was used to assess performance over time. Designing simply to be net zero on day one does not account for the yearly solar variability and annual panel degradation. To ignore these considerations would be shortsighted and likely lead to a facility incapable of reaching its goals.

Conversely, designing for worst-case scenarios and an unlimited timeframe would not be economically nor operationally viable. Nor would it take into consideration local utility requirements for on grid-connected PV system sizing. Rather the array must be sized appropriately with the EUI offset needs and a conservative but realistic eye to the future production.

Based on our experience on previous projects, we have traditionally adopted a PV system sizing baseline of P50 at 10 years. This means simply that we can expect the facility to be operationally site net zero at 50% confidence on solar variability for any given year, even with panel output degradation, recognizing that there are annual variations on the amount of sun the site will receive based on weather conditions.

Figure 4: Illustration of expanded site.

To help work through the complicated design process, the project team brought a third-party PV integrator onboard. They were able to review the basis of design information and verify through their usage of PVSyst Modeling Software and the National Renewable Energy Laboratory's (NREL) regional solar yield dataset. Combined with the project design, the third-party integrator ultimately designed the system to include seven 62 kW Sunny Tripower inverters powered by 1,186 SunPower Maxeon 475-watt panels expected to generate 767 MWh per year. This array will cover nearly the entirety of the facility's roof, making use of every available square foot and providing critical renewable energy generation to make the facility site net zero.

Once operational, it will be important for the project team to validate the design EUI with operational monitoring and metering. To exceed the design EUI would mean the entire project would be at risk of not achieving its site net zero goals. To this end, the design-build team intentionally scaled and sized the PV system to allow for future expansion capabilities (see Figure 4). The inverters as designed have spare capacity to allow for future installation of an added ground mounted array without impacting building operations. While the plan is that the project will exceed expectations, having the ability to correct course ensures that the project will ultimately meet its stated goals.

RESILIENCY AND THE MICROGRID

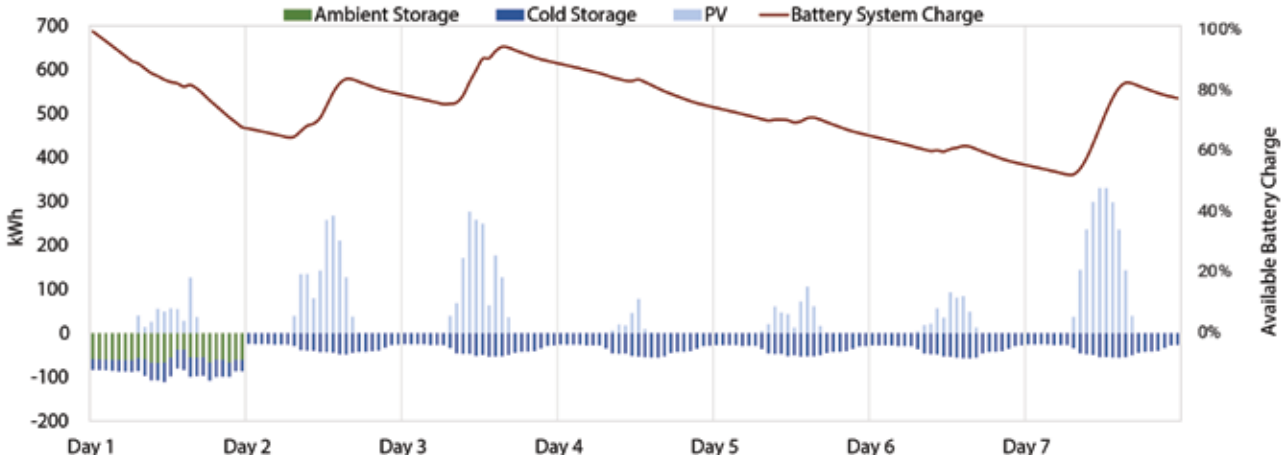
Although the design to this point is expected to meet the requirements that the project be site net zero energy, it would be negligent to leave a cGMP facility of this scale and magnitude without ensuring its critical resiliency. The project priority of eliminating the ability to implement traditional emergency backup systems like diesel or natural gas generators pushed the team to explore lithium-ion battery backup systems. Unlike a traditional generator, which has a theoretical endless supply of backup power, batteries are a finite resource and must be sized specifically for the application. They can be connected to the solar PV systems through a microgrid to be able to recharge when the array is producing a surplus of energy but that is not guaranteed.

A cGMP warehouse and logistics facility like Project Lightyear cannot rely on the expectation that the sun will shine bright to power the PVs and recharge the battery during an extended electrical outage. Consequently, the design-build team worked with operations to determine the worst-case scenario emergency battery backup requirements. Essentially it boiled down to how long the operations team would need to react and reallocate resources if the power went out and the batteries were not able to be recharged from their full charge state.

Simultaneously, the design-build team reached out to the local permitting officials and fire marshal to introduce them to the concept and understand local compliance requirements. Together it was determined that a priority list would be established. The entire building needed to be able to run for 24 hours post outage. From there, loads would be shed for the ambient warehouse, support, and office spaces, allowing only the cold room to remain online for an additional 24 hours. Finally, the team was required to hold an eight-hour tranche of battery power to provide support for the fire pump that feeds the facility, ensuring that in any situation the fire sprinkler system would remain active and operational. Taken together, the loads resulted in a minimum required battery size of 5,310 kWH with 1 MW of peak demand and the ability to operate in "island mode" without utility power.

As had become routine, the team discovered in their research of various battery applications that there was a dearth of potentially applicable systems. The residential-scale market had begun to boom as more homeowners were installing solar panels on their

Figure 5: Battery system projected performance.



It would be negligent to leave a cGMP facility of this scale and magnitude without ensuring its critical resiliency.

roofs and were looking for energy resiliency in markets that encountered regular outages. But residential scale of installation was well below the requirements of Project Lightyear—typically on an order of magnitude of 100 times smaller than required. Similarly, utility scale installations were growing rapidly.

This was particularly so in areas with significant time-of-use penalties or peak-usage charges where utility rate arbitrage is profitable, though these often don't have microgrid capabilities to allow islanding from the grid during an outage. It has also started to become more common as utilities themselves develop significant solar production capabilities and have the need for on-grid storage during times of low or no solar production. The scale of these systems is typically 10 times or larger than Project Lightyear required.

Ultimately, the Project Lightyear team partnered with Tesla to utilize their Megapacks. Each individual Megapack is a self-enclosed modular battery pack that allows for flexibility and resilience and provides 3.1 MWH and 770 kW of capacity. Pairing two provided the required emergency backup for Project Lightyear. The Megapack system was attractive to the project team due to its next-gen lithium iron phosphate chemistry, which greatly reduces the potential for thermal runaway which then reduces potential risk for the project. It comes integrated with an internal cooling system, module inverters connected to an internal 480V AC bus, and independent operation that allows either to support the building load individually. Being a self-enclosed unit, the team was able to locate the system on the exterior of the building, which provided critical code/UL separation requirements and eliminated the need for supplemental fire alarm and sprinkler systems.

The Tesla Megapack is designed to be connected and controlled through a Schneider microgrid control system, allowing it to power the building and recharge when needed. The microgrid switchboard is connected directly to the battery system, rooftop PV inverters, emergency lighting inverter, and building electrical distribution system. Through a detailed building automation system, it is set up to automatically control the potential electrical distribution throughout the facility depending on required use case and battery charge level. As noted previously, it is programmed to shed noncritical loads on demand and as needed to maintain the more critical facilities.

Although the facility was designed for a worst-case scenario of no solar recharge, the design team anticipated that under normal conditions with the fully operational microgrid that the entire facility should stay online for weeks if not months while disconnected from the electrical grid or during an extended outage. Once such example of typical solar production following an extended power outage is shown in Figure 5, with varying amounts of solar production allowing the battery system to recharge fully or

Figure 6: Aerial progress photo.

partially during the daytime. We are hopeful that such a use case is never fully realized and tested but are confident in the ultimate resiliency of this critical facility.

GOING LIVE

Following design and permitting, project construction began October 2021 and is now nearing completion in spring 2023 (see Figure 6). The long path to this point was marked by many challenges, but through close coordination between all project partners, Project Lightyear is expected to be delivered on time, on budget, and fully site net zero. The project team even reached out to our adjacent site net zero energy childcare center to involve the young children in the project in exciting ways. From "touch a truck" days during the heavy civil construction phase to inviting the kids to leave their literal handprints on the final installed crossbeam during the topping out ceremony, this project truly proved to be a learning experience for all.

As on any such groundbreaking project, the lessons learned to take forward are numerous. The most significant lessons learned were based around the microgrid implementation, notably ensuring to design for flexibility in design and having a full understanding of processes during a load shedding scenario.

It is easy to say that only the cold room should be operational if the battery charge drops to a certain level but understanding the operational needs of the cold room widens that boundary. Shipping and receiving must remain operational. Building automation and monitoring systems must remain operational per FDA requirements. Printers and computers need to remain powered on. You cannot just draw a circle around a functional object without understanding the full associated process and cascading affects.

Similarly, we also discovered that the battery backup system did not work as an uninterruptable power source as originally expected but rather responded similarly to a traditional generator. This meant that building systems that needed to remain permanently online required an additional whole-building uninterrupted power supply to cover the few seconds between a power outage and the Megapacks coming online. The late discovery of this issue led to some last-minute design and construction changes that were critical in making sure that the project would be successful.

Working through bleeding-edge sustainable design and integration—most notably with the battery storage and microgrid—would not have been possible without a design team with a clear vision and a local jurisdiction and utility willing to learn along with the project team. Similarly, lingering pandemic-era cost inflation and supply chain issues were mitigated through early subcontractor involvement, critical equipment early release packages, and a design team willing to explore creative and sometimes custom-built solutions when all else failed. Ultimately, the projected is expected to received LEED Gold, LEED Zero Energy, and LEED Zero Carbon certifications.

Our team is eagerly awaiting completing commissioning and validation of Project Lightyear in the coming months and taking final occupancy of the building to begin using this groundbreaking facility. To infinity and beyond!

About the author

Andy Campbell, PE, LEED, AP, is a construction and real estate professional with a combination of experience across commercial construction, sustainable development, green technology, GMP laboratories, and Class A office buildings. Andy received his BS and MS in civil engineering and construction management from Virginia Tech, and is the Senior Project Manager–Corporate Real Estate for United Therapeutics Corp. He has more than 15 years of experience in construction and development and is a frequent speaker at industry conferences on topics related to sustainability, specifically with challenges within the biopharmaceutical industry. Andy has been an ISPE member since 2018.

ISPE 2022 Member of the Year:
Martin Lipa: An Advocate for Knowledge Management

By Marcy Sanford


MARTIN LIPA

When nominating Martin (Marty) Lipa, Executive Director, Knowledge Management, Merck & Co. Inc., for the 2022 Max Seales Yonker Member of the Year Award, Anne Greene, Professor, Technological University Dublin, said, "Arguably the last year has been pivotal for the practice of knowledge management (KM) in the pharmaceutical industry based on new KM frameworks and guidance and resulting engagement by ISPE membership and industry at large. Indeed, one could credit Marty with this advancement as, in addition to significant contributions to educate ISPE's membership on the practice of KM, through his doctoral research he developed several innovative KM-related solutions."

The Max Seales Yonker Member of the Year Award honors the ISPE member who has made the most significant contribution to ISPE during the past year. It is named in honor of a dynamic woman who contributed to ISPE in many different ways and served as a source of inspiration during her battle with cancer.

An active member of ISPE since 2014, Marty was a key contributor to the ISPE *Good Practice Guide: Knowledge Management in the Pharmaceutical Industry. In 2022,* he shared his expertise in knowledge management through an ISPE webinar, an Expert Xchange, articles in *Pharmaceutical Engineering®*, and ISPE's iSpeak blog. He is also a standing member of the ISPE Regulatory Quality Harmonization Committee's Europe-Middle East-Africa Regional Focus Group.

KM BEGINNINGS

Marty has nearly 30 years of biopharmaceutical industry experience and currently leads KM for the Manufacturing Division of Merck & Co., Inc. His prior experience includes various roles in technology, engineering, software validation, and IT. Marty is a Lean Six Sigma Black Belt, has a PhD from Technological University Dublin with a focus on improving KM and its interdependency with risk management, and is an active member of the global KM community as a regular speaker and author.

Marty's journey to becoming an expert in KM started 14 years ago. "I did not know KM was a 'thing' until 2008, which perhaps isn't surprising since KM has only been around for about 25 years now, while quality risk management (QRM) has had 70 years to mature. I was the new IT business partner to Mike Thien, who at the time was the Merck Senior Vice President of MS&T [manufacturing, science, and technologies] and new product commercialization. Concurrently, quality by design (QbD) had introduced the concepts of 'knowledge management' and using 'prior knowledge' and was just taking off, with the release of the associated ICH Guidelines Q8, Q9, and Q10," he said.

"At the time, we had people working in research who were developing models but had no idea how they performed in real-life manufacturing environments," Marty explained. "There was no feedback loop to report what worked and what didn't work. So, there was this discontinuity across the organization between research and manufacturing. Similarly, manufacturing didn't know that research had done troubleshooting on a given problem, or who to contact to find out if they had. There was wasted time and duplicate knowledge creation and inefficiency.

"At the same time, Merck was merging with Schering-Plough Corp.: one day we had 20 manufacturing plants, the next day we had 91, and the right hand truly did not know what the left hand was doing. That really highlighted the need to better connect people across the manufacturing network."

The next steps helped establish a foundation in KM, Marty said. "This led to a year of research and learning about KM, with a heavy dose of benchmarking KM in other industries. An immediate lesson was that KM was not an 'IT thing' but needed to start with a focus on people and process. In time, I had the opportunity to lead the development of our initial KM strategy following a Six Sigma design methodology. A recommendation of the strategy

was to have a dedicated KM group, and I was privileged to be selected as the leader of the newly established KM Center of Excellence."

KM'S VALUE TO THE INDUSTRY

"Of course I'm biased, but I think KM is crucially important to our business—it's indispensable," Marty said. "We are, after all, in a knowledge industry: people create new knowledge, build on the knowledge of others, and think for a living. In fact, almost everyone in our industry is doing KM in some fashion every day, whether it is how we store and search for documents, find experts, capture lessons, transfer knowledge, or connect via communities. But the reality is that most of these KM approaches are highly variable, likely not scalable, and tend to be overwhelmingly localized. These challenges are magnified in larger organizations, but in reality, apply to everyone in our industry given the challenges we face internally (complex products, cutting-edge science, global supply chains, and supply challenges) and externally" (competition, pricing pressures, global markets, and post-COVID-19 expectations for speed).

"I believe there are three distinct and compelling drivers for KM. First, regulatory drivers, starting with KM positioned as an enabler of the PQS in ICH Q10. Second—perhaps with the biggest prize—is leveraging KM for business effectiveness, such as improving process robustness, accelerated problem-solving, more effective technology transfer, and the like. This motivation alone has propelled KM in other industries to a higher level than the pharmaceutical industry has yet to achieve. And the third driver is people. We are in a war for talent with other knowledge industries (and sometimes with each other). I believe those who can help their employees best navigate what their organization knows, to free up their energy to focus on their meaningful work, will have a competitive advantage in attracting and retaining talent."

As part of Merck's KM journey, Marty set up a Virtual Technical Network of more than 25 different communities of practice and more than 5,000 employees joined to ask questions and share knowledge. "Magic happened when people started exchanging ideas. We have had wonderful success stories of saving clinical supplies, cost avoidance, and sourcing urgent equipment and materials. Someone told us, 'I joined the company and thought I just had the people in my office to help me, but then I joined the global community and realized there were more than 200 people willing to help me.' Another engineer said, 'I was always afraid to ask a question, but once I did, I realized people just wanted to help.'"

SHARING KNOWLEDGE

Sharing his knowledge with others comes naturally to Marty. "I am passionate about teaching others about KM for a few reasons. First, it's just in my nature to share and help others. Second, I have found the KM community to be very generous of time, advice, and ideas. I think this is because many of the KM approaches are pre-competitive: there are details and best practices to the 'what to do' but much of the heavy lifting is making these approaches work in the culture of your organization. I have seen our journey come full circle from student to teacher. We have learned from many respected organizations, including Shell, Rockwell Collins, Boeing, American Productivity and Quality Center (APQC), United States Navy Sea, Air, and Land (SEAL) Teams, Microsoft, and many others. As we have thought deeply and worked diligently, we've had great results with savings in excess of $100 million, and have for some time now been asked to share our success stories by the likes of NASA, Corning, the World Bank, Columbia University, and many organizations in our industry."

Knowledge management is crucially important to our business—it's indispensable. Almost everyone in our industry is doing KM in some fashion every day.

Along the way, Marty has also become a teacher as well as contributor to the foundation of KM, as Anne noted her nomination. Marty's "research and contributions are centered on the patient. This research and his other contributions to the practice of KM are ultimately foundational for an effective pharmaceutical quality system and its goals of ensuring safe and efficacious products while also enabling a state of control and the basis for continual improvement. These contributions have also been linked to better decision-making during risk management activities, as well as helping address the drug shortage challenges currently faced by the industry."

Marty thinks that KM holds a huge amount of promise for the pharmaceutical industry's future. "In a time of post-COVID-19 expectations for accelerated product delivery, geopolitical uncertainty, and supply chain challenges, when the external manufacturing world has to be dynamic, there has never been a more important time to connect knowledge and risk."

"I'm proud to be a member of ISPE because it is grounded in the practice of connecting and sharing knowledge," Marty said. The network of people I've been able to meet and interact with is immeasurable. I'm very appreciative of ISPE and humbled to be recognized through this award. I want to acknowledge that I've had many friends and colleagues who have helped me on my journey and would like to thank my colleagues at Merck Manufacturing Division and TU Dublin for all of their support and partnership every step of the way."

About the author

Marcy Sanford is ISPE Publications Coordinator.

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CoP LEADER PROFILES

JAVIER LOZANO

Introducing CoP Leader Profiles

With this issue, *Pharmaceutical Engineering*® launches a new feature in P+E: profiles of Communities of Practice (CoP) leaders. These leaders are central to the success of ISPE's CoPs, which spearhead the generation of ISPE's gold standard content, including Good Practice Guides, *Pharmaceutical Engineering* articles, conference presentations, and training programs.

The new series follows the CoP profiles series published in the magazine during 2022. Behind every CoP are the ISPE members who join CoP Steering Committees and participate in sharing knowledge with ISPE members. We will be highlighting two CoP leaders in each issue of the magazine, and look forward to sharing their stories with you.

Javier Lozano is Chair of the Disposables/Single-Use Technologies Community of Practice (CoP). Originally from Spain, he is now located in Portsmouth, England. After earning a degree in chemical engineering from the University of Valladolid, he joined a pharmaceutical company working with active pharmaceutical ingredients and enjoyed the work so much that he knew he had found the industry he wanted to stay with.

"Most chemical engineers end up working in oil and gas, but the feeling and the satisfaction that you get from working in the pharmaceutical industry to me was much more appealing. I always find it very interesting to hear the patient stories at ISPE's annual meetings. When you see the impact that your daily work has had on someone's life, it is very gratifying."

Over the past 20 years, Javier has worked for large and small pharmaceutical and biopharmaceutical companies specializing in biopharma operations and facility design. He has extensive experience working with different product platforms such as human blood plasma, vaccines, microbial, and mammalian cell cultures.

Currently at PM Group, Javier is Head of Process Engineering and is responsible for managing resources for the company's pharma projects. He is also the in-house subject matter expert on single-use technologies, collaborating and advising on projects across the world.

"Single-use technologies are here to stay and are going to remain a very big part of the way biopharmaceuticals are manufactured. But sustainability is very important and all of the big pharma companies have sustainability goals and net zero and carbon neutral plans; single-use technologies can play a key part in the industry. As with everything, it comes with challenges, but I believe that single-use technology can be part of the solution as we move forward into the next part of the century. One of the things I enjoy most about engineering is that you have a problem, and you have to develop a solution and prove it is the right one."

Javier said that being a member of ISPE and the Disposables/Single-Use Technologies CoP has helped him solve challenges throughout his career. "One of the key things about ISPE is that it links you to a wide knowledge base. I don't think there is any other way that you can reach such a large pool of knowledge in the industry. When you go to meetings and networking events, you meet other engineers and suppliers and those connections help you in your day-to-day work life. You can also ask for advice on the ISPE Engage sites. For me, my ISPE membership has been invaluable."

At PM Group, Javier also mentors new engineering professionals. "I enjoy mentoring and developing the next generation of engineers. My advice to them is to always be open and grab every opportunity that comes your way. It may work, it may not, but if you keep an open mind and challenge yourself, that is going to help you to grow and build relationships, knowledge, and experience."

—Marcy Sanford, ISPE Publications Coordinator

RACHEL OWEN

Rachel Owen is the Chair of the Investigational Products—Europe Region Steering Committee Community of Practice (IPNA-EU CoP). Located in Macclesfield, England, she has more than 22 years of experience supporting clinical trials. With a degree in biological sciences from King's College London, Rachel knew she wanted a career in the science industry, but she did not necessarily want to work in a lab. She found the perfect profession at her first job with Almedica, where she was a project manager for the clinical trial supply chain.

From the beginning, Rachel was successfully tackling challenging projects and sharing knowledge from her experiences with others, like the lessons learned from Shire Pharmaceuticals Project that were presented by the team at the 2008 ISPE Europe Annual Conference.

"The project required us to pack and blind a controlled substance, export from the US, and then re-export to multiple European countries, blinding at the very last stage of processing. New import and export rules had just been issued and at first, we did not even know how to get started. It was a tremendous feeling of accomplishment when the project was complete to know that we'd done something that seemed impossible when we first started it."

After earning her master's degree in pharmaceutical medicine from Hibernia College, Rachel began working at AstraZeneca and is currently Director, Global Clinical Supply Chain Capability and Technology, where she leads a global team that delivers input to clinical trial setup and the lean, business process management, and training frameworks for applicable AstraZeneca clinical trials to enable delivery of new medicines to patients.

"I love the output of our work, that we're developing new medicines, that we're helping people with their quality of life, and changing the course of what were previously incurable diseases. I love what I do, the people I work with, and that we get to experiment and innovate, not only with new products but with industry innovations and new regulations such as direct-to-patient shipping and the EU falsified medicines directive.

The IPNA-EU CoP Steering Committee really helps in these situations by creating cross-industry task teams that can tackle these emerging challenges or opportunities together to influence and shape the way that the industry develops for the future."

Rachel is excited about hot topics and potential task teams being discussed within IPNA-EU CoP, including cell and gene therapy. "Cell and gene therapy is moving us toward more and more personalized medicine, which isn't a new concept, but it is becoming more of a reality.

"The patient will become the precise starting point for the product, which is not something we've been used to before. It's a very different supply chain. These are some of the things we discuss in our CoP, the logistical challenges this shift can bring, the patient data challenges that could arise, and also the chain of custody for the product that needs to be followed from patient back to patient.

Rachel's participation in ISPE began in 2007, when she attended an annual conference, minuting the round table discussions. This sparked an interest in cross-company collaboration.

"It's really enjoyable to be working on cross-industry forums and realize that the problems or challenges you're having are experienced by someone else or they may have managed to solve those issues. By working together, we can hopefully solve problems in a standard way and a shorter time in industry, all of which is to the benefit of the patient, which is why we are here."

—Marcy Sanford, ISPE Publications Coordinator

New Guide Promotes Cultural Excellence

Cultural excellence is the expressed and implied ways in which an organization operates. Excellence in organizational culture is essential for delivering robust and sustained quality performance and ensuring patient-focused outcomes. ISPE's new *Advancing Pharmaceutical Quality (APQ) Guide: Cultural Excellence* provides a quality management framework for assessing and advancing an organization's culture of quality.

"Cultural excellence is not a project, but an ongoing commitment by leaders and individuals to model desired behaviors and hold others accountable to behavioral standards," said Guide Co-Lead Nuala Calnan, CEO, BioPharm Excel Ltd.

"Cultural excellence affects company performance in all areas: quality, operations, and supply chain. A culture of excellence understands patient safety as paramount, as it recognizes quality not as an operational burden or compliance requirement, but a necessity that allows companies to make decisions that best benefit the patient," added Guide Co-Lead Erika Ballman, Associate Director Corporate Quality Systems, Perrigo Company Plc.

The ISPE *APQ Guide: Cultural Excellence* provides a quality management framework for assessing and advancing an organization's culture of quality by evaluating the following aspects: leadership and vision; mindsets and attitudes; Gemba and employee engagement; leading quality indicators—measuring what matters; proactive oversight, review, and reporting; cultural enablers; and critical third-party partnerships.

"To our knowledge, the ISPE Cultural Excellence APQ Guide would be considered the first of its kind in combining industry best practices, a cultural excellence framework with rich content in each dimension, inclusion of key cultural enabling behaviors for employee and leader levels, and an effective Assess, Aspire, Act, Advance model for practical development of action plans," said Calnan.

The ISPE *APQ Guide: Cultural Excellence* is the fifth and final guide in the APQ Guide series that seeks to improve the state of pharmaceutical quality and ensure sustainable compliance. To learn more about APQ Guides and other ISPE Guides, visit ISPE.org/publications/guidance-documents

—Marcy Sanford, ISPE Publications Coordinator

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Articles can be 400 to 1,000 words. Photos are welcome: at least 300 dpit or >1MB. Please submit to ssandler@ispe.org

Meet the ISPE STAFF

Tina Li

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Tina Li, Training Manager, Professional Development.

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

Each day is a different day for me depending on what's going on that week. If there's a week full of training courses, I ensure that my team members and I are ready to facilitate the courses that we're assigned to. Training days consist of me being present during the training session by fielding attendee questions, troubleshooting technical issues, launching applications, and ensuring that the training is running smoothly for everyone. These are usually an all-day event or a half-day event over the course of 2–4 days.

Behind the scenes of a training session or during a non-training week, I go through my emails and get myself organized for the day. I like to set my intentions early in the morning so that I know what actions I need to take to accomplish my goals. Some days are busier than others, but I adjust accordingly to what requires my attention. Besides facilitation, I also manage our email communications, CEU [continuing education unit] certificates, and virtual course creation.

What do you love about your job?

I love that I'm able to help others achieve their professional development goals to go further in their careers. I also love that I'm able to collaborate with people from all over the world and hearing about their experiences and knowledge in the industry.

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

I'm spending time with my husband and my son. I am a first-time mom, so trying to navigate motherhood has been a new adventure for me. I like to be active as much as I can by going on walks and doing some strength training. Lately, I've been trying to hit 10,000 steps a day and recently picked up Pilates. I'm also a big foodie, so I like to try new cuisines around the area and I also enjoy cooking, as I feel that food is a common ground that brings people together.

CONTAMINATION TRENDS AND PROPOSED SOLUTIONS

By Sia Chong Hock, Hong Sheu Dong, Jerrick Teo Chan Rui, and Chan Lai Wah

Contamination is one of the top reasons for medicinal product [1] recall by the US Food and Drug Administration (FDA) despite stringent GMP standards enacted by multiple drug regulatory authorities (RAs) globally. Reports of contaminated products from multiple sources worldwide were gathered to review overall trends and identify challenges. This article proposes recommendations for industry and RAs to address the identified problems.

To date, numerous case studies [2–6] have been completed on contaminated medicinal products and contaminants that may be useful in identifying and evaluating methods to control and manage contamination. However, few studies have analyzed contamination trends to enable a more effective risk-based approach to control contamination in the manufacture of medicinal products.

This article aims to gather reports of contaminated medicinal products from multiple sources, such as PubMed and Embase; GMP standards adopted by the US FDA, China National Medical Products Administration (NMPA), and India Central Drug Standard Control Organisation (CDSCO); and standards from the World Health Organization (WHO) and the Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S). From the findings, the overall trends in contamination of medicinal products—including the types of medicinal products and common contaminants encountered, their causes and origins, preventive measures, and challenges faced by manufacturers and RAs—were identified and recommendations to resolve the identified problems provided.

IDENTIFICATION AND ANALYSIS OF CONTAMINATION TRENDS

Three major recall databases—those of the US FDA, the United Kingdom's Medicine and Healthcare Products Regulatory Agency (UK MHRA), and Australia's Therapeutic Goods Administration (TGA)—were searched to assess contamination trends in the past five years. The contamination trends analysis included the year the contamination event occurred, identity of the product and contaminants/impurities, country of manufacture and product recall (if any), circumstances leading to contamination, and outcome following the contamination event. The number and breakdown by contaminants/impurities are provided in Table 1.

Unfortunately, these databases lacked information about the exact nature of the contaminant/impurity and the circumstances that led to the contamination events. To obtain deeper insight into contamination trends, PubMed, Embase, and Cochrane were searched, and cases from these literature sources were analyzed. The cases covered the same types of contaminants and impurities noted in Table 1: microbial contaminants, process-related impurities, metal contaminants, packaging-related contaminants, drug cross-contamination, and an "unknown" category encompassing other contaminants associated with the manufacturing process, including those from cell culturing.

Microbial Contaminants

From 2007 to 2021, 90 cases of contamination due to microorganisms were reported, with 61 caused by bacteria [5–10], 23 by viruses [11, 12], and 6 by fungi [6, 13, 14]. The most commonly mentioned

Table 1: Contamination-associated recalls from 2017 to 2021.

	Recalls Attributed to Contamination	Contaminant/Impurity					
		Microbial	Process Related	Metal	Packaging Related	Other Drugs	Unknown
US FDA	177	78	41	3	5	13	37
UK MHRA	67	27	27	2	2	2	7
Australia TGA	84	28	22	-	6	-	28

contaminants were Burkholderia species [5, 8] as a whole, and vesivirus 2117 for Genzyme products in 2009 [11].

Microbial contaminants commonly occur during manufacture, often arising from the materials used. For example, bacterial and viral contaminants can occur from the use of animal sera and human plasma components [7]. Bacterial contaminants are also commonly introduced into medicinal products through water-based routes, whether during manufacture of liquid preparations or from external sources [5, 8].

Compounding pharmacies were commonly mentioned as sources of microbial cross-contamination, especially in the US [14, 15]. The regulation of compounding pharmacies in the US has historically been murky because they are not officially considered drug manufacturers, leading to incomplete regulation and non-required adherence to GMP standards [9, 15]. This has led to compounding pharmacies completing high-volume activities such as mass repackaging, thereby increasing the risk of cross-contamination. Similarly, compounding practices such as manual dilution and reconstitution [10] have been associated with cross-contamination by microorganisms.

As demonstrated by the various Burkholderia cepacia outbreaks [5] and the case of Streptococcus mitis/oralis-contaminated Avastin, microbial contamination has the potential to cause widespread and serious infection. The Genzyme case also demonstrates that contaminated medicinal products can lead to severe drug shortages, especially when production is monopolized by single companies [11].

Process-Related Impurities

Over 30 studies were found to be related to contamination with process-related impurities [2, 4, 16–21]. More than 20 of these studies reported genotoxic impurities [2, 4, 16–19] such as nitrosamines [2, 16–18] or ethyl methanesulfonate [4, 19]. Five studies reported that the impurities were entities chemically similar to the drug substance, such as epimers, polymorphs, isomers, or drug derivatives [20].

Although many of these studies did not identify the exact factors leading to contamination, the most common cause appears to be the formation of unexpected reaction byproducts during the changing of reactants during manufacture [2, 16–18]. One example is the switching of tributyltin azide with sodium azide and dimethyl formamide by Zhejiang Huahai Pharmaceuticals (ZHP) in 2012 to reduce waste and to increase yield in the production of angiotensin II receptor blockers, resulting in the formation of N-nitrosodimethylamine (NDMA), a known carcinogenic impurity [18].

Failure in characterizing impurities during the manufacturing stage or in the final product is another cause [19]. Characterization is an important step to identify impurities and is especially crucial when manufacturers revise the manufacturing process. In ZHP's case, omission of this step led to patients inadvertently taking NDMA-contaminated drugs for several years before the eventual detection in 2018 [18].

Poor cleaning practices also contribute to the formation of impurities. In the 2007 Hoffmann-La Roche Viracept incident, the holding tank was cleaned but not dried properly. This led to residual ethanol buildup and the unintentional formation of ethyl methanesulfonate [4].

Although these impurities often do not pose sufficient risk to warrant a recall, mass recalls may be necessary for medicines taken for long-term use in view of the compounded risks [2, 4, 18]. Patients taking these drugs may experience medication shortages, healthcare institutes may have to source safer alternatives, and RAs may be required to inspect the manufacturing premises to assess GMP compliance, suspend manufacturing, or recommend corrective actions [21].

RAs may also have to review the risks of patients taking the contaminated medications [22], especially for manufacturers with large market shares (such as ZHP), which can impact large numbers of patients globally. Notably, in both the ZHP and Hoffmann-La Roche contamination incidents, despite the impurities being carcinogenic, RAs declared the risks "not significant" [22] or that there were "no health risks" [4].

Metal Contaminants

Of the 17 studies reporting metal contamination, various contaminants were identified. They included nickel, chromium, steel, and aluminum, as well as various metals of a wide range of weight and toxicity [23–27].

Metallic particles that inadvertently came off the manufacturing equipment may be due to friction between two pieces of metal in the manufacturing equipment or from wear and tear during production. Noteworthy cases were the inadvertent introduction of grade 316L stainless steel into Moderna's COVID-19 vaccine by the outsourced manufacturer (ROVI Pharma Industrial Services S. A. [25, 26] and visible black specks observed in Johnson & Johnson's Infants' Tylenol products [23–25]. The former highlights the importance of avoiding human error in the handling of manufacturing equipment. In this case, the increased friction was caused by incorrect assembly of the manufacturing equipment due to a technician "visually misjudging the precise 1 mm gap between the star-wheel and the stopper" [25].

In both recalls, metal contaminants took the form of visible "black specks" observed by consumers, which prompted further investigation into the manufacturing process. Although technology exists for the screening of elemental contaminants in pharmaceutical products [27], it appears this screening had not been done during quality control tests by manufacturers.

In the Moderna COVID-19 vaccine contamination case, three lots of the five lots affected, totaling 1.63 million vials [26], had to be recalled and destroyed. In Johnson & Johnson's contaminated Infants' Tylenol incident, the manufacturer was fined US $25 million, and had to recall up to 136 million bottles of pediatric medications [23].

Packaging-Related Contaminants

Eighteen studies reported contaminants from drug packaging. The contaminants included rubber, glass, plastics such as low-density polyethylene, plasticizers such as phthalates, and polymer additives such as Irganox 1010 and bisphenol A (BPA) [28–31].

One key cause was attributed to the incompatibility between the packaging materials and the product [28]. For biopharmaceuticals packed in glass vials, the strong pH and/or buffers may result in the delamination of glass, resulting in glass flakes [28]. Another cause identified was poor storage conditions by manufacturers. Prolonged storage or storage at high temperatures may potentially result in container degradation and the leaching of these impurities into the product [30]. For both causes, manufacturers should assess the toxicology and safety of their products in relation to the packaging materials used, as well as their storage conditions.

Many biopharmaceuticals, ophthalmics, and injectable products [29, 30] are often stored in rubber-stoppered glass vials, disposable plastic syringes, polyvinyl chloride (PVC) bags, or plastic bottles. The accidental injection of rubber particles and glass flakes may lead to circulatory disorders such as vascular occlusion, ischemia, and tissue necrosis, thereby increasing the risk of embolic, thrombotic, and vascular disorders [28]. Current evidence also suggests an association between phthalate exposure and reproductive toxicity, hormonal imbalance, and fetal deformations in humans [31].

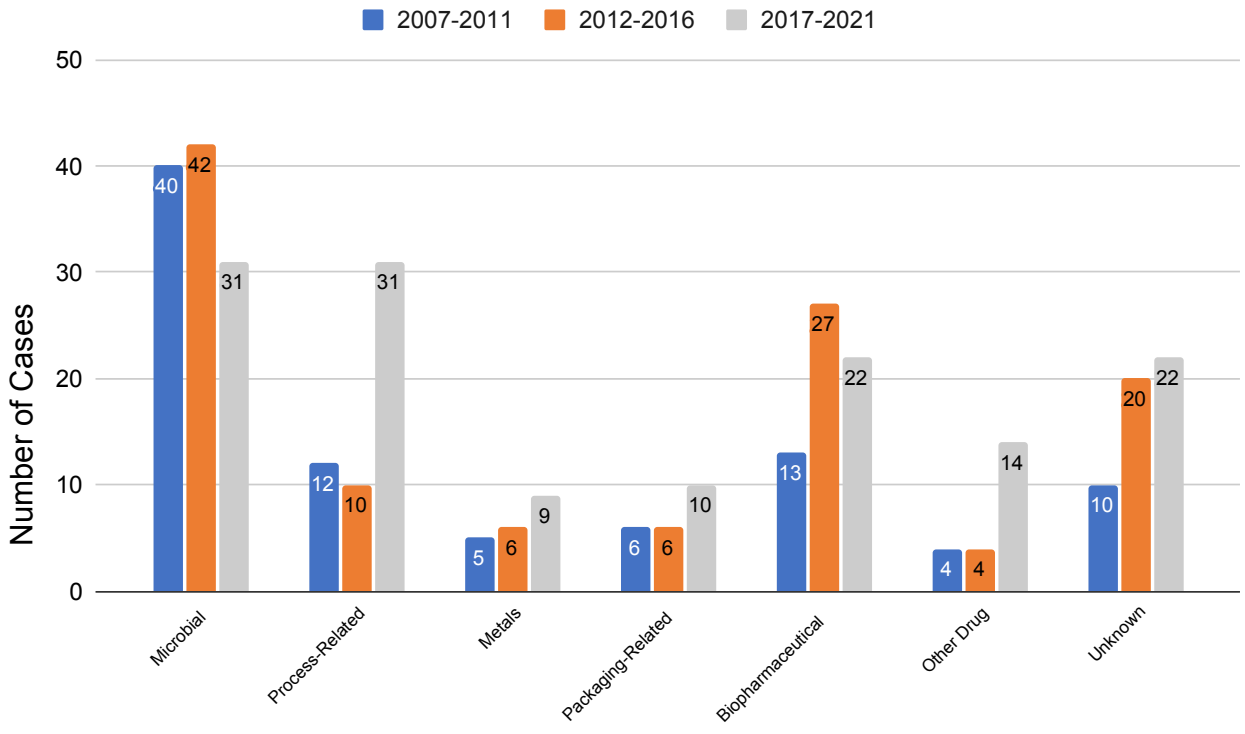
Drug Cross-Contamination

Eighteen papers [32–36] reported cross-contamination with another drug product. One study was a systematic review that covered several cross-contamination cases, reporting eight cases of contamination with hydrochlorothiazide, two with torasemide, and one with triamterene [34]. In the remaining 17 studies, many contaminants were potent prescription-only medications such as antihypertensive drugs including hydrochlorothiazide, olmesartan, and enalapril; anticancer drugs including vincristine; and immune-modulating drugs such as azathioprine.

One key contribution to cross-contamination was the use of shared manufacturing equipment, particularly improper cleaning between the production of different products. Even after proper cleaning, cross-contamination can still occur [33], which highlights areas for improvement in cleaning validation. Another cause identified was human error during production. Personnel shortages and overloaded facilities can result in disorganized equipment and material flow, resulting in mix-ups of products [36].

Diuretics such as hydrochlorothiazide have falsely indicted athletes for doping [32, 34], even when the contaminant was present

Figure 1: Frequency of mention of specific contaminants/impurities in case studies reported in the past 15 years (2007–2021).



in small amounts. In the cross-contamination of itraconazole with rilmazafone, at least 245 patients reported dizziness, intense drowsiness, and loss of consciousness as well as 2 deaths and 38 traffic accident cases [35]. Cross-contamination involving vincristine also led to neurologic symptoms such as weakness and paralysis in at least 107 patients across 12 hospitals in China, despite investigations revealing that vincristine was only present in trace amounts between 0.28 and 18 micrograms per milliliter [33].

Where cross-contaminated drugs were not released into the market, drug shortages can still plague consumers and healthcare institutes. In the cross-contamination of Johnson & Johnson's COVID-19 vaccine with AstraZeneca's COVID-19 vaccine, up to 75 million doses were ordered to be discarded following the incident [36], and vaccine shortages were subsequently reported in South Africa and Germany [37].

Cell Culturing Contaminants

Contaminants associated with the use of cell culturing were widely covered in some studies [38, 39]. Such contaminants included bacterial host cells used in the cultivation of recombinant proteins, their endotoxins, and plasmid DNA [39], as well as tumorigenic stem cells. These studies briefly covered the risks associated with such contaminants, such as immunogenicity [31], but otherwise were more focused on evaluating potential improvements to processes such as identification and purification.

ANALYSIS OF TRENDS BY FREQUENCY

The findings showed that the total number of contamination studies reported over the past 15 years is 344, with 90 in 2007–2011, 115 in 2012–2016, and 139 in 2017–2021 (Figure 1).

Microorganisms are the most common contaminant, followed by biopharmaceutical contaminants and process-related impurities. The number of cases of process-related impurities rose sharply in the 2017–2021 period, due to nitrosamine contamination cases. Notably, aside from biopharmaceutical contaminants, these trends were also observed in the initial study of recall databases of the different RAs. Cross-contamination by other drugs also rose in that same period. The increased number of cases involving these contaminants suggests that closer attention should be paid to the control of cross-contamination and processes involving chemical reactions and the quality of reagents. The importance of segregating production operations in shared facilities should be emphasized. A risk analysis should be carefully conducted when there is any deviation in any of the processes, chemical reactions, and type and quality of the materials, including solvents and reagents.

COUNTRIES COMMONLY ASSOCIATED WITH CONTAMINATED MEDICINAL PRODUCTS

Due to the globalization of the world today, the issue of contaminated medications is an international one. Any major contamination event that warrants a large-scale recall would likely affect patients globally

[2, 40]. Although our analysis hinted at the US being most affected by recalls of contaminated medicinal products [5, 29], this could be explained by the fact that the US FDA regularly publishes alerts and recall notifications on their website to communicate recall information to consumers [41].

Our analysis also showed that besides the US, the countries of origin where contaminated products have been commonly reported include the UK, Europe, Japan, China, and India [40, 42]. The contamination cases appeared disproportionately high for China and India compared to the rest of the world. This observation may not be surprising, given the high production output of these countries where labor costs are lower. Incidentally, the high-profile contamination cases involving nitrosamine-contaminated drugs and heparin also originated from these countries. It is therefore of interest to compare the GMP standards of WHO, PIC/S, and the previously mentioned major countries to better understand the factors that could have contributed to the contamination events.

IMPACT OF GMP STANDARDS ON CONTAMINATION

The following components of GMP standards were identified to be pertinent to contamination control: cleaning validation; water quality; sterility testing; buildings, facilities, and equipment; and personnel. The components of GMP standards from WHO, PIC/S, the US FDA, China NMPA, and India CDSCO were analyzed and these GMP standards are as follows [43–48]:

- **WHO:** GMP for Pharmaceutical Products: Main Principles, GMP for Active Pharmaceutical Ingredients, and GMP for Biological Products
- **PIC/S:** Guide to GMP for Medicinal Products Part I and Part II and Annexes
- **US FDA:** 21 CFR Part 210 Current GMP in Manufacturing Processing, Packing, or Holding of Drugs and 21 CFR Part 211 Current GMP for Finished Pharmaceuticals
- **China NMPA:** Good Manufacturing Practice for Drugs
- **India CDSCO:** Drugs and Cosmetics Act (DCA) Schedule M

The authors' analysis found that the GMP standards from these agencies are fairly consistent. Most points pertaining to the prevention of contamination are similar in concept, with differences in phrasing and content arrangement. Such differences can still create confusion among manufacturers in relation to contamination control and overall GMP compliance.

In this regard, PIC/S has led the way in publishing a revised Annex 1 to its Guide on GMP for Medicinal Products, which will come into effect 25 August 2023. Annex 1 clarifies the clean air classification and microbial monitoring limits that manufacturers of sterile products have to implement for various processing and sterilization operations—such as aseptic processing, terminal sterilization, and finishing of the sterile products—based on a contamination control strategy and quality risk management principles [45].

Another key difference among national and international GMP standards is the level of technical details for cleaning validation. The WHO and PIC/S standards are the most comprehensive, covering changeover between different products, bracketed products, and different batches of the same product. Conversely, national standards of some RAs tend to be devoid of details, leaving discretion to the manufacturers. Improperly validated cleaning procedures for shared production equipment can be a potential source of cross-contaminants, especially during product changeover. Overall, the various GMP standards appear sufficiently comprehensive in terms of contamination control measures. However, the continued occurrence of contamination and cross-contamination events highlights other challenges faced by manufacturers and RAs.

Manufacturer and RA Challenges

Currently there are still differences amongst GMP standards, for example in clean air classification, microbial monitoring limits, cleaning validation, and conditions mandating dedicated drug manufacturing facilities [50]. Although manufacturers may abide by the standards adopted by a certain RA, they may be deemed noncompliant to another.

Even when manufacturers abide by the respective GMP standards, there is still a chance, albeit a small one, for contamination to occur. This is due to the impracticality in performing total quality checks for all product items during batch manufacture and characterizing all impurities in a product. Contamination events can still slip through the cracks and defects may only be spotted after release into the market. The increasing use of biopharmaceuticals adds to the complexity of quality control. Additionally, not all manufacturers have the resources to adopt more effective technology to address contamination issues [49].

Another major problem can arise from the presence of legally ambiguous gray areas. This is best exemplified in the form of large-scale compounding pharmacies in the US; the FDA has limited power to enforce interventions in compounding pharmacies [15] due to ambiguity in whether their activities are considered pharmaceutical manufacturing. Therefore, compounding pharmacies could produce medications in bulk while receiving reduced oversight, leading to various outbreaks of serious contamination [9]. This has highlighted the need to assess the presence of possible equivalent gray areas in countries outside of the US. Both China NMPA and India CDSCO face similar issues [46, 47].

Further, difficulties may arise when overseas inspections of pharmaceutical manufacturers are initiated. These are most notably observable in terms of the activities carried out by the US FDA, ranging from the need to announce inspections in advance, which gives time for manufacturers to rectify any issues [50], to staffing issues that affect inspection capacity and restrictive policies [53]. Collectively, these problems can lead to infrequent overseas inspections. The median inspection frequency between 2011 and 2019 is inadequate and undesirable, standing at approximately two years for high-risk sites and more than three years for low-risk sites [52]. Other RAs face similar staffing and labor issues.

PROPOSED SOLUTIONS

Manufacturers

Contamination can be caused by many factors, including personnel's lack of knowledge and training. The requirement for well-qualified personnel, continual training, and qualification should be strongly emphasized. Manufacturers should embrace a proactive quality culture.

Manufacturers should also be encouraged to harness advanced containment and process analytical technologies, which are already in existence. Manufacturers should be encouraged to harness technology such as quality by design (QbD) when considering problems associated with the final testing of products—from the need to test large numbers of finished products to identify contamination at extremely small percentages to the use of destructive testing—and to place particular emphasis on its practical implementation. A focus on developing and adopting real-time, nondestructive methods of contamination monitoring throughout the manufacturing process is needed, such as by using spectroscopic methods including Raman spectroscopy to improve the speed of contaminant detection.

Contamination issues are a big challenge for compounded medicines. There is a need to reduce the level of human-performed operations, which are a major source of contamination. One possible way to combat this would be to assess which products are most commonly compounded and to create similar formulations to be batch-manufactured, avoiding the need for compounding. Alternatively, the use of robotic compounding and other automated processes could be explored, as these have been shown to reduce contamination rates [53].

RAs

Although all GMP standards share a common aim to guide the production of safe and good quality medicinal products, the contents of these national standards are often organized, arranged, or structured differently. These differences may lead to confusion among manufacturers with regard to GMP compliance, including contamination and cross-contamination control. Some GMP standards still use subjective and vague terms such as *certain drugs, highly active or highly sensitizing drugs*, or *cytotoxics*, which are left to the manufacturers. It would be best to eliminate these vague terms and to characterize drugs in a globally accepted, common GMP standard to avoid ambiguity [54].

A globally harmonized GMP standard for medicinal products in finished dosage forms such as that for the manufacture of active pharmaceutical ingredients (APIs)—namely the PIC/S Guide to GMP for Medicinal Products Part II—can eliminate such ambiguity and confusion. This will go a long way in enhancing overall GMP compliance and quality assurance in the pharmaceutical manufacturing industry. It is also in line with the mission of PIC/S to lead in the international development, implementation and maintenance of harmonized GMP standards.

PIC/S has recently revised Annex 1 of its GMP standard for the manufacture of sterile medicinal products, which goes into effect 25 August 2023. To date, PIC/S has 54 participating authorities and its membership is growing. PIC/S has had success in driving the international harmonization of the GMP standard for APIs. The next challenge is for PIC/S to do likewise for the GMP standard for finished dosage forms, namely the PIC/S Guide to GMP for Medicinal Products Part I.

Through the international harmonization of a common GMP standard, the inspection in large countries such as China, India, and the US can also be more consistent, thereby alleviating the issues of varying inspection standards by local RAs. As outlined in the PIC/S 2023–2027 Master Plan, PIC/S aims to harmonize and standardize GMP training internationally to ensure that its inspectors consistently apply GMP enforcement and inspection to ensure that manufacturers across the world are held up to the same standards regardless of region.

This harmonization also paves the way for mutual recognition agreements and inspection reliance, where any PIC/S member country may recognize the GMP of another PIC/S member country, thus avoiding duplication of inspection which then confers time and cost savings for both manufacturers and RAs. With a harmonized GMP standard, the quality of medicinal products can be assured and be in the best interests of public health. This global cooperation of inspections can also allow for inspections to be done more proactively by eliminating political barriers.

One key issue that remains, however, is the authority granted to inspectors, thereby limiting the routine inspection of overseas manufacturers. As previously noted, US FDA inspectors are not conferred sufficient authority to conduct unannounced overseas inspections, which has contributed to inspections being done infrequently [52]. Aside from GMP harmonization, there should also be more authority granted to PIC/S or WHO inspectors to conduct unannounced inspections to assess GMP compliance.

This would avoid incidents where manufacturers that are notified of an upcoming inspection use the lead time to clean the facility and ensure GMP compliance just before inspection [50], giving a false impression to inspectors. These additional inspections may even go further to assure product quality and strict GMP compliance by mandating routine inspections to be conducted at a specified frequency (e.g., at least one inspection every 18 months), to complement the current risk-based inspections [48].

CONCLUSION

This article has investigated the published literature on the contamination of medicinal products to identify common contaminants and contamination trends. It has further analyzed the GMP standards from the WHO, PIC/S, the US FDA, China NMPA, and India CDSCO, as well as the challenges faced by manufacturers and RAs, before proposing possible solutions. Microbial contaminants and process-related impurities were the most common contaminants, with cross-contamination involving other drugs becoming a problem. There are some minor differences among the GMP standards, but they all embody similar concepts regarding contamination prevention.

The main issues for contamination still occurring today could be attributed to lack of knowledge, noncompliance to GMP, confusion due to differing GMP standards, and ineffective enforcement. Possible solutions include the strict requirement of well-trained personnel, continual training, minimization of compounding activities, adoption of QbD and new technology, and GMP harmonization and standardization. PIC/S has led the way in publishing clearer clean air classification and microbial monitoring limits, which manufacturers of sterile products have to implement for various processing and sterilization operations.

It is hoped that the clarifications in the recently updated PIC/S Guide to GMP for Medicinal Products Annex 1 will eliminate existing ambiguities and will eventually result in lower rates of contamination and a higher level of quality assurance for sterile medicinal products. If this happens, international harmonization to the PIC/S Guide to GMP for Medicinal Products, including Annex 1, could be adopted by all RAs and form the basis of international harmonization. It is acknowledged that the contamination cases captured may not be exhaustive, but collectively, they show certain trends have occurred worldwide. It is also acknowledged that the results might have skewed toward countries with greater information availability, despite efforts to include contamination cases globally.

Regardless, the findings have provided a broad overview on the issue of contaminated medicinal products and potential solutions to counter contamination. Future studies surrounding contamination could focus on categorization of common contaminants to aid in QbD and the promotion of shared interests and greater international collaborations.

References

1. UK Medicines and Healthcare Products Regulatory Agency. "A Guide to What Is a Medicinal Product." March 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/872742/GN8_FINAL_10_03_2020__combined_.pdf
2. Bharate, S. S. "Critical Analysis of Drug Product Recalls due to Nitrosamine Impurities." *Journal of Medicinal Chemistry* 64, no. 6 (2021): 2923–2936. https://pubmed.ncbi.nlm.nih.gov/33706513/
3. Liu, H., Z. Zhang, and R. J. Linhardt. "Lessons Learned from the Contamination of Heparin." *Natural Product Reports* 26, no. 3 (2009): 313. https://pubmed.ncbi.nlm.nih.gov/19240943/
4. Müller, L., and T. Singer. "EMS in Viracept—The Course of Events in 2007 and 2008 from the Non-Clinical Safety Point of View." *Toxicology Letters* 190, no. 3 (2009): 243–247. https://pubmed.ncbi.nlm.nih.gov/19857794/
5. Glowicz, J., M. Crist, C. Gould, H. Moulton-Meissner, J. Noble-Wang, T. J. B. de Man, et al. "A Multistate Investigation of Health Care–Associated Burkholderia Cepacia Complex Infections Related to Liquid Docusate Sodium Contamination, January-October 2016." *American Journal of Infection Control* 46, no. 6 (2018): 649–655. https://pubmed.ncbi.nlm.nih.gov/29329922/
6. Ahearn, D. G., and R. D. Stulting. "Moulds Associated with Contaminated Ocular and Injectable Drugs: FDA Recalls, Epidemiology Considerations, Drug Shortages, and Aseptic Processing." *Medical Mycology* 56, no. 4 (2017): 389–394. https://pubmed.ncbi.nlm.nih.gov/29420758/
7. Wagner, B., and B. Grabein. "Sterility Testing of Blood Components and Advanced Therapy Medicinal Products." *Transfusion Medicine and Hemotherapy* 38, no. 5 (2011): 334–336.
8. Sridharan, S., R. Yamunadevi, P. Senthur Nambi, and V. Ramasubramanian. "Outbreak of B. cepacia Bacteremia Following Use of Contaminated Drug Vials in a Tertiary Care Centre." *Indian Journal of Medical Microbiology* 40, no. 1 (2022): 119–121. https://pubmed.ncbi.nlm.nih.gov/34969551/
9. Watson, C. J., J. D. Whitledge, A. M. Siani, and M. M. Burns. "Pharmaceutical Compounding: A History, Regulatory Overview, and Systematic Review of Compounding Errors." *Journal of Medical Toxicology* 17, no. 2 (2020).
10. Peters, G. F., M. R. McKeon, and W. T. Weiss. "Potential for Airborne Contamination in Turbulent- and Unidirectional-Airflow Compounding Aseptic Isolators." *American Journal of Health-System Pharmacy* 64, no. 6 (2007): 622–631.
11. Qiu, Y., N. Jones, M. Busch, P. Pan, J. Keegan, W. Zhou, et al. "Identification and Quantitation of Vesuvius 2117 Particles in Bioreactor Fluids from Infected Chinese Hamster Ovary Cell Cultures." *Biotechnology and Bioengineering* 110, no. 5 (2012): 1342–1353. https://pubmed.ncbi.nlm.nih.gov/23184768/
12. MacDonald, M. L., S. W. Polson, and K. H. Lee. "k-mer-Based Metagenomics Tools Provide a Fast and Sensitive Approach for the Detection of Viral Contaminants in Biopharmaceutical and Vaccine Manufacturing Applications Using Next-Generation Sequencing." *mSphere* 6, no. 2 (2021). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8546726/
13. Vijayakumar, R., M. Saleh Al-Aboody, and T. Sandle. "A Review of Melanized (Black) Fungal Contamination in Pharmaceutical Products-Incidence, Drug Recall and Control Measures." *Journal of Applied Microbiology* 120, no. 4 (2016): 831–841. https://sfamjournals.onlinelibrary.wiley.com/doi/10.1111/jam.12888
14. Smith, R. M., M. K. Schaefer, M. A. Kainer, M. Wise, J. Finks, J. Duwve, et al. "Fungal Infections Associated with Contaminated Methylprednisolone Injections." *New England Journal of Medicine* 369, no. 17 (2013): 1598–1609. https://www.nejm.org/doi/full/10.1056/nejmoa1213978
15. Pergolizzi, J. V., S. Labhsetwar, and J. A. Le Quang. "Compounding Pharmacies: Who Is in Charge?" *Pain Practice* 13, no. 3 (2013): 253–257. https://onlinelibrary.wiley.com/doi/10.1111/papr.12033
16. Scherf-Clavel, O., M. Kinzig, A. Besa, A. Schreiber, C. Bidmon, M. Abdel-Tawab, et al. "The Contamination of Valsartan and Other Sartans, Part 2: Untargeted Screening Reveals Contamination with Amides Additionally to Known Nitrosamine Impurities." *Journal of Pharmaceutical and Biomedical Analysis* 172 (2019): 278–284. https://www.sciencedirect.com/science/article/pii/S0731708519301864
17. Roberts, S. W., A. Lennard, G. Mohan, J. Bernstein, N. S. Cauchon, S. Cole, et al. "Meeting Report: N-Nitrosamine Impurity Control Strategies in the Pharmaceutical and Biotechnology Industries." *The AAPS Journal* 23, no. 4 (2021): 94. https://pubmed.ncbi.nlm.nih.gov/34258657/
18. Charoo, N. A., A. A. Ali, S. K. Buha, and Z. Rahman. "Lesson Learnt from Recall of Valsartan and Other Angiotensin II Receptor Blocker Drugs Containing NDMA and NDEA Impurities." *AAPS PharmSciTech* 20, no. 5 (2019).
19. Müller, L., E. Gocke, T. Lavé, and T. Pfister. "Ethyl Methanesulfonate Toxicity in Viracept—A Comprehensive Human Risk Assessment Based on Threshold Data for Genotoxicity." *Toxicology Letters* 190, no. 3 (2009): 317–329.
20. Hennigan, M. C., and A. G. Ryder. "Quantitative Polymorph Contaminant Analysis in Tablets Using Raman and Near Infra-Red Spectroscopies." *Journal of Pharmaceutical and Biomedical Analysis* 72 (2013): 163–171.
21. US Food and Drug Administration. "Warning Letter Close-Out Letter Program." Published 29 April 2019. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/about-warning-and-close-out-letters
22. European Medicines Agency. "Lessons Learnt from Presence of N-Nitrosamine Impurities in Sartan Medicines." June 2020. https://www.ema.europa.eu/en/documents/report/lessons-learnt-presence-n-nitrosamine-impurities-sartan-medicines_en.pdf
23. Dunsmuir, L. "Tylenol Maker to Pay $25 Million for Selling Metal-Contaminated Drugs." Reuters. 10 March 2015. https://www.reuters.com/article/us-johnson-johnson-tylenol-idUSKBN0M629S20150310
24. McDonald, J. "Tylenol Maker Pleads Guilty in Case Over Metal Particles in Children's Medicine." WHYY. 11 March 2015. https://whyy.org/articles/tylenol-maker-pleads-guilty-in-case-over-metal-particles-in-childrens-medicine/
25. "Moderna COVID-19 Vaccine Recall Investigation Report–October 2021." Takeda. October 2021. https://www.takeda.com/4a7623/siteassets/ja-jp/home/announcements/2021/report/moderna-covid-19-vaccine-recall-investigation-report--october-2021.pdf
26. Dunleavy, K. "Moderna Report Says 'Human Error' to Blame for Contamination Found in 3 Vaccine Lots from Rovi Plant." FiercePharma. 1 October 2021. https://www.fiercepharma.com/manufacturing/moderna-report-says-human-error-to-blame-for-rovi-releasing-3-vaccine-lots-after
27. Pluháček, T., M. Ručka, and V. Maier. "A Direct LA-ICP-MS Screening of Elemental Impurities in Pharmaceutical Products in Compliance with USP and ICH-Q3D." *Analytica Chimica Acta* 1078 (2019): 1–7.

28. Pillai, S. A., D. Chobisa, D. Urimi, and N. Ravindra. "Pharmaceutical Glass Interactions: A Review of Possibilities." *Journal of Pharmaceutical Sciences and Research* 8, no. 2 (2016): 103–111.

29. US Food and Drug Administration. "Gilead Issues a Voluntary Nationwide Recall of Two Lots of Veklury® (Remdesivir) Due to Presence of Glass Particulates." 3 December 2021. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/gilead-issues-voluntary-nationwide-recall-two-lots-vekluryr-remdesivir-due-presence-glass

30. Wakankar, A. A., Y. J. Wang, E. Canova-Davis, S. Ma, D. Schmalzing, J. Grieco, et al. "On Developing a Process for Conducting Extractable–Leachable Assessment of Components Used for Storage of Biopharmaceuticals." *Journal of Pharmaceutical Sciences* 99, no. 5 (2010): 2209–2218.

31. Latini, G. "Monitoring Phthalate Exposure in Humans." *Clinica Chimica Acta* 361, no. 1–2 (2005): 20–29. https://www.sciencedirect.com/science/article/pii/S0009898105002998

32. Helmlin, H. J., A. Mürner, A. Steiner, M. Kamber, C. Weber, H. Geyer, et al. "Detection of the Diuretic Hydrochlorothiazide in a Doping Control Urine Sample as the Result of a Non-Steroidal Anti-Inflammatory Drug (NSAID) Tablet Contamination." *Forensic Science International* 267 (2016): 166–172. https://www.sciencedirect.com/science/article/abs/pii/S0379073816303590?via%3Dihub

33. Zeng, G., H. Ma, X. Wang, H. Yan, X. Wan, B. Jiang, et al. "Paraplegia and Paraparesis from Intrathecal Methotrexate and Cytarabine Contaminated with Trace Amounts of Vincristine in China During 2007." *Journal of Clinical Oncology* 29, no. 13 (2011): 1765–1770. https://pubmed.ncbi.nlm.nih.gov/21422429/

34. Eichner, A., L. A. Lewis, B. Leonard, R. M. V. Wagoner, D. Eichner, and M. N. Fedoruk. "Generic Pharmaceuticals as a Source of Diuretic Contamination in Athletes Subject to Sport Drug Testing." *Frontiers in Sports and Active Living* 3 (2021). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8635962/

35. Tsuchiya, M., T. Obara, and N. Mano. "Itraconazole Contaminated with Rilmazafone in Japan: A Retrospective Analysis Using the Japanese Adverse Drug Event Report Database." *Drugs–Real World Outcomes* 9, no. 3 (2022): 315–319. https://pubmed.ncbi.nlm.nih.gov/35606678/

36. Kansteiner, F. "How Did 75M J&J Vaccines Get Ruined? FDA Details the Manufacturing Woes at Emergent's Beleaguered Site." FiercePharma. 14 June 2021. https://www.fiercepharma.com/manufacturing/some-j-j-covid-19-doses-now-cleared-from-emergent-but-several-countries-are-already

37. Rushton, S. "Germany and South Africa Demand Action Over Spoiled Johnson & Johnson Covid Vaccines." The National. 14 June 2021. https://www.thenationalnews.com/world/europe/germany-and-south-africa-demand-action-over-spoiled-johnson-johnson-covid-vaccines-1.1241022

38. Ratanji, K. D., J. P. Derrick, I. Kimber, R. Thorpe, M. Wadhwa, and R. J. Dearman. "Influence of Escherichia Coli Chaperone DnaK on Protein Immunogenicity." *Immunology* 150, no. 3 (2017): 343–355. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5290234/

39. Mamnoon, B., T. Naserpour Farivar, A. R. Kamyab, D. Ilghari, A. Khamesipour, and M. Karimi Arzenani. "Quality Control of Widely Used Therapeutic Recombinant Proteins by a Novel Real-Time PCR Approach." *Iranian Biomedical Journal* 20, no. 1 (2016): 56–62. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4689282/

40. White, C. M. "Understanding and Preventing (N-Nitrosodimethylamine) NDMA Contamination of Medications." *Annals of Pharmacotherapy* 54, no. 6 (2019): 106002801989222. https://pubmed.ncbi.nlm.nih.gov/31771343/

41. US Food and Drug Administration. "Recalls, Market Withdrawals, & Safety Alerts." Updated 15 December 2022. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts

42. Schier, J. G., D. B. Barr, Z. Li, A. F. Wolkin, S. E. Baker, L. S. Lewis, et al. "Diethylene Glycol in Health Products Sold Over-the-Counter and Imported from Asian Countries." *Journal of Medical Toxicology* 7, no. 1 (2011): 33–38. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3614107/#:~:text=Diethylene%20glycol%20(DEG)%20is%20used

43. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme. "Guide to Good Manufacturing Practice for Medicinal Products Part II." February 2022. https://picscheme.org/docview/4589

44. Code of Federal Regulations. "Title 21, Chapter I, Subchapter C, Part 225, Subpart A, § 225.1." Published 2014. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-225/subpart-A/section-225.1

45. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme. "Revised Annex 1 (Manufacture of Sterile Medicinal Products) to Guide to Good Manufacturing Practice for Medicinal Products." February 2022. https://picscheme.org/docview/4737

46. Government of India. "State-Drugs-Control." https://cdsco.gov.in/opencms/opencms/en/State-Drugs-Control/

47. Pacific Bridge Medical. "China Regulatory and Market Access Pharmaceutical Report 2014." 2014. http://www.pacificbridgemedical.com/wp-content/uploads/2015/04/China-Regulatory-and-Market-Access-Pharmaceutical-Report-2014.pdf

48. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme. "A Recommended Model for Risk-Based Inspection Planning in the GMP Environment." 1 January 2012. https://picscheme.org/docview/3439

49. Gostin, L. O., G. J. Buckley, and P. W. Kelley. "Stemming the Global Trade in Falsified and Substandard Medicines." *JAMA* 309, no. 16 (2013): 1693. https://jamanetwork.com/journals/jama/article-abstract/1677391

50. White, C. M. "Generic Drugs Not as Safe as FDA Wants You to Believe." *Annals of Pharmacotherapy* 54, no. 3 (2019): 283–286. https://pubmed.ncbi.nlm.nih.gov/31615266/

51. Oehler, R. L. and S. G. Gompf. "Shortcomings in the US Pharmaceutical Supply Chain: Potential Risks Associated with International Manufacturing and Trade-Related Tariffs." *JAMA* 324, no. 2 (2020): 143–144. doi:10.1001/jama.2020.1634

52. Woodcock, J. "Oversight of FDA's Foreign Inspection Program." US Food and Drug Administration. 9 December 2019. https://www.fda.gov/news-events/congressional-testimony/securing-us-drug-supply-chain-oversight-fdas-foreign-inspection-program-12102019

53. Iwamoto, T., T. Morikawa, M. Hioki, H. Sudo, D. Paolucci, and M. Okuda. "Performance Evaluation of the Compounding Robot, APOTECAchemo, for Injectable Anticancer Drugs in a Japanese Hospital." *Journal of Pharmaceutical Health Care and Sciences* 3, no. 1 (2017). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5402647/

54. Petrelli, F., S. Scuri, I. Grappasonni, C. T. T. Nguyen, A. Cocchini, E. Magrini, et al. "Campaign Manufacturing of Highly Active or Sensitizing Drugs: A Comparison Between the GMPs of Various Regulatory Agencies." *La Clinica Terapeutica* 170, no. 1 (2020): e66–73. https://pubmed.ncbi.nlm.nih.gov/31850487/

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CLEANROOM RECOVERY STUDY

Using CFD Methodology

By Elijio Prado and Albert Dyrness

Computational fluid dynamics (CFD) can reduce or eliminate the uncertainty associated with a cleanroom facility as the planned design can be simulated to predict performance to a high degree of accuracy. This article discusses the use of CFD for the purpose of predicting and optimizing the performance of a cleanroom facility in terms of steady-state airborne particulate levels and for estimating the recovery time to a particulate challenge per ISO 14644-3 [1].

An equation is derived to predict the recovery time for a cleanroom that is challenged with 0.5-micron particulates. The results from CFD are compared to the derived equation and to experimental data for a cleanroom waste airlock. A further CFD model of an entire cleanroom facility is made, and the recovery results are compared with the mathematically derived model.

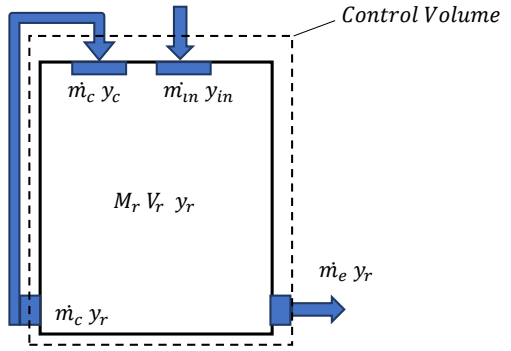
The methodology presented here allows for particulate levels and recovery times to be estimated during the design phase of a cleanroom facility. This study illustrates that CFD is a valuable tool in reducing the uncertainty associated with a cleanroom design. Once created, the CFD model can be used for parametric studies to optimize a design. Design parameters such as air change rates, exhaust rates, supply and exhaust register locations, and supply register types (e.g., laminar, radial) can easily be studied to gauge the impact to particulate levels. These simulations were performed with ANSYS CFX software, version 2021R1.

CFD METHODOLOGY

To gain confidence in the CFD methodology, a cleanroom waste airlock was first modeled for recovery time and compared to a mathematical model and experimental data. Even though a waste airlock is used in this study, the methodology formulated here applies equally to higher grade room classifications, such as an aseptic filling area. This work includes a mesh independence study on the CFD model, which compares particle recovery times for increasing levels of mesh refinement.

After a satisfactory agreement was made between the CFD model and experimental data for the airlock, a more complex facility was modeled and optimized to minimize the overall steady-state particulate level.

Figure 1: Flow diagram for a room with a fan filter units.



This article first analyzes a cleanroom waste airlock and then an entire facility composed of cleanrooms. Design input parameters for the waste airlock came from the as-built/as-left condition (e.g., final air balance, field measurements) to align with the actual conditions. For a new construction, detailed or conceptual design parameters would be used to predict the cleanroom performance.

Mathematical Model

Figure 1 illustrates a typical cleanroom with a recirculation fluid stream that is part of a fan filter unit. The figure shows two filters, one part of the fan filter unit (associated with y_c) and the other part of the outside air (associated with y_{in}).

Assuming uniform particulate levels throughout the room, the concentration mass balance for the control volume in Figure 1 becomes:

$$\frac{dM_r y_r}{dt} = \dot{m}_c y_c + \dot{m}_{in} y_{in} - \dot{m}_c y_r - \dot{m}_e y_r \qquad \text{Equation 1}$$

Where: $\dot{m}_i$ is the mass flow rate for stream i
y_i is the particulate concentration for stream i
M_r is the fluid mass in the room

Further, assuming that the flow is incompressible, in that there is a negligible impact of density as the variation in pressure is insignificant, and the room mass remains constant, Equation 1 becomes:

$$V_r \frac{dy_r}{dt} = Q_c y_c + Q_{in} y_{in} - Q_c y_r - Q_e y_r \qquad \text{Equation 2}$$

Where: Q_i is the flow rate for stream i and V_r is the room volume. A mass balance reveals that $Q_{in} = Q_e$.

In addition, if we let X = 1 – HEPA%, then $y_c = X\, y_r$ and the equation becomes:

$$V_r \frac{dy_r}{dt} = Q_c X y_r + Q_{in} y_{in} - Q_c y_r - Q_{in} y_r \quad \text{Equation 3}$$

Rearranging and integrating, the equation becomes:

$$\int \frac{dy_r}{y_r(Q_c X - Q_c - Q_{in}) + Q_{in} y_{in}} = \int \frac{dt}{V_r} \quad \text{Equation 4}$$

Integrating yields:

$$\frac{1}{(Q_c X - Q_c - Q_{in})} ln[y_r(Q_c X - Q_c - Q_{in}) + Q_{in} y_{in}] = \frac{t}{V_r} + Const1 \quad \text{Equation 5}$$

Solving for time t, the above equation becomes:

$$t = \frac{V_r}{(Q_c X - Q_c - Q_{in})} ln[y_r(Q_c X - Q_c - Q_{in}) + Q_{in} y_{in}] + Const2 \quad \text{Equation 6}$$

At time t = 0, the room concentration $y_r = y_0$ (initial concentration) and thus the Const2 is:

$$\text{Const2} = -\frac{V_r}{(Q_c X - Q_c - Q_{in})} ln[y_0(Q_c X - Q_c - Q_{in}) + Q_{in} y_{in}] \quad \text{Equation 7}$$

Thus, the time equation becomes:

$$t(y_r) = \frac{V_r}{(Q_c X - Q_c - Q_{in})} ln\left[\frac{y_r(Q_c X - Q_c - Q_{in}) + Q_{in} y_{in}}{y_0(Q_c X - Q_c - Q_{in}) + Q_{in} y_{in}}\right] \quad \text{Equation 8}$$

The equation above provides the elapsed time in going from an initial room concentration y_0 to a final room concentration y_r. The equation can be used to estimate recovery times where y_0 = 100 y_r. Note this equation was formulated for a room with recirculation fan filter units but can easily be applied to a single-pass flow system with Q_c = 0.

WASTE AIRLOCK MODELING USING CLOSED-FORM SOLUTION

This waste airlock model consisted of a single-pass system with two doors, one HEPA inlet, and one exhaust. Since the airlock operated as a pressure sink, the model needed to account for the inlet flows across the doors, as this would affect the room particulate concentration. An easy way of accounting for these flows was to make Q_{in} and y_{in} a flow-weighted average of the infiltrated door flows and the HEPA inlet flow. As an example, if the infiltrated door flows are 50 cfm and 100 cfm at a concentration of 1,000 particles/m^3 and 100,000 particles/m^3, respectively, and the inlet HEPA air contains a flow of cfm at a concentration of 50 particles/m^3, then Q_{in} would be set to 650 cfm with y_{in} set at 15,500 particles/m^3.

To estimate the infiltrated door flows, design documentation can be used. Specifically, the differential pressure (dp) between rooms should be known from the pressurization plan, and design drawings can be used to estimate the flow area of the door clearance (gap between door edge and floor or door edge and wall).

In this study, to reduce the uncertainty of this methodology, field measurements were used for both the dp across the doors and the door clearance. The door infiltration flow rate is calculated based on the Darcy–Weisbach equation shown below, with the loss coefficient K simply modeled at 1.5, which is equal to an abrupt entrance + exit loss coefficient:

$$dp = \frac{1}{2}\rho K \left(\frac{Q}{A}\right)^2 \quad \text{Equation 9}$$

Where: dp = differential pressure across the door:

K = loss coefficient across door

A = flow area of door clearance

Q = door infiltration flow rate

ρ = air density

Solving for the flow rate yields:

$$Q = A\sqrt{\frac{2\,dp}{\rho K}} \quad \text{Equation 10}$$

Using the above equation, the door infiltration flows were calculated.

Other field measured data that were used as inputs to Equation 8 are listed below:

1. The HEPA inlet flow per air balance report
2. Initial room concentration, y_0, per field tested recovery study
3. Final room concentration, y_r, per field tested recovery study
4. Measured room volume

The waste airlock was designed as a single-pass system; therefore, the recirculation flow, Q_c, in Equation 8 was set to zero. This equation estimated the waste airlock to take 7.24 minutes to go from an initial concentration of 100x to a final concentration of 1x.

WASTE AIRLOCK MODELING USING CFD

As previously discussed, this room acts as a pressure sink, meaning that it operates at a lower pressure than the adjacent rooms. Thus, there is air infiltration into the room via the door clearances. The CFD modeled the doors in their closed position with air allowed through the bottom door clearance. The same flow rates that were used for the mathematical model were used for the CFD model. Two models were solved: first a flow-only model and then a particulate transient model. It is important to have the flow structure resolved before introducing the particulate challenge, otherwise the results may not be as accurate. The particulate transient started with flow results based on the steady-state flow-only solution with an initial particle concentration at 100x.

Assumptions

The following assumptions were made in our study:

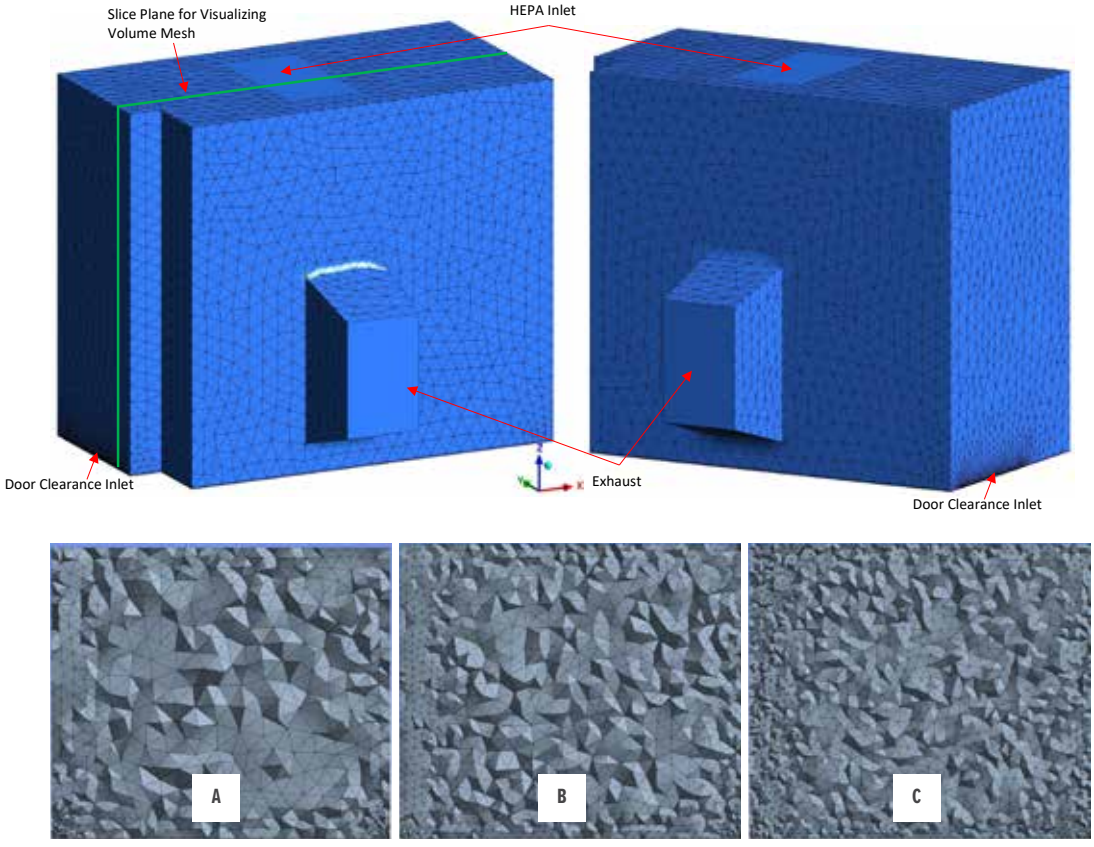
1. The air was assumed incompressible with properties at 25°C (77°F). The pressure changes are minor, so this assumption will not have a noticeable impact.
2. Particle deposition does not typically occur for 0.5-micron-sized particles (medium-sized particles) as they typically flow with the air stream [2], thus particles are assumed to be fully suspended.

Selected Conditions

For this study, the following conditions were used:

1. Isothermal conditions were used because there were no significant heat loads.
2. To model turbulence, the two-equation RNG k-$\mathcal{E}$ model was used with medium turbulence intensity (5%), which is the

Figure 2: Waste airlock coarse surface mesh (top) and fluid volume mesh (bottom): (a) coarse, (b) medium, (c) fine.



recommended CFX option when no turbulence intensity information is available. As a check, the turbulence intensity formula, $I = 0.16Re^{-1/8}$, for fully developed flow within a pipe was solved for the HEPA inlet flow and the door infiltration flows (with a hydraulic diameter = 4 × flow area ÷ wetted perimeter) and an intensity of approximately 5% was calculated.

3. All physical walls contained a no-slip boundary condition, per boundary layer theory.
4. The high-resolution scheme was used for turbulence and advection. This scheme uses second-order numerical modeling and is the recommended scheme to use for final results.

Table 1: Mesh study.

Parameter of Interest	Coarse Mesh	Medium Mesh	Fine Mesh
Number of Elements	70,066	140,427	280,146
Number of Nodes	15,579	30,004	57,418
y+ Area Average	49	39	31
Element Size (inch)	4.7	3.0	2.2
Recovery Time (min)	9.30	9.47	9.45

MESH INDEPENDENCE SOLUTION

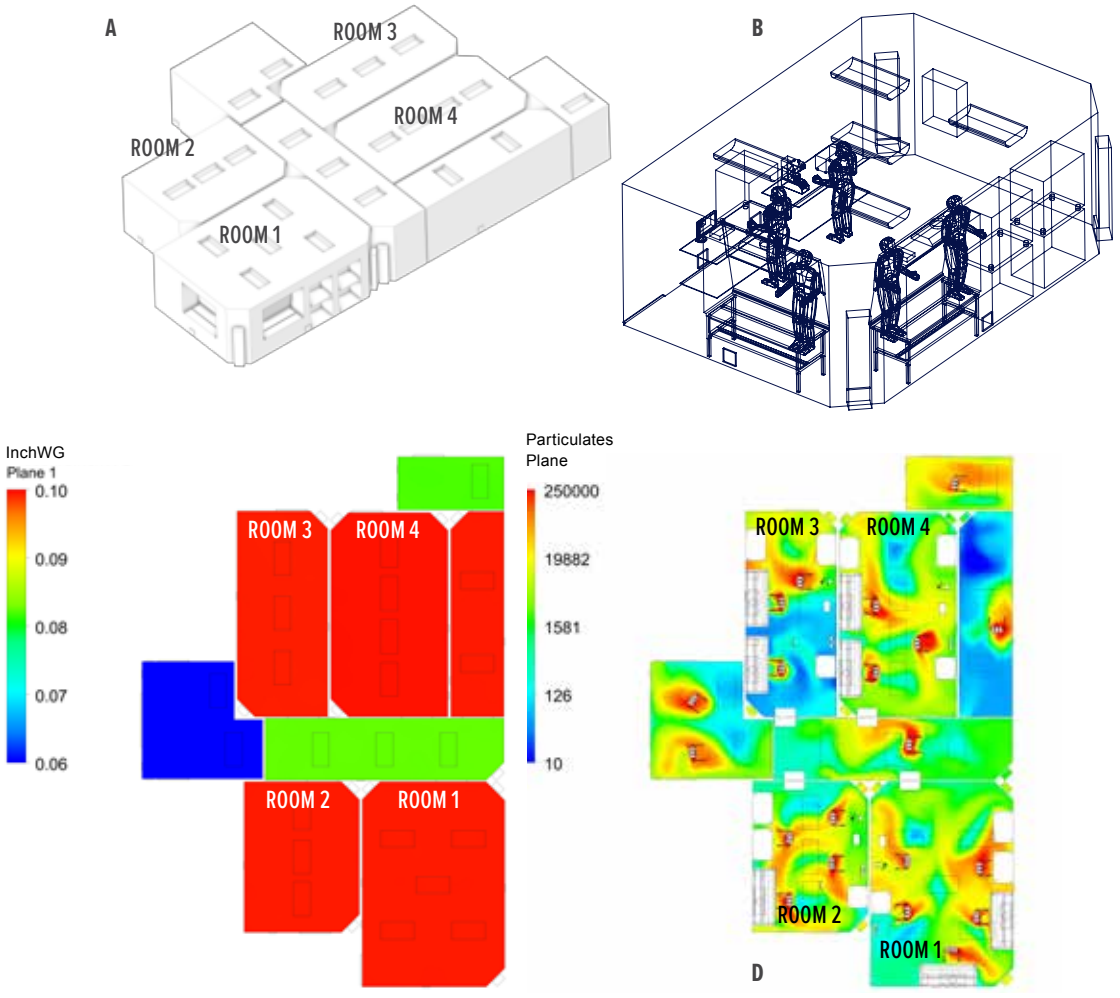
An unstructured mesh using mostly tetrahedral elements was applied with some prisms and pyramids as required. Two layers of mesh inflation using prisms were added off the floor to better capture the high-velocity gradients arising from the infiltrated door flows.

Three separate meshes were created to test mesh independence on recovery time. Successive mesh refinements doubled the total number of elements; the medium mesh had twice the number of elements as the coarse mesh, and the fine mesh had twice the number of elements as the medium mesh. Local mesh sizing was added to the door clearance. The local mesh-sizing parameters on the door clearance and the two-layer mesh inflation thickness did not change across the different meshes, only the global mesh size changed. Figure 2 illustrates surface mesh and volume mesh.

Table 1 shows the results of the mesh study for coarse, medium, and fine on the parameter of interest.

The results suggest that mesh independence was achieved with the coarse mesh, as the medium mesh results differ by less

Figure 3: Grade B facility cleanroom model: (a) isometric view, (b) isometric of Room 1 showing details, (c) pressurization plan view, (d) CFD particulate concentration at working level during normal operations.



than 2% and the recovery time did not significantly change with a further doubling of the mesh density (fine mesh results). Thus, a global element size of 4.7 inches was sufficient to properly capture the flow physics along with the two-layer prisms off the floor and local mesh controls at the door clearance.

MATHEMATICAL MODEL, CFD, AND EXPERIMENTAL DATA

The mathematical recovery time model and CFD agree within approximately 24% (7.24 vs. 9.47 minutes). The mathematical model was based on uniform distribution, and the CFD results were made based on a volume average concentration for an equal basis comparison. Though the CFD model did show that uniform particulate distribution did not exist, it was expected due to the existence of different particle concentrations for the inlet streams and the fact that mixing does not occur instantaneously.

The experimental data was taken at three different points within the waste room at approximately working level or about 3 feet from the floor. The experimental recovery times for these three points were 9 minutes, 10 minutes, and 9 minutes; averaging yields a recovery time of 9.33 minutes. The experimental results and CFD are in close agreement at less than 2% difference. This illustrates that, with the methodology provided in this CFD study, accurate predictions for particulate recovery times may be obtained using CFD.

FACILITY CFD MODEL

The CFD methodology discussed previously was implemented in a much larger cleanroom facility with four Grade B processing cleanrooms, a storage room, an entrance corridor, personal access, and material access, as shown in Figure 3. Radial HEPA supply registers were used in the model, and several rooms contained recirculating fan units.

Table 2: CFD versus experimental data and mathematical model for recovery time.

Room	CFD (min)	Experimental (min)	Difference (%)
Waste Airlock	9.47[a]	9.33	1.5
Room	**CFD (min)**	**Mathematical Model (min)**	**Difference (%)**
Waste Airlock	9.47[a]	7.24	23.5
Processing Room No.	**CFD (min)**	**Mathematical Model (min)**	**Difference (%)**
1	5.32	6.19	16.4
2	5.15	6.02	16.9
3	5.60	5.84	4.3
4	5.27	6.02	14.2

a Using worst case CFD recovery time from Table 1.

The Grade B cleanrooms, shown in red in Figure 3, acted as bubbles, i.e., at higher pressure than adjacent rooms. The arrows shown in the pressurization plan view of Figure 3 illustrate the flow cascade and denote the door locations.

The recovery times were estimated using the mathematical model and CFD. This facility study included the following three elements:

A. An operating study with personnel present to determine steady-state particulate levels; this included several different configurations for cleanroom optimization.
B. A transient with no personnel to capture a steady-state flow condition, based on the final configuration from element A.
C. A transient particle recovery study (no personnel present) with initial flow conditions from element B and a 1E8 particles/m^3 starting concentration.

Element A of the study involved performing several simulations, each with a different configuration (such as different supply and exhaust locations), with the goal of reducing the steady-state particulate level; the final design is illustrated in Figure 3. For this study, personnel were modeled with an applied particulate generation source. A total of 20 personnel working in the facility was assumed, each generating 3,000 particles/second of 0.5-micron size, which was applied uniformly. This particle generation rate was considered conservative because people in Grade B cleanroom coveralls will generate no more than 1,000 particles/sec [3]. To model the particle generation rate, a small velocity (such that it did not affect the room air change rate) was applied on personnel with a particle concentration determined as below:

Particle Concentration = (3,000 particles/sec) ÷ (small velocity × surface area of person)

In addition to modeling personnel, the planned equipment (e.g., biological safety cabinets, tables, chairs) was also modeled. Exhausts contained a pressure boundary condition, which was adjusted to achieve room target pressurization (as shown in Figure 3). Exhaust flows were an output of the CFD model and useful in properly sizing the exhaust ductwork and fan(s). Air communication between rooms was only allowed via a 0.5-inch modeled clearance at the bottom of doors. The final CFD configuration had a maximum particulate level of approximately 2.5E5 particles/m^3 in the Grade B space, which is 30% lower than the Grade B operating limit of 3.5E5 particles/m^3.

As this was a study to show the feasibility of using CFD at the design stage of a project, there is no experimental data. The comparison for the four processing rooms is made between CFD and the mathematical recovery model derived previously.

As can be seen in Table 2, there is reasonable agreement between CFD and the mathematical model; however, CFD is expected to yield the more accurate result.

CONCLUSION

This study showed that CFD is a valuable tool in cleanroom design, with particulate recovery times accurately predicted within 2% of experimental data, as shown in Table 2. This comparison was made based on averaging the experimental results of 9 minutes, 10 minutes, and 9 minutes. The experimental data itself has an 11% spread, which is larger than the CFD prediction.

The mathematical model was not expected to provide as accurate a result since it is based on simplifying assumptions such as equal particulate distribution. Nevertheless, its results are valuable at providing estimates in the initial design phase of a project and acknowledges the need for more sophisticated analysis tools when accuracy is critical.

Several biopharmaceutical companies have adopted the European Union Guideline of a 15- to 20-minute recovery time. As can be seen from the results in Table 2, even the mathematical model could have provided quick guidance to whether a design would meet this recovery time criteria.

The larger advantage of using CFD over the mathematical model is not only to provide more accurate results, but also to perform optimization studies such as rearranging the inlet and exhaust registers in a room or even changing register type (e.g., from laminar to radial) to see the effects not only on recovery times, but also on steady-state particulate levels.

The suggested path for cleanroom design is to use the mathematical model as an initial estimate to establish a minimum required room air change rate. This initial airflow can then be used in a CFD model to determine a more accurate air flow requirement. This approach would eliminate uncertainty in a heating, ventilation, and air conditioning (HVAC) design and reduce the potential of overly sizing an air handling unit (AHU) and/or exhaust fan system.

The following are required design inputs and considerations for building an accurate CFD model:

- Flows for inlet and exhaust registers and infiltration across doors should be considered.
- Each fluid stream should contain its own particulate level. This would come from design inputs at the design stage and may include the outside particulate level being designed to the filters within the AHU (pre and final filters), and the terminal air filter in the cleanroom.
- The room exhaust may be entered as a pressure-specified boundary condition, which can be adjusted as the solution is being solved, to meet target pressurization within the room. The exhaust pressure will not necessarily be equal to room pressure as there may be hydraulic losses, depending on how the exhaust is modeled. From experience and CFD modeling best practices, it is best to avoid modeling an exhaust boundary where recirculation flow may occur.

References

1. ISO Standard 14644-3. "Cleanrooms and Associated Controlled Environments—Part 3: Test Methods." 2019. https://www.iso.org/obp/ui/#iso:std:iso:14644:-3:ed-2:v2:en
2. Tsuda, A., F. S. Henry, and J. P. Butler. "Particle Transport and Deposition: Basic Physics of Particle Kinetics." *Comprehensive Physiology* 3, no. 4 (2013): 1437–1471. doi:10.1002/cphy.c100085
3. Whyte, W., N. Lenegan, and T. Eaton. "Calculation of Airborne Cleanliness and Supply Rate for Non-Unidirectional Airflow Cleanrooms." *European Journal of Parenteral & Pharmaceutical Sciences* 21, no. 3 (2016): 79–88.

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