PHARMACEUTICAL ENGINEERING®

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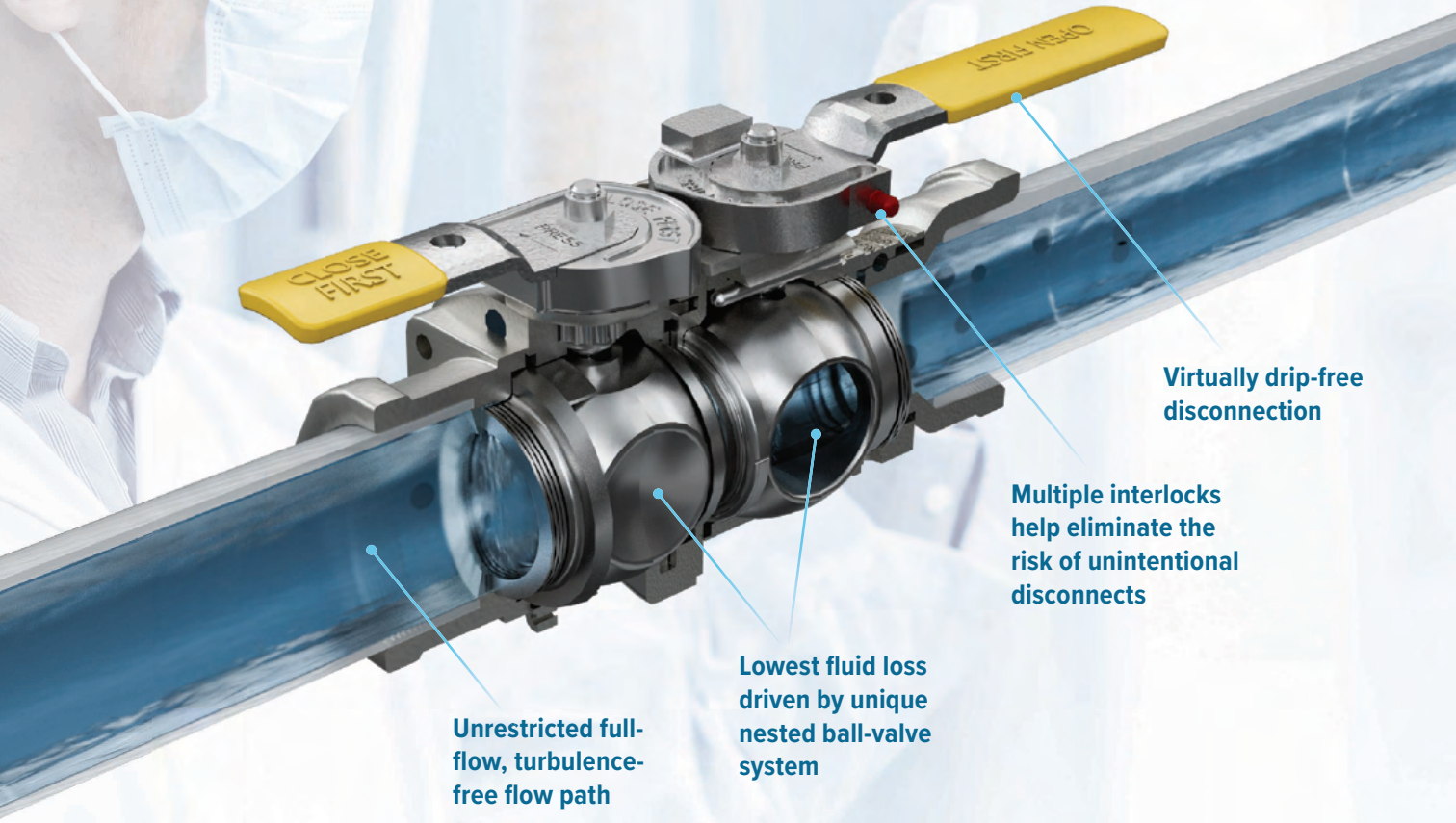

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ON THE COVER The focus of this issue is the Workforce of the Future. The future workforce will be shaped by upskilling, global collaboration, and other factors featured in this issue.

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35 CREATING GLOBAL IMPACT IN INDIA

India's pharmaceutical sector is not only a cornerstone of its national economy, but it's also a pivotal player on a global stage. As of 2023, India ranked as the third-largest producer of drugs and pharmaceuticals by volume, with a 20% global share in the export of generic drugs. Currently valued at US$50 billion, the country has an ambitious goal for the sector: Grow its value to US$450 billion by 2047.

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By Jeffrey A. Biskup, PE


Jeffrey A. Biskup, PE

ISPE's Regulatory, Technical, and Quality Leadership

Our March/April issue focuses on the workforce of the future. This is a critical theme for us: ISPE's vision includes a focus on member and workforce development, as well as technical, regulatory, and quality leadership, as we continue to shape the future of the global pharmaceutical industry. This is particularly important with the industry's growing skills gap.

SUPPORTING LEADERSHIP AND WORKFORCE DEVELOPMENT

ISPE is working to bridge the talent gap and support workforce development—helping the future workforce prepare to drive the industry forward. Workforce development is a critical need: A 2017 study by ISPE and McKinsey & Company found disruptors in pharmaceutical operations, including digitization, advanced analytics, and new product modalities (such as cell and gene therapy), were creating a skills mismatch in more than 80% of pharmaceutical manufacturing companies. In the seven years since that report, additional research has confirmed those gaps persist across the pharmaceutical value chain.

ISPE offers a wealth of resources and opportunities to support leadership development. We recently launched a new column focused on leadership. This topic is at the forefront of our conferences as well. Leadership development opportunities are available through many avenues, including ISPE's Women in Pharma®, the Mentor ISPE program, and the ISPE Emerging Leaders program.

ISPE is expanding its scope of professional development opportunities. This year, we plan to launch a new professional development certificate program; more details will be unveiled later this year. We are also seeing momentum around professional development offerings specifically tailored for ISPE Affiliates and Chapters, thanks to One ISPE.

PROVIDING A WEALTH OF INDUSTRY RESOURCES

With a vast network of over 22,000 members across 120 countries, ISPE supports collaborative, complex problem-solving to address some of the industry's most pressing challenges.

- **Supporting Annex 1 implementation:** The 2024 ISPE Pharma 4.0™ and Annex 1 Conference emphasized Annex 1 implementation and digital transformation.
- **Addressing drug shortages:** The ISPE Drug Shortages Prevention Model was updated in 2023 to account for the COVID-19 pandemic and other large-scale events. ISPE also issued blog posts and online exclusive articles on this topic.
- **Advising on harmonization and the convergence of regulatory expectations:** In 2024, ISPE published a survey report on innovation barriers through its Enabling Pharmaceutical Innovation program.
- **Guiding ICH Q12 implementation:** ISPE's Product Quality Lifecycle Implementation (PQLI)® initiative provides education and training to support ICH Q12 implementation.
- **Providing quality management maturity (QMM) guidance:** The ISPE Advancing Pharmaceutical Quality (APQ) initiative enables QMM with APQ-focused professional development trainings and five ISPE APQ Guides on change management systems, corrective action and preventive action systems, management responsibilities, product quality monitoring systems, and more.

ENABLING REGULATORY, TECHNICAL, AND QUALITY LEADERSHIP

ISPE steadfastly supports enabling regulatory leadership; this is part of our vision statement and a top priority for me as the ISPE International Board Chair. ISPE is uniquely positioned to bring together regulators, manufacturers, and other key stakeholders from across the industry and around the world.

We operate around this mindset: If we knew what regulators were thinking, what they wanted or needed, it would help us do our job better in serving them. We come together so we can understand the challenges and opportunities surrounding regulatory compliance collectively, enabling us to engage in complex problem-solving to make improvements together.

We are actively engaging with regulators. By the third quarter of 2024, our conferences had featured more than 27 speakers from 10 regulatory agencies around the world. Collectively and individually, ISPE has built relationships that drive remarkable benefits to the pharmaceutical industry. Regulators, pharmaceutical manufacturers, service providers, and equipment vendors have all contributed significantly to the industry and ISPE. Many professionals have benefited from ISPE trainings and in many cases, they were the trainer or were involved in developing the training program.

ISPE has delivered 45 years of technical leadership to the industry and continues to make strides in providing novel insights and approaches as the industry grows and evolves. Our technical leadership is apparent in everything we do—starting with our 22 technical Communities of Practices, who inform content from ISPE Guidance Documents to professional development courses to conferences. We are expanding the ISPE community to engage all aspects of the pharmaceutical industry—appealing to and looking beyond our dedicated audience of engineers.

We are also providing quality leadership, which closely ties with our regulatory leadership initiatives. Our regulatory volunteer groups actively submit commentary to regulators, engage in meetings with health authorities, and provide valuable content and insights to inform ISPE Guidance Documents, conference sessions, webinars, articles, blog posts, and more.

As we broaden our scope, we are exploring a wider array of topics, including a focus on biotechnology, with our 2024 ISPE Biotechnology Conference in June and early-stage plans for ISPE Guides focusing on topics like oligonucleotides and mRNA. ISPE also has guides on pharmaceutical compounding and continuous manufacturing. Together, we can advance the workforce of the future and support industry growth with our leadership initiatives, a wealth of resources, and collaborative support.

Jeffrey A. Biskup, PE, is the Executive Chairman of the Board at CRB and the 2024–2025 ISPE International Board Chair. He has been an ISPE member since 1998.

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PHARMACEUTICAL ENGINEERING®

By Lindsay Daniel, PE


Lindsay Daniel, PE

HAVING IT ALL

Being a working mom has shaped my career in unexpected ways. Early in my career, a colleague who had just become a mother told me that you can't "have it all"—a thriving career, a happy home life, and a fulfilling personal life.

Her words resonated with me as I contemplated starting a family and how it might impact my career. However, through Women in Pharma®, I witnessed mothers excelling at work and home, giving me hope that I could "have it all" too. I sought mentorship with these successful working mothers to uncover their secrets.

SECRET 1: CREATE A BALANCE

The first secret I learned was to create balance in my life. At the start of my career, work was my primary focus. I traveled extensively, building biologic and plasma facilities globally, and worked long hours. These years were invaluable for my career growth and allowed me to build relationships worldwide which have molded who I am today. When I considered starting a family, I realized I needed to reshape my professional life to align with my career and family aspirations. This led me to Takeda because of their strong support of women in engineering and working mothers, two of my primary focuses at the time. Transitioning to an engineering role at a local site reduced my travel but as my family grew, I realized I needed even more flexibility. Fortunately, I found the flexibility I needed in a non-technical strategic role, allowing me to work hybrid and avoid on-call work during prime family time.

SECRET 2: FIND WAYS TO MAINTAIN BALANCE

Balance is a tricky thing to maintain as personal priorities are always shifting. While transitioning to a non-technical role, I feared losing touch and confidence in my technical capabilities. This is where ISPE became my anchor. Active participation in local Chapter boards, Communities of Practice (CoPs), and conference planning committees allowed me to stay informed about industry trends and remain at the forefront of technological developments. ISPE has also supported my growth as a leader through opportunities to serve on local executive boards and chair the 2026 Facilities of the Future Conference Planning Committee. Through these experiences, ISPE has provided me with an outlet to stretch myself on my terms and in my time frame, allowing me to maintain my balance.

They say it takes a village, and Women in Pharma is the pub at the center of my village—a place to connect, celebrate successes, and confide in friends when struggling.

SECRET 3: EMBRACE THE BALANCE

Many women say, "I am a better mom because I work," a sentiment that resonates with me. I also believe I am a better employee because I am a mom. Motherhood has broadened my perspective and expanded my thinking. It has encouraged me to take risks and make career shifts I might not have otherwise. The new balance I have created keeps me energized at work and home. It allows my head to be where my feet are—focused on work while at work, and on family while at home. This enables me to be more efficient with my time and reduces the stress of trying to do it all at once. As priorities shift, I remain focused on the balance as I have learned it is the key to my success.

Through my evolving roles at Takeda and ISPE, I have developed my version of "having it all." Each woman has her definition, but for me, "having it all," means creating peace with what I can achieve today and finding, maintaining, and embracing my balance. They say it takes a village, and Women in Pharma is the pub at the center of my village—a place to connect, celebrate successes, and confide in friends when struggling. Most importantly, it's a place I know will always be there when I need it, no matter the problem.

Lindsey Daniel, PE, serves as the Product Operations Strategy and Business Lead at Takeda. She is Chair of the 2026 Facilities of the Future Conference Planning Committee, Vice President of the ISPE Boston Area Chapter, and a member of the ISPE Women in Pharma International Steering Committee. She joined ISPE in 2012.

By Rebecca Roscher


Rebecca Roscher

MASTERING CONSTRUCTIVE DISAGREEMENT IN TIMES OF CHANGE

The expectations for the workforce joining the industry right now are slightly daunting. It can feel like being required to be everything at once: flexible but driven by purpose, extremely adaptable but stable at the core, empathetic but independent, and knowledgeable but versatile.

Young, early-in-career professionals are expected to push progress forward while remaining patient, balancing innovation with tradition, and leveraging creativity and new technologies like artificial intelligence to pave highly efficient new paths.

In all business sectors, employees are asked to take on responsibilities by choice without necessary gain, to become ideal collaborators but also decisive contributors who take charge within dynamic work structures. And naturally, everyone is invited to develop into a modern, vulnerable leader without authority who can empower and motivate all generations with complete confidence. And to complete the list of expectations for the workforce of the future: they shall all embrace change.

In Germany, my home country, there is a saying for this level of expectation: Eierlegende Wollmilchsau, (literally "egg-laying wool-milk-sow"), humorously describing the impossibility of meeting every demand simultaneously. Instead of striving for perfection in every area all at once, why not focus on one crucial skill at a time? One that will help us navigate through stressful periods of intense and frequent changes because it strengthens decisions in teams.

Over the past year, I've realized one skill is often missing. (It's even mentioned as a dysfunctionality pillar by Patrick Lencioni in his book, *The Five Dysfunctions of a Team: A Leadership Fable*.) It is a skill we often used in school during group discussions or interactive lessons, but one that we rarely see in our daily lives as working adults: the ability to disagree and hold constructive critical discussions.

HARNESSING THE ABILITY TO CONSTRUCTIVELY DISAGREE

When normalized, healthy disagreements allow teams to assess risks and identify gaps more quickly. Team members create better solutions instead of signing off on unpolished ideas for the sake of harmony. Hence, they not only work on fostering trust between stakeholders or colleagues to enable open dialogue, but they also empower themselves and others to disagree. This is because a disagreement alone is neutral and represents an opportunity. It does not end in conflict if you do not let it. However, healthy disagreements don't happen by accident in work environments; they require intentional effort and active fostering.

Instead of striving for perfection in every area all at once, why not focus on one crucial skill at a time? One that will help us navigate through stressful periods of intense and frequent changes because it strengthens decisions in teams.

First, ensure everyone understands and aligns to the conversation's shared goal to reducing defensiveness. The power of pre-reads and moderation, especially an aligning introduction, should not be neglected. Once alignment is established, stay attentive during discussions. Watch for signs of disengagement, such as silence or changes in tone, pace, or volume, because they can signal underlying discomfort that needs gentle addressing. For instance, you might say, "I noticed you've gone quiet. Do you feel comfortable sharing your thoughts?" To keep a collaborative dialogue alive, it is helpful to pose only open questions for better

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Lou Schmukler

THE VISIONARY LEADER

Crafting and communicating a vision for the organization is one of the most important and visible jobs of a leader. It is also a difficult job, and executing plans to realize the vision is even more difficult.

"In order to take the organization to the highest possible level, leaders must engage their people with a compelling and tangible vision," said Warren Bennis, PhD, a prominent scholar and author on leadership. Research shows that approximately 71% of managers are not fully aligned with the leader's vision, and only 29% of employees say their leader's vision for the future is aligned with the organization's vision. Plus, a large segment of employees does not believe the organization's vision has been clearly communicated [1]. These are troubling facts that underscore the criticality of this essential leadership responsibility.

THE IMPACT OF VISIONARY LEADERSHIP

We are all likely familiar with some of history's most famous leaders and their visions: Dr. Martin Luther King Jr.'s vision for equality, President John F. Kennedy's vision to land a person on the moon, and Henry Ford's vision to transform the automotive industry. Visions like these often originate as merely a kernel of an idea that eventually evolves into a more vivid picture of a compelling, better, and brighter future.

Visionary leaders are sometimes mocked and ridiculed for what is viewed as a too bold, seemingly impossible idea. Apple's "Think Different" ad campaign from the late 1990s featured a poem that celebrated people who are "crazy enough to think they can change the world." Steve Jobs, former CEO of Apple, envisioned a digital revolution driven by the iPod and iPhone—and the rest of that story is well-known. The visionary leader is a nonconformist. They challenge the status quo, think outside the box, pursue novel ideas, and go against conventional practices to drive significant change.

ORGANIZATIONAL VISION

One of my favorite business maxims is, "If you don't know where you are going, any road will take you there." That said, why is an organizational vision essential? It is essential for several key reasons. First, it provides the organization with a clear path forward, a roadmap to a future state. Second, it serves to motivate, inspire, and engage the organization in the hard work of realizing that future state. The German philosopher Friedrich Nietzsche said, "He who has a why to live can bear almost any how." Third, it aligns everyone in the organization toward a set of shared goals. Fourth, it aids in decision-making by providing a framework. Fifth, it can assist in attracting top talent and gaining external shareholder buy-in. Lastly, I would add that it can differentiate the organization from competitors by showcasing unique aspirations and values. And I have always liked the notion of the vision as the organization's north star, its guiding light.

The visionary leader is a nonconformist. They challenge the status quo, think outside the box, pursue novel ideas, and go against conventional practices to drive significant change.

VISION AS A SKILL SET

In a previous column I wrote that we're not all natural-born leaders, and that leadership skills can be learned. This certainly applies to the skills associated with visioning. Visionary leaders share some common qualities and abilities. They are often imaginative and innovative. They have a communicative and collaborative style. They are goal-oriented risk-takers. They are usually both enthusiastic and persistent.

The visionary leader is sometimes thought of as a charismatic extrovert. But this is not a requirement, nor is it the case with some of the most recognized visionary leaders.

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understanding. I find it helpful to ask for a follow-up-quantification (e.g., "On a scale of 1–10…").

Even if it's difficult, respond positively to disagreement by expressing interest in their perspective. For example, say, "Let's explore it further," or paraphrase their statement to confirm if everything was understood correctly. Further, thank people for sharing differing views, even if their ideas aren't implemented. It took courage and may have paved the way for others to follow.

What should you do when participation is lacking during a discussion and "courteous" silence wrongly infers agreement? In such cases, explicitly invite disagreement. Instead of antagonizing (e.g., "Does anyone see this differently?"), use neutral and open questions like, "What's the downside of this approach?" You might even go as far as assigning a devil's advocate role to team members to facilitate contrasting opinions.

Although these strategies help, a few simple ground rules can ensure discussions remain productive rather than just a series of monologues. These rules could include combining opinions with underlying arguments, using a moderator to summarize the status quo, or not interrupting in video calls while still allowing for interactivity (e.g., by using mandatory cameras). When selecting ground rules, make sure to do so interactively and visually, such as using a whiteboard or PowerPoint presentation, or even lightheartedly asking everyone to sign the rules to increase their acceptance.

Constructive disagreement isn't just a skill—it's a tool for progress that will help us thrive in an ever-evolving industry.

As scholars, we once engaged in critical discussions with ease, challenging ideas to refine them. Let's bring that ability back to the workplace. By fostering trust, normalizing disagreement, and setting clear ground rules, we can navigate the next 40 years of change with confidence. Constructive disagreement isn't just a skill—it's a tool for progress that will help us thrive in an ever-evolving industry.

Rebecca Roscher, MSc, is a trained scientist in molecular medicine specializing in the research and development of immune therapies with a passion for cell and gene therapies and project management. Her interest in pharmaceutical engineering was sparked after joining ISPE in 2020.

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Bill Gates of Microsoft and Larry Page of Google are two prime examples. Studying leaders like these and others can help develop the competency of visionary leadership. Nevertheless, I would submit that this is a skill set that does not always come easy, even for the seasoned leader.

ESTABLISHING A VISION

The process of establishing a vision is the first step on a journey of creation, innovation, improvement, and transformation. There are various approaches and techniques for developing an organizational vision. A 5- to 10-year horizon is a good timeframe to consider. Regardless of whether the vision begins as a leader's flash of insight or emerges over an extended period, a structured set of activities is required to best ensure a successful outcome.

At a macro level, the visioning process has four major steps: preparation, creation, communication, and follow-up activity. Team meetings, retreats, and workshops are a part of each. These processes range from the very formal to the very informal. The effort of shaping an organization's vision does not fall on the leader's shoulders alone. At its core, visioning is a social process. It is a team sport. Selecting the right team members is extremely important. To be comprehensive, the team will need to be inclusive, engage a broader group, and consult various subject matter experts as the work advances. As with any major initiative, celebrating milestones along the way is always a good practice.

LEADING WITH VISION

An effective organizational vision directs, guides, and motivates members to improve organizational performance strategically. In effect, they are saying, "We want our organization to be different from what it is now and better tomorrow than it is today." A vision brings purpose and meaning to work, enabling employees to be a part of something bigger. It should enable the organization to realize its potential, exploit opportunities, and be a source of pride. In the song "Scarlet Begonias," the Grateful Dead sang, "Once in a while you get shown the light, in the strangest of places if you look at it right."

Reference

1. Murphy, Mark. "A Shocking Number of Leaders Are Not Aligned With Their Companies' Visions." *Forbes.* 28 August 2020. https://www.forbes.com/sites/markmurphy/2020/08/28/a-shocking-number-of-leaders-are-not-aligned-with-their-companies-visions/

Lou Schmukler served as Executive Vice President and President of Global Product Development and Supply at Bristol Myers Squibb until his retirement. His pharmaceutical industry career spanned over 40 years. He holds a BS from Temple School of Pharmacy and an MA from Webster University. He joined ISPE in 1993.

A SKILL MANAGEMENT FRAMEWORK for a Pharma 4.0™ Workforce

By Vinzenz Zauner, Kai Reinhardt, PhD, Yvonne Duckworth, PE, and Paige Kane, PhD

Pharma 4.0™ is driving fundamental industry changes and requires a comprehensive approach to workforce development. This article proposes a skill management framework aimed at empowering companies to develop a future-ready workforce, including practical insights within the context of Pharma 4.0™.

The framework includes establishing a skill model and governance, deriving the target state, identifying existing skills, conducting a gap analysis, and developing a skill development roadmap. Organizations can greatly benefit from systematic skill management, which aims to increase operational efficiency, enhance flexibility, and improve employee retention. By fostering innovation and supporting corporate strategy, strategic skill management enables pharmaceutical companies to thrive in the Pharma 4.0™ era. Organizations can greatly benefit from systematic skill management, which seeks to increase operational efficiency, enhance flexibility, and improve employee retention.

RESEARCH MOTIVATION AND CONTEXT

The fourth industrial revolution, marked by the integration of digital, physical, and biological technologies [1, 2], is driving fundamental changes in the global VUCA (volatility, uncertainty, complexity, ambiguity) world [3, 4]. This transformation is particularly profound in the pharmaceutical industry, where technologies such as artificial intelligence, big data analytics, and the Internet of Things (IoT) are reshaping the sector. Members of ISPE have developed a holistic approach to the fourth industrial revolution, Pharma 4.0™, tailored to the uniquely regulated environment of the pharmaceutical industry.

In 2023, ISPE published the *ISPE Baseline® Guide Vol 8: Pharma 4.0™* (First Edition) which highlights the importance of people, organization, and culture in this transformation [5, 6]. Research highlights the "technological-organizational paradigm shift" [7] requiring that companies fundamentally reconfigure their skills and processes to remain competitive [8]. To effectively harness the potential of Pharma 4.0™, pharmaceutical companies must adopt a comprehensive approach to workforce development and the management of its skill landscape.

A mixed author team was assembled for this article, bringing together perspectives and knowledge from technology to human resources (HR) from across academia, consulting end users, to bridge theory and practice. This article proposes a skill management framework designed to empower companies in developing a future-ready workforce. The framework is presented in the context of Pharma 4.0™ to provide practical insight.

BENEFITS OF STRATEGIC SKILL MANAGEMENT

Beyond research interest, organizations can greatly benefit from systematic skill management. Active skill management can be an essential enabler toward the wider aim to cultural excellence [9]. It aims to increase operational efficiency in daily HR, training, and leadership tasks. Further, data-driven insights and transparency unlock new ways to efficient workforce planning [10–12]. If set up successfully, the following impact and use cases are possible.

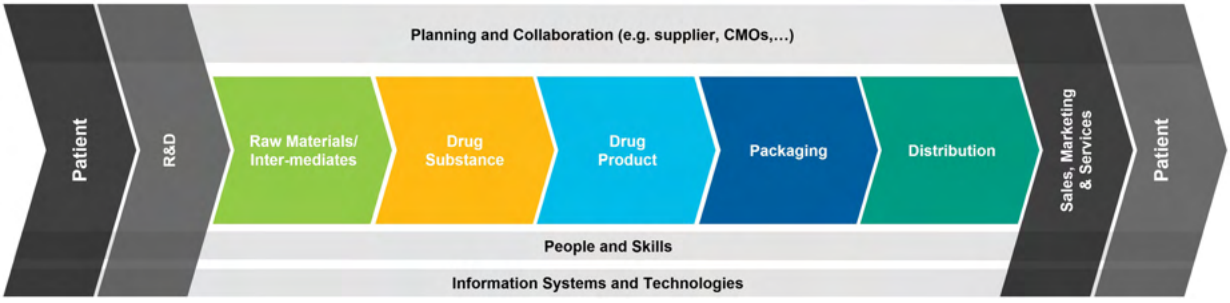
Increased Efficiency

Effective skill management enhances organizational efficiency by ensuring employees possess the necessary skills to perform their tasks effectively. This leads to improved performance, productivity, and operational efficiency, resulting in better-prepared employees who contribute significantly to overall organizational success.

Enhanced Flexibility

In today's dynamic business environment, flexibility is crucial. A robust skill management system allows organizations to quickly adapt to market changes, technological advancements, and evolving

Figure 1: Schematic representation of the end-to-end product supply value chain in the pharmaceutical industry influenced by Pharma 4.0™ [14]



customer needs. This agility helps maintain competitiveness and ensures that the organization can respond promptly to new challenges and opportunities.

Targeted Hiring

With clear insights into existing skills and future requirements, organizations can harmonize job postings and actively source the right talent. This targeted approach to hiring ensures that new employees possess the skills needed to meet current and future demands, aligning with the organization's strategic goals.

Improved Employee Retention

Focusing on skill development creates an engaging and supportive work environment. Employees who see opportunities for growth and development are more likely to stay with the company, which reduces turnover costs and contributes to a stable, experienced workforce. This fosters a culture of continuous improvement and loyalty.

Targeted Enablement

Data-driven insights reveal skill gaps with growing demand. Organizations can develop dedicated courses for relevant individuals, going beyond generic training available in overcrowded marketplaces. This targeted enablement ensures employees acquire the specific skills needed to excel in their roles.

Supported Corporate Strategy

Competency models aligned with the company's strategy ensure that the workforce can achieve long-term goals. By developing the specific skills necessary for strategic initiatives, organizations are better prepared for future challenges and can exploit new opportunities effectively.

Fostering Innovation

Systematic development of new skills promotes a culture of innovation. When employees acquire new skills and knowledge, they are more likely to contribute innovative ideas and solutions. Encouraging innovation helps the organization stay ahead of the competition, respond to changing customer needs, and explore new markets. These are essential for growth and long-term success.

Advanced Staffing

Organization-wide skill insights enable identification and staffing of optimal project teams. A project member chosen for technical expertise might hold that new role for the first time and then upskills in project management. After the project, the employee retains and documents the new skills, making them an identifiable valuable asset for future opportunities.

Embedded Regulatory Understanding

In regulated industries, employees and managers need to be aware of the regulatory framework of their company, processes, and products to meaningfully explore innovation, flexibility, and agility. Actively managing these critical skills helps in finding efficient ways to implement Pharma 4.0™ initiatives while ensuring compliance.

Overall, strategic skill management aims to bring immense value and improvements to workforce management as well as workforce spirit. These benefits make strategic skill management a central component of modern human resource management and organizational development strategies.

FROM STRATEGIC MANAGEMENT TO SKILL MANAGEMENT

Strategic management is paramount in navigating the complexities of global VUCA conditions and the fourth industrial revolution [2]. Building on dynamic capabilities theory [7], organizations must develop both the ability to sense new opportunities and the capacity to transform their operations accordingly. By formulating the business strategy, top management sets the organization's trajectory within this evolving landscape [2].

Changes coming with the adaptation of Pharma 4.0™ resonate throughout the end-to-end pharmaceutical value chain and its respective ecosystem capabilities in the context of people, processes, manufacturing plants, and organizations. This encompasses not only internal operations, but also external stakeholders, including suppliers, research partners, and regulatory bodies [13] (see Figure 1).

Table 1: Skill management impact areas within Pharma 4.0™

Impact Area	Guiding Questions
Digital Literacy and Data Fluency	• To what extent does the workforce understand core digital concepts such as data integrity, cloud computing, cybersecurity, and modular automation? • Are people enabled and willing to work with digital platforms and software commonly used in Pharma 4.0™, such as Laboratory Information Management System (LIMS), Manufacturing Execution System (MES), or Enterprise Resource Planning (ERP) systems?
Technical Skills for Automation and Advanced Technologies	• Does the workforce possess the skills to operate, maintain, and troubleshoot automated equipment, robotics, and other advanced technologies used in pharmaceutical manufacturing? • Is there relevant experience with technologies like artificial intelligence/machine learning (AI/ML) for drug discovery, process optimization, or predictive maintenance?
Skill Gaps and Upskilling/ Reskilling Timelines	• What are the most critical skill gaps hindering the implementation of specific Pharma 4.0™ initiatives (e.g., continuous manufacturing, real-time release testing, personalized medicine)? • Can existing training programs be adapted to address these gaps, or are new programs needed? If so, what is the timeline for development?
Concentration and Availability of Specialized Skills	• Is critical knowledge in areas like drug discovery, bioprocess engineering, or cybersecurity concentrated on few individuals, creating potential bottlenecks, knowledge silos, and risk? • Are these specialized skills resilient within the organization, or is there a need to recruit new talent or collaborate in novel ways?
Future Skills for Emerging Technologies	• How can the organization anticipate and prepare for the skills needed to implement Pharma 4.0™ technologies like 3D printing for drug manufacturing or digital twins for advanced process simulation? • What initiatives can be put in place to monitor technological advancements and proactively identify future skill requirements (e.g., industry partnerships, participation in conferences, horizon scanning)?
Internal vs. External Sourcing of Skills	• Which skills are more efficiently sourced externally through collaborations with technology providers, universities, or specialized consultants (e.g., advanced AI/ML, specialized automation engineering)? • What strategies can be used to balance internal skill development with external partnerships to ensure robust access to the most critical expertise?

At the skill management level, the leadership of each organization faces crucial questions about workforce readiness for Pharma 4.0™ (see Table 1).

Strategic skill management includes methods to address the questions highlighted in Table 1. It enables pharmaceutical companies to proactively identify, prioritize, develop, and retain the skills essential for thriving in the Pharma 4.0™ era.

A FRAMEWORK FOR STRATEGIC SKILL MANAGEMENT IN PHARMA 4.0™

This article proposes a novel framework to systematically implement and operate strategic skill management within an organization. This includes the required governance, identification of target and existing skills, formulation of a consistent roadmap, and sustainable operationalization for lasting organizational success. The framework is universal in nature but is applied and discussed here in the context of Pharma 4.0™.

Existing literature extensively explores the theoretical dimensions of skill management [15–17]. The presented framework bridges theory and practice, providing a sound approach accessible to leaders and professionals, independent of a background in human resource management or organizational psychology (see Figure 2).

Step 1: Establishing a Skill Model and Governance

Skill management functions as a dynamic and integrated decision-making tool for modern management [11, 12]. To start, foundational work is required to ensure success and organizational fit. The initiative can be targeted to specific areas undergoing transformation or applied across the whole organization.

Organizational setup

The organization setup considers the initial implementation project team as well as the later integration into the line organization. The initial setup necessitates a collaborative project approach, incorporating input from the following:

- Top management: defining strategic direction and scope
- HR: designing and implementing the model
- Department heads: identifying specific skill requirements
- Employees: providing input on their skills and needs
- Quality and regulatory: embedding compliance

Data model

The effectiveness of skill management is based on a structured data model. Early definition is required to structure the later data aggregation and usage. The authors propose roles, associated skill sets, and underlying skills. Roles are a powerful tool in

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Figure 2: A strategic skill management framework

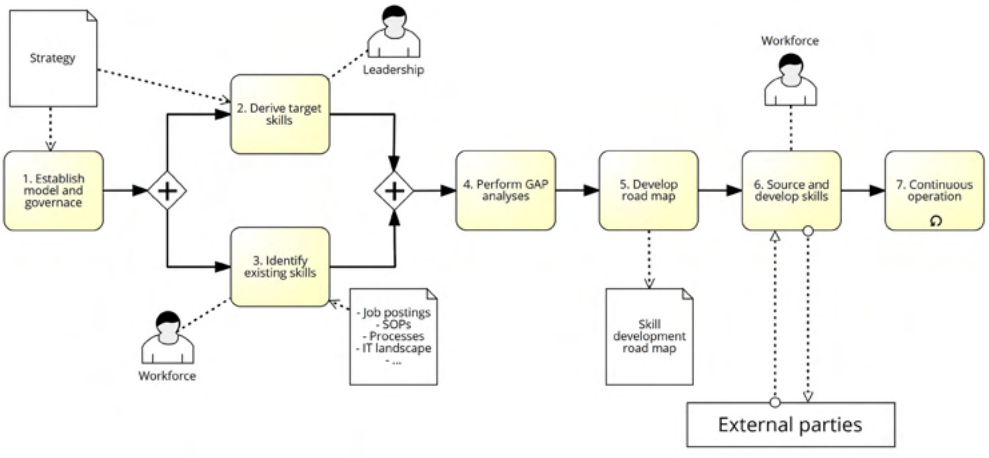
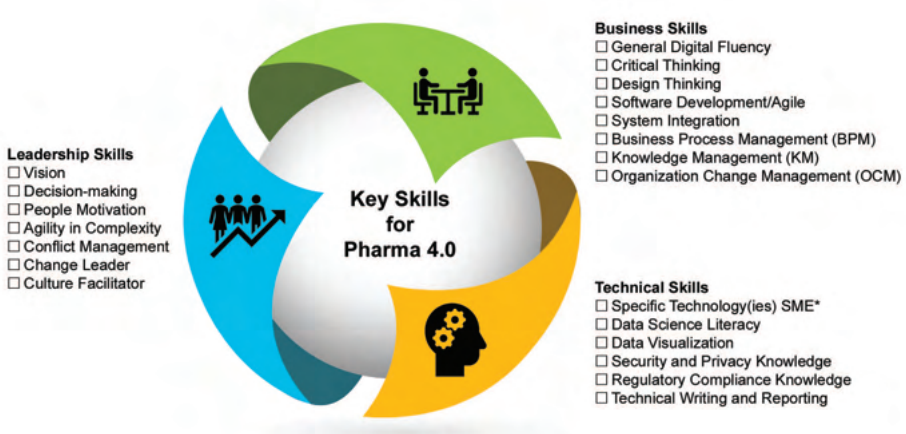


Figure 3: Key skill sets and skills for Pharma 4.0™ [5]



achieving a shift from rigid, power-based hierarchies and static job descriptions to a more agile and dynamic organizational structure. A person can hold one or more roles, and roles should be held by multiple people to avoid knowledge concentration. A role typically holds multiple skill sets, reflecting areas of knowledge relevant to the organization and providing a structuring middle layer.

A skill set consists of multiple skills. Skills form the foundational level. They are tangible, described in detail, and subject to individual development and evaluation. For example, the role "digital compliance specialist" might hold a skill set "regulatory" with a skill in "International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use regulations" and a skill set "digital" with skills in "data integrity" and "Rust programming." An example of this logical structure is provided in the *ISPE Baseline Guide Vol. 8: Pharma 4.0™ (First Edition)* [5] (see Figure 3).

In addition, the scope of the skill model is to be defined. There are multiple dimensions to categorize discussed in literature [10, 18, 19]. One example is shown in Table 2.

Data management

Strategic skill management produces and requires the management of large amounts of data. Although a spreadsheet can support initial pilots or small organizations, leveraging software for skill management is recommended. Common corporate workforce management applications such as SAP SuccessFactors, Workday, Oracle HCM, and Personio, as well as dedicated providers such as Growify, ensure relevant data structure. Data become an actionable asset with searches and reports, such as skill bubble maps, skill

Table 2: Differentiation of skills across different dimensions with definition, examples, and importance

Dimension	Definition	Examples	Importance
Technical Skill	Referring to the specialized knowledge and practical skills	• Mastering Java or Python • Understanding aseptic processing or freeze drying	Fundamental for any professional role; influences the ability to effectively perform specialized tasks
Methodological Skill	Ability to apply appropriate techniques and methods	• Applying Scrum or Lean Six Sigma • Document and transfer insights into knowledge	Essential to promote innovation, strategic thinking, and investigation of deviations
Social Skill	Skills for effective interpersonal interactions	• Promoting collaboration • Mediating team conflicts • Inspiring leadership	Important in environments that rely on teamwork, dynamics, and culture
Self-Skill	Ability to manage oneself in various professional contexts	• Adapting to a fast-paced work environment • Working productively under pressure • Independent decision-making	Crucial in roles requiring a high degree of autonomy, such as leadership positions or independent work environments

matrices for team staffing, and skill timelines indicating when skills will leave the organization. These insights provide immediate value by enabling data-driven decisions in daily operations.

Dedicated change management

Implementing effective change management strategies is crucial to ensure smooth transitions and minimize resistance. Clear communication of the "why" with benefits and goals helps align all stakeholders, foster a supportive environment for change, and increase workforce motivation. Effective communication and change management strategies are vital to fostering a culture that embraces innovation and continuous improvement. Current employees may be accustomed to legacy systems and processes, making it essential to address resistance to change.

The use of highly skilled employees as early adopters of change is an opportunity to develop skills in the workforce. These individuals might view sharing knowledge as weakening their position. Building a culture of proactive knowledge sharing (e.g., by taking on an apprentice) is a necessity for advancement. At the end of this step, the implementation project is planned, the new line function is envisioned, and the data model developed.

Step 2: Deriving the Target State

Once the governance is in place, the target state is detailed. Input for the roles, skill sets, and skills should come from strategy and from across relevant business functions. When exploring the organization's target skill setup, it is beneficial to differentiate on relevant dimensions. This, for example, involves temporary organizational needs versus permanent skills for sustained operational effectiveness.

Models can be developed from templates or created from scratch [20] and should differentiate between the borrowed approach, the borrowed-and-tailored approach, and the tailored approach. From the first to the latter, the level of individualization and resources rises. Although each extreme might come with downsides in either being too generic or requiring too much development effort, companies face the decision where to balance themselves in between. At the end of this step, the skill model is filled with described target roles, skill sets, and skills. Skills are evaluated on a scale with the defined target level.

Step 3: Identifying Existing Skills

Identifying the current skills is carried out in parallel with, and in alignment to, the definition of the target state. Multiple sources are available for skill identification, greatly varying in required resources and insight. Some are centrally accessible and can be reviewed by the project team. Starting points are existing job profiles, organizational charts, and training materials. In the pharmaceutical industry, standard operating procedures are critical for quality and compliance and can be another valuable resource. In addition, established business process management (BPM), enterprise architecture management (EAM), or knowledge management (KM) systems should be leveraged to derive insight into existing skills.

Typically, these inputs are disconnected, resulting in a fragmented understanding on the skill landscape. To gain a complete picture and strengthen accountability, the workforce should be involved. Here, a combination of self-assessment and external evaluation is recommended. This ensures that the data collected is more representative of the entire organization.

Self-assessment empowers employees to reflect on their own skills, fostering ownership and responsibility for personal development. This method can be facilitated through questionnaires, competency matrices, or online platforms designed for self-evaluation. External evaluation provides an objective perspective on skills across the organization, often conducted by supervisors, peers, or

Table 3: Type of skill outlook with examples from Pharma 4.0™

Skill Outlook	Examples in Pharma 4.0™
I. Future Skills	• AI for drug discovery • Data analytics for clinical trial optimization • Cybersecurity expertise for protecting sensitive patient data
II. Increasingly Important Skills	• Quality control and data integrity • Process control and optimization using digital twins • Cybersecurity awareness and best practices for all employees • BPM • EAM • Organizational change management (OCM) • Knowledge Management
III. Stable Skills	• Core scientific knowledge (organic chemistry, pharmacology, toxicology) • Manufacturing practices and regulatory compliance expertise (GMP) • Project management
IV. Decreasingly Important Skills	• Manual data entry and traditional documentation practices • Certain laboratory techniques where inline measurement takes over
V. Phasing Out Skills	• Skills related to legacy manual work to be replaced by automated systems • Legacy software or systems expertise

external assessors. This can involve observation, interviews, skills tests, or 360-degree feedback mechanisms.

At the end of this step the existing roles, skill sets and skills are identified. Each member of the workforce is assigned to its roles and has their skills evaluated.

Step 4: Conducting Gap Analysis

After building a structured foundation, a gap analysis should be completed. A gap analysis is a systematic comparison of the organization's current skill set with the defined target skills. This analysis reveals discrepancies and highlights areas where skill development initiatives are needed. Depending on the applied tools, this can involve out-of-the-box analytics and reports or may require manual data processing. This data-driven approach provides reliable results for the upcoming management discussions and reflects on the readiness toward Pharma 4.0™. At the end of this step, the skill gaps are identified.

Step 5: Developing a Skill Development Roadmap

In the journey toward achieving the target state, developing a comprehensive roadmap is essential. This roadmap must address identified gaps and clearly differentiate between skills required on a short-term, project-based basis, and those that will become integral to the new line organization in the long term. In addition, the time dynamic of skills should be considered (see Table 3).

Another dimension should focus on the spread of skills across the organization. Although some skills may have existed in the organization for some time (like data integrity), with wider adoption of additional technology, there is a need for more individuals to become fluent, and for knowledge to not just be concentrated within a few experts. Here an individual categorization from universal skills to expert skills is recommended.

These additional dimensions align with the concept of organizational ambidexterity, which emphasizes the importance of simultaneously exploring new opportunities and exploiting existing capabilities [21]. By fostering ambidexterity in skill development, pharmaceutical organizations can effectively balance the need for innovation and adaptation with the need to maintain operational efficiency and leverage existing expertise from experts.

Implementing a robust skill development roadmap or workforce development program is crucial for equipping employees with new skill sets. This includes careful selection of appropriate training methods such as on-the-job training and focused apprenticeships to facilitate practical learning. Leveraging skills from other industries can bring diverse perspectives and expertise, enhancing the overall capability of the workforce.

One of the greatest challenges in skill development is preventing silos and eliminating redundancies. Adopting a matrix organization or establishing a Center of Excellence can provide specialized support at various points within the organization, promoting efficiency and collaboration. Emphasizing cross-functional training and development ensures that skills are transferable, and that knowledge is shared across the organization.

Special focus is required in brownfield facilities, which are existing sites undergoing modernization. Here skills of type IV and V are present, which require well-established teams to be upskilled or reskilled to adapt to new technologies and processes. This needs a strategic approach to training and development, ensuring that employees are equipped with the necessary skills to thrive in a digitally transformed environment.

In contrast, greenfield facilities, which are new sites built from the ground up, offer a blank slate for skill development. These facilities require building a workforce from scratch with the required skills of the present and future. Beginning staffing early, like during the planning phase, ensures alignment with the goals and allows for challenges and opportunities to be identified and proactive measures to address them to be enabled. At the end of this step, a dedicated skill development roadmap is developed, approved, and communicated.

Step 6: Sourcing and Developing Skills

During enablement, holistic alignment with the ecosystem's capabilities is required. For externally sourced skills, strategic partnerships with specialized providers are best suited. Effective vendor management involves setting clear expectations,

maintaining open and transparent communication channels, and implementing rigorous qualification processes. For ensuring long-term organizational success and stability, managing internal skills is indispensable. This process involves creating customized learning paths that are tailored to various skills.

In the special case of a new greenfield facility, introduction to the community is a critical step in building local support and attracting talent. Establishing partnerships within the local community, such as with educational institutions and industry organizations, can create a robust pipeline of skilled workers in line with identified needs. Additionally, seeking support from the wider organization ensures consistency and leverages existing resources.

For training, external sources for skill development include industry-specific training centers like the Jefferson Institute for Bioprocessing in Pennsylvania, the National Institute for Bioprocessing Research and Training in Dublin, the Biomanufacturing Training and Education Center in North Carolina, and the European Aseptic and Sterile Environment facility in Strasbourg, France, with cooperation to ISPE. These offer numerous training programs with state-of-the-art facilities to systematically address, develop, and identify future skills. Conferences from ISPE and other professional organizations provide networking opportunities with peers, instructors, and industry professionals who foster valuable relationships for development and collaboration. At the end of this step, strategic skill management is implemented and aligned with the aims of the organization. After initial setup, continuous operations are transferred to the line organization.

Step 7: Implementing Continuous Operations

Strategic skill management is an ongoing process that requires continuous assessment and adaptation. Identifying gaps and new or unexpected roles that may arise is essential to stay ahead of industry changes. New insights or strategic changes should feed back to the now established system. For line integration, it is recommended that the department responsible for training, often part of HR, holds administrative responsibility, whereas the individual functions in scope of the strategic skill management initiative are responsible for the content and up-to-date assessment.

Strong integration in operations and management ensures value and continuous commitment from leadership and workforce. The continuous operations cycle is summarized in Figure 4. From monitoring the dynamic internal and external environment, new demand emerges. Identified and planned adjustments to the skill landscape are communicated in the organization. Impacted members of the workforce take part in evaluation. Finally, insights and data-driven actions are taken to execute precise development.

This step does not end and ensures continuous excellence in strategic skill management.

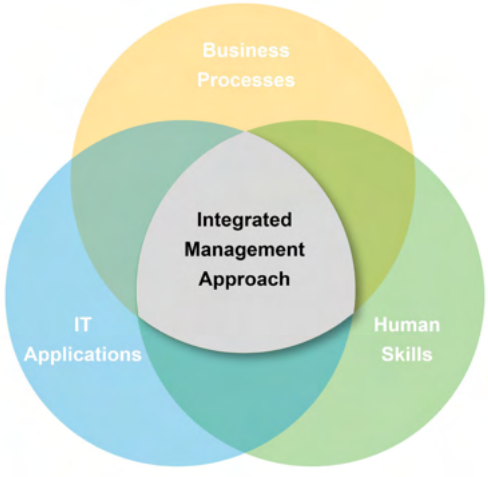
CONCLUSION

This article presents a framework for strategic skill management and details the steps from initial setup to sustainable integration. Initial execution is resource-intensive. Top management must demonstrate commitment and provide oversight while the project team executes. By embedding clear structures for roles and skills within a dynamic governance framework, pharmaceutical organizations can effectively manage their skill landscape while maintaining the high-quality standards essential to pharmaceutical manufacturing.

This framework empowers organizations to strategically manage skill development with data-driven methods. By implementing targeted solutions and leveraging the expertise of specialized consultants, companies can ensure their workforce is

Figure 4: Strategic skills management operating model

Figure 5: Integrated approach for management of processes, applications, and skills



prepared for future challenges. This forward-thinking, strategic approach helps build a dynamic and adaptable organization, while ensuring the organization continuously evolves and meets the demands of an ever-changing market.

Depending on an organization's readiness, an integrated approach combining business processes (BPM), IT applications (specifically, Enterprise Asset Management), and skills can leverage synergies (Figure 5). Each area includes mapping both current and future states and is characterized by holistic landscapes. During Pharma 4.0™ transformation, all three areas are deeply intertwined. For example, implementing a new manufacturing technology impacts business processes, IT applications, and required workforce skills. This integrated management approach fosters the organizations transformation management capabilities.

In summary, the framework provides a comprehensive approach to skill management, underpinned by strategic planning and coordination. This is vital for navigating the complexities of modern business environments and achieving sustained success. By proactively investing in strategic skill management, organizations position themselves to respond effectively to emerging challenges and opportunities, thereby securing a sustainable competitive advantage in the marketplace.

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EMBRACING THE HUMAN SIDE of Manufacturing

By Cyril Buckley, Cole Brunson, Javier Garay, and Elizabeth K. Strutz

For companies focused on producing lifesaving treatments, the positive effects of employee health, well-being, and satisfaction can be easily overlooked, but those positive effects are real. An investment in people results in better research, testing, and manufacturing processes, which leads to more efficient delivery of therapies and treatment to patients worldwide.

In the biopharmaceutical industry, it is expected that corporations emphasize the primacy of the patient in their mission statements, reflecting the core focus of the field. However, it is less common to observe one of the world's largest pharmaceutical manufacturing facilities placing significant emphasis on the health and satisfaction of its employees. This focus on employee well-being plays a crucial role in the effective delivery of therapies to patients.

Embracing the fundamental idea that there is an explicit connection between the well-being of employees and the health of the patients it serves, Takeda planned its Georgia Manufacturing Facility with a human-centered approach. The 1.1-million-square-foot facility was deliberately designed to support employee health, well-being, and resiliency.

In planning the facility, Takeda viewed these ideas not as additional benefits but as key factors to increase efficiency and efficacy and ultimately accomplish its goal of delivering plasma-derived therapies for people living with serious and complex health conditions.

With over 1,300 full-time employees, the facility is arranged to encourage collaboration and foster human connections and relationships. Amenities such as on-site nurses and sports courts that support wellness, paired with a design that reflects a culture of transparency, make clear the intention to draw a bright line connecting the health of Takeda's employees and the health of the patients they serve.

HUMAN-CENTRIC DESIGN

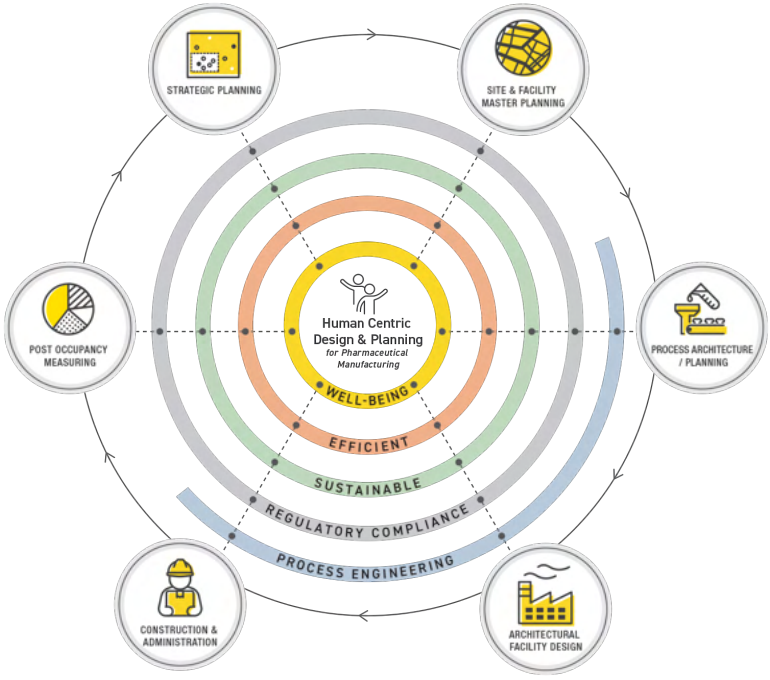
The initial planning and design of a successful pharmaceutical manufacturing facility includes many considerations, such as maximizing production and volume, process and environmental controls, and cleanroom classifications, to name a few. For large manufacturing facilities such as this one, the human experience is often overshadowed by the focus on production yield and the bottom line.

When Takeda engaged Flad Architects to master plan the facility, they considered the project's ability to create a positive impact on both patients and Takeda employees. From the employee perspective, the key objectives for the project were attracting and retaining talent; improving employee health; promoting diversity, equity, and inclusion; and fostering lifelong learning and growth. To accomplish these objectives, Takeda placed a major emphasis on human-centric factors and how the building occupants would experience the space (see Figure 1).

This focus informed decisions for all aspects of the buildings at all phases of the project, from site selection and early concepts through final design, construction, and occupancy. The human-centric focus encompassed not only the administration and collaboration spaces, but also, and more importantly, manufacturing and manufacturing support spaces.

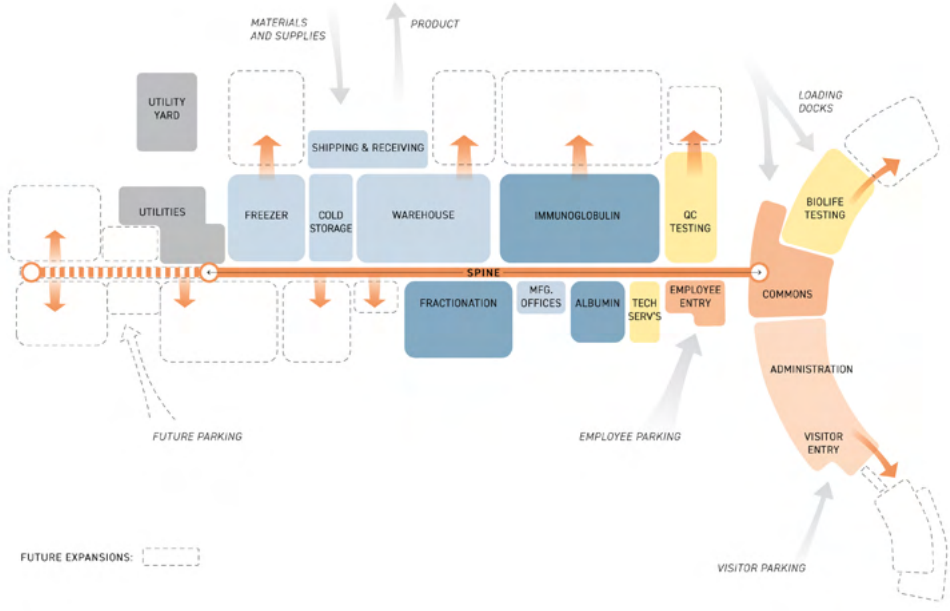
Supporting health and well-being includes physical considerations such as opportunities for physical activity in daily work life, air quality, temperature, natural light, glare control, and noise level. It also includes less tangible — but just as important — factors such as a sense of community and a connection to both the organization's mission and nature.

Figure 1: Enabling the mission: integrated human-centric planning and design process



Credit: Flad Architects

Figure 2: Site organizational diagram



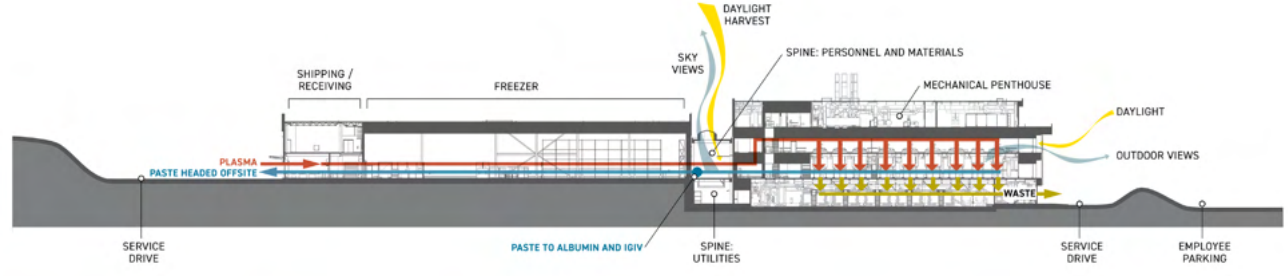
Credit: Flad Architects

The site's paramount purpose is the processing of human plasma and fractionation of plasma proteins to yield albumin and immunoglobulin. Plasma fractionation is the first step of the manufacturing process and the second largest user of materials coming from the warehouse, after the immunoglobulin process, filling and packaging operations. Therefore, the four-level fractionation space, comprising 187,000 square feet, is located directly across from the warehouse (see Figure 2). The albumin operations, located in a four-story building, house the equipment needed to purify specific proteins from the fractionation area. This includes buffer solution vessels, centrifuges, and filter presses used to separate distinct proteins from human plasma.

Figure 3: The Commons serves as heart of the campus

Credit: Jim Roof Creative, Inc.

Figure 4: Cross section of manufacturing space featuring process flows daylight and outdoor views



Credit: Flad Architects

To achieve optimal efficiency among each of the program elements, the design team considered the most logical flow of materials and product, as well as how people would move through the facility. Extra care was taken with the placement of primary and support areas, maintaining the most vital adjacencies of various production functions.

To reach human-centric planning goals such as Takeda's requires thoughtful consideration at every stage of the project. Starting with initial planning, the focus on the idea of engaging employees and collaboration is evident in the floor plans. The design team considered how and where employees would interact with each other; and what they should see, feel, and experience. This includes access to natural light and views to the outside as well as the length of time to de-gown and move to the cafeteria, restrooms, or parking lot.

In addition to situating the manufacturing offices centrally within the process areas, the plan positions the units that generate the most samples and have the most employees as close to the quality control labs as possible. The Commons (see Figure 3), a two-story space that acts as the facility's "Times Square," is the heart of the campus. It's an active area where people pass through from all directions. The cafeteria is located on the ground floor with a 360-degree balcony overlooking it. A coffee corner, fitness center, sports courts, and shared computer stations are located just off the balcony area.

This series of conscious decisions allowed for the creation and optimal location of the heart of the campus, where all employees can share a common experience, filled with natural light and views. This provides ample opportunities to collaborate and build community as people dedicated to improving the health of patients.

Figure 5: Plasma fractionation conducted in a naturally lit space with wide views to nature

Credit: Jim Roof Creative, Inc.

Figure 6: The spine is naturally lit, enhancing the employee experience and health

Credit: Jim Roof Creative, Inc.

DESIGN TO SUPPORT HEALTH AND WELL-BEING

Most employees in manufacturing spaces are physically active throughout the day, doing important work that requires focus. For the sake of safety and to avoid contamination, these workers are often wearing personal protective equipment and, in a typical manufacturing plant, may find themselves in an isolated, contained working space. To help these employees remain inspired and engaged, the design team focused on providing access to daylight and views to the outside and adjacent spaces within the building. Exposure to natural light and the outdoors has been proven to significantly improve mood and reduce stress, with the added benefit of boosting productivity and cognitive function. The building design maximizes every opportunity to provide natural light to employees using large windows and glass walls, including floor-to-ceiling windows in some areas. This includes admitting natural light into (and views out from) even the cleanest and most regulated cGMP manufacturing suites (see Figures 4 and 5). In addition to boosting employee well-being, the extensive use of glass also provides a literal window into the facility's intricate processes for the benefit of passing employees, visitors, and regulators to the facility.

For the central spine, which runs between warehouses, freezers, and manufacturing spaces, windows to the exterior were not an option. Instead, it features a skylight system to infuse natural light (see Figures 4 and 6). This 400-meter corridor spanning the length of the facility serves as the link that connects all operational and administrative spaces. The lower level of the spine carries all the major utilities for the campus. Along the upper-story spine, the controlled not classified (CNC) offices are adjacent to the manufacturing spaces that they serve. Central placement of CNC offices allows members of the different manufacturing support teams to collaborate and build relationships that could potentially lead to new ideas and process improvements and innovations.

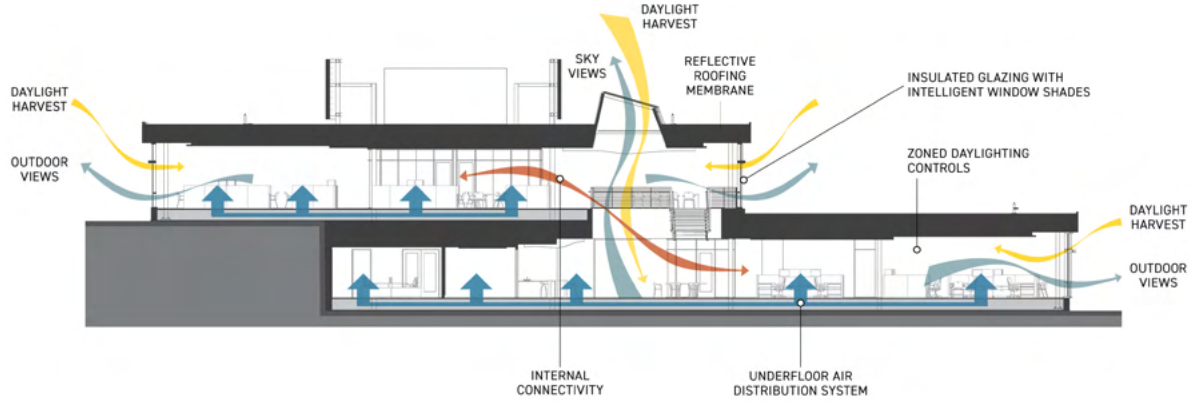
Focusing on physical transparency also supports a culture of transparency. Providing views into the functional areas promotes a sense of community and enables passive supervision and communication as well as improved employee safety. Transparent designs allow management and staff to visually connect, verify safety, and rapidly identify and respond to any issues. It allows each team member to pursue their individual tasks while being visually connected to the overall team. With functional areas exposed to outside views without the need to gown or de-gown, the transparency also facilitates regulatory inspections with minimal disruption to ongoing operations.

ENABLING PHYSICAL HEALTH: STAIRS AND INTERACTIVE SPACES

Although occupants of the administrative spaces may not be on their feet physically exerting energy all day, the negative health effects from sitting for long periods of time are well documented. People with inactive lifestyles are at higher risk of hypertension, high blood sugar, and obesity [2], so the building design incorporates "design-led intervention" strategies [3] to encourage activity. Research published in the *Journal of the Royal Society of Medicine* indicates these "design-led interventions can make better (healthier) choices easier or constrain (less healthy) behaviors by making certain actions more difficult" [3].

Stairs and interactive spaces that minimize the use of elevators are strategically placed throughout the facility to help promote physical activity, movement, and interaction. In addition to these collaboration nodes, walking paths and a wide range of workspaces encourage people to get up from their desks and move around. The design also provides the opportunity to tailor their work to the

Figure 7: Strategically located open stairs promote physical activity and interaction



Credit: Flad Architects

Figure 8: Communicating stair and interaction hubs with access to daylight and outdoor views

Credit: Jim Roof Creative, Inc.

type of environment that they need, whether it's a private, quiet, or collaborative space.

The two levels of the administrative wing (see Figure 7) are fully interconnected by three light-filled atriums that include communicating stairs (see Figure 8), providing connectivity to an already open, collaborative, and transparent office environment. These elements that encourage physical movement and interaction are congruent with design recommendations based on recent research on well-being and its relationship to health [4]. Additional features were implemented to maximize air quality and comfort, such as zoned lighting controls, intelligent shading devices that improve light quality and reduce glare, and an underfloor air distribution system with localized controls to optimize thermal comfort.

POST-PANDEMIC ADDITIONS

During the pandemic, Takeda switched to a hybrid work model, with employees going into the facility two days a week. In 2023, employees began returning to the office more frequently, and by fall of 2024, the facility had returned to a full-time in-person workplace.

The quality of the space in the facility, with its human-centered design, was key in the success of the return-to-work strategy after the pandemic. In addition, Takeda implemented a number of additional amenity spaces including tennis and pickleball courts, ping pong tables, a barbecue smoker, and a giant TV wall. The TV is used to build collaboration and culture by displaying employees of the month, pets of the month, and information about upcoming events. Other additions include an on-site recycling

plant that supports an ambitious zero-waste-to-landfill goal and a patient mural, reinforcing the impact of the work done at the manufacturing facility.

THE ULTIMATE CONNECTION: BUILDING DESIGN — EMPLOYEE WELL-BEING— PRODUCTIVITY

Do happier, healthier employees do better work? Two studies out of the United Kingdom suggest they do. Economists at Warwick University found a causal link between human well-being and performance: three different experiments showed a 12% increase in productivity by happy workers against a 10% decrease by unhappy workers [5]. Additional research performed by University College London found "a clear, positive, and statistically significant relationship between the average level of job satisfaction at the workplace and workplace performance"[6]. Warwick researchers also noted that happy workers proved to be more effective collaborators, and there is evidence to suggest that a more collaborative environment leads to greater work satisfaction.

A post occupancy survey conducted by Takeda and Flad Architects found that the majority of employees in the Covington facility are satisfied with building attributes. A 15-question survey was sent out to employees to understand the impact of the facility on employees' overall wellness. The survey had a 60% response rate.

Asked to rate their level of satisfaction of building attributes on a scale from one to five, with one representing very dissatisfied and five representing very satisfied, employees gave "access to natural light and views" an average rating of 4.38. For "overall visual connections between spaces," the average rating was 4.12, and "accessibility to co-workers" received an average rating of 4.09. Over 55% of respondents said the design of the new environment positively contributed to their overall job satisfaction. Meanwhile, 70% of respondents said they use the open collaborative spaces at least once a week. Another 67% said they use those spaces multiple times a week.

Prospective hires in Georgia have demonstrated the facility's value as a magnet for recruitment. During hiring, participants in a recruiting program are nine times more likely to return after pre-assessment testing when the testing was held inside the Takeda Covington facility than when the testing was held at nearby facilities operated by Takeda's partnering agency.

Among the many benefits that accrue to businesses that invest in employee satisfaction are gains in yields, a heightened ability to spot trends and potential problems, and more effective processes for maintaining quality—which can help, for example, attain US Food and Drug Administration approvals. Taken together, these are bottom-line benefits that add up to an ability to meet market demand more quickly. Links between the quality of an environment and the health of the people within is being researched by the International WELL Building Institute (IWBI). Viewing buildings "as a platform for public health intervention...and recognizing the importance of a data-driven approach" [7], IWBI is hoping to further establish what Takeda and others have begun to see: the clear connections between employee health and the health of patients.

CONCLUSION

For companies focused on producing lifesaving treatments—a process in which protecting against waste, controlling capital expenditures, and maximizing operational efficiency are a must—the potential for the positive effects of employee satisfaction can be easily overlooked. However, those positive effects are real. Investing in workers makes them better collaborators, problem-anticipators, and problem-solvers. An investment in people results in better research, testing, and manufacturing processes. That, in turn, leads to a greater impact with more efficient delivery of therapies and treatment to patients worldwide.

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NURTURING A CULTURE of Collaboration and Growth

By V.J. Venkatraman

Organizations must continually evolve and adapt in order to grow, sustain, and stay competitive. No organization survives for a long period of time if it does not change with the times. The pace of change is accelerating, and the scale of disruptive market forces is growing by the day.

Many companies have failed, created more problems, and wasted investments in their initiatives to restructure, re-engineer, right-size, and implement total quality management [1, 2], etc. Research shows that one of the main reasons for such failures is neglecting to change and nurture a culture of collaboration and growth.

INNOVATIVE COMPANY SUCCUMBS TO CULTURAL CHALLENGES

Digital Equipment Corporation (DEC), founded in 1957 by Ken Olsen and Harlan Anderson, was a major manufacturer of minicomputers known for playing a leading role in the introduction of interactive computing. By 1990, it grew to US$14 billion in revenue with over 120,000 employees.

DEC was the largest minicomputer manufacturer and second-largest overall computer manufacturer in the country, after IBM. In 1998, the company ran into severe financial difficulties and was acquired by Compaq Computer Corp. DEC was very adept at responding to changes in the technology landscape and developed a line of personal computers widely considered to be technologically superior to other personal computers on the market. Yet, DEC failed and was pushed out of the technology map. There were many reasons for its demise, but an analysis conducted by Edgar Schein and colleagues pointed to its culture as being primarily responsible for its rise and fall [5, 7].

DEC's strategy was to develop a technologically superior computer to compete with IBM. The company was organized as a product management matrix structure. This structure was conceptualized to encourage autonomy and innovation. It provided so much autonomy that more than one product development team emerged, competing with each other—internally focused versus externally focused. This resulted in three different, incompatible personal computer product lines. Even though technologically they adapted fast, product teams and leaders were operating within the company's existing corporate culture of the mainframe and minicomputer. This misalignment of sub-cultures with the overall corporate culture, leadership styles, and non-collaborative culture played a vital role in the demise of DEC [7].

Longevity and stability in the workplace are no longer the norm. Technological, societal, and economic development demand change. But adaptation is not easy. It requires both leaders and followers to buy into large cultural shifts while sustaining critical talent at every level.

Cultural dynamics are among the most challenging elements of an organization to manage. Done poorly, large changes can tear organizations apart. But done well, culture change initiatives can yield massive returns on investment. Effective cultural change impacts various factors, including leadership style, personal change, talent development, and other growth strategies and frameworks.

This article describes an integrated approach to leading cultural change by understanding:

- The importance of organizational culture
- Leadership style as a key component of the change process
- How individual change is the key component of cultural growth and sustainability

CULTURAL CHANGE AND MANAGEMENT

Culture is the living, breathing personality of an organization. It encompasses the beliefs, values, preferences, and practices affecting individual and group behavior. It is an embedded social order that shapes the behaviors and attitudes of individuals and groups at every level of the organization [3, 8, 9]. When properly aligned with personal values, principles, and needs, organizational culture can be an engine of durable growth [3]. Organizational cultures are:

- Collectively held, at least by some subset of society or organization,
- Socially transmitted by members of the organization through their internal and external interactions,
- Built over time, especially values and beliefs, and
- Impact long-term growth and sustainability.

Why should organizations care about cultural change now more than ever? We are deeply interconnected, so any external force results in organizations facing both external and internal pressures to manage leadership transitions, business expansions, and market contractions. Culture needs to keep up because when an organization's culture grows stale, the organization as a whole becomes rigid and unable to stay competitive and sustainable.

Figure 1: Integrated approach to cultural change

DRIVERS OF CULTURAL TRANSFORMATION AND MANAGEMENT

Globalization of Economies

The trade landscape has changed significantly since World War II. With increasing globalization, organizational existence, and performance have been subjected to fierce competitive international pressure—even for domestic companies. As organizations expand their operations across borders, they encounter a variety of beliefs, values, and practices that challenge their existing culture. However, these challenges also present opportunities to build a new, more inclusive, diverse, and innovative culture that can adapt to new markets and conditions.

Mobility of Resources and Talents

The migration of human resources has significantly impacted the composition and quality of talent that organizations can draw upon. Resources and talent migrating within and between organizations have significant impacts on the culture of those organizations. Poorly managed, a lack of cultural cohesiveness can cause tension in teams and result in organizational silos. But when managed well, organizations can purposefully migrate talent dynamically while maintaining a collaborative, innovative, engaging, and growth-oriented environment across their functional areas.

Advancement of Technology

Technology has grown leaps and bounds in the past decade and is not slowing down. Organizations with a poor culture struggle to keep up with the pace of change and fall behind. However, strong organizational cultures lead managers and employees to search for innovative ways to implement technology in their practices. Done well, technology-oriented cultural change can lead to a more data-driven decision-making environment, a flatter hierarchy, increased employee autonomy, and a more dynamic workplace.

Exponential Growth in Information

Information is more abundant than ever before. Organizations produce and consume more information than ever before, thanks to the development of information technology. Poorly equipped organizations can drown in a sea of information. However, organizations with strong cultures know how to sift through the information available to them effectively, educate their workforce using new technologies, and use the massive amounts of knowledge they produce effectively.

Organizations of all types and sizes have an urgent need to create unique competitive advantages to stay successful in today's environment of dynamic change and scarce resources, Organizations face internal and external challenges to sustain their continued existence in the global landscape. On the external front, organizations encounter increasing financial performance, growth, product/service innovations, and competitive threats. Internally, they face more pressure to retain talent, improve efficiency, implement process changes, and adapt to technological innovations to cater to changing customer needs.

Firms should focus on every aspect to improve their effectiveness and efficiency, particularly critical drivers of culture, leadership, and talent management. It's important to create a unique competitive advantage and an environment for innovation in order to stay ahead of the growth curve. The driving forces previously addressed here put a lot of pressure on the organization's survival and growth. In the following sections, I outline an integrated approach that provides guidance and a framework for developing a roadmap and strategy for the future.

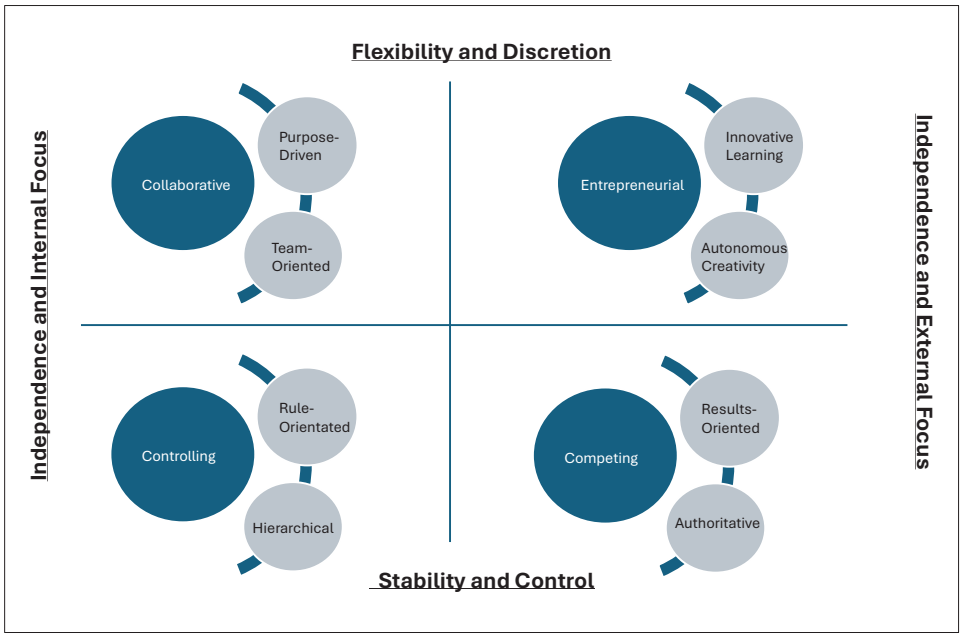
AN INTEGRATED APPROACH TO CULTURAL TRANSFORMATION

Few organizations successfully integrate their components to function as one. Most are a loose collection of silos, kept separate by cultures, workforces, leadership styles, geographical locations, products, and service offerings (to name a few). Many organizations could benefit from a major realignment and transformation.

For example, consider a global pharmaceutical company with facilities around the world that manufactures products with complex processes. This company has huge investments in facilities and equipment, including information technology infrastructure, among other operational divisions. Monitoring the performance of each product line, facility, and equipment takes a lot of integration, process improvements, and data management, even for one site. The management of siloed operations, even within one site, is challenging, and coordinating all global operations to work together is even more challenging. Each department within a site operates in its own silo, providing management their own perspective on performance. There is a significant duplication of efforts at this company leading to suboptimal use of talents and other resources, particularly systems and technology.

Siloed operations create roadblocks that hinder the development of innovation-centric organizations. To address this issue, an information integration program was initiated at this company with efforts to optimize processes, integrate data, and harmonize

Figure 2: Cultural environment and characteristics [3]



systems. One potential solution required an integrated application to synthesize information from multiple different sources and to provide stakeholders and the leadership team with insights into their decision-making framework. The adoption of the integrated solution slowed significantly because of the existing siloed culture, misaligned leadership, and the individual personality differences. The culture was not conducive to accomplishing the vision of being an innovative organization. The leadership team recognized the need to transition to more of an entrepreneurial and learning culture where collaboration and innovation are fostered in all aspects of science and operations.

The key takeaway: The company needs a cultural transformation strategy. Leadership and personnel must align to successfully adopt solutions, ultimately fostering innovation, agility, and synergy within the organization. Some key questions to consider before starting a cultural transformation journey:

- How can we transform our culture to meet the future needs of business today?
- How can we get employees or teams to effectively execute our strategic goals?
- How can we align organizational performance with employee engagement and customer experience?
- How can we promote cross-organizational collaboration to drive innovation and agility in fast-changing markets?

Effective cultural change that supports sustainable growth requires aligning three major forces: (1) the cultural environment, (2) leadership styles, and (3) personal skills and traits. For a growth and sustainable model, all three elements must be integrated and continuously iterated (see Figure 1). In an integrated approach to cultural change and management, all three elements need to be carefully nurtured and managed to ensure growth and sustainability.

The next three sections of this article explore each element of effective change and outline the strategic process map for ongoing cultural evolution to achieve a unique competitive advantage.

CULTURAL ENVIRONMENT AND CHARACTERISTICS

According to the Competing Values Framework (CVF) developed by Kim S. Cameron and Robert E. Quinn in 1983, organizational cultures can be classified into categories along the following two dimensions.

Vertical Axis: Flexibility and Discretion vs. Stability and Control

The movement along the vertical axis is determined by how people respond to change. Organizations scoring high on control are at the bottom of the axis and tend to have many documented procedures and processes that must be followed. Less regimented organizations are located higher on the vertical axis of control.

Horizontal Axis: Interdependence and Internal Focus vs. Independence and External Focus

The movement along the horizontal axis is influenced by how people interact with each other and the environment. Firms focusing externally tend to be concerned with the market, new customers, and competitors. Organizations that focus internally are concerned with employee morale and how work is accomplished. Existing customers remain important as the company prioritizes processes over new business.

FOUR WORK CULTURES

Organizations generally fall under one of four cultures: collaborative (clan), entrepreneurial (adhocracy), controlling (hierarchy), and competing (market) (see Figure 2):

Collaborative (Clan)

Organizations with this culture exhibit characteristics of flexibility, inward focus, teamwork, employee involvement, collaboration, shared goals, and a sense of camaraderie. These organizations believe in a strong commitment to customers and empower employees to run operations effectively. In this culture, employees feel as part of a close-knit family, with a strong sense of collaboration, teamwork, shared values, and talent development. This culture focuses heavily on relationships, mutual trust, and working for a greater cause. Leaders of this culture follow the T.R.U.S.T. Leadership Model: Teamwork, Respect, Understanding, Sincerity, and Tolerance.

Entrepreneurial (Adhocracy)

This culture values flexibility and discretion, but unlike clan cultures, it has an external focus. This environment motivates and encourages members to brainstorm new ideas, innovate, create, and take risks. Teams adapt quickly to respond to changing external conditions. Members of this culture are flexible, expansive, explorative, creative, and comfortable when dealing with changing market and economic conditions. They are always ready for changes to the organizational structure and future direction. Change is the only constant for this culture. The work environment is trusting and open-minded, where people are not afraid to try new ideas and explore alternatives. Leaders of this culture encourage innovation, risk-taking, learning, and exploring unchartered water.

Controlling (Hierarchy)

This culture shares some characteristics of the collaborative clan culture, but emphasizes centralized management with strict rules and processes. Regulatory-compliant organizations, such as government entities, biotechnology and pharmaceutical companies, typically fall under this cultural environment. People are expected to follow policies and procedures, doing work the correct way with an emphasis on efficiency and smooth-running operations. The main characteristics of this culture are decisions, information, and communication flowing down the chain of command. This structure inherently restricts the free flow of communication between employees and upper management, which can result in a lack of enthusiasm from employees leading to reduced job satisfaction. These organizations respond effectively and efficiently to routing business but are slow to respond to unique situations. Leaders of this culture are very regimented in planning, maintaining the chain of command, and following long-standing customs.

Competing (Market)

This culture emphasizes centralized control with a strong external and customer focus. It encourages employees to be laser-focused on being efficient, productive, and competitive. Leaders of this culture manage the organization by measuring performance and growth in empirical terms, such as market share and financial performance. Employees are expected to be results-oriented and are evaluated against each other using both qualitative and quantitative results. Leaders of this culture are very goal-focused, customer-centric, and are focused on gaining a competitive advantage.

There is a greater sense of urgency to create an environment where people feel connected, contribute to a greater cause, bring out the best in themselves, and increase the happiness index — both at home and in the workplace. Understanding the type of organizational culture that represents an organization's current environment, and future changes or transformations, will enable better alignment of leadership styles. This will facilitate leaders in influencing and inspiring their employees for future growth. Defining the type of leader and talents to represent the cultural brand is essential for success and growth.

Cultural environments have massive impacts on the day-to-day operations and long-term growth of an organization. So, who is in the best position to steer the culture of an organization? Leaders can emerge in an organization both positionally (i.e., promotion to the C-suite) and socially (i.e., members of the organization who have informal authority). The differences between these types of leaders and their specific influence over organizational culture is outside the scope of this article. But no matter which type of leader, leadership style is critical to shaping your organization's cultural environment.

LEADERSHIP STYLE AND CHARACTERISTICS

Understanding various leadership styles is crucial in achieving alignment between leadership style and cultural shifts. This will empower leaders to manage talent and build high-performing teams. There is no one right way to lead in a way that is suitable for all situations — it depends on skills, experience, the team itself, and the task at hand. The two extreme styles are visionary thinking (creating value in places not previously considered) and rules-based system thinking (sustaining and bringing about change designed to maintain and improve performance). Leadership means different things to different people and is situated within an organization's cultural context.

Four Primary Styles of Leadership

- **Democratic:** Also called participative, a democratic leadership style encourages team members to take a more active role in decision-making. Team members are encouraged to share ideas and opinions without fear of judgement. Teams feel more engaged and creative. Collaboration is encouraged and rewarded. This style works best in situations where team members are skilled, motivated, self-starters, and eager to share their knowledge. By listening to concerns and diverse perspectives, and incorporating varied ideas, leaders demonstrate confidence in team members and send positive vibes suggesting that opinions matter and con-

Table 1: Cultural and leadership styles [1, 9]

Cultural Style	Leadership Style	Characteristics	Work Style	People Interaction
Collaborative	**Democratic** • Laissez-faire • Delegates	• Team builder • Facilitator • Coach and mentor	• Patient • Creates a comfortable environment • Values personal relationships • Establishes a collaborative workplace	• Encourages employee input • Active listener • Supportive • Works well with teams • Empathetic
Entrepreneurial	**Transformational** • Portray a sense of integrity and trustworthiness • Charismatic • Strategic • Motivational	• Passionate • Adaptive • Innovative • Visionary	• Outgoing • Risk-taker • Dreamer • Spontaneous • Possesses persuasive skills • Transparent • Defines goals • Clearly expresses expectations	• Inspires people to take risks • Encourages new ideas • Generates excitement • Naturally attracts followers
Controlling	**Authoritative** • Autocratic • Bureaucratic • Sets clear guidelines	• Micromanager • Organizer • Rigid • High expectations • Doesn't delegate	• Highly analytical • Makes decisions independently • Task-oriented • Calm and rational • Disciplined • Rule-based	• Expects employees to be disciplined • Encourages decisions based on facts • Mandates others to think before acting • Follows the chain of command
Competing	**Transactional** • Situational • Diverse	• Competitive • Results-oriented • Customer-focused	• Works independently • Take charge • Likes control • Very pragmatic	• Keeps the group focused on organizational goals • Obsessed with growth and performance

tributions are valued. This gives employees a sense of ownership and responsibility.

- **Transformational:** These are leaders who exhibit integrity, charisma, and trustworthiness, which inspires and motivates followers. They set clear goals and expectations, and maintain transparency in communications across teams. Transformational leaders are packed with multiple skills, making them exceptional entrepreneurs who are highly valuable in dynamic environments.
- **Authoritative:** This leadership style thrives in a highly structured environment with rules, process, and procedures. It centers on setting clear guidelines. These leaders provide clear explanations of tasks, process, procedures, timelines, and expected behaviors and outcomes. There is a clear distinction between the leader and followers. Autocratic leaders independently make decisions with minimal or no input from the rest of the group. Leaders with this style motivate team members by connecting their work to the broader oganizational strategy, helping them see how their daily tasks contribute to a greater purpose.
- **Transactional:** This leadership style is characterized by a cost-benefit transaction between leaders and employees, where leaders control the exchange of value based on the needs of followers. Transactional leaders define goals and objectives, and communicate effectively to organize tasks and activities with the cooperation of team members to ensure that broader organizational goals are met. It centers on trusting employees to work towards a shared vision with autonomy and creatively, which leads to high employee engagement and increased job satisfaction.

Research suggests that a congruence between culture and leadership style ensures success and growth of an organization. However, leaders are often promoted despite having beliefs, values, styles, and behaviors that are not aligned with the cultural needs of the business. This misalignment results in suboptimal performance and long-term damage. The highest performing leaders tend to have a good mix of skill sets enabling them to comfortably operate and succeed in each quadrant.

PERSONAL TRANSFORMATION

We have just discussed cultural environments and leadership styles, two foundations of cultural transformation upon which the success and sustainability of an organization depend. No change process or strategy will produce the desired results unless mindsets, behaviors, skills, and competencies are modified. This happens only through personal transformation. Organizations should create an environment conducive for learning and growing to accomplish individual dreams and goals.

Figure 3: Personal transformation: The journey to perfection [8]

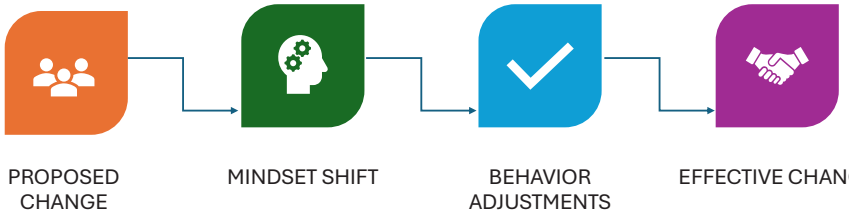


Figure 4: Cultural transformation and sustainability framework

What does personal transformation involve? How can it be integrated into an organization's culture? The steps involved in this process include:

- **Awareness**: Begin with a deep understanding of the current state of affairs. Acknowledge where you stand and where you aim to go.
- **Desire for change**: Fuel your journey with a passion for making meaningful transformations. Let this be your guiding light.
- **Imagination**: Realize the power of imagination as the catalyst for change. Envision the desired outcome and chart a course accordingly.
- **Visualization**: Picture the desired end goal and visualize the journey required to reach that goal. Let this mental imagery propel you forward.
- **Living the change**: Experiment with living the change you desire, making it an integral part of your daily life.
- **True transformation**: Embrace changes you wish to see in your thoughts, actions, and demeanor for permanent transformation from within.
- **Manifestation**: Through consistent effort and dedication, witness the transformation unfold. What once seemed merely imagined now becomes a tangible reality.

Harnessing the power of personal transformation ignites a ripple effect within organizational culture, fostering growth, innovation, and resilience. Embrace this journey and watch as your organization flourishes amidst change.

Any journey towards change and perfection starts with a need for change in future behavior. Behavioral change will occur only when there is a mindset shift for any proposed or perceived changes. Once these changes are internalized and implemented, they will provide opportunities for further changes. This continuous change process, when adopted as a personal culture, provides the platform for both personal and organizational growth.

CULTURAL TRANSFORMATION AND SUSTAINABILITY FRAMEWORK

In many organizations, there exists a gap between existing and aspired realities. To bridge this gap, the orgaizational culture must support and advance the organization's vision, mission, goals, and strategies. Traditionally, owners or senior leadership were considered responsible for establishing an organization's culture. In a new culture-building framework, the responsibility for cultivating and managing organizational culture rests with every member of the organization.The four foundational pillars for cultural transformation and growth are: a clear long-term strategy, a leadership style that nurtures the organization, an organizational design that creates an environment for success, and talent development for long-term sustainability and innovation. To ensure these foundational pillars are robust enough to withstand future changes, the overall framework and processes must address organizational readiness, leadership and values, and personal transformation. This approach will ensure the organization becomes a learning and innovative organism.

Factors Affecting Cultural Change

- **Organizational readiness:** Develop an understanding of past and current culture, its origins, and reason for being. Determine the preferred future culture based on business needs. Assess if the organization is ready for change by analyzing the gap between the present and proposed cultural transformation needs using the such as the Organizational Culture Assessment Instrument (OCAI) tool developed Cameron and Quinn [2].

Figure 5: Drivers of cultural evolution

- **Leadership readiness:** As often stated with other programs, top management must be committed to the change and should lead by example. Future leaders need to be skilled, theoretical, and strategic thinkers. Leaders must have deep integrity and intellectual openness, find new ways to create loyalty, lead increasingly diverse and independent teams over which they may not always have direct authority, and empower collaborative approaches inside and outside the organization.
- **Organizational transformation:**

Vision and purpose: Identify forces pushing an organization to change culture and the cultural elements that must be changed. Communicate these clearly.

Strategy and goals: Develop a strategy aligned with the new environment. Include employees at all levels as much as possible.

Mindset change: Create a framework for ongoing improvement by changing the mindset and behaviors of leaders, contributors, and groups.

Integration of culture: Integrate cultural styles within the organization to get the best of all styles. Align cultural styles with leadership and personal styles as the cornerstone of success.

Organizational design: Build the organizational structure. Define clear roles and responsibilities to build an inclusive workplace, and be nimble.

Talent development: Implement programs to enhance individual cognitive processes. Consider cross-pollination of talents, employee training at different stages, and develop a succession plan.

STRATEGIC PROCESS FOR CULTURAL EVOLUTION — CONTINUOUS IMPROVEMENT

Developing a new corporate takes time. The strategy must be visionary, and the change management process should be progressive. There is a saying that "culture eats strategy for breakfast." All the efforts to develop strategy, improve processes, data integration, system harmonization, and talent development initiatives will not yield ROI if the organization does not create a culture supporting growth, sustenance, and learning [3, 4].

Culture is a powerful differentiator for gaining a unique competitive advantage as it is closely aligned with leadership, talents, and strategy.

CONCLUSION AND OPPORTUNITIES

The pharmaceutical industry landscape is rapidly evolving due to globalization of economies, regulatory improvements, international support for delivering lifesaving medicines, technological advancements, and capital infusions. The ability to meet growing global demands depends on the capacity to innovate and adapt rapidly. Recent disruptions like the COVID-19 pandemic, inflation, geopolitical shifts, and digitalization, highlight the need for long-term strategies to sustain and grow.

In today's turbulent business environment, pharmaceutical companies are quickly realizing the need for an innovative-centric culture. Established processes won't sustain competitive advantage. A flexible culture that encourages creativity, supports innovation, and fosters an environment of collaboration is essential for continuous growth and sustainability.

Industry leaders have a crucial role in delivering sustainable value and growth, whether organically or through acquisitions. This

In today's turbulent business environment, pharmaceutical companies are quickly realizing the need for an innovative-centric culture. Established processes won't sustain competitive advantage.

equires strategic prioritization and nurturing cultures at all levels. While encouraging an entrepreneurial and collaborative culture (Figure 2), leaders must manage the controlling and competing cultures of divisions dealing with regulatory compliance and fiscal obligations. Subcultures should support organizational needs and integrate into the overall corporate culture of growth and sustainability.

Individual talent is the cornerstone for cultivating an innovative and entrepreneurial culture. Individuals bring new ideas, seek opportunities, and explore new markets. Organizations must foster an environment of learning, creativity, collaboration across subcultures, effective communication, and teamwork, while also planning for strategic succession and implementing talent development plans.

"Cultural transformation" has become a buzzword, with many companies embarking on this journey without robust planning. Often, it involves a quick survey and a new initiative to satisfy the C-suite. However, true transformation only occurs if the organization is prepared for continuous change. Strategically minded leadership must take responsibility for preparing the organization for cultural transformation.

Culture is a powerful differentiator for gaining a unique competitive advantage as it is closely aligned with leadership, talents, and strategy. The integrated framework presented in this article could be a catalyst for developing, nurturing, and continuously adapting to a culture that remains aligned with the company's vision in a constantly changing world.

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INDIAN PHARMACEUTICAL INDUSTRY: Creating Global Impact

By Lata Harish, Prema Desai, and Kaushik Desai

India's pharmaceutical sector is not only a cornerstone of its national economy, but it's also a pivotal player on a global stage. As of 2023, India ranked as the third-largest producer of drugs and pharmaceuticals by volume, with a 20% global share in the export of generic drugs. Currently valued at US$50 billion, the country has an ambitious goal for the sector: Grow its value to US$450 billion by 2047.

The country's strength in manufacturing high-quality generic drugs has made it a reliable supplier to over 200 countries and regions, including highly regulated markets of the United States, United Kingdom, and European Union. This success is driven by a skilled workforce, cost-efficient production methods, and a regulatory framework that supports business growth. India's commitment to research and development, along with its emphasis on high-quality generic medications, has reinforced its status in the global pharmaceutical market.

The Federation of Indian Chambers of Commerce and Industry projects the total market size of the Indian pharmaceutical Industry will reach US$120 billion by 2030 [11], fueled by a heightened focus on innovation and growing export opportunities. With government initiatives aimed at enhancing local manufacturing and attracting foreign investment, India is set to emerge as a global leader in pharmaceutical production. This will allow substantial contributions to both the economy and the healthcare system.

INDIA: FIRMLY ESTABLISHED IN THE GENERIC DRUG SPACE

Now, as a key global player in the pharmaceutical industry with a vital role in producing and distributing medications worldwide, India has one of the world's fastest-growing economies and is on track for becoming one of the world's top three economic powers in the next decade, according to the India Brand Equity Foundation. The development of a robust pharmaceutical supply chain network with manufacturing facilities has been a key factor in fueling the Indian economy.

As of 2023, India ranked as the third-largest producer of drugs and pharmaceuticals by volume, with a 20% share in the export of generic drugs [1], 5.71% of the global share of all pharmaceutical exports [1], and a 60% share in the supply of low-cost vaccines [15], according to the Indian Pharmaceutical Alliance (IPA).

The sector has the potential to exceed US$120 billion by 2030 [11]. Leading Indian pharmaceutical companies have strategically positioned themselves as strong contenders in the expanding generic market in North America. Additionally, many Indian companies have firmly established themselves in the specialty medicines market. For example, the oncology drug market in India is expected to reach US$1.98 billion this year [17].

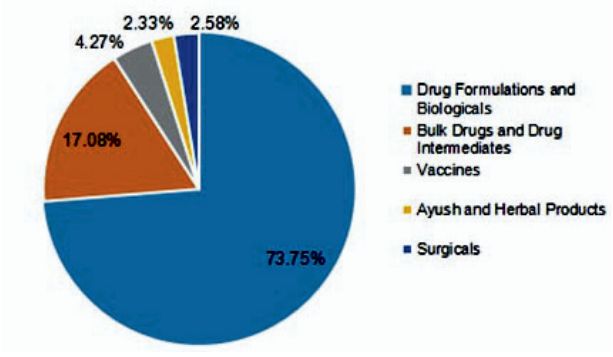
Figure 1: **India's pharmaceutical exports have shown significant growth over the past decade. In FY 2013–2014, pharmaceutical exports were valued at US$15 billion, which compares with US$26.5 billion in FY 2023–2024. Custom Market Insights [29] reports that the Indian pharmaceutical industry in 2022 was valued at US$59.63 billion and is expected to reach US$129.49 by 2032. This growth highlights India's expanding role in the global pharmaceutical market.**

Indian Pharmaceutical Exports Grow 57% Over 10 Years

US$15 billion FY 2013–2014

US$26.5 billion FY 2023–2024

Figure 2: Breakdown of India's export categories



Indian pharmaceutical companies have achieved global recognition through competitive pricing and their ability to manufacture cost-effective generic alternatives, with many benefiting from economic factors that support the industry, including competitive land rates, low resource expenses like water and electricity, and affordable machinery costs.

Between FY 2018 and FY 2023, the Indian pharmaceutical industry saw steady growth, with a compound annual growth rate (CAGR) of 6%–8%, primarily driven by an 8% increase in exports and a 6% rise in the domestic market [6]. This sector has attracted significant foreign direct investment (FDI), crossing the US$20 billion mark in September 2022, with FDI inflows increasing fourfold over five years [12].

On 17 December 2024, the Ministry of Chemicals and Fertilizers in India announced that for FY 2023–2024 (which closed 31 March 31 2024), the pharmaceutical market was valued at US$50 billion [6] with domestic consumption accounting for US$23.5 billion and drug and pharmaceutical exports US$26.5 billion [15], which compares with US$15 billion in exports for FY 2013–2014 [14] (see Figure 1). The sector is projected to achieve a turnover of US$130 billion by 2030 [6].

INDIA'S DOMESTIC PHARMACEUTICAL MARKET

India also boasts a strong domestic pharmaceutical industry. This industry plays a crucial role in providing medications to the Indian population and other countries. With a wide-reaching network of drug companies and manufacturing facilities, India's pharmaceutical sector significantly contributes to the nation's economy and healthcare system. The country is home to over 3,000 drug companies and approximately 10,500 manufacturing units. These include [7]:

- More than 2,000 units hold World Health Organization (WHO) GMP approval
- 253 plants are approved by the European Directorate of Quality Medicines
- 1,105 units possess Europe's Certificate of Suitability (CEP)
- Over 950 units comply with the Therapeutic Goods Administration guidelines
- 500 are approved by the US Food and Drug Administration (the highest number outside of the US)

INDIA'S DIFFERENTIATORS

Indian pharmaceutical companies have achieved global recognition through competitive pricing and their ability to manufacture cost-effective generic alternatives, with many benefiting from economic factors that support the industry, including competitive land rates, low resource expenses like water and electricity, and affordable machinery costs. Notably, India's drug manufacturers integrate various components, such as intermediates, Active pharmaceutical ingredients (APIs), and formulation companies, while adhering to international safety and quality standards. The contract manufacturing sector plays a significant role in positioning India as a top global player by production volume.

India is often referred to as the "Pharmacy of the World." Indian pharmaceutical sector supplies over 50% of global demand for various vaccines, 40% of generic demand in the United States and 25% of all medicine in the United Kingdom. The domestic pharmaceutical industry includes a network of 3,000 drug companies and 10,500 manufacturing units," per the India Brand Equity Foundation (IBEF) [6].

The industry offers a wide range of 60,000 different generic brands across 60 therapeutic categories, including generic drugs, over-the-counter (OTC) medicines, APIs/bulk drugs, vaccines, contract research and manufacturing, biosimilars, and biologics [2, 8].

There are a number of noteworthy pharmaceutical companies listed on the National Stock Exchange (NSE) in India, including Sun Pharma Industries Ltd., Divi's Laboratories Ltd., Cipla, Mankind Pharma, Dr. Reddy's Laboratories, Zydus Lifesciences

Ltd., Torrent Pharmaceuticals Ltd., Aurobindo Pharma Ltd., and Alkem Laboratories Ltd. [16]. India also excels in the production of APIs, with the Confederation of Indian Industry ranking the country's API industry as the third-largest globally, contributing around 57% of APIs to the World Health Organization's (WHO) prequalified list [6].

The government's initiatives to boost local manufacturing, particularly through the Production Linked Incentive (PLI), has gained momentum. Amid disruptions in the supply chain due to the COVID-19 pandemic, the government has introduced initiatives to support the production of bulk drugs and medical devices for domestic use and export. Under PLI, the government sanctioned funds for developing bulk drug parks to world-class infrastructure facilities that have common amenities like solvent recovery plants, distillation plants, power and steam units, and effluent treatment plants.

The Indian government has made modifications to the Pharmaceutical Technology Upgradation Assistance Scheme to improve quality upgradation for small and medium-sized enterprises [17]. This scheme, which is a part of the country's "Strengthening Pharmaceuticals Industry" initiative, provides financial assistance for upgrading manufacturing facilities to meet international standards [18]. India's focus on research and development aims to foster innovation and propel the nation toward becoming a global leader in pharmaceutical manufacturing.

The Indian pharmaceutical sector comprises of five key verticals: contract research and manufacturing services (CRAMS), APIs, formulations, biologics and biosimilars, and vaccines.

CRAMS

The contract development and manufacturing organization (CDMO) industry plays a vital role in the global drug development due to specialized expertise, cost efficiency, and ability to accelerate the drug development process. They also ensure regulatory compliance, offer scalable production, and allow pharmaceutical companies to focus on their core competencies, leading to faster and more efficient market entry for new drugs. The CDMO market in India is forecasted to reach US $44.6 billion by 2029 from an estimated size of US $22.5 billion in 2024 [21]. In the US, nearly 50% of all new drug application (NDA) approvals involve contract-manufactured drug products, and over 50% of small-molecule NDA products involve contract-manufactured drug substances. The CDMO industry has enabled rapid expansion in the bio/pharmaceutical sector, with 80% of drugs for emerging companies and 60% for midsize companies being manufactured by CDMOs [19].

CRAMS is undergoing substantial growth. It's expected to grow by 6.2% annually from 2021 to 2026, reaching about $170 billion. Biologics-based CRAMS is set to grow even faster, at 11% annually from 2020 to 2026, due to an increasing number of medicines in development and the limited manufacturing expertise of respective companies. Small molecules also play a big role, with around 6,000 molecules currently in development [20].

Many international pharmaceutical companies are using CRAMS and outsourcing research and clinical trials to developing nations as a strategy to address increasing costs and regulatory limitations in developed markets. This approach enables companies to concentrate on branding, tap into specialized product expertise, and mitigate risks while ensuring the delivery of top-notch medications to the market.

APIs

India's APIs market was valued at US$11.8 billion in FY 2021 and is projected to grow at a CAGR of 12.24% from 2021 to 2027 [22]. Numerous Indian companies contribute to API manufacturing, with this growth driven significantly by the expanding biopharmaceutical sector in the country.

Formulations Development

Globally recognized for high-quality generic medicines, India's largest pharmaceutical companies are major players in manufacturing and exporting generics. They rank among the largest generic medicine producers worldwide.

Biologics and Biosimilars

The biologics and biosimilars [6] segments are gradually gaining traction in India. As of 2021, India held an 8% share of the global biopharmaceutical market [6]. The global biosimilars market is projected to reach US$1.3 trillion by 2032 [23], with Indian manufacturers producing US$500–$600 million in a US$12 billion market. India, could potentially, own 15%–20% of the global market [24].

Vaccines

India is the world's largest vaccine supplier, providing 62% of global demand. Currently, two-thirds of its vaccine production is exported. The Indian vaccine market was worth US$95 billion in 2021 and is projected to reach US$256 billion in 2030 [9].

MEDICAL DEVICE MANUFACTURING AND INNOVATION

2023 marks a significant milestone for India's medical technology industry with the introduction of the National Medical Devices Policy (NMDP) [25], which aims to promote the Indian medical devices sector and position the country as a global leader in medical device manufacturing and innovation. The goal is to grow the sector to a point in which India owns 10%–12% of the global market over the next 25 years.

The NMDP outlines strategies for phased manufacturing of critical components and utilizes initiatives like the Public Procurement (Preference to Make in India) Order 2017 and the Aatm Nirbhar Bharat Abhiyan, or the Self-Reliant India Mission [26] to bolster domestic manufacturing. It charts a roadmap focusing on accessibility, affordability, quality, patient-centered care, preventive health, security, research, innovation, and skilled labor development.

The government is supporting medical device manufacturing

India is on the right path to capitalize on this opportune time, with key factors aligning to drive pharmaceutical manufacturing in the country. It has built a robust scientific and technological foundation through decades of extensive collaboration with pharmaceutical companies and research institutions worldwide.

in India through regulatory frameworks and industry-friendly policies. Initiatives like the production-linked incentive (PLI) scheme to encourage entrepreneurs to establish domestic facilities, possibly in collaboration with global partners. The integration of smart connected care, advancements in diagnostics and therapy, and improved clinical outcomes are shaping the market for medical devices and diagnostics. Growth areas include smart medical devices, digital therapeutics, AI-based solutions, predictive analytics, and wearable technology. India is one of the top 20 countries in demand for medical devices, but its local industry is still developing and relies heavily on imports of advanced medical technologies such as, cancer diagnostics, medical imaging tools, ultrasonic scans, high-value cardiology devices, hearing aids, and orthopedic implants.

"For sustainable development of the medical devices industry and safeguarding the interests of patients, India needs to actively reflect and work towards addressing the need for timely availability of crucial lifesaving medical technologies to citizens, without any discrimination, to deliver better patient outcomes, and also to keep our medical faculty and students updated on the latest medical technologies," states the 2023 report, "Ensuring Equitable Access to Critical Medical Technologies for Indian Citizens" by the Public Health Foundation of India and the Indian Medical Parliamentarians' Forum (IMPF)]32].

By launching research and development initiatives and allowing 100% foreign direct investment (FDI), India aims to become a top manufacturer of medical devices in both local and global markets. Additionally, they aim to ensure their citizens have fair access to critical care medical devices [26].

The report focuses on several key areas: analyzing current regulations for medical devices in India, assessing the demand for advanced medical devices, evaluating the procurement process, examining the cost-effectiveness of new medical devices, looking at how health technology assessment (HTA) is used globally, and reviewing new procurement methods like value-based procurement (VBP).

As India progresses toward becoming a global medical technology hub, fostering stronger alliances, leveraging technology effectively, and establishing clear policy frameworks are crucial. Initiatives such as developing more medical device parks, partnering with industry and academia to address skill gaps among healthcare professionals, and prioritizing mental health support for healthcare workers can further enhance India's position as a medical device powerhouse. Success in seizing these opportunities will define India's stature in the global medical technology industry.

EVOLVING BUSINESS MODELS AND OPPORTUNITIES

Pharmaceutical companies worldwide have numerous opportunities to enhance their investments in India. With a growing trend toward collaborative business approaches, Indian companies are expected to play a vital role as partners. Indian pharmaceutical companies are advancing toward more valuable endeavors. Overseas corporations are increasingly utilizing India's growing research capabilities in addition to its manufacturing expertise. They collaborate through entering into licensing agreements, franchising, or joint ventures to tap into the Indian market. Among these, joint ventures are an increasingly popular option for companies aiming to take advantage of opportunities in India.

Foreign companies are seeking local partners to expand their presence in the country. Domestic partners offer valuable local expertise, knowledge, and networking capabilities. These advantages—coupled with cost-effective production, skilled labor, and expedited drug development—greatly benefit western pharmaceutical companies entering the Indian market.

Other companies are using local branches to establish their own sales and marketing operations, either through internal growth or acquisitions. GlaxoSmithKline (GSK) has 20 contract manufacturing organizations, and regional and sales hubs in India. In 2024, Novartis AG announced that it is conducting a review of Novartis India Limited, noting that it is "deeply committed to India with a footprint that has expanded significantly in recent years."

MAJOR PHARMACEUTICAL CLUSTERS IN INDIA

India is recognized as a global pharmaceutical hub, providing affordable and high-quality drugs that improve health worldwide. Many multinational companies have invested heavily in India and are growing their presence in different parts of the Indian pharmaceutical market. They are also expanding into smaller cities and rural areas to make healthcare more accessible to more people.

Regulators have supported the industry by introducing PLI schemes and specialized industrial zones (bulk parks) for APIs, which help Indian API manufacturers compete on an equal footing. These measures have also reduced the cost difference between India and China for APIs.

India's pharmaceutical hubs present diverse investment opportunities in APIs, biosimilars, vaccines, nutraceuticals, and contract research. In March 2024, under the PLI Scheme, the Indian Ministry of Chemicals and Fertilizers inaugurated 27 Greenfield Bulk Drug Park projects and 13 Greenfield Manufacturing Plants for Medical Devices.

In 2022, the bulk drug park in Una, Himachal Pradesh, began construction. It is expected to attract investments of US$1.35 billion and create 20,000 jobs.

In southern India, at over 19,000 acres, Hyderabad Pharma City (HPC) in Telangana's Ranga Reddy district (including Kandukur, Yacharam, and Kadthal Mandal) is reported to be the world's largest integrated cluster for pharmaceutical industries in both research and manufacturing. Recognized as a National Investment and Manufacturing Zone by the Government of India, HPC holds significant national and international importance.

In Andhra Pradesh, Jawaharlal Nehru Pharma City—located in Visakhapatnam and developed by Visakha Pharmacity Ltd. (a joint venture between Ramky Group and Andhra Pradesh Industrial Infrastructure Corporation)—is India's first pharmaceutical hub for bulk drugs. It spans 2,400 acres and hosts Pfizer, Mylan, Aurobindo, Lupin, Biocon, and many other companies [27].

VISION PHARMA: 2047

India is on the right path to capitalize on this opportune time, with key factors aligning to drive pharmaceutical manufacturing in the country. It has built a robust scientific and technological foundation through decades of extensive collaboration with pharmaceutical companies and research institutions worldwide. The government has adopted policies and initiatives, such as financial incentives, regulatory support, and infrastructure support, to drive innovation and support manufacturing and development. Plus, manufacturing costs are low and India has a strong consumer base at home.

In 2022, the Indian Department of Pharmaceuticals (DoP) introduced Vision Pharma 2047, a long-term strategy designed to transform Indian's pharmaceutical sector into a global leader in manufacturing affordable, innovative, high-quality pharmaceutical and medical devices. They are pursuing more collaborations with pharmaceutical companies and researchers in drug development, medical devices, and digital technologies.

Although the conditions are right for growth, there are many challenges that lie ahead [28], including regulatory hurdles, international compliance standards, protecting intellectual property, securing funding for research and development, developing and retaining a skilled workforce in the life sciences and digital technologies, building and maintaining state-of-the-art infrastructure, implementing sustainable manufacturing practices, and competing with established global companies.

The Indian government addresses these challenges, and solutions, in the Promotion of Research and Innovation in Pharma MedTech Sector (PRIP), a US$675 million scheme introduced in 2023 [3] by the DoP. The ultimate goal is to shift pharmaceutical manufacturing in India from being cost-based orientated to an innovation-based model.

The ambitious vision of Vision Pharma 2047 aligns with the principle of "Vasudhaiva Kutumbakam," a Sanskrit saying that means "the world is one family." India aims for its pharmaceutical industry to reach a value of US$450 billion by 2047.

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PROCESS ARCHITECTURE AND INTEGRATED DESIGN
in the Pharmaceutical Sector

By Donato de Vivo

Large engineering companies specializing in the industrial production sector have increasingly been adding process architects to their teams to address the need for expert designers in this specialized field. Process architects play a key role in designing industrial plants, particularly for pharmaceutical production facilities.

In fact, these sites must meet architectural criteria while addressing complex technological needs with particular attention to integrating various disciplines, such as Process Engineering and Mechanical, Electrical, and Plumbing (MEP) Engineering, while ensuring compliance with Good Manufacturing Practices (GMP) and Health, Safety, and Environment (HSE) regulations.

Architects are accustomed to working in multidisciplinary teams, and on intricate projects. They have strong three-dimensional thinking and act as design integrators, collaborating across the diverse disciplines involved.

A process architect can play a significant role in making designs more sustainable and help reduce environmental impact (e.g., water and energy consumption, emissions, and solid waste). By using a "Value Engineering and Cost Reduction" design approach, they reduce the consumption of water and energy, reduce emissions, and manage solid waste more effectively. Additionally, they can integrate sustainability principles into the design process, aligning with the concept of the "Facility of the Future," which focuses on innovative, efficient, and sustainable facility designs.

BACKGROUND

Process architects are becoming more important in the life sciences industry because their evolving role as systems integrators aligns with the demand for modular solutions, promising enhanced quality, reduced costs, and expedited project delivery. There is not a specific degree and educational path for this professional role—it is an expertise that would be achieved and consolidated through years of professional experience. This is why it is usually hard for engineering societies to find a process architect within the job market, especially considering that specialized professionals are usually only motivated by certain types of projects.

Process Architect Role and Responsibilities

The responsibilities of a process architect consist of the following: assessing the site; planning the facility; establishing a benchmarking repository to define parameters and objectives; managing project development and process analysis; defining material and personnel flow; overseeing feasibility studies; completing presentations and processing documentation for approval; issuing construction drawings and producing specifications; estimating cost, reviewing and approving workshop drawings; and managing and supervising construction.

At the beginning of a project, it is essential to define the role and responsibilities of the process architect on the team. That definition leads to better building and process as well as better customer and user outcomes.

EQUIPMENT

When developing the layout, it is essential to address the integration of the equipment in the early stages of the design process. Once equipment is selected—usually together with the clients—then operating heights, maintenance access, flows, and delivery logistics are addressed. Initial design is typically based on generic equipment drawings or, if parameters are unknown, using worst-case scenarios. In particular, personnel and materials into and out of the production area determine the room adjacencies.

CONTAMINATION CONTROL

Developing strategies for clothes changing and washing should be defined and simplified according to the local customs and clients' internal procedures, always keeping contamination control in mind. Concerns about sterility should be reviewed with all interested parties, including the HSE. One interesting example case relating

The process architect often works in the modernization of existing plants. Modifications and renovations represent a different set of challenges. These include feasibility studies and constructability reviews, aiming to define move in/out of equipment, and definitions of temporary partitions for process segregation.

to general lockers is the idea of flexible lockers. These lockers could have mobile partitions between dedicated changing rooms for men and women, with the possibility to move these partitions according to a facility's employee numbers.

Circulation spaces for transferring materials and personnel within the facility require large amounts of expensive space. Planning an adequate number of airlocks requires accurate information on the current required current GMP (cGMP) zone classifications, biocontainment, and required pressurization.

OTHER DESIGN CRITERIA

Other design criteria to examine include the ergonomics of the machines and the degree of product handling, as well as biological and toxicity levels for hazardous products such as flammable corrosives. In case of ATEX (explosive atmospheres) considerations, the type of finishes and the layout for the room should be carefully considered, especially if these rooms occur in a classified production area.

DESIGN PROCESS

The design process could be described as follows:

- Collect user requirements (URS)
- Establish context
- Complete adjacency diagrams
- Define project scope
- Develop options
- Finalize the selected option
- Develop the layout
- Determine equipment allocation and ergonomics
- Determine classes
- Verify personnel and material flows
- Ensure spatial interdisciplinary coordination

The design process of a laboratory is similar, but flows are different and could not be required in a GMP assessment.

MODERNIZATION AND RENOVATION

The process architect often works in the modernization of existing plants. Modifications and renovations represent a different set of challenges. These include feasibility studies and constructability reviews, aiming to define move in/out of equipment, and definitions of temporary partitions for process segregation. This is to guarantee the functionalities of the existing department for client sustainability goals (an increasingly significant factor).

In some case studies, process architects evaluate the flexibility of layout with respect to scale-up considerations. For example, if the clients evaluate to proceed with a 600/900 -liter bioreactor, the layout should incorporate enough wide corridors, big doors, and proper ceiling height to allow the bioreactor in and out. Further, operational space for maintenance on top of the bioreactor should be considered by the process architect by designing a ceiling with enough height in certain areas of the room.

SUSTAINABILITY

In the context of a facility design, sustainability could be addressed in many ways; for example through the box-in-box approach and modular design; closed process and ballroom layout, the use of disposable equipment instead of stainless steel; integrating a plug and play approach; reduced rooms segregation and areas classification (e.g., heating, ventilation, and air conditioning [HVAC]); and risk analysis and Lean design.

PRODUCT CONSIDERATIONS

The facility is designed and built to ensure and test the product and, ultimately, to provide a safe, effective product. Multiple decisions impact facility design. These include decisions made regarding filling format, technology, regulations, and batch size, among many other things. For example, deciding between using a restricted access barrier systems (RABS) or isolator is probably the single largest decision that can be made regarding facility design.

Another example is the final product format (e.g., vials, cartridges, or syringes; liquid or lyophilized; aseptic or terminally sterilized; single or muti-product). Moreover, commercial decisions determine the reason for the facility. For example:

- Who is the customer?
- Will it involve clinical trials?
- Is it a commercial product?
- Is it liquid or lyophlized? Aseptic or terminally sterilized?
- Is it a single or multi-product?

Process Architect Knowledge

The process architect is responsible for understanding, defining, and prioritizing the needs and expectations of the customer. This includes considering how format and batch size decisions impact facility design, as well as the specific requirements of different customer markets (e.g., EU, Japan, US). Therefore, the process

Figure 1: Regulations

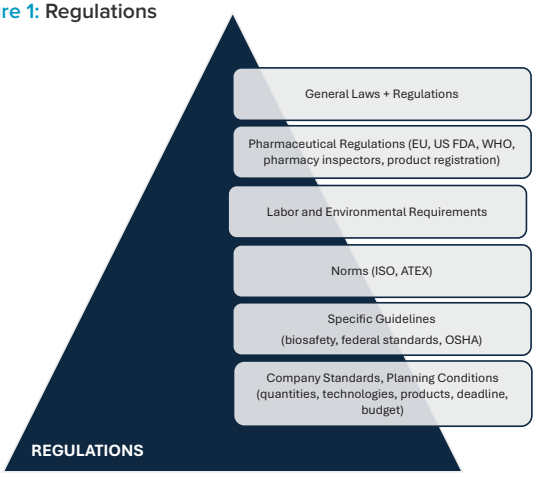


Figure 2: Area classifications and nominal operating pressures

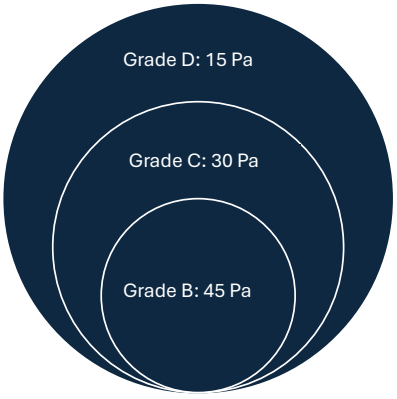


Table 1: Checklist of process architect knowledge requirements

General	• Definition of the project scope • Adjacency diagram (hand drawings, sketches, etc.) • Sizing of spaces and machines, GMP classes, flows, etc. • Knowledge of the project areas • Focus on sustainability • Contamination control • Maintenance spaces and accessibility (access to sampling points, equipment technical areas, and integrated ceiling devices)
Flows	• Classification of spaces • Contamination control strategy • Airlock requirements/strategy gowning philosophy • Material flows • Personal flows • Equipment
Finishes	• Integration of finishes • Use of glass partitions • Walkable false ceilings • Finishes workshops and case studies • Chemical resistance/cleaning chemicals specifications • Cleanability (i.e., smoothness of surfaces and expansion joints, lack of edges, use of coved corners)
Coordination with Technical Disciplines	• Process • HVAC • Electrical • Piping • Automation, data, and security • Not passing ductwork or piping through process rooms
Maximum Personnel Requirements	• Lockers • Offices • Canteen • Parking
Tools	• IT tools • SketchUp • Autodesk Revit • CorelDRAW or Adobe Illustrator/InDesign • Equipment library in Revit and SketchUp

architect must possess a specific set of skills and knowledge. It is helpful to propose a checklist of the required knowledge (see Table 1).

Project User Requirement Specifications

The layout of a pharmaceutical manufacturing plant should be designed based on the needs of the facility. The needs of the structure are identified during the planning phase, where the company must clearly define its actual needs. It is essential that we separate "must have" objectives from non-strategic objectives, which may require conducting a formal decision analysis. This is often a very time-consuming endeavor, since each department needs to weigh what is truly necessary for their business versus those items that are not essential to operations. A facility should be designed to anticipate its needs in two-, five-, and ten-year increments.

The architectural design must consider optimal room finishes, client standards, local customs, environmental and safety considerations, and compliance with building and fire regulations. Additionally, the external structure and finishes of buildings should account for the internal environment, minimizing the use of columns and expansion joints within in clean areas of production facilities. The layout must be an integrated project meeting the following requirements:

- Project cost and schedule
- Compliance with GMP
- User requirements
- Equipment layout and equipment requirements
- Personnel and material flows (product, component, and raw material)
- Operational access requirements
- Maintenance access requirements
- Cost considerations in layout design

USER REQUIREMENTS

The designer must first understand the requirements of the product and the process, precisely clarifying the number and dimensions of

Figure 3: A process architect's involvement in each project phase

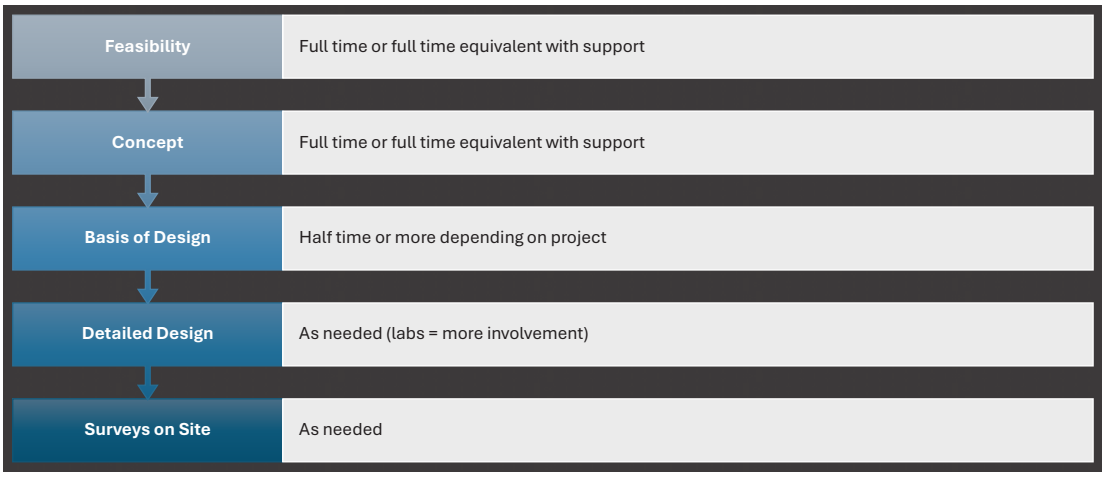
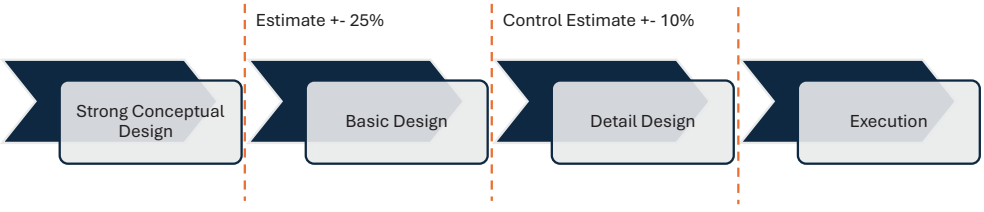


Figure 4: Project phases and estimates



The process architect has a role in defining the layout, particularly during the initial phases. This involves privileged interactions with the customer and various disciplines, as well as overseeing the spatial coordination of structures, equipment, and systems.

the rooms that will be required; relationships between the groups of rooms; finishes, equipment, and furniture suitable for carrying out the various functions; and the environmental conditions (temperature, humidity, air movement, sound insulation, etc.).

EQUIPMENT LAYOUT AND REQUIREMENTS

Equipment layouts, also called logic diagrams, and equipment requirements ensure the optimum flow of materials and personnel. They should define all the areas that can influence the operations necessary for production, as well as the relationships between them. These are derived from program and equipment sizing needs and can be developed once the process is known. Equipment sizes are indicated using blocks and room groups are assembled based on necessary adjacencies and process requirements.

DRESSING REQUIREMENTS

Dressing rooms play a fundamental role in layout. Locker rooms have two grades (or, levels) of changing rooms. Low standard, which includes normal (civilian) clothes to factory (clean) clothes. High standard includes clean clothing to full coverage coveralls.

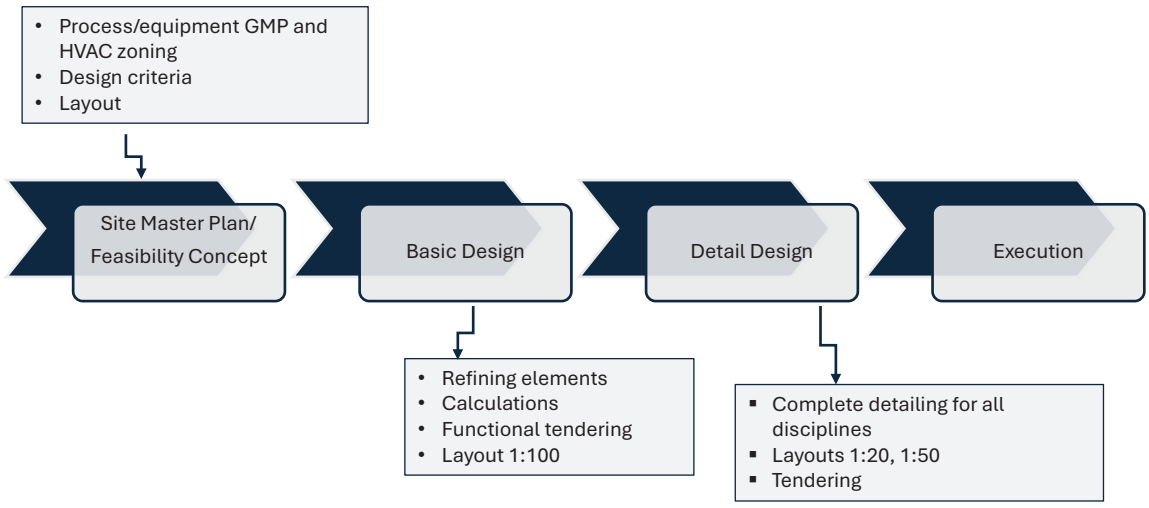
Project Phases

It is extremely important not to skip design levels. The strategic decision to invest in a strong conceptual design leads to the following advantages:

- Low initial costs
- Feasibility study
- Advance clarification of the main project themes
- Stronger decision-making tool
- Possibility to develop alternatives/brainstorming
- Customer orientation

Based on the process outlined in the workflow diagram (see Figure 5), the project engineer interfaces directly with the

Figure 5: Workflow diagram of design and planning process



technical disciplines, responding to the pharmacy manager for the correct flow of project information.

The process architect has a role in defining the layout, particularly during the initial phases. This involves privileged interactions with the customer and various disciplines, as well as overseeing the spatial coordination of structures, equipment, and systems (i.e., space management).

Final Considerations

It is worth focusing on the current state of the process architect profession and on future market trends in the field of industrial production, especially sustainability goals. The evolution of the life science sector is driving the need for new manufacturing paradigms based on advanced technologies. As a result, process architects must transform themselves into systems integrators to best meet customer needs for fast manufacturing facilities.

For example, the constant introduction of new and innovative modular manufacturing solutions is creating significant opportunities for the lifespan and costs of future manufacturing facilities. Today, process architects are expanding their role as systems engineers and integrators focused on finding the best way to execute a project using modular and pre-engineered systems, through the design of the structure with the clear objective of improving quality while reducing costs and time needed to deliver a project. The demand for this enhanced role is highlighted by requests from numerous companies asking for modular platform and system designs that take advantage of modular, pre-engineered components.

A modern pharmaceutical production plant must be flexible and adaptable, not only to have the ability to scale up inventories to meet growing market demands, but also to have the flexibility needed to accommodate changes in production machinery needs.

The evolution of the life science sector is driving the need for new manufacturing paradigms based on advanced technologies. As a result, process architects must transform themselves into systems integrators to best meet customer needs for fast manufacturing facilities.

Process architects should come to understand clients corporate culture and their short- and long-term goals, whether a new facility is being designed or an existing facility is expanded or updated. In fact, design often takes place while production processes are still in the development phase. Thanks to this knowledge, process architects can act as true technical coordinators.

About the author

Donato de Vivo, MArch, BE, EMPM, is a CoE Process Architect with Exyte in Agrate Brianza, Lombardia, Italy, where he leads the biopharma and life sciences team in building conception and layouts through planning, engineering, architectural design and integration, procurement, follow-up, and construction. He holds advanced degrees in the field from POLIMI Graduate School of Management in Italy, the University of Florence in Italy, and Budapest University of Technology and Economics in Hungary. He joined ISPE in 2018.

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2025 ISPE Europe Annual Conference: Network and Explore New Technologies

By Heather Watson

The 2025 ISPE Europe Annual Conference will be held 12–14 May in London, England, and virtually. Heather Watson, the Conference Chair, offers advice and shares what attendees can expect at the upcoming event.

What are the top three reasons you would recommend attending this conference?

Attendees will have the chance to hear from industry leaders and regulators who will share their perspectives on some of the most important topics the pharmaceutical industry is facing: sustainability and drug shortages, digital transformation, GAMP®, biotechnology in large molecules, cell and gene therapy, advanced therapeutical medicinal products (ATMPs), good engineering practice, and investment management.

They can also participate in workshops, which are being included as part of the conference program for the first time this year. The sessions will cover:

- Integration, Innovation, and Advancing Pharmaceutical Quality (APQ)
- Quality and Regulatory
- Digital Transformation and GAMP
- Sustainability: Titanium Dioxide, Ethylene Oxide, PFAS, Nitrosamines, Softeners, Urban Wastewater Directive

As with other ISPE conferences, there will be several opportunities for you to expand your network, including the exhibition area and a networking dinner on Tuesday evening.

What are you most looking forward to?

I'm very interested to hear from our keynote speakers, attend the regulatory panel discussions, learn from the case studies that are going to be presented, and, of course, make new friends and contacts thanks to the networking opportunities.

What suggestions do you have for making the most out of the conference?

The conference will be an exhilarating and unmissable event. Prepare to engage with a remarkable mix of academic, industry, and health authority leaders, covering a diverse range of topics in the pharmaceutical sector.

This event is not only an opportunity to learn but also to connect. Attendees will get the chance to network, exchange insights, and preview the latest technologies and services in the exhibition area, so make sure you make the most of everything that is available at the conference.

Register for attendance at one of the workshops: space is limited, so make sure you register when they become available. Review the agenda prior to attending the conference to identify the sessions you would like to attend.

What prompted you to take on the role of Conference Chair?

When I was invited to be the Conference Chair, I was honored to have been recognized as a volunteer in a leadership role and to be considered for such an important position. I have been a member of the ISPE Europe Annual Conference program committee since it started several years ago and have enjoyed watching the committee strengthen the conference year after year, with attendee numbers increasing with each year that the conference is held. All of the conferences that I have participated in have helped me grow and increase my knowledge and understanding of the pharmaceutical industry.

In the role of Conference Chair, I'm involved in more aspects of the organization of the conference, rather than just focusing on the GAMP track that I had previously co-led. This is the first year that the ISPE Annual Europe Conference has had a Chair and I'm really looking forward to helping deliver an outstanding and successful event with the support of a very enthusiastic program committee.

Why do you enjoy being a member of ISPE?

I'm a member of several Communities of Practice, primarily with GAMP. I enjoy the variety of networking opportunities, which help me learn and connect with other individuals with similar interests in the pharma industry. I've made some great friends through ISPE, and I now have a huge network of people that I interact with. Some of my highlights have been leading the GAMP Global Steering Committee; co-leading the team that produced *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* (Second Edition), and being a recipient of the ISPE Committee of the Year award for the GAMP Global Steering Committee in 2016 and 2022 and the ISPE Europe Annual Conference in 2019.

Heather Watson is a Director of TenTenTen Consulting Limited based in the UK, where she is responsible for delivering specialist computer system validation consulting services on a global basis within the life science industry by providing advice and support to overcome the business and regulatory challenges to patient safety, product quality, and data integrity. Heather has over 30 years of experience working in the pharmaceutical industry and worked at GlaxoSmithKline until 2022. She joined ISPE in 2002.

Roger Nosal Receives 2024 ISPE Distinguished Achievement Award

By Marcy Sanford

Long-time ISPE member Roger Nosal was honored with the ISPE Richard B. Purdy Distinguished Achievement Award at the 2024 ISPE Annual Meeting and Expo in Orlando, Florida, US.

An ISPE member since 2007, Roger Nosal has dedicated his career to bringing global regulators and pharmaceutical industry professionals together to bring lifesaving medicines to patients worldwide. So, it was especially fitting that he was honored with the distinguished achievement award—the highest honor bestowed by ISPE on a member. The award, named for one of the Society's founders and most esteemed presidents, recognizes an ISPE member who has made significant, long-term contributions to the Society.

BACKGROUND AND EXPERIENCE

A Principal Consultant with Roger Nosal PharmaCMC Regulatory Consultants, Nosal also serves as Head of Regulatory Strategy for NGT BioPharma Consultants, a consortium of experienced experts and leaders in the development of pharmaceutical products. Before that, he was Vice President and Head of Global Chemistry, Manufacturing and Controls (CMC) at Pfizer, where he was accountable for all global regulatory CMC strategies and applications for innovative products and medical devices. He is the co-author of 24 patents and has publicly presented and published on a wide variety of regulatory and pharmaceutical policy initiatives and topics.

Nosal graduated with degrees in geology and studio art, and he worked briefly for a mining company in Montana before beginning his career in the pharmaceutical industry. "Over a 40-year span, I went from process chemistry to medicinal chemistry. In 1994 at G. D. Searle and then Monsanto, after it was acquired, I was asked to take on a role in regulatory because I had drafted CMC sections for a couple of investigational new drug applications. I learned about regulatory requirements/expectations while I assembled the CMC sections for different products that we were moving through the development pipeline."

"At the time, CMC was emerging as a distinct regulatory discipline in the industry. I basically grew up with it and learned it," he said. "I also had a chance to formulate it in the companies that I worked for. At Pfizer, I learned a tremendous amount over the course of several years, not only about the development approach that companies take, but also how to apply that and use that information in the right way for engaging with regulatory authorities and conveying information to them, not just for small molecules, but for just about every molecular entity.

"When I first got into regulatory, the industry had somewhat of an adversarial relationship with regulatory authorities. At least from the vantage point that I had. At the time, I did not know a lot of people who worked at regulatory authorities, but as I got to know them, I realized that what they did was not very different from what the regulatory colleagues at my company did. They were just looking at things from a different perspective than we were. I took it upon myself to work with other colleagues in the industry who were establishing collaborative approaches with regulatory authorities because it was the most effective way to improve regulatory applications and interactions," Nosal said.

Over the course of his career, Nosal led the CMC team that received global regulatory approvals for Celebrex, a medicine used to manage the pain of osteoarthritis and rheumatoid arthritis. He collaborated with colleagues at Wyeth and Merck to implement Quality By Design (QbD) through US Food and Drug Administration (FDA) pilot program applications, ultimately leading to improved process understanding and post-approval regulatory flexibility.

In 2013, he was awarded the Pharmaceutical Discovery, Development and Manufacturing Forum Award from the American Institute of Chemical Engineers (AIChE) for outstanding contributions to advancing QbD in the pharmaceutical community. From 2018 to 2021, he co-led PhRMA engagement with the US FDA and meetings with the International Pharmaceutical Regulators Programme to address concerns regarding appropriate control for nitrosamines in pharmaceutical products. He also worked on many innovative pharmaceutical technology projects including regulatory approval and the introduction of portable continuous modular manufacturing. He also provided crucial leadership in the global development, distribution, and commercialization of the chemistry, manufacturing, and controls (CMC) for Pfizer's COVID-19 mRNA vaccine.

As a consultant, Nosal provides regulatory strategy and support for companies that have drug candidates in development. "I really enjoy the fact that there's not always a right regulatory answer, but there are answers that are very close to minimizing the risks that a lot of companies encounter in their development. Understanding how to minimize and address those risks, and work with regulatory authorities to ensure they are assessed and understood, is probably the best part of this job. Science benefits by building on itself and

I think we're seeing academia, industry, and governments come together to find alternative ways to put together medicines that will not only address the symptoms of disease or deal with diseases, but, in some cases, potentially eliminate them. I think that's really remarkable. It seems there's an opportunity for us as an industry to collaborate more effectively with regulators in a way that allows for one regulatory authority to serve as the lead in evaluating an application in a way that other regulatory authorities would be able to approve the same application based on the original approval. During the COVID-19 pandemic, we would not have been able to get vaccines out to all the countries that we did if the regulatory authorities had not collaborated and mutually relied on the approvals that had been granted," he said.

A VOLUNTEER AND LEADER

Nosal has been a leader and member of ISPE policy initiatives and Communities of Practice, was the co-founder and past chair of the Regulatory Steering Committee, and served as chair of the *Pharmaceutical Engineering*® Committee and Product Quality Lifecycle Implementation (PQLI®) Task Teams. In her nomination of him, ISPE Regulatory Steering Committee Chair Sarah Pope Miksinski, PhD, Executive Director, CMC Regulatory Affairs, Gilead Sciences, Inc. wrote, "Roger has demonstrated sustained and impactful presence at the interface of regulators and industry. He frequently contributes and leads efforts related to highly complicated issues, and he has been and remains a recognized thought leader across ISPE membership and within the field.

"In 2023 Roger led [and continues to lead] a highly critical and visible ISPE program geared toward global harmonization. He has repeatedly served as a moderator of global regulatory town hall events at ISPE annual meetings. Roger is frequently sought out as a mentor to both industry and regulatory colleagues alike, which strongly supports his capability in the collaboration zone between industry and regulators. In situations that require a leader with the ability to create a safe space for global regulators and industry colleagues to discuss contentious topics, his name is often at the top of the list," Miksinski said.

"I find it a privilege to be a member of ISPE. I try to put in as much effort as I can because I enjoy the work that I get to do with other ISPE members. I've met outstanding people who collaborate with others to deliver very solid approaches that can be used and adopted throughout the industry," Nosal said.

ISPE International Honor Awards recognize and celebrate dedicated professionals who volunteer countless hours to support ISPE in its mission. For more information, visit ispe.org/membership/international-honor-awards

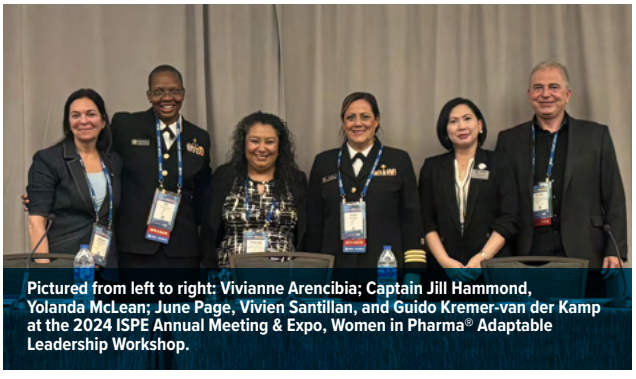
Marcy Sanford, ISPE, Production Manager

ISPE Women in Pharma®: Adaptable Leadership Workshop

Women in Pharma® Hosts Transformative Leadership Workshop at 2024 ISPE Annual Meeting & Expo

by Miriam Kremer-van der Kamp

At the 2024 ISPE Annual Meeting & Expo, Women in Pharma® hosted the transformative Adaptable Leadership Workshop. This three-hour session brought together over 60 attendees eager to improve their leadership abilities, team dynamics, and regulatory interaction strategies.



Pictured from left to right: Vivianne Arencibia; Captain Jill Hammond, Yolanda McLean; June Page, Vivien Santillan, and Guido Kremer-van der Kamp at the 2024 ISPE Annual Meeting & Expo, Women in Pharma® Adaptable Leadership Workshop.

Moderated by Guido Kremer-van der Kamp, Senior Consultant, Merck Chemicals GmbH, the workshop explored adaptable leadership, team-building techniques, and regulatory interaction , particularly in the context of audits. Key presenters included Yolanda McLean, Senior Director, Quality, Strategy and Operations, Alnylam Pharmaceuticals, and Captain Jill Hammond, Director of Training and Regulatory Science, US Food and Drug Administration (FDA).

The workshop concluded with an in-depth panel discussion that delved into real-world examples of effective audit strategies and the human dynamics of regulatory interactions. Other panelists included:

- Vivianne Arencibia, Vice President, Global Quality Systems and Compliance, Moderna
- June Page, Senior Regulatory Officer, US FDA
- Vivien Santillan, Regional Director, Asia, Novatek International
- Tonya Wilbon, Assistant Director, Division of Industry and Consumer Education and Branch Chief, Center for Devices and Radiological Health, US FDA

SESSION I: ADAPTABLE LEADERSHIP

Kremer-van der Kamp opened the workshop with a compelling session on adaptable leadership. Drawing from his extensive experience in the global biopharmaceutical industry, Kremer-van der Kamp emphasized that adaptability is crucial in an era marked by constant regulatory and operational changes and stressed that leaders need to view change not as an obstacle but as an opportunity for growth. Change, as he explained, is inevitable in regulatory environments, particularly in the pharmaceutical sector, where evolving standards and unexpected challenges demand flexibility. Leaders who can adapt to these shifts will not only survive but thrive, fostering innovation and continuous improvement within their teams.

A key component of adaptable leadership is resilience. Kremer-van der Kamp pointed out that resilience allows leaders to weather setbacks and maintain focus under pressure. During audits or compliance challenges, leaders must remain calm and composed, setting a positive example for their teams. This resilience not only boosts team morale, but also builds confidence during high-stakes audits.

Kremer-van der Kamp further discussed the role of proactive leadership. Being proactive, he explained, means anticipating challenges before they arise and taking steps to mitigate them. Whether it's preparing for a regulatory audit or adjusting to new compliance standards, proactive leaders ensure that their teams are always one step ahead. This strategic foresight allows organizations to maintain operational flow and avoid disruptions.

One of the most valuable takeaways from Kremer-van der Kamp's session was the focus on fostering a culture of ideation within teams. Leaders should encourage their team members to share new ideas and innovative solutions, which can help navigate complex regulatory landscapes. This open dialogue leads to creative problem-solving and ensures that teams are well-prepared to tackle any challenges that come their way.

Finally, Kremer-van der Kamp highlighted the importance of trust-building in leadership. Trust is the foundation of any successful

team, particularly in high-pressure situations like audits. Leaders who build trust within their teams foster an environment where members feel confident and supported. This trust also extends to interactions with regulators, as transparency and honesty build credibility and ensure smoother audits.

SESSION 2: WE ARE ALL HUMANS

McLean guided the audience through the human aspects of regulatory interactions. In this session, she shared insights into effective audit behavior, demonstrating how building trust between auditors and auditees is critical to compliance and the success of audit outcomes.

McLean emphasized that effective audit behavior is essential to building cooperative and transparent relationships. Audits should not be viewed as confrontational, but as opportunities to collaborate and enhance quality systems. Key to this success is the ability to communicate openly and effectively with auditors, ensuring that all parties are aligned in their goals.

McLean outlined several key behaviors that contribute to positive interactions during audits. Among them:

- Open communication: Clear, ongoing dialogue with auditors ensures that both sides understand each other's expectations, reducing the likelihood of misunderstandings.
- Transparency: By being transparent and open about processes and challenges, companies can build trust with auditors. This openness proves that there is nothing to hide, fostering a collaborative environment.
- Professionalism and respect: Maintaining a professional demeanor throughout the audit process ensures smooth and productive interactions.
- Avoiding defensiveness: McLean stressed that defensiveness could escalate tensions during an audit. Instead, teams should focus on collaboration, welcoming feedback as an opportunity for improvement.

McLean also highlighted best practices for audit success:

- Ensuring that the right inspection team is selected, including subject matter experts who can speak knowledgeably about the processes being audited.
- Adequately preparing subject matter experts for the audit by ensuring they understand the expectations and can clearly articulate their processes.
- Maintaining transparency throughout the audit process, ensuring that auditors have full access to documentation and information.
- Ensuring accessibility so that auditors feel supported and can ask for additional information as needed.

McLean's session reinforced the importance of human connection and mutual understanding during audits. By fostering positive interactions and focusing on collaboration, companies can achieve better audit outcomes, enhancing both compliance and operational success.

SESSION 3: TRAINING FOR REGULATORY EXCELLENCE

In her session, Hammond focused on the role of training in achieving regulatory excellence. She provided an in-depth overview of the US FDA's Compounding Quality Center of Excellence and the strategies the US FDA adopted during the COVID-19 pandemic to continue delivering critical training to industry professionals. Hammond provided a background on the Compounding Quality Center of Excellence, which was established in 2019 to address the growing need for high-quality compounded drugs produced by outsourcing facilities. These facilities must adhere to Current Good Manufacturing Practices (cGMPs), and the Center plays a crucial role in ensuring compliance.

The mission of the Center is to build the capacity of outsourcing facilities to meet the increasing demands of healthcare providers while maintaining the highest quality standards. Hammond outlined several key initiatives undertaken by the Center, including:

- Training on cGMP and compounding policy
- Conferences to discuss emerging trends and share best practices
- Research and analysis to better understand the challenges facing outsourcing facilities
- Regulatory science to examine complex technical questions and provide clarity

One of the most significant challenges the Center faced was the shift to virtual training during the COVID-19 pandemic. Hammond discussed the strategy change that was implemented to adapt to the worldwide shutdown, ensuring that training could continue uninterrupted. Despite the challenges of virtual delivery, the Center successfully transitioned to online platforms to deliver online instructor-led and self-guided courses. Hammond shared that maintaining engagement and effectiveness in the virtual environment was a top priority, and the Center developed interactive courses to ensure that participants remained involved and enthusiastic.

From 2020–2024, the Compounding Quality Center of Excellence achieved several major milestones under Hammond's leadership, including:

- Developing and delivering six instructor-led trainings
- Offering virtual training for more than four years, with more than 13,000 course completions
- Expanding educational opportunities through recorded webinars and self-guided online trainings on topics such as environmental monitoring, process validation, and sterile drug compounding

The session offered attendees a comprehensive understanding of how the US FDA has adapted its training programs to meet the evolving needs of the pharmaceutical industry while continuing to deliver high-quality education to professionals.

PANEL DISCUSSION: NAVIGATING AUDIT CHALLENGES

The workshop culminated in an engaging panel discussion, moderated by McLean, bringing together US FDA representatives

CONTINUED ON PAGE 52

Building trust between the US FDA and companies was another essential theme. The panel discussed how transparency is fundamental to this relationship. Trust is built over time through open communication, honesty, and a commitment to improvement.

and compliance experts. This interactive session allowed attendees to ask questions and engage directly with experts about the challenges of audits and regulatory compliance.

One of the central themes raised during the discussion was the importance of collaboration. Hammond, Wilbon, and Page emphasized the US FDA's role is to find gaps to help collaboration, not to penalize. US FDA inspectors want to partner with companies to identify areas for improvement. Audits should be seen as opportunities for learning and growth, rather than confrontations.

The panel highlighted the need for effective communication during audits. Misunderstandings often arise, but panelists stressed the importance of seeking clarity rather than becoming defensive. Asking follow-up questions instead of assuming intentions allows for smoother dialogue. Page particularly emphasized that defensiveness could escalate situations unnecessarily, making audits more challenging for both parties. Approaching audits with openness and a willingness to learn ensures more productive outcomes.

A significant point that emerged was the value of emotional intelligence during audits. Emotions run high on both sides, and maintaining composure, especially during stressful moments, can make a huge difference. Panelists discussed how managing emotional dynamics and creating a calm, supportive environment can ease tensions. Emotional intelligence is critical on both sides to facilitate cooperation and collaboration, Kremer-van der Kamp stated.

One key piece of practical advice shared by the panel was ensuring the right people are in the room during audits. Too often, companies place managers who are not the process experts in front of inspectors, which leads to ineffective communication and delayed responses. Panelists agreed that it is essential to have subject matter experts (SMEs) present—those who are directly involved in the processes under inspection. Arencibia stated that having SMEs present ensures that auditors get accurate, insightful information that can help move the audit along more efficiently.

The concept of involving a technical translator during audits was also discussed. Experiences in the Asia-Pacific region suggest that having someone who can explain complex technical details in simpler terms to auditors—without losing accuracy—can be crucial. This person can bridge communication gaps, ensuring that both parties are on the same page.

Building trust between the US FDA and companies was another essential theme. The panel discussed how transparency is fundamental to this relationship. Auditors and companies need to trust one another, and this trust is built over time through open communication, honesty, and a clear willingness to improve. Keeping logbooks of document requests and questions is important on both sides for maintaining transparency and ensuring smooth progress throughout the audit, Page stated.

Another crucial topic that emerged was about team structure during audits. Successful audit teams typically involve two key players: a quality assurance lead, who oversees communication and manages the flow of information, and a runner, who logs document requests and questions. This combination ensures that audits are handled efficiently, and that no information is missed. The US FDA speakers said this kind of team structure can help train colleagues internally by demonstrating best practices for audit handling.

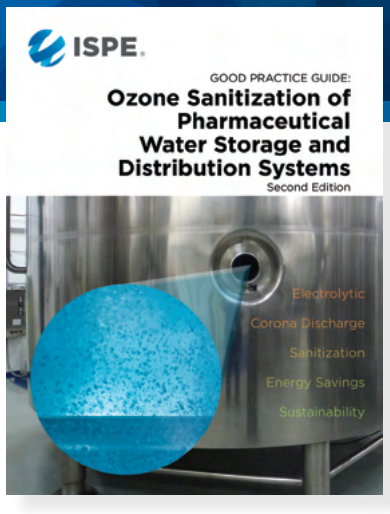
Panelists discussed the stress involved on both sides during audits, noting that emotions can easily escalate, especially when pressure is high. Emotional intelligence is vital, not only in navigating the stress of the situation, but also in creating an environment of mutual respect and understanding. Arencibia added that human interaction and empathy should always be part of the equation, emphasizing that both regulators and company representatives are under pressure and must work together to manage emotions constructively.

The panel wrapped up with a discussion about how companies can prepare for audits. Confidence comes from preparation, panelists agreed, and this confidence helps foster trust with regulators. Well-prepared teams project competence and readiness, which makes auditors feel reassured. Preparation is not just about technical readiness but about ensuring the right team members are involved, that everyone is briefed and confident, and that processes are well understood.

Miriam Kremer-van der Kamp is a Business Developer for VILS Switzerland GmbH. She is the Emerging Leader Liaison of the Women in Pharma International Steering Committee. She joined ISPE in 2022.

New Edition of Ozone Sanitization Good Practice Guide

By Marcy Sanford



The second edition of the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Storage and Distribution Systems* offers comprehensive guidance on designing and operating pharmaceutical water storage and distribution systems that utilize ozone for sanitization, outlining key principles for implementing an effective sanitization approach.

Ozone has been utilized for more than 100 years to sanitize municipal drinking water supplies, ensuring its potability and reducing organic content. It has also been used for more than 40 years in pharmaceutical water storage and distribution systems. In 2012, ISPE published the *ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Storage and Distribution Systems*.

Since then, the use of ozone in the pharmaceutical industry has significantly increased as the knowledge base regarding its use has expanded. The second edition of this ISPE Good Practice Guide provides comprehensive guidance on designing and operating pharmaceutical water storage and distribution systems that use ozone for sanitization, outlining key principles for implementing an effective sanitization approach.

The microbial content of water is important to product manufacturing, cleaning, and some laboratory activities in pharmaceutical and biopharmaceutical facilities. Systems that produce and distribute these waters must generally maintain continuous control to minimize microbial content, biofilm buildup, and endotoxins. Controlling microbial presence and proliferation in pharmaceutical water storage and distribution systems is typically achieved through heat, chemical sanitants, or ozone. This Guide focuses on the use of ozone as a sanitizing agent.

"Ozone initially faced resistance in the pharmaceutical industry because many did not know how to properly apply it," said Brian M. Hagopian, CPIP, President, Clear Water Consulting Inc. Hagopian is a chemist who served as a co-lead of the Guide. "During its initial use in the industry, companies may have introduced too much ozone and did not realize that being such an aggressive chemical, ozone not only eliminated bacteria (which is its intended purpose), but it also attacked elastomers, leading to leaks."

"Now the understanding of ozone has improved," he said. "Coupled with the widespread regulatory acceptance of membrane-based technologies to produce water for injection (WFI) grade water, the use of ozone as a sanitant is expected to increase across the industry in the future. During the industry review of this Guide, the authoring team received valuable comments and feedback, which was incorporated to make this Guide more comprehensive, well-rounded, and inclusive."

"The Guide discusses ozone-specific requirements, including associated advantages and disadvantages," said Philip E. Sumner, Jr., PE, Senior Manager, Pfizer Global Engineering. Sumner served as a co-author of the Guide. "It also guides the reader through system design, operation, and control. As with any system design, it is the responsibility of the owner and the design team to evaluate ozone's applicability, taking into consideration the design guidance provided in this Guide. Ozone sanitization has many benefits, including fewer and shorter interruptions to manufacturing due to water system sanitization, cost savings due to less energy use, and reduction in carbon footprint."

"An additional advantage of ozone as a sanitization method is its ability to reduce biofilm, which heat does not," said Rod Freeman, Associate Director, Quality Engineering, Kite Pharma, Inc. Freeman served as a co-lead on the development of the Guide."It can also provide a safer environment for workers by avoiding exposure to scalding pipes or clamps, and it offers an ambient temperature sanitization alternative that eliminates the need to heat the water up and cool it back down. The expert team of authors who worked on the Guide shared their knowledge and experience to help develop best practices that expand the use of ozone sanitization based on knowledge of its principles and benefits."

For more information about the *Ozone Sanitization of Pharm Water Storage & Distribution Systems Good Practice Guide*, visit ispe.org/publications/guidance-documents

Marcy Sanford, ISPE, Production Manager

VOLUNTEER
PROFILE

TRISH MELTON, PHD

GUIDANCE DOCUMENTS COMMITTEE IMMEDIATE PAST CHAIR

Trish Melton, PhD, has over 30 years of experience in the pharmaceutical industry, working in both manufacturing and service organizations. She is the Founder and Managing Director of MIME Solutions Ltd., a consultancy that has been providing support to the global pharmaceutical industry for 21 years in areas such as project, quality, and risk management, as well as in developing organizational strategies, such as corporate sustainability.

A member of ISPE since 1997, Melton led the team that wrote the *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry* and is mentoring the team working on a guidance document about sustainability. In addition to her volunteer work with ISPE, she currently serves as the Chair of the Institution of Chemical Engineers Sustainability Hub.

Melton holds a Doctor of Philosophy in chemistry, a Master of Business Administration, and a Master of Arts in Dance Education. Her research focus is on the development of tap dance teaching and learning and its link to music-making, somatic practices, and the history and culture of tap dance. She is currently a doctoral candidate in tap dance pedagogy at Coventry University in England and runs Tap Team Ireland, a tap dance team that competes in international competitions.

How did you become interested in working in the pharmaceutical industry?

My first degree was in chemical engineering. For my PhD, I began looking at applications of aerosols and how we can target where the aerosol goes, specifically for respiratory diseases, and that really piqued my interest. It made me realize how much science was connected to people and solving the problems they were facing. I decided I wanted to go into the pharmaceutical industry because there are always big problems to solve, and I wanted to be involved in solving them and was excited to do something that changes people's lives for the better.

What was your first job out of college?

I lectured for a few years, but my first job in the pharmaceutical industry was with Eli Lilly in Liverpool as a process/project engineer. It was real baptism of fire because I was working on the manufacturing side, but I was also helping develop the drug. So, I was doing manufacturing support, looking at the drug development, and looking at the quality implications of things we were scaling up. It was a drug that needed a lot of development, and I was there at the right time to be involved in many different aspects of the entire drug development process. I also started to get involved with how we document and send information to regulators for approval. I got my first taste of real cross-functional teams because I was working with quality professionals, regulatory professionals, scientists, engineers, and operators.

Tell me about your current role.

I get to do what I love: solve problems for a living. It's been exciting because I work for large and small pharmaceutical companies and their suppliers, looking at problems. Sometimes it is setting up a new project, sometimes it is looking at a tricky project, sometimes it is how we talk about this to our regulators. Because I have the quality and project management background and am an engineer, I can play a lot of different roles, whether it is running a Lean Six Sigma project or a new facility project, for example.

Now, in addition to process improvements, I'm also doing a lot of work with sustainability. That's become a big part of my role. Organizations are trying to determine how to incorporate sustainability into their strategy and daily operations; not just thinking about today, but also about tomorrow and next year.

How has your volunteer work with ISPE benefited you?

I think the most important volunteer position I've had has been chairing and being a member of the Guidance Documents Committee (GDC). In this committee, we look at what knowledge members need by examining industry best practices and current hot topics. We've got experts from across the industry who volunteer their time to say, "That's good. We need to look at that." I've written many guides, presented at conferences, and done a lot of different volunteer work for ISPE, but I think the most satisfying has been working with the GDC and Publications Department. It has been great to find a group of like-minded, curious people.

— Marcy Sanford, ISPE, Production Manager

VOLUNTEER
PROFILE

FERDINANDO E. ASPESI, PHD

PHARMACEUTICAL ENGINEERING® COMMITTEE CHAIR

Ferdinando E. Aspesi, PhD, is a Senior Partner at Bridge Associates International, LLC, New Jersey, USA, where he advises pharmaceutical companies on quality strategy, organizational design, and quality and compliance issues. In his more than 44 years of experience in the industry, Aspesi has worked in active pharmaceutical ingredient (API) and drug products quality assurance and quality control, pharmaceutical research and development, and analytical development.

Aspesi has held positions as Global Head of Quality for Aventis and Wyeth Pharmaceuticals and led the Wyeth Pharmaceuticals Global Regulatory Affairs Chemistry and Control organization. In addition to the United States, he has worked in South Africa, United Kingdom, Germany, France, and Italy. He has led up to 5,000 people and been part of executive management teams at Aventis, Wyeth, and Novartis.

He has been active in external industry initiatives for many years. He engaged with the US Food and Drug Administration (FDA) on process analytical technology (PAT) and the initiative "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach." He's been recognized by the US FDA as an industry leader for the implementation of PAT and manufacturing science approaches.

How did your career journey unfold?

I graduated from the University of Milan in Italy with a degree in organic chemistry. I stayed at the university as an assistant professor and was working on research about compounds or molecules to fight obesity. After four years there, I joined a pharmaceutical company that later, through three mergers and acquisitions, became Sanofi. My passion has been always to help provide new and proper treatments to patients.

What projects are you most proud of?

There are many projects I've worked on that I am proud of but a few that stand out include building a greenfield pharmaceutical manufacturing plant in South Africa, being part of the team that built a $2 billion plant in Frankfurt, Germany, to produce the first recombinant DNA human insulin, and, on the compliance side, one of the companies I worked for had a major issue with European health authorities. I led 500 people in 5 different countries to file 3,200 marketing authorization variations to bring 5 plants back to compliance.

I'm also proud of the mentoring I've done. Until recently, I worked with Dr. Tony Moreira with the University of Maryland, Baltimore County; Purdue University; and the University of California, Davis, to provide students with opportunities and new courses taught by industry experts to help prepare the students to join the pharmaceutical industry and navigate the work world.

What advice do you give students?

Some might find this advice shocking, but one thing I think is particularly important for emerging leaders to be, is to be humble enough to learn as much as possible, both about technical issues and people management. Continuing education and knowledge improvement is very important. You have to build your soft skills and be willing to challenge yourself or change when needed.

How do you benefit from volunteering with ISPE?

I serve as Chair of the *Pharmaceutical Engineering* Committee (PEC) where our goals are to ensure the committee has international representation and that major industry topics, especially from a manufacturing standpoint, are considered.

When you are in a certain position of responsibility, you need to have a basic understanding of the technical issues your company might face because you are going to make decisions that could impact the company at the level of billions of dollars. *Pharmaceutical Engineering*, for me, has always been a reference to understanding what else was going on in the pharmaceutical engineering industry. It gave me the chance to read articles that were pertinent to what I was doing, which helped me better understand certain issues. I have always seen the magazine as a positive tool for my job.

ISPE is a great place for networking and personal advancement. When emerging leaders ask, "How can I improve myself?" I tell them to become a member of ISPE. There, you'll find anything you want: more insights into your job, the industry, science, and technology as well as a great people network.

— Marcy Sanford, ISPE, Production Manager

ISPE FOUNDATION NEWS:

International Women's Day

In honor of International Women's Day, join the ISPE Foundation in supporting women students pursuing academic degrees in a STEM field.

By Isabella Stoup

As we celebrate the 114th anniversary of International Women's Day in March, the ISPE Foundation continues to champion women and underrepresented groups through Women in Pharma® (WIP). This initiative bridges gaps in the pharmaceutical industry, empowering professionals. Programs like Mentor ISPE have transformed careers by connecting students and recent graduates with experienced leaders.

One such student is Sarah Dubin, who is currently pursuing both a Doctor of Pharmacy (PharmD) and a Master of Science in regulatory affairs (MRA) at the University of Georgia's College of Pharmacy. Women in Pharma has supported her academic journey through the Women in Pharma Scholarship, which provides funding toward tuition costs associated with pursuing STEM degrees (science, technology, engineering, and mathematics).

Sarah Dubin, recipient of an ISPE Women in Pharma scholarship

The Women in Pharma Scholarship program is vital, as financial barriers are still a significant factor in why many choose not to pursue college degrees. Additionally, women and marginalized groups continue to be underrepresented in STEM-related careers, often due to social and economic barriers. This underrepresentation hinders the pharmaceutical industry's ability to build a talented workforce representative of our global population and their diverse needs.

"I am so grateful for the opportunity this scholarship has given me to continue my education," Dubin said after receiving the scholarship. "I plan on using the Women in Pharma Scholarship to fund my academic career throughout the summer months, where I'll continue my studies in regulatory affairs and work toward my Doctor of Pharmacy. I hope to gain a fellowship at the end of my academic journey, allowing me to further explore the many facets of the pharmaceutical industry."

By donating to support the Women in Pharma Scholarship program, you are not only advancing the careers of women and underrepresented groups in the pharmaceutical industry, but also contributing to the development of a healthier global community. Your support can make a significant difference in the lives of the recipients and the future patients their work will impact. Help us bridge the gap and create a more inclusive and innovative future.

In recognition of International Women's Day, donate today and empower the next generation of STEM leaders by visiting ispefoundation.org/donate

Isabella Stoup, ISPE Foundation, Senior Coordinator, Development

ISPE REGULATORY NEWS:

ISPE Drug Shortages Initiative

By Carol Winfield

The ISPE Drug Shortages Initiative team was invited to present an overview of ISPE's body of work in drug shortage prevention to the European Medicines Agency (EMA)'s Medicine Shortages Single Point of Contact (SPOC) Working Party at the October 2024 meeting in Amsterdam.

The presentation was delivered by Diane Hustead, Chair of the ISPE Drug Shortages Initiative. Hustead highlighted ISPE's global expertise and longstanding commitment to drug shortage prevention [1], publications, recent activities, and near-term priorities. She emphasized that the industry is in a transformational period for product-availability risk management, or shortage prevention planning, and that many global harmonization opportunities exist, as identified in the team's recent article, "Drug Shortages Global Convergence Opportunities," published in the September/October issue of *Pharmceutical Engineering* [2].

The SPOC Working Party is composed of single points of contact for medicines shortages from the national competent authorities of EU Member States responsible for human and veterinary medicines. The Working Party is responsible for monitoring events that could lead to public health emergencies impacting the supply of human medicines in the EU and reporting them to the EMA's Executive Steering Group on Shortages and Safety of Medicinal Products. Additionally, the Working Party drafts specific critical medicines lists for major events and public health emergencies, tracks demand and stock levels of these medicines, and reports shortages (along with potential alternatives) to the EMA.

QUALITY MANAGEMENT MATURITY INDUSTRY STUDY

ISPE is partnering with the University of St.Gallen, Switzerland, to conduct an industry study on International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) "ICH Harmonized Tripartite Guideline Q10: Pharmaceutical Quality System" maturity and quality practices, including culture. The study is based on the ISPE Advancing Pharmaceutical Quality™ (APQ) Program [3] with St.Gallen pre- and post-assessments.

ISPE's APQ program is an industry-led quality management maturity assessment and benchmarking initiative that offers a practical set of tools and systematic approaches to help organizations enhance the effectiveness of their pharmaceutical quality systems. The program is aligned with international initiatives that promote quality excellence, as well as with the US Food and Drug Administration (FDA)'s focus on quality management maturity and rating the maturity of manufacturing facilities. Study participants will receive individualized analytical reporting benchmarked against industry. For more information, or to enroll, contact matteo.bernasconi@unisg.ch

For more news on ISPE's regulatory activity, visit ispe.org/initiatives/regulatory/newsletter

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Carol Winfield, ISPE, Senior Director, Regulatory Operations

Meet the ISPE STAFF

ISABELLA STOUP

Hometown: Holiday, Florida

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Isabella Stoup, the ISPE Foundation, Senior Coordinator, Development.

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

My job is to raise funds for the ISPE Foundation's pillars. Day-to-day, I partner with internal and external stakeholders to write impact stories and blogs, apply for grants, generate proposals, and disseminate quarterly appeals to ISPE members. I also plan and manage the logistics of our events, such as the annual ISPE Foundation golf tournament.

What do you love about your job?

My favorite part of my job is the opportunity to invite others into the work we do to help those in underserved groups get access to ISPE resources. Each day, I know the work I do will benefit the career trajectories of students and recent graduates, support building equity in emerging markets, and bridge other gaps within the pharmaceutical industry. To be able to share about this exciting work and let others know how they can be a part of it is truly rewarding.

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

My favorite thing to do is spend time with my husband, our puppy, and our family and friends. I also enjoy running, reading, hiking, and surfing. I recently completed my first half marathon, and met my goal to read 20 books in 2024. One of my favorites was *The Great Alone*, a historical fiction novel by Kristin Hannah. It's set in the 1970s and tells the story of a family that moves to the wilderness in Alaska.

IDENTIFYING OUT-OF-TREND DATA in Stability Studies

By Prasanth Sambaraju

Drug stability data that deviate from an expected trend when compared to other stability batches or historical data collected during stability studies are considered out-of-trend (OOT) results. According to the US Food and Drug Administration's "Investigating Out-Of-Specification (OOS) Test Results for Pharmaceutical Production Guidance for Industry," OOT results should be limited and scientifically justified.

However, the US FDA guidance does not specify the process for identifying OOT results in stability data [3]. Different approaches have been historically used to identify OOT results, including:

- Three consecutive results are outside the prescribed limits
- The difference between consecutive results is outside of half the difference between the prior result and the specified limit
- The current result is outside ± 5% of the initial result
- The current result is outside ± 3% of the previous result
- The current result is outside ± 5% of the mean of all the previous results

These approaches are easy to understand and implement. They also do not require different limits for each time point. The major disadvantage of these approaches is that they lack statistical basis [4], which raises questions about the reliability of these approaches to clearly and precisely detect OOT.

METHODS FOR DETECTING OOT RESULTS

The following three methods are outlined and illustrated by the Pharmaceutical Research and Manufacturers of America (PhRMA) Chemistry, Manufacturing, and Control (CMC) Statistics and Stability Expert Teams for detecting OOT results [4, 5].

- Regression control chart method
- By-time-point method
- Slope control chart method

The first method is suitable for both comparisons within-batch and between-batch comparisons, whereas the second and the third methods are only suitable for comparisons with other batches.

Regression Control Chart Method

In the regression control chart method, data within a batch or data among batches are calculated. The control chart limits bracket the regression line along the length of the stability study. This method assumes that the data are normally and independently distributed with a constant variability across all time points, as shown in Figure 1. A common linear slope for all batches is also required for this method. For comparisons within a batch, a regression line is fit to the data for that batch.

For comparisons among batches, a regression line is fit to the historical data for the product, assuming a common slope but different intercepts for different batches. The fit obtained will provide an estimate of the intercepts, the slope, and the square root of the mean square error. A common slope estimate and standard error from the regression from historical batches can also be used. An estimate of the expected result at any given time point for a given batch is specified by the following equation:

$$\text{Expected result} = \text{intercept} + (\text{slope} \times \text{time})$$

The control limits at a given time point are given by the expected result ± ($k \times s$), where k is the multiplier obtained from normal quantiles at a desired level and s is the square root of the mean squared error from regression. These limits are also called Shewhart limits [5]. Stability data points outside the control limits at a given time point are considered OOT, and such data

Figure 1: Independent normal distributed hypothetical stability data with constant variance

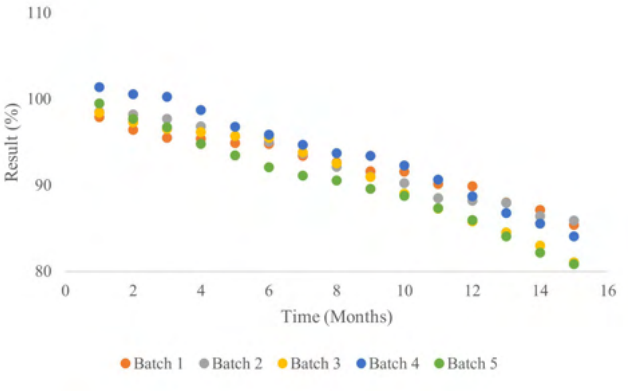


Figure 2: Regression control chart using hypothetical historical data with upper and lower control limits, regression line, and test data

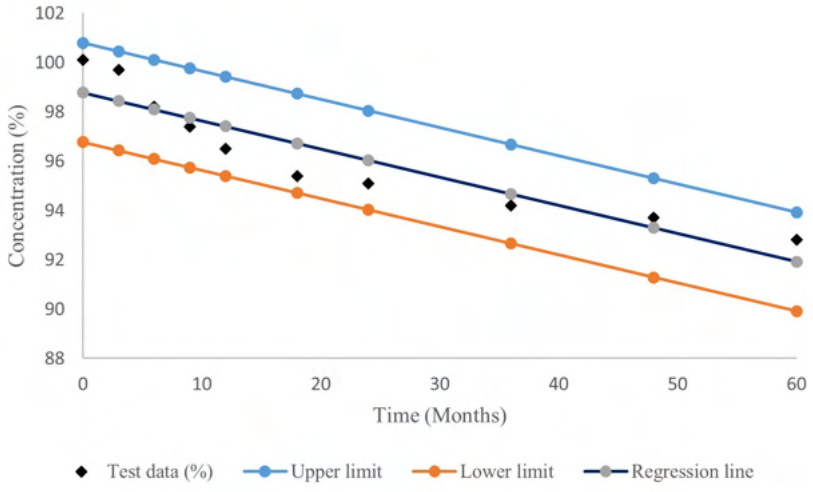
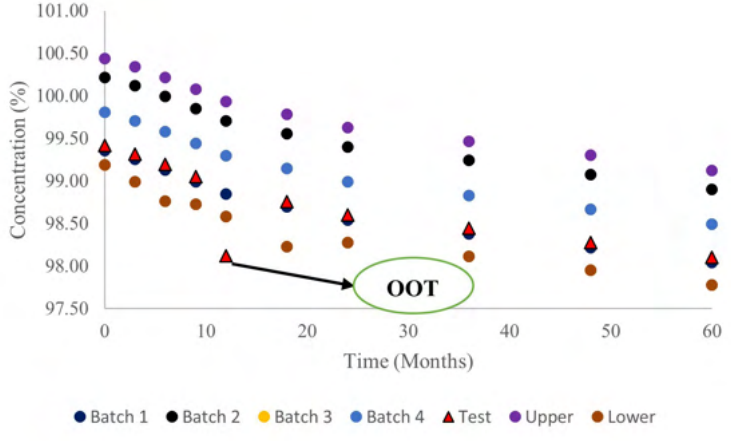


Figure 3: OOT trend across test batch by-time-point method using tolerance intervals (upper and lower) for each time point generated from historical batches data. Both test and historical batches are from simulated data.



points are investigated further [4]. A regression control chart for hypothetical historical data with upper and lower limits and test data is shown in Figure 2.

By-Time-Point Method

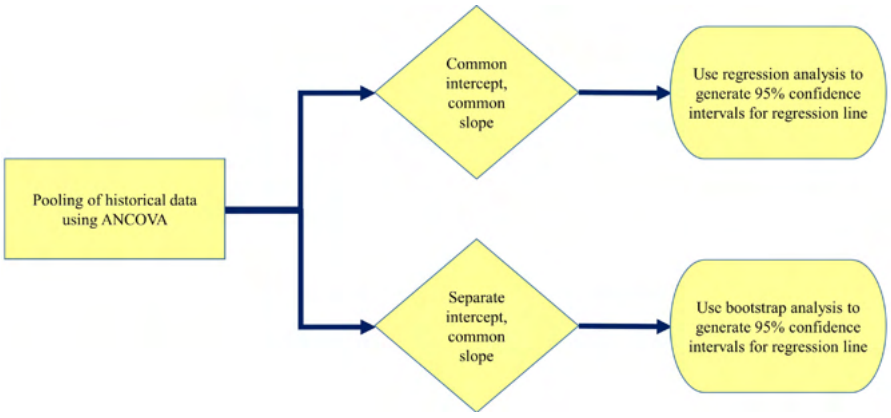
In this approach, data from historical batches are used to compute a tolerance interval for each stability time point. The tolerance interval can be based on the stability results or by using the difference from the initial stability result to minimize the effect of time zero differences among the tested batches. To calculate a tolerance interval, mean ($\bar{x}$) and standard deviation (s) for each time point are calculated.

The intervals are then calculated as $\bar{x} \pm ks$, where k is the multiplier value obtained from tables or approximation. The width of the interval depends on the number of historical batches and the levels of confidence and coverage desired, as shown in Figure 3. Data points outside these limits are considered OOT. The advantages of this method are that it requires no assumptions about the shape of degradation and it is used when different time points have variability [4].

Slope Control Chart Method

For each time point, a least squares regression fit is generated that includes all data up to that time point. The slope estimate for each batch is used to find the overall slope and control limits. As the slopes are normally distributed, OOT limits for the slopes at each time point are obtained from the tolerance interval ($\bar{x} \pm ks$), in which the value k is chosen to obtain the desired

Figure 4: OOT identification based on the proposed method



coverage. Further, $\bar{x}$ and s are the mean and standard deviation of the historical slope values [4].

The goal of this article is to create a new method to identify OOT based on the regression control chart method. In the first step, data from all the historical batches are tested for pooling using analysis of covariance (ANCOVA). If the historical batches can be pooled using the common intercept and common slope (CICS) model, then regression analysis of data from historical batches is performed and the 95% confidence intervals (CI) for the regression line are obtained. If any data points from the test batch fall outside the 95% CI limit, the data are considered OOT.

If the historical batches can be pooled using the separate intercept and common slope (SICS) model, bootstrap analysis is performed on the historical data to generate 95% CI for the regression line. If any data points from the test batch fall outside the 95% CI limit, they are examined as OOT. This method cannot be applied if the data from historical batches cannot be pooled: In this case, the separate intercept and separate slope (SISS) model would be used for ANCOVA analysis. The schematic outline of this method is shown in Figure 4.

The 95% CI, for the dependent variable (y_i) for a given independent variable (x_i), is given by the following equation [6]:

$$(mx_i + b) \pm t(\alpha, n-2) \times S_{yx} \times \sqrt{\frac{1}{n} + \frac{(x_i - \bar{x})^2}{\sum_{i=1}^{n}(x_i - \bar{x})^2}} \qquad [2]$$

Where m equals slope, b equals intercept, a equals significance level (0.05), n equals number of observations, and S_{yx} equals the standard error of the predicted y value for each x in the regression. It is a measure of the amount of error in the prediction of y for an individual x. This value can be obtained by STEYX function in Microsoft Excel [7].

ANCOVA

A covariate is a variable that is not the variable of research interest, but may affect the dependent variable and its relationship with the independent variable. The effect of a covariate variable is controlled by changing the variance of dependent variables. It is also controlled by the relationship between the dependent variable and the covariate at different levels of variables being analysed.

ANCOVA analysis is a statistical method that involves combination of analysis of variance (ANOVA) and regression analysis for adjusting the linear effect of covariate. The main advantage of using ANCOVA is its ability to uncover variance changes of the dependent variable due to change in the covariate and to discriminate it from the changes in variance due to changes in the levels of the qualitative variable. ANCOVA reduces errors in dependent variables and increases analytical power [8].

Materials and Methods

Data in Table 1 reported by Mihalovits and Sándor containing eight batches of historical data and the ninth batch as test data were used to demonstrate this approach [5]. The historical data were tested for pooling criteria using ANCOVA method in Microsoft Excel. Based on the model used for pooling historical data, 95% CIs for the regression line were obtained. Hypothetical data in Table 2 containing three historical batches and one test batch were used.

Data Pooling Using ANCOVA

The use of Microsoft Excel to test the equality of slopes and intercepts using ANCOVA for three batches was described by LeBlond [9]. When the number of test batches is greater than three, the test for equality of slope and intercepts using Microsoft Excel was described by Sambaraju [10]. In these tests, a significance level of 0.05 was used as the criterion for pooling. Based on ANCOVA analysis results, the SICS model was used to pool the data from historical batches.

Bootstrap Method

The bootstrap method was employed to generate 95% CIs for the regression line. The bootstrap method was introduced by Efron in 1979 to assess the statistical accuracy of the estimator [1]. It is

Figure 5: Bootstrap method illustration

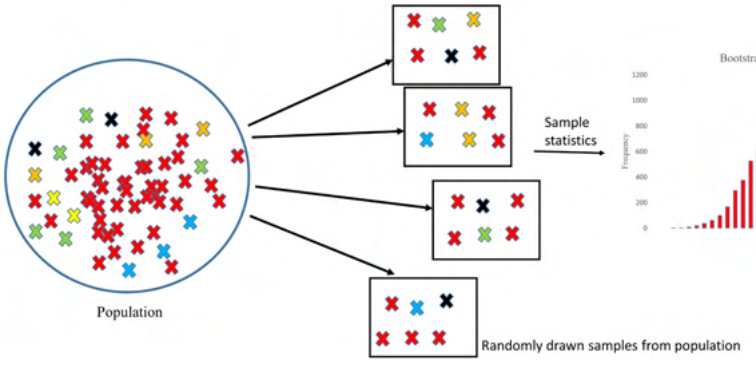
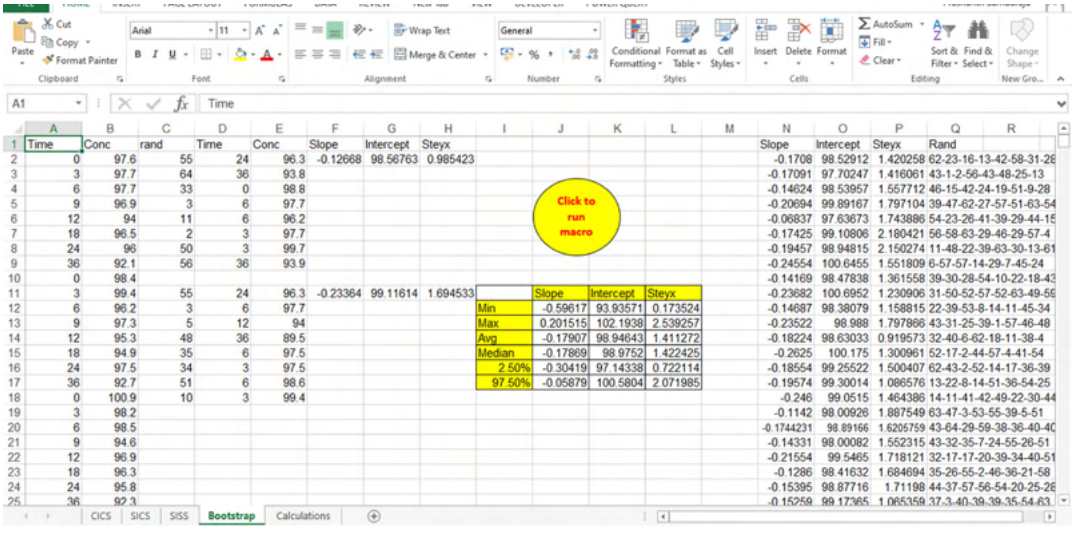


Figure 6: Results of summary statistics from bootstrap samples



Identifying OOT in stability studies is a challenge in the pharmaceutical industry. The historical methods used to identify OOT are not sensitive enough to identify a true OOT or may have high false-positive OOT results.

a computer-based resampling technique that uses new samples with repetition from original sample data to estimate the relevant properties of the population.

The main advantage of this technique is its simplicity, reliability, and ability to check the stability of results [12]. Figure 5 shows an illustration of the bootstrap method. The Visual Basic for Application (VBA) code to generate bootstrap samples in Microsoft Excel is included in Table 3. The CICS model was used based on the results obtained for pooling of historical data in Table 2 using the ANCOVA method in Microsoft Excel.

Results and Discussion

The results of summary statistics from bootstrap samples are shown in Figure 6. The 95% CIs for regression were generated using equation 2 and are shown in Figure 7. After the test data (ninth batch) were overlaid on this plot, data points that are outside the 95% CIs are considered as OOT. In this case, the 18-month time point data are considered as OOT. The results reported by Mihalovits and Sándor concluded that data from time points 9 to 36 months are OOT using Shewhart limits and data from the 18-month time point are OOT according to prediction limits and confidence limits. No data are OOT as per the tolerance limits method [5].

Figure 7: Upper and lower 95% confidence intervals for historical data overlaid with test data

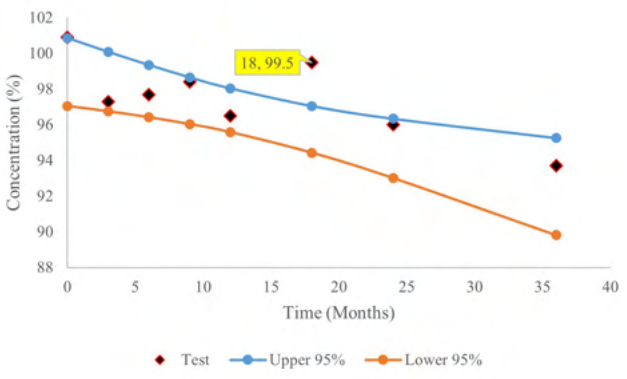
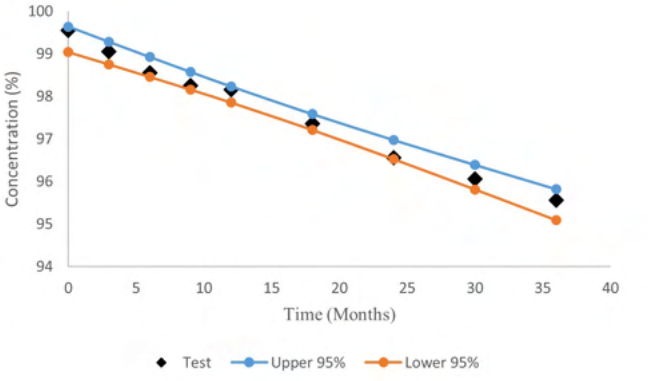


Figure 8: Upper and lower 95% confidence for hypothetical data overlaid with test data



In case of hypothetical data, it can be observed that the test data points are within the 95% CIs, as shown in Figure 8. No test data point was considered as OOT. The Excel formula used in these calculations is shown in Figure 9.

CONCLUSION

Identifying OOT in stability studies is a challenge in the pharmaceutical industry. The historical methods used to identify OOT are not sensitive enough to identify a true OOT or may have high false-positive OOT results. The modified regression control chart method provides another statistically rigorous alternative approach that is not too complex and has limits that are not too narrow, unlike Shewhart limits.

This method can mitigate the incorrect use of tolerance intervals, which would widen the acceptance interval. This article provides a method for identifying OOT using Microsoft Excel with modest programming skills (see Figure 9A and 9B). This study also highlights the necessity of regulatory guidelines for identification of OOT results while performing stability data studies to enable a harmonized way of OOT identification.

Figure 9A: Excel formulas used in random sampling and summary statistics calculations

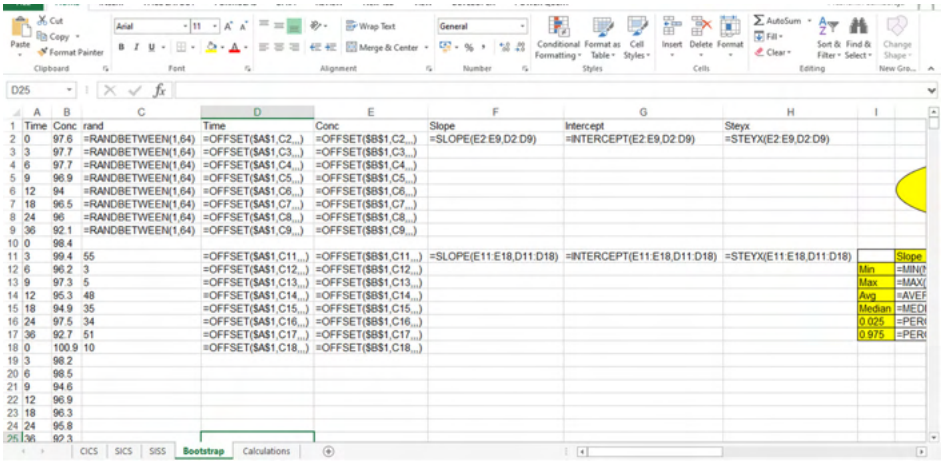


Figure 9B: Summary statistics of slope, intercept, and Steyx using Excel formulas after random sampling

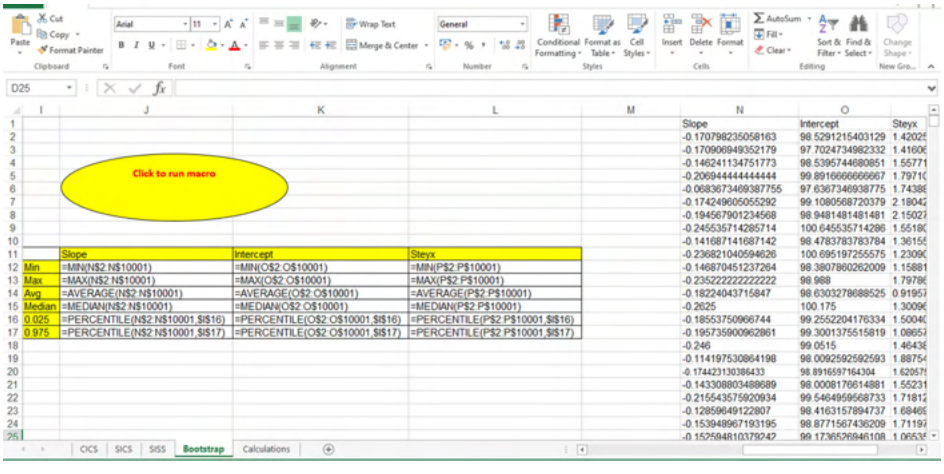


Table 1: Historical stability data (Batches 1 to 8) and test data (Batch 9)

Time (month)	Active drug (%)								
	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9
0	97.6	98.4	100.9	98.7	98.8	100.5	100.3	101.5	100.9
3	97.7	99.4	98.2	95.8	97.5	96.5	99.7	100.1	97.3
6	97.7	96.2	98.5	96.7	97.5	96	98.6	99.5	97.7
9	96.9	97.3	94.6	97.5	98.9	96.3	98.3	99.6	98.4
12	94	95.3	96.9	94.7	97.5	98.3	96.8	98.3	96.5
18	96.5	94.9	96.3	93.7	96.5	94.1	96.7	95.2	99.5
24	96	97.5	95.8	93.1	96	92.5	96.3	97.1	96
36	92.1	92.7	92.3	91.3	92	89.5	93.9	93.8	93.7

Table 2: Hypothetical historical data (batches 1 to 3) and test data

Time (Months)	Batch 1 (Conc %)	Batch 2 (Conc %)	Batch 3 (Conc %)	Test (Conc %)
0	99.80	99.64	99.61	99.55
3	99.30	99.14	99.11	99.05
6	98.80	98.64	98.61	98.55
9	98.30	98.14	98.11	98.05
12	97.80	97.64	97.61	97.55
18	97.30	97.14	97.11	97.05
24	96.80	96.64	96.61	96.55
30	96.30	96.14	96.11	96.05
36	95.80	95.64	95.61	95.55

Table 3: Excel visual basic code to generate bootstrap resamples

```
Option Explicit
Sub bootstrap()
Dim i As Long
Application.ScreenUpdating = False
Application.Calculation = xlCalculationManual
On Error Resume Next
' In case if cells in Range("N2", Range("N2").End(xlDown).End(xlToRight)) are empty
Range("N2", Range("N2").End(xlDown).End(xlToRight)).ClearContents
' To clear previous bootstrap resamples
For i = 1 To 10000
Application.StatusBar = "Processing " & i & " of 10000"
Application.Calculate
Range("F2:H2").Copy
Range("N" & Rows.Count).End(xlUp).Offset(1, 0).PasteSpecial (xlPasteValues)
Range("Q" & Rows.Count).End(xlUp).Offset(1, 0).Value = Range("c2").Value & "-" & Range("c3").Value
& "-" & _
        Range("c4").Value & "-" & Range("c5").Value & "-" & _
        Range("c6").Value & "-" & Range("c7").Value & "-" & Range("c8").Value & "-" &
Range("c9").Value
'Trace slope, intercept & STEYX values in case if there is any error
Next i
Application.ScreenUpdating = True
Application.Calculation = xlCalculationAutomatic
End Sub
```

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USING ISOLATORS AND BIO-DECONTAMINATION

to Future-Proof CGT Processes and Facilities

By Donald Singer, David Root, and Chris Berridge`

The production of Advanced Therapy Medicinal Products (ATMPs) can have many complex manual steps, which necessitates meticulous aseptic processing conditions to ensure the product is sterile, which is critical for patient safety. Closed isolator systems provide a consistent, compliant, and cost-effective solution, and can play a critical role in ensuring the safety of ATMPs.

To further the understanding of biopharmaceutical or human cell therapy process development to include improvements of advanced, automated technologies and digital monitoring (e.g., Pharma 4.0™), the following objectives should serve as constant criteria: patient safety, access to therapies, scalability, speed of production, and compliance with current GMPs (GMPs). To meet these criteria, a steady and repeatable strategy is essential.

To reduce the risk of contamination, the industry needs to work toward the following:

- Closed process design
- Thorough understanding of where human operators interact with the process
- Reduction of human operator interaction in critical areas of the process
- A contamination control strategy that encompasses process, equipment, people, and facilities with risk-mitigating approaches

Expertise and risk assessment can set a foundation for evaluating and making ongoing improvements to ensure patient, product, and business risks are mitigated. The following discussion will offer options for approaches to contamination control using technology, expertise, and a culture of quality improvement. These options have historical experience in successfully handling biopharmaceutical and cell therapy materials.

RETHINKING PHASE APPROPRIATE COMPLIANCE

Current Guidance

For this industry, current GMPs are constantly under scrutiny to stay up-to-date with new technology. Some guidance and GMPs have global impact. Specifically:

- *Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S): Annex 2A, Manufacture of Advanced Therapy Medicinal Products for Human Use to Guide for Good Manufacturing Practice for Medicinal Products* [1]
- The European Commission:
  - EudraLex, Volume 4: *Good Manufacturing Practice (GMP) guidelines. Part IV: Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products* [2]
  - EudraLex Volume 4: *EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.* Annex 1: Manufacture of Sterile Medicinal Products [3]
  - EudraLex Volume 4: *EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.* Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use[4]
- The US Food and Drug Administration:
  - *Sterile Drugs Produced by Aseptic Processing – Current Good Manufacturing Practice: Guidance for Industry* [5]
  - *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products* [6]
- *International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, ICH Harmonized Guideline.* Q9 (R1): Quality Risk Management [7] (this has become the reference approach for quality risk management justification)
- Other regional guidance has its own versions of the latter regulatory perspectives.

From a microbiological perspective, contamination control spans from small-scale manufacturing for clinical trials to larger-scale approved commercial manufacturing. Compliance with GMPs and a contamination control strategy are essential at all phases.

Sterility Assurance and Contamination Control

Aseptic manufacturing has always been a highly scrutinized process. In some cases, the lack of a product sterilization step (e.g., in cell therapy because cells are too large to pass through a sterile filter) has led to high-risk concern for assuring proper, robust processes and procedural design for contamination control. The common sources of contamination in aseptic manufacturing are people, materials and equipment, and the environment. The risk assessment approach can map the potential origins of microbial contamination, determine the level of risk to mitigate, and holistically examine the integration of process steps, along with the design of equipment and cleanroom space, to decide how to mitigate the risks.

From a microbiological perspective, contamination control spans from small-scale manufacturing for clinical trials to larger-scale approved commercial manufacturing. Compliance with GMPs and a contamination control strategy are essential at all phases. Appropriate microbiological validation (qualification) is a fundamental requirement, in contrast to other types of validation development, to ensure no harm to the patient. The earlier an automated system can be included in process development, the less validation and change management will be required during scale up to commercial approval.

Design of a process and the cleanroom space surrounding it becomes a significant factor to sterility assurance. Closed systems, robust material transfer, and separation of operators from product within classified areas are design parameters to consider. Complexity of design can lead to higher costs. Considerations for the latter will influence the cost of goods in the long run (i.e., from clinical manufacturing to commercial-scale manufacturing). Leading industry organizations, such as ISPE, have encouraged manufacturers to view isolators as an appropriate new containment design consideration for aseptic processes (including sterility testing) that could replace the use of open biological safety cabinets and laminar air hoods, where possible.

A balance between manual processing and automated processing is possible with currently available technology. The intended design improvements can eventually lead industry to fully automated processing. Although autologous processes are currently a combination of manual and automated (using closed instrument systems with one or more steps), scientists are attempting to develop allogeneic processes in platform approaches for consistency of the larger-scale volumes. Depending on the location of manufacturing (e.g., offsite or bedside for autologous) and volume of therapy batch (as for allogeneic), designing a fully closed system that can maintain aseptic control is a primary consideration. Progression from clinical to commercial should consider ways to minimize changes in design and maintain consistency in contamination control.

It is important and valuable to consider options for a critical process, such as cleaning and bio-decontamination, because your choice will influence both contamination control and the cost of goods. Cleaning and bio-decontamination is more than just a routine program. These processes consist of selecting effective, compatible, and regulatory compliant cleaning and disinfecting agents, proper and relevant application of the chemical agents, and application at an appropriate frequency to meet efficacy and contamination control requirements. Manual cleaning and disinfection have inherent variability, which should be supplemented by more consistent, validated approaches, where possible. This is where options for improvement by automation using hydrogen peroxide vapor should be a strong consideration, for equipment, process, and cleanroom spaces.

ISOLATOR ADVANTAGES FOR CLOSED SYSTEMS

The production of ATMPs can have many complex manual steps, which necessitates meticulous aseptic processing conditions to ensure patient safety and product efficacy. Although traditional open systems like laminar flow hoods (LFHs) and biosafety cabinets (BSCs) have found widespread application due to their low cost and ease of use, these systems possess inherent limitations. The advantages of closed isolator systems as a compelling alternative for ATMP manufacturing are emphasized by their ability to enhance contamination control and streamline production processes.

OPEN SYSTEMS LIMITATIONS

Open systems, although effective to a certain extent, rely on rigorous operator aseptic techniques and stringent cleanroom maintenance for contamination control. This translates to increased operational costs due to multiple layers of operator gowning, energy consumption from the heating, ventilation, and air conditioning systems, additional environmental monitoring, and frequent cleanroom decontamination cycles. In addition, the inherent openness of these systems necessitates constant

vigilance to prevent airborne contaminants from compromising product sterility.

CLOSED ISOLATOR SYSTEMS: A PARADIGM SHIFT

Isolator systems offer a transformative approach to ATMP manufacturing. They function as self-contained units, physically separating the critical processing zone from the operator environment. This physical barrier significantly reduces the risk of contamination from human intervention. In fact, one particular study from an autologous cell therapy manufacturer that was using both LFHs and isolators to produce their product found that the batch failure rate in the LFH was 10%, whereas in the isolator it was only 3% [9]. Furthermore, isolators utilize a cascaded pressure differential system similar to cleanroom design principles, as well as unidirectional airflow over the product/process. This creates a controlled aseptic zone within the isolator, minimizing the influence of external contaminants.

Isolators can be hosted in a lower-grade cleanroom than an open LFH or BSC. This is evidenced by EU GMP Annex 1, which states in section 4.4 that grade B is required as the background cleanroom for grade A (where it is not an isolator), i.e., an LFH or BSC, and that grade C and D is the background for isolators [3]. Downgrading from a grade B to grade C/D cleanroom results in substantial cost savings from reduced gowning, environmental monitoring, cleaning and disinfection, and energy consumption. In fact, one study which investigated the running costs between different cleanroom grades found that grade C/D cleanrooms resulted in 30% lower running costs than grade B cleanrooms [10].

ENHANCING ASEPTIC PROCESSING WITH INTEGRATED TECHNOLOGIES

Modern isolator systems are equipped with advanced features that bolster aseptic processing. This includes being integrated with hydrogen peroxide vapor (H_2O_2) bio-decontamination technology. This automated process demonstrably achieves a 6-log sporicidal reduction in bioburden on the isolator chamber surfaces as well as the surfaces of incoming materials, ensuring a high degree of microbial inactivation prior to product introduction.

The bio-decontamination process consists of four distinct steps:

- Conditioning: The hydrogen peroxide vaporizer heats up to the necessary operating temperature for effective vaporization, and the instruments being decontaminated warm up and stabilize ensuring they are ready for the next steps.
- Gassing: Hydrogen peroxide liquid is vaporized and dispersed throughout the chamber. The vapor reaches the dew point and micro-condensation forms on surfaces.
- Dwell: The hydrogen peroxide vapor is either maintained at a constant level or the vapor is distributed without additional vapor.
- Aeration: The hydrogen peroxide vapor is catalytically converted into water vapor and oxygen.

The bio-decontamination process outlined previously is typically validated with *Geobacillus stearothermophilus* biological indicators (BIs), which are placed at strategic challenge locations within the isolator (i.e., corners, equipment, hot/cold locations, and filter faces). Furthermore, calibrated chemical indicators can be used to verify cycle performance on an ongoing basis.

In the ATMP sector, not all incoming materials can undergo hydrogen peroxide vapor bio-decontamination. Due to its small molecule size hydrogen peroxide can permeate through some bags. This is generally a consideration for any living material such as the cells being processed because they can be damaged or even killed by the hydrogen peroxide. For such sensitive living materials, alternative methods may need to be explored to transfer them into the isolator. This topic will be explored later in the article.

Additionally, isolator systems can be seamlessly integrated with other technologies, such as environmental monitoring (EM) equipment, audit trail software to support compliance with 21 CFR Part 11 [8], and glove integrity test equipment to further provide peace of mind on the operations conducted within. EM typically consists of two components. The first is an integrated viable air sampler that draws a validated volume of air from the isolator over an agar plate to collect any airborne microorganisms that may be present. The second is a continuous particle monitoring system, which has three main elements: an air feed from the isolator chamber via an isokinetic cone, a particle counter through which the extracted air is passed, and a computer to log the particle counter operation and results.

When combined with standard operating procedures, the comprehensive approach of using isolators for aseptic processing provides a robust framework for maintaining aseptic conditions throughout the ATMP manufacturing process.

STREAMLINING WORKFLOWS WITHIN A CLOSED SYSTEM

While ATMP processing within an isolator will vary depending on the application, a typical workflow generally involves a multi-stage decontamination process. Initially, the entire isolator system undergoes a bio-decontamination cycle with no materials inside. This "system empty cycle" targets the chamber surfaces and achieves a validated 6-log bio-decontamination. This cycle focuses on high-frequency touchpoints like gloves, sleeves, chamber floors, and racking, minimizing potential contamination sources.

Following the system bio-decontamination, necessary tools and materials are transferred into the isolator via a designated transfer chamber. These tools and materials then undergo a dedicated rapid bio-decontamination cycle tailored to the specific material loading being introduced. This may encompass flasks, pipettes, agar plates, and other process-specific items. These items should be hung on racking to maximize exposure to the hydrogen peroxide vapor.

Finally, after both the isolator and incoming materials have been bio-decontaminated, the living/cellular material is introduced into the chamber via an alternative material transfer method to avoid any exposure to hydrogen peroxide vapor, which could adversely impact it. Depending on the process, this may involve rapid transfer ports, liquid transfer ports, or manual transfer via a dedicated airlock and manual disinfection of the outer surfaces.

Figure 1: Typical isolator decontamination workflow

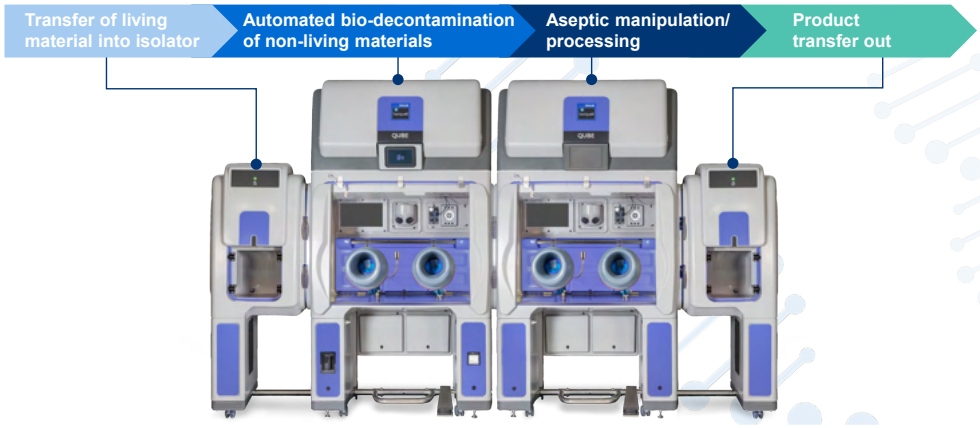

Figure 2: Demonstration of the ingress testing method developed by Ecolab

(©Ecolab)

The use of these transfer mechanisms minimizes operator intervention and the associated risk of contamination. All materials will be transferred into a working chamber where the aseptic process will be conducted, and an additional airlock can be used to allow egress of materials without losing the aseptic conditions within the working chamber. The diagram in Figure 1 outlines the typical workflow described.

ADDRESSING POTENTIAL CONCERNS

Although the advantages of isolator systems are clear, some initial hesitation regarding their implementation is understandable. Cost is a common concern. However, advancements in isolator technology have made them more budget-friendly and the initial cost can be offset by the reduced running costs that are delivered by operating a lower-grade cleanroom.

Additionally, some isolators are designed for easy integration into existing spaces without room modifications and can be configured to fit the space constraints that may have previously prevented their use. Isolator manufacturer's validation engineers can validate isolators in days instead of weeks, speeding up system use and reducing the burden on site staff. A potential concern is working through glove ports. But as technology evolves, glove systems become more lightweight and easier to work with.

Another concern, which was already outlined, is the robust transfer of living materials (cells) into isolators using a method that will not damage the cells or bring contamination into the

aseptic environment. Before exploring other transfer methods, it's necessary to first establish whether the ideal method of bio-decontaminating with hydrogen peroxide vapor risks penetrating the container housing living materials and damaging them. This can be determined by performing ingress testing. The process involves running de-ionized water through the entire procedure to be performed in the isolator, in place of the drug product, and then measuring the levels of hydrogen peroxide (if any) in the de-ionized water.

Using a horseradish peroxidase (HRP)-based assay, levels in the water as low as 15 parts per billion (ppb) can be detected. If no hydrogen peroxide is detected at these low levels, it provides evidence that there is no ingress of hydrogen peroxide during the bio-decontamination process. Thus, the living material is highly unlikely to be detrimentally affected. Ingress testing should be performed using the same load and preferably the same isolator system in which the aseptic process is taking place to accurately simulate the process.

If testing reveals significant ingress into the container housing the living materials, alternative material transfer methods should be used to minimize contamination risk in the aseptic environment and reduce the risk of damage to the living material.

CONCLUSION

Closed isolator systems represent a future-proof strategy for ATMP manufacturers seeking to enhance contamination control and streamline aseptic production processes. By offering a consistent, compliant, and cost-effective solution, isolators can play a critical role in ensuring the safety and efficacy of ATMPs. This will help pave the way for advancements in this rapidly evolving field.

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THE POWER OF FLEET MANAGEMENT in Distributed Manufacturing

By Maria Amaya, PhD, Ryan Farley, Toby Groathouse, Joe Jerkins, Line Lundsberg-Nielsen, PhD, Jacob Holst Madsen, Richard Panton, Christian Siegmund, PhD, and Inger Soerensen

The pharmaceutical industry faces significant challenges in rapidly expanding production capacity to meet the needs of patients. Traditional centralized manufacturing models are increasingly seen as inflexible and slow to adapt to the dynamic demands of modern healthcare. This article proposes a regulatory framework for distributed manufacturing using the concept of fleet management to address these challenges.

Fleet management involves creating a network of standardized manufacturing units or equipment that can be efficiently managed and replicated across one or multiple sites. This approach draws inspiration from the principles of standardization that revolutionized other industries, such as automotive manufacturing.

The proposed approach offers significant benefits, including improved regulatory efficiency, reduced drug shortages, and enhanced environmental sustainability. This approach calls for collaboration between regulators and industry stakeholders to refine and implement this innovative framework, which will pave the way for a more resilient and responsive pharmaceutical manufacturing ecosystem.

CHALLENGES

Pharmaceutical companies often encounter significant challenges when investing in processing equipment due to the industry's stringent standards and need for customized production solutions. Collaboration with technology vendors frequently leads to the creation of bespoke systems designed to meet company-specific requirements. Although these tailored systems provide short-term benefits, they also introduce long-term complexities. Each system evolves uniquely through multiple iterations and adaptations to different production environments, resulting in diverse configurations that carry distinct risks, especially with respect to supply chain design and technology transfer. These specialized failure modes demand expert knowledge to manage, adding layers of complexity to the equipment's life cycle. Furthermore, the lack of standardization in these systems presents significant challenges for the manufacturers and the regulators, who must invest additional time to assess each solution. This variability complicates production transfer between sites, raising operational costs and slowing down manufacturing processes. As the pharmaceutical industry progresses, there is a growing recognition of the need to move beyond traditional manufacturing approaches. The currently well-established centralized production model nonetheless has certain barriers that can lead to longer lead times, increased transportation costs, and supply chain vulnerabilities.

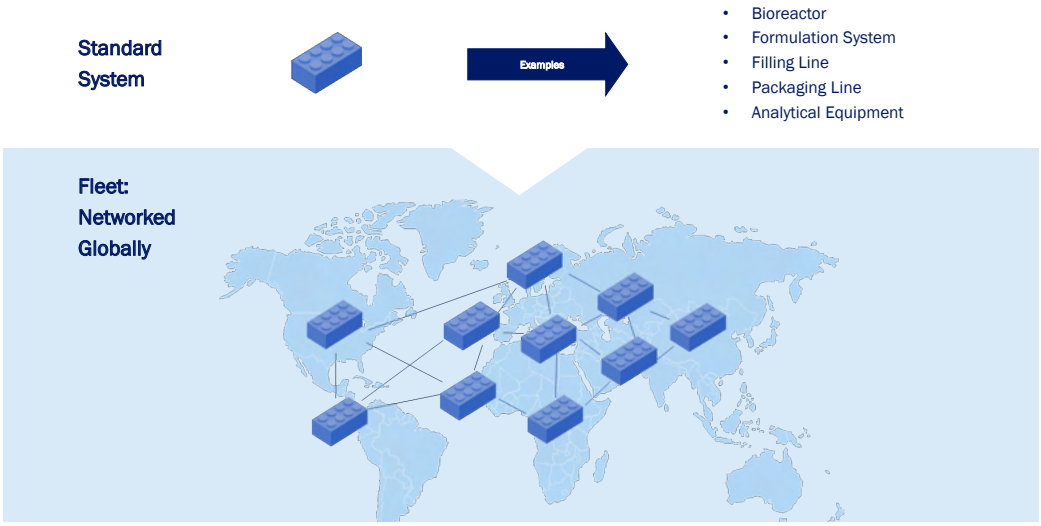
To address these challenges, the pharmaceutical industry is increasingly shifting toward a more agile manufacturing framework that combines the efficiency of large-scale production with the adaptability of smaller, distributed facilities. Regulatory agencies, including the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), are actively creating guidelines to facilitate this transition, labeling it as decentralized manufacturing (EMA) [1] or distributed manufacturing (FDA) [2–3]. In this article, we will refer to it as "DM."

FLEET

Central to this evolution is the concept of "fleet," a DM operative model that represents a transformative approach to pharmaceutical production. Fleet is founded on the principles of standardization that gained prominence during the Industrial Revolution, emphasizing the creation of uniform systems that can be efficiently replicated and managed across multiple sites. This approach draws parallels with the automotive industry's journey, where innovators like Ford revolutionized manufacturing through standardized processes that drastically reduced costs, enhanced quality, and facilitated knowledge sharing [4].

In the pharmaceutical field, similar advantages have been noted in technologies like fermentation units, freeze dryers, and autoclaves, where uniform design and operation have improved efficiency and minimized complexity. Fleet aims to push these principles further, advocating for a standardized methodology that transcends site-specific differences. This will help foster consistency and uniformity across all production facilities.

Figure 1: Fleet concept, founded on the principles of standardization



Implementing the fleet concept, illustrated in Figure 1, involves establishing rigorous controls and standardized procedures to ensure system equivalence across locations and throughout the life cycle. A key aspect is a central quality system within a network of sites to maintain product quality and regulatory compliance through standardized protocols (e.g., qualification/validation, calibration, maintenance). Developing a comprehensive oversight framework is essential for managing the entire life cycle of the fleet, including procurement, operation, and decommissioning.

This framework should encompass detailed documentation, regular audits, and continuous training for personnel. By integrating risk management strategies and leveraging real-time data analytics, organizations can proactively address potential issues. Fostering collaboration among stakeholders enhances communication and promotes best practices, ultimately leading to improved operational efficiency, reduced variability, and consistent delivery of high-quality products in the pharmaceutical industry.

This article outlines the core elements of the fleet approach. It focuses on its organizational structure, its key components, and the strategic benefits of efficient fleet management within the DM framework. Through an exploration of DM's fundamental principles, we demonstrate how the fleet can boost production efficiency, mitigate drug shortages, and drive innovation within the pharmaceutical sector.

The primary definitions are summarized in Table 1. We aim to offer a thorough understanding of DM's potential to revolutionize pharmaceutical manufacturing, ensuring adherence to regulatory standards while maintaining exceptional product quality. Additionally, it proposes a progressive regulatory framework that emphasizes current GMP (cGMP) compliance, safety, and traceability, highlighting the need for adaptable regulatory strategies to meet the dynamic demands of modern manufacturing.

Table 1: Primary definitions

Term	Definition
Centralized Pharmaceutical Quality System (PQS)	A PQS that employs a grouping strategy or family approach to the specification, design, procurement, qualification, operation, equivalency, and life cycle management of the systems and equipment.
Equivalency	State in which manufacturing systems remain identical in critical aspects (e.g., specification, design, function, operation, and qualification approach) required for cGMP manufacturing execution.
Equivalent Manufacturing Systems	Manufacturing systems are defined as equivalent if they are identical in critical aspects (e.g., specification, design, function, operation and qualification approach) required for cGMP manufacturing execution to deliver robust process performance and consistent product quality over the life cycle.
Fleet	Group of equivalent systems that are constructed and installed to the same specifications across multiple manufacturing facilities across different locations, networked and operated by a central PQS.

BACKGROUND

The Regulatory Landscape and Its Challenges

Existing pharmaceutical regulatory standards are designed to ensure the safety, efficacy, and quality of medicinal products, established

by various international regulatory bodies such as the US FDA and EMA. These standards encompass comprehensive guidelines that cover the entire life cycle of a pharmaceutical product, from research and development to manufacturing, marketing, and post-market surveillance.

Key components include cGMP, which enforces strict controls on production processes to maintain consistency and compliance with quality specifications. Additionally, the frameworks prioritize thorough clinical trials and rigorous approval processes to ensure that new drugs are safe and effective for their intended use. However, these regulations are primarily tailored to traditional manufacturing models, which can pose challenges when applied to the complexities of DM networks that aim to reach more patients efficiently.

Under the current regulatory framework, pharmaceutical manufacturers face stringent requirements when expanding or establishing new locations within a production fleet. This includes demonstrating bioequivalence, generating analytical comparability data, and validating methods and processes for each site. However, when manufacturing units can be proven equivalent in design, qualification, and operation, the necessity for duplicating extensive data for every new site may be reevaluated, as equivalency of the fleet members minimizes risks to drug product quality.

A significant limitation in the current system is the lack of a clear regulatory pathway for submitting and approving DM networks. Despite having a central PQS, existing guidelines [5] tend to treat each site and product as unique, without a defined framework for managing quality control and validating processes across multiple locations. This gap highlights the urgent need for updated regulatory guidance that outlines submission categories, strategies, and documentation requirements specific to DM. This is because the absence of such updates complicates ensuring the safety, efficacy, and quality of products manufactured through distributed systems.

The industry and health authority responses to the COVID-19 pandemic showcased the potential for innovative thinking and operational changes beyond traditional pharmaceutical models. During the pandemic, industry supply chains largely met their goals, and governments demonstrated a willingness to intervene to ensure the security of pharmaceutical supplies. These actions exemplify how regulators and industry collaborated to quickly enhance manufacturing capacity and effectively distribute medicinal products to the public. Drawing on these experiences, there is an opportunity to work jointly with health authorities to develop a DM regulatory framework that prioritizes global access of medicines and patient needs.

DM in the Pharmaceutical Industry

There is a growing trend toward the localization of supply chains and a push for regional or national self-reliance. This shift is driven by several factors, including changes in the globalization model, the diminishing relevance of global trade agreements, and an increased emphasis on sustainability—all elements that can affect industry supply chains. As a result, unpredictable shocks in the future are likely to reinforce the trend toward supply chain flexibility, and to develop faster product transfers to achieve higher adaptability and product availability.

Portfolio trends are driving significant shifts in the traditional pharmaceutical model, with one of the key factors being the rise in competition. As patents on existing drugs expire, biopharmaceutical companies increasingly focus on boosting manufacturing efficiency to reduce costs. With each new medicine aiming to surpass its predecessors, the emphasis on high-quality production processes continues to grow.

Furthermore, the increasing prevalence of complex biologics requires specialized approaches to manufacturing, storage, and handling, necessitating a precisely managed supply chain. In this context, achieving manufacturing excellence through innovation is essential to ensure adaptability, uphold quality standards, and meet cost-efficiency goals in response to these changing dynamics.

Challenges Establishing a Regulatory Framework for DM

Developing a regulatory framework for DM poses significant challenges in maintaining product quality and patient safety across multiple sites. A key issue is ensuring system equivalence when different manufacturing locations have varying processes and environmental conditions. To address this, robust criteria and advanced technologies like real-time monitoring and data analytics are recommended to standardize quality metrics and quickly identify deviations.

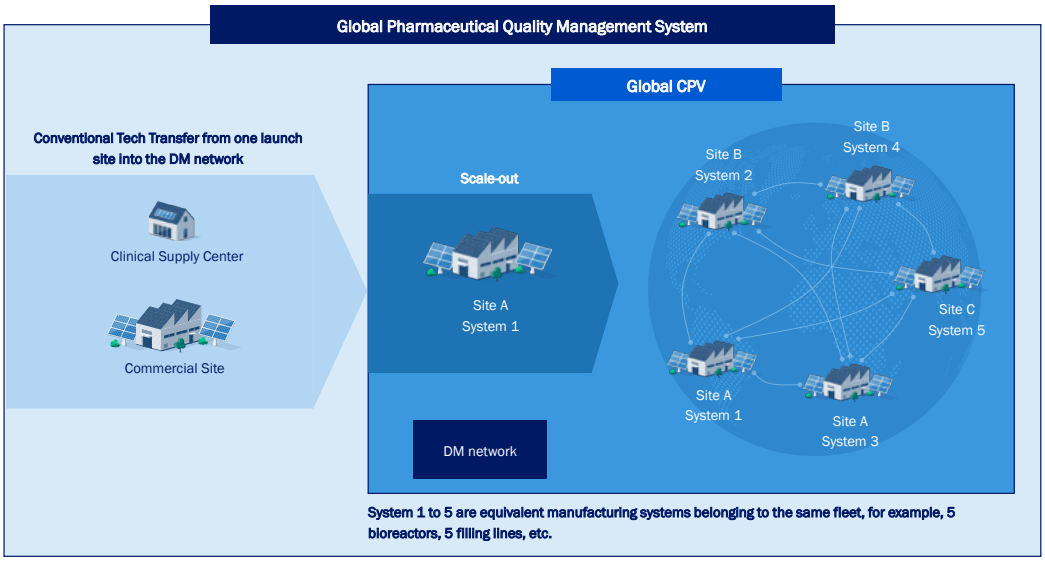
Establishing standardized protocols for equipment qualification, calibration, and validation, as well as implementing consistent training programs, will further support quality assurance. Effective collaboration between regulatory agencies and manufacturers is essential to create clear guidelines for assessing variability without compromising product quality.

Another challenge is creating a centralized PQS that ensures consistency and regulatory compliance throughout the DM network. This system requires harmonized protocols that account for the unique conditions of each site while maintaining uniform quality standards. Regulatory bodies must consider their inspection practices to determine whether to inspect sites individually or collectively, balancing thorough oversight with efficiency. Open communication and best practice sharing among sites will be crucial for the success of this centralized PQS, as it enables real-time monitoring and proactive adjustments across all locations.

Implementing new manufacturing processes within a DM network adds complexity for the initial unit, requiring careful planning and seamless integration to avoid disruptions; however, it ultimately streamlines operations at the network level and therefore to the additional fleet members. Future DM guidelines from regulatory agencies might focus on assessing and validating these changes to ensure they do not compromise product safety or efficacy.

Current data submission requirements also present challenges,

Figure 2: Impact of the fleet approach on technology transfers



as they can be time-consuming and costly. A more flexible, risk-based regulatory approach could be established that considers the specific conditions and performance of each fleet member together with the knowledge and understanding from the DM network's fleets. This would streamline the process while maintaining high standards of quality and safety, allowing for more agile and cost-effective manufacturing expansion.

PROPOSED FRAMEWORK FOR DM

The philosophy behind DM is the concept of "design one, build many" (copy/paste) and is operationalized using fleets. The fleet concept serves as a key mechanism to ensure the standardization of equivalent manufacturing systems across various sites, regardless of location, throughout the entire life cycle of the fleet. A central governing body is responsible for maintaining these standards across all stages of the fleet's life cycle, ensuring uniformity and compliance across different facilities. This approach fosters continuous improvement, allowing for cross-network problem solving, knowledge sharing, and enhanced process robustness.

The fleet concept enables a more streamlined and accelerated qualification process, making ramp-ups faster and more efficient. A comprehensive fleet management system ensures that all fleets, regardless of their geographic location, adhere to established fleet standards. With a highly connected digital network, fleet performance is monitored and controlled in real or near real time, ensuring alignment and consistency across the entire DM network.

Establishing a fleet of equivalent manufacturing systems across multiple sites allows systems within a fleet to leverage data, knowledge, and understanding from other fleet members to expedite the risk-based approval and implementation of subsequent members. This reduces the need for extensive validations, stability studies, and comparability studies, as well as the frequency and scope of inspections, as health authorities can rely on the data and experience from other fleet members. The fleet approach simplifies the initial technology transfer process and ensures consistent operations across the DM network. New members can be seamlessly integrated into the network, as subsequent technology transfers are efficiently handled through the company's PQS (see Figure 2), reducing the need for further regulatory reviews.

Table 1: Potential benefits of systems within a fleet

Potential benefits of utilizing the fleet concept
• Faster delivery from equipment suppliers
• Reuse of standards and documents
• Leaner and faster science and risk-based qualification and validation activities
• Reuse of process flows, SOPs, job instructions, and training setup
• Fast technology transfers keeping CMC off the critical path for launches
• Efficient health authority inspections
• Faster product approval
• Supply chain agility incl. fast capacity adaptation
• Strong equipment supplier relationships
• Improved execution efficiency and process robustness
• Increased quality maturity through cross-network problem-solving and knowledge sharing

The systems within a fleet will benefit across various phases, including procurement, design, construction, qualification, validation, operation, ramp-up, and production. Table 1 highlights the potential benefits of fleet systems.

A Centralized PQS

The International Council for Harmonisation of Technical

Requirements for Pharmaceuticals for Human use (ICH) "ICH Harmonised Tripartite Guideline Q10: Pharmaceutical Quality Systems" guidance [5] was introduced to bridge the gap between traditional cGMP and the evolving demands of modern PQS. ICH Q10 fosters a culture of innovation and quality by design (QbD), where companies can proactively address potential risks, optimize processes, and implement corrective and preventive actions (CAPAs) effectively. In doing so, companies not only meet compliance requirements but also reduced time-to-market and enhanced patient safety.

Several pharmaceutical companies already have a global quality management system or centralized PQS, which establishes standards and expectations that apply uniformly across all locations, guiding the development of any local procedures. A centralized PQS contains the four core pillars described in ICH Q10, which are essential for fleet management, supporting each stage of the product life cycle:

- Process performance and product quality monitoring system
- CAPA system
- Change management system
- Management review of process performance and product quality

Implementing fleets of standardized production systems across multiple sites requires a shift from local to global thinking. Each site must operate as part of a broader, interconnected network, aligning technically and culturally to ensure that actions taken at one site are informed by the performance of the entire fleet. Highly integrated process performance and product quality monitoring systems is essential to provide near-real-time visibility across all sites, enabling proactive tracking of trends, identification of deviations, and prompt responses to variations.

Effective coordination across a manufacturing fleet relies on a robust change management process with clear roles and accountability. Fleet-wide visibility into process performance allows for the early detection of risks and the implementation of global CAPAs instead of localized solutions. Consistent change management fosters continuous improvement, ensuring product stability, safety, and quality while promoting a unified approach across the network.

A well-integrated PQS is crucial for managing changes across sites. Leveraging PQS tools like annual product quality reviews and trend analysis for continued process verification (CPV) (US FDA terminology) or ongoing performance verification (OPV) (EMA terminology) helps identify variations that could indicate emerging risks. Strong governance, combined with structured change management and a focus on fleet-wide equivalency, ensures consistent product quality and safeguards the integrity of the manufacturing process across all locations.

The cGMP oversight requirements for a centralized PQS mirror those for overseeing multiple manufacturing sites, contract manufacturing organizations, and suppliers. The key difference lies in leveraging advanced digital technologies, which enable real-time monitoring and oversight of remote units, ensuring that quality standards are maintained across the board despite geographical separation.

The establishment of enterprise and cloud-based systems—such as a manufacturing execution system, laboratory information management system, change management or deviation tracking platforms—that can be accessed globally allows for centralized control and oversight. These systems will contain historical records for each member of the fleet, enabling comprehensive tracking and trend analysis across the entire network. This approach strengthens consistency in quality and compliance.

ICH Q10 specifies that the effectiveness of the PQS can typically be assessed during a regulatory inspection conducted at the manufacturing site. In the context of a fleet approach, the PQS could be inspected by health authorities as a single unified entity, irrespective of the number and geographical distribution of the fleet members. This inspection process would be based on a risk-based approach, considering the overall maturity and performance of the fleet.

The centralized PQS, along with data and information shared between the central organization and individual fleet members, would play a critical role in guiding this evaluation. The high level of connectivity between fleet members allows authorities to not only assess the performance of individual sites but also review the overarching fleet governance system.

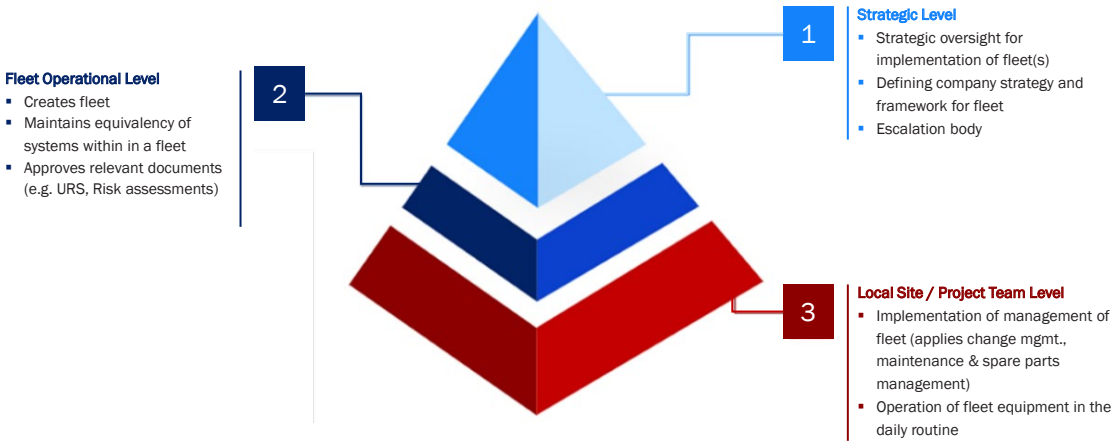
This ensures that consistent standards, procedures, and quality controls are applied across all locations. By leveraging this centralized approach, the inspection process becomes more streamlined, enabling regulators to focus on system-wide compliance rather than conducting redundant inspections at each site. Furthermore, the ability to monitor performance metrics and procedures across the network ensures that inspections are more targeted, potentially reducing the time and resources needed to complete them. This leaner inspection process can lead to more efficient regulatory oversight while maintaining rigorous quality assurance standards across the DM network.

A targeted, streamlined inspection process could further support reliance among health authorities. For example, if a health authority inspects site A, which has specific equipment within a fleet used across multiple sites, then another health authority might not need to focus on that equipment during an inspection of site B. This approach could reduce redundant inspection efforts, promote resource efficiency, and enhance collaboration among health authorities by allowing them to rely on each other's findings. This would ultimately contribute to a more cohesive and efficient regulatory oversight process.

Fleet Management

Fleet management is the process of defining and establishing a standard for a manufacturing system, replicating the standard across multiple sites, and maintaining the standard over the life cycle of the fleet. Fleet management begins when defining a consistent system design and user requirement specifications of a particular system to be replicated.

Figure 4: Example of fleet governance structure



To ensure consistency and compliance across the DM network, a robust governance framework must be established to manage changes, as well as external factors such as environmental conditions, utility systems, personnel qualifications, and procedures. Managing the impact of surrounding areas needs to be taken into consideration during the definition of the border and interfaces of a specific fleet equipment.

The governance framework should ensure the standardization and alignment of key aspects of the manufacturing environment to meet the operational needs of all fleet members. To achieve consistency across the fleet, a well-defined organizational structure that integrates both global and local roles is essential. This structure typically includes at least three tiers within the pharmaceutical company: strategic, fleet operation, and local site/project team levels, as depicted in Figure 4.

Strategic Level

This level functions as a strategic interface between the fleet management program and the company's top management. It also serves as a liaison with parts of the manufacturing processes that follow the traditional approach rather than the fleet model.

Operational Level

The network group is the main body to maintain a fleet, especially maintaining the equivalency of equipment within a fleet. The global network group at this level could include:

- System owner
- A role per site owning a fleet equipment representing operations
- A role per site owning a fleet equipment representing quality
- Network, local subject matter expert (SME) representing a specific topic (e.g., regulatory, engineering) as required

Site representatives (operation and quality) act as an interface between the global network groups and the sites and should bring in the needs and requests from the sites into the global network group for discussion. They also have technical oversight for implementation of the fleet within their sites.

Local Site and Project Team Level

The local site and/or project teams are in close collaboration with the site representatives in the global network group. The local team operates fleet equipment or executes any work on fleet equipment.

Building a Global Fleet

Creating a standardized system design is a fundamental step toward achieving consistency in pharmaceutical manufacturing processes. This involves clearly defining essential components like user requirements and engineering specifications. Following this, the development of standardized documentation and validation practices, including templates for protocols, test plans, and reports, is crucial. Operational procedures are also aligned across the board, covering job instructions, process flows, training, and maintenance protocols. To ensure these standards are maintained consistently, a system owner is appointed to oversee the system's life cycle across all locations, guaranteeing a unified approach.

After the standard design is established, it sets the stage for building a fleet of systems that strictly adhere to the specified criteria. This fleet consists of systems that are meticulously aligned in their design, functionality, and core processes, allowing only minimal variations. A System Owner oversees this fleet, ensuring that all systems perform cohesively, maintaining consistent manufacturing operations and product quality. This coordinated management approach ensures that the organization's fleet operates as a unified entity, supporting reliable production outcomes.

Fleet qualification employs a science-driven, risk-based strategy to streamline qualification activities. Once the first system in the fleet is qualified, data and knowledge from this initial effort can be efficiently utilized to expedite the qualification of subsequent systems, reducing test documentation preparation, testing, and overall timelines. Performance metrics, tied to critical process

By establishing a network of manufacturing sites equipped with standardized processes and equipment, companies can swiftly adjust production locations to meet unforeseen demand spikes or local disruptions.

parameters (CPPs) and critical quality attributes (CQAs), guide the continuous monitoring of fleet performance. Additionally, maintaining a fleet master plan as a dynamic document helps track fleet status, equipment details, and system boundaries. Regular updates to this living document ensure that any new equipment installations or system retirements are accurately reflected, keeping the fleet's information up to date and fostering continuous improvement.

Change Request Process

To maintain the equivalency of a specific fleet, a stringent change control process is of utmost importance. The impact of each change must be analyzed accurately for the equivalency of the fleet members. A deep knowledge of the equipment, materials and processes are fundamental to making decisions upon impact of changes. If a change influences the equivalency, the change must be implemented on each piece of equipment within the fleet to maintain the equivalency. Therefore, the benefit of a change versus the requirements to implement in the fleet must be evaluated very carefully.

The global network group will be responsible for fulfilling this task. It is elementary that the people representing the sites in this group are well integrated in their sites to make sure that any events at a specific site impacting fleet equipment (e.g., changes, deviations, shutdowns, maintenance, internal audits) are reported to them in a timely manner, so that they can escalate it into the global network group for further evaluation or assessment. Any decisions impacting the equivalency of equipment within a fleet should be made within the global network group, balancing out pros and cons and impacts for each site. Specific topics need to be escalated to the next level, in case strategic decisions are required.

Independently of maintaining the equivalency within a fleet, continuous improvement is still an important aspect within the life cycle of this equipment. Continuous improvement should be performed at the supplier of fleet equipment as well as within a company using fleet equipment. The fact that there is more than just one machine within a fleet offers the possibility to gather more information and data about equipment and processes that are due to the equivalency directly comparable. Based on the availability of comparable data, improvements can be identified and implemented more quickly and efficiently to create more robust processes.

Knowledge Management (KM) in a Fleet

KM is crucial for maintaining fleet standards, ensuring equivalency, and enhancing overall performance across the fleet. ICH Q10 defines KM as a systematic approach to acquiring, analyzing, storing, and sharing information related to products, manufacturing processes, and components. In the context of a fleet, this involves applying and managing knowledge related to both the fleet and its individual members. Combined with the CPV/OPV program, KM plays a key role in driving performance improvements and ensuring operational consistency.

Building and Sharing Knowledge

A comprehensive fleet knowledge base should be developed to capture both explicit data and tacit knowledge from global network groups. This information must be systematically collected, organized, and shared across the fleet organization to ensure it reaches the right teams at the right time. The aim is to equip teams with the necessary insights to operate, support, and manage fleet members and their processes effectively. Advanced digital tools and connectivity enhance the management and flow of this data, creating a robust framework for knowledge sharing and decision-making.

Integrating advanced data analytics within the fleet transforms data into actionable knowledge, enabling strategies like early troubleshooting, impact analysis, and predictive maintenance to prevent equipment failures. This analytical approach drives

continual improvement, optimizing fleet performance, training, and operations. Knowledge sharing across the network also extends to external stakeholders, such as quality professionals and regulators, fostering a collaborative culture and informed decision-making throughout the fleet organization.

Operational support across the fleet is seamlessly integrated through standardized processes, equipment, standard operating procedures (SOPs), and work instructions. This consistency allows colleagues and subject matter experts to quickly step in when issues arise. Digital tools like virtual reality and augmented reality can enhance interactive support experiences. When breakdowns occur, local teams provide the first response, while the global network offers additional support, ensuring comprehensive solutions that are consistently applied throughout the fleet.

Training

Standardized training across the fleet and the DM network ensures that all personnel follow the same protocols, assessments, and quality standards, equipping staff with consistent skills and knowledge. This unified approach enables effective support regardless of location and promotes seamless cooperation among team members, maintaining high-quality operations across the network. Specific roles and responsibilities are clearly defined, with dedicated training programs tailored to each role, continuously reviewed, and updated to reflect new developments and best practices. This standardized approach ensures that personnel adhere to consistent procedures and also facilitates efficient cross-site collaboration, enabling teams to provide effective support and adapt quickly to challenges.

CPV/OPV and Fleet Evaluation

Every pharmaceutical product requires a CPV or OPV program to confirm that the manufacturing process remains under control during commercial production. Typically aligned with the PQS, these programs use statistical tools to analyze CQAs and CPPs. When fleet members are digitally connected, CPV/OPV can be conducted across the network, enhancing the ability to monitor and improve the entire fleet's performance.

Automated data collection and analysis provide real-time and near-real-time insights into both individual fleet member performance and overall fleet operations through a cloud-based system that integrates data from multiple sources. This setup enables continuous monitoring of product quality, equipment functionality, and fleet consistency. It also facilitates quick responses to deviations, implementation of global CAPAs, and initiation of improvement measures to maintain the fleet's robustness.

The global availability of data from all fleet members is a critical factor in leveraging validation activities across the fleet, making the fleet management system uniquely effective. This comprehensive data access allows for better-informed decision-making and enhances the capability to maintain uniform standards and continuous improvement across all manufacturing sites.

Life Cycle Management

The management of fleet members within the DM network requires a comprehensive strategy to ensure the equivalence of manufacturing systems and equipment throughout their entire life cycle within a manufacturing network. One of the main challenges is overseeing equipment that may remain in use for decades, requiring meticulous maintenance, updates, and compliance checks to align with evolving standards and technologies.

The "design one, build many" approach offers a solution by promoting the use of standardized equipment across sites, which can streamline operations and reduce variability. Although this concept isn't entirely new, what distinguishes the fleet management concept is its extension beyond the initial handover from project to operations, ensuring that standardization is maintained throughout the entire life cycle of the equipment. In pharmaceutical manufacturing, equipment life cycles often extend beyond a decade, during which evolving production needs or technological advancements may require additional equipment purchases. It's crucial to have a long-term plan to maintain equipment equivalency, whether through upgrades to existing units or the introduction of a new fleet.

This approach poses challenges for pharmaceutical equipment suppliers, as they must strike a balance between providing versatile "off-the-shelf" solutions and offering highly customized options. Prioritizing the development of next-generation models over frequent modifications to standardized equipment may be more efficient. Effective fleet management, however, requires a strong partnership between suppliers and the pharmaceutical industry to ensure consistent performance, compliance, and operational efficiency across the entire network.

Effective management of supply chain quality is essential for the successful operation of manufacturing fleets, ensuring consistent quality and availability of critical raw materials such as drug substance precursors, single-use technologies, and assay reagents. A reliable network is key to maintaining equivalency across the fleet, supporting the broader manufacturing strategy, and ensuring that data from different locations are comparable.

Although cGMP facilities rigorously test incoming materials to verify their identity, purity, and quality, DM faces added complexities due to its reliance on local suppliers, which must be carefully managed to maintain consistency. These challenges could be addressed by the adoption of advanced analytical techniques, such as process analytical technology (PAT), real-time monitoring and control technologies, and strengthened supplier qualification processes. Effective communication with suppliers and solid contingency planning are also crucial to mitigate potential disruptions and uphold supply chain integrity.

A robust PQS is crucial for effectively leveraging the tools outlined in ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Life Cycle Management [6] to manage the integration of new fleet members. Successful implementation of ICH Q12 tools necessitates a well-organized industry framework that draws on existing knowledge, scientific principles, and innovation.

The fleet concept simplifies regulatory processes by standardizing data and procedures across multiple sites, reducing societal costs through streamlined production, decreased regulatory burdens, and improved drug supply reliability, ultimately benefiting all stakeholders involved.

By employing the tools and enablers of ICH Q12, organizations can enhance fleet management throughout the product life cycle through a risk-based approach that specifies the appropriate level of regulatory oversight.

This proactive strategy, which includes post-approval change management principles, allows for better anticipation of future changes and their related reporting requirements, ultimately streamlining the regulatory process. Furthermore, a robust PQS, combined with effective KM and proactive quality risk management practices, can significantly improve operational flexibility, enabling the manufacturing process to adapt to changes while maintaining quality. This approach also ensures supply continuity by minimizing the risk of disruptions, thereby guaranteeing consistent product availability.

Additionally, fostering an innovative culture becomes more attainable as a well-managed PQS facilitates the effective integration of new fleet members, ensuring compliance and responsiveness to market demands throughout their life cycle. Aligning with ICH Q12 principles, where structured KM supports life cycle management, further enhances proactive change management and drives continuous improvement in the fleet operating model.

BENEFITS OF DM

DM manufacturing offers significant advantages, including enhanced patient safety, greater reliability and consistency in supply, speed in delivering medicines, improved compliance, and reduced societal costs. Enhanced patient safety is a core benefit of DM, made possible by the ability to share and leverage data, lessons learned, and best practices across multiple sites. This collaborative approach allows for broader perspectives, more comprehensive data analysis, and improved safety and performance across the network.

Drug shortages have become a pressing concern in the pharmaceutical industry, and DM offers a significant advantage in addressing this issue. One of the key benefits of the fleet concept is the enhanced reliability and responsiveness in patient supply. By establishing a network of manufacturing sites equipped with standardized processes and equipment, companies can swiftly adjust production locations to meet unforeseen demand spikes or local disruptions.

This interconnected approach bolsters supply chain robustness by creating "interchangeable sites" that can quickly adapt to changes in demand or supply challenges. Additionally, the capacity to share data and experiences across these sites further enhances overall performance and reliability. This collaboration not only facilitates a smoother rollout of new technologies but also helps to mitigate the risk of stockouts during emergencies, ensuring that patients have continuous access to essential medications.

DM fosters innovation and accelerates the delivery of medicines to patients by enabling a more agile and scalable production approach. Through the incremental rollout of fleet members across the network, continuous improvements can be applied in real time, minimizing trial and error and optimizing processes for smoother multisite implementation.

As discussed earlier, this approach not only enhances the overall efficiency of the network, but it also supports faster technology transfers between sites, which boosts flexibility and ensures a coordinated strategy across the entire fleet. As a result, the need for extensive comparability studies is significantly reduced, streamlining regulatory approvals and shortening the time-to-market for new medicines, ultimately improving patient access to life-saving treatments.

Another benefit of DM is its potential to enhance environmental sustainability within the pharmaceutical industry. By localizing production closer to end users, this approach significantly reduces the carbon footprint associated with long-distance transportation of goods. Additionally, DM often allows for the use of renewable energy sources at localized sites, further minimizing environmental impact.

Furthermore, the decentralized nature of DM fosters innovation in sustainable practices, as each site can implement localized strategies for waste reduction, recycling, and energy efficiency that align with community goals. This alignment not only supports corporate sustainability initiatives but also enhances corporate social responsibility, ultimately contributing to a more sustainable and resilient supply chain.

Finally, health authorities benefit from DM through reduced inspection demands, streamlined review processes, and a more robust supply chain that lowers the risk of stockouts. The ability to quickly adapt manufacturing to meet demand, scale out production processes, and enhance process reproducibility with replicated equivalent manufacturing systems supports regional production and improves patient access to essential medicinal products.

CONCLUSION

In this article, we outlined a comprehensive framework for the fleet concept as an operational model for DM. By focusing on the principles of scaling out and the copy/paste approach, we highlight how these core elements can significantly enhance compliance and minimize variability in the production of medicines. This alignment between industry practices and health authority objectives ensures the delivery of safe and effective drugs, whether they are new candidates in clinical trials or established therapies. The fleet concept simplifies regulatory processes by standardizing data and procedures across multiple sites, reducing societal costs through streamlined production, decreased regulatory burdens, and improved drug supply reliability, ultimately benefiting all stakeholders involved.

The flexibility inherent in this framework makes it also suitable for emerging modalities. By adopting the approaches presented in this article, manufacturers can significantly reduce waste and optimize resource efficiency while creating a production system that is agile and responsive to fluctuations in demand. This adaptability not only enhances inventory management but also ensures the consistent availability of critical products across global markets.

By fostering collaboration between regulators and industry stakeholders, we can work toward establishing a clear and robust regulatory environment that facilitates the implementation of these innovative manufacturing models. We have previously had informal yet constructive discussions with regulators from the US FDA and EMA about creating a suitable regulatory environment for the fleet concept, and both parties expressed support for continuing this dialogue.

We encourage regulators to keep engaging with industry sponsors to further refine and implement the ideas presented in this article. A well-defined regulatory framework that embraces the principles of the fleet concept will be crucial for advancing flexible, on-demand small or large volume production solutions, ultimately leading to a more efficient and responsive healthcare delivery system on a global scale.

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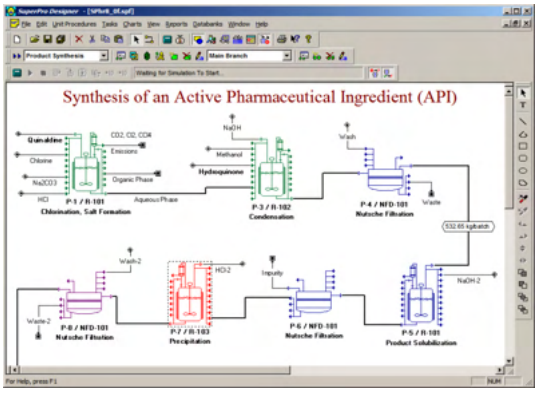

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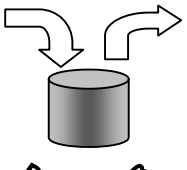

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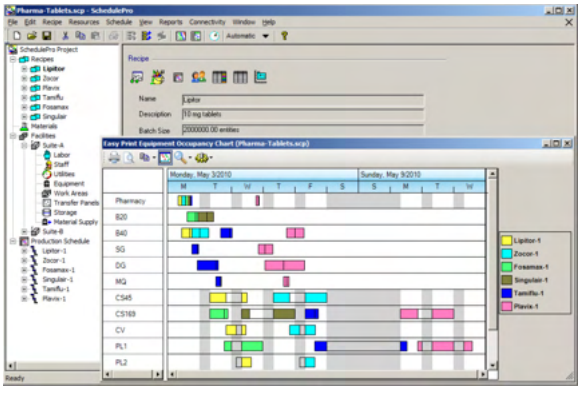

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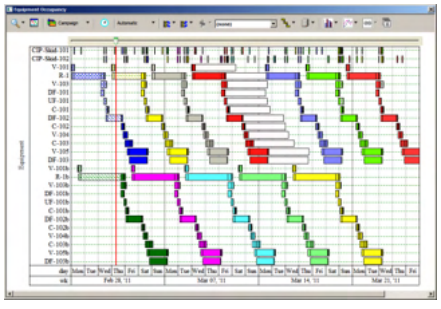

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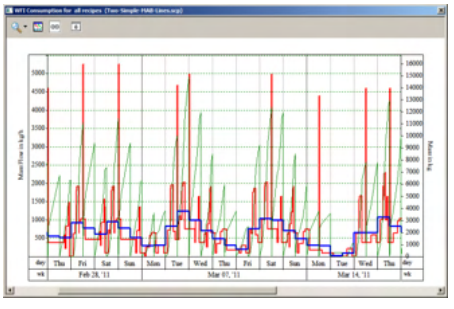

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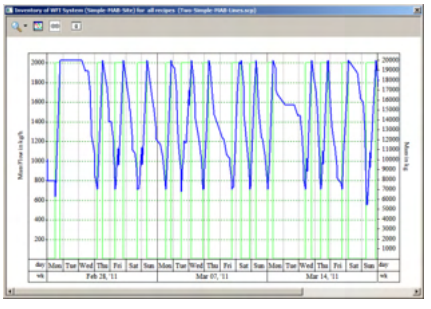

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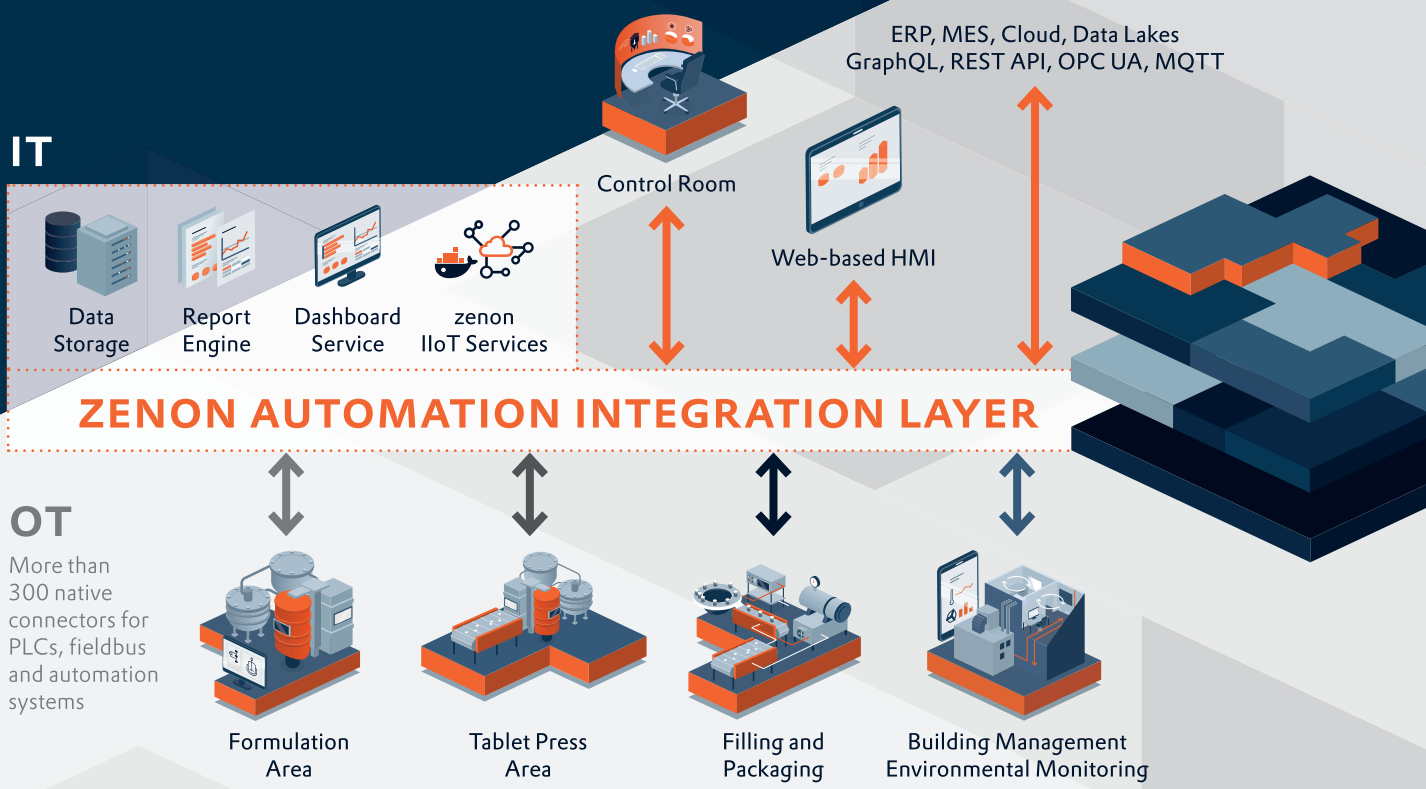

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