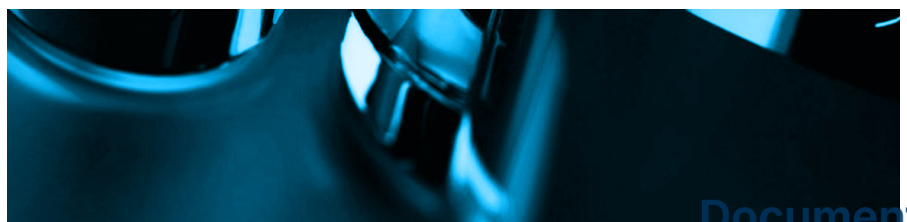


2023 ISPE Drug Shortages Prevention Model



Guidance for Drug Shortage Prevention Excellence





This guide aims to provide recommendations intended to diminish the occurrence of drug shortages caused by manufacturing and quality issues. ISPE cannot ensure and does not warrant that systems managed in accordance with this guide will reduce or eliminate drug shortages nor that activities recommended by this guide will be acceptable to regulatory authorities. Further, this guide does not replace the need for hiring regulatory and quality professionals, engineers, or technicians.

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Content Outline

Performance Domain 1 Pharmaceutical Quality System (PQS)

- The International Council for Harmonisation (ICH) [\[1\]](#) provides essential guidance on quality topics for pharmaceutical systems.
- Quality beyond baseline compliance improves reliability of drug supply.
- Multiple ISPE initiatives focus on quality systems and guidance.

Performance Domain 2 Cultural Excellence

- There is elevated regulatory interest in moving to excellence beyond compliance.
- Cultural alignment, both internally and with external organizations, is key.
- A healthy quality culture promotes continual improvement.

Performance Domain 3 Workforce Capability

- Management leadership and commitment to workforce capability is integral to success.
- The dynamic manufacturing climate requires an evolving workforce.
- Global competition for a limited workforce is increasing.

Performance Domain 4 Supply and Distribution Resilience

- Expectations for reliability of supply are increasing globally.
- Resiliency approaches should be diversified and include a rapid response system.
- Organizational preparedness is critical to optimize supply resiliency approaches.
- Resiliency is closely linked to all *ISPE Drug Shortages Prevention Model (DSPM)* performance domains.

Performance Domain 5 Risk Management Planning

- Risk Management Plans (RMP) manage risks to supply for disruptive events.
- ICH Q9 [\[2\]](#) provides essential guidance for risk management activities and principles.
- Global regulatory expectations for RMPs are increasing.
- RMPs require enterprise-wide engagement and a periodic refresh.

Performance Domain 6 Data Analytics

- Metrics are essential to drug shortage rapid response and continual improvement.
- A metrics standard to universally identify drug shortages remains unavailable.
- Predictive modeling may provide transparency to supply chain vulnerabilities.

Performance Domain 7 Advanced Technology

- Advanced technology can increase manufacturing agility and improve drug shortage prevention.
- Technical risks and regulatory challenges present challenges to implementation.
- Distributed and Point of Care Manufacturing (DM and PoC) strategies could radically transform the way medicines are delivered to patients.

Performance Domain 8 Digital Solutions

- Digital solutions will transform global supply chains. Key examples: blockchain, electronic labeling
- Digital solutions can offset drug shortages with improved quality and efficiency.
- The [ISPE Pharma 4.0™](#) initiative is intended to enable manufacturers to fully leverage digitalization for the benefit of patients.

Performance Domain 9 Sustainability

- Like drug shortage prevention, sustainability is a multidisciplinary, multifaceted challenge.
- Advancement of sustainability is being pursued by many of the larger pharmaceutical manufacturers and may be key to long term drug product availability and access.
- Some sustainability activities may achieve drug shortage prevention goals in tandem.

Performance Domain 10 Lifecycle Management

- Lifecycle Management (LM) ensures optimal operational strategy for the present and the future and should be refreshed over time.
- Attention to LM is particularly important for drug shortage prevention of sterile products.
- LM is closely connected with regulatory considerations.

Performance Domain 11 Regulatory Execution

- Engagement with Health Authorities (HAs) can be pivotal to prevent a drug shortage.
- Multiple markets have requirements for drug shortage reporting.
- Proactive regulatory actions may be instrumental in mitigating or avoiding a drug shortage (e.g., Post-Approval Change Management Protocol (PACMP), streamlined approvals via structured content)
- Leveraging regulatory assistance should be pursued whenever appropriate.

Performance Domain 12 Evolving Regulations

- International governments and organizations are increasingly pursuing strategies to prevent drug shortages.
- Regulatory intelligence is key for holistic prevention and mitigation plans.
- Global harmonization or convergence presents a significant opportunity to bolster drug shortage prevention.

ISPE Drug Shortages Prevention Model (ISPE DSPM)

Background

The International Society for Pharmaceutical Engineering (ISPE) published the *ISPE Drug Shortages Prevention Plan (ISPE DSPP)* [3] in 2014 and has been guiding progress in drug shortage prevention ever since. The original *ISPE DSPP* continues to be applicable to drug shortage prevention. At this time, however, the ISPE Drug Shortages Initiative team sees an opportunity to present expanded guidance in the framework of the *ISPE Drug Shortage Prevention Model (ISPE DSPM)* because best practices have evolved, and new perspectives have emerged. Experience with large-scale events, such as Hurricane Maria and the COVID-19 pandemic, and more recent geopolitical events, have cast a wider lens on global supply chain and distribution vulnerabilities. In parallel, public and civic demand for change has been accelerating new regulatory requirements in some markets and increased pressure is being placed on manufacturers for supply chain resiliency globally.

Contemporaneous, industry-wide, and global insight to the reasons for shortages remains unavailable. The latest publicly available data reflects that manufacturing/quality issues continue to be the main drivers for drug shortages [4,5]. Regardless of the main drivers, drug shortages can and do result from an abundance of reasons and may be attributable to more than one root cause. The onset and lifecycle of the COVID-19 pandemic vividly demonstrated that the challenges today may not be the challenges tomorrow. Therefore, vigilance to pharmaceutical manufacturing excellence and continual improvement is essential to drug shortage prevention. We must learn from the drug shortage experiences and the large-scale events that may contribute to them (e.g., natural disasters, cyberattacks,

pandemics/epidemics, geopolitical issues) and adapt to the evolving regulations that are keeping pace with these events.

Like the original *ISPE DSPP*, the *ISPE DSPM* covers the quality, technical, and regulatory aspects of drug shortage prevention. Other areas that may contribute to drug shortages, including but not limited to insufficient financial incentives, pricing issues, equity challenges, and geopolitical issues that may affect patient access, are beyond the scope of ISPE and the *ISPE DSPM*. Other than brief remarks for context, they are not addressed.

All markets were included in the scope of the original *ISPE DSPP* and the same applies for the *ISPE DSPM* presented herein. While examples of specific market or regional regulatory expectations are provided throughout the *ISPE DSPM*, it is important to note that not all markets have regulatory expectations. Further, for the markets that do have regulations, definitions and expectations are not always aligned. The business climate or political landscape within certain markets or regions may also influence approaches for drug shortage prevention. For example, some manufacturers in Africa, Asia Pacific, and Latin America supply finished drug product to only their market or region instead of exporting globally. Several markets in Africa have minimal-to-no local manufacturing and rely solely on imported drug product supply from multinational companies. Still other markets, such as those in the European Union (EU), US, Canada, Australia, and the UK, typically have both local and global supply, and strong generic competition such that dramatic changes in market share with potential for unexpected shortages may occur in short periods of time. To ensure the greatest success in drug shortage prevention, companies should consider both applicable regulatory expectations and regional/local dynamics of end markets.

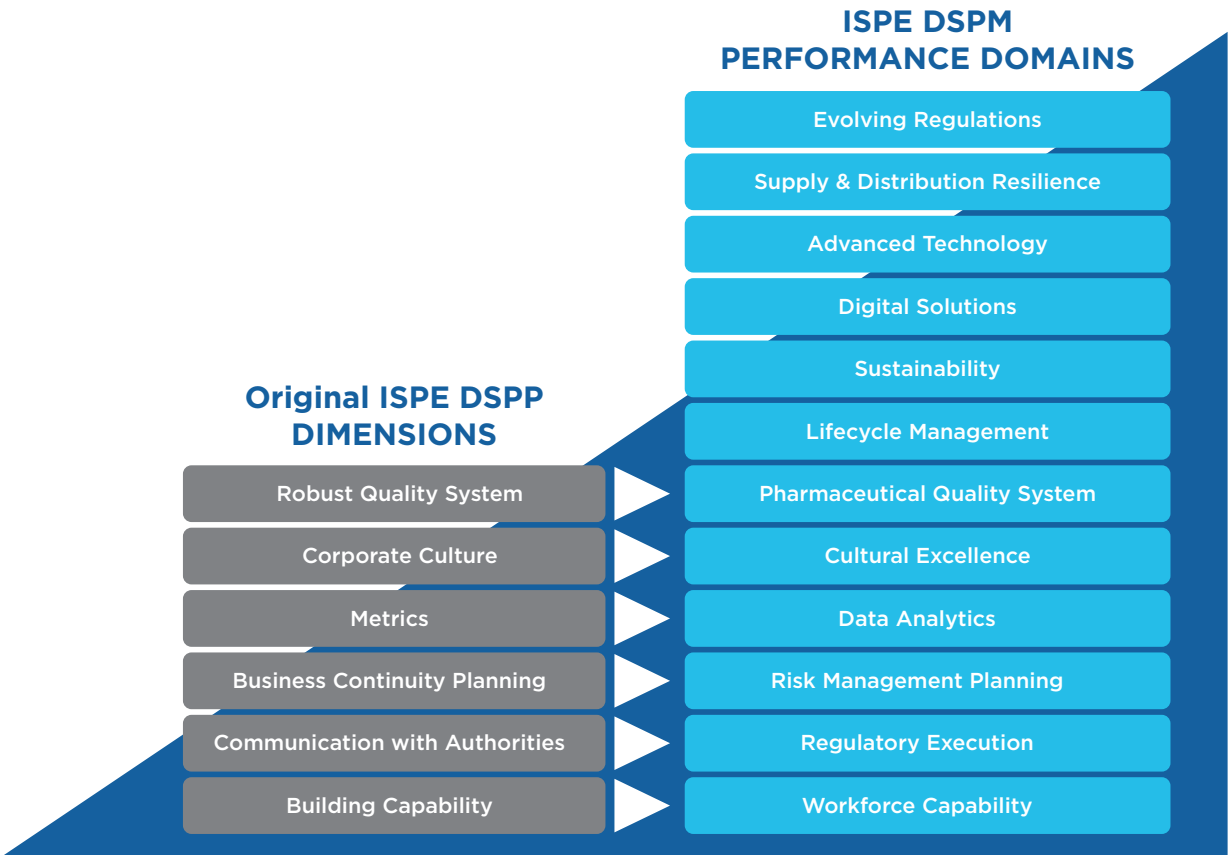
Figure 1: The ISPE Drug Shortages Prevention Model (ISPE DSPM)



As shown in Figure 1, the *ISPE DSPM* has 3 foundational areas for accountability and 12 performance domains. This new model does not supersede the original *ISPE DSPP*, but rather complements it. Every element of the original 6 dimensions may be found in the new *ISPE DSPM* performance

domains. Figure 2 shows the progression of topics in the *ISPE DSPP* and where an original dimension may be included within a differently titled performance domain within *ISPE DSPM*.

Figure 2: Progression of the ISPE Drug Shortage Prevention Plan (ISPE DSPP) to the ISPE Drug Shortage Prevention Model (ISPE DSPM)



Enterprise-wide Nature of Drug Shortage Prevention

For robust drug shortage prevention preparedness, companies should strive to excel in each of the foundational performance domains of the *ISPE DSPM*, all of which include risk management opportunities at organizational, operational, and product-specific levels. Therefore, developing and implementing robust drug shortage prevention is an enterprise-wide endeavor.

All organizations should have a company-wide policy for drug shortage prevention to ensure that the necessary awareness and partnership is achieved. Larger organizations that have distinctions between functional areas need to ensure that the cross-functional alignment and execution of drug shortage prevention goals is sufficient. Success may require additional workforce readiness measures and support to ensure adherence to a drug shortage prevention policy. Examples of the many areas that typically support drug shortage prevention or event mitigation are:

- Customer relations
- External business partnerships
- Legal
- Manufacturing
- Medical affairs
- Procurement
- Quality
- Regulatory affairs
- Research and Development*
- Sales and marketing
- Supply chain
- Technical/manufacturing operations

*Note: Ensuring uninterrupted supply of critical medicines for all patients should be prioritized, regardless of the approval status of the product. Therefore, clinical supplies should also be considered when developing drug shortage prevention plans.

ISPE DSPM Architecture

Because of the depth and breadth of the many areas that contribute to robust drug shortage prevention, the *ISPE DSPM* is presented as a high-level guide and not intended to be an exhaustive resource for knowledge within each performance domain. Additionally, some of the performance domains have interconnections with one or more other domains. To ensure clarity of why the performance domains were selected for inclusion in the *ISPE DSPM* and to convey the appropriate level of orientation of what they are, each of the performance domain descriptions were constructed to address the following questions:

1. What is the performance domain?
2. Why is the performance domain important to drug shortage prevention?
3. What resources does ISPE offer on the topic(s)?

Accordingly, this document may serve as a navigational guide and sections may be reviewed in any order and on an as-needed basis. To determine which section may provide the most meaningful insight for your organization, evaluate your organization's drug shortage prevention readiness by asking the *ISPE DSPM* top drug shortage prevention questions ([see Appendix 1](#)).

The ISPE Drug Shortages Initiative team has developed the *ISPE DSPM* to assist ISPE membership and industry to reduce drug shortages globally. The team includes global, multidisciplinary experts whose areas of expertise cover a wide range of pharmaceutical technology and manufacturing, quality, and regulatory topics. We actively monitor developments related to drug shortages by regularly seeking HA input and engagement with key stakeholders on drug shortage prevention. Focusing forward, the ISPE Drug Shortages Initiative team in partnership with the many ISPE Communities of Practice (CoPs) and other experts, continues to pursue opportunities to provide additional guidance and instructional opportunities to ISPE membership and industry on each of the foundational performance domains described in the *ISPE DSPM*. The ISPE Drug Shortages Initiative team is available to respond to any associated questions and we welcome input on best practices for drug shortage prevention. Contact regulatoryaffairs@ispe.org.

Twelve Performance Domains for Drug Shortage Prevention

Quality and Manufacturing Maturity

1. Pharmaceutical Quality System

A robust quality system, generally referred to by ICH as a Pharmaceutical Quality System (PQS) [6], should ensure appropriate pharmaceutical quality at any time over the lifecycle of a drug product. Ideally, quality systems should foster quality beyond compliance expectations to ensure not only consistent quality, but also consistent drug product supply. As a result, the level of maturity of an organization's PQS can provide insight into the potential for drug shortages.

A robust PQS, the elements of which are Process Performance and Product Quality Monitoring, Corrective Action/Preventive Action (CAPA) System, Change Management System, and Management Review, with the enablers Knowledge Management and Quality Risk Management, facilitates the identification and evaluation of improvement opportunities. It also ensures that process performance is achieved and guarantees that knowledge is continually expanded and shared throughout the pharmaceutical manufacturing organization [6].

The primary reference guidance for a PQS may be found in several ICH documents. Notably ICH Q8 [7] ICH Q9 [2], and ICH Q10 [6], on driving pharmaceutical quality and modern pharmaceutical quality systems based on science e.g., Quality by Design (QbD), risk management (e.g., Quality Risk Management [QRM]) and knowledge (e.g., Quality Management System [QMS]). Building and maintaining a robust quality system is significantly important to drug shortage prevention because supply disruptions associated with manufacturing or product quality problems are one of the primary contributors to drug shortages. A robust PQS is crucial to achieve product

realization, to establish and maintain a state of control, to facilitate continual improvement, and ultimately, to proactively prevent and manage drug shortages. Quality issues that can generate drug shortages include:

- a) Delays in regulatory approvals due to quality inspection findings
- b) Delays in the manufacturing of Active Pharmaceutical Ingredients (APIs) or finished drug product due to quality issues
- c) Lack of cGMP compliance
- d) Issues with transfer qualification and validation of analytical methods

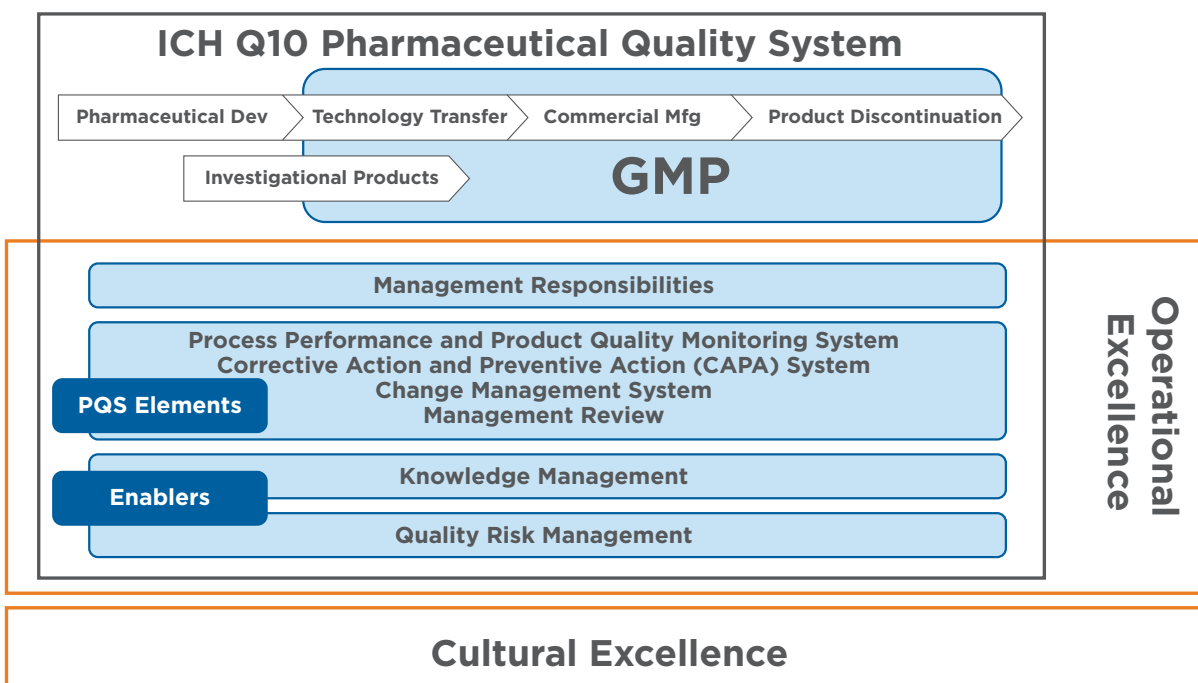
ISPE has had a long-standing commitment to providing guidance and communicating best practices regarding the principles of robust quality systems. Two ISPE initiatives that extensively focus on quality systems and guidance thereof are [Advancing Pharmaceutical Quality \(APQ\)](#) and [Product Quality Lifecycle Implementation \(PQLI\)](#)[®].

The APQ initiative is building industry-for-industry tools and programs to help companies assess and improve their quality operations. It integrates quality management maturity, cultural and operational excellence principles, tools, and approaches (see Figure 3). Achieving success in robust quality systems can deliver a competitive advantage because it helps to promote year-over-year uninterrupted supply. The overarching goals of the APQ Program are to [8,9]:

- Foster industry ownership of quality beyond compliance
- Promote effective and efficient use of resources
- Support and incentivize manufacturers and suppliers' continual improvement

- Enable structured benchmarking, knowledge sharing, and learning among companies
- Increase the reliability of supply for quality products

Figure 3: APQ Program Links to the ICH Q10 PQS Model [8]



Through PQLI, ISPE assists industry and regulators in advancing manufacturing sciences across the product lifecycle to achieve excellence in drug development and pharmaceutical production. It was created to facilitate the introduction and provide guidance on practical implementation of the concepts described in ICH guidelines, focusing on Q8 [7], Q9 [2], Q10 [6], Q11 [10], and Q12 [11] to help ensure product quality throughout a product lifecycle, leading to continual product improvement. Today, PQLI technical teams are developing solutions in emerging regulatory and scientific topics related to Chemistry, Manufacturing, and

Control (CMC) and GMP approaches to ensuring product quality [12].

The following ISPE groups are recommended for further assistance:

- [ISPE Advancing Pharmaceutical Quality \(APQ\) Team](#)
- [ISPE Product Quality Lifecycle Implementation \(PQLI\)[®] Committee](#)

2. Cultural Excellence

Cultural Excellence in the pharmaceutical industry is essential for ensuring a culture of



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quality and is key to continual improvement and business continuity. The establishment of a strong cultural excellence requires time and dedicated management commitment, and often involves a change in the mindset of the organization: moving from a culture solely focused on compliance to an excellence-led culture of quality. Cultural excellence plays a significant role in ensuring that an effective PQS is in place within an organization and drives successful uninterrupted supply for patients, manufacturing innovation, and employee engagement.

Regulatory authorities are emphasizing the importance of quality culture in the continual improvement of processes. A consistent and strong quality culture is based on quality values and the behavior of the individuals within the corporate quality strategy, from the shop floor to upper management. The World Health Organization (WHO) [13] and other organizations have noted key features of quality culture that are foundational: 1) leadership is responsible for providing the environment to establish, maintain, and continually improve the quality culture and 2) the quality culture within the company must encourage personnel to be transparent about failures, which includes a reporting mechanism inclusive of investigation and follow-up processes. These aspects build cultural excellence based on trust and a “one-team” mindset within a manufacturing organization that ensure focus on the product and the patient [14].

An additional important aspect of cultural excellence and the prevention of drug shortages is the relationship between pharmaceutical companies and their third-party organizations. Understanding the cultural differences and similarities between the sponsor and the third party facilitates the establishment of well-structured and well-defined communication pathways with decision-making autonomy that has clearly defined escalation pathways. Leaders of the organizations involved in the partnership should set expectations to ensure that they understand and share the

same values and standards when it comes to sustainability, ethics, and the environment. There are significant challenges in the relationships between sponsors and third-party organizations, however a strong quality culture and expectations around it will facilitate understanding between the companies and will help meet deliverables. A clear line of sight to the patients must be maintained at all times and boundaries between the internal and external parties should not constitute a barrier for cultural excellence and knowledge flow.

Culture affects the organization’s ability to identify and act upon near-miss shortages, ensure transparent problem escalation, and strive for operational excellence. A healthy quality culture promotes continual improvement and a strong risk-management framework, which are key to the proactive identification and prevention of poor-quality outcomes and, by consequence, drug shortages. Quality culture can play a central role in preventing drug shortages by designing organizations that have a cross-functional ownership of quality, clear escalation pathways for issues, a speak-up culture, and that provides psychological safety that promotes transparency [15,16].

The following ISPE programs and resources are recommended for further assistance:

- [ISPE Advancing Pharmaceutical Quality \(APQ\) Program](#)
- [ISPE Cultural Excellence Report \[15\]](#)
- [ISPE APQ Guide: Cultural Excellence \[16\]](#)

3. Workforce Capability

For the pharmaceutical industry, workforce capability ensures operational success and continuous supply of essential medicines. It is interconnected with robust governance, organizational design, and talent management. Because of the resources and strategy required to accomplish the overall infrastructure necessary for workforce capability, management leadership and commitment is particularly pivotal to its success.

As described in the original *ISPE DSPP* [3], workforce capability results from developing individual employees through training, learning, and mentorship, relying on effective knowledge management. The development of individual employees is not only helpful for the activities they will complete in the near term. Constructive, inspirational workforce development can be motivating and contribute to greater productivity, retention, and continuity of staffing for critical operations over time.

An important element of workforce capability is the readiness of all employees to act on or escalate product or PQS [6] issues that may contribute to a supply disruption. A preparedness mindset should be developed with all employees because drug shortage events can be multifaceted and cross-functional or company-wide in nature. Therefore, for the purposes of holistic drug shortage prevention and the quickest possible response time for mitigation or prevention efforts, a company-wide policy and related procedures for drug shortage mitigation or prevention should be created, maintained, and included in ongoing training, learning, and mentorship activities.

It is essential that all companies have a dynamic focus on building workforce capability to ensure employees stay current with and prepared for evolving technology, quality, and regulatory expectations. Companies should consider that the workforce of the future will include emerging talent that will need formative training, learning, and traditional mentorship, as well as experienced staff. Experienced staff may require retraining to move to new roles if former activities become obsolete by technology, quality, or regulatory progress [17,18]. or possibly reverse-mentoring relationships, where emerging talent mentors experienced staff, to foster exchange of fresh ideas that may be critical to bridging generational gaps and improving organizational alignment. Additionally, there is increasing global competition for a limited workforce [19,20]. As a result, success in

building, leveraging and transferring skills of capable employees to new professional roles will attract and retain available talent for critical operations and optimal drug shortage prevention.

ISPE is passionate about supporting the next generation of pharmaceutical professionals and has created many resources for students and young professionals through its [Workforce of the Future](#) program.

The following ISPE groups and initiatives are recommended for further assistance:

- [ISPE Affiliates and Chapters](#)
- [ISPE Emerging Leaders](#)
- [ISPE Women in Pharma®](#)
- [ISPE Foundation Workforce of the Future](#)

4. Supply and Distribution Resilience

Resiliency has become one of the fastest growing topics in the pharmaceutical industry due to supply [chain or distribution] vulnerabilities that have been identified or magnified through impactful circumstances in the past few years (e.g., COVID-19 pandemic, natural disasters, geopolitical events) [4,21,22]. There has been a longstanding expectation for manufacturers to supply pharmaceutical product of appropriate quality. Due to the increased focus on supply chain vulnerabilities, there are now developing expectations and corresponding regulatory framework to ensure reliability of pharmaceutical supply [2,23]. Among other considerations, the reliability, or sustained availability, of pharmaceutical supply depends on manufacturing or distribution logistics' resiliency in the face of unexpected events. Foundational practices for resiliency may be found primarily in the area of supply chain management and therefore maximizing or expanding the application of supply chain management and related best practices is more critical than ever. Examples of how to achieve supply resiliency include: