ISPE

Drug Shortage

Assessment and Prevention Tool

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Disclaimer

This ISPE *Drug Shortage Assessment and Prevention Tool* provides a structured, risk-based approach to the assessment of potential vulnerabilities across the supply chain, consistent with the principles of International Conference on Harmonisation's (ICH) Q9. [4] It will enable the identification of specific risks or products which might need to receive priority attention. ISPE cannot ensure and does not warrant that a system managed in accordance with this tool will be acceptable to regulatory authorities. Further, this tool does not replace the need for hiring professional engineers or technicians.

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1 The Task Team of ISPE's *Drug Shortage Assessment and Prevention Tool* developed a framework to organize the Drug Shortages Prevention Plan's (DSPP's) six dimensions to highlight the strategies and challenges associated with operationalizing each and also show the potential interactions that may exist between them. The order presented in this document therefore differs from that in the DSPP.

Preface

Welcome to the *Drug Shortage Assessment and Prevention Tool*, ISPE's latest contribution to address the global problem of drug shortages. I'm proud to be associated with this member-driven initiative, which focuses on better serving the needs of patients through the reliable provision of medicines.

As I talk to our industry members, regulators, and patients all around the world, they ask me "What's different?" What's new?" Well, what's different is that ISPE has developed this tool that provides the first simple but enduring route to reducing the chances of a disruption to the supply of medicines. Ever since ISPE started its work on drug shortages with its 2013 survey on the root causes of drug shortages, it has been abundantly clear that these problems could only be solved through a combination of guidance and tools that broadly address the totality of a company's operations and systems, including its organizational culture.

Having previously worked with patient organizations in many different countries, I am well acquainted with the growing complexity and geographical diversity of modern supply chains. It is rewarding to be able to show members that at last there is one tool that enables them to address supply chain risks with a common framework, no matter what their size, capability, or location might be. Hot spots and weaknesses can be quickly identified and, through the use of maturity level indicators, remediation plans prioritized and progress readily monitored.

We do still have a lot to do before we can declare success. Many pharmaceutical professionals, even those with decades of experience, look at all the rules and regulations, their own quality systems, the many inspections that occur both at home and abroad and question the need for additional guidance and tools. Some organizations—by which I mean the management of some organizations—don't always recognize their limitations in process, governance, or skills, nor are they sufficiently prepared to manage a disruption in supplies. "After all," they say, "we've implemented a quality system according to ICH Q10, and it has been inspected repeatedly without issue. Why do we need something else?"

Unfortunately, the data tells us that it is indeed needed, as evidenced by the shortages that still occur as a result of manufacturing or quality issues.

The good news is that many ISPE members around the world have contributed their time and expertise to develop ISPE's *Drug Shortage Assessment and Prevention Tool*, building on the best practices described in our Drug Shortages Prevention Plan, guidelines such as those issued by ICH, and standards from organizations such as ISO. This dedicated cadre of volunteers has assembled a holistic contribution to support a better understanding of industry and supply partner weaknesses, and provide concrete steps to put continual improvement plans into action.

I feel passionately that this comprehensive, multifaceted approach is the way forward. We can no longer adopt ad hoc solutions and ought to consider going beyond a product-by-product approach. We must address all the dimensions that can contribute to the interruption in supplies of medicines.

Finally, I most sincerely thank my industry colleagues and the many regulators who have contributed to the preparation of this seminal document and tool. I hope you do indeed find this a valuable addition to your management and organizational processes, and that you will use it to the benefit of patients all around the world.

John Bournas
President and CEO, ISPE

An Introduction

First Things First

The International Society for Pharmaceutical Engineering (ISPE) Drug Shortages Prevention Plan (DSPP) [3] was released in October 2014. It was developed as part of a cross-industry association initiative in response to a November 2013 request from the European Medicines Agency (EMA) to present proposals addressing the prevention of drug shortages caused by manufacturing and quality issues. Concurrently, discussions with representatives from other agencies, such as the US Food and Drug Administration (FDA); Japan's Ministry of Health, Labor, and Welfare; and Health Canada, demonstrated a need to move the discussion from questioning to implementation of best practices.

The DSPP was the logical next step for ISPE, following its 2013 Drug Shortages Survey [1] to determine the root causes of drug shortages. ISPE used the survey as its starting point to:

- Provide a holistic view of vulnerabilities within industry operations and supply chains
- Present recommendations for improvement
- Develop a structured approach by which industry could develop strategies and practices for each of the DSPP's six dimensions

An executive summary of the DSPP may be found in the Appendix.

From Theory to Practice

This ISPE *Drug Shortage Assessment and Prevention Tool* provides a structured, risk-based approach to the assessment of potential vulnerabilities across the supply chain, consistent with the principles of International Conference on Harmonisation's (ICH) Q9. [4] It will enable the identification of specific risks or products which might need to receive priority attention. The tool is being made available to help industry, especially manufacturers and marketing authorization holders, chart a path toward its "desired state." [2] It should be useful to anyone involved in the operation of a pharmaceutical supply chain for investigational or commercial products. The principles and processes described in the tool will also be useful to those engaged in product distribution.

The ISPE *Drug Shortage Assessment and Prevention Tool's* new and unique benefit makes it especially valuable: it identifies points to consider when assessing the gap between current operations and the desired state of a robust quality system, supportive quality culture, appropriate business continuity plans in place and well-qualified and -trained employees.

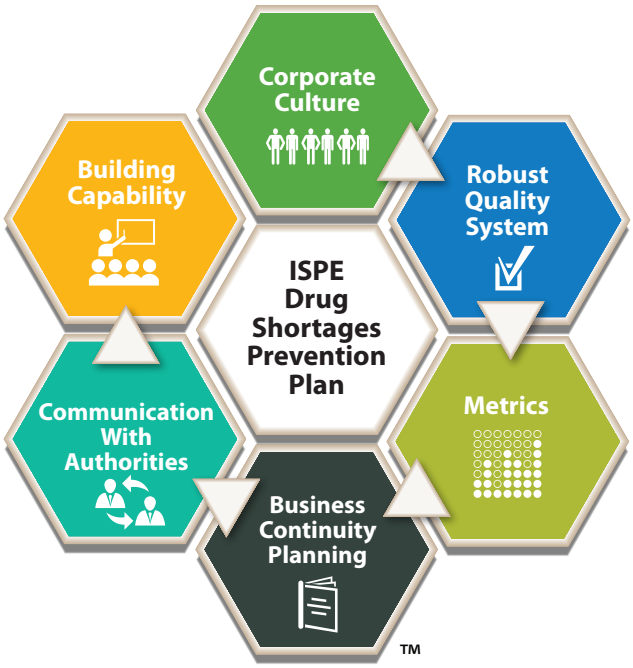
Each chapter of the *Drug Shortage Assessment and Prevention Tool* is organized in the same way. For each of the DSPP's six dimensions, regulatory insight is followed by a summary of the desired state and the relevant questions that need to be asked to determine your organization's maturity against that desired state (see Figure 1). **It is worth noting that in some instances, yes-or-no answers may be insufficient, and an organization will have to identify their evolution along a particular step, using maturity level**[2] indicators. [25]

Assessment results can become the foundation for an action plan to improve the robustness of the product supply chain.

2 "A maturity level is a defined evolutionary plateau for organizational process improvement. Each maturity level matures an important subset of the organization's processes, preparing it to move to the next maturity level. The maturity levels are measured by the achievement of the specific and generic goals associated with each predefined set of process areas. The five maturity levels, each a layer in the foundation for ongoing process improvement, are designated by the numbers 1 through 5."

—"CMMI for Development, Version 1.3," Carnegie Mellon University

Figure 1: Six Dimensions of the ISPE Drug Shortages Prevention Plan



Maturity Levels

The ISPE *Drug Shortage Assessment and Prevention Tool* provides a mechanism by which organizations can evaluate their ability to minimize the risk of a drug shortage by controlling the root causes of drug shortages.

The gap assessment questions contain a series of challenges in each identified area of drug shortage prevention control. Some challenges are straightforward and only require a "Yes/No" response; other controls, however, lend themselves to an assessment of the controls' maturity. The results of the assessments can become the foundation of an action plan to improve the robustness of the product supply chain.

Where an evaluation of maturity might be beneficial, the tool requests the entry of a maturity score from 1 to 5, one being the least level of maturity and 5 the highest level.

While the model is here illustrated by reference to Capability Development, a similar approach is applicable to selected or all the dimensions impacting an organization's operations and hence shortages. Alternatively, many companies may already have in place their own established maturity definitions which can then be applied to the controls defined within the gap assessment questions. The best approach is left to the discretion of the organization conducting the assessment. However, such is the value of maturity assessments, it is recommended that they are 'owned' by senior management and become an integral part of the organization's continual improvement program.

Table 1 provides some guidance as to how the maturity assessment may be applied.

Table 1: Maturity Assessment Model—Building Capability Example

GENERAL DEFINITIONS	
Level 1	Initial: Controls unpredictable and reactive
Level 2	Managed: Controls applied to specific initiatives, organizations, activities, projects
Level 3	Defined: Controls applied consistently across the organization against company policies and standards
Level 4	Quantitatively managed: Controls' effectiveness is measured
Level 5	Optimizing: Controls are improved and optimized across the organization
BUILDING CAPABILITY	
Level 1	Ad hoc training
Level 2	> Some organizations have training plans in place > Attendance at training is monitored
Level 3	> Capability development policies and processes in place > Staff development plans are in place and monitored > Role-based training is delivered > Competency assessments are conducted with follow-up > External supply partners are assessed
Level 4	> Staff development plans are aligned to company strategies, plans and roles > Supply chain partners are assessed and monitored against service level agreements > Staff performance metrics are in place and reported to senior management
Level 5	> Organization resourced to meet workload demands > Active collaboration across functions / departments > Effective knowledge management program > Varied learning methods focused on specific development needs > Development aligned to company strategies, plans and organizational roles > Metrics used to measure effectiveness of staff development and performance > Effective evaluation, monitoring and partnering with supply chain partners > Reporting of capability metrics to executive management > Implementation of improvement opportunities

Assessing the Gaps

The *ISPE Drug Shortage Assessment and Prevention Tool* is designed to help organizations assess their drug shortage preparedness. It outlines a five-step process to facilitate improvements across supply chains and increase supply reliability. In order to ensure the maximum effectiveness of the assessment for drug shortage mitigation, the outcomes from the gap assessment should be embedded and implemented within the pharmaceutical quality system and monitored periodically.

Step 1 Commit to a shortage-prevention culture across the organization.

Step 2 Conduct the self-assessment.

Step 3 Remediate.

Step 4 Implement new procedures and goals as part of the corporate culture and incorporate into the pharmaceutical quality system.

Step 5 Engage with stakeholders, including regulatory authorities, to inform them of the impact of changes implemented as appropriate.

Step 1 is self-evident. Unless leadership and senior management agree to address supply availability and potential for disruption and then improve the robustness and responsiveness of the supply chain from end to end, the organization will find it difficult to realize its full potential. Table 2 provides an overview of what a drug shortages prevention framework within an organization could identify.

Table 2: Desired State of Drug Shortages Prevention

DRUG SHORTAGE PREVENTION CONTROL FRAMEWORK
Is a shortage-prevention control framework in place for each product in the supply chain?
1. A well-developed definition of potential drug shortage within the organization and everyone in the entire supply chain is aware of this definition
2. A signal-detection mechanism in place from operations, planning, logistics and quality for a potential drug shortage and a communication tree to transmit the notification
3. Formal and multidisciplinary failure modes and effects analysis (FMEA) or other formal structured analyses to determine vulnerabilities within product-specific end-to-end supply chains
4. Vigilant monitoring program of suppliers, especially suppliers of key raw materials and components, critical equipment spare parts and critical quality control consumables, with particular attention to sources outside one's geographic base
5. Identification and mitigation of sole-sourced raw materials and components
6. Adequate product shelf-lives pertain when factors such as product quality control testing and release process, sample logistics, shipment, storage and distribution are accounted for
7. Defined minimum inventory recovery times associated with product recalls
8. Internal self-assessment groups focused on evaluating the risks of product-specific shortages
9. A control framework is reviewed and updated periodically, based on drug shortage metrics, including near-miss shortages
10. Evolving regulatory standards are reviewed and the impact analyzed relative to potential drug shortage
11. The external environment is monitored to identify and assess the impact of factors such as market dynamics, alternative suppliers/withdrawals and the overall balance of supply and demand

Step 2 is included in the ISPE *Drug Shortage Assessment and Prevention Tool*. Each section includes sets of questions that can be used to assess the gap between current operations and the desired state to minimize the opportunity for shortages. The output and feedback from this assessment could support annual product quality reviews.

Step 3 uses gap assessment results (probably via a multidisciplinary team) to address potential vulnerabilities across the supply chain in materials suppliers and contract manufacturing organizations (CMOs). The more detailed DSPP may help organizations address these vulnerabilities.

Step 4 completes the internal cycle. The recommendations become part of the business and corporate culture, reflecting management responsibility and commitment. This could include assessments by senior management (and other staff) that demonstrate success in maintaining an uninterrupted supply of product.

Step 5 engages external stakeholders in the improvement effort. For example, external suppliers, wholesalers, hospitals etc., may be interested to know what has been put in place, or the metrics being used to assess or monitor potential threats to supply. Regulatory agencies may also be interested to be alerted to preventive actions being implemented which may impact upon filings or site operations, or where the gap assessment has highlighted a particular vulnerability which may need to be addressed, and more especially a shortage avoided or mitigated: an update to the site master file could be envisaged.

Collaborating to Better Meet Patient Needs

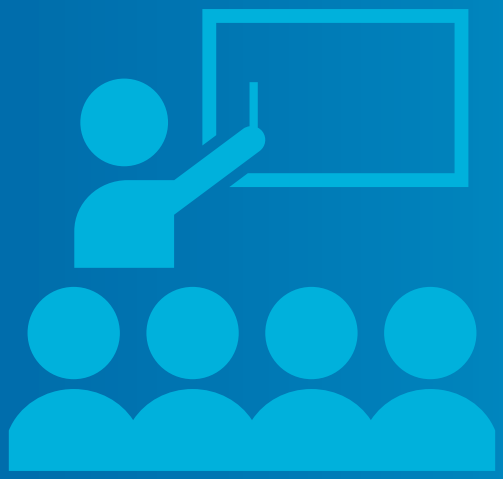
The ISPE *Drug Shortage Assessment and Prevention Tool* recognizes the endeavors of other organizations committed to the prevention and mitigation of drug shortages, including the Parenteral Drug Society's (PDA) Technical Report 68, "Risk-Based Approach for Prevention and Management of Drug Shortages," [22] and the AESGP/EFPIA/EGA/PPTA paper "Quality and Manufacturing Driven Supply Disruptions: Industry Communication Principles to Authorities." [18] The ISPE tool builds on these and other elements to present a holistic approach to preventing drug shortages. In subsequent editions of this tool, ISPE anticipates more contributions from its diverse member base so that the *Drug Shortage Assessment and Prevention Tool* and the principles it espouses may become universally understood.

As its name suggests, ISPE's *Drug Shortage Assessment and Prevention Tool* can make a valuable contribution to ongoing discussions aimed at helping organizations better understand their limitations—in process, governance, or skills—and determine what they must address and overcome to take advantage of the solutions offered by the DSPP.[3] By focusing resources on the identified weaknesses and driving the right priorities, organizations can significantly reduce their vulnerability to supply disruptions and ultimately better meet patient needs.

The ISPE *Drug Shortage Assessment and Prevention Tool* does not aspire to be the singular answer to an issue that is as complex as it is widespread. It is, however, a practical tool for professionals to embrace, as the industry struggles to maintain the supply of critical medicines to patients around the world.

3 Because industry and regulatory standards evolve, this guide is not a definitive standard operating procedure for preventing drug shortages or supply disruptions. It reflects the findings of the Drug Shortages Survey and the DSPP. ISPE cannot guarantee that following this guide will prevent questions from or observations by regulatory agencies. However, using this guide will support a more formal assessment of an organization's preparedness to avoid or manage a disruption in product supplies.

ISPE recognizes that differing requirements among regulatory authorities may warrant region-specific actions. While the guide does not attempt to customize solutions by region, it does provide a baseline for discussion, allowing readers around the world to identify opportunities for implementation.



01 Building Capability

1 Building Capability

1.1 Regulatory Background

Quality systems vary from one organization to the next. While most will use global quality systems, they can also vary among an organization's sites, depending on local good manufacturing practice (GMP) regulations [26] and corporate culture. As a rule, regulators expect that an organization's sites around the world will have:

> Sufficient staff and expertise to cope with production and quality issues

> Proactive responses to production and quality issues

> Appropriate change management processes to address capability issues

> Capable supply chain partners

1.2 Desired State for Building Capability

Regulators have indicated that human resource issues, and training in particular, are among the top ten GMP deficiencies. [21] This implies that a key challenge for senior management should be managing the organization's capabilities, as well as its processes and people.

When considering drug shortages an organization's capability must be designed to understand drug shortage risks; it must also address and mitigate such risks at the appropriate hierarchical level. Yet workforce capability means more than just training; optimal organizational structures, cross-functional linkages, clear and dedicated resources in key areas, and relevant metrics are all required. Organizations must know what talent and technical skills they need, and put appropriate learning, development and retention programs in place.

1.3 Developing Capability

1.3.1 Effective capability building

The capability of an organization is based on a number of dimensions:

> Having the right quality culture [27]

> Having the right quality systems [41]

> Having the right organizational capability: [28]

  > Effective organizational structure and collaboration across the organization

  > Effective leadership

  > Resources that are authorized, available and knowledgeable

  > Retention of capable and experienced staff

> Having effective supply chain partnerships [30] and avoiding contractual complexity based on operational preference rather than minimum quality standards

1.3.2 Organizational capabilities

A well-designed organization provides a clear and consistent model for operating and organizing resources to achieve strategic objectives and operational plans. To minimize the risk of drug shortages, an organization's structure should be designed to ensure:

> Effective leadership and management

> Availability of resources to meet work demands and responsibilities

> Decision-making accountability at each level of the organization

> Clear definition of roles and responsibilities

> Skills and training to enable effective decision making and fulfill roles and responsibilities

> Effective engagement with supply chain partners

Business process design should ensure effectiveness and consistency of operations, integrated supply chains, and collaboration across the organization in order to support the entirety of the product portfolio throughout the totality of the life cycle.

1.3.3 Leadership and management

An organization's leadership and management must:

- Define clear goals aligned to the organization's strategies and plans, including drug shortage avoidance
- Maintain awareness of, and provide resources to, compliance-focused activities to reduce risk of shortage arising from regulatory action
- Make risk-based decisions to mitigate the risks associated with drug shortages
- Recognize and manage according to the strengths of the organization's resources
- Motivate resources to identify and mitigate potential drug shortage risks
- Promote integrity and transparency including reporting of drug shortage risks
- Communicate organizational strategies and plans relating to drug shortages

Such leadership skills should be promoted throughout the organization from senior executives through organizational and shop-floor managers and supervisors.

1.3.4 Internal skills and capability development

Effective staff development programs are created and conducted by qualified learning program developers, trainers and subject matter experts (SMEs).

Capability development programs should be based on organizational strategies, plans, and individual roles relating to drug shortages. Development plans should identify the skill level to be attained and should be tailored to the address the skills gaps of the organization and its workforce. Regarding drug shortages, the extent and depth of development should be adjusted for each individual role. For example, employees indirectly involved in supply chain continuity may require communications or awareness training, while those directly involved in ensuring supply reliability would receive more comprehensive development programs.

Capability development programs should consider a variety of learning approaches, including but not limited to:

Training

- **Informational or awareness:** Employees are not learning a specific process or skill, but they are raising their awareness of a given topic.
- **Web-based:** The delivery of educational content via the internet, a private intranet, or an extranet. Web-based training can provide links to other learning resources, synchronous, or asynchronous content.
- **Read and understand (R&U) procedures:** The procedure is determined to be at a level that will allow the employees to read and completely understand and be able to demonstrate the skill.
- **Instructor-led (ILT):** Classroom training that uses lecture and exercises, games or other materials to allow employees to practice what they are learning. These trainings are taught or overseen by a qualified trainer and require training documents and knowledge assessment. [29]
- **On-the-job (OJT):** A structured activity with very clear, predetermined outcomes. This type of training is delivered by a qualified SME and will require one or multiple skills assessments.
- **Learning management system (LMS):** LMSs are becoming commonplace within organizations in order to plan, organize, facilitate and effectively track the development of individuals and organizations. [31]

Mentoring and coaching

Mentoring and coaching is based on the use of one-to-one discussions to enhance an individual's skills, knowledge or performance.

Social media

Social media channels are used to exchange knowledge and experiences.

Self-learning

Using ISPE's knowledge base, such as Good Practice Guidelines, to enhance subject matter knowledge.

Attendance at industry conferences and seminars

Enable access to subject matter experts and sharing of organization and personal experiences, and may increase employee awareness.

It is essential that learning objectives and work-performance targets be established so that competence and performance of individuals may be evaluated as well as the learning tool's efficacy.

While each organization must define and establish its own staff management and development strategy, a mixed-learning model can enhance effective capability building. Staff should understand the "whats" as well as the "whys" of their roles. While this document is not intended to recommend one approach over another, by allowing both employees and managers to define individual strengths and development opportunities, staff development may be enhanced.

1.3.5 Supply chain partner capability

An organization's capability is not limited to internal resources. Third parties support all aspects of the supply chain from raw material supply to validation services and can have a considerable impact on the supply chain and risk of drug shortages. Capable third parties will understand supply-chain risks, and their impact on drug shortages. They will have in place appropriate organizations, processes, resources and skills to minimize such risks. Indeed, there can be significant value in the sharing of formal risk assessment between all supply chain partners, leading to the potential development of a common risk assessment framework across the entire supply chain.

Organizations must fully understand the capability of third parties so that they can appropriately evaluate, educate and monitor supply chain partners. Such education should include an appreciation of the medical priority of the products being manufactured. Supplier contracts and agreements should address the specific roles and capabilities required of the organization to ensure the effective supply of services and products. The sharing and discussion of maturity level indicators with supply chain partners during inter-company audits can be extremely useful in identifying potential weaknesses or vulnerabilities and stimulation appropriate remediation measures.

1.3.6 Knowledge management

Knowledge management should be seen as a key vehicle for recognizing and preventing drug shortages. Knowledge management is not limited to technical content; it also includes developing decision-making capabilities in complex situations. Staff should have a holistic view of decisions relating to legal and regulatory requirements, patients' health and safety, and of the supply chain. Team exercises and mentoring of young professionals can be supportive elements of knowledge management. Transfer of product and process know-how and transfer of knowledge between know-how owners and their delegates and/or successors should be transparent and documented. Information relating to product market criticality should be visible.

Knowledge management should be driven like a quality system, from planning for execution to reporting and documentation. It should be a part of everyone's job and woven through the fabric of an organization. And while there should be a responsible owner for a knowledge management program, it is important to have resources and capabilities with expertise in knowledge management

to develop the processes and systems that further enable a Pharmaceutical Quality System as described in ICH Q10. [5]

These concepts form the basis for the Capability Building gap analysis, shown in Table 3.

1.4 Gap Analysis of Capability Building

Table 3: Gap Analysis of Capability Building

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Organizational Capability			
Does the way the organization is structured enable the communications needed to proactively detect a potential drug shortage?			
Has your company invested in building the capabilities and/or hiring the right resources that will help detect and/or prevent drug shortages?			
Are resources at all levels of the organization empowered to make decisions relevant to their role and skills level?			
Do these resources have the tools needed to empower them to identify shortages and alert management of the risks?			
Does your organization operate processes that evaluate and provision resources to meet ongoing work demands?			
Does your organization evaluate job satisfaction and take action to address concerns and aspirations of staff?			
Does your organization monitor staff turnover in order to evaluate and address the impact on your organization's capability?			
Does your organization define and measure performance targets based on organization strategies, plans and roles?			
Does your organization expect and assess maturity level indicators for all your supply chain partners?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Do performance targets include the identification and reporting of drug shortage root causes, as identified by the DSPP?			
Leadership and Management			
Do your leaders and managers define clear goals aligned to the organization's strategies and goals relating to drug shortages?			
Do your leaders and managers make effective risk based decisions to mitigate the risks associated with drug shortages?			
Do your leaders and managers recognize and manage according to the strengths of the organization's resources?			
Does leadership have the tools to make sure that the right personnel are assigned to tasks that if not executed properly, will lead to a shortage?			
Do your leaders and managers actively promote integrity and transparency including reporting of compliance issues and drug shortage risks?			
Do your leaders and managers communicate organizational strategies and plans relating to drug shortages?			
Does leadership build alliances and partnerships to strengthen the organization's capabilities?			
Does leadership recognize the need for capabilities, internal or through partnership, aimed at identifying and managing drug shortages?			
Internal Skills and Capability Development			
Are your organization's learning plans related to performance targets, organization strategies, plans and roles relating to drug shortage prevention?			
Does your organization define target skills levels for each role and evaluate current skills levels of individuals?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Are your organization's learning programs aligned to evaluated skills gaps?			
Do defined skills and learning objectives address non-technical and technical skills across key areas, including drug shortage prevention?			
Do your company training strategies address cross training?			
Are development plans and training curricula developed and executed by qualified course developers, trainers and subject matter experts?			
Are development plans and training curricula in place for each position within the product supply chain?			
Is the training curriculum offered focused on avoiding drug shortages?			
Do the programs help trainees understand the link between the supply chain and drug shortage; the importance of compliance and ensuring a continuous supply of product?			
Do development plans and training curricula include the elements defined in the drug shortage prevention control framework?			
Are development and skills metrics part of the quality indicators and periodically reported to site- and corporate managers?			
Is development and training planning compliance monitored and enforced?			
Do learning programs include examples of near-miss shortages, or reviews of actual shortages?			
Is a drug shortage near-miss reporting program in place and included in the training curriculum?			
Do learning programs address continuity in an emergency situation?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Are learning objectives within a curriculum clearly documented and measurable?			
Does your organization use a variety of learning and training methods to ensure the effectiveness of staff development, e.g.: > Role-based training > Web-based training > Read and understand > On-the-job training > Instructor-led training > Conferences > Social media channels > Self-learning			
Does your organization provide dedicated mentors and coaches to support the ongoing skills development of individuals?			
Do learning programs require an assessment of competence against learning objectives?			
Supply Chain Partners			
Do you have a program to ensure that your supply chain partners understand the risks their services and products present to the supply chain?			
Are supply chain partners made aware of the potential impact of their services and products on drug shortages?			
Do supply chain partners openly report known risks to the supply chain arising from the services and products they supply?			
Do you evaluate the capabilities of supply chain partners?			
Does your organization track the effective resolution of supply chain partner assessment observations?			
Are supply chain partners subject to ongoing performance reviews?			
Does your organization include an evaluation of staff skills development during supplier assessments?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Knowledge Management			
Is knowledge management recognized as enabling the prevention of drug shortages?			
Is there a process or group to coordinate knowledge management activities and ensure they are built into the workflows of the business)?			
Does your organization have a process in place to assess the medical necessity of a given product against the risk of its shortage?			
Does leadership include knowledge management as an initiative or enabler of the organization's drug shortage strategy?			
Are knowledge flow processes, such as Communities of Practice, Lessons Learned and After Action Review embedded in the organization's management systems?			
Is drug shortages prevention a recognized knowledge management component with defined activities, investigations, data and information supporting root cause identification and resolution?			
Are knowledge management efforts and trends regularly assessed, benchmarked, and analyzed?			

02 Corporate Culture

2 Corporate Culture

2.1 Regulatory Background

As an organization builds its capability to identify, assess, and mitigate drug shortages, its corporate culture is its greatest ally. "Corporate culture," refers to the expressed and implied ways in which an organization operates. You may often hear reference to a "quality culture" – but there is not a separate quality culture – there is one culture at an organization or at a site. The corporate culture reflects an organization's "culture of quality"– or the lack thereof. As such, corporate culture affects both quality performance and supply chain excellence, and is critical to the prevention of shortages.

Corporate culture is driven by leadership example and, in the case of drug shortages, affects the ability to identify and act upon near-miss shortages, assure transparent problem escalation, and the drive for supply-chain resiliency. A healthy corporate culture also requires management ownership and accountability, performance metrics that promote continual improvement, and a strong risk-management framework. All are key to the proactive identification and prevention of shortages.

While no regulations currently describe expectations for a corporate culture, there is growing regulatory interest [32, 33] in promoting quality more broadly within the context of corporate culture. During ISPE's April 2015 conference on quality metrics, Dr. Janet Woodcock, director of the US FDA's Center for Drug Evaluation and Research, described her intent to move both industry and the FDA along the "continuous improvement pathway" by adding metrics and a quality management system to the FDA's risk-based approach. [6,7] The interest in metrics as a vehicle to assess quality performance is reflected in an equivalent interest in understanding and measuring an organization's quality culture.

The implied focus and interest in quality culture signals a shift from a focus solely on regulatory compliance to include a focus on continual improvement where there is deep understanding throughout an organization of what is critical to product quality.

2.2 Desired State for Corporate Culture

Corporate culture can play a central role in the prevention of drug shortages[4] and should not be adversely affected or overtaken by immediate business needs. Reality often differs from policy, however, and people may make decisions that undermine quality. [6]

The corporate culture gap analysis outlined in Table 4 is based on the work of ISPE's quality culture team. It has developed a holistic framework, "Six Dimensions of Cultural Excellence," which was introduced at the ISPE Quality Metrics Summit in April 2015. The framework acknowledges that each organization will have a different context, within which their corporate culture exists, based on organizational ownership, supply-chain configuration, maturity, product mix and regional influences. Knowledge of this context is critical to assessing the influence and current health of the culture within a given organization. The six dimensions of cultural excellence, shown in Figure 2, facilitate a holistic assessment of those elements required to foster, develop, monitor, measure, learn and ultimately improve an organization's corporate culture.

4 Speaking at the April 2015 conference, Woodcock also noted that "fear of reporting problems internally within an organization and fear of negative repercussions from reporting them to the agency drives behaviors that are not just nonproductive, but anti-productive."

Figure 2: Six Dimensions of Cultural Excellence Framework[5]

The six dimensions of cultural excellence include:

1 Leaders establishing and engendering the vision for the organization through leading by example

2 Periodically surveying for employee attitudes and mindsets through employee engagement tools

3 Assessing and coaching for the desired behaviors using Gemba walks [34] and other face-to-face assessment tools

4 Ongoing monitoring and surveillance of the key triggers and leading indicators of quality [35] across the supply chain

5 Oversight, reporting and reviews by the 'learning leaders' to proactively establish current status and direct resources to drive improvement

6 Building capabilities [28] for the structural enablers of a healthy culture, such as:

> Learning organization development

> Developing learning teams

> Influencing and recognizing organizational change

> Proactive problem solving

> Getting to true root cause

These concepts form the basis for the Corporate Culture gap analysis, shown in Table 4 below.

5 Reprinted with permission from the ISPE Quality Culture Team, which, operating under the auspices of the current ISPE Quality Metrics Initiative, launched their Six Dimensions of Cultural Excellence framework at the Quality Metrics Summit held in Baltimore, Maryland, US, in April 2015.

Calnan, N. (2015a). "Culture of Quality: More than a Slogan." In ISPE (Ed.), Quality Metrics Summit, Baltimore.

Calnan, N. (2015b). "Protecting the Patient: Enhancing the Quality of Pharmaceutical Products." Thesis.

2.3 Gap Analysis of Corporate Culture

Table 4 will help organizations conduct a high-level assessment.

Table 4: Assessment of the Health of the Current Corporate Culture

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO EVIDENCE OF SUPPORTING DOCUMENTATION	COMMENTS
Leadership and Vision			
A corporate policy exists that articulates the organization's expectation for quality excellence. The vision, regarding the organization's commitment to quality excellence, is available and clearly understood by all within the organization.			
This vision is also available and clearly understood by your external partners across the supply chain of your products.			
Leadership at your organization takes purposeful steps to systematically demonstrate their commitment to the vision through their behaviors and leading by example.			
Mindsets and Attitudes			
Employees have job function training that is competency based as well as training in good manufacturing practices.			
Job descriptions reflect references to the importance of upholding GMPs and continual improvement.			
There are formal processes to observe and assess employees' mindsets and attitudes within your organization.			
Employees report that they understand how their roles affect quality.			
Employees and management acknowledge a culture of "speak up without penalty," whether through a whistleblower policy or an ombudsman's office.			
There is evidence from employee surveys that employees are comfortable raising concerns and believe management will act on them.			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO EVIDENCE OF SUPPORTING DOCUMENTATION	COMMENTS
Gemba and Shop Floor Assessments			
There are both formal and informal processes in place to ensure management visit the shop floor to observe, assess, listen and coach the employees, such as Gemba walks			
There is evidence from these assessments and Gemba walks to confirm that the desired behaviors are actually in practice across the supply chain on a day-to-day basis.			
Monitoring and Measuring			
The organization has a set of relevant KPIs and metrics that clearly link the desired behaviors to the critical quality outcomes for the organization, the product and the patient.			
These measures are clearly understood by all and current progress against targets is visible to all within your organization, e.g.: visual management boards, functional meeting updates.			
The measures incorporate a blend of leading and lagging indicators to promote the desired behaviors and outcomes and monitor for triggers that alert the existence (or potential) for non-desirable behaviors and outcomes.			
Management Oversight and Reporting			
Aligned quality objectives are established and are linked to organization goals.			
Senior Management routinely conducts reviews of the pharmaceutical quality system.			
There is a policy and expectation for transparency and the escalation of significant events.			
There are formal processes for action-oriented oversight and reporting against the triggers and metrics.			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO EVIDENCE OF SUPPORTING DOCUMENTATION	COMMENTS
The oversight and reporting activities are systematically applied to both internal and external partners within your supply chain.			
Structural Enablers for Culture			
There are formal processes for capturing improvement suggestions, reporting near misses and actively seeking insights and shared learning.			
Leadership champions organizational change, and also actions, enables, encourages and ensures its effectiveness.			
There are knowledge management processes in place to support the effective sharing of insights and learning across the organization. They include processes to enable knowledge flow across external organizational boundaries.			
There are formal organizational development processes in place to build the capabilities necessary to foster a learning organization: proactive problem solving, transparency, accelerated team-based learning, enabling change and continual improvement.			
Programs for recognizing and rewarding individual and group quality performance are in place.			

03 Business Continuity Planning

3 Business Continuity Planning

3.1 Regulatory Background

There are documented regulatory expectations regarding business continuity for certain elements of pharmaceutical activities and quality systems, such as pharmacovigilance. There do not appear to be many, however, that are specific to supply chain resilience.

Improving business continuity was one of the goals defined in the EMA's 2013 publication "Reflection Paper on Medicinal Product Supply Shortages Caused by Manufacturing/ Good Manufacturing Practice Compliance Problems." [11]

In that same year, EMA published a document for the benefit of regulators—also arguably related to business continuity planning—entitled "Points to Consider for the Overall Assessment of a Supply Shortage of a Medicinal Product due to GMP Noncompliance/Quality Defects." [12] In it, the EMA recommends an assessor discuss the following with the marketing authorization holder (MAH):

- Provide a technical report of problems in the manufacturing or quality area that have given rise to the possibility of a shortage. Ask the MAH to provide analytical data and discuss its relevance, including:
  - What is the root cause of the supply interruption?
  - Where in the manufacturing process does it occur?
- What preventive and/or corrective actions has the organization taken to avoid and/or resolve the shortage?
- What is the current stock situation/ member state?
- Are there any buffer stocks at distributor or hospital sites?
  - Forecasted demand rates and estimated stock out dates should be provided.
  - Request a discussion on the feasibility of stock rotation between member states to cover and any other measure to prevent the shortage.
- What is the estimated lead time before the product reaches out-of-stock level?
  - Provide lead times and a timetable for (a) manufacture and supply utilizing the batches in question and (b) manufacture and supply utilizing new batches.

In June 2015, Health Canada, the federal department responsible for health in Canada, issued Regulations Amending the Food and Drug Regulations (Shortages and Discontinuation of Sale of Drugs) [24] in which it proposes a mandatory drug shortage and discontinuation reporting system by a third-party website. The intent is to "provide patients, practitioners, and other health care stakeholders with reliable and trustworthy information in a timely fashion, as well as a more accurate picture of which drugs are actively being sold on the Canadian market."

3.2 Desired State for Business Continuity Planning

As stated in Section 1.3.1, avoiding drug shortages requires a multidimensional approach. While many of the solutions explored in the DSPP center on improving quality systems and governance structures across an organization, the ISPE team also identified the supply chain as a critical component. This is especially true as organizations rely increasingly on suppliers and manufacturers around the world.

The supply chain must be integrated with an organization's quality and governance systems for it to function most effectively. This builds a robust supply chain that not only detects shortages, but offers visibility and increased transparency as well. These enable organizations to either address the issue proactively or fix it quickly. Both reduce manufacturing downtime.

To ensure that a supply chain retains its robustness, the organization must analyze its manufacturing operations and suppliers to determine where the supply chain is most vulnerable. Once the risks have been identified, the organization should support its supply chain with backup and redundant systems.

Finally, the DSPP suggests that organizations test their supply chains using scenarios and simulations. These will further strengthen management's ability to make decisions that keep the supply chain redundant and robust, when and where needed.

Some noteworthy points about business continuity planning:

- **Achieve robustness:** Integrate *internal and external* supply chain networks with a robust quality system
- **Build redundancy:** First assess each product proactively to understand vulnerabilities and identify areas where redundancy may be needed. On the basis of this evaluation, plan for additional capacity, a backup facility, a second supplier, and additional inventory.
- **Establish resiliency:** Develop crisis management plans to identify and remediate weaknesses or gaps in the quality system before an issue occurs.
- **Develop facility response plans:** These will restore operations if an event occurs.

These concepts form the basis for the Business Continuity Planning gap analysis, shown in Table 5, below.

3.3 Gap Analysis of Business Continuity Planning

Table 5: Gap Analysis of Business Continuity Planning

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
General Considerations			
Is there a clear commitment from the top management to prevent supply disruptions?			
Are products evaluated and categorized based on their medical necessity and the availability of therapeutic equivalents?			
Is there a robust risk assessment program that can anticipate potential failure points and areas of risk for product supply?			
Is the risk assessment documented with clear mitigation plans, regular reporting and change management?			
Is risk assessment institutionalized to survive in-licensing, out-licensing, divestiture, change of control?			
Resilience			
Have demand forecasts, including potential upsides, been evaluated against available capacity?			
Have demand forecasts been appropriately communicated to suppliers to assure continued supply of necessary materials?			
Are supply metrics in place to provide early warning for supply shortfalls?			
Is there an appropriate process in place to assess market conditions and indicators that may impact drug supply?			
Have lean manufacturing principles been applied to achieve short cycle times, improve machine turnover and increase ability to respond to interruptions?			
Have safety stock levels been established at adequate levels to assure supply during unforeseen increases demands, or interruptions in supply?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Robustness			
Is your manufacturing operation integrated with your quality systems?			
Is your clinical department integrated with your manufacturing operations?			
Has the partnership between manufacturing and quality organizations been firmly established?			
Has your organization been able to integrate its quality systems with its partners while respecting the partner's need to serve multiple customers and manage their internal complexity?			
Are systems in place that would allow information generated at partners (or manufacturing sites) to be fed back to your organization's quality group?			
Does your organization have metrics in place to help measure the interactions between quality and manufacturing?			
Are products evaluated annually to understand process variability, failure rates and important product quality trends?			
Where product evaluations indicate that there are product quality risks, are appropriate corrective actions put in place in a timely manner?			
Redundancy			
Is there a process in place to assess each product proactively, understand vulnerabilities and identify areas where redundancy may be needed?			
Does your organization have a process in place to assess the medical necessity of a given product against the risk of its shortage?			
Does the risk assessment process address critical products individually (e.g., by SKU)?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Does the risk assessment process address redundancy by product by unit operations? Is redundancy or ease/difficulty of transferring of dispensing, blending, tableting, primary, secondary, or tertiary packaging operations across the supply chain considered?			
Does the risk-assessment process address redundancy requirements based on supply chain elements?			
Are the following elements considered?			
> API, raw materials, critical components?			
> CMOs?			
> Capacity across sites?			
> Validated cold chain capabilities?			
> Controlled or hazardous transportation channels?			
> Distribution channels?			
Is the competitive landscape understood for your products and have you assessed shortages with respect to competitive capacity?			
Has a comprehensive business continuity plan been established, which includes an assessment of redundancy opportunities?			

04 Robust Quality Systems

4 Robust Quality Systems

4.1 Regulatory Background

Pharmaceutical manufacturers are required to establish effective pharmaceutical quality systems to comply with the various legal and regulatory requirements in place around the world. And while regulations may vary from one country or continent to the next, there are regulatory instruments that provide common ground.

The ICH Q10 [5] is a tripartite guideline that describes a comprehensive model for an effective pharmaceutical quality system that can be implemented throughout the different stages of a product life cycle. It has been adopted in the European Union, Japan, the United States, and Canada, and, as of May 2015, in Australia.

In the United States, the FDA issued guidance in 2006 [10] to help manufacturers implement modern quality systems and risk management approaches to meet the requirements of the FDA's CGMP regulations [36] and the Code of Federal Regulations (CFR) Title 21, parts 210 and 211. The guidance describes a comprehensive quality systems (QS) model, highlighting the model's consistency with the CGMP regulatory requirements for manufacturing human and veterinary drugs.

In June 2015 Health Canada issued Regulations Amending the Food and Drug Regulations (Shortages and Discontinuation of Sale of Drugs) [24] in which it proposes a mandatory drug shortage and discontinuation reporting system by a third-party website. The intent is to "provide patients, practitioners, and other health care stakeholders with reliable and trustworthy information in a timely fashion, as well as a more accurate picture of which drugs are actively being sold on the Canadian market."

In Europe, Articles 46 and 47 of the European Council's directive 2001/83/EC [8] require compliance with the principles and guidelines of GMP. These principles and guidelines are found in EudraLex Volume 4: *Good Manufacturing Practice (GMP) Guidelines*. [9] Chapter 1 of the Eudralex Volume 4 was updated and renamed "Pharmaceutical Quality System" for operation from 31 January 2013. [23]

4.2 Desired State for Robust Quality Systems

Robust and well-established quality systems are critical to quality performance. Organizations rely upon the universal implementation of quality management systems, from early development through commercial launch and the supply chain life cycle.

Table 6: Building Blocks of Robust Quality Systems

Basis	> Factories/facilities/infrastructure > Material > Equipment > Experts > Environment
Pharmaceutical Quality Systems	> Management review and responsibilities > Process performance/product quality/continual improvement > Deviation/Investigation management and root-cause analysis > Corrective action/preventive action (CAPA) > Change management > Inspection and internal audit management > Outsourced activities management > Complaints management > Training
Enabler	> Quality risk management > Knowledge management

However, even the best-implemented quality system needs well-designed and -maintained factories, infrastructure, material, and equipment, as well as a controlled environment. It needs sufficient expertise and human resources for a good understanding of products and processes. Finally it needs "enablers" to control a constant level of quality and compliance: quality risk management and knowledge management. A well-developed quality culture and good management oversight provide its framework.

The gap analysis for robust quality systems is structured according to the building blocks in Table 6.

The various elements of a quality system are generally well considered and detailed in most pharmaceutical organizations. Yet, the quality system structure is often established with emphasis on activities that proceed well and according to plans. Adverse situations, such as an interruption of supply and the potential development of a shortage, are not always anticipated or detailed as well as they could be.

These concepts form the basis for the Robust Quality Systems gap analysis, shown in Table 7, below.

4.3 Gap Analysis of Robust Quality Systems

Table 7 lists a number of questions in each sector of the quality system, which organizations may use to ensure that sector and its aspects are appropriately addressed in the event of a shortage situation.

In addition, there are references made to a variety of sources, including: ISPE good practice guides, Baseline® Guides or other ISPE Guides that contain more background, ICH standards, EudraLex Volume 4: *Good Manufacturing Practice (GMP) Guidelines*, [9] and CFR Title 21, parts 210 and 211.

Table 7: Gap Analysis of Robust Quality Systems

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Production Factors			
Factory/facilities/technical infrastructure			
Is an ongoing risk-management process or system in place to evaluate facility and utility systems, which enables life cycle management of the drug manufacturing facility, equipment and utilities and could be defined as continual risk management?			
Material			
Are incoming ingredients and materials monitored to ensure they are from approved sources, using the selected supply chain?			
Does a material review board (or equivalent) exist and make decisions to minimize material related risks?			
Is there a definition of critical materials? Is there a list of critical materials? Are there contingency plans for critical materials that may be sole-sourced or coming from suppliers with poor quality, compliance or service level?			
Equipment			
Is there an ongoing process within a risk management framework to assess manufacturing equipment on a routine basis?			
Is there a process for maintaining oversight of critical equipment spares, and stock holding of parts with extended lead times			
Is there a risk-based investment plan available to determine in-time needs for substitution of old equipment?			
Is an equipment reliability program in place that prevents equipment failures and identifies trends in equipment reliability performance?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Is the preventive maintenance program data evaluated routinely to ensure that facilities and equipment are appropriately maintained?			
Experts			
Have leadership and senior management committed sufficient and appropriate human resources?			
Have SMEs for products and manufacturing processes been identified?			
Are resources reviewed periodically to map knowledge and capabilities vs. workload and capacity vs. workload?			
Environment			
Is there a cross-functional team that regularly reviews environmental monitoring trends and subsequent engineering needs?			
Pharmaceutical Quality Systems			
Management review and responsibilities			
Does a quality policy exist and is it readily available to the entire workforce?			
Does the quality policy address the obligation to avoid drug shortages?			
Does the quality policy define quality as a mandated value across the entire organization?			
Are there corporate standards and tools providing the minimum requirements for all quality-system-related activities: laboratory, materials, facilities and equipment, production, packaging, etc.?			
Have you identified senior managers responsible for shortage prevention and/or mitigation?			
Have responsibilities of functional managers been defined?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Are individual and collective roles defined and understood by all?			
Does a timely and effective communication and escalation process exist to raise quality issues?			
Is there a formal process for drug shortage leading indicators and drug shortage problem escalation?			
Does management review process performance and product quality and of quality system conducted at established time points?			
Do you conduct performance reviews of supply disruptions?			
Is there a formal process for periodic management reviews?			
Is there an integrated approach to assessing drug shortages systems in place that support monitoring of the potential impact of internal and external factors?			
What is the management notification process for potential shortages or near misses?			
Have you set annual targets and incentives related to the avoidance of drug shortages?			
Process performance, product quality, and continual improvement			
Do you advocate continual improvement?			
Are manufacturing processes and control strategies based on principles of continual improvement?			
Do you have a life cycle and continual improvement strategy for existing products?			
Are production processes subject to regular revision and revalidation to reconfirm process performance? Do validation procedures require continual process verification and what are the conclusions?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Are procedures in place to ensure commercial manufacture maintains state of control?			
Are work orders trended to detect problematic equipment or systems? And what are the resultant actions if a trend is detected?			
Are pharmaceutical development activities consistent with ICH guidelines?			
Do you use an enhanced (QbD) approach for product development?			
Are critical quality attributes (CQAs) and critical process parameters (CPPs) available?			
Are CPPs monitored and within Process Acceptance Ranges (PARs) and No Acceptance ranges (NORs)?			
Is the Annual Product Review and the Product Quality Review subject to regular Pharmaceutical Product Life Cycle measures and actions in order to keep products well maintained and to reduce the impact on drug shortages?			
Deviation, investigation, and root cause analysis			
Is there a process to resolve root cause?			
Is “human error” refused as a root cause?			
Is “single event” refused as a root cause?			
Have you named a final approver of investigations?			
Who is the final approver of investigations and does this person have the requisite knowledge and experience to perform this activity?			
Corrective action and preventive action (CAPA)			
Are there procedures in place to address recurring deviations/CAPAs related to a specific product, process or equipment?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Is there a statistical trend analysis available to ensure that the total amount of CAPAs will decrease?			
Is it possible to open up unresolved and overdue CAPAs in the IT system, using a new title?			
Are CAPAs reviewed by an un-biased/ independent individual?			
Are processes in place that could mitigate the unexpected, such as natural disasters, or economic motivated adulteration of materials, which could impact drug shortages?			
Complaints management			
Are complaints systematically checked for creating potential drug shortages?			
Is the unavailability of drugs accepted as a rationale for complaints?			
Is the geographical origin of complaints systematically evaluated in order to challenge potential drug shortages?			
Change management			
Is priority setting in place for change management applications and approvals related to drug shortages?			
Is the regulatory affairs department actively involved in drug shortages crisis teams?			
Is there an active communication process regarding approvals for urgent changes with the regulatory authority?			
Are registration variations in multiple markets coordinated in order to reduce impact to commercial manufacturing plans and subsequent drug shortages?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Inspection management			
Does the organizational set up ensure there is a consolidated and holistic view between inspection findings and internal quality risk-management processes?			
Outsourced activities			
Do you have a policy to govern outsourced activities services, material and suppliers?			
Have you assessed all outsourced activities and material suppliers for suitability, competence and ability to maintain supplies using principles of quality risk management? Do you monitor them?			
Do you have processes that ensure CMOs are held to the same quality standards as internal operations and that CMO issues are communicated promptly to the appropriate decision makers?			
Training			
Do you have a drug-shortage-prevention training plan?			
Are there effectiveness checks done for training?			
Enablers for Pharmaceutical Quality System ICH Q 10			
Quality risk management			
Do you conduct regular reviews of end-to-end supply chain to ensure ongoing ability to avoid supply disruption?			
Is there a definition of critical or sole-sourced materials?			
Is there a list of critical or sole-sourced materials?			
Are there contingency plans for unavoidably critical or sole-sourced materials?			
Do you evaluate future risks to product supply?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Do annual product reviews (APRs) include a statistical evaluation of process capability value (CPK), critical quality attributes (CQAs), and critical process parameters (CPPs) to identify improvements?			
Do APRs include site-review and cross-site (end-to-end) product reviews?			
Is product demand trended to detect patterns or indications that may affect supply?			
Knowledge management			
Do you have a formal procedure for technology transfer?			
Does your organization have a process in place to assess the medical necessity of a given product against the risk of its shortage?			
Have you identified potential threats to supply, as well as actions assigned and executed during technology transfer?			
Have you established metrics to evaluate technical transfers and scale-ups?			
Are there metrics evaluating technical transfers and scale ups and a determined period or number of batches following these events? If the results are substandard what corrective actions are taken?			

05 Metrics

5 Metrics

5.1 Regulatory Background

Pharmaceutical organizations can choose from a wide range of metrics, yet determining which are appropriate as part of a quality system has yet to be decided upon. This chapter will discuss the quality indicators ISPE has previously shared with regulators and include recommendations from ISPE workshops on this topic. [37]

5.2 Desired State for Metrics

Inadequate governance and metrics within a quality system have previously been demonstrated to be a potential root cause of supply disruptions. [1] Additionally, more recent work by ISPE [2] provided insight into the benefits of utilizing quality metrics to monitor performance, create transparency and inform improvement of pharmaceutical manufacturing, which in turn can provide line of sight to supply chain reliability.

When establishing a set of robust metrics, it is worth noting that metrics are measures used to gauge a quantifiable performance component, such as a division, a site product or process performance. Metrics should be specific and meaningful, and therefore limited to the critical few that enable focus on identified priority areas. Additionally, due to the differences in quality system and supply chain maturity, organizations must select their own metrics to monitor and identify areas of potential shortage vulnerability.

Evaluation, analysis and governance of quality metrics are essential elements of ensuring the ongoing value of the identified metrics. They should be thoughtfully established, based on an assessment of risk, monitored and matured over time according to the evolution of the quality system, product and or supply chain robustness. Indeed, carefully selected metrics can support the better monitoring of the quality system and provide signals for issues such as shortages. It should also be noted that metrics most reliably function as potential indicators of drug shortage when other pharmaceutical quality system elements are robust.

Some points to consider when determining metrics for monitoring shortage vulnerability:

- While metrics are not a solution to shortages per se, they do have the potential to prevent shortages because they can point to a potential supply constraint.
- Supply chain metrics (cycle time, customer service, etc.) should be considered for inclusion.
- Manufacturers and distributors should be able to demonstrate the effectiveness of the metrics they adopt to monitor shortage vulnerability; these could include measures related to on-site shortage procedures, such as audits and “dummy shortage” investigations.
- Metrics to monitor site culture are currently not well established, yet organizations can select objective and quantifiable quality culture metrics that have been demonstrated, through research, to have a strong relationship with culture.

- Sites should examine their selected metrics to determine if they point to a specific or general shortage trigger—such as a lack of investment, budget constraints, business needs or shortage in resources.
- Organizations can explore real-life shortages and how other industry leaders addressed them; this allows them to evaluate the effect of corporate quality culture in organizations that avoided drug shortages. Additionally, organizations are encouraged to review actual shortages experienced to understand whether a metric could have been predictive, identify it, and consider the utility of such a metric for adoption.
- To assess and demonstrate effectiveness, the application of metrics adopted to monitor shortage vulnerability should follow principles of continual improvement.

5.2.1 Clear definitions

The pharmaceutical and biotechnology industries as well as several sectors within them, have not traditionally shared a common dictionary of terms. Consequently, the need to ensure that the standardized definitions to support each metric under consideration are specific, clearly understood and meaningful across and within organizations is critical to the success of any metrics program.

Standard language with universal usefulness, as in publications by the World Health Organization (WHO) or the CFR, should be used to maximize the likelihood of consistent current operational understanding of the terminology used in the metric's definition.

Experientially, the process for establishing metrics is highly iterative, with lengthy discussion related to ensuring crisp yet explicit definitions; this most often occurs in a singular language, such as English. Additional vigilance and governance needs to be brought to bear should the metric be translated into other languages.

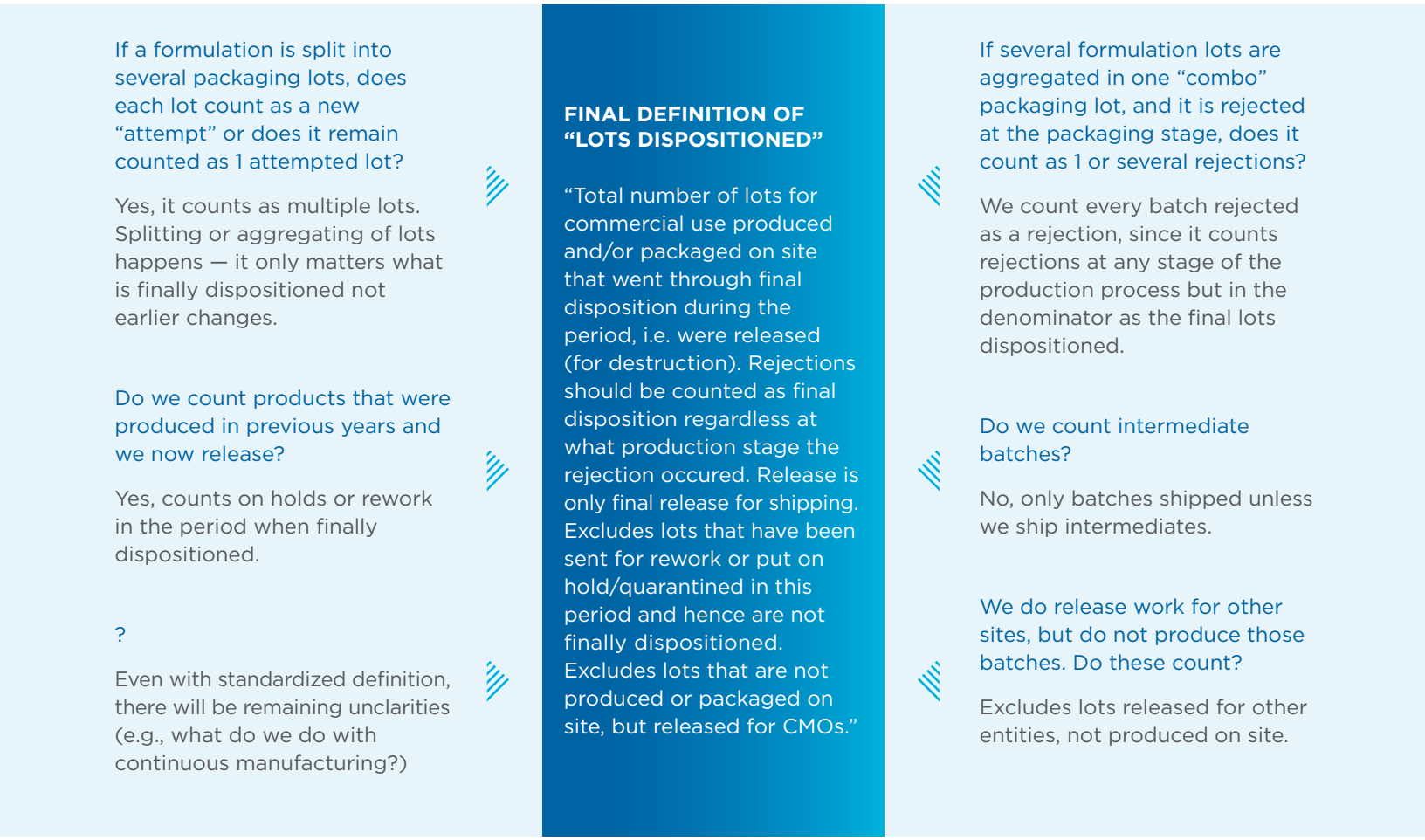
Metrics are most valuable when they are leading indicators. Nevertheless, lagging indicators also have potential for high value when monitoring for directional change, rather than a focus on the absolute value at a point in time.

5.2.2 Clarity of scope

The definition of a metric also should be detailed and outline exactly what is intended to be measured and within which parameters. This will maximize the likelihood of consistency in collection of the data behind any established metric.

As highlighted in Figure 3, *Example Definition of Lots Dispositioned*, the definition considered many facets and its actual definition provides two definitive "excludes" provisions.

Figure 3: Example Definition of "Lot Dispositioned"



5.2.3 Data normalization to maximize comparative utility of the metric

A key step in defining a metric to ensure its utility is maximized—for comparative and trending purposes across sites or products, and processes in the quality system and supply chain—is considering how the data can be put into context, with careful consideration given to the selection and definition of the numerator and denominator. This minimizes any unanticipated influencers into the metric that may dilute the correlation of the metric to its area of focus.

5.2.4 Critical few

The number of metrics should be limited to the critical few needed to monitor the potential for supply disruption. This will ensure optimal utilization of resources as well as value from a metrics program,

One approach is to limit the metrics to those select key performance indicators (KPIs), with underlying diagnostic measures established as a second tier of metrics to be monitored in additional depth in the event that the KPI provides a signal of performance change. [27] Selecting measures such as some of these critical few can provide a perspective on the underlying culture while leveraging

the established relationship with quality performance and providing an ability to monitor signals that could be indicative of a potential for supply disruption.

Another approach is to conduct an in-depth risk analysis of the product portfolio, quality or operational business processes and supply chain to develop targeted metrics corresponding to the high-risk areas.

Table 8 is included for illustrative purposes only as a tool to guide considerations of possible measures, commensurate with assessment of level of risk. As noted above, each organization, supply chain and product portfolio is unique, therefore, while measures adopted to monitor potential vulnerability in the supply chain may be unique to that organization, product or node in the supply chain, they should be designed to maximize their utility from an insight as well as utilization of resources to gather and monitor same.

Table 8: Possible Measures to Consider and Commensurate Levels of Risk

API RISK AREAS		
Raw Materials		
High Risk		> Single source > Unique product > Lengthy timeline for delivery > Poor quality and delivery performance > HA compliance concerns > Geographic risk due to regional political or environmental climate
Medium Risk		> Limited sources > Uncommon product > Delivery timeline is critical > Sporadic quality and delivery performance
Low Risk		> Multiple sources > Common product > Predictable quality and delivery performance
Measures for Consideration	High	> Safety stock levels > On-time in full-delivery performance
	Medium	> Safety stock levels > On-time In full-delivery performance
	Low	> Incoming lot acceptance rate

DRUG PRODUCT RISK AREAS		
Manufacturing		
High Risk		> Single source > Unique product > Essential medicines > Highly potent compounds > Lengthy timeline for delivery > Highly outsourced > Poor quality and delivery performance > Complex manufacture > Limited experienced personnel > New technology > Old registration dossier, “legacy” product > HA compliance concerns > Geographic risk due to regional political or environmental climate
Medium Risk		> Limited sources > Uncommon product > Delivery timeline is critical > Sporadic quality and delivery performance > Manufacturing complexity is low
Low Risk		> Multiple sources > Common product > Good quality and delivery performance > Manufacturing complexity is minimal-straight forward
Measures for Consideration	High	> Safety stock levels > Manufacturing/delivery performance plan adherence > CAPA effectiveness rate > RFT/human error rate > Systematic product quality review of legacy products
	Medium	> Safety stock levels > Manufacturing/delivery performance plan adherence
	Low	> Lot acceptance rate
MANUFACTURING FACILITIES RISK AREAS		
Building and Utilities		
High Risk		> Aged facilities/utilities > Multipurpose facilities > Region with high potential for environmental impact
Medium Risk		> Relatively new facility > At least one back-up facility
Low Risk		> New facility > Multiple facilities > Contingency plan established and tested

Measures for Consideration	High	> Safety stock levels > Unplanned/corrective maintenance activities > Re-capitalization spend > Environmental monitoring action level excursions
	Medium	> Unplanned/corrective maintenance activities
	Low	> Unplanned/corrective maintenance activities
Equipment		
High Risk		> Aged and/or unreliable equipment > Limited flexibility
Medium Risk		> Aged equipment > Limited flexibility
Low Risk		> Reliable equipment with adequate capacity alternates
Measures for Consideration	High	> Safety stock levels > Unplanned/corrective maintenance activities > Recapitalization spend
	Medium	> Safety stock levels > Unplanned/corrective maintenance activities > Recapitalization spend
	Low	> Unplanned/corrective maintenance activities
Supply Chain Capacity		
High Risk		> Volatility in planning process > Complex integration of internal vs external resources
Medium Risk		> Short-term planning horizon > Reasonable level integration of internal vs. external resources
Low Risk		> Robust S&OP process
Measures for Consideration	High	> On-time delivery performance > Overtime
	Medium	> On-time delivery performance
	Low	

Testing		
High Risk		> Contract labs > Unique or aged equipment/ methods > Aged methods, low robustness > Inexperienced personnel > High number of OOS
Medium Risk		
Low Risk		> State of the art equipment > Highly trained experienced personnel
Measures for Consideration	High	> Audit outcomes > Confirmed OOS > Re-capitalization spend > RFT/human error
	Medium	
	Low	

These concepts form the basis for the Metrics gap analysis, shown in Table 9. This tool provides a framework for consideration and should not be considered exhaustive. As noted previously metrics most reliably function as potential indicators of potential drug shortage when other pharmaceutical quality system elements are robust.

5.3 Gap Analysis of Metrics

Table 9: Metrics for Consideration in Monitoring Potential Shortage Vulnerability

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Leading Indicators in Place			
Lot acceptance rate: Total lots released for shipping out of total dispositioned for commercial use.			
Right first time: Total lots that have not been through rework or reprocessing out of total released lots for commercial use.			
Recurring deviations rate: Number deviations with same root cause within same process or work area in same 12-month period.			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
CAPA effectiveness rate: Number of CAPAs evaluated as effective out of all CAPAs.			
Equipment reliability: Number of overdue and/or corrective maintenance activities or work orders.			
Near misses for drug shortages and root causes.			
Lagging Indicators in Place			
Complaints rate: Total complaints received normalized by number of products released (divided between total and critical.)			
Confirmed OOS			
Product recall events			
Environmental monitoring (sterile aseptic sites): Total sterile lots with investigations related to action limit excursions out of all sterile lots dispositioned.			
Process deviations within the first 24 months of product launch.			
Trend of critical equipment availability or mean time between failures (MTBF).			
Number of drug shortages and root causes.			

06 Communication with Regulatory Authorities

6 Communication with Regulatory Authorities

6.1 Regulatory Background

Given the rise in drug shortages over the past few years, the majority of regulatory authorities have now implemented reporting or notification requirements for potential or actual drug shortages. [38, 39]

In June 2015, for instance, Health Canada issued Regulations Amending the Food and Drug Regulations (Shortages and Discontinuation of Sale of Drugs) [24] in which it proposes a mandatory drug shortage and discontinuation reporting system by a third-party website. The intent is to "provide patients, practitioners, and other health care stakeholders with reliable and trustworthy information in a timely fashion, as well as a more accurate picture of which drugs are actively being sold on the Canadian market."

Consequently, organizations should be familiar with the particular requirements for the different regulatory authorities that regulate its products. [38, 39]

This chapter outlines a proactive approach an organization can use before, during, and after a drug shortage when communicating with a regulatory authority. Information contained in the preceding chapters should be included in an organization's regulatory communications plan, as should applicable information from local or regional sources (e.g., trade associations) depending on the organization's location. [40]

If developed and executed correctly, a regulatory communications plan demonstrates that an organization has the appropriate proactive communications strategies and underlying quality systems in place to work closely with regulators and ensure the best possible outcome for patients in need of medicines.

6.2 Desired State for Communicating with Regulatory Authorities

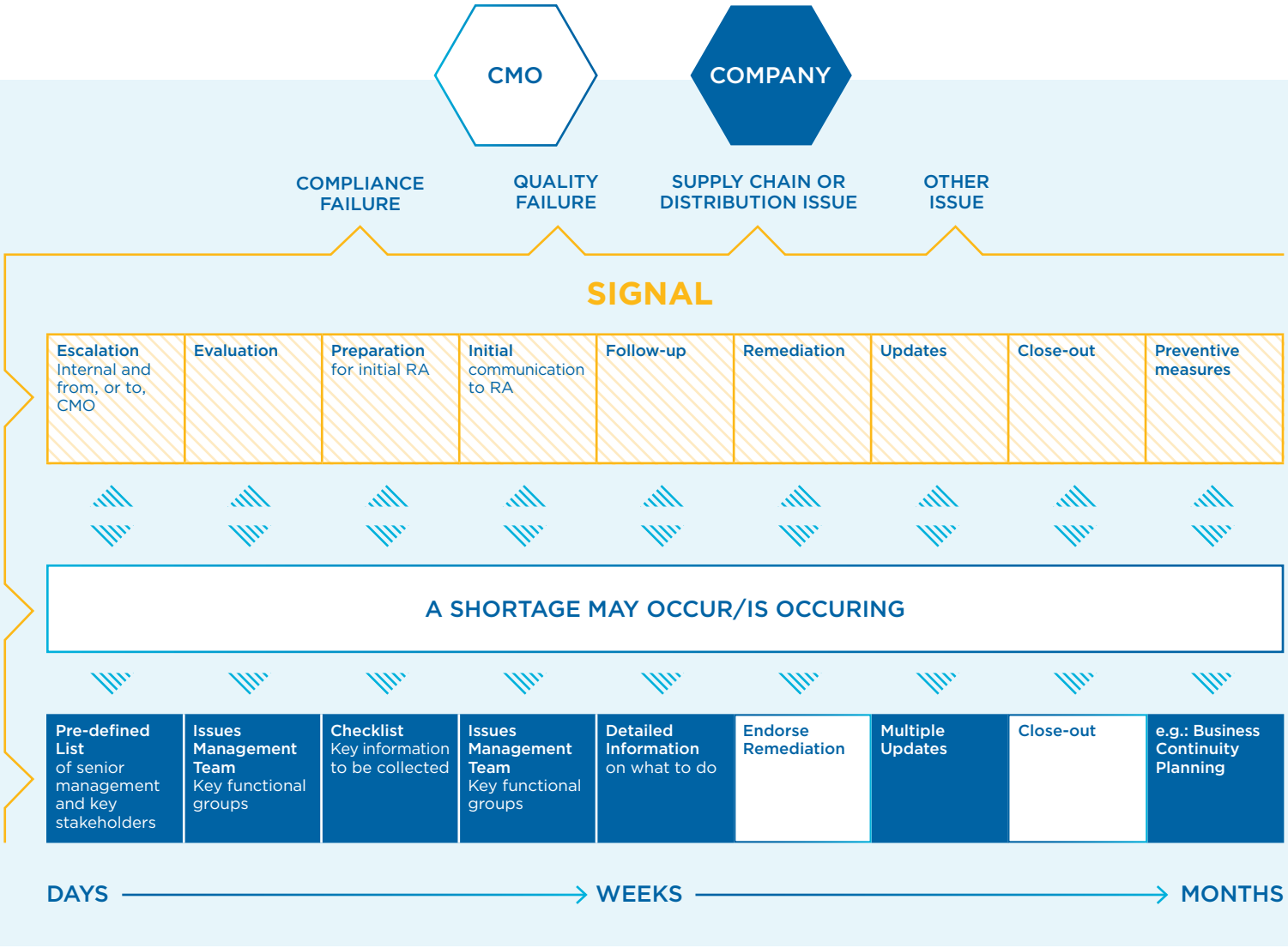
This section describes typical activities that may occur when a drug shortage occurs and highlights several proactive processes that an organization should develop to respond in a timely fashion.

6.2.1 Managing a drug shortage

Effective communication with regulatory authorities requires both planning and day-to-day management and is typically undertaken by an organization's issues management team.

Figure 4 provides a decision-making algorithm once a drug shortage is identified. It identifies the actions and interactions of the organization with regulatory authorities and CMOs, if applicable.

Figure 4: Managing a Drug Shortage



Organizations should have processes in place to monitor signals and quickly escalate supply restrictions or potential drug shortages to senior management. A predefined list of designated individuals from senior management should be established to provide sponsorship, guidance, and, ultimately, be the key decision makers. A response team made up of the key functional groups should be established to investigate the issue, gather information to evaluate the interruption, and recommend remediation activities.

This team should be prepared to answer myriad of questions when communicating with regulators about a potential shortage of a patient-critical product. Many questions relate to obvious items such as product information, alternative products available, time frames for supply interruptions, and stock conservation. Others, however, are far less obvious—such as patient benefit-to-risk analyses and pharmacovigilance aspects that may be specific to the shortage situation or to the product.

6.2.2 Preparation to notify regulatory authorities

Transparent communications with regulatory authorities is critical and requires both planning and day-to-day management and communication. Predefine checklists should be prepared for key information necessary to provide to the regulatory authority. (A template is provided in Table 11.)

Additional references are also available, such as recommendations for notifying European authorities, in the AESGP/EGA/EFPIA/PPTA paper on supply disruptions. [18] Organizations should be prepared to answer questions about a variety of topics, such as product identification, therapeutic indications, countries affected, cause of shortage, current inventory and expected date of depletion, health hazard evaluation (HHE), and potential impact to patients. [20] The AESGP paper proposes a standard reporting form, which could assist in collecting appropriate information.

6.2.3 Notifying regulatory authorities

There needs to be a proactive approach to regulatory engagement—early notification is essential. The initial notification should occur within a short timeframe (days) once the abnormal disruption in supply and/or shortage is known by the organization even if only limited information may be available at the time. The goal is to establish a close working relationship with the regulatory authority to determine the best solution to remediate the problem and prevent a shortage.

6.2.4 Follow-up

It will be necessary to establish a regular follow-up process with regulatory authorities. Organizations should expect follow-up meetings and activities to continue for weeks and in many cases, several months until the situation is resolved and eventually, closed.

6.3 Gap Analysis of Communication with Regulatory Authorities

Table 10 below provides a list of questions that address the basics an organization should have in place to manage a potential shortage in a timely manner.

These concepts are adapted from ISPE's DSPP [3] and form the basis for the Communications with Regulatory Authorities gap analysis.

Table 10: Communication with Regulatory Authorities

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Are processes in place to manage a drug shortage?			
Does this process cover:			
> Signal identification			
> Escalation to senior management			
> Evaluation of root cause			
> Communicating with regulatory authorities			
> Remediation			
> Close out			
> Implementation of future preventive measures?			
Signal Detection and Identification			
Are processes in place to monitor for drug shortage signals?			
Are there effective communications and coordination processes if signal arises from CMOs or key suppliers? Are these covered in the technical agreements?			
Escalation to Management			
Are key decision makers identified?			
Are the following senior managers/key stakeholders involved:			
> Quality			
> Operations			
> Supply chain			
> Medical (e.g., officer, affairs, safety)			
> Regulatory affairs			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
> Legal			
> Compliance			
> Communications			
Are roles and responsibilities defined for key staff involved in the shortage mitigation process?			
Is there a detailed procedure for:			
> Forming an investigative team			
> Gathering information			
> Evaluating supply interruption			
> Evaluating remedial action			
Preparation (Evaluation of Root Cause)			
Is there a detailed and comprehensive methodology for evaluation of root cause?			
Are corrective actions defined?			
If a root cause has not been defined are the most probable causes and mitigation actions defined and resolved?			
When and How to Communicate to Regulatory Authorities			
Does a standardized checklist exist for determining what information needs to be communicated to regulatory authorities?			
Is this checklist appropriately comprehensive (refer to Table 11, below, for suggested examples.)			
Are there defined roles and responsibilities for collating and holding checklist information?			
Initial Communication with Regulatory Authorities			
Is there a risk selection process for the type of meeting required (i.e., phone, document, or face-to-face)?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
When multiple regulatory authorities are involved, is the justification and rationale for determining which regulatory authority should be notified first fully understood and communicated?			
Will the justification on the timing of events be discussed, particularly if a delay in reporting occurred?			
Is there a process to determine what information on short-term and long-term actions will be taken?			
Are actions outlined to ensure establishment of close working relationship with regulatory authorities (e.g., what group will be the lead in communicating with the regulatory authorities)?			
Is there a detailed procedure to assure the following information is covered?			
> Contact names			
> Timelines			
> Agreement on any future meetings			
> Documentation to share with regulatory authorities			
Follow-Up/Remediation/Updates with Regulatory Authorities			
Is the process for follow-up meetings documented?			
Are the appropriate SMEs identified and engaged?			
Is there a process for determining the appropriate length of time needed for scheduling meetings?			
Is there a process for determining when a close out meeting is appropriate?			

DESIRED STATE	MATURITY LEVEL (1-5)	REF. TO SUPPORTING DOCUMENTATION (REPORTS/SOPS)	COMMENTS
Closeout			
Implementation process for preventive measures			
Are changes to systems (product design, quality system, facilities) captured and documented? (See Chapter 4)			
Are processes to properly communicate and implement appropriate system changes included?			
Does your organization have a process in place to assess the medical necessity of a given product against the risk of its shortage? Have the results of this process been checked e.g. by engagement with the National Health Authority?			
Are training processes established to improve employee practices?			

Section 6.2.2 recommended a checklist approach to assembling the key information ahead of initiating communications with an authority. Table 11 is one approach that can aid the assembly of the necessary information.

Table 11: Ensuring Your Checklist Is Complete

SUBJECT	DATA
Product Information	
Name of generic or active ingredient	
Drug strength and formulation	
Route of administration and package size(s)	
Therapeutic category	
Patient impact and HHE (benefit/risk analysis)	
Regulatory reference number (e.g., PL (EU) or NDC (US))	
Alternative products available	

SUBJECT	DATA
Potential Supply Interruptions (Manufacturing and Quality Issues)	
If possible, describe the root cause of the drug shortage.	
Describe if the issue is related to product or process.	
Describe if the issue is at an internal or external (CMO, supplier) site.	
Describe if the issue could affect other products.	
Describe if alternative manufacturing sites are available and what time is required to bring these on line.	
Time Frames	
Describe when and how the shortage occurred.	
Describe estimated duration of the shortage.	
Describe when the shortage may begin to affect patients.	
Supply information:	
Inventory currently available	
Inventory in distribution	
Sales forecast (burn rate)	
Actions taken to conserve existing stock	
Market share (estimated)	
Markets and regions affected	
Actions Taken	
Describe short-term and long-term actions to mitigate shortage (e.g., CAPAs).	
Describe rationale for actions and associated risk assessments.	
Describe the quality of inventory available (In process/WIP/approved/on hold).	
Describe any interim controls (e.g., use of in-line filters for sterile products).	

SUBJECT	DATA
Discuss if a recall of the product is necessary and/or planned.	
Discuss if any formal regulatory reports will be submitted (e.g., US Field Alert Reports).	
Discuss communication strategy to patients and providers (taken and/or planned).	
Pharmacovigilance Considerations	
Is there a known safety profile or new safety signals?	
Are there any spontaneous reports?	
Is there a need for any enhanced pharmacovigilance monitoring?	
Potential Actions Needing Input from Regulatory Authorities	
Market supply strategy	
Criticality to patient needs	
Alternative resources	
Regulatory strategy	
Communications strategy	
Communication with other regulatory authorities	

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8 Appendix

Drug Shortages Prevention Plan—Executive Summary

The International Society for Pharmaceutical Engineering (ISPE) *Drug Shortages Prevention Plan* (the Plan) was developed as part of a cross-industry association initiative in response to a request from the European Medicines Agency (EMA) in November 2013 to present proposals addressing the prevention of drug shortages due to manufacturing and quality issues. Concurrently, discussions with representatives from other agencies, such as the United States Food and Drug Administration (FDA); Japan's Ministry of Health, Labor and Welfare (MHLW); and Health Canada, demonstrated a need to move the technical discussion from questioning to implementation of best practices. With this in mind, ISPE's intent was that the Plan would provide an opportunity to emphasize synergies between the EMA and the FDA. Accordingly, the ISPE Drug Shortages Task Team was formed to use the results of its 2013 Drug Shortages Survey [1] as a starting point to develop a framework that could be used by industry to develop strategies and practices for each of the six dimensions of the Plan.

While the survey pointed towards a few key areas to avoid shortages – such as developing quality systems and strong management controls – the Task Team worked to identify further strategies based on a more detailed review of the survey data as well as interviews with industry and regulatory leaders. This analysis helped dispel some of the common perceptions behind shortages, such as an excessive number of recalls, non-availability of material, or poor product quality caused shortages. Instead, the Task Team identified strategies that could help address the underlying root causes behind shortages, whether due to inadequately maintained facilities, lack of product or process robustness, poor corporate quality culture, or other behavioral aspects that could result in the flawed design or inadequate execution of a company's quality system.

ISPE recognizes that there are many other factors that may impact the supply of drugs, including regional economic factors, differing regulatory requirements, insurance programs, and government procurement procedures; however, these are outside the scope of the *Drug Shortages Prevention Plan*.

With regard to the different regulatory requirements among the various regulatory authorities, ISPE recognizes that these differences may warrant region-specific actions. And, while the Plan does not attempt to customize solutions by region, ISPE hopes that by providing a baseline for discussion readers will be able to identify opportunities for more global implementation.

The Task Team set out to identify ways in which the gaps initially highlighted by the survey could be resolved. As these strategies began to take shape, and mechanisms to operationalize and implement these strategies were discussed, the Task Team was able to shed light on questions that remained unanswered after the initial analysis of the survey results. For example:

> Why did some of the companies that focused on Information Technology (IT) systems have drug shortage prevention plans that failed?

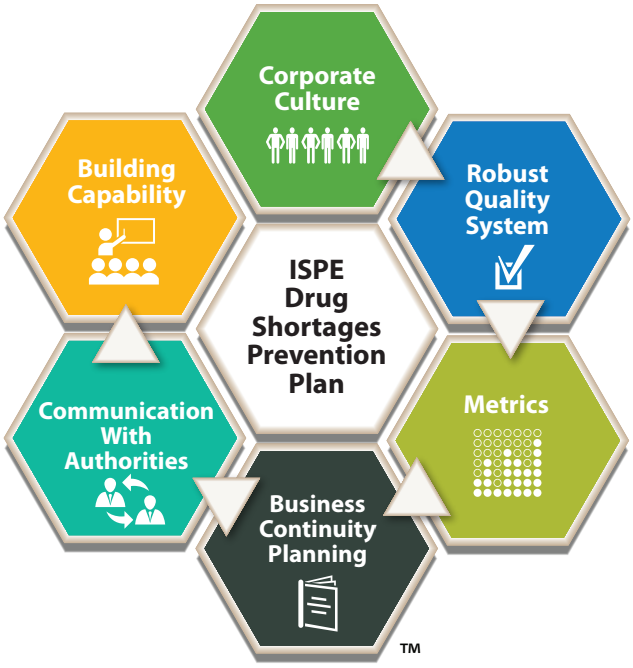
> Similarly, why did some companies that focused on building in redundancy not able to avoid shortages?

> Why did some companies that focused on areas that did not include IT and redundancy build programs that helped to prevent shortages?

Discussions with industry and regulators pointed to a number of additional dimensions that should be considered when attempting to unravel complex issues that contribute to supply shortages.

The proposed framework developed by the Task Team and the six dimensions are illustrated in Figure 1.

Figure 1: Six Dimensions of the ISPE Drug Shortages Prevention Plan



The Task Team developed a framework to organize these six dimensions in such a way that not only helped highlight the strategies and challenges associated with operationalizing each, but also demonstrated the potential interactions between them. The latter point is important and one that ties into the complexity of the shortage issue and the need for preventive strategies both holistic in nature and able to cross multiple functional areas in an organization. The Task Team also recognized that many of the insights and recommendations are already implemented in most companies, although it is clear from the survey that the extent of understanding and implementation varies. Therefore, the Plan is not a guide intended to be read sequentially from cover to cover. Rather, it is a multi-dimensional tool-kit from which one may select the most relevant chapters or subsections to support improvement activities.

A summary of each of the six dimensions constituting the ISPE *Drug Shortages Prevention Plan* is provided below.

Corporate Quality Culture describes the importance of organizations being designed in such a way as to foster cross-functional ownership of quality so that quality is not viewed as a hindrance for success, but an absolute necessity for the company to collectively make decisions to best benefit patients [2]. The Plan suggests that avoiding supply disruptions requires not just a compliant quality system, but one that helps drive the overall quality of the product throughout its lifecycle by integrating it and focusing on a number of key processes. These processes include:

> Cross-functional cooperation

> Management controls and problem escalation

> Communication and transparency

Robust Quality System – highlights the ability of the company's quality system to integrate applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q9 [3]. This integration is a necessary foundation for companies to create more and better opportunities for the "the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities."

In order to achieve a robust quality system, the Plan proposes structuring the approach to developing strategies across a few key elements, including governance, culture, and management controls, as well as improvements to overall production and process-related factors contributing to shortages. The Plan argues that this integration will enable stronger and more consistent decisions that will ultimately drive higher levels of quality. These decisions, in turn, may help drive the following improvements:

> Process Related Elements

  > Corrective and Preventive Actions (CAPA) and Deviations – as a result of improved product characterization and process understanding, reduce the total number of deviations and CAPAs identified during a campaign.

  > Investigations – due to the greater process understanding of the product, reduce the time needed to identify the root cause behind an issue and identify a systemic solution that will address it.

  > Knowledge Management – create better and more opportunities to capture information about the process; information that can be used to better understand and define the product, control the product, and over time, improve it. All of these characteristics will help prevent drug shortages.

- Production Related Elements
  - Product – allow the supply chain to be designed around the product. Suppliers can be chosen based upon the characteristics of the molecule as well as a supplier's experience working with similar products.
  - Factory – better detect the need for maintenance and, when needed, upgrade the factory's systems and processes. A sound preventive maintenance plan attached to the quality system is a good indicator of issues that could later, if not addressed, result in shortages.
  - Material – ability to detect when materials are needed to manufacture a drug are in short supply; identify when materials may not be meeting specifications.
  - Machine/Equipment – similar to the benefits related to material availability, integrating the supply chain with the quality systems will help companies better detect the need to take the steps to update plant machines and equipment.
  - Experts – make sure that all parties responsible for delivering quality and compliance will have the tools to do so.

Metrics – are measures put in place to determine the performance of not just the quality system, but also of other operational elements – such as supply chain and culture – that may indicate the potential for a drug shortage. Depending on the site quality system, some quality metrics and other indicators can be predictive of the overall ability to reliably supply quality products. This section was supplemented with a series of case studies to help illustrate how drug shortages might be avoided by defining and implementing a well-defined set of metrics across the organization.

Cases explored the following:

- What a company did to develop and use a series of risk assessments, metrics, and simulations to help determine the amount of strategic reserves (safety stock) to maintain in order to protect against shortages.
- A company's ability to integrate both supply chain and quality systems-related metrics, such as batch yields, batch release and stability cycle time performances, rejection rates and rationales, to create more accurate visibility into operational performance and proactively identify potential shortage risks.
- How a company used a "reliability room" to predict risks across the supply chain more consistently and efficiently so that executives could take action and mitigate any risk of shortage or stock-outs for life saving and unique products.

Business Continuity Planning – explores how companies have established supply chains that are robust, redundant where appropriate, and resilient to ensure continuity of supply by: (a) achieving product realization; (b) establishing and maintaining a state of control and; (c) facilitating continual improvement (ICH Q10) [4]. Solutions developed in this section revolve around the following:

- Achieve Robustness: integrate the supply chain network (from development to commercial manufacturing) with a robust quality system, including governance and management strategies and decisions used to help achieve a robust supply chain.
- Build Redundancy Across the Supply Chain: communicate the successful strategies in place today to monitor the supply chain for risks and develop the solutions needed.
- Test and Refine: identify mechanisms to test and monitor potential issues with the supply chain; weaknesses that, if not addressed, could lead to a shortages.

Cases also were used in this section to help illustrate various solutions, such as:

> What a company did to create a dual source system within the company's own manufacturing network allowed the company to provide assurances to its customers that their products could be provided by multiple manufacturing sites across the network.

> How a company managed to create a more robust quality system by integrating it with the supply chain and, in turn, helped improve the ability to manage the suppliers critical to its ability to avoid shortages.

Communication with Authorities – examines what companies can do to improve communication with the various regulatory agencies across the globe. This includes looking at: (a) what can be done to drive a consistent and transparent message between the company and its regulators to help reduce the chance that a shortage will occur and; (b) if there is a compliance driven supply disruption, reduce the amount of manufacturing downtime needed to get the site compliant and back up and running.

Specific areas explored include:

> The role of regulatory agencies/health authorities – proposes how both companies and regulators can work together to deliver a consistent message; one that is transparent to all parties and helps facilitate a rapid response to mitigate the shortage and address the impact to patients.

> Managing an abnormal restriction in supply – examines not just the signals that may point to a shortage, but also potential escalation paths that should be in place to make sure that if a signal is identified the right steps can be taken to address and resolve the pending issue.

Both of these areas are backed up with several examples of how companies facing a shortage were able to work with the appropriate regulatory authorities as well as their own management to make the decisions needed to allow a solution to be developed and implemented rapidly and efficiently.

Building Capability – summarizes the capability needs required for each of the elements described in the ISPE *Drug Shortages Prevention Plan* to be realized. The capabilities discussed revolve around the following areas:

> Training

> Learning

> Knowledge Management

> Mentorship

The Plan argues that much of a company's ability to put these processes in place and execute them consistently will rely heavily on the capabilities of the organization and its personnel.

All of these combined elements offer what the ISPE Drug Shortages Task Team believes to be a holistic plan and a valuable contribution to ongoing discussions aimed at preventing drug shortages. By the application of often limited company financial resources to the identified key areas within a quality system, companies can significantly reduce their vulnerability to drug shortages and ultimately improve patient care. Just as importantly, these discussions will help an organization understand what its limitations are – whether in process, governance, or skills – and what they need to address and overcome in order to take advantage of the solutions offered by ISPE's *Drug Shortages Prevention Plan*.

References

[1] Report on the ISPE Drug Shortages Survey, International Society for Pharmaceutical Engineering (ISPE). 2013. http://www.ispe.org/drug-shortages-initiative/about-the-survey.

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[4] Pharmaceutical Quality System – Q10, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH). www.ich.org.

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