

ISPE Drug Shortages Prevention Plan

Introductory Summary



August 2014



Introduction

The International Society for Pharmaceutical Engineering's (ISPE) *Drug Shortages Prevention Plan* is aimed at guiding the pharmaceutical and biopharmaceutical industry in establishing reliable, robust, and resilient supply chains that can, without interruption, provide quality medicines to patients. The Plan was created from a cross-industry initiative in response to a 2013 request from the European Medicines Agency (EMA) to address the prevention of drug shortages caused by manufacturing and quality issues.

ISPE announced in April, 2014 that it would work with global stakeholders and other industry associations to produce a Drug Shortages Prevention Plan – its second major effort in its continuing efforts on the topic. The ISPE Drug Shortages Task Team used the results of ISPE's 2013 Drug Shortages Survey¹ as a starting point for developing strategies and practices to prevent shortages.

This Introductory Summary is aimed at highlighting important areas of the Team's work. The full ISPE Drug Shortages Prevention Plan will be published in October 2014.

The Plan is organized around a “six dimension” framework: Corporate Quality Culture; Robust Quality System; Metrics; Business Continuity Planning; Communication with Authorities; and Building Capability, each of which are interlinked.

Work on the Plan engaged Team members with leaders from more than 30 major pharmaceutical companies. The Team also utilized information offered at recent ISPE conferences held in Frankfurt, Germany (April 2014) and Baltimore, Maryland, USA (June 2014) and other conferences and workshops where presentations included valuable information from members of industry, as well as from regulators, regarding how drug shortages might be mitigated or prevented.



How should the Plan be used?

Avoiding or mitigating drug shortages is a crucial issue, and the Task Team Members who compiled this plan hope that it will find wide use in industry and be a valuable guide for solving drug shortage problems and preventing the interruption of supplies due to manufacturing or quality issues, thereby focusing on the prevention of events that may lead to drug shortages.

The Plan may be thought of as a “reflection paper” to help industry members look holistically across all elements of their company and evaluate whether their current drug shortage prevention strategies,

¹ Report on the ISPE Drug Shortages Survey (ISPE), 2013, <http://www.ispe.org/drug-shortages-initiative/about-the-survey>.

as well as their policies and procedures, meet current challenges, or whether changes need to be implemented and processes improved.

Team members also suggest that the Plan could be seen as a “toolbox” that companies may use to select the proper tool for the appropriate problem that may potentially cause a drug shortage. That toolbox has six dimensions, each of which can be utilized as needed, whether to measure and test the integrity of the supply chain, build a robust quality system, enhance corporate quality culture, or find ways to better communicate with regulators.

Dimension 1 – Creating a Corporate Quality Culture to Prevent Drug Shortages

Drug shortages are often perceived as resulting from material non-availabilities or product recalls. However, the root causes of drug shortages are many and often involve a trigger in production factors or technical processes that can set into motion a cause-and-effect chain that can lead to a shortage. Lack of controls and human errors contribute to root causes, as do problems and insufficiencies in manufacturing, infrastructure and materials. However, a general failure to implement a robust quality system across the life cycle of the product, as reported in 2013 by the ISPE Survey, is considered to be a critical factor for causing drug shortages.



The Plan cites the responsibilities of leadership and management to implement robust quality systems by creating an effective Corporate Quality Culture, one that encompasses an organization’s practices, central values and philosophy with regard to quality, and requires that employees at every level subscribe to its requirements. A company’s Corporate Quality Culture is an indicator of its ability to routinely provide quality service and products and must be supported by management principles and practices aimed at quality. It is up to the CEO and other executives to communicate the concept of Corporate Quality Culture to all employees.

Dimension 2 – Developing a Robust Quality System

In the search for the *true root causes* of drug shortages, questions regarding what makes a quality system robust and, conversely, what triggers can affect the supply chain and lead to a drug shortage, are important. Accordingly, this section discusses what is needed to develop a robust quality system.



Validation – a key tool in the industry, and for which the principles are well-known – is aimed at demonstrating that a process operates effectively, consistently and produces the expected and desired results, which in this case are robustness and quality. Validation, also a legal GMP requirement, needs to occur in the context of continual improvement during the product’s lifecycle.

Corrective and preventive actions (CAPAs) are key tools in creating a robust quality system, and CAPA processes need to be actively managed in such a way that their appropriateness is endorsed by senior management, complete with a process for escalating problems to top managers.

Robustness and quality can be achieved by compliance with preventive maintenance programs for facilities and equipment used in pharmaceutical manufacturing as equipment failures (as revealed in the ISPE Survey) can often lead to production interruption.

All this should be embedded in a Pharmaceutical Product Life Cycle management in the sense of continual improvement as outlined in ICH Q10, “The Pharmaceutical Quality System,” for all marketed products, including legacy products.

This chapter of the Drug Shortages Prevention Plan also includes a discussion of subject matter experts and the role they may play in helping to create robust quality systems.

Dimension 3 – Using Metrics to Track Quality

This chapter examines parameters for measuring and tracking performance and offers metrics for discovering any weaknesses that may be in process or product. The chapter emphasizes that there is no “one size fits all” metric. Rather, there are a variety of tools and the right one needs to be chosen.



While many companies use metrics as part of their Quality System Management Review (as driven by ICH Q10 Ch 4), this chapter discusses quality indicators provided by and recommended to the U.S. Food and Drug Administration (FDA) by ISPE, and the collective knowledge gained from many discussions held at conferences and workshops over the past two years.

The ISPE Survey revealed that well-defined metrics, tailored to identify potential shortages risks, can help mitigate them. Both lagging and leading indicators are needed to measure the overall quality performance of a site and the products it produces. In relation to drug shortages, appropriate metrics need to be present across the quality system to: 1) identify and allow mitigation; 2) monitor supply and demand within the supply chain; 3) monitor and predict actual shortages in terms of scope, duration and patient impact and; 4) demonstrate corrective action for future prevention.

The ISPE Plan recommends that companies leverage their CAPAs, Annual Product Quality Review (APQR) and Quality System Management Review (QSMR) programs to pull the appropriate metrics for improving the prediction of shortages. Which metrics to use as predictors, whether leading or lagging, is a key question addressed in the chapter.

Case studies are presented to demonstrate the use of metrics to anticipate, prevent, and solve problems of product quality and supply chain integrity:

- A company that experienced problems with its supply chain and experienced shortages uses metrics to overcome challenges.
- Another company experiences supplier disruptions that led to a shortage. Learn in this chapter how one company established a “reliability room” to help prevent shortages by gaining more insight into supplier and a product performance.

The chapter notes that in June, 2014, ISPE launched its Quality Metrics Pilot Program to test sets of metrics for relevance and effectiveness. A system of metrics is offered in this chapter as examples of “relevant indicators of the quality system for preventing drug shortages.”

Dimension 4 – Business Continuity Planning

The ISPE Survey suggested that to avoid drug shortages, companies should develop drug shortage mitigation programs built around production and process. Production includes product, factory, material, machines and equipment and experts. Process includes environment, production and behavior and human error. The chapter makes suggestions on how to achieve robustness, evaluate the value redundancy and test, monitor and refine the supply chain.



The chapter also recommends how to integrate the supply chain network (from development to commercial manufacturing) with a robust quality system, especially important at a time when supply chains have become global and more complex. The importance of having good governance systems across the organization, IT systems, the use of metrics and organization design receive consideration as do materials, machines and equipment, and technology transfer as topics that are related to business continuity planning. The chapter offers several objectives for attaining continuity as well as “real world” case studies gathered from industry members and illustrating by situation not only the challenges

but the application of principles aimed at meeting the challenges and strengthening the continuity of business. The objectives and case study results are linked to the three important aspects of building continuity – robustness, redundancy and resilience.

Case studies include:

- A pharmaceutical company faced significant quality issues and subsequent recalls. True root causes were discovered by an end-to-end assessment of the company’s operations.
- A major supplier of pharmaceutical excipients consolidating manufacturing and supply sites found that one site was responsible for supplying 20 percent of the market and that disruptions took up to one year to correct. Find out how they mitigated these problems.

Dimension 5 – Communication with Authorities

In parallel with the development of a plan to address shortages resulting from manufacturing and quality issues, the European Federation of Pharmaceutical Industries (EFPIA) and the European Generic Medicines Association (EGA) led an initiative also requested by EMA to propose an EU-wide process for informing regulatory agencies of a “meaningful interruption to supplies.” Complementing this initiative, the ISPE Drug Shortages Prevention Plan addresses what companies can do to improve their communication with regulatory agencies and make certain that all communication is carried out using consistent and transparent dialogue aimed at identifying problems quickly and notifying regulators of a shortage in a timely manner. Examples in this chapter describe how several companies facing shortages were able to effectively communicate their long-term and short-term goals with regulators.



In collaboration with other industry associations, such as EFPIA and EGA, the chapter focuses on communication with regulators both in the US and in the EU with an emphasis on the importance of informing regulators about problematic issues – whether with the site or a CMO – early-on and quickly. How problems can be more quickly escalated to top management and key decision-makers (also a communication issue) is also discussed.

What kinds of communication work best? The Team offers insight into call centers and “media message maps” and explains how to use them. Again, a number of real world case studies are offered to highlight good communications strategies and practices.

Case studies include:

- Problems with a sterile injectable made at a CMO required discontinuation after an inspection. However, quick and effective communication with Health Authorities lessened the impact on patients. Find out what steps they took.
- A year after a company discontinued manufacturing a product, the FDA asked them to resume production because of a problem in the supply chain. What steps did they take to ensure a reliable supply for patients?
- Visible particulate matter showed up in one kind of container. A recall of the product loomed, plus the shelf expiration date had to be changed from 24 months to 12. How did this problem work out for the best thanks to good communication between the manufacturer and the Health Authority?

Dimension 6 – Building Capability

The final chapter summarizes capability needs for each of the other chapters described in the Plan. This dimension encourages a holistic approach, which means looking at production, quality, supply chain integrity, the commitment of all employees to quality and, most importantly, using that analysis to better build the capacity to meet the variety of challenges and root causes of drug shortages, whether they are derived from issues of process, governance or skills.



The chapter notes that 60 percent of recent warning letters cite “weak organizational effectiveness” as the cause behind the citation. How organizational effectiveness can be improved is the key issue tackled in Dimension Six. Attention is also paid to how staff members can better understand the “what” and the “why” of their roles.

This chapter specifically outlines how improvements in capability building can be made and summarizes the capability needs that other chapters highlight. The chapter is forward looking by recommending potential courses and conferences that could be developed regarding training, knowledge management and mentorship to identify, prevent, or mitigate drug shortages.

Conclusion

The Plan concludes with recommendations taken from each of the chapters relevant to each dimension. The Team re-emphasizes that there is “no one size fits all” solution to ensuring supply and preventing drug shortages. However, the recommendations, gleaned from each chapter, also emphasize, and are linked to “real world cases” where quality, management responsibility, and knowing capabilities couple with proactive risk management and crisis management to play a strong role when it comes to preventing drug shortages.

The Plan ends with a chapter that promises to make the necessary “Next Steps” in making drug shortages an important topic at the top of ISPE conference agendas in order to continue raising awareness of drug shortages and further the effort to make them a thing of the past. ISPE will continue to provide resources aimed at that end.

**To learn more about ISPE’s Drug Shortages Initiative,
visit www.ISPE.org/DrugShortages or contact Carol Winfield,
Director of Regulatory Operations, cwinfield@ispe.org.**

**Don’t miss the worldwide release of the
ISPE Drug Shortages Prevention Plan at the
2014 ISPE Annual Meeting.**

Tuesday, 14 October, 13.00-14.30

Hear directly from the Plan’s creators describing how every employee, every leader and every organizational function impacts successful outcomes preventing drug shortages.

