ISPE Drug Shortages Prevention Plan

A Holistic View from Root Cause to Prevention

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Connecting a World of Pharmaceutical Knowledge

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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.

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.

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

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*.

Introduction

The International Society for Pharmaceutical Engineering (ISPE) announced in April 2014 that it would work with its global stakeholders and other industry associations to produce a *Drug Shortages Prevention Plan* to guide the pharmaceutical and biopharmaceutical industry in establishing reliable, robust and resilient supply chains that can, without interruption, provide quality medicines to patients [5].

This *Drug Shortages Prevention Plan* is ISPE's second major continuing effort on this topic since launching its Drug Shortages Initiative in 2011. Over the past two years, ISPE and a Task Team of industry leaders have been working on ways to understand better the root causes and possible mitigations for drug shortages that result from manufacturing quality issues. ISPE also has engaged leaders from more than 30 major companies, regulators from health authorities, and regional industry associations to ensure that ISPE is comprehensive in its approach to the problem of supply disruptions caused by manufacturing quality shortfalls.

The *ISPE Drug Shortages Prevention Plan* builds upon data from ISPE's 2013 Drug Shortages Survey [1], which provided clear evidence that mitigating shortages requires a holistic approach that encompasses both the organizational and technical issues affecting drug manufacturing and quality. The Drug Shortages Survey also highlighted the need for industry to conduct an appropriate examination of the underlying technical, scientific, manufacturing, quality, and compliance issues associated with a company's supply chain as it relates to its ability to source, manufacture, and distribute products.

Based on the results of the ISPE Drug Shortages Survey and stakeholder feedback at recent ISPE conferences in Frankfurt, Germany (April 2014) and in Baltimore, Maryland (June 2014), the ISPE Drug Shortages Task Team defined the following "building blocks" for a sustainable drug shortages prevention plan, known as the "Hexagon Model. The model includes:

- Corporate Quality Culture
- Robust Quality System
- Metrics (specific to drug shortages)
- Building Capability – for example, organizational and personal competencies
- Business Continuity Planning – for example, crisis management
- Communication with Authorities

The *ISPE Drug Shortages Prevention Plan* uses this model to serve as a "roadmap" to assist the pharmaceutical industry in identifying, managing, resolving and preventing constraints in manufacturing operations which may result in abnormal restriction in supply. The Plan also addresses optimal organizational strategies, such as aligned governance and proactive communication practices, effective manufacturing and integrated quality systems, and appropriate measures of supply chain robustness.

After reviewing the *ISPE Drug Shortages Prevention Plan*, the reader should better understand the regulatory expectations regarding interruptions to drug supplies caused by manufacturing or quality issues and their potential to result in drug shortages; key elements from the ISPE Dug Shortages Survey; and specific building blocks to help industry and health authorities collaborate on reducing drug shortages globally. However, it is important to recognize that the Plan is not intended to be read from cover to cover or indeed in any particular order. The plan will be most useful if considered a reflection paper against which manufacturers and Contract Manufacturing Organizations (CMOs) can compare their entire supply chain and challenge their current processes, systems and practices in order to identify gaps and opportunities for improvement. Secondly, the Plan is a tool kit from which individual tools may be selected as appropriate. While it is essential to recognize the inter-relationships of the six dimensions, many readers will find that one or two dimensions provide the greatest insight and value, especially when considering the discussion points and industry examples.

SECTION 1

1 The Holistic View of Underlying Root Causes

Drug shortages initially might be perceived simply as consequences of a non-availability of materials for production or an inability of the manufacturer to manufacture or release a product to the market or due to a market recall of a medical drug.

A particularly insightful report into the situation in Europe was provided by the birgli® management consulting platform in the report commissioned by the European Association of Euro-Pharmaceutical Companies and published in 2013 [6]. The birgli® report summarized the reasons for shortages in three main categories. Manufacturing, and the pharmaceutical supply chain, comprise just one element of the shortages picture.

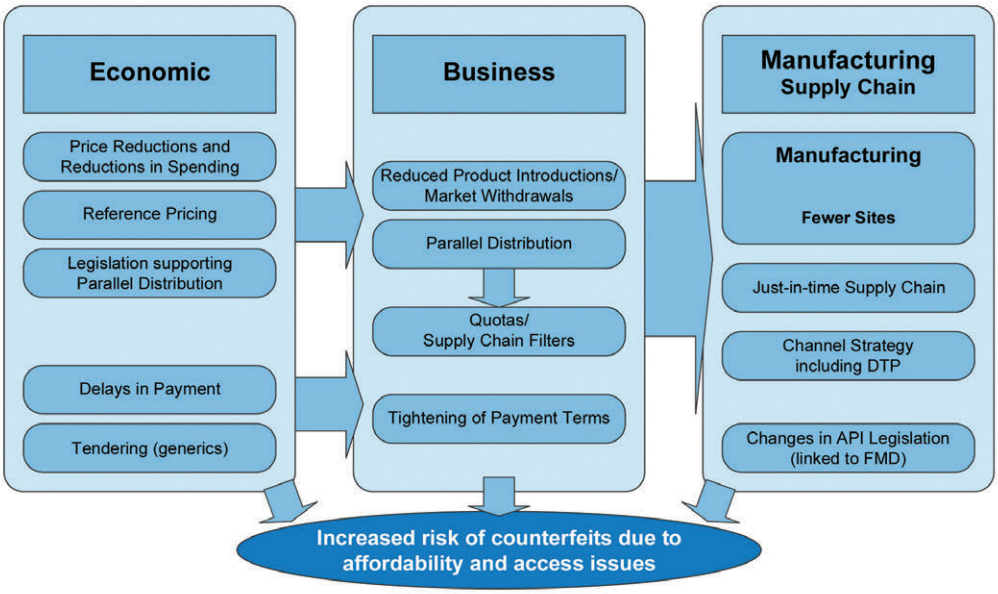


Figure 1.1: birgli® Summary of the Causes of Shortages (Source: birgli® ag. Used with permission.)

As can be seen from the birgli® report and reports from other regulatory bodies [7], manufacturing quality issues are just one source of potential shortages. The *ISPE Drug Shortages Prevention Plan* addresses the root cause technical issues within manufacturing, but in a holistic and comprehensive manner since all six dimensions comprising the Plan's framework need to be considered if the resilience and robustness of the supply chain are to be increased. And while there will be some differences in other regions, the underlying factors will be very similar.

The manufacture and supply of medicines is a complex and lengthy process with many material and component (excipient and active ingredient) sources, and increasingly, multiple organizations executing just a part of the manufacturing or distribution, often in geographically diverse regions.

Therefore, within manufacturing operations and the supply chain, underlying root causes for drug shortages can be multifactorial and often not transparent to an outside view. Normally there is a so-called "cause-and-effect chain" leading to a drug shortage. And, even the first "root cause" has a "trigger" which might not be immediately understood to have the potential to lead to an underlying root cause. An example is the

functionality of an HVAC system in an old building. The following cause and effect chain can happen: if the old building suffers from vibrations caused by heavy machines, those vibrations can lead to leakages in the filtration system. As a consequence, contaminated air can penetrate a sterile room. These contaminations may not be discovered during production, as the testing scheme is not designed to reveal such unexpected leakages. The contamination can be discovered later in the product, which cannot be released to the market. Investigations take time until the underlying root cause is identified and Corrective and Preventive Actions (CAPA) measures are realized. The CAPA measure might be remediation of leakages, which is not sustainable because the real underlying root cause is the inability of an old building to maintain a filtration system in optimal condition. The trigger leading to the cause and effect chain in this example is the investment plan, which does not address the age of the building over time. As products and processes are based on regulatory approval, a change of building needs a new approval process, which takes time. Consequently, there should be a risk assessment in place addressing such risks in order to be able to start re-investment.

As the ISPE Drug Shortages Survey [1] indicated, underlying root causes for drug shortages are not easily isolated from a very complex picture. Figure 1.2 indicates which elements and triggers may underlie root causes. Figure 1.2 also addresses which cause and effect chains exist from a trigger point through a longer chain of consequences, to the final consequence of a drug shortage.

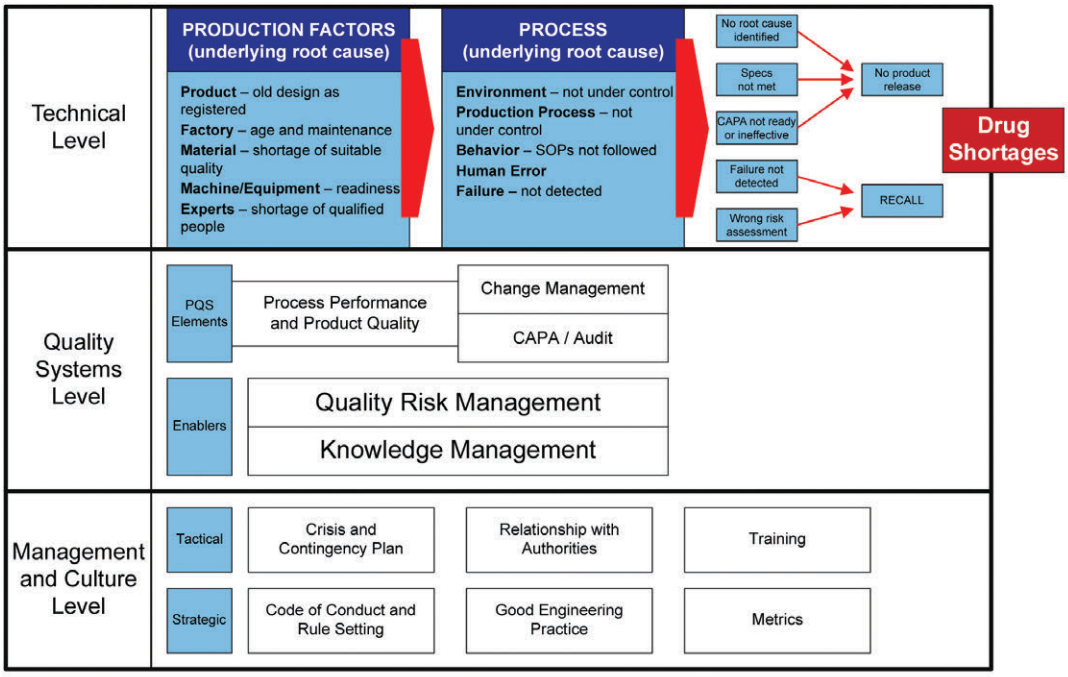


Figure 1.2: Holistic View of Elements with Potential for Causing Drug Shortages

When examining the causes of supply disruptions that could lead to drug shortages, there are three levels to consider: the technical level, the quality systems level, and the management level. The overall "cause framework" is related to the *Corporate Quality Culture*.

1.1 Technical Level

From a technical perspective, it has been reported that sub-robust technology transfers of products and processes have resulted in start-up, validation and supply issues based on the ISPE Drug Shortages survey results. It is essential that the transferring and receiving sites work seamlessly to understand their product, share knowledge, and perform the necessary development work to assure robust products and methods are transferred in a continuous, uninterrupted manner to the market. A detailed understanding of the Critical Quality Attributes (CQAs) and significant process parameters and material inputs are essential. Controls should be in place to monitor and maintain these key parameters within Proven Acceptable Ranges (PARs) or within the developed design space. All of this is especially important when working with Contract Manufacturing Organizations (CMOs) and other companies internationally. With respect to products that have been on the market for some time, a company should take a retrospective look at the process performance, significant process parameters and material inputs and CQAs to optimize, where appropriate, and/or install enhanced controls to assure that robust products are more consistently produced.

Within the technical level, there are both production factors and technical process related factors. Both can have a major impact on product quality.

Often, underlying root causes are linked with the capability for managing processes or process understanding, such as:

- Environmental control
- Process control
- Human capabilities/human error / failures not detected
- Sub robust product introductions during technology transfer

Sometimes triggers leading to underlying root causes are covered in managing and investing in production factors, such as:

- Factories / buildings / infrastructure
- Machines / equipment
- Material / quality and availability
- Availability of resources

Managerial experience and functional experience is needed to identify these factors on the technical level as cause-and-effect chains that lead to “true” root cause can be very complex.

1.2 Quality Systems Level

The ISPE Drug Shortages Survey found that a failure to implement a robust quality system across the life cycle of the product is the main reason for abnormal disruptions in supply. Figure 1.2 shows the elements of an ICH Q10-based [4] quality system critical for avoiding such interruptions. These include: change

management, CAPA, and monitoring. Knowledge management and risk management are important enablers. However, these enabling factors must be based on scientific and technical standards as well as specific knowledge at all organizational levels. They include:

1. Describing a needed methodical approach to determining true root cause of an issue.

2. Assuring that the investigations fully utilize all aspects of the pharmaceutical quality system and assuring appropriate documentation and communication to all involved functions in order to learn from the findings and assure the issues do not reoccur.

3. Assuring adequate management oversight to ensure that all expectations are clear, that necessary tools are in place, and that communication channels are clearly defined. It is important that management awareness and effective communication processes take place cross-functionally and across management levels and between-levels both internally and externally.

4. Across each of these areas, in-depth knowledge of the product and the process is needed to assure high quality and that safe and efficacious products are reliably manufactured.

If one of these elements is missing or if the basic adherence to GMP compliance is missing interrelated to a false or insufficient Corporate Quality Culture, cause-and-effect chains will be triggered with the ultimate risk of drug shortages.

1.3 Leadership and Management Level

It is the responsibility of company leaders and management to implement a robust quality system and have trained and capable staff in place. This is important because on occasion there is uncertainty with regard to how regulations and guidelines should be interpreted. At inspections, this uncertainty can lead to a misunderstanding or conflict between the manufacturer's assessments and the regulators' expectations.

On a strategic and proactive level, ISPE supports industry with products, conferences, seminars, training and guidances, all focused on innovative technical solutions and helping to avoid drug shortages.

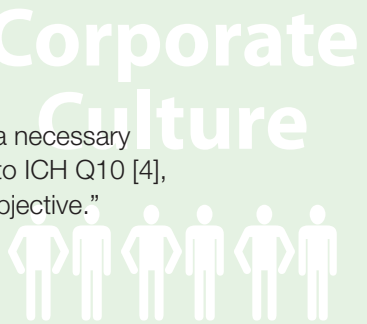
A Corporate Quality Culture sets priorities for the quality system and the entire organization. This was the strong message from participants in ISPE conferences held in 2014 in Frankfurt, Germany and in Baltimore, Maryland, US. At these conferences, regulatory agencies and members of industry have seen supply problems in the manufacture of products with a low-profit margin, where there is a diminished incentive to invest in systems, personnel, facilities, and equipment. These issues can be indicative of a poor quality culture.

Section 2 will detail the elements identified by the ISPE Drug Shortages Task Team for a sustainable *Drug Shortages Prevention Plan* and discuss the triggers that can initiate cause-and-effect chains with the potential to lead to drug shortages.

SECTION 2

2 Corporate Quality Culture

2.1 Introduction



Purpose

Data from the ISPE Drug Shortages Survey [1] made it clear that *Corporate Quality Culture* is a necessary foundation for – and key enabler of – a well-functioning and robust quality system. According to ICH Q10 [4], the definition of an "enabler" is "a tool or a process which provides the means to achieve an objective."

Objectives and Scope

Because technical guidance does not generally address the concept of Corporate Quality Culture, ISPE has asked industry for input on how a quality culture is defined by their companies and what elements are considered essential for establishing a good Corporate Quality Culture.

Inputs

For the aforementioned conferences, ISPE organized executive forums and plenary sessions to collect and discuss input from various target audiences, including industry, regulators, consultants and others.

Various definitions of Quality Culture exist. One definition suggests that Corporate Quality Culture encompasses an organization's practices, central values and philosophy as well as the concentration of all people and resources engaged in a never-ending quest for greater quality and service throughout every dimension of the organization.

Within a culture based on quality, there are many elements, such as opinions, beliefs, traditions and practices concerning product and service quality. In addition, the behavior of people, based on norms, dominant values, rules and the "climate" within the organization, play a role.

The most relevant elements of a robust and effective Corporate Quality Culture are the following:

- Each individual takes ownership for quality performance.
- Decisions are made based on what is best for patients.
- Staff is proactive.
- Everyone is focused on continual improvement.
- Business needs do not drive patient-based quality decisions.
- All employees know and care about why a certain process has to be applied.

Some unfounded beliefs related to a Corporate Quality Culture are that "quality can be tested in," or "if it passes specifications, it is acceptable," or "quality can be inspected in." Also "traditional audits, internal or by a regulator, can demonstrate that product quality will consistently be acceptable" and that "strong controls can mitigate all risks."

In reality, testing, inspection and other controls are not enough to produce a true Corporate Quality Culture. There are elements of "basic compliance," such as meeting the minimum requirements, but this is not enough to assure reliable quality. Robust quality systems are required. As described in ICH Q10 [4], based on process performance, product quality monitoring [8], change management and management review are necessary. In addition, a fully functioning supply system must be supported by a culture in which the understanding of "why a certain process has to be applied" can lead to good decision making. This suggests another level of quality, one beyond the idea that simply following fixed procedures can create quality. A deep and thorough mechanistic understanding of quality includes the mentality for continual improvement.

Discussion

A company's Corporate Quality Culture is an important indicator of their ability to routinely provide a quality service or product and foundation to support change.

While thousands of decisions are made daily by all employees, not all can be predicted or described precisely in Standard Operating Procedures (SOPs). Thus, it is up to each responsible person to make decisions in the light of rules, guidances, SOPs and risk management principles that are consistent with the overarching culture of a company.

A good Corporate Quality Culture has to be supported by appropriate management practices such as:

- Cross-functional and cross-level communication, for example, feedback loops to assure that CAPAs are effective and that qualified personnel complete the tasks at hand.
- Problem escalation to management where required.
- Professional communication; accepting bad news without "shooting the messenger."
- Rule setting.
- Both philosophical and financial support from executive management to robustly implement communicated policies.

2.2 Cross-Functional and Cross-Level Cooperation

Quality and compliance are the responsibility of everyone in the company, not just the quality department staff or those in technical operations functions. Ultimate responsibility for quality culture lies with the CEO of a company; however, the CEO and all executives must communicate a sense of responsibility to every employee. The communication needs to be clear, strong and regular and its effectiveness must be measured.

Ensuring successful quality and compliance management is the ultimate and fundamental responsibility of top management. Communication is key and must take place between all functions related to a business process, between all management levels – from shop floor over middle management – to functional

heads and senior management as well as all participants in the supply chain. Only regular and appropriate communication can help to avoid hidden problems which, if allowed to continue undiscovered, in time can grow into significant issues.

2.3 The Need for Problem Escalation to Management and Organizational Aspects

To manage the complexity of a modern business environment, management philosophies emphasize "delegation." However, where problems with quality and compliance may lead to drug shortages, escalation to top management is critical. The escalation must be "fear-free" without "shooting the messenger," reprisals, or punishing people who report bad news. Only in a true culture of transparency, where there is a strong team spirit, and where individuals help each other and cooperate, can quality problems be prevented.

Successful communication for problem escalation is related to how well the reporting lines are organized, and how well the organizational structures can respond to a trigger that might lead – over a chain of impacts – to drug shortages. Good communication and well-organized reporting lines can help "harmonize" quality systems over the various sites of the same production network, and the independence of the quality function over other functions can help to prevent drug shortages.

In larger companies with international subsidiaries and local sites, it can be difficult for the quality systems from each site to harmonize with one corporate standard. Also, the history behind acquisitions and mergers can affect a site's quality standards without a harmonization process across the new company. Globally harmonized quality systems are strongly recommended.

Some companies may interact with foreign sites according to the "at arm's length" principle, which gives such sites a very high independence when making local decisions, but without a focus on one global, corporate standard. In such cases, local quality systems are often not sufficiently challenged and as such cannot develop. "Corporate does not understand our local situation" might be a defensive phrase often used in local sites in a defensive way. In such cases, companies should assess their practices and consider the associated risks.

Discussion

The organizational position and defined responsibility and accountability of a Corporate Quality Culture can have a significant impact on local quality systems. Companies should demonstrate the reporting line of the head of quality to the highest possible level and the complete independence. Reporting to the CEO highlights the CEOs accountability, but not the complete independence of the quality head. Some companies have a dual reporting line of quality head to the board of directors to address the independence of the quality head.

Recently, health authorities have done more to directly address CEOs to help ensure that a global company has one and the same understanding of quality among and between sites. In addition, and independent of legal responsibilities to a local regulatory authority, a local head of quality should have a direct reporting line to the global head of quality in order to focus on international standards and guarantee independency.

The global quality function has the ultimate responsibility of coordinating global and local teams for drug shortages prevention. Quality functions must be integrated into the whole supply organization and employees for quality and compliance need to be part of the supply chain organization, but report to the global quality head. Otherwise, there is the risk of having a "silo mentality" where each function looks to the goals of the head of the function while quality and compliance have only second priority.

2.4 Professional Communication

Many corporate cultural environments have developed a consensus culture in order to organize life and collaboration and for avoiding aggressive or poor behavior. A consensus culture means that bad news is not welcomed; therefore, people tune out bad news so that they instead "shine positive." In a consensus culture, risks are always described as "manageable" and hope dominates, preventing management from making tough decisions. Even in corporate incentive systems, the social compatibility of an individual can be wrongly interpreted lead to hiding conflicts or trade-offs. Another concept is that having good social skills means (mistakenly) that people should avoid conflict under all circumstances. However, having people in managerial positions who avoid all conflict can lead to fatal consequences for a quality system when conflicts grow to such a dimension that they cannot be managed.

Perfectly designed quality systems and drug shortages prevention plans can be untenable if the organization's communication does not address potential or active problems in a timely manner and escalate them to senior management. If escalation occurs in timely manner, top management can make the right decisions and allocate skilled resources to address problems in a proactive way.

Rules for the rapid and transparent communication of issues to the right committees and functional heads, and between all actors in the supply chain, may need to be generated. For urgent cases, special communication pathways should be well-defined.

2.5 Rule Setting

To ensure meeting the needs of patients by maintaining a continuous supply of medications, the Corporate Quality Culture and compliance should be described in a code of conduct based on an underlying set of principles.

Generally, codes of conduct afford quality and compliance the highest priority.

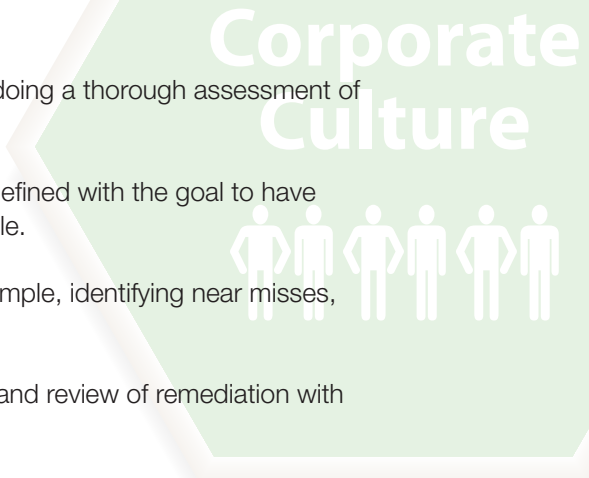
Principles and rules can specifically address the avoidance of drug shortages in the market by defining and assigning functional roles, responsibilities and accountabilities. For example, there should be no batch release before related investigations are closed and that "human error" is rarely accepted as an underlying root cause of a deviation.

Principles and rules must be clearly stated, appropriately communicated, and made available to all employees. Management must include compliance with these rules in the corporate incentive system by goal and objective setting. Verification that the principles and rules underlying the code of conduct are effective is also necessary.

2.6 Conclusion

Having a Corporate Quality Culture plays central role in drug shortages prevention and should not be impacted by business needs. However, reality is often different from what is written in policies and people may make decisions that negatively affect quality.

How to measure a Corporate Quality Culture was discussed in a presentation made by Carol Bye, Vice President, Quality Assurance, Pfizer, at the ISPE European Annual Conference (April, 2014). She referred to Quality Culture Maturity Assessments and highlighted instances of what could go wrong, where management welcomes identification of risk and bad news and decision-making and behaviors at all levels of the organization every day.



Recommendations

- *For quality culture,* companies should demonstrate "walk the talk" by doing a thorough assessment of their quality culture.
- *For management style and behavior,* there should be good practices defined with the goal to have defined formalized and transparent decision making processes available.
- *For proactive management,* there should be principles applied, for example, identifying near misses, weak signals and trends.
- *For problem escalation,* there should be formal processes of high risk and review of remediation with senior leadership.
- *For crisis management,* there should be a focus on management capabilities to manage challenging issues; for example, significant deviations, recalls used already in the recruitment process for key people.
- *For issue management,* there should be cross functional task forces or rapid response teams defined for rapid consultation as soon as a production problem has occurred.
- *For senior management awareness,* there should be a regular quality review meeting with representatives from all management levels as well as Subject Matter Experts (SMEs).
- *For the supply chain,* there should be a holistic view applied to the end to end robustness and resilience.
- *For metrics,* there should be leading metrics demonstrating over time effectiveness and sustainability of actions taken.
- *For systems and processes ability,* there should be a regular management check in place.
- *For professional communication,* there should be a formal process established for escalation and decision making based on standard agendas.
- *For outsourced activities,* there should be ownership of all outsourced activities demonstrated, for example, using a contractor risk dashboard.
- *For risk management,* there should be real time assessments of quality and compliance risks undiluted by business risks.

3 A Robust Quality System

3.1 Process-Related Root Causes

In this chapter, all relevant elements of a quality system as described in ICH Q10 [4] will be considered. Questions considered include: what makes a quality system robust or resilient? What triggers can affect the supply chain and lead to a drug shortage?

3.1.1 Product and Process Development

Stable processes and a well-defined product quality control strategy based on continual improvement are basic to preventing abnormal disruptions in supply and drug shortages.

Products are expected to have their Critical Quality Attributes (CQAs) identified and the impact upon these CQAs by the Critical Process Parameters (CPP) be understood. A systematic and risk-based approach is preferred, i.e., Quality by Design (QbD). However, legacy products may not have benefitted from such a systematic approach.

The majority of batch-based processes require scale-up and technology transfer to final commercial locations. ISPE's Drug Shortages Survey [1] showed that technical issues encountered in routine commercial manufacture are often revealed, but not addressed, during technology transfer [9].

Discussion

Technology transfer and scale-up are key diagnostic opportunities during which potential problems can be identified and resolved prior to routine manufacture. Accordingly, manufacturers should be encouraged to use these exercises for knowledge transfer and problem identification prior to filing. Good engineering and scientific principles need to be applied and conclusions made and evaluated via analysis of statistically powered data sets.

Risk-based approaches to development, process and methods of transfer should be applied with the goal of determining CQAs and CPPs. All results should be evaluated prior to declaring the transfer a success, and controls must be put in place before concluding that the product is ready for validation and commercialization. By employing a holistic approach to development and technology transfer, a company can more fully understand their product and the process that will result in minimal drug shortages. Utilizing a life cycle approach to development and commercialization is also encouraged. A company is encouraged to understand all retrospective learnings to feed the information back to the product and process, thereby ensuring continual improvement and monitoring throughout the entire product life cycle. The application of regulatory tools for re-registration, such as "sunset clauses" for legacy products, may support this process. Robust product transfer and a development process following ICH guidelines will prevent some of the problems observed in a number of past drug shortages. (Refer to ISPE Guidance Documents listed in Appendix II.)

3.1.2 Validation

The purpose of validation is to demonstrate that a process operates effectively, consistently and produces expected results and quality. The principles of validation are well known; they have been around for many years and have been regularly updated. Numerous guidelines and guidances (see also Appendix II) are available, for example:

- ISPE Discussion Papers on Process Validation
- ISPE Guide: Biopharmaceutical Process Development and Manufacturing
- PQLI® Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products, *Journal of Pharmaceutical Innovation* (2009) 4:4–23.
- Quality by Design (QbD) for Legacy Products (in development by the ISPE Spain Affiliate)
- European Medicines Agency (EMA) Guideline on Process Validation for Finished Products – Information and Data to be Provided in Regulatory Submissions
- Food and Drug Administration's Guidance for Industry – Process Validation: General Principles and Practices

The EMA's Guideline on Process Validation states that "Process validation should not be viewed as a one-off event. Process validation incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production." [10] The US Food and Drug Administration (FDA) Process Validation Guidance states: "With a lifecycle approach to process validation that employs risk based decision making throughout that lifecycle, the perception of criticality as a continuum rather than a binary state is more useful. All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or in-process material, and re-evaluated as new information becomes available. The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output. In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk. The Agency recognizes that terminology usage can vary and expects that each manufacturer will communicate the meaning and intent of its terminology and categorization to the Agency." [11]

Poorly validated processes, or outdated validation, can be a trigger for deviations in the manufacturing or testing process, or for not meeting specifications. A soundly-validated process should be able to withstand the rigors of varying lots of raw materials and Active Pharmaceutical Ingredient (API), varied shifts, and varied employees. Quite often, a transferring site that has all the knowledge validates with an experienced crew by assessing each detail and guiding the lots through a successful validation. If the transferring group did not perform all the necessary development work and/or all prior knowledge has not been summarized and shared with the receiving site, commercialization issues and product shortages could result when the development team leaves and the site manufacturing organization commences manufacturing. This applies to both development group-to-site transfers for new products as well as site-to-site transfers for existing products.

Validation must be regularly checked with respect to on-going changes. Manufacturers are expected to demonstrate to health authorities that they have sufficient understanding of the manufacturing process to ensure its validity and that it is in a state of control.

Discussion

Product and process data need to be collected continuously in order to evaluate that state of control and assess the need for further validation exercises. This process is called "continued process verification" in the United States and "ongoing process verification" in the European Union.

At a minimum, data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. Other metrics, such as Process Capability Indicators (CPK), should be established to identify unstable processes with the potential to lead to unstable production, deviations, non-release and, as an ultimate consequence, to drug shortages. These possibilities demonstrate the need for a holistic (end-to-end) consideration of potential cause-and- effect-chains (see also Chapter 4 of the *ISPE Drug Shortages Prevention Plan*).

Identified products not meeting process stability criteria should undergo a rigorous and risk-based decision making process for remediation. A recommended metric is the availability and the transparent use of such a process.

In product remediation, all attempts to identify true root cause are necessary to correct any issues to maintain continuity of supply and eliminate drug shortages. One of the main qualifiers should be sustainability of measures with no suboptimal "quick fixes" that do not address the underlying issues, such as probability of recurrence of the same problem. These issues should be addressed in Corrective Actions and Preventive Actions (CAPA) measures.

3.1.3 Deviations and Investigations

Poor deviations and investigation processes have been one of the major root causes of compliance enforcements and also indirect contributors to drug shortages. (Reference is made to published warning letters in the US, and Good Manufacturing Practice (GMP) non-compliance statements of regulatory agencies in Europe and the equivalent documents in other countries.)

A frequent impediment to reliable production can be a process deviation in manufacturing or testing, or in environmental monitoring. There are many factors, including human factors, affecting the process parameters and driving variation. The concept of QbD seeks to understand these factors so that they can be controlled; however, the majority of pharmaceutical products on the market are not yet based on QbD-driven development principles and may only include some of the elements of a QbD approach.

Discussion

The level of investigations conducted – in terms of quality, robustness, and completeness – needs to attempt to identify the true root cause behind the issue at-hand and incorporate the required corrective actions. This also means completing any necessary documentation and developing training programs aimed at preventing the problem from reoccurring.

An appropriate management review process should be established to monitor the deviations being raised as well as to help identify trends and potential issues. Additionally, management should assess if the proposed corrective actions are adequate and based on data and sound scientific judgment. Reviews should focus on the following questions:

- Will the deviation cause a drug shortage?
- Has a real or true root cause been identified?
- Has the scope of the deviation been identified to include all lots and all products affected?
- Is the measure taken both sustainable and able to prevent recurrence of the same problem?

- Is the root cause investigation carried out within an appropriate time frame and has progress been clearly communicated?

- Is there a probability for successful preventive action in due time?

Process deviation reports are an important contributor to continued process verification; therefore, it is important to have clear procedures for the assessment of deviations and subsequent investigations. False reaction, or unscientific investigation, may lead to an interruption of production and create drug shortages.

Processes for notification of deviations from all levels of staff within a company, and from suppliers outside of the company, should be established. In case of deviations, clear rules for a "quality stop" must exist. Procedures should define qualifiers for the criticality of deviations in order to 1) guard against either a failure to identify undesirable process variability and deviation as well as 2) avoid an over-reaction to an individual event.

Investigations of deviations should be performed by qualified Subject Matter Experts (SMEs) working in cross-functional teams with integrated members from various functions. The result of investigations should be subjected to management review. These investigations should include information on any necessary corrective actions to current procedures or controls (see below).

There should be a formal and transparent decision making process available that includes senior management. If no root cause can be identified, production batches should not be released. Human error as root cause is unacceptable, but these kinds of errors do occur since humans do make mistakes. If a human error occurs, it should not be systematically categorized as the root cause, and an investigation should take place to reveal the true root cause, e.g., lack of:

- Robust process design, and/or

- Clear procedures, and/or

- Organization capabilities

In a worst case scenario, where a root cause is not identified, marketing activities for that particular product should stop. If this step has the potential to give rise to a drug shortage, a crisis plan should be immediately activated (see below). Ultimately, the product might need to undergo re-development, or phase out from the market.

3.1.4 Corrective and Preventive Action (CAPA)

Linked to the deviation and investigation process is the subsequent determination of Corrective and Preventive Actions (CAPAs). Each must be effective, efficient and sustainable in order to avoid recurrence of the same problem, which might result in more unreleased batches, and as an ultimate consequence, lead to a drug shortage.

CAPAs are key tools in a quality system; however, many also will start through non-conformances, annual product reviews, complaints and re-validation. This will be further exacerbated if the proposed actions are overdue due to capacity or "know-how" constraints, or if the measures are not sustainable.

On some occasions, corrective or preventive actions are not completed and verified as scheduled, or are ineffective. There are findings in published warning letters supporting this [12].

Improved ability to meet established quality standards requires improved product and process understanding. For new products, this understanding is generally gained during product realization. Key enablers to explore and to help facilitate an increased level of product realization include improved knowledge management systems (for legacy products see also Section 3.1.5 of the ISPE Drug Shortages Prevention Plan).

Discussion

CAPAs should be addressed in proportion to patient risk. CAPA processes need to be actively managed in such a way that their adequacy is endorsed by senior management, that overdue activities are challenged, and that there is an escalation process. Hard due dates should be set for successful remediation measures.

Using a corporate-wide standard tool, a systematic risk-based approach for CAPAs is recommended. Management review should monitor metrics closely. Useful metrics include successful completion by due dates, backlogs, and numbers of CAPAs according to a simple classification, and on the availability of a challenging decision process driven by management. The metrics also should indicate the qualifications of a CAPA team and the SMEs.

3.1.5 Knowledge Management

Management of deviations, investigations and CAPAs require the know-how and experience of capable employees on all levels. Therefore, the skill sets of people and the management of the available know-how for products, systems and processes are key trigger points for avoiding abnormal disruptions in supply.

Knowledge Management is one of the two fundamental success factors (ICH Q10 calls them “enablers”) in the pharmaceutical quality system. Knowledge is not a given. It must be actively managed. In the past, scientific know-how was focused mainly on development divisions. Today, in production and engineering divisions, the technical and scientific know-how and knowledge management is key to producing consistent drugs of high quality. In addition, engineering and scientific know-how, the knowledge of manufacturing technologies for production processes, and regulatory expectations, are key elements.

Knowledge management systems can help track, record, and store knowledge associated with a product from its initial development through the overall commercialization stages and into product discontinuation. Often, a product is much longer in the market than its developers or producers who may have retired or left the company. A product also may be sold to another manufacturer without the transfer of the product’s history. Products may have lower margins and, as a consequence, do not allow for modernizing due to a lack of cost-effectiveness.

Low-margin products will eventually not finance the product updates required in a registration process. On the other hand, a product withdrawal from the market is sometimes not accepted for economic reasons. If this is the case, all technical measures proposed in this plan will not be taken.

ISPE Members believe that a regulatory environment in which manufacturers are encouraged to invest in improving their understanding of legacy products that lack quality robustness is necessary. If adopted, this consideration will be a significant challenge in cost-pressured manufacturing. While there would be regulatory support for this, pressures from low-margin manufacture may be an issue in terms of this investment.

Discussions in the 3rd Annual ISPE-FDA cGMP Conference (June, 2014) highlighted this problem. While economic considerations are not subject to this *ISPE Drug Shortages Prevention Plan*, they cannot be overlooked in developing a complete picture of underlying root causes for drug shortages.

Discussion

The ISPE Drug Shortages Survey showed that there is a danger in companies focusing on Information Technology (IT) solutions and metrics rather than the more fundamental business imperative of implementing a robust quality system with knowledge management as its enabler.

Key elements of knowledge management are as follows

- Owners should be defined, as should direct delegates and backups.
- SME profiles and qualification plans should exist.
- Metrics should focus on an overview and the ownership for systems, processes and content, and should drive business requirements.
- Appropriately selected metrics should escalate through the management chain to senior management score cards.
- Regular training should be monitored, regular checks of training success should be performed, and the whole recorded.
- Specific training programs for management and key decision makers on avoidance of drug shortages should be in place.
- Training should be recorded and reported.

3.2 Production Factor-Related Root Causes

3.2.1 Product Related

Pharmaceutical products have long life cycles with some living over many decades. However, they may need to be updated according to new process technologies in order to meet current expectations for process control and compliance. When older products are not updated, drug shortages can result. It is a concern, particularly for aseptic products, that there are still registered processes in use involving classical fill and finish processes, allowing manual interventions with the risk of contamination in the process or product. Those processes are at higher risk and require the tightest of controls [13].

Discussion

Some products were registered many years ago and utilize processes and technologies that are no longer state-of-the-art. Post-approval change management and redevelopment of such products are lengthy administrative processes and Marketing Authorization Holders (MAHs) and Manufacturing Authorization (MAs) holders may decide to continue to produce such products unchanged. With no formalized mechanism for regular updating of these processes within the current regulatory systems, manufacturers can continue to manufacture according to the once-registered, but now suboptimal processes.

Nevertheless, compliance should focus on current engineering and scientific applications and constantly strive to be current taking advantage of newer learnings and new technology when appropriate [14].

As defined in ICH Q10, there is a requirement (under legal incentive) to execute continual improvement. There is also a need for manufacturers to update outdated manufacturing processes, especially those with marginal economics. Without a facile, harmonized dossier updating procedure, manufacturers will likely terminate supply rather than risk the costs and delays associated with a re-submission.

Consequently, there must be practical and applicable rules for regularly updating the pharmaceutical dossiers supporting the principle of continual improvement as defined by ICH Q10 in order to maintain processes in a state-of\-the-art level. Metrics can focus on compliance with new technological standards, as defined in numerous ICH standards, guidelines and guidances, for example, from ISPE and other associations.

3.2.2 Factory Related

Facility suitability, age, and maintenance, as well as adequacy of equipment and utilities, can have a significant impact on product quality. For example, vibrations in weak building structures might lead to the inability to keep an HVAC system functioning properly. Also, poorly designed layouts might lead to an uncontrollable airflow with the consequence of causing permanent problems in environmental monitoring. The consequences of these permanent problems are deviations and subsequent investigations without sustainable solutions. When followed by quality stops and an inability to deliver products to the market, these issues can cause drug shortages. Also, expansion of product portfolio (capacity and type) over time can cause sub-optimal process flows. Adaptability is worthy of consideration early-on at the new build stage or when considering facility upgrade options.

Discussion

Audits and scheduled Preventive Maintenance (PM) programs should be in place for all equipment, facilities and utilities used in the manufacture of pharmaceuticals. Audits results and PM findings need to have leadership visibility with regard to issues revealed and what is being done to correct them and when. This information can be utilized by site leadership to determine if manufacturing should continue or be stopped. By paying attention to this important area, a company can prevent costly manufacturing stoppages and prevent stock-outs. Those performing audits or executing the PM program should be well-educated, qualified, and trained pharmaceutical professionals.

Audits could be considered part of process control to avoid triggering a cause and effect chain that may lead to drug shortages.

3.2.3 Material Related

This topic is related to Section 3.2.1, but addresses individual components of a drug, such as excipients and packaging material.

Most specifications for actives, excipients, and packaging material are fixed within the development and the submission approval process of a drug. Yet, there is often only a minimal understanding of the potential variations in quality of starting materials and their impact. The impact on the final product may not be known until after the product has been on the market for some time. It would be helpful if a better understanding of a material's variability and potential impact on the finished product was clarified during product development.

If that initial assessment does not reveal potential impacts, what has been learned through many years of the legacy product's production needs to be integrated into both product and process updates as well as filing updates.

Discussion

Within the pharmaceutical quality system, a life cycle management process should be in place to assure that a comprehensive understanding of raw material, API, and component variability is developed during the development stage. Where legacy products are manufactured, retrospective analysis and understanding of variability ranges is important. Experience gained from successful products should be applied and controls put in place as may be appropriate to remain in a state of control and avoid the use of starting materials of unsuitable quality that can lead to the inability to produce a product (see also Validation above).

Regularly updated systematic lists can indicate the criticality of a starting material or component and the related contingency measure. There also should be routinely monitored actions for remediation of critical materials with results assessed as part of on-going quality risk-management and crisis plans. For critical materials, such as those that are sole-sourced, there should be suitable contingency plans in place to avoid drug shortages.

3.2.4 Machine and Equipment Related

Equipment failures can lead to production interruption and subsequent drug shortages may occur. Such failures are often linked to a lack of preventive maintenance or poor equipment capability. When preventive maintenance intervals are not respected due to tight production schedules or very limited capacities of other production factors, cumulative breakdown of machines, equipment or essential parts of infrastructure may result. Old equipment and the lack of availability of spare parts also may lead to lengthy down times while a fabricator customizes a part. Substandard equipment capability also may be the cause of manufacturing problems.

Discussion

Non-compliant preventive maintenance programs can lead to cumulative breakdown of machines, equipment, or essential parts of infrastructure. Regular inspection based on criteria defined during commissioning, factory acceptance tests and machine end equipment qualification can help avoid the risk for manufacturing equipment break-downs. Life cycle measures, such as maintaining fixed exchange intervals for critical spare parts, can help avoid production shut downs.

Because complex machines and equipment are subject to critical skill sets, company plans should be in place to identify the SMEs and the obligations and ownerships they have.

In addition, metrics should be available to indicate whether preventive maintenance has been performed and identify where actions may be overdue.

Maximum lead times for obtaining spare parts should be available as internal standards. If such standards are extended, they should be based on a formal risk analysis and release process in a controlled document.

When equipment is nearing its end-of-life or found to be of poor capability strategic plans need to be in place for planning and budgeting for equipment upgrades or replacements.

3.2.5 *Lack of Knowledge-Related Subject Matter Experts*

Lack of expertise in the product, its manufacturing process, associated technologies or management processes, can be underlying root causes of drug shortages. If a company lacks SMEs or the experts do not have adequate capabilities, skill-sets, or resources, investigations may be of poor quality or incomplete. This lack of expertise could affect the quality or outcome of an investigation and ultimately, lead to a drug shortage (see also Chapter 7 of the *ISPE Drug Shortages Prevention Plan*).

Discussion

A systematic list can be maintained regarding the levels of knowledge and expertise required for particular roles and used to determine where gaps exist and require attention. It can be valuable to maintain a matrix of expertise and qualifications together with completed training in order to give access to the appropriate SMEs at short notice. SMEs do not always need to be organizational employees. Consultants can fill requirements as appropriate. However, to be prepared for personnel turnover, SMEs need backups and substitutes. SMEs should have a definite role in the management decision processes and be actively involved. These backup SMEs also can be utilized in the event of staff illnesses, accidents, or family and health problems.

There also should be a mapping of the knowledge landscape available, and a list of SMEs and their available delegates or substitutes. Another important factor to consider is the number of part-time staff allowed in production areas. The maximum number allowed should be limited according to the criticality and complexity of processes and equipment.

3.3 Third Party Quality Oversight

A robust quality system must have business processes to control any third party involved in the drug manufacturing process, such as suppliers for starting material and packaging material, graphic artwork offices, chemical and microbiological laboratories, bulk and finished dosage manufacturers, distributors, wholesalers, traders and brokers.

Current GMP and Good Distribution Practices (GDP) requirements, for example, in the European Community, allocate this task to both the Qualified Person and the Responsible Person at Supply chain stakeholder level.

3.4 Conclusion

A robust quality system is essential for preventing meaningful interruptions to supply and subsequent drug shortages. Robustness is achieved when a quality system requires and ensures:

- Deep mechanistic understanding of the cause and effect chains and the triggers (for example, budget situation, investment decisions) starting such a cause and effect chain.
- Identification of the role of business impact on quality relevant decisions.
- Adequate qualification of SMEs.
- Usage of tools and guidances for technical expertise as available in the market (for example, from various industry associations).

Recommendations

- *For product and process development,* there should be defined business processes organizing the product life cycle management of transfer, phase-in, marketing period and phase- out of pharmaceutical products.

- *For validation,* a process should be established that enables product and process data to be collected continuously to evaluate that state of control and assess the need for further lifecycle validation interventions ("continued process verification" in the US and "ongoing process verification" in the EU).

- *For deviations and investigations,* there should be an appropriate management review process to monitor the deviations being raised to help identify any trends and potential issues.

- *For root cause-and-effect chains,* there should be transparent root cause-and-effect chains established as a result of investigations and as a starting point for remediation.

- *For CAPA,* there should be business processes in place ensuring that no accumulation of "overdue CAPAs" occurs and that CAPA measures are effective and sustainable.

- *For knowledge management,* this should be set up like a quality system with the main elements of regular training, know-how transfer, collecting experience and defined skill set to improve the capabilities to use a quality system adequately.

- *For good engineering practice,* there should be evidence of the usage of science and risk-based approaches.

- *For factories, buildings, machines and equipment,* there should be business processes available creating evidence of inherent potential to be a trigger for a cause and effect chain leading to major risks of unavailability to manufacture products. There should be metrics available indicating whether preventive maintenance is performed in time and where there are overdue actions. Maximum (lead) times for spare parts should be available as internal standards. If such standards are extended, this should be based on a formal risk analysis and release process in a controlled document. Strategic plans need to be in place for a company to plan for and budget for equipment replacements when the machine or equipment is at the end of its life.

- *For starting materials and packaging materials,* there should be regularly updated systematic lists in place which indicate the criticality of a starting material or component and the related contingency measure. There should be routinely monitored actions for remediation of critical materials. The results should be assessed as part of on-going quality risk management and crisis plans. For unavoidably critical, sole-sourced materials there should be suitable contingency plans in place to avoid drug shortages.

- *For SMEs,* there should be a mapping of the knowledge landscape available, and a list of SMEs and their available delegates or substitutes. Another important factor is the number of part timer staff allowed in production areas. The maximum number should be limited according to the criticality and complexity of processes and equipment to control.

4 Metrics

4.1 Introduction

This chapter examines various parameters for measuring or tracking performance against quality standards to determine whether the standards are meeting expectations. Tracking quality metrics can reveal weaknesses in process or product operations and alert a company to the need for quickly correcting deficiencies. While some measures may be used together to help prevent or mitigate drug shortages, the extent and range of monitoring will vary among companies and the selected measures may differ depending on what is being tracked. Metrics allow a greater understanding of the issue at-hand and offer the operator an opportunity to make informed decisions.

An inadequate quality system and lack of governance, in particular, have been identified as root causes behind supply disruptions and drug shortages. As the ISPE Drug Shortages Survey [1] revealed, companies investing in strong quality systems will be more likely to succeed in preventing drug supply interruptions and shortages as a result of driving compliance and by achieving sound governance and metrics. The ISPE Drug Shortages Survey also revealed that support from senior management to drive the drug shortages prevention programs, and well-defined metrics tailored to proactively identify the potential risk of a shortage, will help mitigate looming shortages. Hence, it is important to examine metrics across the operations and determine the strength of a company's Corporate Quality Culture. These efforts will help to determine which potential issues can be predictive of the overall ability to reliably supply quality products without interruption. Additionally, there is a need for a reporting system based on "meta data" that can indicate whether the quality system in place is complete and well managed across all management levels. Some of these measures may already exist at a company as per implementation of Q10 [4]. What are important are the similarities, as well as significant differences, between "meta data" and specific metrics and indicators necessary when investigating the causes of drug shortages.

Today, many pharmaceutical companies may choose from a wide range of metrics as part of their quality system management review (as driven by ICH Q10 Chapter 4). Finding the appropriate metrics is an ongoing discussion and ISPE continues to contribute to the US Food and Drug Administration (FDA)-triggered quality metrics initiative [15]. Accordingly, this chapter will discuss quality indicators provided and recommended to the FDA by ISPE and also take into account many discussions and ISPE workshops on this topic.

Purpose and Scope

The focus of the metrics initiative has been on quality and compliance elements. Both lagging and leading indicators are needed to measure the overall quality performance of a site and the products it produces. Taken together, these quality metrics can be predictive of the overall ability to reliably supply quality products.

A retrospective analysis of the root causes of shortages could indicate which specific metrics need to be routinely monitored. Unfortunately, conclusive data on the root causes of shortages is not readily available. The ISPE Drug Shortages Survey encouraged companies to leverage Corrective and Preventive Actions (CAPAs), Annual Product Quality Review (APQR), Quality System Management Review (QSMR), process performance, and product quality monitoring system [8], and to selectively pull metrics from these activities that can be predictive of shortages. However, questions remain as to which specific metrics will be the best predictors of potential shortages.

In relation to drug shortages, appropriate metrics need to be present across the quality system to:

- Identify and allow the mitigation of a potential drug shortage.
- Monitor demand and supply of particular drugs to identify risks to the supply chain.
- Monitor and predict an actual shortage: its scope, duration and patient impact.
- Demonstrate corrective action in preventing a similar future shortage is effective.

Metrics

Within a site's quality system, there may be many procedures that develop the level of control associated with the various operational systems. Statistical control is often used when considering these aspects. However, it is not possible for documented procedures to capture all possible eventualities within particular systems, and problems can arise where inherent control relies heavily on the involvement of staff members and their level of knowledge, experience, capability, and the degree to which compliance is important to them.

Metrics to monitor site culture are currently not well-developed. However, this chapter will identify some specific quality indicators that need consideration.

While global regulators require notification of potential shortages, notification has not yet been universally standardized. Moreover, such information is often classed as "commercial in confidence" and as such, in some countries, cannot be placed into the public domain. This may change with the adoption of a standardized reporting system and the potential publication of anonymized data by regulators. Therefore, there is currently little other than anecdotal industry reports regarding which specific metrics are best monitored to identify and prevent potential shortages.

Metrics associated with underlying root causes leading to drug shortages are different depending on which triggers might have the potential to lead to underlying root causes for drug shortages (see the example given at the start of Section 1). Metrics for triggers tend to be at a higher level to underlying root cause metrics. Once sites have identified and selected appropriate metrics that would demonstrate shortages, this step needs to be followed by a review to determine if there is any one factor that gives rise to any of these shortage metrics, i.e., seek to identify a more general or overall trigger. No guidance on this is provided as this will depend on the specific metrics selected and whether such a trigger may or may not be present.

It is also well recognized that there are supply chain metrics utilized and tracked by companies. Supply chain metrics are predictive of product demand and can be leveraged with quality metrics to prevent shortages or plan for remediation actions.

Sites may vary even where the same quality system is utilized within a larger multi-site company; however, the maturity of the quality systems may be different between those sites. Thus, it is not surprising that an examination of anecdotal evidence – as one-on-one discussion with regulators would suggest – that it is highly likely that no one set of metrics data fits all. What is more important is that companies maintain a system of monitoring and that they are making efforts to identify the quality metrics, quality culture, and supply metrics most appropriate for their operations. This chapter will address these topics.

Objectives

Given that no one set of metrics fits all, the objective of this chapter is to present a range of possible metrics to assist companies in selecting measures and indicators appropriate for them. The primary focus will be to examine metrics in the quality system supply chain and discuss the importance of Corporate Quality Culture. During 2014, there were a number of important industry conferences that highlighted the importance of quality metrics to assist in predicting potential drug shortages. Accordingly, this chapter recognizes these many contributions (such as from the Brookings Institute, the FDA, ISPE, and McKinsey and Co.) and presents a summary of these contributions. By tackling these objectives and by providing actual examples of how shortages are being addressed by industry leaders, the chapter strives to help both the regulator and industry better identify potential issues. With this information, one may proactively identify issues that may impact supply and ultimately, the patient.

Discussion

4.2 Quality Metrics

Categorizing a measure is highly subjective. Any given metric can be either leading or lagging based on how it is used. In order to ensure selected metrics are proactive rather than reactive in identifying potential shortages, companies have adopted measures that are leading indicators rather than lagging indicators. The definitions for leading and lagging are:

- A leading indicator may be predictive of future performance.
- A lagging indicator identifies or signifies past and up-to-the present performance.

Similar definitions can be found in various texts (for example, ICH Q10) [4].

These indicators are listed below along with their associated high level definition. This list is for reference only as these metrics are currently being evaluated in an ongoing ISPE project (see discussion below) and their applicability will be evaluated further into that project.

Metrics generally assigned as leading indicators:

- *Lot acceptance rate* – total lots released for shipping out of the total finally dispositioned lots for commercial use in the period.
- *Right first time (rework/reprocessing)* – total lots that have not been through rework or reprocessing out of the total finally released lots for commercial use in the period.
- *APQR completed on time* – number of APQRs in the period that were completed by the original due date normalized by all products subject to APQR.
- *Recurring deviations rate* – number of deviations that have occurred during the preceding 12 months period with the same root cause within the same process and/or work area out of all deviations in the reporting period.

- *CAPA effectiveness rate* – number of CAPA evaluated as effective (the quality issue subject of the CAPA was resolved and/or has not reoccurred, and there have been no unintended outcomes from the CAPA implementation) out of all CAPAs with effectiveness check in the reporting period.

- *Technology specific* – Media fill (for sterile) – number of media fills dispositioned as successful out of all media fills to support commercial products dispositioned during the period.

Metrics generally assigned as lagging indicators:

- *Complaints rate (total and critical)* – total complaints received in the reporting period related to the quality of products manufactured in the site normalized by the number of products released. Critical complaints (indicating a potential failure to meet product specifications, impact product safety and/or lead to regulatory actions), normalized by the number of products released.

- *Confirmed Out-of-Specification (OOS)* – total confirmed OOS (test results that fall outside the specifications or acceptance criteria) out of all lots tested during the period.

- *Recall events.*

- *Stability Failure rate* – total confirmed OOS related to stability testing out of all stability lots.

- *Invalidated OOS rate* – total unconfirmed OOS out of all lots tested by the lab during the period.

- *Environmental monitoring (sterile aseptic sites)* – total sterile lots with investigations related to action limit excursions out of all sterile lots dispositioned. Total sterile lots rejected due to action limit excursions out of all sterile lots dispositioned.

ISPE Quality Metrics Pilot Program

Following the passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 [16], the FDA was authorized to collect manufacturing quality data from pharmaceutical manufacturers. The FDA plans to use the "quality metrics" as an input to modify various aspects of its inspection models and to help predict possible drug shortages. To that end, the FDA invited input from industry on which metrics manufacturers use and have been found to be effective for assessing processes and risk.

In December 2013, ISPE developed a white paper proposing an initial list of quality metrics linked to the six systems inspected by the FDA. In June 2014, ISPE launched a Quality Metrics Pilot Program [15]. The pilot program's primary objectives are aimed at testing the set of metrics based on industry and FDA input, the harmonization of metric definitions, and the feasibility of data collection across different companies.

Quantitative and survey-based metrics with associated definitions have been selected by the ISPE Quality Metrics Team to cover a range of quality indicators. The list of quantitative metrics will measure the performance of the site, product, and quality system, and has been designed to be a blend of leading and lagging indicators to provide a balanced objective view of quality performance. The metrics described in the white paper include:

- Batch Rejection Rate

- Rework and Reprocess Rate
- Confirmed OOS Rate
- Unconfirmed OOS Rate
- Critical Complaints Rate
- Percent of APQRs Completed on Time

Metrics

The FDA has established a program with a goal of developing and implementing a standardized set of quality metrics across the pharmaceutical industry. As part of this initiative, the Engelberg Center for Health Care Reform at the Brookings Institute and the FDA held a workshop on 1-2 May, 2014 with industry experts to focus on identifying and defining standardized metrics. The metrics listed in Table 4.1 are some of the metrics discussed at the meeting that are of most value in demonstrating shortage vulnerability.

Metric Name	Available Factors	Inputs	API Relevance	PDF Relevance	QC Lab Relevance	Packager Relevance	Shortage Vulnerability	Leading or Lagging for Shortage	Leading or Lagging for Site Selection
Lot Acceptance Rate		# lots attempted; # lots rejected	Yes	Yes		Yes	Yes	Leading	Possibly Both
Stability Failures		# lots studied and # tests (including all timepoints) in protocol; # of tests and lots failed	Yes	Yes			Yes		
Environmental Monitoring/ bioburden		TBD	Yes	Yes			Yes	Leading	Leading
Right First Time		# lots reworked or reprocessed	Yes	Yes			Yes	Leading	Leading
Lot Disposition Rate or Time		# lots not receiving final disposition, or high, low, average SD	Yes	Yes	Yes	Yes	Yes	Leading	Leading
Lot Yield		High, low, average, and SD lot yield	Yes	Yes		Yes	Yes		Possibly Both
Product Quality Complaint Rate		# quality complaints; # lots released (aggregated by all sites)	Yes	Yes		Yes	Yes		Lagging
OOS Rate		# of OOS; # of release tests conducted	Yes	Yes			Yes	Leading	Possibly Both
Invalidated OOS Rate		# of OOS invalidated; # of release tests conducted and/or total # OOS			Yes		N/A	N/A	Possibly Both
Recall Rate (Class I, Class II)	Recalls/ Seizures	Available	Yes	Yes		Yes	Yes	Leading	Lagging
	Product Type	Available	Yes	Yes		Yes	N/A	Static	Static
	Facility Type	Available	Yes	Yes	Yes	Yes	N/A	Static	Static
	Time Since Last Inspection	Available	Yes	Yes	Yes	Yes	N/A	N/A	N/A
	Inspection Outcome	Available	Yes	Yes	Yes	Yes	Yes	Leading	Lagging
	Establishment Site	Available	Yes	Yes	Yes	Yes	N/A	Static	Static
	Product Market Share	Available					Yes	Leading	N/A
# of Products produced by site		Number of SKUs produced at site	Yes	Yes	Yes	Yes	N/A	N/A	Possible Both

Table 4.1: Key Metrics for shortages. Adapted from "Measuring Pharmaceutical Quality though Manufacturing Metrics and Risk-Based assessment," Quality Metrics Meeting Summary, Brookings Institute, May 2014 (Source: Used with permission of US FDA.)

Quality Culture Performance Indicators

The ISPE Drug Shortages Survey highlighted the importance of receiving support from senior management in order to implement quality system programs and link corporate quality goals to preventing drug shortages. The survey also established the importance of having dedicated resources for prevention and tying incentives to preventing shortages. This step reinforced how important it is for companies to not only have a dedicated Drug Shortages Prevention program in place that is "owned" by an organization's senior members, but to also create the attitude and set of values needed to improve the levels of quality in its service and products. This is what is referred to as having a Corporate Quality Culture.

ISPE, in collaboration with McKinsey, will conduct a survey on company Corporate Quality Culture. To better understand how a quality culture could be determined more objectively, the ISPE pilot includes a survey of site personnel – conducted anonymously – that poses 15 agree/disagree questions in five dimensions – Mind-set, Integrity, Leadership, Governance and Capabilities.

Most of these key areas – and many of the details associated with each – have already been described in other chapters. However, it is important to note that the lack of attention paid to these key areas, and the lack of monitoring of one or more of the detail points, is often cited as a major contributory factor for shortages by those companies who have experienced them.

Discussion

How the above quality metrics and performance indicators are best used will vary with each site. Most will be familiar with "Quality Dashboards" and "Balanced Scorecards." Classical quality dashboards are focused on lagging indicators and some leading indicators. Usually, they report statistical figures that need interpretation and comments in order to place them into the right perspective. The balanced score card system was developed to transfer corporate strategy into action by applying a holistic view to all functions of a company. This method does include quality aspects, but is not intended to be a systematic way of reporting on a quality system. While various approaches and metrics are utilized by companies for different products and plants, what is most important is that each site has a defined set of metrics that serve the intended purpose. It is for companies to determine which metrics best serve their quality system. By careful selection of appropriate indicators from a small range of metrics, companies should be able to determine which metrics are the most appropriate for indicating the potential for shortages within their quality system.

A system of metrics is recommended in this chapter (Table 4.2). It is important to note that these are simply examples and that the metrics utilized will depend on what is most appropriate for a specific quality system. The table is included to demonstrate that any system of metrics will utilize a wide range of metrics that may include indicators from the quality system, from the quality management and quality culture indicators. It is also important to reflect on and incorporate metrics on the "state-of- play" of your own shortage procedures and "dummy" incident investigations (see Metrics Case Study 3 below and Chapter 6 of the *ISPE Drug Shortages Prevention Plan*).

Relevant Indicators of the Quality System for Preventing Drug Shortages
Systematic risk management according to ICH Q9 and a common framework applied by all operators in the supply chain availability (for example: Failure Mode and Effects Analysis [FMEA], Ishikawa)
Contingency plans to be activated in case of near or potential drug shortages (for example: safety stocks, second sources for critical material, etc.) available
Crisis plans for all personnel in the supply chain available
List of qualified Subject Matter Experts (SMEs) available
Periodical production releases are performed for buildings, infrastructure, machines and equipment based on pre-defined performance checklists
Preventive maintenance is performed, maximum usage times (and replacement) for critical spare parts are defined
Quality Management Indicators for Drug Shortages
Management involved in all decision making processes
Overall responsibility of senior management, including the CEO, is defined
Regular cross-functional and cross-level quality review meetings are in place
Qualification of individuals in drug shortage teams defined
Qualification of drug shortage team defined (for example: at least four different disciplines)
Decision making processes defined
Regular training for drug shortage teams and functions performed
Corporate quality function reporting lines work effectively
Quality stop philosophy in case of observed deviations implemented
CAPAs are sustainably managed
APR and PQR are regularly reviewed by upper management, product design problems are identified and sustainable actions are taken
Supply Chain Indicators for Drug Shortages
List of sole-sourced products available and updated on a regular basis
List of life saving products available and updated on a regular basis
List of critical suppliers available and updated on a regular basis
Regular reporting on status of supply for critical products
Sourcing strategy for critical starting materials identified
Quality Culture Indicators
Quality policy addresses avoidance of drug shortages and allocates quality as an obligation for the whole organization
Code of conduct addresses cross-functional and cross-level communication (for example: escalation and notification of potential and actual drug shortages to assure ownership at all levels of an organization)
Dedicated set of rules for the avoidance of drug shortages available (“golden rules“)

Table 4.2: Suggested System of Performance Indicators

4.3 Supply Chain Practices and Supply Metrics

Chapter 5 of the *ISPE Drug Shortages Prevention Plan* introduces three important aspects of the supply chain – resilience, robustness and redundancy – as key practices that can enable pharmaceutical companies to proactively characterize and plan for potential drug shortages. The following examples of key supply chain metrics have been recommended to enable companies to be alert to problems and to managing potential drug shortages [17]:

- *Supply chain cycle time:* the total time (in days) taken to satisfy a customer order for a product if all inventory levels were zero. It is calculated by adding up the longest lead times in each stage of the cycle from planning, sourcing, manufacturing, and delivering the product to the customer.
- *Order fulfilment cycle time by line:* average actual cycle time (in days) to fulfil customer orders for all products manufactured at each line at a facility. For each individual order, this cycle time starts from the order receipt and ends with customer acceptance of the order.
- *Inventory Months of Supply (components, Active Pharmaceutical Ingredient [API], drug product):* it is the ratio of inventory on-hand and average monthly usage for a product (the average monthly usage is typically the yearly forecast for the product divided by 12).

It could be that the metric adopted here is as simple as the control of stock and the coordination between the manufacturer and the Marketing Authorization Holder (MAH).

As with quality metrics, it is probable that no one set of supply metrics fits all quality systems so distributors will need to identify which are the most suitable for assessing shortage vulnerability.

4.4 Case Studies

Metrics Case Study 1: Using Supply Chain Metrics to Avoid Shortages

Situation

A global pharmaceutical company had significant issues with its supply chain management and inventory planning. The company repeatedly failed to meet forecast targets, which in turn, led to product shortages in the market. Multiple quality and performance issues along the manufacturing process were impacting product yield. In addition, product release took longer than usual cycle times, which were not originally accounted for during forecast goals/targets.

What was not clear to the company was whether the shortage issues could be solved by simply improving control over supply chain planning activities or if other elements might be contributing to the issues they faced.

Approach

The company conducted an assessment to understand the key "pain points" within its supply chain continuum to develop mitigations and implement solutions needed to reduce lost sales and shortages. While some of the inventory shortfalls were due to limited planning, other factors involved poor yields due to quality-related issues (such as time lost investigating OOS events and batch failures). Management created a cross-functional team to define metrics across both the supply chain and quality systems. If looked at in tandem, the metrics could help point to potential shortages before they were realized. In addition, the company also factored in more financial-based metrics (cost of manufacturer, percentage of sales and revenue) to better understand the mitigations to address any risks identified across the supply chain. Some of the supply chain metrics examined included the following:

- Inventory days of supply
- Batch yields
- Scrap percentage
- Inventory turns
- Plant capacity and utilization

Once these elements were in place, the company set out to understand the risks across the network that might cause a shortage if one of its plants or suppliers shut down or faced reduced production levels. Identifying risk was based on the following metrics:

- Product Revenue (percentage of overall portfolio)
- Product Complexity
- Percentage of Sole Source Suppliers
- Capital investment needed for facility expansion/upgrade
- Identified compartmentalized practices and objectives with little cross functional synchronization between functions

Solution and Results

Management refreshed its approach toward supply chain and inventory management strategy. By integrating traditional supply chain metrics with operational quality metrics, management had better visibility into operational performance, including batch yields, batch release and stability cycle time performances, rejection rates and rationales. The company implemented an end-to-end structured inventory methodology comprised of inventory planning controls, replenishment strategies, batch quantities, site planning, and parameters alignment. The resulting "de-compartmentalization" of practices and cross-functional synchronization (between quality and supply chain) led to improved targeted product forecast achievements across all major markets.

Metrics Case Study 2: Robustness with Reliability Rooms

Situation

A pharmaceutical company experienced major supplier disruptions that impacted their ability to provide lifesaving drugs to patients. While the issues were related to the quality of their Contract Manufacturing Organizations (CMOs) and suppliers, the disruptions exposed the need for transparency in information and metrics. The company subsequently conducted an assessment to understand the true root causes behind the problems, and more importantly, to develop potential solutions.

Approach

A company conducted an end-to-end assessment of the operations, including looking at the overall supply chain and the controls over third party manufacturers. Management identified the need for investing in creating "reliability rooms" for managers in the supply chain to gain access to all the data on suppliers and a product's performance during manufacturing.

Solution and Results

The company established "reliability rooms" at all plants with adequate controls on major suppliers. Each room was designed to contain a sensitive set of metrics with leading indicators that could result in reliability issues at supplier. Metrics included delivery performance, non-conformances, and "right first time." These metrics were correlated to the performance issues of the supplier so that potential supplier risks could be proactively identified. These reliability rooms enabled risk prediction more consistently and quickly for the supply chain managers to take action to mitigate any risk of shortage or stock-outs for life-saving and unique products. Because of the success of the program, the Company expanded the reliability room process existing for internal plants to the external network.

Metrics Case Study 3: Creating Strategic Reserves (Redundancy)

Situation

A global pharmaceutical company with multiple life-saving and unique products proactively worked to prevent stock-outs and shortages as a strategic goal. The company had established back-up sources that were qualified and registered. However, based on learnings from some events related to life saving products, management realized that it was not a "true" back-up unless these back-ups were kept "warm" by giving them some volume (10 to 20 percent of total) and then use this as a strategic reserve for the company. In other cases where dual sourcing was not viable, having strategic reserves for key components and products was critical to preventing shortages and stock-outs of life-saving products.

Approach

The company employed risk assessments for each product where the marketplace is analyzed for therapeutic equivalents and other competitors/players. The assessment was based on a robust risk management system that "pressure tested" the supply chain network for each product by reviewing the capabilities, redundancy, and continuity plans of all Tier-1 suppliers and their supplier's key suppliers (Tier 2) including distributors.

The risk assessment leveraged a combination of scorecards, audits, and simulations to conduct scenario planning and sometimes a planned disruption was created to test all elements of the supply chain. At each plant, evaluation of back-up plans for equipment, including power sources, was implemented. Based on this evaluation, validation of additional equipment was carried out. Other factors that could impact operations at facilities (such as natural disasters and labor issues) also were considered as part of the scenario planning.

Solution and Results

The company established seven to eight quantitative dimensions in the risk management program with rankings, metrics, algorithms, and weight-ages to generate a risk score on a per product basis. This score was used to help decide which trade-offs would be made between investing in redundancy vs. keeping strategic inventory. For one of the products in women's health (although the product was not significant in terms of revenue there is no alternate in the market) the company strategized to hold more inventory since it would not be financially viable to qualify another back-up source.

Additionally, in the event of a shortage or stock-out, the company proactively took steps to notify its competitors so that these manufacturers would have the opportunity to ramp-up production volumes as required to avoid a future shortage of these products. While the company evaluated a range of qualitative dimensions to develop mitigation strategies to prevent shortages – the weight-age on cost and revenue are lower compared to the other dimensions, although unlimited insurance is not available.

4.5 Conclusion

There are a number of learning points arising from the above:

- Metrics are an aid in dealing with shortages; they are not necessarily the solution to shortages.
- Due to the differences in maturity of site quality systems, companies must select their own metrics to highlight shortage vulnerability.
- Shortage metrics can arise from quality metrics and be statistical in nature; however, a range of quality culture indicators is probably also required.
- A range of potential metrics was presented and some guidance on those that may be best at identifying shortage is given above.
- Shortages do not always arise at the manufacturing site; supply chain metrics also are important for monitoring shortage vulnerability.
- Manufacturers and distributors should have a system to demonstrate the effectiveness of the metrics they adopt to monitor shortage vulnerability; shortage metrics should include measures related to on site shortage procedures, for example, audits and "dummy shortage" investigations.
- Sites should look closely at the metrics they select to demonstrate shortage vulnerability to determine if they are pointing to a specific or more general shortage trigger, for example, such a lack of investment budget constraints, business needs, shortage in resources or others.
- There is value in evaluating how real life shortages are addressed by industry leaders and how companies that were successful in avoiding drug shortages had a strong Corporate Quality Culture.

Metrics

Recommendations

- Companies should select their own metrics as indicators of an effective quality system and potential shortage vulnerability. Shortage metrics can arise from quality metrics, product performance reliability, and be statistical in nature (process variability), however, a range of quality culture indicators are probably also required.
- Supply chain metrics (cycle time, customer service, etc.) also need to be considered when monitoring shortage vulnerability.
- The application of metrics should follow principles of continual improvement to assess and demonstrate the effectiveness of the metrics they adopt to monitor shortage vulnerability.

5 Business Continuity Planning

5.1 Introduction

Purpose

The ISPE Drug Shortages Survey [1] identified a number of problems that contribute to drug shortages. Specifically, the following areas for improvement were identified.

- Less than robust Pharmaceutical Quality Systems
- Limited governance and oversight at a cross-functional level

The survey suggested that companies that developed mitigation programs focusing on these areas within their organizations were best able to avoid shortages. Through subsequent discussions with ISPE Members, ISPE was able to further discern how companies were able to use strong quality systems and governance systems and structures to both ensure reliable supply and prevent shortages by identifying potential risks across the following areas:

- Production
    - Product – work to identify optimal product designs/old design as registered; in addition, improve the overall technology transfer process by better characterizing the product (and process) when it is transferred from development to manufacturing.
    - Factory – identify factories across the network in need of upgrade due to age and high maintenance costs or low capability.
    - Material –develop systems to identify potential issues with ingredients (for example, Active Pharmaceutical Ingredient (API), excipients, etc.) that – if not addressed – will lead to shortage of suitable quality.
    - Machine/Equipment/Utilities – help ensure that suitable materials and equipment needed to manufacture products were available when needed for production runs.
    - Experts – address the shortage of qualified people.
- Process
    - Develop systems to communicate what processes needed to be developed to help determine the specifications and parameters required to control the following elements:
        - Environment
        - Production
        - Behavior and human error

Integration of governance processes and quality systems was found to be important company-wide. Through interviews and bench marking with key and knowledgeable corporate executives and global regulators, and through a more detailed analysis of the study results, the supply chain was identified as another area that needs to be added to a company's drug shortage avoidance strategy. During these discussions, feedback included comments related to a lack of quality and the need to improve the overall quality systems. However, many of those interviewed referred to challenges around the supply chain. Some of the highlighted areas of challenge and comments from those interviewed are as follows:

- *Slow manufacturing ramp-up:* ability to overcome regulatory hurdles and the ability to operationalize the production planning systems needed to make sure that planning, demand, and manufacturing stays in synch with one another. This is especially important in light of the reliance on outside vendors and third-party manufacturers.

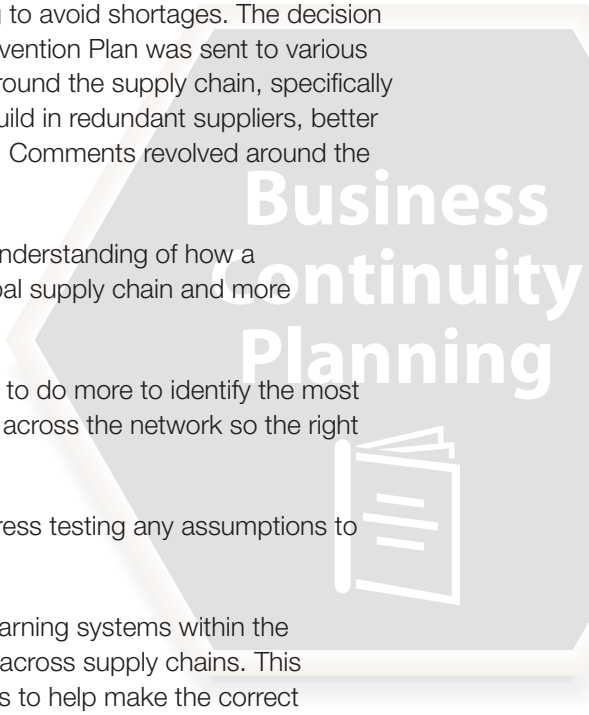
- *Sourcing issues:* challenges to identify alternative/redundant and equivalent sources of products, raw materials and components to address deficiencies quickly in order to restore manufacturing activities. While many companies have identified back-up manufacturers, these manufacturers must give some assurance of their being able to keep up with predicted demands and capabilities and to quickly address issues and/or expand capacity for critical drugs when needed.

Both producers and purchasers of APIs should strengthen their understanding of the regional legislative requirements [18] and regulatory expectations as outlined in various Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) guidelines around the world and the associated quality standards and how they should be implemented. Steps also should be taken to develop supply chain resilience around these drug component types – whether quality or supply chain-related. This should be implemented as a model requiring specific metrics which are commonly reported across all supply chains or metrics used as part of a manufacturer's PQS and supplier oversight, which may vary, but are meaningful to each product/organization – the system is then under control. For critical excipients and packaging materials, suitable contingency plans should exist.

A new type of supply chain- focused audit may help here. These audits should be carried out against the requirements of the various new GDP guidelines (for example, those of the World Health Organization (WHO) or European Medicines Agency (EMA) or others on national basis) for all stakeholders of the international supply chain. It could be done either by organizations, by manufacturers, or by agencies and based on mutual recognition agreements. These supply chain-related challenges were supported by findings from the ISPE Drug Shortages Survey. Where companies reported failed mitigation programs, respondents were asked to rank which of the factors they had chosen to emphasize as part of their drug shortage programs. When this list of factors was compared to the list of factors from successful mitigation programs, a marked difference was apparent.

Rather than indicating that their priorities revolved around strong quality systems, governance, metrics, and incentives, the failed programs focused on areas such as building Information Technology (IT) systems to help identify potential shortages as well as efforts to establish redundancy in the supply chain and manufacturing operations. While companies with successful programs did not appear to emphasize this point, it is unclear whether this was because redundant systems had already been established or if this was an area that companies felt was less critical than other factors in preventing shortages [1].

ISPE decided to focus on the supply chain to understand its role in helping to avoid shortages. The decision to do so was validated when the first draft of the ISPE Drug Shortages Prevention Plan was sent to various regulatory agencies for review. Many of the comments tended to revolve around the supply chain, specifically asking ISPE to help identify ways that the supply chain could be used to build in redundant suppliers, better alerting mechanisms, and overall greater transparency across the network. Comments revolved around the following themes:



- *Integrate Supply Chain with the Quality System:* "There is insufficient understanding of how a pharmaceutical quality system should be implemented across the global supply chain and more guidance is needed."

- *Identify the Risks to Build Appropriate Redundancy:* "Companies need to do more to identify the most critical risks (manufacturing, testing, raw material sourcing) associated across the network so the right decisions can be made."

- *Quickly Adapt to "Shocks" to Enable Resilience:* "Develop and build stress testing any assumptions to further the strategic objective of resilience and robustness."

- *Develop Alerts to Ensure a Proactive Approach:* "Develop early alert/warning systems within the supply chain with integrated crisis communication and rapid reporting across supply chains. This includes quickly assembling a senior level of functional decision makers to help make the correct decisions quickly." The reader is directed to the European Federation of Pharmaceutical Industries and Associations (EFPIA) Good Practice – October 2013, *Reducing Risk for Drug Products Shortages* [19], for a further discussion of early alert/warning systems within the supply chain.

To address this need, ISPE created a team dedicated to better understanding the key supply chain elements that should be developed and built into a company's drug shortage mitigation strategy. In addition to leveraging the ISPE Drug Shortages Survey findings and feedback from ISPE members and regulators, the team identified a number of senior executives responsible for supply chain operations to get their perspectives on the challenges they have faced. Discussions were focused on the solutions implemented as they worked to develop and build a supply chain that would help prevent shortages – one that was robust, redundant, and resilient. The following elements would help to understand how the desired objectives could be met.

- *Robustness:* supply chain has been integrated within an organization's Quality System. By achieving this integration, the organization will be in a better position to identify and proactively address potential issues. This may include helping to identify opportunities to update "old" product designs as a result of capturing performance knowledge from the manufacturing arena, converting this knowledge into improvement opportunities, and then implementing them – whether improvements to the product/analytical method or the processes or facilities used to manufacture the product.

  The integration between the supply chain and the quality system also will help better integrate the concepts related to Quality by Design (QbD) across the development of new products as knowledge can be shared between development and manufacturing in a more proactive manner.

  Having a robust supply chain also will help leverage the learnings from across the supply chain network to identify improvement opportunities. In addition, a robust supply chain is one that includes well-defined metrics that could be used to help proactively alert management of an problem with the supply chain that might, in turn, cause a shortage.

- *Redundancy:* a key element needed to ensure that a company could protect itself from factors that may cause an interruption of supply. Companies that have taken the steps to understand the risks across their supply chain will be in a much better position to identify where specific mitigations strategies should be implemented, including additional manufacturing sites, back-up equipment, dual source suppliers, or safety stock inventory.
- *Resilience:* once the supply chain has been developed – one that is robust and redundant – steps need to be taken to test the supply chain to assure it remains redundant and resilient. Resilient supply chains can overcome a number of issues that threaten to reduce product supply. Finally, these supply chains have been designed with the feedback loops to help monitor and identify improvements across the quality system and supply chain.

Note, ISPE is not suggesting that each of these elements should carry an equal amount of weight as companies strategize how to develop solutions related to shortages. Indeed, it will be up to each company to decide how to balance the solutions across each of these three areas.

5.2 Objectives

The following objectives have been defined for this section, specifically looking to see how companies have established supply chains that are robust, redundant, 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].

1. Integrate the supply chain network (from development to commercial manufacturing) with a robust quality system, including governance, management strategies, and decisions used to help achieve a robust supply chain.

2. Communicate the successful strategies in place today to monitor the supply chain for risks and develop the solutions needed.

3. Identify mechanisms to test and monitor potential issues with the supply chain and weaknesses that, if not addressed, may lead to a shortages.

Objective #1: 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.

As a result of an increasingly global economy, supply chains have become more global and complex, reaching from the supplier's supplier to the customer's customer. Accordingly, the need to integrate operations with the quality organization becomes critical in helping to avoid shortages. Without integration, the company increases the risk of a shortage as negative elements will "seep" into the system, such as:

- An inability to capture information that can be used to make better decisions related the supply chain.
- Poor visibility-related to issues with equipment, material, etc., as well as overall supplier base.
- Limited cross-functional collaboration that may cause compliance issues to go unnoticed by the organization.

Supply chain organization should include managers – not only from sourcing, manufacturing, and logistics – but also from product and service development, marketing and sales, finance, sustainability, and ethics and compliance.

Doing so will ensure that the operations are compliant, but also will help the organization identify potential issues that if left unaddressed will lead to a shortage. One executive who commented on a company's ability to generate significant advantages across the supply chain as a result of integrating it with the overall quality system said that:

- Improved technology transfer and scale- up capabilities have not only helped reduce the delays with these activities, but also helped the operational group to better understand characteristics related to the product. They achieved better process understanding.

- Achieve the appropriate* production and material controls that, as a result of the greater degree of process understanding, work to help improve the ability of the organization to stay compliant and improves quality starting upstream in the process (material receipt) and throughout the production process. It will be important to select the appropriate Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) and to have a control strategy to monitor them.

*To prevent a shortage of material at times, if there were wider limits on raw materials that were deemed acceptable technically, more material would be available for the product. Similarly, if in-process controls can be loosened after we have enough experience under our belts that, as well, would help prevent shortages. However, we stress that any loosening has to come with data review and compliance to the submission.

- Achieve a true "closed loop" system so that when product issues are identified the quality system is able to capture them and communicate to all parties involved, including operations.

Key elements – a summary of what is required includes the following: achieving this objective will require companies to develop key capabilities across their supply chain, including their third-party suppliers and manufacturers. Capabilities will include the following [20]:

- *Governance Systems:* develop the proper levels of governance across the organization that will allow information to get to the right people at the right time. This will help make sure that decisions can be made in a quick and efficient manner and help resolve issues that potentially may lead to a shortage. The governance structures should be set up to enable transparency related to the ongoing operations, whether related to quality, inventory levels, or manufacturing yields. As a result, company executives will be able to make better decisions when it comes to resolving a potential shortage issue.

- *Processes:* develop integrated supply chain processes and systems that interface efficiently with the rest of the enterprise. These processes should extend into third-party suppliers and manufacturers. This would include developing and putting in place agreements with the various partners that specify requirements and expectations related to quality of products and continuous supply. In addition, this is where a robust knowledge management process can be helpful.

- *Organizational Design and Capabilities:* develop and maintain organizational structure and skills to define and manage the supply chain of the future. Consider context, culture and complexity when designing your supply chain organizational structure, whether centralized, decentralized or hybrid.

- *Metrics:* use metrics to measure the health of each core supply chain process and identify problem areas. The metrics will focus on measuring not only compliance issues, but also issues that may lead to a shortage (see Chapter 4 of the *ISPE Drug Shortages Prevention Plan* for a list of potential metrics to consider). Once these metrics are established, executives also will be able to measure the overall performance of the supply chain and use any learnings to help make the system more operationally efficient while still maintaining overall compliance and high levels of quality.
- *IT Systems:* new technology and analytics can make the supply chain transparent, enabling companies to adjust quickly to changes. The better the information companies have at-hand, the more responsive their supply chains can be. However, information from the supply chain may be slow to reach managers, and suppliers may complicate matters by using different software programs and data formats.

  Companies with the appropriate IT capabilities can capture this information and analyze it for trends and/or disruption patterns. Signals that may point to an issue with the supply chain's ability to deliver the correct quantities of product can put a company in a better position to avoid shortages. The trends may help identify actionable insights, some of which may be specifically related to where the sponsor company may need to intervene to help resolve a potential issue, whether it is related to operational efficiency or a compliance-related risk.

  These trends or disruption patterns may include the following:

  - Reduction in yield (compared to the average level of production).
  - Inventory is approaching safety stock levels.
  - Upstream suppliers are starting to slip related to ability to deliver critical components to the downstream processing plants.
  - Potential issues with quality based on trends picked up related to Out-of-Specification (OOS) and batch failures.
  - Supplier audit results may give the sponsor company a potential signal that a supplier has a compliance issue that may lead to a shortage.

  These trends and patterns can help ensure that the supply chain stays integrated with the quality system and will indicate if systems can catch potential issues. This level of integration also will help resolve potential issues that may go unnoticed as a result of the limited visibility. Issues may include:

- *Production*

  - Product – allow supply chain to be designed around the product. Suppliers can be chosen based on the characteristics of the molecule as well as potentially, a supplier's experience working with similar products.
  - Factory – better detect the need for maintenance and upgrade the factory's systems where necessary. Without integration, systems will either not pick up the needs for the upgrades, or the upgrades may potentially be made without the input from quality, which opens up significant compliance risks. A sound preventive maintenance plan attached to the quality system is a good indicator of issues that could later result in shortages if not addressed.

- Material – integrating the supply chain with the quality system will help the organization identify two key elements that often are "lost" when the two systems operate independently to: a) have the ability to detect when materials needed to manufacture a drug are in short supply and b) be able to identify when materials may not be meeting specifications. Without this integration, communication between operations and quality is limited and in turn, increases the risk of releasing non-compliant product or running out of supplies.

- Machine/Equipment – similar to the benefits related to material availability, integrating the supply chain with the quality systems will help detect the need to take the steps to either update plant machines and equipment.

- Experts – shortages of qualified people can contribute to the potential for compliance risks across the supply chain. Developing the capabilities across quality as well as operations will help address this. Specifically, make sure that all parties responsible for delivering quality and compliance have the tools to do so. The advantage of developing the personnel across the elements of both operations and quality has the added benefit of helping to identify potential improvements across the supply chain.

- *Process*

  - Environment – the facilities that support the supply chain processes are built to meet the needs of the processes without failure from manufacture of raw materials through delivery of product to customers. Validation is performed to assure key parameters are met.

  - Production process – by integrating operations with the quality system, deviations to the process will not only be more easily identified, but operational personnel will be more likely to understand that the issue needs to be addressed. By working closely with the quality personnel, the collaboration between the two groups will be stronger and the solution needed more readily identified. In the end, issues on the shop floor will be better understood by the shop floor Subject Matter Experts (SMEs) – so having these individuals involved in helping to resolve the issues side-by-side with quality will help identify a solution that is complete and systemic in nature.

  - Technology Transfer Process – taking steps to make the technology transfer process more robust also will help avoid shortages. By defining the characteristics of the drug earlier in the process (i.e., identifying the critical attributes and parameters) the product that is transferred will be better understood. Provided this information is transferred in a complete manner to manufacturing, as a result of the improved product characterization, a number of benefits should be achieved:

    - Shorter transfer times

    - Greater first time batch success

    - Reduced time needed to close out any investigations needed

    - Greater chance of identifying continual improvement opportunities

- *Behavior* – training people to have a quality mind-set will help reduce risks across the supply chain. Due to the expanding nature of the supply chain, the ability to create and sustain a quality culture can be lost. It is important that efforts are taken by companies to communicate expectations related to quality and

emphasize how quality needs to be integrated across the supply chain. Successful teams have found ways to do this by creating core groups that are cross-functional in nature and work together to improve quality and overall compliance. The added benefit of these integrated teams is that opportunities to improve both the overall system and degrees of efficiency can often be gained.

Objective #2: Communicate the successful strategies in place today to monitor the supply chain for risks and applying the necessary solutions.

To protect the supply chain from potential disruptions, it is important that a risk assessment is employed to identify areas where redundancies are needed to reduce the risk of a shortage. While the risk assessment should be used to help identify potential weaknesses across the supply chain that would warrant a back-up or redundant system, other risks should be factored in as well, as they relate to impacting a company's ability to ensure a continuous supply of product. This might include several risks:

- Operational Risks: How would a transportation disruption impact business? How would a natural disaster impact the supply chain?
- Financial Risks: Are any key suppliers financially unstable? What are the carrying costs associated with inventory levels?
- Geopolitical Risks: What impact would a labor strike at a key port have on business? How would an increased import tariff impact supply chain costs?

Other risks to consider when attempting to identify and determine where redundant systems are needed are identified in Table 5.1.

Sample Risk Category	Illustrative Risk Events
Supplier Risks	• Supplier financial crisis • Supplier regulation non-compliance • Supplier IT systems disruption • Supplier counterfeit parts
Environmental Risks	• Natural disasters (e.g. earthquake, flood) • Pandemic • Terrorism • Industrial accidents
Product Risks	• Raw material price fluctuation • Currency fluctuation • Product development delays • Product quality impact
Process Risks	• Equipment breakdown • Under/over capacity • Material Scarcity
Transportation Risks	• Air/sea port disruption • Freight capacity shortage • Inter-partner communication break down

Table 5.1: Supply Chain Risk Categories (Source: Supply Chain Resilience Model. Used with permission from PricewaterhouseCoopers.)

Redundant systems can take a variety of different forms, whether by identifying additional third party suppliers/manufacturers or taking the steps to identify the additional facilities across the enterprise that may be able to support the manufacturer of additional product in the event of a disruption. There has been a recent emphasis in the industry to have a "Just in Time" inventory practice. Inventory means money.

However, while establishing redundancy is important – and a critical piece of any supply chain – the areas in which redundancy is built across the supply chain are just as important. In other words, it is not financially prudent, or operationally efficient, for a company to build in a redundant system across the full supply chain. This was confirmed during the ISPE Drug Shortages Survey where participants who had developed successful mitigation strategies did not rank "redundancy" as a top priority. Many of the participants with failed mitigation strategies had ranked the ability to develop redundant systems as something their company had spent time developing.

This finding speaks to the importance of establishing a robust quality system before setting out to develop a redundant system. As mentioned at the 3rd Annual ISPE-FDA cGMP Conference (June, 2014), "it does no good to build a second warehouse if it is going to be used to store product that is out of specification."

Companies that have established redundant systems have effectively taken the steps to identify the risks across their supply chain and in turn, developed the redundancy needed based on identifying critical areas that may lead to a supply disruption. Our executive interviews have confirmed this aspect and also highlighted that in their experience, it has been noted that, "leading companies have more mature supply chain risk-management capabilities and are more resilient to supply chain disruptions." These companies tend to recover quicker and are able to limit any disruptions to the drug supply as a result of these redundant systems.

Other important elements that need to be included and integrated across the supply chain and quality systems include:

- Sensing mechanisms – demanding customers, different order-to-delivery times, and the need to tailor products to different segments will require flexibility.

- Reporting channels – what are the early warning systems? Check points along the supply chain – field alert to the supply chain to let it know there are issues.

Objective #3: Identify mechanisms to test and monitor potential issues with the supply chain and weaknesses that, if not addressed, will lead to a shortage.

When asked about the various mechanisms to test the supply chain, executives highlighted not just the processes used to test the quality systems, but also tested the operational "resilience" associated with the supply chain. Companies that claimed to have the most success were those that highlighted the steps taken to test and monitor both the quality systems and operational in an integrated manner. For example:

- *Demand Fluctuations:* to test the ability of the supply chain to handle an increased demand on the product. Executives commented that the company would take the results of the testing to identify "holes" in the supply chain – that is, areas within the network that would not be able to absorb an increase in demand. Armed with this information, the operational elements would work with the quality counterparts to identify the solutions needed; solutions might revolve around the following:

- Increase Manufacturing Capacity: increase the number of third party vendors and manufacturers that could manufacturer products; anticipate the demand and use information to work with quality to shift its resources so it could prioritize the approval of new sites. Identify ways in which the vendor/ manufacturer could quickly come up to speed on the product so technology transfer could be carried out in a quick and efficient manner, thereby reducing the time needed to initiate commercial operations.

- Regulatory Risks (Internal as well as Supplier Related): use a site and/or supplier's regulatory history to better anticipate which issues may cause: (a) a site to shut down or (b) the need to proactively work with the regulators to identify solutions and agreements to keep the facility running as the compliance issues are being resolved. The close communication and coordination between operations and the quality group is critical for this to take place.

- Redundant Systems: executives developed tests to help determine the various trade-offs that would need to be considered when designing a supply chain. By executing the tests, trade-offs between cost and flexibility could be better identified. Building redundancy – while important – needs to be done based on the risks. Making sure that these risks as assessed against the impact on quality will help make sure that the supply chain and ops groups do not make any decisions that would sacrifice quality in an attempt to either increase flexibility or reduce costs.

Tests across each of these areas can be conducted using a number of different scenarios that help to identify risks (as outlined as part of the Objective 2 discussion) are summarized in Figure 5.1.

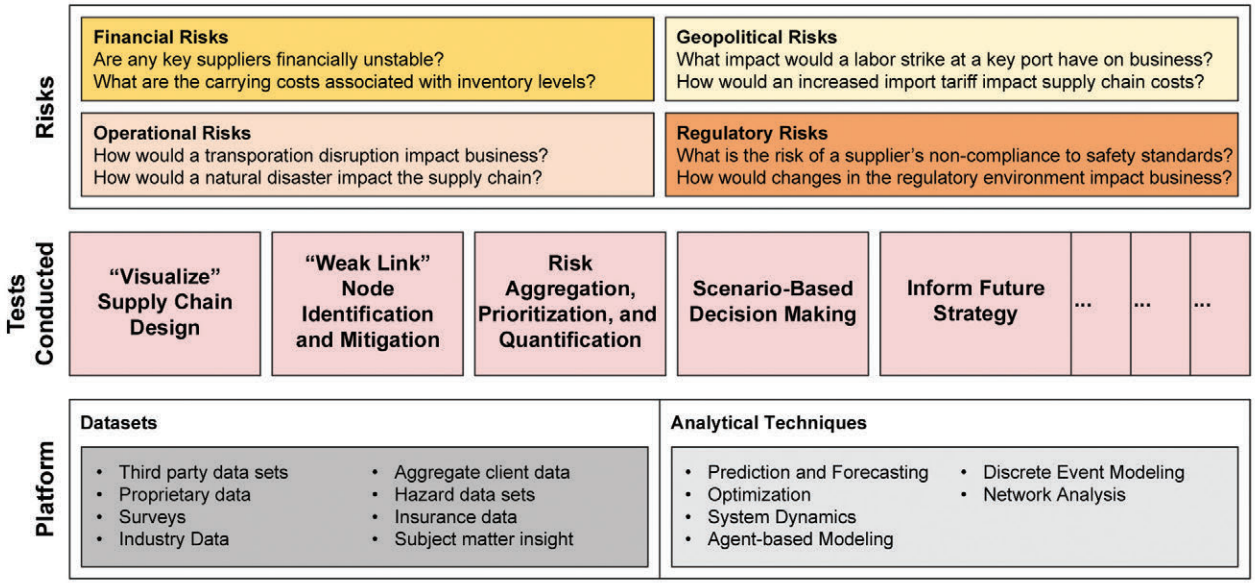


Figure 5.1: Supply Chain Simulation Factors to Consider (Source: Supply Chain Resilience Model. Used with permission from PricewaterhouseCoopers.)

As Figure 5.1 shows, the key to allowing these simulations to be conducted depends on a combination of datasets and analytical techniques, tools that allow for modelling and scenarios related to shortages to be developed.

5.3 Case Studies

Introduction

The executive interviews yielded insights into some of the key leading practices that companies were putting in place as part of their efforts to reduce drug shortages. While many practices revolved around traditional supply chain characteristics, such as formal demand and supply planning practices, others layered in the practices that would help integrate the quality system and the supply chain. As a result, companies were able to get a higher level of visibility into supply chain operations and also better understand how elements might get impacted based on quality related issues. In addition, the integration of these two systems helped improve the ability to be more proactive and develop potential solutions when a shortage issue was identified.

Business Continuity Planning Case Study 1: Achieving Robustness

Situation

A pharmaceutical company was facing significant problems with the quality of its products, and that led to a number of recalls which, in turn, led to shortages in the market. While quality was initially blamed for the issues they faced, the company conducted an assessment to better understand the true root causes behind the issue and more importantly, to develop the solution needed to mitigate the problems.

Approach

A company conducted an end-to-end assessment of their operations, including examining the overall supply chain and, specifically, the controls over third party manufacturers. They identified limited supplier controls as a result of operations taking steps to identify and select suppliers without bringing quality into the loop. In addition, because of the lack of controls, there was a risk that suppliers would be able to make changes to their respective materials without the necessary oversight.

Solution and Results

Management revamped supplier management processes so they could be integrated with the company's quality system. Because of the integration, quality had more control and visibility into the suppliers selected and was able (via audits) to better understand the risks associated with each of the suppliers. Supplier agreements were set up to define expectations related to initiating product changes. The agreements also included expectations related to more traditional supply chain/operational metrics – that "forced" the suppliers to maintain a certain level of inventory on hand to help mitigate shortages. This information was communicated to operations. This helped the effort to make improvements in quality as well as emphasized the need for the suppliers to increase the safety of stock on hand.

Business Continuity Planning Case Study 2: Creating a Redundant Set of Systems

Introduction

Executives were asked about strategies in place to determine redundancy, specifically to make sure that the appropriate trade-offs between risk and costs were taken to help identify just where across the supply chain it made sense to put in redundant systems. One executive commented that "it goes beyond just looking at the risk a site may have a compliance issue. Our algorithm also factors in the economic element as well.

Specifically, how much of revenue does a plant contribute to the bottom line? If high, we may consider adding in a second source supplier. If low, our risk threshold may rise somewhat." Other factors highlighted by executive would impact redundancy included:

- Available skill set and capabilities to support a second source.
- Cost of manufacturing – the higher the cost, the less likely that a second source might be used.
- Proprietary versus non-proprietary technologies, products, or products.
- Ability to get a new site approved.
- Ability to ramp up new suppliers.
- Complexity of product.
- Recovery time needed to ramp-up manufacturing if an issue were to be identified.
- Potential risks associated with a supplier based on past quality-related issues.

Business Continuity Planning Case Study 3: Creating Redundant Systems

Situation

A major supplier of pharmaceutical excipients had spent the last few years consolidating its supplier and manufacturing sites in an effort to cut costs. While the company was able to save on costs, in an effort to understand the risks to the business, the Operations function conducted an end-to-end review of the supply chain network, one that had manufacturing facilities spread throughout the globe. The results of the review showed that one facility was responsible for supplying more than 20 percent of the market. The analysis also indicated that any disruptions would take close to one year of recovery time. Realizing the risk that this posed to the company's customers – many of whom had faced shortages in the past – the company took action.

Approach

Building a new facility to help spread the risk was not an option given the costs and regulatory burdens the company would need to overcome. Too, contracting a facility outside of the network would potentially create regulatory challenges for its customers, and also provide an external company access to its proprietary technology. The company initiated efforts to identify which sites could serve as back-up sites to one another. (They found that manufacturing site X could provide the same product to customers as manufacturing site Y).

Solution and Results

In this case, a dual-source system within a company's manufacturing network allowed the company to provide assurances to its customers that their products could be provided by multiple manufacturing sites across the network. In terms of cost, the company was able to identify creative ways that allowed manufacturing sites to share the costs of this dual source system, a move that allowed the company to justify this strategy to management

Business Continuity Planning Case Study 4: Designing a Robust, Redundant and Resilient Supply Chain

Situation

A company was aware of potential weaknesses in its quality systems and governance and that the weaknesses may lead to a negative impact on continuous market supply. The weaknesses took the form of a suboptimal set-up of supply chain design. Examples given varied, but included:

- A lack of overview as to regulatory status and compliance of some products and some sites
- Upcoming importation regulations or probable market entry barriers and enforcement for domestic manufacture in different countries around the world
- Additional QC analysis in receiving countries

Approach

The company approach was to look at three different key areas:

- *Achieving product realization in the early stage of product life cycle* – this was supported by dual sourcing of key starting materials, chemical intermediates, APIs, or key packaging components, bulk manufacturing and packaging activities (end-to-end supply chain set-up) as well as the introduction of a definition of a safety margin to cover a volatile forecast. The concept comprised the definition for which products are designated as "essential medicines."
- *Establishing and maintaining a state of control* – for the active product portfolio management, this included, for example, transfer of a robust production process to a further production site, a flexible QC concept, and the installation of a proactive product risk management approach.
- *Facilitating continual improvement* – involved the use of ICH Q9 [3] and ICH Q10 [4] guidelines to provide tools for continual improvement. This included product design review, FMEA, and a close monitoring of upcoming regulatory requirements, as well evaluation of deviations within own production and ensure the control of product status. Subsequent definition of measures for improvement, as well as the governance for implementation, was necessary.

Solution and Results

- *Robustness* – in the early life cycle, robustness was reached via stocks at different levels in the manufacturing stages. Later, technology and network flexibility played a role. Clearly assigned roles and responsibilities for decisions on product allocation (internal, external) based on capacity, technology evaluation (core, special, niche technology), and target markets were precondition and were introduced. Defining safety stocks was based on an end-to-end knowledge of the supply chain and the lead time for rebuilding or reconstructing. Risk management, according to ICH Q9(3) steps, was put in place. Senior management was involved to ensure that supply network committees were established and were the governing bodies for strategic supply and lifecycle topics:
    - Operations network strategy, including internal and external site missions.

- Product specific supply chain designs, including all product allocation within supply network.
- Supply chain risk management, including supply chain integrity.
- Product transfers within and between internal and external sites.
- Operations launch activities.
- Strict separation between supply strategy, governance, and production execution.

- *Redundancy* – this was assessed per product family in the context of special formulations (raw materials or excipients), technology, and of knowledge of "critical" production steps." The redundancy concept took the infrastructure and key equipment into consideration, such as WFI water loops, steam preparation, power shortages, supply of trays, transportation within a location, QC capacity, capacity, and equipment for visual inspection.

- *Resilience* – to enable the appropriate and early identification of a potential drug shortage event, it was necessary for business units to know the individual, downstream supply chain set up. In supply chain view, this drug shortage meant stock outs occurred at level L-1 (level before patient level), by applying the most critical path, in general hospital. Up-stream supply chain resilience was found to required knowledge of supplier situation regarding finance, quality and compliance, geographical, geopolitical and overall market situation. Any transportation or importation ban had to be reported in a timely manner. Cross-functional, "early warning" demand management, supplier management, and Quality Assurance/ Quality Control (QA/QC), forecasting and purchasing, was set up.

Challenges included:

- Having knowledge and insight of the overall market situation, competitors and generics available.
- Having a regulatory strategy for early and accelerated access.
- Regulatory approval timelines for first submission and approval or variations.
- Robustness of quality systems with regard to increasing regulatory requirements.
- Increased regulatory scrutiny with an increase of different demands from various authorities.

Support required:

- Authorities and industry had a common goal that product is available to the patient.
- Close cooperation with health authorities on drug shortage was maintained.
- Harmonized internal "reporting duties" on potential drug shortages for all products versus reporting essential medication shortages.
- Timelines for reporting in advance and as feasible.

5.4 Conclusion

Avoiding drug shortages requires a multi-dimensional solution. While the solutions explored in the *ISPE Drug Shortages Prevention Plan* center on improving the quality systems and governance structures across an organization, the ISPE team identified another dimension to explore – one that revolved around an organization's supply chain. Through various stakeholder interviews, the supply chain was identified as "a critical component" to avoiding drug shortages, especially as companies have started to rely more on suppliers and manufacturers around the globe to manufacture the drugs needed to meet the demands of its expanding customer base. It is important to note that The *ISPE Drug Shortages Prevention Plan* looks at each of these elements in an integrated fashion. For the supply chain to operate in a most effective manner in terms of preventing shortages, it must be integrated with a company's quality system and governance systems. Doing so would create a "robust" supply chain, one that is not just able to detect shortages that may be brought on as a result of compliance issues, but also one that offers the visibility that executives will gain as a result of the increased transparency. These steps will enable companies either to (a) proactively address the issue or (b) quickly fix the issue so that the amount of manufacturing downtime will be reduced.

In addition, the Plan suggests that to ensure that a supply chain retains its robustness, it must be supported by a redundant set of systems – one where the company understands the risks associated with the supply chain so it can best determine where to put in back-up systems with manufacturers and suppliers to help mitigate against shortages.

Finally, to make sure that the supply chain remains robust and redundant as it grows and evolves over time, the Plan suggests that various scenarios be designed to test the supply chain. Simulations will help further strengthen management's ability to make decisions related to how the supply chain is designed so it will continue to remain robust, when and where needed, as well as redundant.

Recommendations

- *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 where risks may exist* – redundancy can be achieved by either planning for additional capacity, a back-up facility, a second supplier, and additional inventory of raw materials, bulk product, or finished product. Each product should be proactively assessed to understand vulnerabilities and therefore areas where redundancy may be needed.

- *Establish resiliency* – develop prospective crisis management plans to test the Quality System and help identify and remediate weaknesses/gaps before an issue takes place (i.e., natural disaster, fire protection, theft, vandalism, breakdown of equipment, etc.)

- *Develop Facility Response Plans* – develop prospective plans needed to resume operations once an event does take place.

6 Communication with Authorities

6.1 Introduction

Purpose and Scope

This chapter provides guidance for managing a supply interruption from the initial signal of a potential issue through the notification to health authorities, remediation, and close out. The ISPE Drug Shortages Survey [1] found that a success factor for companies that avoided shortages due to manufacturing or quality issues was the quality of their interactions with regulatory authorities. In the event of a drug shortage, it is important to begin rapid and transparent communication with health authorities and to understand their expectations and capability for working with companies to find solutions for mitigating the shortage as quickly as possible. The industry reporting to European authorities on potential supply disruptions arising from quality and manufacturing issues, the so-called "privileged communication," is the subject of a submission to the European Medicines Agency (EMA) by a joint industry association task force of the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Association of the European Self-Medication Industry (AESGP), the European Generic medicines Association (EGA), and the Plasma Protein Therapeutics Association (PPTA); the reader is referred to this submission [24] for more definitive guidance on the actual reporting process. Before a report can be made to a regulator in any region; however, many activities need to be initiated, information assembled, and plans developed. These steps are the focus of this section since, without them, shortages resulting from manufacturing or quality issues will not be prevented.

This chapter builds on the experiences of many companies that have suffered manufacturing supply interruptions and suggests ways to manage the remediation process. It includes recent information about health authority requirements and processes for dealing with supply interruptions, possible solutions to the potential resultant shortage, and recommended follow-up activities as well as lessons-learned for preventive measures. Case studies are provided to both illuminate the complexities and also share best practices for implementing a robust drug shortage mitigation process. The purpose of this chapter is to provide the information needed to proactively prepare for possible supply interruptions and to improve the process for communicating with health authorities and managing remediation and efforts to mitigate the crisis.

6.2 The Role of Regulatory Agencies/Health Authorities

Drug shortages are a global problem. Most abnormal restrictions in supply will require communication with multiple health authorities [21]. Because most countries require notification regarding shortages of medicinal products, manufacturers, Marketing Authorization Holders (MAHs), or other operations within the supply chain, companies should familiarize themselves with all national and international reporting requirements. A consistent message from all health authorities is that rapid and transparent communication is required between companies and the health authorities in order to foster optimal cooperation for mitigating a shortage as well as assessing and addressing its impact on patients.

This section is focused on manufacturing supply interruptions and potential drug shortages from the point of view of regulatory authorities, both within the EU and the US. Other regulators in other areas of the world, such as Pharmaceutical and Medical Devices Association (PMDA), Therapeutics Goods Administration (TGA), Health Canada, and others, are likely to provide similar specific regulations and guidelines for dealing with drug shortages. The reader should ensure their full awareness and remain in compliance with local regulatory agency regulations and guidances on how to handle shortage notification. The remaining parts of this chapter should be taken as a generic approach to dealing with shortages and regulatory interaction.

Communication with different regulators in different parts of the world can be both efficient and effective, and it is logical for regulators in different parts of the world to discuss potential shortages of critical patient medicines with the local national regulatory agency. For this reason, it is particularly important that the regulatory authority that has responsibility for site approval is fully informed of a potential shortage before this is discussed with regulatory authorities in other parts of the world.

Although quality and manufacturing issues are often complex and may require a significant amount of time to address, discontinuing production to determine root cause of an issue, and to then implement corrective measures, may not always be the best decision. When quality and manufacturing issues arise, companies can work with health authorities to decrease the impact of shortages of medically necessary drugs. This is recognized in EMA/314762/2013 [22] which discusses the potential need for temporarily keeping a product on the market even in the case of Good Manufacturing Practice (GMP) issues. Thus, health authorities are available to discuss with industry the contingency plans for use of other manufacturing sites, production lines, or suppliers to help prevent shortages of medically necessary drugs. Some of the actions may include:

- Expediting review of submissions from manufacturers (for example, new applications or modifications to existing applications)
- Expediting inspections of new or existing facilities
- Expediting review of new or additional sources of raw material (for example, approve new Active Pharmaceutical Ingredient (API) suppliers or alternative suppliers of other raw materials)
- Consulting with and advising sponsors on resolution of manufacturing or quality issues
- Exercising regulatory discretion

For more specific information about the requirements in different countries, visit the health authority's website. Some examples are listed below:

- **European Medicines Agency (EMA)** – http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000588.jsp&mid=WC0b01ac05807477a5

Within the European Union, the licensing system is such that product-specific issues are generally dealt with via the MAH; site-specific issues are generally dealt with via the Manufacturing Authorization (MA) holder. The entries in the following sections assume that the MAH and the MA are one in the same. Where this is not the case, companies should ensure that an appropriate level of communication exists with the MA and that the technical agreements in place clearly set out their respective roles and responsibilities.

Companies (both MAs and MAHs) need to work closely with local regulators to help prevent drug shortages. This need has been referred to earlier and is referenced in EU legislation. For further details of these EU regulations, the reader is referred to the Legal Obligation section of the EFPIA/EGA/AESGP/PPTA paper, *Quality and Manufacturing Driven Supply Disruptions: Industry Communication Principles to Authorities* [24]. As referenced earlier, this should take the form of specific points of contact and roundtable professional discussions.

- **US Food and Drug Administration (FDA)** – http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm

In the US, the passage of the *Food and Drug Administration Safety and Innovation Act* (FDASIA) [16] broadened the scope of reporting requirements regarding drug shortages. FDASIA requires all manufacturers of all covered prescription drugs (approved or unapproved) that are "life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition," to notify the FDA of a permanent discontinuance or an interruption of the manufacture of such a drug when that is likely to lead to a meaningful disruption in the supply. The notification must be submitted at least six months prior to the discontinuation or supply interruption, or as soon as possible. FDASIA also allows the FDA to require early notification of discontinuances or interruptions in manufacturing of biologics. In November 2013, the FDA published a new proposed rule to extend the present notification requirements to most manufacturers of biological products and made it available for public comment to help implement FDASIA's expanded notification requirements.

The FDA drug shortages website also provides information from manufacturers about all actual shortages. This posting allows the public and health care communities to stay current on shortage situations. It is important to note that the FDA does not – unless authorized by law – disclose trade secret or confidential commercial information in connection with a drug shortage.

The pharmacists in the FDA's Center for Drug Evaluation and Research (CDER), Office of Communications (OCOMM), and Division of Drug Information (DDI) have prepared an online video that discusses the management of drug shortages and how the FDA's role has changed in recent years. This video is part of FDA Drug Info Rounds, a series of training videos for practicing clinical and community pharmacists. To watch this video, visit: http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm400243.htm

- **Japan** – http://www.pmda.go.jp/english/about/index.html
- **Australia** – http://www.tga.gov.au/hp/msi-general.htm
- **Canada** – http://www.hc-sc.gc.ca/dhp-mps/prodpharma/shortages-penuries/index-eng.php

6.3 Managing a Drug Shortage

ISPE supports the development of a standardized checklist or template containing information that industry can use to assist the health authorities in addressing any drug shortage. Figure 6.1 illustrates activities that may occur when a drug shortage is identified. It shows the actions of the company or MAH and interactions with health authorities and Contract Manufacturing Organizations (CMOs) where applicable. Although the diagram is linear, in most cases, these actions and interactions occur concurrently.

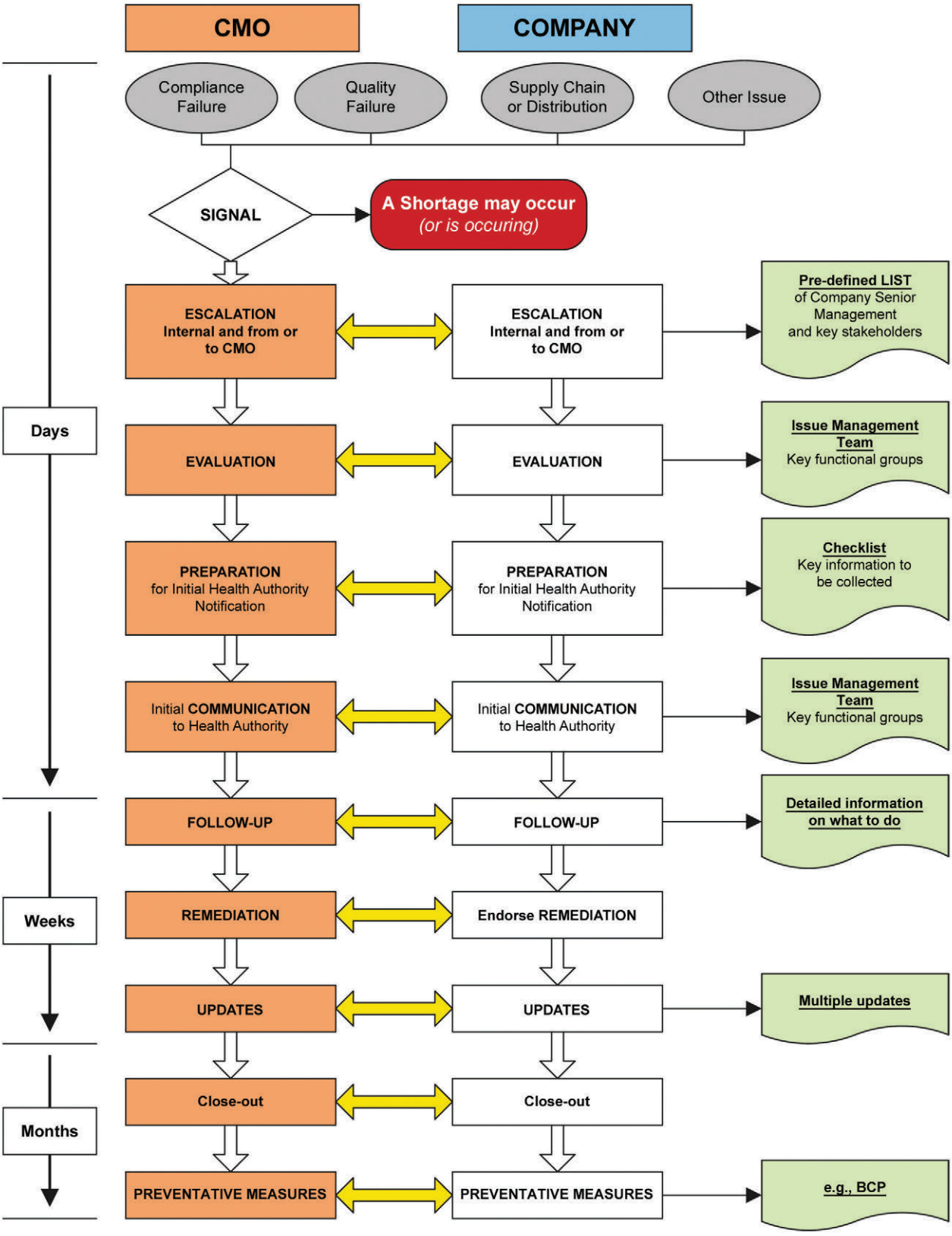


Figure 6.1: Managing a Drug Shortage

6.3.1 Signal that a Shortage May Occur or is Occurring

Drug shortages may develop for many reasons; including manufacturing problems internally or at a CMO, compliance failures, quality failures, supply chain or distribution issues. When a company receives a signal that an abnormal restriction in the supply has occurred or may occur, the company, or their CMOs, should have processes in place to monitor signals and quickly escalate supply restriction or possible drug shortages to senior management. The quality unit/Qualified Person (QP) is responsible for the release of product and should consider the supply implications of any shortage event impacting recently distributed product. If the quality unit/QP determines that an event represents an actual or potential major or critical supply interruption of a medically necessary product, they will escalate accordingly.

- Supply monitoring systems and unforeseen event escalation of events that stop manufacturing, or place inventory in question, are key elements to ensuring continuity of supply.
- When a CMO is involved, it is important to establish an escalation process to facilitate communication and coordinate actions between the company (for example, MAH) and the CMO. Optimally, this is effectively managed through a collaborative and transparent relationship often governed in detail through contractual and quality agreements.

6.3.2 Escalation Internally: Roles and Responsibilities

Companies should have an established escalation process in place to notify senior management of abnormal interruptions in supply. Designated individuals from senior management will provide sponsorship, guidance, and will ultimately be the key decision makers. Their functions will vary, but those key people may include:

- Quality Head or Officer
- Operations Head or Officer
- Supply Chain Lead
- Medical Affairs Head
- Medical Safety Head
- Regulatory Affairs Head
- Medical Officer
- Legal
- Compliance Head
- Communication Head

The internal escalation process will trigger the formation of a team (such as an issues management team) made up of the key functional groups to investigate the issue, gather information to evaluate the interruption, and recommend remediation activities. The functions will vary, but may include the following:

- Communications
- Regulatory Affairs
- Quality Assurance (and QP or equivalent, where applicable)
- Customer Management
- Global Planning
- Medical Affairs
- Operations
- Subject Matter Expert (SME)

The communications unit is responsible for the creation of call center and media message maps for managing all pro-active media communications. The communications lead will prepare the core message map to be used in preparation for external communications, which may include notifications to trade customers, health care providers and users, health authorities, and press with input from the issues management team. Any external communications need to be handled with great care, and may need to be considered as a safety communication. This is outside the scope of this Plan and the reader is referred to the EFPIA/EGA/AESGP/PPTA paper, *Quality and Manufacturing Driven Supply Disruptions: Industry Communication Principles to Authorities* [24].

The regulatory affairs unit is responsible for coordinating all non-routine regulatory activity, such as those activities not in the scope of the field action or advisory notice Standard Operating Procedures (SOPs), and those related to escalated issues. Global regulatory affairs may be responsible for preparing communications to the health authority as required by the regional regulations.

The regional or local Quality Assurance (QA) unit or the Qualified Person (QP) may be required to communicate non-routine regulatory activity to local health agencies. It is still the responsibility of CMC regulatory affairs or equivalent function to coordinate these activities globally.

The customer management unit is responsible for coordinating all communications with internal marketing companies. They also are responsible for ensuring consistent content in the communications and for the management of communications timing. Additionally, the management unit should collaborate with QA if there is a quality issue that needs to be communicated.

The global planning unit is responsible for leading and coordinating all activities associated with the product supply management unit and product allocation plans.

The global medical safety unit is responsible for providing the Medical Impact Assessment in accord with, for example, EMA/314762/2013 [22], and for collaborating on any notification to health care providers (“Dear Healthcare Provider Professional Letters”). See also the Guideline on good pharmacovigilance practices, Annex II [23].

6.3.3 Evaluation

One of the most critical steps in preventing manufacturing or quality disruptions to the supply of medicines is carrying out a comprehensive evaluation which includes a root cause investigation. If the root cause investigation is not thorough or conducted without using an appropriate root cause analysis tool [25], the investigation could conclude prematurely without the true corrective and preventive action being identified so as to avoid reoccurrence of the true root cause.

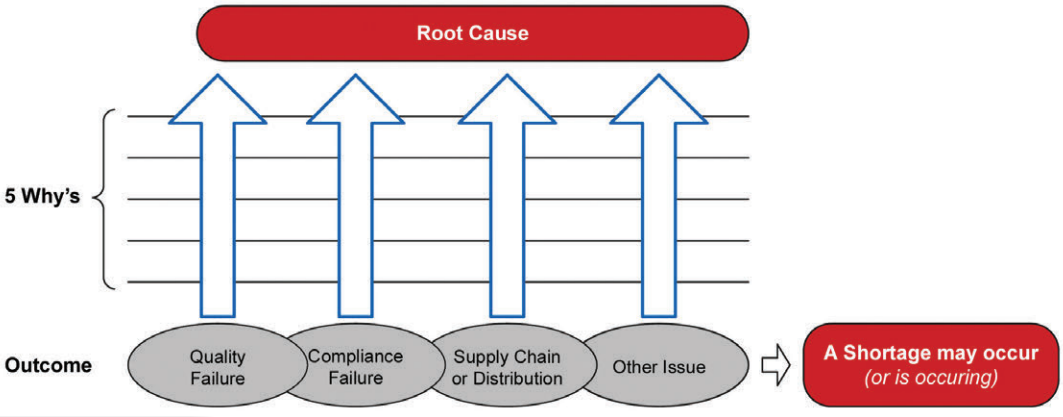


Figure 6.2: Importance of Determining Root Cause when possible

6.3.4 Preparation for Initial Health Authority Notification

Transparent communications with all health authorities is critical and requires both planning and day-to-day management and communication, typically by the issue management team. This is a resource of intensive activity for both the company and the health authority. The benefit for this activity is in creating a combined team with a goal to ensure continued supply of the product to patients. The initial notification should occur within a short timeframe (days) once the abnormal disruption in supply and/or shortage is known by the company even if only limited information may be available at the time.

Industry's recommendations for notifying European authorities of an abnormal interruption in supply are presented in the EFPIA/EGA/AESGP/PPTA paper, *Quality and Manufacturing Driven Supply Disruptions Industry Communication Principles to Authorities* [24] to which the reader is referred. The company should be prepared to answer a variety of questions, such as identification of product, therapeutic indications, countries affected, cause of shortage, current inventory and expected date of depletion, Health Hazard Evaluation (HHE), and potential impact to patients, for example, whether the medicine considered to be critical (EMA/314762/2013) [22]. A standard reporting form is proposed in the EFPIA/EGA/AESGP/PPTA paper which could assist in collecting the appropriate information.

This information may include the following:

- Product information – product description and presentation – name, dosage form and strength.
- Therapeutic categories – patient population and major indications (pharmacological action).
- Benefit/risk analysis – patient impact (to be determined in collaboration with the medical affairs unit). What makes the product critical to patients (include patient population affected, for example, children,

elderly or other high-risk groups; life-supporting, life sustaining, treats debilitating disease or condition)? What is the benefit risk analysis for patients switching to alternatives?

- What are the alternatives?
- How many patients will be impacted?
- Has an HHE been performed?
- Are "similars" or generics available in the market place locally or globally? What is the need for enhanced pharmacovigilance monitoring and reporting if possible defective product remains on the market to minimize the shortage?
- What activities would be carried out by the company to minimize the shortage of the medicinal product (for example, importation of non-registered product)? The company should actively participate in the solutions.

Potential Supply Interruption Scope for Manufacturing or Quality Issues

- Has a root cause been identified? If not, how do you plan to find it, and what are your intentions for updating authorities with your investigations?
- Is the issue related to the product or component?
- Is the issue at your site or another site, such as the supplier's?
- Do you have another site that could make the affected product?
- Could this issue affect other products?
- Which markets and regions will be affected?

Time frames

- When did you know about the interruption?
- Explanation of any (necessary) delay in reporting (for example, investigations)?
- Estimated duration of interruption? When might it start to impact patients?
- Communication strategies planned, including other health authorities and what communication has taken place to date (for example, Dear Healthcare Professional letter)?

Supply Information

- Inventory – How much stock is "in hand"?
- Sales forecast/burn rate
- What has been done to conserve existing stock?

What is being done specifically to correct this situation?

What do you plan to do in terms of short-term and long-term plans?

- What is the rationale for this action and associated risk assessments?
- What corrective actions are planned at your site, at your supplier's site, and at alternative sites, such as distribution hubs?
- What is the quality of the inventory – is it processed or WIP, approved, or on hold?
- Is recall of the product necessary? Describe potential replenishment and recall strategy if not immediate recall possible.
- What is the communication strategy to regulators, patients, distributors?
- Are there future planned preventive action?
- Describe the interim controls.
- What paperwork will you provide the health authority about the supply interruption regarding investigations and communication with suppliers?

Pharmacovigilance considerations

- What is the known safety profile or new safety signals?
- Are there spontaneous reports?
- What is the need for enhanced pharmacovigilance monitoring and reporting if possible defective product remains on the market to minimize a shortage?

What action do you want the regulator to take?

- Agree to the market supply strategy?
- Agree that the product is critical to patient needs?
- Agree with the alternative resource being introduced? Agree with the regulatory strategy for any variations needed.
- Agree with the communication strategy?
- Communicate with other health authorities?

6.3.5 Initial Health Authority Notification

Communication with health authorities regarding a supply interruption should occur as soon as possible as there may be some cases when immediate measures can be taken to help bridge the situation until the

company is able to resupply the markets. A meeting or teleconference with the health authority should occur within days of the signal. The early goal is to establish a close working relationship with the health authority to determine the best solution to remediate the problem and prevent a shortage.

6.3.6 *Follow-Up*

As more detailed information becomes available, follow-up meetings with the health authority or multiple health authorities will be necessary to establish a regular follow-up process with health authority for updates on the remediation plan's progress. Possible actions were discussed previously in this chapter and may include expediting review of submissions or facilities. Although the initial notification will probably be within days, the follow-up meetings and activities will likely continue for weeks and in many cases, several months until the situation is resolved. (See the examples at the end of this chapter to get a better perspective on the various actions, timelines and potential solutions).

6.3.7 *Close-Out*

When the supply interruption or shortage situation is resolved, a final meeting with the health authority is recommended to summarize the corrective actions, actions to prevent future shortages, and findings from enhanced pharmacovigilance monitoring.

6.3.8 *Preventive Measures*

Lessons learned from the event should be used to improve product design, quality systems, and facilities so as to prevent future drug shortages. This information also should be used to improve business continuity plans as well as improvements to employee practices, drug shortage processes and procedures.

6.4 Industry Inputs

Working with Heath Authorities in Drug Shortage Situations: Case Study 1

Product type: *Sterile injectable/small molecule*
Patient impact: *Lifesaving drug – sole source*
Countries impacted: *Global*
Cause for drug shortage: *Facilities and Equipment Systems*

Continued manufacturing problems with a sterile injectable product manufactured at a CMO resulted in supply interruptions. After a significant regulatory inspection, production by the CMO was discontinued. The company's first priority was to communicate with heath authorities and heath care professionals and to manage the remaining inventory in the best interest of the patients. At the same time, alternate manufacturing solutions were evaluated.

Three possible manufacturing solutions – short-term, medium and long-term – were developed, all of which required close coordination with health authorities. Regular communications were held with several health authorities to discuss expedited review of regulatory submissions, inspections, and exercising enforcement discretion. In some cases, input from health authorities on quality investigations was requested to allow for release of product while corrective actions were implemented.

- In the US, the FDA expedited approval of a generic product to provide patients with an alternative product and also exercised enforcement discretion for the New Drug Application (NDA) product by allowing expedited transfer of the aseptic filling process to another site pending approval of an NDA supplement. Following this expedited transfer, batches of the NDA product were released under regulatory discretion.

- In Europe, a bioequivalence waiver was granted allowing for faster supply from a second manufacturing site. Several other health authorities expedited regulatory submissions for approval of two additional manufacturing sites.

Today, the product is available worldwide from two manufacturing facilities with a third facility currently manufacturing validation batches and awaiting approval of the site.

Recommendations for having good communications with health authorities include:

- Initial notification
    - Rapid communication – notify health authorities as soon as possible of a drug shortage or potential drug shortage. This is an expectation by most health authorities and in some cases a legal requirement.
    - Required information – cause of the shortage, current inventory, days of supply, patient impact, alternative products, affected markets, and when supply may be restored.
    - Corrective actions – be prepared to discuss probable actions to mitigate the shortage.
    - Transparency – when supplying product to multiple regions it is important to share information with all health authorities involved assuring alignment.
- Mitigation activities
    - GMP compliance – establish detailed remediation plans that address primarily the quality gaps and demonstrate product quality will be delivered. In addition, companies need to develop appropriate interim controls to address these compliance gaps. The FDA and major health authorities can apply discretion for compliance related gaps if the company can demonstrate: 1) benefits of using the product outweigh the risks of the quality defect; 2) interim controls are in place; and 3) appropriate oversight and monitoring is in place to ensure sustainability.
    - Regulatory submissions – discuss filing requirements and timing of submissions.

Working with Heath Authorities in Drug Shortage Situations: Case Study 2

Product type: *Sterile injectable/small molecule*
Patient impact: *Lifesaving drug*
Countries impacted: *US*
Cause for drug shortage: *Competitors in marketplace unable to supply*

Following a product and process assessment, a company made the decision to discontinue a product because other manufacturers were able to supply product to the marketplace. More than a year later, the company was contacted by the FDA drug shortages staff who indicated that there were issues with supply in

the marketplace and inquired as to the ability of the company to reintroduce the product in an effort to help avoid a drug shortage.

The company immediately began to determine what efforts were needed for reintroducing the product. It was determined that efforts would require significant changes to the process and a Prior Approval Supplement (PAS) to be filed. The FDA drug shortages staff indicated they would recommend expedited review and approval of the product due to the nature of the market shortage. The company created a timeline that indicated they would need six months to complete the required product and process work to submit the filing.

The product was remediated and stability data submitted as PAS (with request for expedited review) in six months. The PAS was approved in seven months. During the time from the submission of the PAS to approval, the company began building inventory of this product and prepared to "re-launch" it immediately upon receipt of the approval letter. As a result of this planning, the product was available to ship to customers the day of approval, allowing patients access to this medication.

Today, the product is available from multiple manufacturers. In this example, while a drug shortage was unable to be completely avoided, open and rapid communication with the FDA drug shortages staff allowed the shortage to be minimized.

Working with Heath Authorities in Drug Shortage Situations: Case Study 3

Product type: *Sterile injectable/small molecule*
Patient impact: *Lifesaving – sole source*
Countries impacted: *US*
Cause for drug shortage: *Complex Investigation for Particulate Matter*

During a routine 12 month commercial stability testing time point, an Out-of-Specification (OOS) was generated when it was found that product had begun to exhibit visible particulate matter. As a result, an investigation was initiated and a field alert was filed. Upon confirmation of the OOS, the FDA drug shortages staff was contacted to advise them of a potential market action (recall) that the company – the sole-supplier of the product – was considering.

The company held several conference calls with the FDA drug shortages staff and the FDA Office of Generic Drugs (OGD) during this time to provide them with the updated findings from the investigation. As part of the investigation, it was determined that the particulate matter was only forming in the final drug product 12 months after the manufacture date. The shelf expiration dating was approved for 24 months. Additionally, it was confirmed that the particulate matter was forming in only one of the two kinds of approved primary containers. Based upon the investigation, and in collaboration with the FDA, it was determined that the company would need to immediately submit a Change Being Effected (CBE), which changed the shelf life of the product to 12 months and, concurrently, to recall all product on the market that was older than 12 months and manufactured in the problematic primary container. Additionally, a hold was placed on any previously un-released inventory of this product, as it was labelled with a 24 month expiration date and would no longer be in compliance with the newly submitted CBE that changed the shelf life from 24 to 12 months.

As a result of the recall, the product quickly went into a drug shortage situation. Re-supply to the market would not occur until a new product was manufactured and labelled with the 12 month expiration date, a process that would take several months. The situation prompted additional discussions with the FDA drug shortages staff and OGD regarding one lot on hold in the firm's inventory that had been manufactured approximately one year earlier and labelled with 24 month expiration date. It had never been released to the

market. This lot also had been manufactured in the primary container that had not shown particulate matter. It was confirmed by the company that the quality of the lot was acceptable, that the lot had not exhibited any Out-of-Trend (OOT) or OOS with respect to particulate matter, and suggested that, with regulatory discretion, it could be released to the market with the current 24 month expiration date to avoid a complete market depletion until such time that the newly manufactured product became available. As part of the discussions, OGD requested the company to provide visible and sub-visible test results (real-time) for the lot in inventory, as well as any other lots of this product on commercial stability. This and other relevant retention sample information was provided to OGD for their review and consideration.

Within several days of submitting the requested information, the FDA drug shortages staff and OGD confirmed with the company that there were no quality concerns with this product and that they would allow this lot to be commercially distributed with a commitment to perform additional ongoing particulate matter testing at specified time points and notification to the Agency should any OOT or OOS be observed.

While a drug shortage was unable to be completely avoided, open communication with the FDA allowed the shortage in the marketplace to be minimized. It also required planning as well as regular interaction and collaboration with the Agency. While it was labor-intensive for both the company and the FDA, the effort was well worth it to ensure patient supply.

6.5 Conclusion

Rapid, open and clear communication with regulators is extremely important when dealing with a drug shortage situation, and in this case, the process was facilitated by establishing a dedicated shortage team. The team dealt with the quality issues and kept the regulator informed with the progress of their root cause analysis. Steps to monitor appropriate stock metrics and ensure corrective and preventive actions were carried out to prevent future events for all products.

Recommendations

Companies should be prepared by developing processes to manage the various activities that are likely to occur during a shortage.

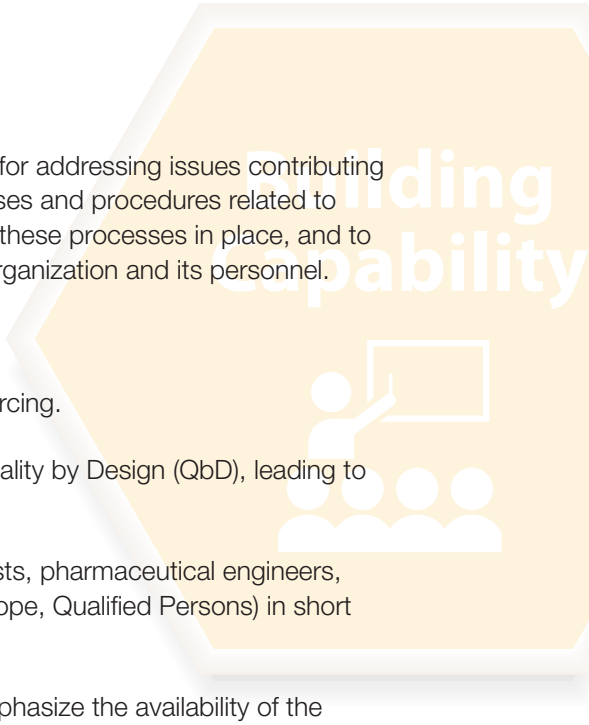
- Establish processes to manage a shortage such as:
    - What are the signals?
    - Escalation to management
    - Evaluation (for example, identify root cause)
    - Working with the CMO when applicable
    - When and how to communicate to health authorities
    - Remediation
    - Close out with the health authorities

To prevent future supply interruptions, use these recommendations and lessons learned to proactively prepare for supply interruptions, which may include developing prevention plans.

7 Building Capability

7.1 Introduction

The *ISPE Drug Shortages Prevention Plan* identifies a number of solutions for addressing issues contributing to drug shortages. While many of these solutions involve improved processes and procedures related to improving a company's quality system, much of a company's ability to put these processes in place, and to execute them in a consistent manner, depends on the capabilities of the organization and its personnel.



The catalysts of the changes are:

- Change business models from vertical integration to diversified outsourcing.
- Focus on operational excellence, including lean manufacturing and Quality by Design (QbD), leading to higher complexity but fewer people.
- Develop and retain key talent, such microbiologists, validation specialists, pharmaceutical engineers, quality engineers, data analytics specialist and statisticians (and in Europe, Qualified Persons) in short supply.
- In Europe, the new Good Distribution Practice (GDP) requirements emphasize the availability of the "responsible person" at each stakeholder of the supply chain to ensure supply chain integrity and transparency.
- Create the capability to analyze and trend data which is lagging or is insufficient. This is a critical capability to prevent and predict potential shortages.
- Develop publically accessible Information Technology (IT) based tools to give overview to products in the market place, not only in the supply chain.

While many of the improvement areas are related to traditional quality systems, ISPE's model has identified a new skill set focused on areas such as IT and Supply Chain operations that need to be enhanced in order to help reduce or avoid shortages.

Purpose and Objectives

This section describes the capabilities and skills across an organization that are needed to address issues presented in the previous chapter and highlights ISPE products that can help companies to develop a robust, capability building program.

Scope

This section summarizes the improvement opportunities identified throughout the *ISPE Drug Shortages Prevention Plan*. Based on the improvements identified, the section will highlight potential vehicles that can be developed and used to help address any capability or skill gaps that may be preventing necessary solutions from being implemented. Where relevant, ISPE has identified the various tools developed by its Members that can be used to help address capability gaps. Where tools are not available, the section will highlight potential courses and conferences that could be developed over the course of the next few years to help personnel build the skills needed to address drug shortages.

Finally, this section will cover solutions across the following categories, each of which can be applied across the elements of the plan to help make improvements:

- Training
- Learning
- Knowledge Management
- Mentorship

Key Inputs

- ISPE Drug Shortages Survey [1]
- Industry feedback at ISPE conferences in 2013 and 2014
- Regulatory feedback

Discussion

In the US, some 60 percent of recent warning letters cite weak "organizational effectiveness" elements, such as governance, organization design, and talent management, as the cause behind the citation. In 2011, PIC/S organized a workshop to discuss the top 10 deficiencies cited by its members. The fourth consideration was "personnel issues – training." Consequently, a key challenge and purpose of senior management should be managing capability, which covers the organization, its people, and processes.

Workforce capability means more than just training. Optimal organizational structures, the harnessing of cross-functional linkages, clear and dedicated resources in key areas, and relevant metrics are all needed. In addition, identifying an organization's talent needs, technical skills, learning and development, retaining and development of staff at all levels are fundamental to success.

While it is the responsibility of each organization to define and establish its own staff management and development strategy, effective capability building can be enhanced by a "mixed learning" model. Staff should not only understand the what of their role, but also the why of their role. While it is not the purpose of this document to recommend one approach over another, the development of employees can be enhanced through the use of competencies by which employees and their managers can more easily define an individual's strengths and development opportunities.

A robust capability building program is a key enabler of a strong and sustainable quality system, and represents a fundamental pillar of the ISPE Drug Shortages Prevention Plan. It should include the activities listed in Figure 7.1.

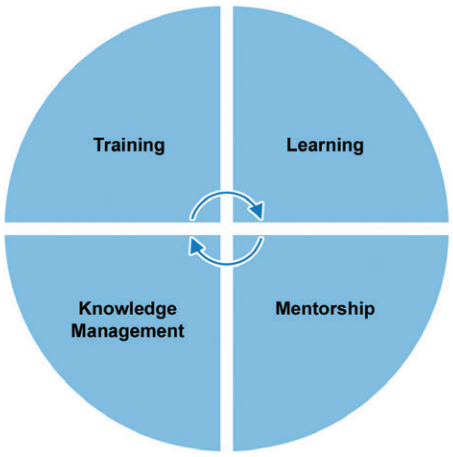


Figure 7.1: Elements of a Capability Building Program

7.2 Training

Training and measuring the effectiveness of training is fundamental to both successful business performance and regulatory compliance. Training focuses on the acquisition of new skills and knowledge as well as the foundational knowledge necessary to bring learners up to a basic performance competency level. Training usually involves a formalized curriculum and a structured learning environment, often accompanied by an exam or an assessment tool to gauge the knowledge of the participant. To be effective, training initiatives should be straightforward, well-organized and have planned curriculums with clear expectations. Such programs can be systematically implemented throughout an organization.

Key Training Resources offered by ISPE include:

- ISPE Training Courses
- ISPE eLearning
- ISPE Onsite Training

7.3 Training vs. Learning

Once basic training needs have been satisfied, learning and understanding how that training is put into action and why it is important is critical for achieving permanent changes in behavior. Learning enhancing capabilities are associated with current roles as well as preparing people for future roles and responsibilities. As with training, with learning there is a focus on a positive change in knowledge and skills. Unlike training, learning involves a more gradual and less-structured opportunity to achieve the changes through both personal experience and practice. Effective development methods include coaching, internships, and team participation. Learning extends the idea of personal development to beliefs, values, wisdom, compassion, emotional maturity, ethics, and integrity, all of which are essential building blocks for companies that want to achieve a *Corporate Quality Culture*.

Key Learning Resources offered by ISPE:

- ISPE Continuing Education Conferences
- ISPE Publications
- ISPE Guidance Documents
- ISPE *Pharmaceutical Engineering* magazine
- ISPE Glossary of Pharmaceutical Terminology
- ISPE's Communities of Practice (COPs) Online Discussion Forums
- ISPE Affiliate and Chapter events and publications

7.4 Mentorship

Good, guided development and the maximization of learning and knowledge management can move simple compliance with an organization's rules and regulations toward a competitive advantage of engagement, innovation and creativity.

Key Mentorship Resources offered by ISPE:

- Participation in ISPE Committee, Councils, and Task Teams
- Participation in ISPE's Communities of Practice (COPs)
- ISPE's Young Professional Program and those offered by local ISPE Affiliates

7.5 Knowledge Management

Since 2008 and the publication of ICH Q10 [4], the importance of the role of *knowledge management* has been clearly positioned as one of two key enablers necessary for the successful implementation of an effective pharmaceutical quality system. With high-level expectations set by regulators, industry is still struggling with how to "manage knowledge." All too often, an organization focuses on institutional knowledge management, perhaps by establishing an IT system to manage the learning within the organization. However capable such a system might be, the knowledge and know-how of individuals is all important.

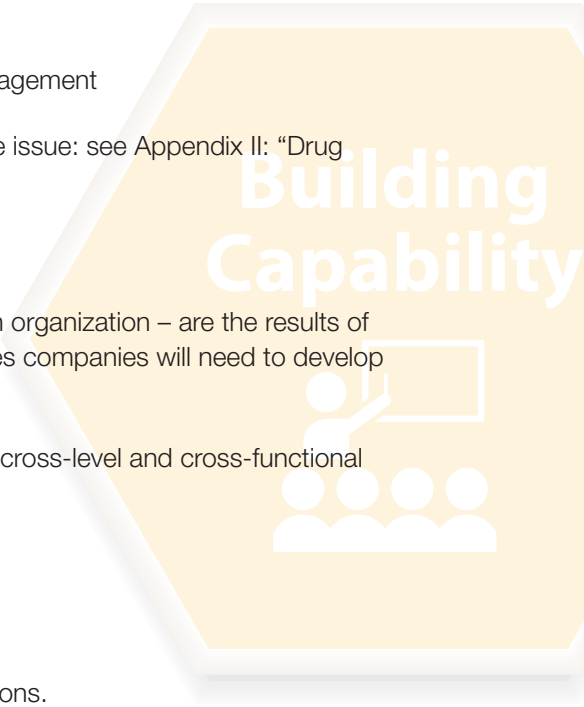
Knowledge management should not be limited to technical content. It also should include developing decision-making capabilities in complex situations. The impact of legal and regulatory requirements, the impact of decisions on patients' health and safety and on compliance, and the supply situation should be considered in a holistic way. Team exercises and mentoring of young professionals can be supportive elements of knowledge management.

Know-how transfer of product and process, specific know-how between know-how owners and their delegates or successors, should be carried out in a transparent and documented way. Knowledge management should be driven like a quality system, from planning for execution, to reporting, and documentation.

Key Knowledge Management Resources offered by ISPE:

- *Pharmaceutical Engineering* electronic supplement on knowledge management

Effective knowledge management requires a thorough understanding of the issue: see Appendix II: "Drug Shortages Industry Awareness" educational offering from ISPE.



7.6 Conclusion

Capabilities – comprised of the collective skills, abilities, and expertise of an organization – are the results of investments made in staff development. Below is a list of the key capabilities companies will need to develop to achieve organizational effectiveness.

- Awareness building at all management levels and internal and external cross-level and cross-functional communication for quality problems.
- Knowing how to measure progress of a successful improvement.
- Knowing how to learn good decision making processes.
- Using case-based learning to find the right decisions in complex situations.
- Using knowledge management as a quality system.
- Developing supply chain professionals such as "responsible persons."
- Using data analytics and early detection of potential drug shortages signals (from operations, planning, logistics, quality).

In Europe, there also may be a need to upgrade the Quality Person (QP) training certification program and enhance the education of QPs. This can potentially make use of newsletters and other means to ensure that QPs are kept up-to-date in the area of drug shortages, especially when it comes to key risk management decisions to be taken with the endorsement of European Medicines Agency (EMA) or the member-state health authorities.

Recommendations

- *Cross-functional training* – define and implement training programs for needed capabilities, recognizing that training is a combination of education, personal experience, and class room learning. For example, ensure the supply chain team and the quality team both understand the relevance of each other's roles, the dynamic tensions between the two organizations, and have joint objectives to ensure quality supply.
- *Ongoing learning and knowledge management* – being committed to continuously learning is ever important as requirements and expectations evolve across the industry. Sharing case studies with open discussion is an excellent tool to effectively learn from prior challenges. Companies should have a clear system for knowledge management.

- *Mentorship* – good, guided development and the maximization of learning and knowledge management can move simple compliance with an organization's rules and regulations toward a competitive advantage of engagement, innovation and creativity. Employing principles of mentorship within a company can be enhance by leveraging ISPE and their resources with participation in industry meetings and groups to further build capability.
- *Utilize resources available via ISPE and other industry forums.* See Appendix II for a listing of ISPE programs and resources.

Building Capability

8 Recommendations and Next Steps

ISPE believes its *Drug Shortages Prevention Plan* provides a structure for how companies may consider their plans for ensuring supply and preventing drug shortages.

Ensuring supply and preventing drug shortages are the foundation of the supply chain sector of the pharmaceutical industry. As mentioned earlier, there is no "one size fits all" solution to the prevention of events leading to drug shortage, and the approach to preventing shortages may vary from company to company, or among sites within the same company.

A summary of recommendations and points to consider from each element constituting the ISPE Drug Shortages Prevention Plan is provided below.

Corporate Quality Culture and a Robust Quality System

The Plan provides key elements in the prevention of drug shortages. A corporate quality culture and a robust quality system are foundational to each other. Ensuring a robust quality system requires a holistic lifecycle approach to product quality and is gained by focusing on a number of key processes.

Recommendations for Corporate Quality Culture

- *For quality culture,* companies should demonstrate "walk the talk" by doing a thorough assessment of their quality culture.
- *For management style and behavior,* there should be good practices defined with the goal to have defined formalized and transparent decision making processes available.
- *For proactive management,* there should be principles applied, for example, identifying near misses, weak signals and trends.
- *For problem escalation,* there should be formal processes of high risk and review of remediation with senior leadership.
- *For crisis management,* there should be a focus on management capabilities to manage challenging issues; for example, significant deviations, recalls used already in the recruitment process for key people.
- *For issue management,* there should be cross functional task forces or rapid response teams defined for rapid consultation as soon as a production problem has occurred.
- *For senior management awareness,* there should be a regular quality review meeting with representatives from all management levels as well as Subject Matter Experts (SMEs)
- *For the supply chain,* there should be a holistic view applied to the end-to-end robustness and resilience.

- *For metrics,* there should be leading metrics demonstrating over time the effectiveness and sustainability of actions taken.
- *For systems and processes ability,* there should be a regular management check in place.
- *For professional communication,* there should be a formal process established for escalation and decision making based on standard agendas.
- *For outsourced activities,* there should be ownership of all outsourced activities demonstrated, for example, using a contractor risk dashboard.
- *For risk management,* there should be real time assessments of quality and compliance risks undiluted by business risks.

Recommendations for Robust Quality System

- *For product and process development,* there should be defined business processes organizing the product life cycle management of transfer, phase-in, marketing period, and phase-out of pharmaceutical products.
- *For validation,* a process should be established that enables product and process data to be collected continuously to evaluate that state of control and assess the need for further lifecycle validation interventions (“continued process verification” in the US and “ongoing process verification” in the EU).
- *For deviations and investigations,* there should be an appropriate management review process to monitor the deviations being raised to help identify any trends and potential issues.
- *For root cause-and-effect chains,* there should be transparent root cause- and-effect chains established as a result of investigations and as a starting point for remediation.
- *For Corrective and Preventive Actions (CAPAs),* there should be business processes in place ensuring that no accumulation of “overdue CAPAs” occurs and that CAPA measures are effective and sustainable.
- *For knowledge management,* this should be set up like a quality system with the main elements of regular training, know-how transfer, collecting experience and defined skill set to improve the capabilities to use a quality system adequately.
- *For good engineering practice,* there should be evidence of the usage of science and risk based approaches.
- *For factories, buildings, machines and equipment,* there should be business processes available creating evidence of inherent potential to be a trigger for a cause-and- effect chain leading to major risks of unavailability to manufacture products. There should be metrics available indicating whether preventive maintenance is performed in time and where there are overdue actions. Maximum (lead) times for spare parts should be available as internal standards. If such standards are extended, this should be based on a formal risk analysis and release process in a controlled document. Strategic plans need to be in place for a company to plan for and budget for equipment replacements when the machine or equipment is at the end of its life.

- *For starting materials and packaging materials,* there should be regularly updated systematic lists in place that indicate the criticality of a starting material or component and the related contingency measure. There should be routinely monitored actions for remediation of critical materials. The results should be assessed as part of on-going quality risk management and crisis plans. For unavoidably critical, sole-sourced materials, there should be suitable contingency plans in place to avoid drug shortages.

- *For SMEs,* there should be a mapping of the knowledge landscape available and a list of SMEs and their available delegates or substitutes. Another important factor is the number of part timer staff allowed in production areas. The maximum number should be limited according to the criticality and complexity of processes and equipment to control.

Metrics

It has long been established that successful companies utilize "dash boards" and metrics to monitor performance and drive improvement. Regulators also have expressed interest in leveraging metrics to establish compliance risk and risk of drug shortage. The marriage between quality performance metrics, quality culture metrics, and supply chain metrics is introduced within the drug shortage prevention plan element to be predictive of the overall ability to meet quality standards for reliably supplying quality products.

Recommendations

- *Metrics selection* – companies should select their own metrics as indicators of an effective quality system and potential shortage vulnerability.

- *Metrics range* – shortage metrics can arise from quality metrics, product performance reliability, and be statistical in nature (process variability) however a range of quality culture indicators are probably also required.

- *Supply Chain metrics (cycle time, customer service, etc.)* – need to be considered when monitoring shortage vulnerability.

- *The application of metrics* – should follow principles of continual improvement to assess and demonstrate the effectiveness of the metrics they adopt to monitor shortage vulnerability.

Business Continuity Planning

Ensuring supply is important to our patients and customers. Business Continuity Planning is a prospective risk management process to ensure a robust supply chain. Business continuity planning has many levers to ensure supply.

Recommendations

- *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 where risks may exist* – redundancy can be achieved by either planning for additional capacity, a back-up facility, a second supplier, and additional inventory of either raw materials, bulk product, or finished product. Each product should be proactively assessed to understand vulnerabilities and therefore areas where redundancy may be needed.

- *Establish resiliency* – develop prospective Crisis Management plans to test the Quality System and help identify and remediate weaknesses/gaps before an issue takes place (i.e., natural disaster, fire protection, theft, vandalism, breakdown of equipment, etc.)

- *Develop Facility Response Plans* – develop prospective plans needed resume operations once an event does take place.

Communication with Authorities

Having clear processes for conducting rapid and clear communications with the various regulatory agencies around the globe is an important element in ensuring robust supply and avoiding or mitigating drug shortages. 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 shortage, reduce the amount of manufacturing downtime needed to get the site compliant and back up and running.

Recommendations

- *Develop Escalation and company internal systems* – for identification and escalation of product supply risk is essential in preventing drug shortage. You cannot fix what you do not know.

- *Initial notification*

    - Rapid communication – notify health authorities as soon as possible of a drug shortage or potential drug shortage. This is an expectation by most health authorities and in some cases a legal requirement.

    - Understand information likely to be requested by health authority – cause of the shortage, current inventory, days of supply, patient impact, alternative products, affected markets, and when supply may be restored.

    - Corrective actions – be prepared to discuss probable actions (both short term and long term actions) to mitigate the shortage.

    - Transparency – when supplying product to multiple regions it is important to share information with all health authorities involved assuring alignment.

- *Mitigation activities*

    - Good Manufacturing Practice (GMP) compliance – establish detailed remediation plans and interim controls that address primarily the quality gaps and demonstrate product quality will be delivered.

    - Regulatory submissions – discuss filing requirements and timing of submissions.

Building Capability

Building capability is an important element both within the Pharmaceutical Manufacturing system and for any drug shortage prevention plan. Capabilities are comprised of the collective skills, abilities, and expertise of an organization—they are the results of investments made in staff development needs that are required for each of the elements described in the ISPE Drug Shortages Prevention Plan to be realized and sustained. Companies should ensure capability across all elements of the drug shortage prevention plan – again, there is not a "one size fits all" approach – but ensuring capability in key elements for a company specific or site specific plan is critical to success.

Recommendations

- *Cross-functional training* – define and implement training programs for needed capabilities, recognizing that training is a combination of education, personal experience, and class room learning. For example, ensure the supply chain team and the quality team both understand the relevance of each other's roles, the dynamic tensions between the two organizations, and have joint objectives to ensure quality supply.

- *Ongoing learning and knowledge management* – being committed to continuous learning is ever-important as requirements and expectations evolve across the industry. Sharing case studies with open discussion is an excellent tool to effectively learn from prior challenges. Companies should have a clear system for knowledge management.

- *Mentorship* – good, guided development and the maximization of learning and knowledge management can move simple compliance with an organization's rules and regulations toward a competitive advantage of engagement, innovation and creativity. Employing principles of mentorship within a company can be enhance by leveraging ISPE and their resources with participation in industry meetings and groups to further build capability.

- *Utilize resources available via ISPE and other industry forums.* See Appendix II for a listing of ISPE programs and resources.

Conclusion

The *ISPE Drug Shortages Prevention Plan* has identified the need for companies to increase capability in several key technical areas. ISPE's body of knowledge contains resources in these areas for both industry and regulators that can help individuals and organizations reach their full potential. Appendix II lists those resources. We encourage companies to utilize the DSPP Plan and the associated ISPE resources as a selection of tools available to the extent that they meet individual company or site needs.

Next Steps from ISPE

ISPE will continue to act as global facilitators and integrators in the effort to prevent shortages through ongoing projects with other associations; holding forums with industry leaders and regulators; and helping companies build capability through the development of guidance documents, training and education programs.

- In November 2014, *ISPE's Drug Shortages Prevention Plan* will form part of an inter-association action plan to be submitted at the request of the European Medicines Agency (EMA).

- In 2015, the inter-association task force will assess the impact of what was achieved in 2014 and complement it with further deliverables as indicated.
- In 2015, ISPE's Drug Shortages Initiative will enter its third phase, which will consist of delivering solutions based on the Plan's recommendations in ISPE conferences, including:
    - ISPE European Annual Conference: May, Frankfurt, Germany
    - Pharmaceutical Quality Week: June, Washington D.C., US
    - ISPE Annual Meeting: November, Philadelphia, Pennsylvania, US
- ISPE will develop educational offerings on Drug Shortages Industry Awareness based on the Plan, designed to increase companies' staff awareness of shortage prevention.
- Key elements from the Plan will be considered for development into ISPE Training Courses, Guidance Documents, and other publications.
- ISPE's Quality Metrics initiative will continue with the publication of initial results from the Quality Metrics Pilot Wave 1, and the launch of the pilot's Wave 2 which will expand number of companies participating as well as expanding on the use of metrics.

Appendix I – Regulatory Perspectives

I.1 Introduction

Global efforts to address the causes of drug shortages have escalated in response to a US Food and Drug Association (FDA) workshop in 2011 [26], the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012 [16], and a European Medicines Agency (EMA) Reflection Paper in 2012 [27] These events provided the impetus for conferences and workshops and, ultimately, for the ISPE Drug Shortages Survey [1]. As industry associations around the world raised awareness of drug shortages and began collaborating to prevent and mitigate them, an industry association task force was asked by EMA to develop initial proposals for preventing drug shortages and improving communication. The end "product" and strategic objective for these efforts is a "resilient end-to-end supply chain."

In November, 2013 ISPE and the Parenteral Drug Association (PDA) agreed to deliver to the EMA a proposal plan that addressed the prevention of drug shortages due to manufacturing issues. The European Federation of Pharmaceutical Industries and Associations (EFPIA), the Association of the European Self-Medication Industry (AESGP), the European Generic medicines Association (EGA), and the Plasma Protein Therapeutics Association (PPTA). EFPIA, AESGP, EGA, and PPTA are developing a complementary project on communication.

The industry association project was initiated in January, 2014 and will run through November, 2015. Phase I, delivered in January, 2014, created an inventory of existing activities. Phase II ended in January, 2014 with the delivery of a proposal to EMA with key findings and recommendations. Phase III, completed by November, 2014, include an executable plan. Phase IV, to be carried out through 2014-2015, includes training activities (as informed by Phase III plan) and is intended to be executed jointly with regulators. Phase V, ending in November, 2015, will be an evaluation of effectiveness.

Given the common goal of industry and regulating agencies to prevent drug shortages, consensus has been reached not only regarding better communication with authorities, but also regarding the need for capacity building by improving the scientific and technical knowledge of individuals and organizations. Input from Regulators, as already seen, has reinforced/reinforces the need for communication and collaboration with health authorities in the event of potential drug shortage situations.

In this Appendix, selected presentations made by regulators concerned about the drug shortage problem are summarized. The presentations were selected from those made at recent ISPE conferences in two different international settings – Frankfurt, Germany and Baltimore, Maryland, US. Drug shortages also have been a topic at many other ISPE and industry events.

I.2 European Medicines Agency (EMA)

Initiatives on Product Shortages Due to Manufacturing/Good Manufacturing Practice (GMP) and Quality Issues

(Summary of a presentation delivered by Brendan Cuddy, Scientific Administrator, EMA, at the ISPE Europe Annual Conference held April 28-30, 2014 in Frankfurt, Germany)

The European Union has a legal framework relating to drug shortages and their manufacturing-based causes. The framework includes "obligations" for Marketing Authorization Holders (MAH), manufacturers, and distributors to ensure continued supplies of medicinal products so that the needs of patients in Member States are covered. Obligations specific to manufacturers are the requirement that the national competent authority be informed of any defects that could lead to a recall or supply restrictions.

"If the product ceases to be placed on the market of a Member State – temporarily or permanently – the MAH has to notify the Member State's competent authority no less than two months before the interruption on the market," explained Cuddy. "The MAH also has to notify the competent authority of the reasons for the action and notify the Member State concerned of any action to withdraw a medicinal product from the market."

Cuddy noted the increase in supply chain complexity and subsequent perceptions of an increase in the number of shortages due to manufacturing quality and compliance problems in the supply chain. "It is a complex path," he said, "and at every stage a problem can arise."

The results of a supply chain disruption could have an economic impact (increased costs) and a concomitant decrease in public confidence in the organization.

"The ISPE Report on Drug Shortages [1] made it clear that companies that have successfully avoided drug shortages focus on strong quality systems and involve senior company leadership," he noted, adding that improved relationships and interactions with regulatory authorities can mitigate the likelihood of a shortage.

EMA actions on the drug shortage issue have included the publication of the EMA's seminal reflection paper in November, 2012, discussions at major conferences and workshops and have served to provide a framework for assessing the problem, raising awareness and seeking solutions.

EMA's Implementation Plan has helped develop both a common understanding of "essential" medicines and a decision tree for use by national competent authorities. Criteria for defining a "critical" medicinal product have been developed and rules for escalating action from the national to EU level have been developed. A communication plan has been agreed upon and an assessment template and assessment resources have been developed.

Progress on the Implementation Plan has included a revision of Chapter 5 of the EU GMP Guide to address "appropriate and continued supplies" (5.68) and Chapter 8, regarding "abnormal restrictions in the supply" (8.14). The Community Procedure for handling reports of serious non-compliance with EU GMP has also been updated.

Industry can do more. We expect:

- Shift focus from reactive to proactive risk management.
- More explicitly assess supply chain and transport risks, such as a lack of temperature control, diversion and counterfeiting.
- Improve pre- and post-incident communication on disruptions between the operators of the supply chain and to regulatory authorities.
- Industry associations can develop and share methodologies for assessment and information sharing.

- MAHs should focus on developing supply chain resilience.

"Public health and patient safety are our main concerns," advised Cuddy. "Both are linked to supply chain security. Initiatives have been taken and are being taken by regulators. Now it is up to the pharmaceutical industry to engage with the goal of building more resilient supply chains and establish more effective communication processes."

Summary

Public health and patient safety are linked to supply chain security. Industry needs to shift its focus from reactive to proactive risk management to better assess supply chain and transport risks and generally engage with the goal of building a more resilient supply chain.

I.3 Medicines and Healthcare Products Regulatory Agency (MHRA)

Drug Shortages – the UK Response

(Summary of a presentation delivered by Gerald Heddell, Director, Inspection, Enforcement and Standards, MHRA at the 3rd Annual ISPE-FDA CGMP Conference held 2-4 June 2014 in Baltimore, Maryland, USA)

Drug shortages are a global problem. Challenges to global drug supply chain integrity include: the complexity of the supply chain, distances, supervision, shipping issues, and contractors with multiple clients, according to Heddell. The UK has responded by providing key points of guidance. They include:

- Pharmacies should receive medicines within 24 hours.
- There should be regular communication between manufacturers and wholesalers so that all parties have a good understanding of the supply and demand for particular products.
- Arrangements should be in place to verify that if a medicine is required for a genuine UK patient, they should be sensitive to the workload implications for dispensers and, as part of these arrangements, dispensers should not disclose patient or prescriber identifiable details.
- There is a need for the supply chain to have contingency arrangements in place to source supply when there are supply difficulties.

Illustrating through a case study, Heddell discussed a regulatory dilemma related to drug quality and shortages requiring regulators to balance public safety with the patient's need for medicines. Is a potentially defective product better than no product? Should the potentially defective supply be recalled? Or allowed to continue on the market? The EU solution has been to allow release of quarantined batches subject to a positive risk assessment in EU countries with no alternative product, but to recall and restrict supplies in EU countries where alternatives are available.

Heddell cited regulatory changes in the MHRA approach to the drug shortage problem that would increase awareness of potential shortages throughout the EU regulatory network through a Compliance Management Team charged with anticipating supply chain/compliance risk; early compliance intervention/escalation; and improving compliance-related communications.

Other changes included: coordination of action; sharing information; revisions to EU GMP Guide Chapters 5 and 8; and revisions to procedures for managing non-compliance.

Summary

Recognizing that drug shortages may put patients at-risk, the MHRA has responded with the UK Department of Health and key industry and pharmacy stakeholders to the drug shortage problem by providing key points of guidance for managing supply and aimed at protecting the integrity of the supply chain. Anticipation of supply chain compliance risk, early compliance intervention and improving compliance communication, are essential.

Quality Risk Management and Shortages

(Summary of a presentation delivered by David Churchward, Expert GMDP, Inspector, MHRA at the ISPE Europe Annual Conference held 28-30 April 2014 in Frankfurt, Germany)

"How can non-compliance impact drug shortages?" asked Churchward. Compliance impacts medically critical products, but also affects a company's market share, sites of sole supply, causes supply restrictions and necessitates regulatory action.

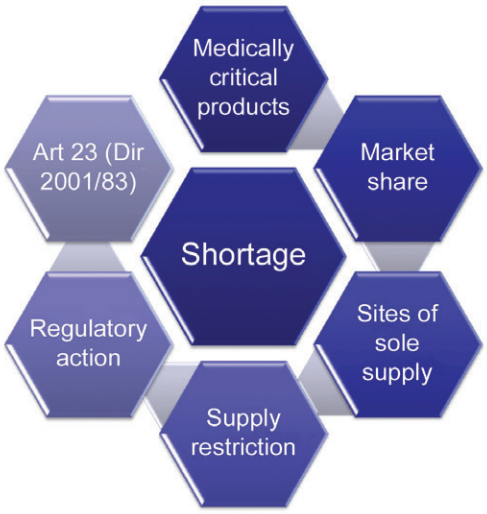


Figure I.1: How can compliance impact shortage? (Source: Used with permission from MHRA.)

The cost of non-compliance affects patients and industry alike. For patients, unavoidable regulatory action caused by non-compliance may lead to less effective and more expensive alternative treatments, treatment errors, and even an inability to treat. The cost of non-compliance for industry affects both Contract Acceptors and Contract Givers. Contract Acceptors risk additional regulatory burdens and the costs of remediation plans while Contract Givers risk shortages and the "uncomfortable position" of having to source critical products from a non-compliant Contract Manufacturing Organizations (CMOs). They also risk loss of market share and share price, diminished reputation, and recalls.

Non-compliance also can cause regulatory dilemmas regarding whether to recall a product. Should regulators issue a recall? Or should regulators allow potentially defective products onto the market rather than have no products available for patients?

For creating a risk-based, market-specific approach to regulatory action, Churchward noted the effectiveness of the European Union's use of Quality Risk Management (QRM). "Limited approval is given to permit the release of quarantined batches in EU countries with no alternative product," explained Churchward. "However, the EU recalls and restricts supplies in EU countries where alternatives are available." The QRM approach is taken through a process of global regulatory collaboration where there is agreement for the review of batches considered by MAH to be suitable for release and where the risk/benefit balance is found to be positive.

In one case of non-compliance, resolution saw company proposals for corrective action accepted (although they would take six months to implement). Subsequent re-inspection confirmed improvements and eventually the restrictions on supply were lifted for new batches. The previous product that had remained on the market was recalled when the first 'compliant' batches were released.

Improving the visibility of compliance issues is important, said Churchward. Increased awareness of potential shortages throughout the EU regulatory network can facilitate better sharing of information and coordination of action. Likewise, revisions to Chapters Five and Eight of the EU GMP Guide can improve procedures for managing non-compliance. The MHRA has found that the use of a proactive Compliance Management process can be beneficial.

Churchward recommended that industry consider the costs of non-compliance, do not delay actions, and review Technical Agreements. Regulatory interaction and information sharing means greater awareness of critical supplies and the ability to develop strategies for action while reducing shortage impacts.

What if something does go wrong? Churchward recommended determining the impact, determining the scope, and informing the regulators in a timely manner to discuss plans for action.

Summary

There are costs to both industry and patients as a result of drug shortages caused by non-compliance. QRM can help manage the supply, but requires improving the visibility of compliance and regulators world-wide sharing information with each other.

I.4 US Food and Drug Administration (FDA)

Response to Drug Shortages

(Summary of a presentation delivered by Douglas C. Throckmorton, MD, Deputy Director, Regulatory Programs, FDA/CDER at the 3rd Annual ISPE-FDA CGMP Conference held 2-4 June 2014 in Baltimore, Maryland, USA)

"Drug shortages pose a significant threat to public health," said Throckmorton. Among these are manufacturing problems that can include:

- Sterility: bacterial and fungal contamination
- Particulates: glass, metal or fiber in vials
- Crystallization: drug may form crystals

- Precipitation: reaction between drug and container or diluent
- Impurities: can be toxic (heavy metals)
- Degradants: lead to less effective drug product
- Equipment breakdown, need for remediation
- Natural disasters

In singling out one drug shortage issue, Throckmorton noted that shortages of sterile injectables are caused by manufacturing problems. According to Throckmorton, small numbers of manufacturers make up most of the market. Yet, many of these small manufacturers also are contracting out manufacturing, a practice that can lead to a variety of problems. Shortages also occur because of a lack of redundant manufacturing, multiple products made on existing manufacturing lines, and 24/7 production with no "time cushion."

The FDA's response to drug shortages has been to develop a Strategic Plan created by a taskforce of FDA personnel. The Strategic Plan, released 31 October 2013, has two overarching goals:

- Strengthening the FDA's ability to respond to notices of disruption in the supply, including improving mitigation tools and communication
- Developing long-term prevention strategies to address the underlying causes of supply disruptions and preventing drug shortages

Strengthening the FDA's drug shortage response potential means:

- Responding promptly to shortage notifications
- Performing risk-based analyses to find ways to address shortages, and
- Communicating effectively with stakeholders

Long-term efforts at preventing drug shortages include: developing methods to incentivize and prioritize manufacturing quality; using regulatory science to identify early warning signals of shortages; and increasing knowledge to develop new strategies to address shortages.

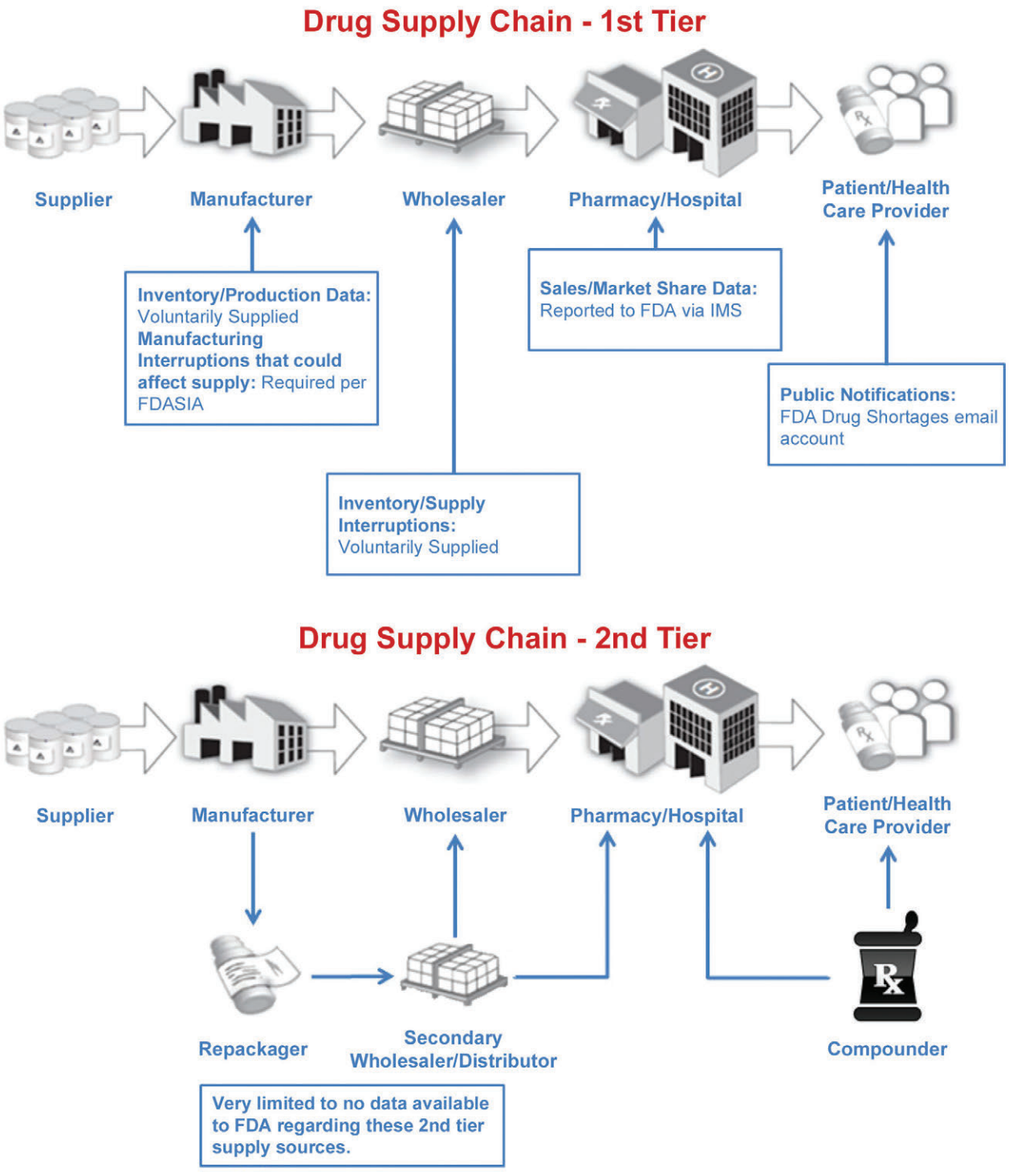


Figure I.2: Drug Supply Chain 1st and 2nd Tier (Source: Used with permission from the US FDA.)

Throckmorton described a two tier drug supply chain in which a second tier differed from the first by including "repackaging" and a secondary wholesaler/distributor, and a compounding component. "We have very limited to no data available to FDA regarding these second tier supply sources," explained Throckmorton.

The future of drug shortages must focus on cooperation. "No one party can solve drug shortages," he said. "FDA can only prevent shortages if problems are reported."

An emphasis for the FDA will be on persistent drug shortages and to develop new tools to speed their resolution. The FDA also will continue to analyze the root causes of the persistent shortages to determine how they may differ from shortages that resolve more quickly.

Industry needs a focused commitment to a manufacturing "culture of quality" that includes better manufacturing practices, methods, and quality testing. Needed as well is more production redundancy and appropriate facility updates to plants. Industry needs to report and correct even small production and quality problems and continue discussions with the FDA about ways to support quality manufacturing.

Summary

An FDA response to the drug shortage problem has been to create a task force charged with strengthening the FDA's ability to respond to notices of disruption in supply, improve mitigation tools and communication between manufacturers/marketing authorization holders and the FDA and develop long-term prevention plans that would address the underlying causes of supply disruption and prevent drug shortages.

I.5 Conclusion

The preceding chapters in *ISPE's Drug Shortages Prevention Plan* have focused attention on and helped clarify aspects of the root causes of drug shortages caused by manufacturing problems as well as problems that can occur anywhere along the supply chain. This Appendix is comprised of four summaries of presentations made by regulators at recent ISPE conferences. The summaries not only reflect regulatory concern over the causes of drug shortages, but also offer the presenters' suggestions for preventing and mitigating shortages. Better communication between industry and regulators is a key theme throughout the presentations.

Appendix II – ISPE Resources

ISPE's Body of Knowledge contains numerous resources in the areas identified in this Plan as key to preventing and mitigating drug shortages. Below is list of select resources.

- **Drug Shortages Industry Awareness: the ISPE Drug Shortages Prevention Plan and its Background**
    - This educational offering, which will be based on the Plan, is in development and will be designed to increase companies' staff awareness of shortage prevention.
- **Continual Improvement and Life Cycle Management of Products and Processes**
    - Online Training: Product Quality Lifecycle Implementation® (PQLI®) 101: Vision, Status and Next Steps
    - Training Course: Turning QbD into a Practical Reality; Process Validation Lifecycle – Integration to the Pharmaceutical Quality System
- **Knowledge Management**
    - Concept Paper: Implementing Knowledge Management in Bioprocesses: A QbD Driven Approach Turning Data into Knowledge in Reference to the CMC A-Mab Case Study
    - *Pharmaceutical Engineering* electronic supplement on Knowledge Management
- **Maintenance**
    - ISPE Good Practice Guide: Maintenance
- **Process Validation**
    - ISPE Guide: Biopharmaceutical Process Development and Manufacturing
    - Concept Paper: Stage 2 Process Validation: Determining and Justifying the Number of Process Performance Qualification Batches
    - Concept Paper: Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products
    - Concept Paper: Lifecycle Approach to Biotech Process Validation
    - Training Course: Process Validation Lifecycle – Integration to the Pharmaceutical Quality System; Process Validation in Biotechnology Manufacturing
    - Online Training: Understanding Process Validation in Biotechnology Manufacturing; Process Validation

- **Quality by Design**
  - ISPE PQLI® Guides:
    - Overview of Product Design, Development and Realization: A Science- and Risk-Based Approach to Implementation
    - Part 1 – Product Realization using Quality by Design (QbD): Concepts and Principles, including Overview, Criticality, Design Space, and Control Strategy
    - Part 2 – Product Realization using Quality by Design (QbD): Illustrative Example
    - Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System
    - Part 4 – Process Performance and Product Quality Monitoring System (PP&PQMS)
  - Knowledge Brief: Overview: Quality by Design
  - Training Course: Turning QbD into a Practical Reality; Process Validation Lifecycle – Integration to the Pharmaceutical Quality System
  - Online Training: Product Quality Lifecycle Implementation® (PQLI®) 101: Vision, Status and Next Steps
  - Quality by Design (QbD) for Legacy Products (in development by the ISPE Spain Affiliate)
- **Quality Risk Management**
  - Training Course: Applying Quality Risk Management
  - Online Training: Risk Management and QRM Webinars
- **Technology Transfer**
  - ISPE Good Practice Guide: Technology Transfer (Second Edition)
  - Training Course: Practical Application of Technology Transfer

Appendix III – Acronyms

API	Active Pharmaceutical Ingredient
APQR	Annual Product Quality Review
CAPA	Corrective and Preventive Actions
CBE	Change Being Effected
CDER	Center for Drug Evaluation and Research
CMO	Contract Manufacturing Organization
COP	Community of Practice
CPK	Process Capability Indicators
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DDI	FDA Division of Drug Information
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic medicines Association
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HHE	Health Hazard Evaluation
IT	Information Technology
MA	Manufacturing Authorization
MAH	Marketing Authorization Holders
MHRA	Medicines and Healthcare products Regulatory Agency

NDA	New Drug Application
OCOMM	US FDA Office of Communications
OGD	FDA Office of Generic Drugs
OOS	Out-of-Specification
OOT	Out-of-Trend
PAR	Proven Acceptable Range
PAS	Prior Approval Supplement
PDA	Parenteral Drug Association
PM	Preventive Maintenance
PMDA	Pharmaceutical and Medical Devices Association
PPTA	Plasma Protein Therapeutics Association
PQLI®	Product Quality Lifecycle Implementation®
QA	Quality Assurance
QC	Quality Control
QbD	Quality by Design
QP	Qualified Person
QRM	Quality Risk Management
QSMR	Quality System Management Review
SME	Subject Matter Expert
SOP	Standard Operating Procedures
TGA	Therapeutics Goods Administration
WHO	World Health Organization

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Acknowledgments

This ISPE Drug Shortages Prevention Plan advocates a holistic approach to avoiding and mitigating drug shortages caused by manufacturing and quality issues. Therefore, it is fitting that it was developed by a multi-disciplinary, multi-cultural team of industry experts which included professionals with expertise in quality systems, manufacturing, and regulatory compliance.

ISPE Drug Shortages Team

- François Sallans, Vice President and Chief Quality Officer, Johnson & Johnson – *Chairman, ISPE Drug Shortages Team*
- John C. Berridge, PhD, ISPE Advisor
- Peter T. Bigelow, President, XCell Strategic Consulting, LLC
- Paul N. D'Eramo, Vice President Pharmaceutical Regulatory Compliance, Johnson & Johnson
- Joseph C. Famulare, Vice President Global Compliance and External Collaboration, Pharmaceutical Technical Quality, Genentech Inc.
- Donna Gulbinski, Senior Vice President Global Quality & EHS, Bristol-Myers Squibb Co.
- Karen Hirshfield, RPh, Senior Compliance Specialist, Genentech
- Stephen C. Mahoney, Senior Director Global Quality and Compliance, Genentech.
- Sam Venugopal, Partner, PricewaterhouseCoopers LLP
- Christine Wells, Vice President, America Compl. Prod. Quality, Teva Pharmaceuticals
- Bryan J. Wright, ISPE European Regulatory Advisor
- Frances M. Zipp, President, Lachman Consultant Services Inc.
- Thomas G. Zimmer, PhD, Vice President European Operations, ISPE

Other Contributors

- Kankshit Bheda, Senior Associate, PricewaterhouseCoopers LLP
- Randolph Fillmore, Florida Science Communications, Inc.
- George P. Millili, PhD, Senior Principal Technical Advisor, Genentech
- Christopher Potter, PhD, ISPE Advisor
- Snehal Srikrishna, Manager, PricewaterhouseCoopers LLP

ISPE Staff

- Nancy Berg, President and CEO (2012 – 2014)
- John Bournas, President and CEO (2014 –)
- Carol Winfield, Director of Regulatory Operations

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- Mark Birse, Group Manager, GMDP, IES, MHRA
- David Churchward, Expert Inspector, GMDP, IES, MHRA
- Brendan Cuddy, Scientific Administrator, EMA
- Richard L. Friedman, Associate Director of Risk Science Intelligence and Prioritization, FDA/CDER
- Gerald W. Heddell, Director, Inspection, Enforcement and Standards, IES, MHRA
- Isabelle Izzard, Principal Pharmaceutical Officer, UK Department of Health
- Valerie Jensen, R.Ph., Associate Director, Drug Shortages Task Force, FDA/CDER
- Amparo Noguera, Head of Service, Pharmaceutical Inspection and Enforcement Department, AEMPS
- Jouhayna Saliba, Pharm.D., Team Leader, Drug Shortages Task Force, FDA/CDER
- Bernadette Sinclair Jenkins, Regulatory Unit Manager, IES, MHRA
- Emily Thakur, R.Ph., Team Leader, Drug Shortages Task Force, FDA/CDER
- Douglas C. Throckmorton, M.D., Deputy Director, Regulatory Programs, Drug Shortages Task Force, FDA/CDER
- Associations participating in the cross-industry association task force:
    - Association of the European Self-Medication Industry (AESGP)
    - European Federation of the Pharmaceutical Industries and Associations (EFPIA)
    - European Generic medicines Association (EGA)
    - Parenteral Drug Association (PDA)
    - Plasma Protein Therapeutics Association (PPTA)

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ISPE Headquarters
600 N. Westshore Blvd., Suite 900
Tampa, Florida 33609 USA
Tel: +1-813-960-2105
Fax: +1-813-264-2816
Email: ASK@ispe.org

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