Report on the ISPE Drug Shortages Survey

June 2013

I. Background/Introduction

The prevention and mitigation of drug shortages are critically important to public health. As a key stakeholder in the global pharmaceutical industry, the International Society for Pharmaceutical Engineering (ISPE or "the Society") believes efforts to address the complex and multi-faceted problem of drug shortages require close technical collaboration and clear communication between the pharmaceutical industry and global health authorities.[1]

As an organization of pharmaceutical professionals and regulators involved in drug manufacturing, ISPE continually aims to provide leadership in solving complex technical issues affecting drug manufacturing and quality. Consequently, ISPE formed a Drug Shortage Task Force (Task Force) in late 2012 in order to help stakeholders better understand the root causes for global drug shortages and to define mitigation strategies that can help prevent drug shortages. In our approach to the challenge of drug shortages, we focused on technical and quality systems topics. In doing so we strove to keep our inquiries broad and our approach open to ensure that no aspects of the problem were overlooked.

Causes for Global Drug Shortages

After reviewing the current literature regarding global drug shortages, the Task Force identified several recurrent messages including:

- The number of drug shortages across the globe has increased significantly in recent years.[2]
- The majority of recent drug shortages have involved sterile injectable products.[3]

Not surprisingly, the Task Force also found significant variation in the proposed root causes for these drug shortages. Consider the following:

- The U.S. Food and Drug Administration (FDA) found that quality problems (e.g., contamination, presence of foreign particles) are the most common cause of drug shortages, accounting for nearly 46% of all drug shortages in 2011.[4] However, FDA also lists other causes for drug shortages including inadequate capacity, raw materials issues, and packaging component problems.
- The European Medicines Agency (EMA) identified the globalization of drug manufacturing and complex supply chains as factors that increase the risk of drug shortages.[5]
- The Biotechnology Industry Organization (BIO) cited a number of contributing factors to drug shortages including unanticipated shifts in market demand, manufacturing production and quality problems and limited manufacturing capacity.[6]
- The European Association of Pharmaceutical Full-line Wholesalers listed several potential causes for drug shortages including the potential impact of the Falsified Medicines Directive, lack of market attractiveness for (older) medicines and stringent supply quotas imposed by pharmaceutical manufacturers.[7]

Based on this research, the Task Force understands there are many factors that may affect the supply of drugs and impact drug shortages. However, given ISPE's technical expertise, the Task Force determined that the Society would be well suited to focus on manufacturing and quality issues, the biggest causes for drug shortages in 2011 according to FDA.[8]

In response to the growing global concerns, the Task Force aimed to discover whether one or more manufacturing or quality-related root causes/mitigations could be identified that would assist industry and regulators in avoiding drug shortages. The Task Force Members understood that the issues involved in drug shortages are complex, and the number of possible elements affecting the identified scope of manufacturing and quality issues is vast. Hence, the Task Force's intent was to identify key areas or aspects of the drug shortage problem on which to focus immediate attention as well as to identify promising areas for future development and exploration.

Study Scope and Approach

To explore these technical issues, the Task Force developed and launched an anonymous survey aimed at identifying the root causes of manufacturing and quality problems that have led, or could lead, to drug shortages, and to seek respondents' input into potential solutions both industry and regulators may wish to adopt. The intent of the survey was not to define the ideal solution that would be required to help reduce the number of drug shortages observed. However, the Task Force felt that by focusing on fundamental technical issues, pharmaceutical quality systems, and organizational efforts, the outcomes could, at least, help provide insight into whether or not the steps taken by industry and the regulatory agencies seem to be working.

ISPE's Drug Shortage Survey, conducted over February and March 2013, focused on understanding and identifying the technical and GMP compliance-related issues that are potentially responsible for contributing to the drug shortages currently faced by the pharmaceutical industry. Overall, the Task Force hoped the results of this study would provide ISPE with unique industry data regarding drug shortages. Through this report and subsequent activities, ISPE plans to provide the pharmaceutical industry and health authorities with much needed data to support additional discussion and the development of science and risk-based approaches to mitigate shortages.

Specific survey objectives were to:

- Identify and collect views from companies and individuals on a global basis to evaluate findings from both a technical and an organizational perspective.
- Confirm or determine root causes of shortages in support of developing a risk-based approach to mitigating shortages.
- Compare and contrast companies that had fully prevented or avoided a drug shortage with those that had experienced a "near miss" or actual shortage.
- Determine any distinctions between sterile and non-sterile products.

In developing the survey, as well as in receiving responses from Members and industry stakeholders, the Task Force benefited greatly from valuable input provided by representatives of regulatory agencies in Europe, the USA and Canada as well as from trade associations such as the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The survey questions were structured around the major elements of pharmaceutical quality systems as described in inspection programs and International Conference on Harmonization (ICH) guidelines and defined in Section III of this report. In addition to gathering data on the major elements, the Task Force attempted to delve more deeply into the sub-elements within the quality systems that were helping with, or detracting from, companies' abilities to maintain their supply chain. Since data in this field of research is presently limited, great care was taken to keep the questions in each area of focus broad and to encourage respondents to provide more specific details in open-ended comments. This was done with the intent of capturing as much information as possible and using the body of collected input to inform decisions on the direction of future research. **See Figure 1.**

Figure 1: Quality System Manufacturing Focus Areas

Quality Records
- Inadequate review of risks to patient
- Inadequate review of failure investigations
- Inadequate review of trends/quality indicators

Facilities & Equipment
- Cleaning and maintenance
- Facility layout or compliant design
- Container Closure
- Support Utilities (Water, HVAC)

Packaging and Labeling
- Control system for implementing changes in the packaging or labeling operations
- Investigation of discrepancies
- Inadequate control of packaging and labeling operations

Production Equipment
- Aseptic processing equipment
- Stopper washer
- Capping equipment (vials)
- Post-fill visual inspection/automated inspection equipment
- Sterilizers
- Lyophilizers
- Isolators
- Restricted Access Barrier System (RABS)
- Blow-Fill-Seal (BFS) Technology
- Reactor, centrifuge, dryer, mill

Production System (Sterile)
- Media fills or process simulations
- Sterile filtration (aseptic processing)
- Sterilization and depyrogenation of containers, closures and processing equipment
- Lyophilization
- Sealing of vials
- Terminal sterilization
- Parametric release of terminally sterilized drug product
- Inspection of injectable products
- Personnel (e.g., gowning, training, aseptic techniques)
- Environmental and personnel monitoring

Production System (Non-Sterile)
- Inadequate batch records (for example, missing or incomplete records)
- Nonconformance to established in-process controls, tests, or specifications
- Control system for implementing changes in processes
- Process validation

Lab Controls (Non-Sterile)
- Control system for implementing changes in the laboratory operations
- Investigation of discrepancies
- Analytical methods or procedures
- Out-of-specification (OOS) procedures

Material Systems (Sterile)
- Processed gas
- Pre-washed/ready to sterilize closures
- Microbiological and endotoxin testing of component, container and closures
- Verification of container and closures
- Container and closure integrity

Material Systems (Non-Sterile)
- Components (for example, inadequate testing or validation of suppliers test results)
- Water and process gas (for example, inadequate validation, operation or maintenance)
- Containers and closures

Lab Controls (Sterile)
- Sterility Testing
- Limulus amebocyte lysate (LAL) testing, including product specific validation
- Environmental monitoring
- Personnel monitoring
- Efficacy of disinfectants
- Assessment of the suitability, efficacy and limitations of the disinfecting agents
- Identifying microorganisms
- Environmental monitoring samples as specified by your company
- Microbiological media, including the preparation, sterilization and growth promotion testing of the media used in performing tests
- Biological Indicators (BI)
- Biological cultures used in sterilization validation studies

Industry participation in providing information for this study was good. Some 264 individuals and companies took the time to respond to the lengthy and complex survey instrument covering over 100 items in four sections (General Information, Underlying Causes of Drug Shortages, Company Strategies to Prevent or Alleviate Shortages, Regulatory Bodies and their Ability to Prevent/Help Avoid Drug Shortages). Because the resulting data set is so vast, this report focuses on the key findings the Task Force discerned from a high level review of the data. Subsequent analysis will be ongoing, and more detailed findings will be made available through future presentations and publications. The remainder of this report summarizes our key findings and recommendations for future study.

II. Demographics

ISPE deployed the Drug Shortages Survey to its global database of Members and non-Members. The organization also worked with several reporters and publications covering the pharmaceutical industry to ensure maximum outreach and participation by industry participants with direct knowledge of actual drug shortages and shortages that had been narrowly avoided. In addition to seeking respondents to answer the survey items based on their individual experiences and opinions, ISPE also encouraged companies to compile an enterprise-level response and to designate a member of their staff to enter the information into the electronic survey system. In this way duplication of data was minimized while still allowing individuals in the industry to share their personal (i.e., non-company) views.[9] Complete anonymity was assured for all respondents.

Participation

The survey generated participation by 175 individuals and 37 companies from around the world for a total of 212 total respondents providing data concerning an actual drug shortage or a near miss. The resulting breakdown met the team's requirements for a representative sample of respondents as shown in **Figure 2** and **Figure 3.**

Figure 2: Respondents Experiencing a Shortage or Near Miss

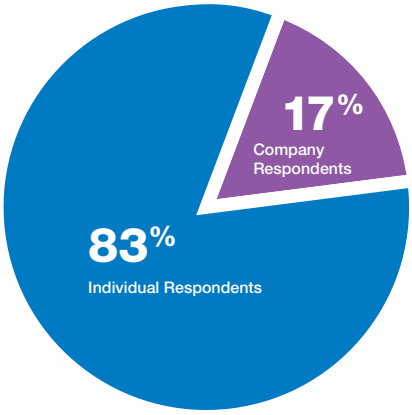
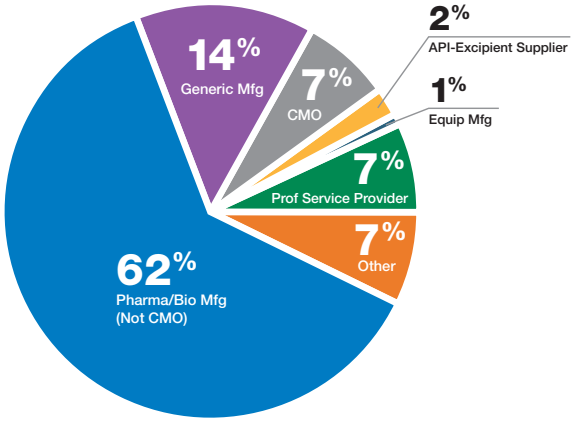
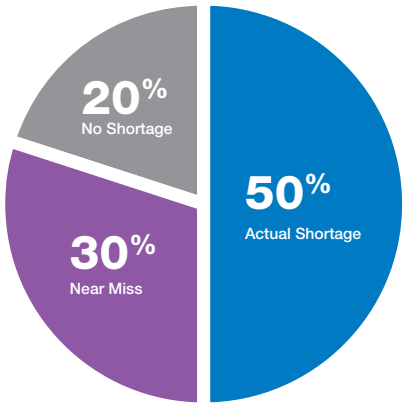


Figure 3: Shortage/Miss Respondents by Company Type



In addition to the 212 respondents who experienced either a shortage or near miss and completed the survey section focused on the underlying causes of shortages, some 52 additional respondents whose companies had avoided a shortage or miss provided data regarding mitigation strategies and experience with regulatory bodies. The respondent pool as a whole is depicted in **Figure 4.**

Figure 4: Respondent Experience with Drug Shortages



III. Underlying Causes of Drug Shortages

The ISPE Drug Shortage Survey was designed to examine the underlying causes of drug shortages related to quality and manufacturing issues. Specifically, the survey examined the following six manufacturing and testing systems (collectively known as Quality Systems) to gather technical insights into underlying root causes:

- **Quality System** – the system that assures overall compliance with cGMPs and internal procedures and specifications. The system includes the quality control unit and all of its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports, etc.).
- **Facilities and Equipment System** – the system that includes the measures and activities which provide an appropriate physical environment and resources used in the production of the drugs or drug products.
- **Materials System** – the system that includes measures and activities to control finished products, components, containers and closures (including water or gases) that are incorporated into the product.
- **Production System** – the system that includes measures and activities to control the manufacture of drugs and drug products including batch compounding, dosage form production, in-process sampling and testing, and process validation.
- **Laboratory Control System** – the system that includes measures and activities related to laboratory procedures, testing, analytical methods development and validation or verification, and the stability program.
- **Packaging and Labeling System** – the system that includes measures and activities that control the packaging and labeling of drugs and drug products.

While data has been gathered concerning the underlying impact all of these systems may have on drug shortages, for our present high-level report, we would like to highlight survey data from several questions regarding overall Quality Systems (Figure 5), the Production System (Figures 6-7), and the Facilities and Equipment System (Figures 8-10) since these data illustrate the study findings that our Task Force deemed most significant with respect to underlying causes.

Key Findings Related to the Underlying Causes of Drug Shortages

By examining the six key manufacturing and testing systems that collectively are known as the "Quality Systems," the Survey identified underlying systemic issues that may have contributed to drug shortages or near misses.[10] Notably, the survey's findings included the following:

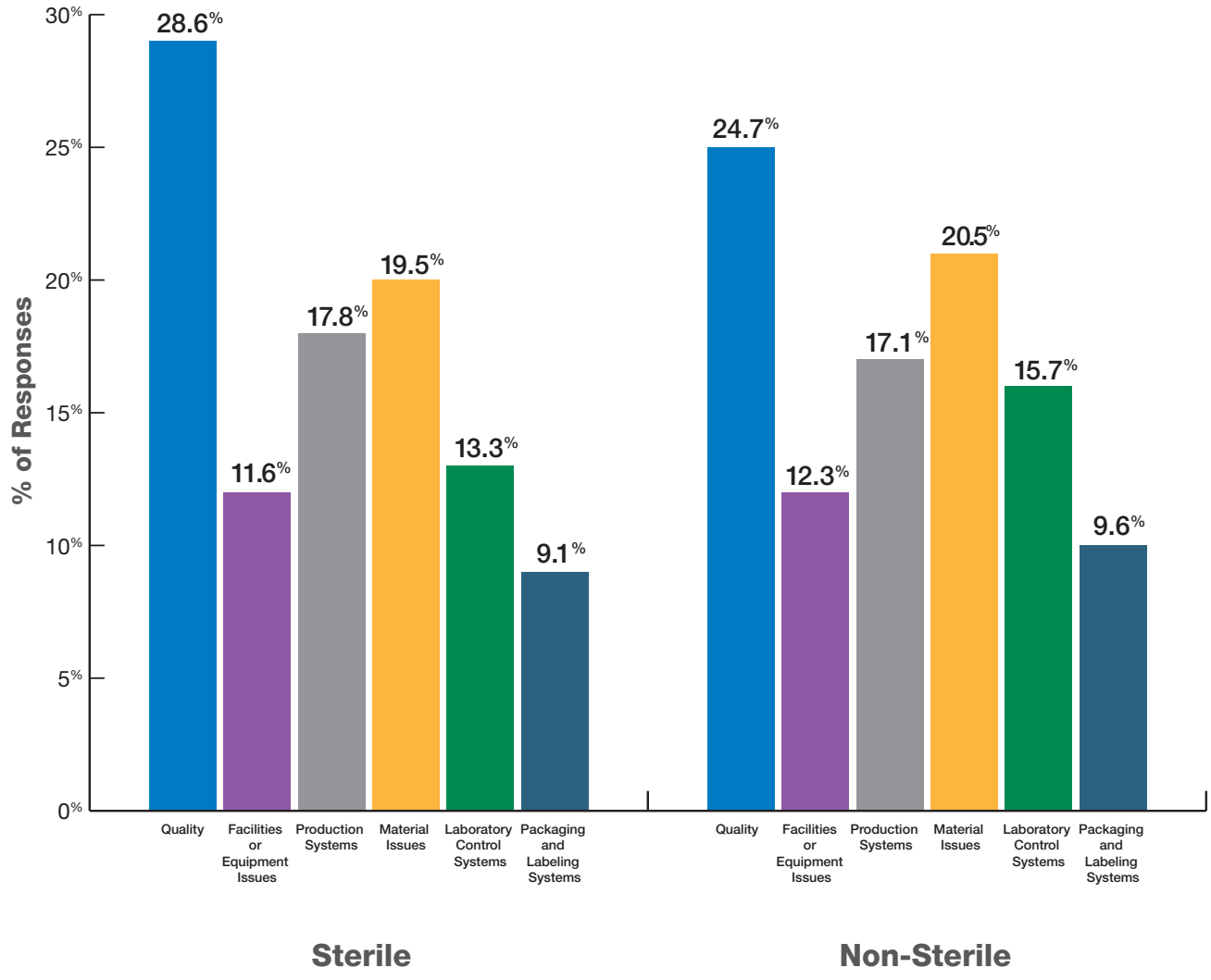
- Aseptic processing equipment was identified as a significant factor in drug shortages, for both individual responses and company responses.
- Production system issues leading to drug shortages or near misses were present during technology transfers or product development according to a small but significant number of respondents.

These findings were derived from an examination of the data provided in response to the following survey questions.

Q: Which manufacturing and testing system likely contributed the most to the drug shortage or near miss at your company?

Data related to the underlying causes of sterile and non-sterile shortages was surprisingly similar. The priority order of the systems' contributing impact on shortages was identical for sterile and non-sterile drug manufacturing, with only slight variations in the weight for each system. As shown in **Figure 5**, in both manufacturing environments the order of importance is found to be (1) Quality System, (2) Material System, (3) Production System, (4) Laboratory Control System (5) Facilities and Equipment System, and (6) Packaging and Labeling System.

Figure 5: Responses to Quality Sub-Systems Questions for Sterile and Non-Sterile Products

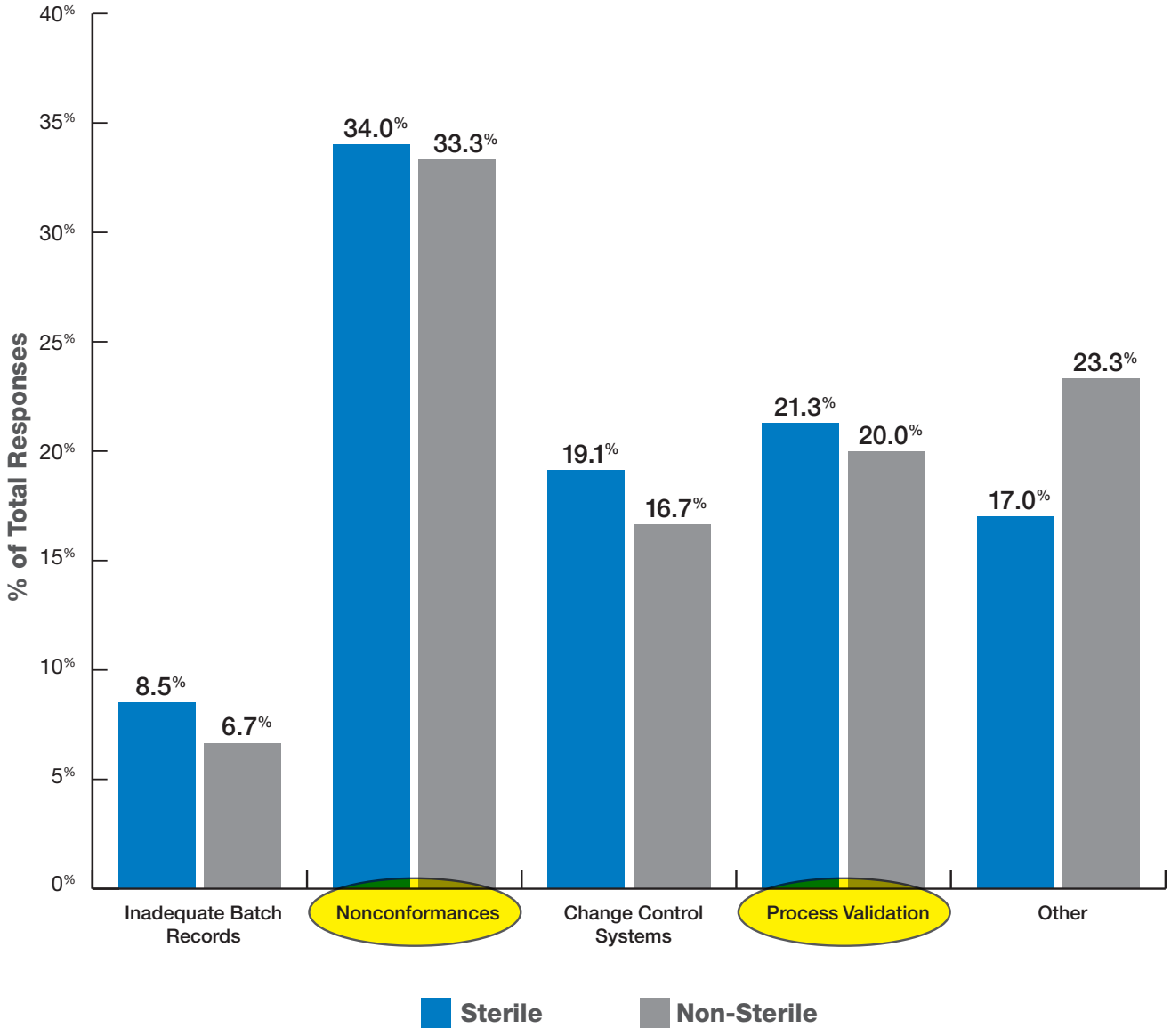


Q: Which one of the following [production system] areas likely contributed the most to the drug shortage or near miss at your company?

This question was asked only of respondents who identified areas in the production system as likely contributing to the drug shortage or near miss at their company.

Within the production system, the most prevalent issues reported were non-conformances (34% for sterile shortages/misses, 33% for non-sterile shortages/misses), process validation (21% for sterile shortages/misses and 20% for non-sterile shortages/misses) and change control systems (19% for sterile shortages/misses and 16% for non-sterile shortages/misses). **See Figure 6.**

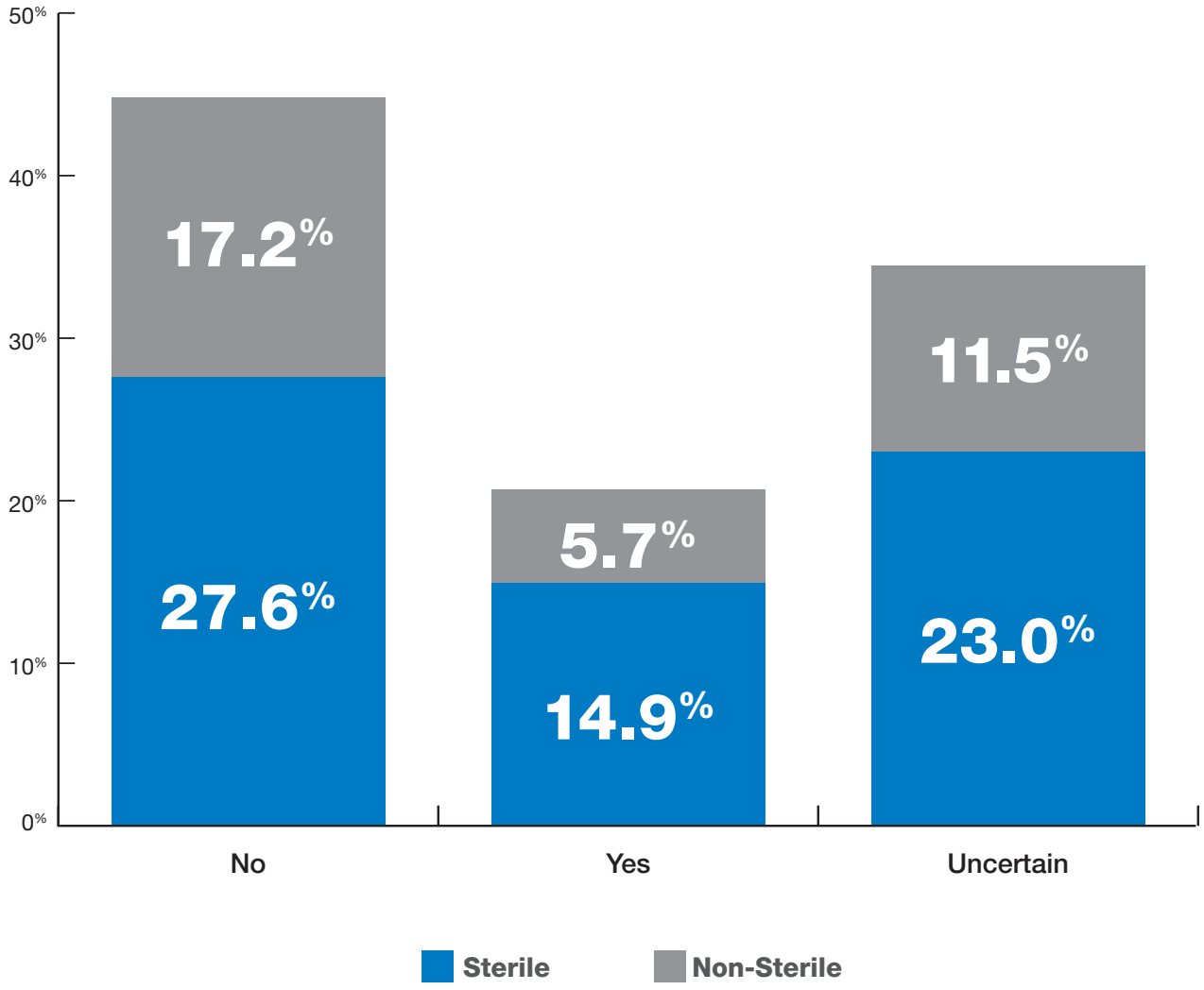
Figure 6: Production System Issues for Sterile and Non-Sterile Products



Q: For any of the issues identified in the prior question, were similar problems observed at your company during development or technology transfer?

Interestingly, a small but significant number of respondents answer "yes" to this question, both for sterile and non-sterile. ISPE recommends more discussion on this topic. **See Figure 7.**

Figure 7: Were Similar Problems Present During Drug Development or Tech Transfer?

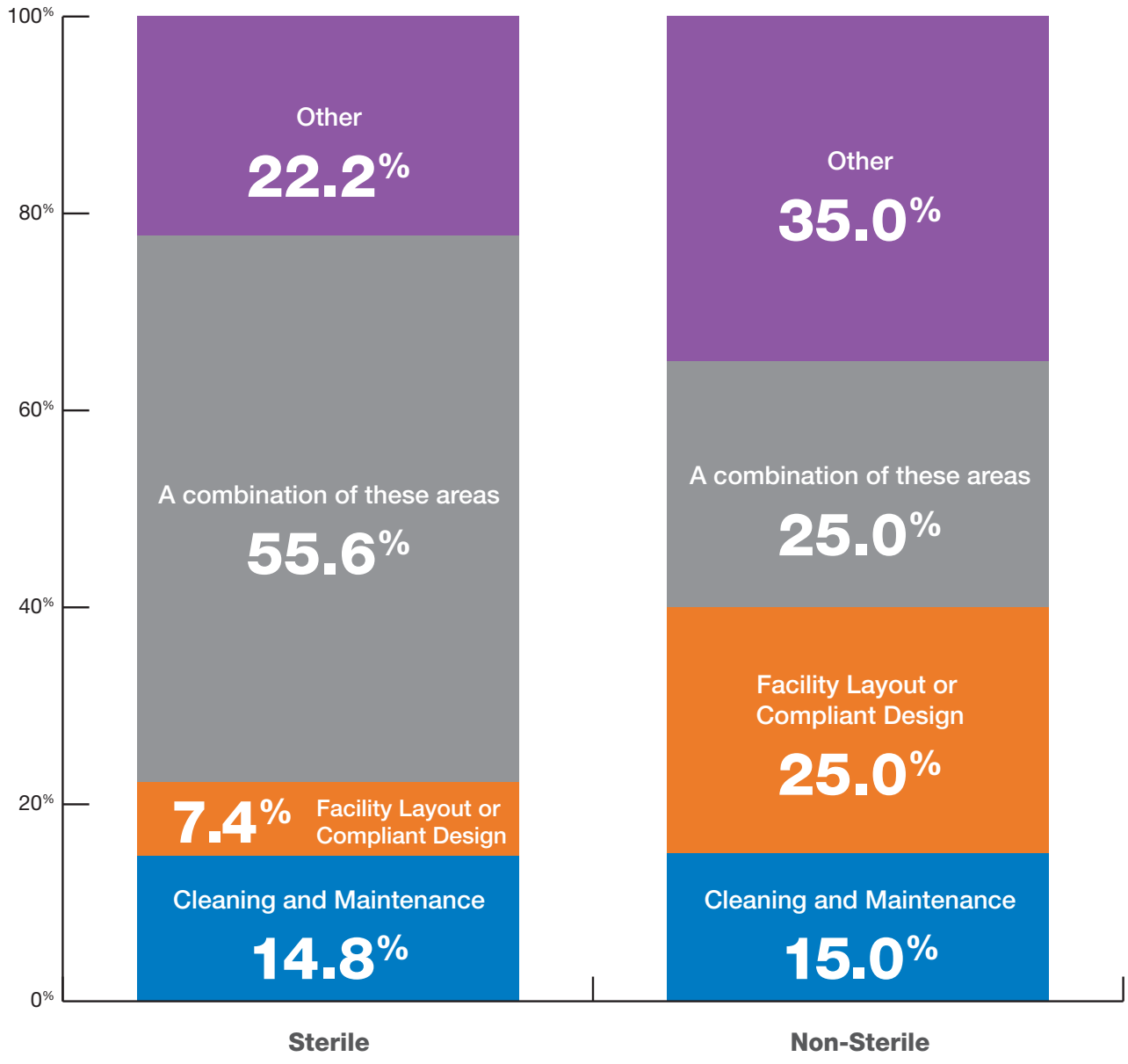


Respondents who identified areas in the facilities and equipment system as likely contributing the most to the drug shortage (or near miss) at their company answered the following questions.

Q: When you consider your facilities issue, which of the following areas likely contributed the most to the drug shortage or near miss?

In general, the issues were often viewed as multi-factorial in nature, but there were significantly more specific issues with facility layout or compliant design in non-sterile facilities than sterile facilities. **See Figure 8.**

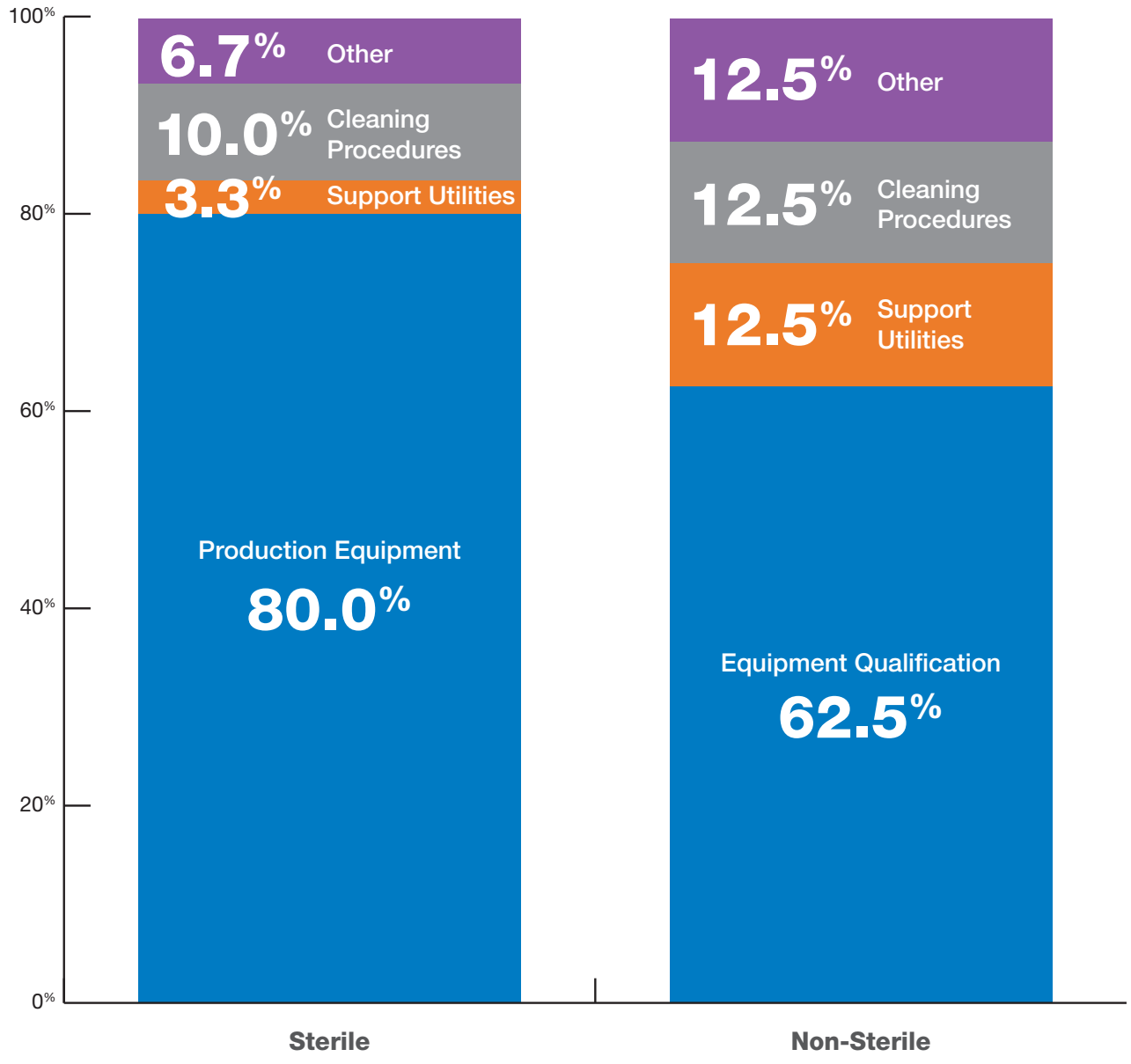
Figure 8: Facility Issues



Q: What type of equipment problem likely contributed most to the drug shortage or near miss at your company?

Data provided concerning equipment problems revealed that production equipment was the major source of issues for sterile products (80%) while equipment qualification was the major source of issues for non-sterile products (62.5%). **See Figure 9.**

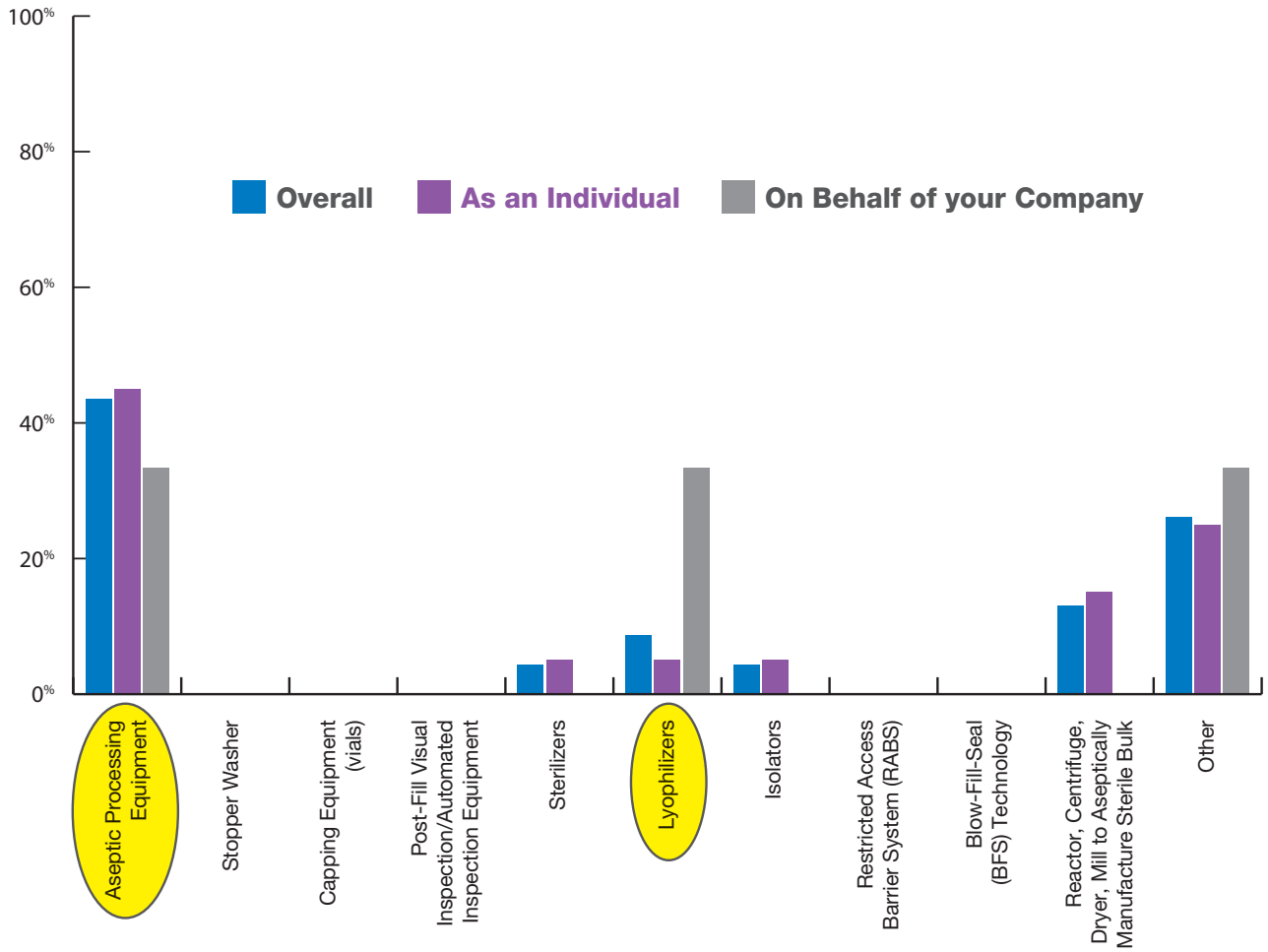
Figure 9: Equipment Issues



Q: What is the one type of [sterile] production equipment that likely contributed most to the [sterile] drug shortage or near miss at your company?

As might have been expected, aseptic processing equipment was the major piece of production equipment reported as posing problems by both individual and company respondents. Note also the prevalence of responses on lyophilizers. **See Figure 10**.

Figure 10: Production Equipment: Drug Shortage Contributors



Areas for Future Development and Exploration Related to the Underlying Causes of Shortages

While the ISPE Drug Shortage Survey answered many questions about possible root causes for drug shortages, the data overwhelmingly confirmed the multi-factorial nature of this global problem. Consequently, ISPE strongly recommends that the pharmaceutical industry and global health authorities further collaborate on this important public health issue and use data from this Survey as one tool to explore these complex issues further. For example:

- What are the specific issues regarding the aseptic processing equipment highlighted in the survey responses? What would lead to more proactive updating and modernization of this equipment for continual improvement?
- What are the product development or technology transfer issues highlighted in the survey that can be mitigated?
- What are the unique issues in facility layout or compliant design that contribute to non-sterile drug shortages? How can these issues be alleviated?
- How can the pharmaceutical industry and health authorities promote more rapid continual improvement (e.g., harmonization of global regulatory change management requirements)?

Extensive data has been gathered through the survey regarding the other component systems that together comprise the manufacturing quality systems. Although the nature of this high level report does not lend itself to a thorough review and analysis of that information here, ISPE intends to continue examining these data sets for possible areas of further study. It is our intent to work with and through other industry stakeholders to advance our collective understanding of the underlying causes of drug shortages which can be traced to each system—or combination of systems—as well as to assist in developing mitigation strategies for them.

IV. Drug Shortage Mitigations

In addition to looking at the potential root causes behind drug shortages, the survey also set out to reveal what mitigation strategies companies were putting in place to help prevent drug shortages from occurring. Respondents were asked questions involving key operational enablers in an attempt to confirm or provide alternatives to the following hypotheses typically associated with drug shortage prevention programs.

- **Quality Systems:** Companies that invest in strong Quality Systems will be more likely to succeed in preventing drug shortages as a result of driving compliance and by achieving sound:
    - **Governance and Metrics:** Support from Senior Management to drive the drug shortage prevention programs as well as well-defined metrics tailored to proactively identify the potential risk of a shortage will mitigate shortages.
    - **Resource Management and Incentives:** Adequate resources to drive the drug shortage prevention programs in place coupled with efforts to tie specific goals related to preventing shortages to performance incentives will mitigate shortages.
- **Supply Chain Operations:** Building redundancies into a company's supply chain is an important—if not essential—element required to prevent drug shortages.

Key Findings related to Drug Shortage Mitigations

Respondents were asked to identify whether or not they had a dedicated program in place to prevent drug shortage and if so, how many of these programs had been successful in preventing a shortage. This was done both to gain a better understanding of how prevalent these types of programs are within the industry and attempt to identify any key characteristics of these programs that contributed to their success.

To this end, 142 survey respondents (54%) affirmed that they had a drug shortage prevention program in place. Of these 142 respondents, 77 (54%) indicated that despite the programs put in place the company was still unable to prevent a drug shortage.

To gain a better understanding of why certain programs were successful, the 65 respondents whose programs were successful in preventing a drug shortage (43%) were asked to indicate which "success factors" were the most important. The top 10 responses are listed in **Figure 11.**

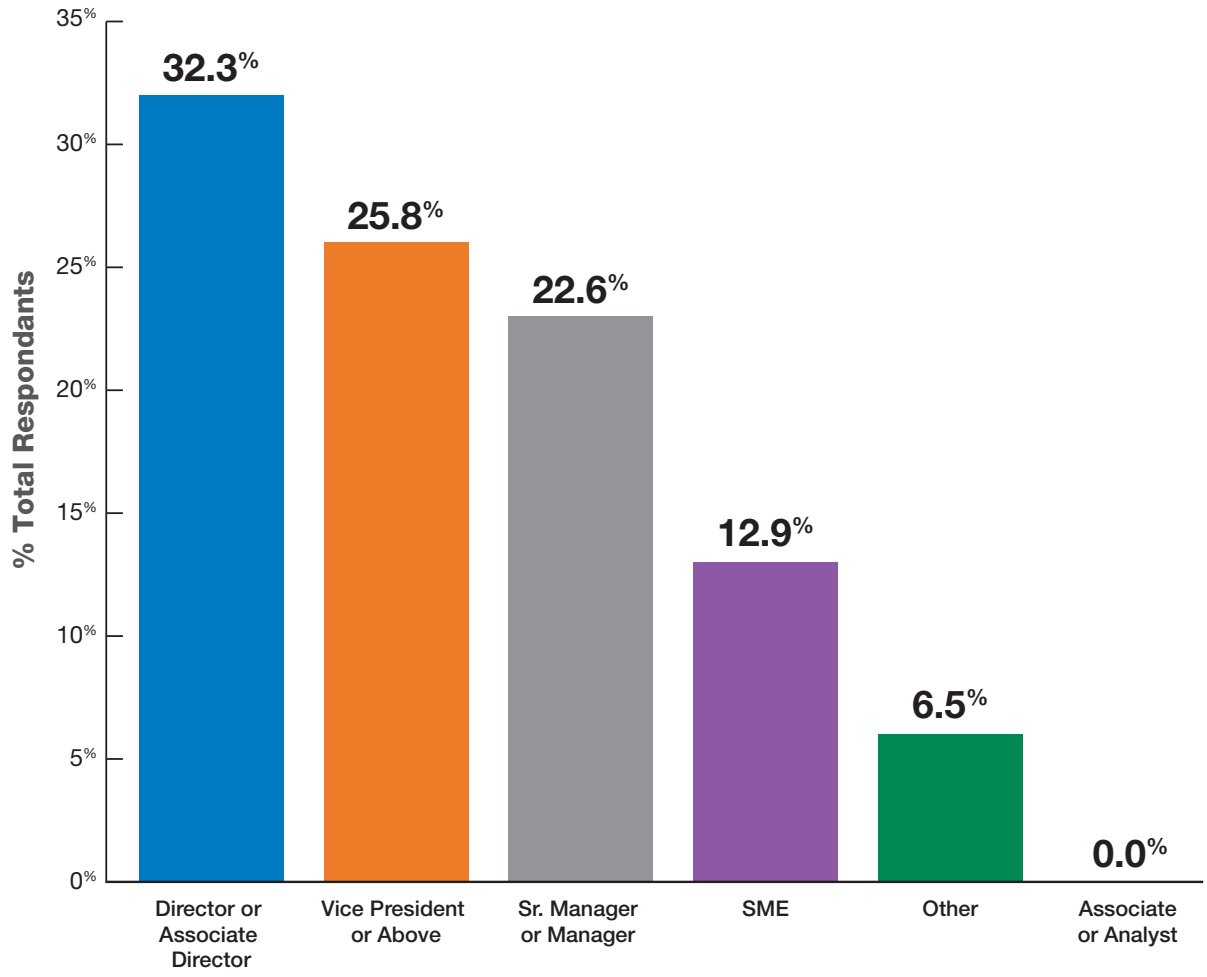
Figure 11

Cited Success Factors in Preventing Drug Shortages	Rank of Success Reason
Strong Quality Systems ➔ Ensure Compliance to Manufacturing Regulations	1
Avoiding Drug Shortage Documented as Corporate Goal	2
Strong QS Track Record and GMP Inspection History	3
Corporate Goals Tagged to Drug Shortage Prevention	4
Ability to Quickly React to Drug Shortages	5
Strong Relationship With Regulatory Authorities	6
Strong Communication Link With Regulatory Authorities	7
Dedicated Resources Focused on Preventing Drug Shortages	8
Incentives Tied to Preventing Drug Shortages	9
Metrics Defined Around Drug Shortages	10

Based on the rankings, the survey confirmed the overall importance of a company's strong Quality System, i.e., "Strong QS Track Record and GMP Inspection History" (ranked #3) in developing a successful drug shortage prevention program. The list of top 10 factors also highlights the importance of receiving support from senior management to implement these programs in a way that links corporate goals to the prevention of drug shortages (ranked #2 and #4) along with establishing dedicated resources to prevention (ranked #8) and tying incentives to preventing shortages (ranked #9).

The fact that internal governance and leadership was ranked so high is not unexpected and offers insight related to how important it is for companies to have not only a dedicated drug shortage prevention program in place but one that is owned by senior members of the organization. Indeed, in looking at the results, companies with a strong mitigation program appear to have authorized manager level staff or above to address/prevent future drug shortages. About 58% of prevention programs were led by senior members of the organization (Directors and Vice Presidents), lending support to the idea that responsibility on mitigation plans and prevention needs to be held at a high enough level in the company to be effective. See **Figure 12** below:

Figure 12: Staff Level Authorized to Address/Prevent Future Drug Shortages in Companies with Strong Mitigation Programs



In addition, the ranking of the top 10 success factors highlights the importance companies with successful programs placed on building strong relationships with regulatory authorities and ensuring strong communication links with regulatory authorities (ranked #6 and #7 respectively). Note: the relationships with regulatory authorities will be explored further in section V of this report.

Finally, the rankings confirmed the importance of defining metrics around drug shortages (ranked #10) which ties to the importance the respondents placed on being able to quickly react to drug shortages (ranked #5).

Similarly, where companies had failed 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 was compared to the success factor list above a marked difference was apparent. Indeed, rather than indicating that their priorities revolved around strong quality systems, governance, metrics, and incentives, the failed programs focused on areas such as building IT systems to help identify potential shortages as well as efforts to establish redundancy in the supply chain and manufacturing operations.

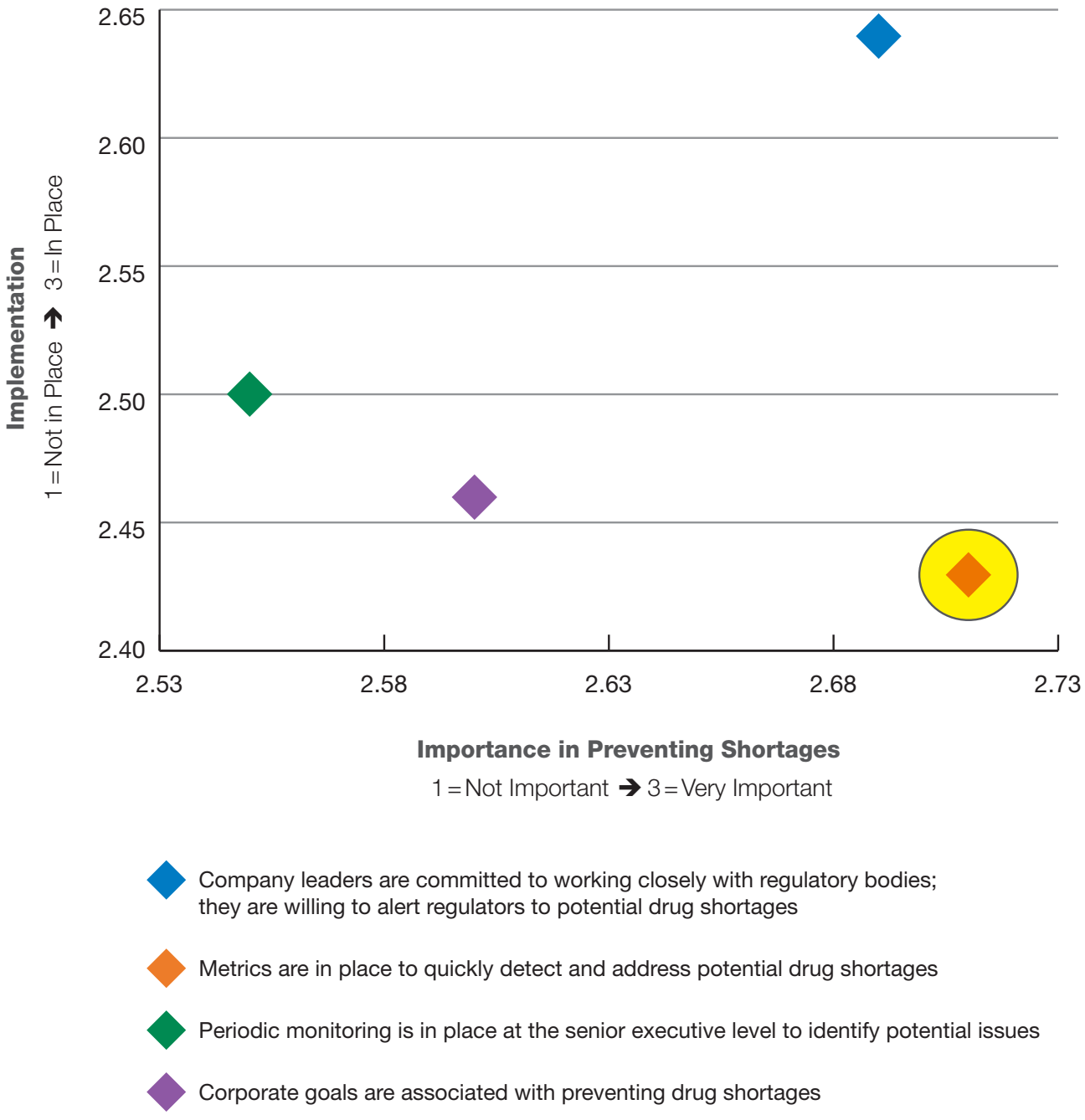
Areas for Future Development and Exploration Related to Drug Shortage Mitigation

The study identified metrics to detect and address shortages as a potential improvement opportunity. The data showed a substantial gap between the degree to which metrics are viewed as important in the prevention of shortages and the degree to which appropriate measures for quickly detecting and addressing drug shortages have been implemented as shown in **Figure 13.**

Strategies for identifying and implementing appropriate quality and/or other alerting metrics within organizations may prove to be a very important aspect of preventing or mitigating future drug shortages. This area should be explored further to understand why some companies are struggling to get metrics in place that can predict shortages and what solutions might be needed to overcome the current challenges.

Similarly, the importance of building in redundancy into a company's supply chain should also be explored further, given varying responses received related to this area. 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.

Figure 13: Mitigation Strategies—Corporate Management Review and Governance



V. Impact of Regulatory Activities

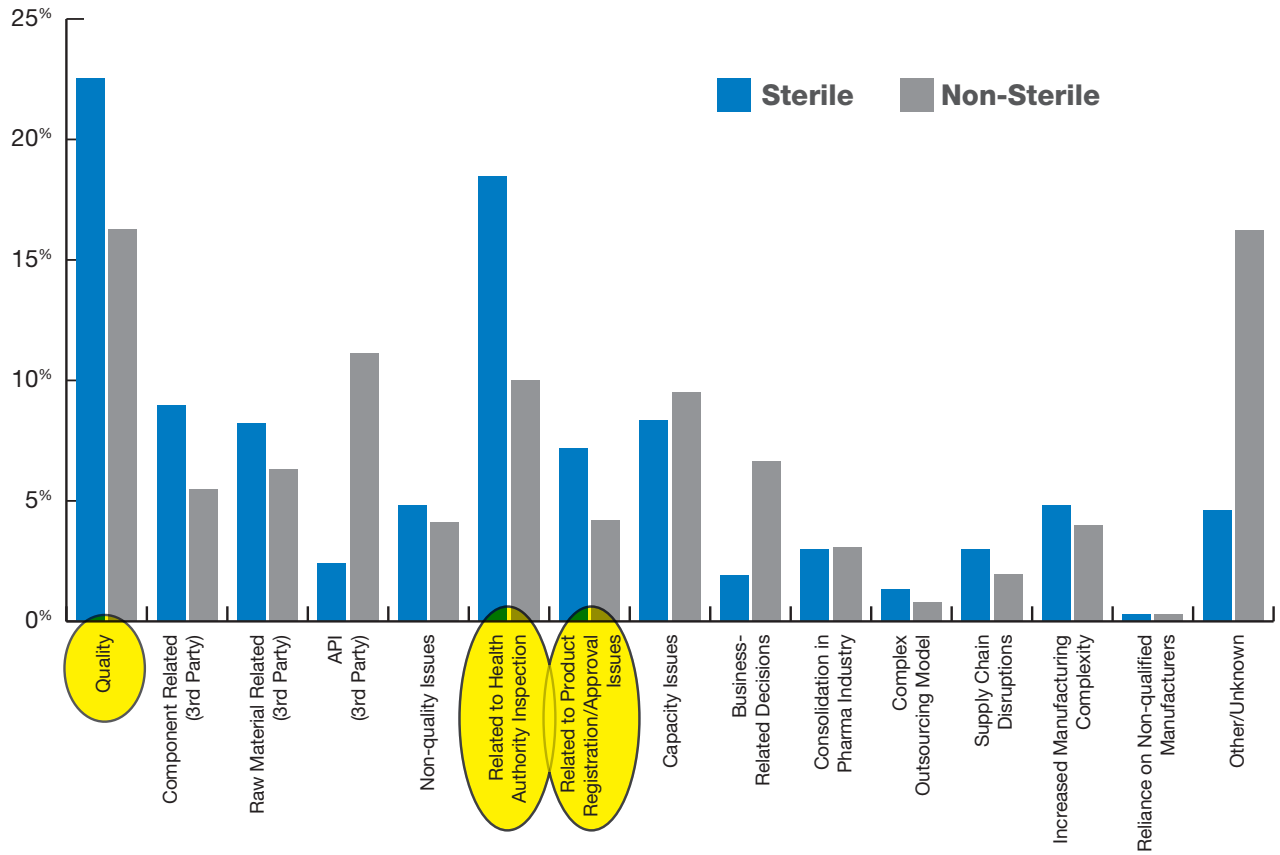
The study explored whether companies considered that the quality of interaction with regulatory authorities played an appropriate preventative role with respect to drug shortages. A series of questions sought more insight into the impact and opportunities that ensued from interactions with the authorities around these issues. Opinions were also sought on potential future regulatory initiatives, in particular those proposed by the European Medicines Agency (EMA) in their 22 November 2012 paper EMA/590745/2012, "Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems."[11] It was also of interest to examine whether the root causes identified by the survey correlated with top compliance citations from global inspection activities.

Role of Quality and Health Authorities in Relationship to Drug Shortages

The survey invited respondents to allocate 100 points across 15 diverse issues, weighting each to represent the extent to which they believed the issue contributed to the actual drug shortage or near miss that was their point of reference for responding to the survey. For sterile products, Health Authority issues collectively received the highest allocation (25.6%), followed by Quality issues (22.5%). For non-sterile products, Quality issues (16.3%) were closely followed by "Other/unknown" (16.2%), then Health Authority issues (14.2%) and Active Pharmaceutical Ingredient from third party (11.2%).

While it is clear that an effective quality system and strong GMP profile remain essential to preventing shortages, respondents indicated that inspections and, to a lesser extent, product registration are significant factors in drug shortages, particularly for sterile products. See **Figure 14** below.

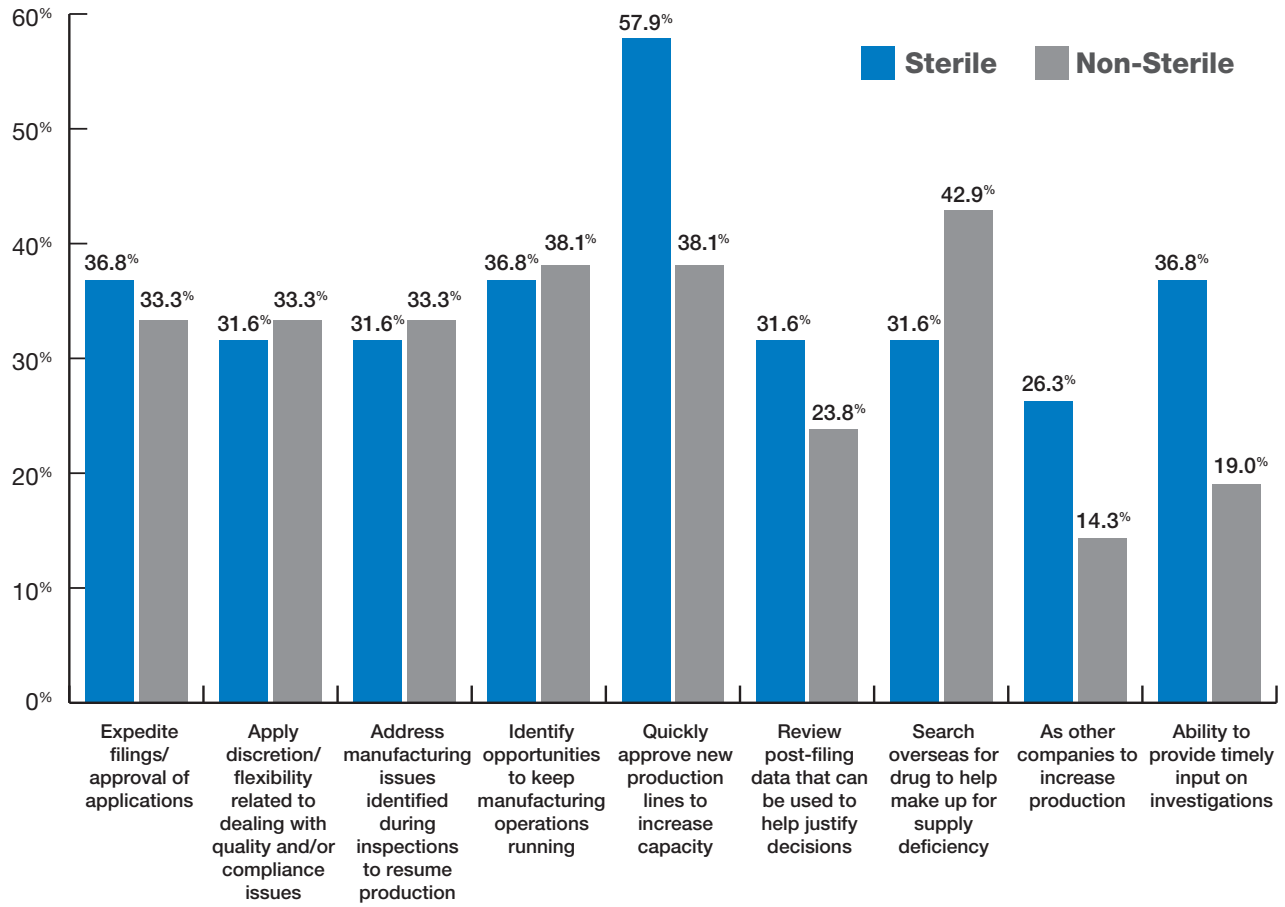
Figure 14: Factors Contributing to Drug Shortage and Near-Misses



In addition to the quantitative data in Figure 14, respondents who perceived health authority inspection-related issues to be a contributing cause to drug shortages and near-misses shared more specific information in response to open ended questions concerning this issue. We then reviewed both the quantitative data and the verbatim comments and analyzed them as a whole.

This analysis revealed that companies experiencing shortages and near-misses perceived that the level and quality of communications with regulatory bodies could be improved. In the case of sterile production this applied most when approving new production lines to increase capacity (57.9%). In the case of non-sterile production it applied most when identifying opportunities to keep manufacturing operations running and when approving new production lines to increase capacity (38.1% in both cases). **See Figure 15.**

Figure 15: Percentage of Respondents who Felt the Level and Quality of Interaction with Regulators Could Be Improved in Defined (or Similar) Areas



Based on the survey responses, it would appear regulators' activities are not currently optimal from the perspective of industry professionals involved in preventing or ameliorating drug shortages. Consistently, a third of respondents in this survey found that the quality and level of interaction between their company and the regulators could be significantly improved

The study also provided valuable industry commentary on the different approaches being taken by regulators. For example, in the February 2013 Federal Register Notice, the US FDA requested information from companies in order to better understand what can be done with respect to the use of metrics to help improve overall quality, the development of redundancy in manufacturing operations, enabling expedited review of regulatory submissions, expediting inspections, exercising enforcement discretion, and working to improve overall communications with the Agency to improve ability to reduce impact of drug shortages.[12] Through this study and related activities, ISPE received and provided comments to the Agency as requested, and the Society has constituted a separate task force to consider these topics in greater depth.

In its recent Reflection Paper, the EMA is proposing to, "Promote better and proactive risk management by Marketing Authorization Holders (MAHs) by requiring submission by all MAHs of a risk-analysis of their manufacturing process identifying any weaknesses and, depending on the severity, [to] provide a contingency plan and proposals to strengthen the identified weaknesses." The EMA also proposed to develop international cooperation so that there is sharing of information on specific shortages as well as on best practices in risk management and prevention strategies. ISPE believes our survey provides unique insight that could be considered as part of this initiative and that it would provide stimulating substrate for international discussion.

Relationship Between Inspection Findings and Drug Shortage Manufacturing/Quality Root Causes

In order to understand how the root causes identified by the survey respondents that led to drug shortages or near-misses compared against the most common inspection observations cited by the authorities, two comparative analyses were conducted. The first was against FDA warning letters, and the second analysis was against information produced by a workshop held by the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Co-Operation Scheme (PIC/S) in 2011.

A comparison of the most frequently cited 21 CFR 211 subparts in warning letters versus the survey root cause results showed that Records and Reports, Production and Process Controls and Laboratory Controls were the most frequently cited sub-parts by the FDA in their warning letters between 2010 and 2012. The sub-sections within both of these latter sub-parts were identified as major root causes from the survey results. However, Packaging and Labeling Controls, which was also identified as a significant root cause from the survey (see Figure 5 above), was not very frequently cited by the FDA in their warning letters.

PIC/S held a workshop in November 2011[13] on the similarities and differences in the top GMP deficiencies cited by PIC/S members. Deficiencies or problems in facilities, and production systems and laboratory control (quality control), are ranked highly by both our survey and PIC/S. Within facilities, there are also some parallels between the survey and PIC/S: facility design and cleaning are two examples. However, packaging and labeling is not a top cited GMP deficiency.

Areas for Future Development and Exploration Related to Interaction with Regulatory Authorities

The survey data suggest that there is opportunity for Industry and Regulators to work more closely together to prevent or recover from drug shortages. The survey asked, "In your opinion what has been your experience regarding regulators' ability to help avoid/mitigate a potential drug shortage issue by helping to execute/facilitate the following activities?"

As shown in **Figure 15**, more than a third of respondents felt the level and quality of interactions with health authorities regarding key regulatory strategies such as the expediting of filings and flexible approaches were in need of improvement. Even greater opportunities for working together would seem to exist in the areas of rapid approval of new production lines and the timely input on investigations. Between 38.1% (non-sterile) and 57.9% (sterile) of respondents indicated the level and quality of interactions with authorities could be improved in these areas.

Respondents' perceptions of the level and quality of interactions with regulators concerning sterile and non-sterile products were about the same in five of nine areas surveyed. In the other four areas, significant perception gaps were revealed between respondents working with sterile products and those working with non-sterile products. The figures below represent the percentage of respondents who indicated a need for improvement in these areas:

- **Quickly approving new production lines to increase capacity** – 57.9% sterile versus 38.1% non-sterile, nearly a 20% gap as noted above.
- **Ability to provide timely input on investigations** – 36.8% sterile versus 19% non-sterile, a 17.8% gap.
- **Requests for other companies to increase production** – 26.3% sterile versus 14.3% non-sterile, a 12% gap.
- **Search overseas for drugs to help make up for supply deficiency** – 31.6% sterile versus 42.9% non-sterile, an 11.3% gap.

The reasons for these gaps and their significance should be explored further.

Further discussion will be needed to understand the quality-related issues no matter if self-identified by the company or resulting from inspection findings. The goal will be to determine ways proactive sustainable quality, compliance, and continual improvement can be achieved. The discussion should also include regulatory filing requirements as to how they can become streamlined and harmonized to facilitate this goal i.e. is the burden for filing Chemistry, Manufacturing and Controls (CMC) changes too burdensome and time consuming to facilitate timely improvements then factored with different requirements from multiple health authorities.

VI. Conclusions, Implications and Recommendations

Consistent with information published by health authorities,[14] respondents to the ISPE Drug Shortage Survey identified that manufacturing-quality issues (quality) were among the most prevalent causes leading to drug product shortages (both sterile and non-sterile drug products). Not unexpectedly, no single technical or manufacturing root cause for drug shortages was identified. Common themes emerge, however.

The survey gives clear evidence that there is scope for industry and regulators to review and improve current working practices. For example, a collection of best practices to drive standardization and harmonization should be considered to help expedite the process of identifying solutions to overcome shortages. Specifically,

- Work is needed to identify a process that would allow firms to quickly identify alternative mechanisms needed to overcome a potential shortfall.
- The merits and value of building redundant capacity need further evaluation, since the survey results were inconclusive with respect to this strategy.
- Industry and regulators need to identify methods to help improve overall communication and opportunities for industry and the authorities to work together to enable more rapid approval of new production lines and the timely input on investigations. For example, for those drugs identified to be at risk of facing a shortage, steps could be taken to identify mechanisms to improve overall communication and in turn define any difference in the regulatory expectations for manufacturing and quality.
- Work is needed to identify proactive steps for continual quality improvement and to align these steps with efforts to harmonize various regional requirements for CMC filings and GMP interpretation.

The ISPE Task Force concurs with the survey findings that the implementation of an effective quality system, consistent with the ICH Q10 guideline, is likely to be one of the most significant factors that can prevent or mitigate drug shortages. While the ICH guideline defines the components of a comprehensive quality system, it does not help in its implementation. There is clearly scope for industry-led guidance, developed in collaboration with regulators, to assist in the establishment and operation of an effective quality system.

Next Steps

As stated elsewhere, this report is intended as a high level overview of the key findings of ISPE's drug shortages survey. Data analysis continues and further findings will be presented or published in the future. For example, sterile and non-sterile products show clear distinctions in the perceived causes of drug shortages, and some of these differences were unexpected. The Task Force will continue to explore this area to discern which differences may hold promise for mitigation strategies across product types. In addition:

- ISPE will organize a global industry-regulatory network to engage in discussion on the findings of this survey and to encourage dialogue, innovation and enhancement of current manufacturing and regulatory practices, as well as to provide technical and scientific support to further harmonization efforts for quality requirements. ISPE will continue to leverage the subject matter expertise in its Communities of Practice, Regulatory Compliance Committee and the Product Quality Lifecycle Initiative. This provides the opportunity to continue and add to our education program and technical documents to the benefits of health authorities and our Members who produce these important pharmaceuticals. These teams will report annually on discussions and progress at the ISPE Global Quality Week events each June.

- ISPE will collect additional information from its Members and present a White Paper to regulators describing Members' perceptions about approaches to streamlining regulatory approvals. This might result in improved quality and, potentially, a more reliable supply of medicines. One important area of focus for Members' comments could be about potential ways to streamline regulatory approvals of new equipment which might have a significant impact on mitigating drug shortages.
- ISPE will convene meetings of industry leaders through the International Leadership Forum (ILF) and other collaborative groups to discuss the survey findings related to corporate governance and leadership as well as the establishment of metrics that could help to predict potential shortages.
- ISPE will use its education resources in the areas of training, certification, publishing and networking to continue to raise awareness on the importance of critical success factors and best practices throughout the lifecycle to ensure all stakeholders are fully informed and equipped for success.

ISPE thanks all those who contributed to the development of the survey, and to those individuals and companies that provided responses. We look forward to continuing collaboration towards achieving our aim of an enhanced science and risk-based approach to the prevention and mitigation of drug shortages across the globe.

To learn more about ISPE's Drug Shortages initiative visit:
www.ispe.org/drugshortages
or download this report:
www.ispe.org/drugshortages/2013JuneReport

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End Notes

1. *See* Letter from U.S. Department of Health and Human Services, U.S. Food and Drug Administration to U.S. House of Representatives, Committee on Oversight and Government Reform (July 23, 2012).

2. *See, e.g.*, Kweder & Dill, *Drug Shortages: The Cycle of Quantity and Quality*, Clin Pharmacol. Ther., at 245 (2013) (stating that drug shortages in the United States are becoming more severe as well as more frequent); Press Release, EMA, European Medicines Agency provides plan to help deal with manufacturing-related medicines shortages (Nov. 26, 2012) (stating the occurrence of shortages of medicines has increased over the past few years), http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001663.jsp&mid=WC0b01ac058004d5c1 (last visited Apr. 8, 2013).

3. *See, e.g.*, Kweder & Dill, *supra* note 1 at 246 (reporting that majority of U.S. drug shortages in 2011 involved sterile injectable products); Woodcock & Wosinska. *Economic and Technological Drivers of Generic Injectable Drug Shortages*, Clin Pharmacol. Ther., at 170 (2013) (stating that sterile injectables constitute lion's share of current U.S. drug shortages); Letter from U.S. House of Representatives, Committee on Oversight and Government Reform to FDA (Mar. 13, 2013) (describing federal oversight of shortages of generic injectable drugs).

4. *See, e.g.*, Kweder & Dill, supra note 1 at 247 (reporting that quality issues caused approximately 46% of all drug product shortages in 2011).

5. European Medicines Agency; "Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems." (Nov. 22, 2012). http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf

6. Biotechnology Industry Organization, Comments to FDA Docket FDA-2011-N-0690: CDER Approach to Addressing Drug Shortages (Dec. 23, 2011). http://www.bio.org/sites/default/files/2011-12-23%20BIO%20Drug%20Shortages%20Comments%20FINAL.pdf.

7. European Association of Pharmaceutical Full-line Wholesalers, Reflection Paper: Medicines shortages in Europe and their impact on patients (Feb. 2013). http://girp.eu/cms/index.php/eng/content/download/4225/21115/file/Medicines%20shortages%20reflection%20paper%20including%20exec.%20summary%20FINAL.pdf.

8. The Task Force also has not attempted to determine the relative frequency of the many causes of drug shortages.

9. As part of this survey, ISPE also gathered information on respondents' personal experiences with drug shortages from the point of view of a patient or consumer. The analysis of that information is out of the scope of this report since it does not pertain to the root causes or mitigations for drug shortages.

10. The ISPE Survey defined the following six systems in the survey: (1) Quality System; (2) Facilities and Equipment System; (3) Materials System; (4) Production System; (5) Laboratory Control System; and (6) Packaging and Labeling System. See FDA's Compliance Program Guidance Manual 7356.002 – Drug Manufacturing Inspections Program.

11. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf

12. Federal Register/Vol. 78, No. 29 /Tuesday, February 12, 2013/Notices Page 9928 (http://www.gpo.gov/fdsys/pkg/FR-2013-02-12/pdf/2013-03198.pdf)

13. Hans Smallenbroek, Boon Meow Hoe, PHARMACEUTICAL TECHNOLOGY Volume 36, Issue 4, pp. 135-137 (http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=768876)

14. *See e.g.*, U.S. Food and Drug Administration (FDA) Basics Webinar on U.S. Drug Shortages dated Sept. 20, 2011 (citing 54% of drug shortages in 2010 for injectables were due to product quality/significant cGMP issues), http://www.fda.gov/AboutFDA/Transparency/Basics/ucm272223.htm