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# Drug Shortages

An exploration of the relationship between U.S. market forces and sterile injectable pharmaceutical products: Interviews with 10 pharmaceutical companies

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PricewaterhouseCoopers was commissioned by Pew to conduct the research presented in this report. The report's conclusions are based on the data captured during the interviews with the participating companies.

## For further information, please visit:

<http://www.pewtrusts.org/en/research-and-analysis/collections/2014/11/drug-shortages>

<http://www.ispe.org/drug-shortages-initiative>

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# 1. Overview

National drug shortages, defined by the U.S. Food and Drug Administration (FDA) as a period of time when the demand or projected demand for a drug within the United States exceeds the supply of the drug,<sup>1</sup> remain a complex and multilayered issue in the U.S. health care delivery system. For the period 2011-14, FDA announced that there were 456 instances of drugs in shortage,<sup>2</sup> a circumstance that can cause adverse outcomes for patients, including substitutions (alternate drugs) or modifications to treatment. In addition, the U.S. Government Accountability Office (GAO) reports that 6 out of 10 health care associations say the situation is static or worsening.<sup>3</sup>

Drug shortages result in nearly \$230 million in additional costs annually for hospitals because of the higher costs of substitute drugs.<sup>4</sup> The majority of the shortages—more than 72 percent<sup>5</sup>—were in the sterile injectable category, and the affected product categories or therapeutic classes ranged from anti-infective and anesthetic drugs to cardiovascular and oncology treatments.

The importance of preventing drug shortages, and the need to identify solutions, is evident from a July 2016 GAO report, which determined that multiple factors—including quality, manufacturing complexity, speed of regulatory reviews, decreased margins of certain drugs, and inventory-related issues—were associated with creating shortages.<sup>6</sup>

A number of papers have examined drug shortages with a key focus on the quality-related root causes behind supply interruptions.<sup>7</sup> For example, the International Society for Pharmaceutical Engineering (ISPE) conducted a survey of its membership and found that compliance, together with manufacturing and product quality issues, represented the single most important factor leading to drug shortages.<sup>8</sup> And although other papers have explored the root causes of shortages outside of quality,<sup>9</sup> this report explores the market dimensions and investments influencing supply chain and business continuity decisions, and their relationships to drug shortages.

The Pew Charitable Trusts and ISPE (Pew/ISPE) launched a research collaboration to identify the multidimensional set of drivers behind shortages of sterile injectable drugs in the U.S. and to find out whether the decisions companies made to reduce risks of future shortages were influenced by correlations between drug shortages and elements other than quality-focused factors. The collaboration included the exploration of elements related to market uncertainties and product margins; supply chain network design; demand forecasting; and relationships between manufacturers and key stakeholders, including purchasing organizations and regulators. The results are presented in this report.

The study examined the following factors:

- **Market forces.** Aspects such as demand fluctuations, market uncertainties, the introduction of replacement products, and margins that inform a company's ability to make investments in systems and facilities that can add more and/or redundant manufacturing capacity to address shortages.
- **Business continuity planning.** Decisions and plans that drive the ways companies design and structure their manufacturing networks to reduce the risk of supply interruptions by identifying backup manufacturing facilities, building new manufacturing lines within existing facilities, and/or establishing dual-source suppliers to react quickly to sudden, unexpected spikes in demand.
- **Supply chain management.** Capability of a company's inventory management, demand planning, and forecasting accuracy to enhance the organization's ability to proactively avoid a supply interruption by aligning the predicted demand volumes with the material inventory levels needed.

This study was designed to identify insights into the contributing factors behind shortages and the suggested areas for further exploration. The study was not designed to produce a statistically significant sample, given that the main objective was to understand key trends and identify the directional focus for future research.

More than 50 executives from 10 companies that collectively manufacture a mix of branded, branded-generic, and generic products participated in the research. The findings result from discussions with those executives, driven by a set of questions developed by Pew and ISPE, and also from 29 drug shortage examples, cited in the report as “reference products,” that the participating companies provided during the discussions.

The terms “companies” and “participating companies” are used interchangeably throughout this report. Similarly, “shortages” and “drug shortages” are used interchangeably.

Refer to the [appendices](#) for details on the research methodology, participating companies and executives, interview questions, and reference products.\*

## Summary of findings

Study results indicated that quality-related compliance issues are not the only factors driving the high number of shortages. The following are also key elements identified by these 10 companies:

- **Market withdrawals.** Market withdrawals, which reduced the number of manufacturers supplying a drug to the market, played a role in causing shortages. Companies highlighted a number of reasons that may have encouraged one or more manufacturers to exit a market, and therefore reduce the number supplying a drug to that market: quality issues, the introduction of replacement drugs into the market, and company decisions to realign a portfolio to focus on products with either greater margins or a higher risk of shortage. *Refer to section 3.1 for details.*
- **Supply chain design.** Companies identified the need to enhance their overall supply chains and in particular plan for and meet the estimated demand for a product by coordinating processes involving sales, demand planning, inventory management, and production. And even though companies said they had taken steps to build additional capacity—such as backup manufacturing or identification of dual-source suppliers—into their respective supply chains, not all products received the same level of manufacturing redundancies. Instead, companies established levels of redundancy based on manufacturing complexity, return on investment, and impact on patients if a shortage occurred. *Refer to section 3.2 for details.*
- **Purchaser-manufacturer incentives.** Companies said they needed incentives, either in the form of guaranteed-volume contracts or the ability to retain contracts, to mitigate the risks of making investments to prevent shortages. They said a lack of such incentives prevented them from entering a market to resolve a shortage issue or build the systems needed to prevent shortages. *Refer to section 3.3 for details.*
- **Limited market insights into future demands.** Without accurate information about the expected demand for a product, especially low-volume, low-margin products, companies felt reluctant to invest in setting up additional manufacturing capabilities to protect against future shortages. Participating companies commented on the need to improve both internal operations, such as sales and operations planning or demand forecasting, and the accuracy of external systems and programs they depended on for the market landscape information (such as how long a competitor would be out of the market). *Refer to section 3.4 for details.*

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\* The cumulative sales volume of the sterile injectable products manufactured by the participating companies reflects the overall composition of the U.S. injectable market. *Refer to section 5.1 for details.*

- **Managing regulatory expectations.** Companies said regulatory challenges contributed to shortages given the timescales and costs incurred in order to obtain approval to expand manufacturing capacity or upgrade a piece of equipment. They said the risks of a shortage increased when these regulatory challenges dissuaded them from making changes, especially to products developed 10 to 20 years ago, that might help meet an anticipated increase in demand. *Refer to section 3.5 for details.*

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The study results indicate that, in addition to improvements in product and manufacturing quality and current Good Manufacturing Practice (cGMP) compliance, drug shortages could be reduced with improvements in internal-demand-forecasting abilities; overall supply chain maturity; and the relationships between a manufacturer, a provider, and regulators.

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## 2. Quality issues continue to be a driving force behind shortages

For the purposes of this report, “quality issues” are a combination of cGMP compliance violations and matters related to product development or manufacturing that led to lower-than-expected product yields. These issues remained a primary contributor to shortages; of the 29 reference products reviewed for this report, 13 (45 percent) experienced shortages due to quality issues.

Examples of quality issues that contributed to shortages include:

- A company experienced delays in getting regulatory approvals for a drug because of quality issues identified during an FDA inspection of the manufacturing site.
- A product’s active pharmaceutical ingredient (API) manufacturing site was subject to quality gaps that caused a delay in production.
- There were FDA violations as a result of the company’s final product contract manufacturing site not following certain cGMP regulations.
- Issues arose in the transfer of the product from development to commercial manufacturing, reducing the product yields.
- Delays occurred in developing and transferring the analytical methods needed to support the transfer of a legacy product (a drug typically developed 10 to 20 years ago) to a new manufacturing site.

Participating companies said these quality issues created vulnerabilities across a product’s supply chains, from manufacturers of active pharmaceutical ingredients, components, and final products. This included both internal and contracted manufacturing units. All the companies said they had curtailed the manufacturing of a product at some point in order to address a quality issue, resulting in a shortage.

In addition, participating companies said they had withdrawn a product from the market at some point in order to deal with a quality issue.

Seven of the 10 companies said they were discouraged from upgrading the facilities and equipment needed to meet cGMP requirements by the high costs of doing so—which, in turn, led to quality problems. This was especially true, they said, for low-margin, low-volume products and legacy products developed 10 to 20 years ago.

When asked to comment on opportunities to reduce quality issues, nine companies said they had systems in place to communicate risks to quality across the manufacturing facilities. However, these systems were reactive in nature, reporting only issues that had already occurred. They proposed improving systems to proactively identify issues before they lead to shortages, and offered the following examples of such proactive systems or processes:

- **Periodic risk assessment reviews.** Reports that identify the potential compliance risks across a company’s manufacturing supply chain.
- **Trending reports.** Studies that review past supply chain data trends to forecast potential issues and trigger additional risk assessments.
- **Issue management communication system.** A method that communicates the potential compliance risks across an organization’s functional groups and external partners.





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Companies also commented on the need to improve their process and analytical methods development programs in order to ensure more robust technology transfers to commercial facilities, which improves the opportunity to consistently demonstrate conformance to the established product specifications.

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### 3. Multiple factors outside of quality contributed to drug shortages

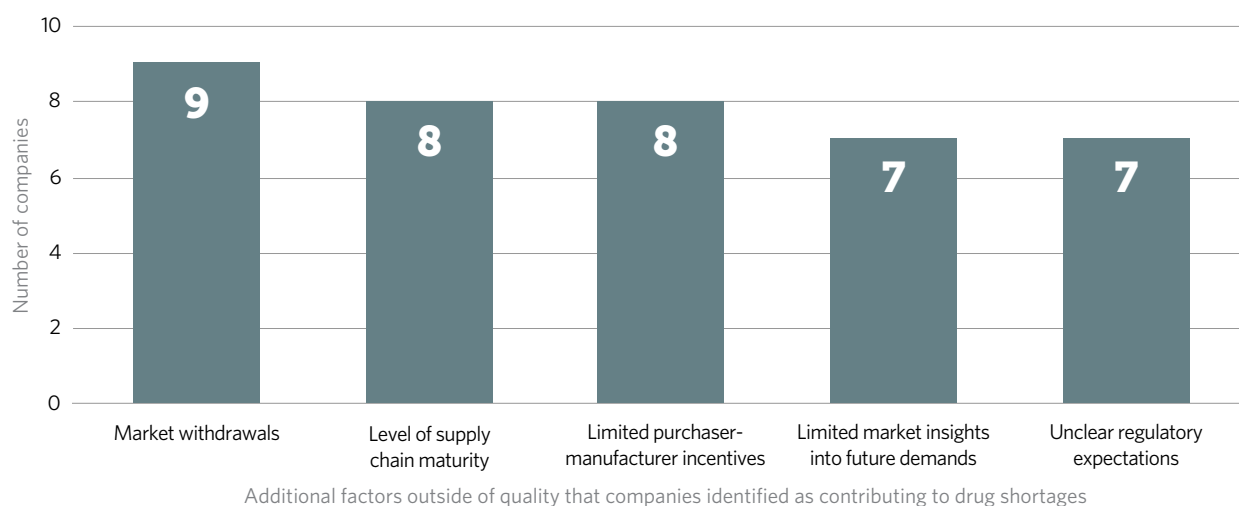
The interviews indicated that no single predictor identified whether a product was at risk of a shortage. Companies identified a set of issues outside of quality that contributed to drug shortages, including the inability to ramp up production when a competitor leaves the market. Other factors cited were lack of purchaser-manufacturer incentives that would benefit manufacturers when they could produce the product needed to meet demand and prevent a shortage.

Finally, companies also cited operational-related elements such as their ability to design predictable, flexible, and redundant supply chains that react quickly to changing demands and/or problems with specific manufacturing sites; predict future demands by improving market insights; and navigate regulatory expectations.

Companies' responses are summarized in Figure 1 and further discussed in sections 3.1 to 3.5.

Figure 1

#### Factors Cited by Companies That Contributed to Drug Shortages, Other Than Quality



Note: Results derived from responses by 10 companies that participated in the survey. Companies answered the question, "What were other factors, besides quality, that led to drug shortages?" The respondents identified multiple elements; therefore, there are more than 10 responses.

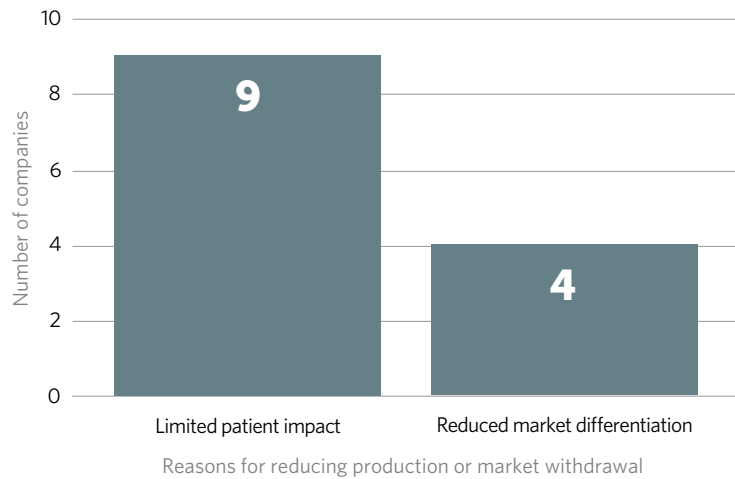
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### 3.1 Market withdrawals

Companies were asked for factors that could lead to a reduction in production or withdrawal from the market. The reasons identified, other than quality, are illustrated in Figure 2.

Figure 2

#### Factors Other Than Quality That Companies Said Contributed to Whether a Product Would Be Withdrawn From the Market



Note: Results derived from responses by 10 companies that participated in the survey. Companies answered the question, “What factors contributed to a manufacturer’s decision to reduce production or withdraw a product from the market?” Respondents identified multiple elements; therefore, there are more than 10 responses.

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Nine companies said patient impact (influenced by the number of replacements on the market) was a major factor they considered before exiting a market or deciding not to invest in additional facilities and/or equipment. The companies said that investments made to prevent drug shortages were not exclusive to high-margin products and that they would evaluate investments to help protect low-margin products from shortages, especially for drugs that had only limited replacements on the market. But they said that if a product had multiple replacements, meaning that patients’ needs could be met by other manufacturers, they would limit investments and potentially withdraw a product from the market. All the companies noted that they prioritize the production of legacy products that have no replacements on the market, even when products had low margins and low sales volumes, since continuing to produce the legacy product would limit the potential impact on patients and also protect the company’s brand.

The companies noted, however, that even the existence of multiple suppliers does not negate the potential of a shortage, since each manufacturer could experience difficulties in ramping up operations when a competitor withdrew from the market.

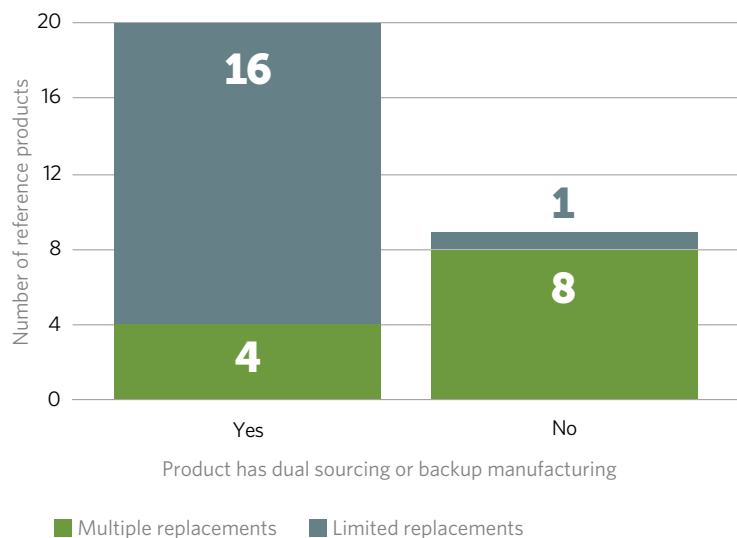
Four of the companies indicated that their emphasis had shifted from dual sourcing and backup manufacturing options for products to a network with limited sourcing and fewer manufacturing options when products went off patent.

And four of the companies said that they adjusted their portfolios by looking for higher-margin options should the market differentiation and associated margins for their products be reduced. This finding is consistent with the July 2016 GAO report finding that prices and profit margins declined for generic drugs as the number of suppliers increased, leading suppliers to exit the market.<sup>10</sup>

### 3.1.1 Reference product examples of drug shortages of sterile injectable products: Influence of replacement products

During the interviews, companies said they were less likely to invest in a backup manufacturing facility and/or a dual-source supplier when replacement products were available (Figure 3).

Figure 3  
**Comparison of Whether Reference Products Had Dual Sourcing and/or Backup Manufacturing Based on the Availability of Replacements**



Note: Results derived from 29 reference products for which shortages occurred. Figure 3 may suggest the effect of the availability of replacements in the market on manufacturers’ decisions to invest in redundant systems (dual sourcing and/or backup manufacturing) for their products; that is, those with multiple replacements were less likely to have redundant systems.

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The analysis also indicated that the ability of another firm to replace a product that goes into a shortage may be a more significant factor than sales volume as a predictor of a company’s investment in redundant systems.

- Sixteen of the 20 reference products with dual-source or backup manufacturing had limited replacements, suggesting that companies prioritized their risk-mitigation strategies and applied them to products that would have larger impacts on patients if shortages occurred. Five of these products had limited replacements and sales of less than \$10 million, suggesting that companies were willing to invest in adding the redundancies needed to protect patients from shortages.
- Eight of the 9 products that did not have dual-source or backup manufacturing had multiple replacements, indicating that these manufacturers did not invest in dual-source or backup manufacturing because the impact to the patient would be low if these companies had a supply issue.



We would invest in a low-margin product that had no alternatives to protect unmet patient need in the market.”

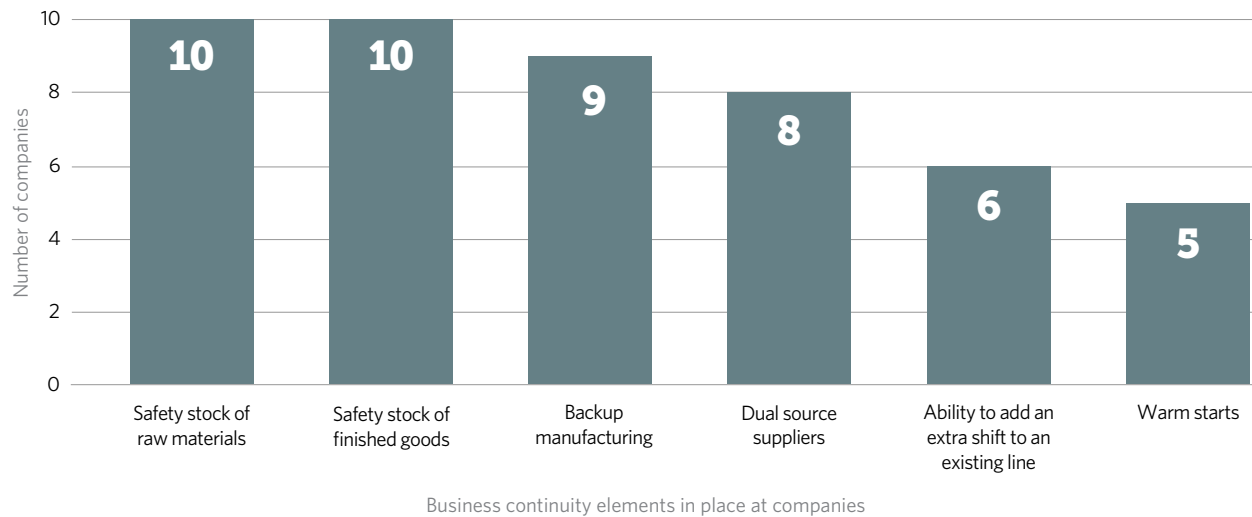
Supply chain team, *small pharmaceutical company*

### 3.2 Supply chain design

Companies said they reviewed and identified gaps across the supply chain management processes and in turn identified areas for prevention of future shortages. These companies identified the following business continuity elements involved in protecting against a sudden and unexpected demand for a product. Each company had in place at least one type of business continuity plan for reducing the risk of a supply interruption (Figure 4).

Figure 4

#### Business Continuity Elements Identified by Companies for Protecting Against Shortages



Note: Results derived from responses by 10 companies that participated in the survey. Companies answered the question, “What elements make up the business continuity plans?” Respondents identified multiple elements; therefore, there are more than 10 responses.

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The companies said they did not implement these elements in a standardized and consistent manner across various products; instead, they select the appropriate business continuity element for products in their portfolios based on the product characteristics, the investment required, the impact on patients, the length of time needed to ramp up operations, or the technical complexity of the manufacturing process.



We must structure our business continuity plans in a way that best meets the market characteristics of each product. Revenue is just one dimension we consider in identifying, developing, and applying business continuity plans for each product.”

*Vice president, global supply chain, large pharmaceutical company*

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Companies described the elements of their business continuity plans as follows:

- **Safety stock of raw materials.** All companies said they maintain buffer or extra stocks of raw materials, such as excipients (inactive ingredients) and vials needed to meet rapid and unexpected increases in product demand.
- **Safety stock of intermediates and finished goods.** All companies said they store backup inventory of finished products at their packaging sites to protect against unexpected product demand. Eight companies said they also maintain backup inventory of key drug intermediates. All companies said that calculating these safety stocks is an area that could be improved.
- **Backup internal and external manufacturing facilities.** Nine companies each had two or more facilities in place to manufacture final products. The remaining company did not invest in backup manufacturing for products that required dedicated facilities, a decision that the company made based on the expected rate of return and limited sales volume anticipated for the products.
- **Dual-source suppliers.** Eight of the companies had second-source suppliers in place to provide the components, vials, stoppers, and raw materials needed to manufacture final drug products. But the companies highlighted that despite having this safeguard in place, they still experienced supply interruptions due to their suppliers’ quality issues.
- **Ability to add a shift to an existing manufacturing line.** Six companies had processes in place to swap the manufacturing of one product with one at risk of a shortage. The companies noted that this strategy risked creating a shortage for the product that was replaced.
- **Warm starts.**<sup>†</sup> Five of the companies applied warm-start strategies to one or more of their products to protect against future shortages. Such warm starts enabled a company to ramp up operations at a contract manufacturer to help meet unexpected and sudden surges in demand. When asked why more companies did not take that approach, all, including the ones that practiced warm starts, said the resources needed required significant investment. As a result, companies found they had to limit this approach to drugs that had annual sales of more than \$10 million or more than 50 percent market share. This was confirmed when looking at the 29 reference products. Of the 29 reference products that experienced a shortage, only eight had warm-start agreements in place. And those eight had either annual sales of more than \$10 million or market share of more than 50 percent.

Some product classes, such as antibiotics, hormones, and/or cytotoxic drugs, may require dedicated manufacturing facilities, an added challenge for these products. Six of the companies said manufacturing facilities requiring segregated, self-contained, or specialized lines prevented the establishment of redundant capacity due to the investments that would be required for products where demand might not be stable on an annual basis and

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<sup>†</sup> Warm start is used typically with contract manufacturing organizations (CMOs) to initiate manufacture of the finished dosage form of a product in a short amount of time. Companies said that to accomplish it, they had established (i) contracts in advance and (ii) qualified lines, along with trained staff for the products to be manufactured. Warm starts require that companies commit volumes to a CMO so that it keeps in place the processes for manufacturing a drug on short notice as well as trained staff to run the operations.

might have low margins. When companies were asked what additional steps they took to protect against supply interruptions when dealing with these dedicated manufacturing facilities, all said they invested in improving the equipment and/or expanding the manufacturing lines.

Given that all 10 companies had business continuity plans in place, they were asked why shortages were still an issue. Example responses cited include:

- The company's backup supplier experienced quality issues, suggesting that manufacturers need to do a better job of measuring and monitoring the quality systems that they and their suppliers use to guard against such failures.
- While the manufacturer had backup systems in place, it was challenged with ramping up backup lines quickly enough to avoid interruptions due to the inability to get information that more supply would be needed.
- The manufacturer built the backup capabilities after it faced a shortage. And even after these were in place, the ability to prevent shortages was challenging due to issues with forecasting demand.
- The risk of a shortage might be calculated incorrectly because of ineffective processes used to predict demand, and, as a result, the appropriate business continuity plan might not be applied to a specific product. *Refer to section 3.4 for details.*

### 3.2.1 Supply-chain-related cost reduction strategies.

Manufacturers of low-margin or end-of-market-life-cycle products were asked what supply chain strategies they used to achieve lower costs and stay competitive. When a branded product nears the end of its life cycle, it is nearing the end of its patent. For a generic, the end of the life cycle is when the product starts to compete with an increasing number of products, which drives down the price of that generic. Such manufacturers provided the following responses:

- Seven of the companies said they either relied on a single-source strategy or purchased products from a single vendor. The lack of a backup supplier put the products at risk of shortage.
- The same seven companies also said they sourced raw materials and components from low-cost countries, adding that they had experienced product shortages as a consequence of this supply strategy.
- All the companies said they used contract manufacturers. Of the 29 reference products, shortages in six cases were caused by quality issues that led to a supply interruption at the contract manufacturing sites.
- All the companies said they shifted the manufacturing of at least one low-margin product to a low-cost country in order to lower costs for the U.S. market and open up domestic capacity for the manufacture of higher-margin products. They said they experienced shortages of the low-margin products because of issues at the manufacturing facilities in the low-cost countries.

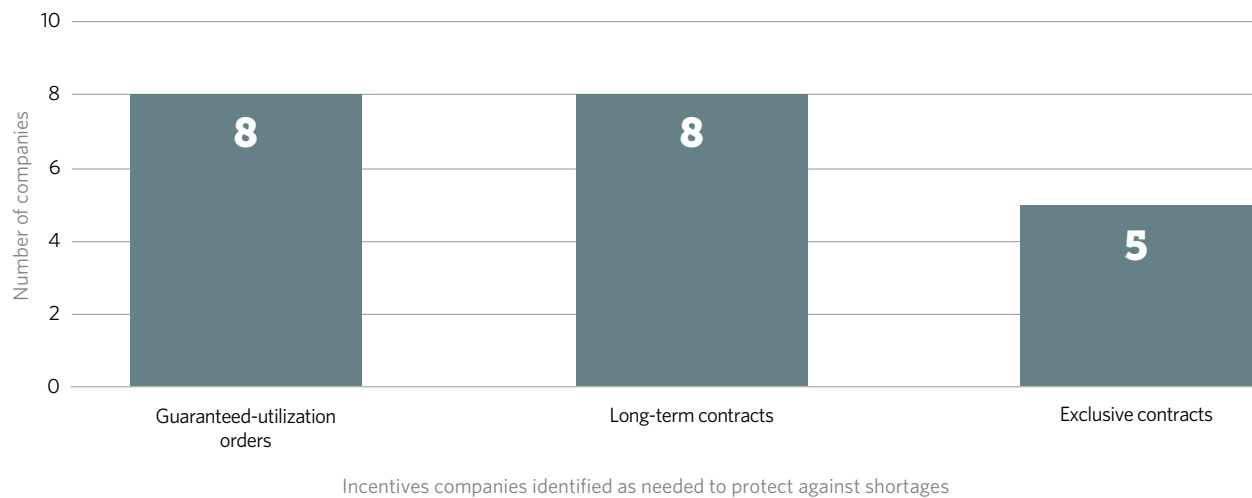
Eight companies said they typically applied these strategies to products with multiple replacements, since the potential impact of an interruption would have a limited impact on patients.

### 3.3 Purchaser-manufacturer incentives

The companies said that because they worried that sales volumes would end up lower than predicted at the time they made decisions to expand capacity, the lack of purchaser-offered incentives in the form of long-term contracts or volume guarantees deterred them from making the investments needed to prevent future shortages. Figure 5 shows the incentives companies discussed during the interviews.

Figure 5

#### Incentives Companies Identified That Would Help Reduce the Risk of Future Shortages



Note: Results derived from responses by 10 companies that participated in the survey. Companies answered the question, “Are there other mechanisms purchasers can or should take advantage of to recognize and reward supply reliability and supply resiliency?” Respondents identified multiple types of mechanisms; therefore, there are more than 10 responses.

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- **Guaranteed-utilization orders.** Eight companies said that if Group Purchasing Organizations (GPOs) were to provide guaranteed-utilization orders (a commitment to order a specific amount annually) to manufacture lower-margin, lower-volume products, they could reduce shortages of those products, especially those without predictable demand. They added that guaranteed orders could provide the incentives companies need to invest in backup facilities or new manufacturing lines as a way to protect against potential shortages. None of the eight currently has guaranteed-utilization orders.

The remaining two companies said they did not think guaranteed-utilization orders would help, since such orders might lead to reduced competition.

- **Long-term and exclusive contracts.** Companies with branded products said they had long-term contracts with GPOs but that the contracts were not exclusive and did not include volume purchase agreements. Eight of the companies said they would likely invest in building additional manufacturing capacity if they had long-term contracts in place. Of the two remaining companies, one said such contracts might prevent other firms from entering the market, because of the challenge of winning new business. The remaining company had no opinion on this question.



Five of the companies said they would like to see exclusive contracts put in place to provide them with the financial incentives needed to develop mitigation strategies and backup manufacturing capacity. One of the participants in the cohort said exclusive contracts might not help because such contracts might prevent competition. The remaining participants did not offer comments about the use of exclusive contracts.

While the study focused on identifying ways to prevent future shortages, companies also pointed out that an incentive would help reduce the length of a shortage.

- **Retention of contracts.** Five companies said they were less likely to increase production of a drug in shortage by adding or repurposing a line at an existing manufacturing facility because of the likelihood that they would not retain contracts when the competitor's product returned to market. The companies said they should be able to maintain contracts they were granted to manufacture a drug during a shortage, for a time agreed upon by both parties in advance. Four of the companies identified situations in which they had taken over a contract to address a shortage caused when a competitor stopped manufacturing a product. However, when the competition came back online, the contracts reverted to the competitor, leaving the company that reduced the time of the shortage to write off unused inventory.

The remaining five companies felt that retaining contracts was not an option since the purchasing organizations, responsible for buying the products, would want to maintain their flexibility when it came to negotiating prices.

### 3.4 Limited market insights into future demands

The research examined the ways companies anticipated demand and identified and mitigated potential risks, including the need for a sudden increase in production in order to meet a shortfall caused by another manufacturer. This included understanding the supply chain management practices (sales and operations planning (S&OP), inventory management, and forecast accuracy) companies followed for predicting and anticipating demand. All the companies said they applied S&OP to meet expected demand for a drug. However, eight said their respective S&OP processes needed improvements to drive better coordination between the group responsible for communicating expected demand and the one needed to manufacture the drug.



We can achieve much of our ability to avoid shortages by improving our internal processes—specifically, the ones connecting our sales organization with the manufacturing group.”

*Director, procurement, large generics company*

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Companies referred to improvements in demand forecasting, cross-functional interaction, and collaboration with GPOs as levers to optimize the S&OP processes. Two of the companies said no changes to their S&OP processes were needed because they were effective in predicting and meeting demand.

Results from the interviews indicated that improvement by companies of their ability to gain market insights would help them better predict demand and reduce the risk of shortages. Seven companies said they received insights into market trends from purchasers or distribution partners. In addition, they commented on their internal efforts to conduct analyses of the market so they could identify the product levels needed to meet demand.

Four of these companies said they needed improvements in the accuracy and timeliness of information they receive about shortage durations and the number of manufacturers looking to enter or exit the market to address shortages, which would help them anticipate unexpected market demand and make decisions about the investments needed to address shortages. Overall forecasting improvements would also contribute to the sector's collective ability to provide a steady supply of products.

The better the systems to highlight potential issues that could lead to a shortage, the more likely a company would be to decide to invest in the infrastructure to address it, especially for those products for which shortages frequently occur. Companies said a lack of information, or incorrect information, about shortages carried the risk that actions taken to expand capacity would lead to manufacturing lines they didn't use or to product inventory they would have to write off—especially legacy products with low volumes and low margins.

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“ There is no economic reason to continue manufacturing products that have low volumes and margins, but we do so to protect patients. But we can't do more to protect against shortages because we don't have accurate information on whether the competition will return and thereby reduce the value of our investment. ... For legacy products with low margins and low volumes, we have to know what the competition is doing so we can plan better and ensure a constant and reliable supply. Without that knowledge, we won't make the investments needed.”

*Product manager, large pharmaceutical company*

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### 3.5 Managing regulatory expectations: Legacy product challenges

Seven of the companies said regulatory hurdles that had to be overcome when expanding a facility or upgrading equipment further hindered their companies from investing. And because of either perceived or real challenges associated with developing backup manufacturing sites, companies with legacy products in their portfolios said they were less likely to invest in the backup capacity needed to protect against future shortages if those drugs had multiple replacements on the market.

Seven companies said they did not want to either incur the costs of submitting new or supplemental filings or risk current regulatory scrutiny and associated delays for taking actions required to upgrade a facility or the equipment.

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“ We're not sure we want to spend the money to qualify a new site—or even a new line—because of the regulatory guidelines we'd have to meet or the filings required that we'd have to submit.”

*Quality vice president, large pharmaceutical company*

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Companies commented that the time required to get an application approved also contributed to their decisions not to invest in the facilities or equipment that could prevent a shortage. This is consistent with the July 2016 GAO report findings that even with a prioritized review, the median approval time for an Abbreviated New Drug Application (ANDA) is over a year. The GAO concluded that prioritizing ANDA reviews to address drug shortages, while generally not a strategy for addressing shortages in the short term, could be a helpful approach if FDA is notified as early as possible about potential shortages.<sup>11</sup>

Six companies said they decided to limit investments in facilities manufacturing legacy products because of challenges with maintaining cGMPs—due mainly to each company’s need to understand the products’ development histories. These development histories were often not available for legacy products, either because of multiple company acquisitions or because the products were developed 10 to 20 years ago, creating challenges for companies when updating marketing authorizations to meet today’s regulatory expectations.

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“Manufacturers are invariably reluctant to make quality upgrades to packaging material or invest in a more expensive stopper or spend on new stability programs for legacy drugs that may not be moneymakers. Such investments are generally made for branded products, which are higher-margin drugs.”

*Head, corporate quality division, midsize pharmaceutical company*

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Companies also traced supply interruptions to issues with analytic methods they used for detecting impurities, saying they had decided not to revalidate the analytic methods—with their reasons ranging from high costs to concerns over the potential rejection of a resubmitted regulatory application.

The participating companies also highlighted the challenges in improving their process and methods development programs when the development histories for legacy products were not as robust as those of newer, more recently developed products.

These companies said that some form of regulatory discretion and increased collaboration would enable them to reduce the risk of a future supply interruption by building more resilient supply chains—including upgrading facilities, building new manufacturing lines, or adding new contract manufacturers in a more efficient manner, in particular for legacy products.

## 4. Conclusions and recommendations

Results from the interviews of more than 50 executives across 10 companies suggest that drug shortages result from multiple underlying factors, with quality issues paramount, and could be prevented or mitigated with specific improvements. The report's conclusions and recommendations are therefore that the industry should:

- A. Develop systems to proactively identify and resolve quality issues.** It was apparent from the interviews as well as a review of the 29 product examples that quality remains a primary driver behind shortages—one that the industry must address. Improvement opportunities should focus on strengthening quality and also development and implementation of systems that proactively identify, measure, and monitor risks across the manufacturer's overall supply chain. This includes cGMP compliance risks as well as issues that may develop when there are less than robust development and/or manufacturing processes in place. Manufacturers should be diligent in selecting suppliers and, when necessary, partner with them to help improve their quality systems.
- B. Understand the risks across the supply chain.** Despite uncertain market demands, companies should have (1) systematic approaches in place for evaluating the risks across their supply chains and (2) the ability to predict the amount of product needed. That would help them understand and apply the right mitigations across their portfolios by product type. These risk evaluations should look beyond a mere understanding of the compliance and specific individual product risks and instead be broadened to include a review across multiple dimensions. For example, ISPE's Drug Shortages Prevention Plan identified the following dimensions that should be reviewed to understand the risk of a potential shortage: corporate culture, quality systems, metrics, business continuity planning, communication with authorities, and building capabilities.<sup>12</sup>
- C. Improve market forecasts.** Industry, regulators, and purchasers must begin working together to improve the accuracy of the information related to the risk of a shortage that they collect and communicate. Without these market insights, companies are not making the investments necessary to expand facilities or upgrade equipment to create the additional manufacturing capacity that would protect against future shortages. The ability to predict a drug's expected demand is especially important since having multiple replacements for a product does not protect it from experiencing a shortage.  
  
Although companies won't share specific market strategy information with their competitors, purchasers, or even regulators, they need a system to improve the accuracy of volume predictions for annual manufacturing, especially when it comes to low-volume drugs that have multiple replacements and variable annual demand cycles. Companies would be more likely to build the mitigations they need to reduce the risk of shortages if levels of confidence in the information provided were to increase.
- D. Improve overall incentives between purchasers and manufacturers.** Purchasing groups should offer incentives such as long-term, exclusive contracts or guaranteed orders to motivate companies to invest in backup manufacturing facilities. The investments needed to build such facilities or develop dual sources can be significant, and incentives would help companies reduce the risk of building capacity they would not use.
- E. Improve collaboration with regulators.** While the companies said that relationships with regulators had improved, they also cited the need to continue identifying ways of addressing disconnects that limit the ability of the manufacturer—because of the time needed to obtain approval and implement changes—to expand capacity or invest in new equipment. In addition, a solution that enables a more effective way to update market authorizations for legacy products is needed. Putting such a solution in place would make it easier for manufacturers of these products to update their market authorizations and create the capacity needed to protect against shortages.

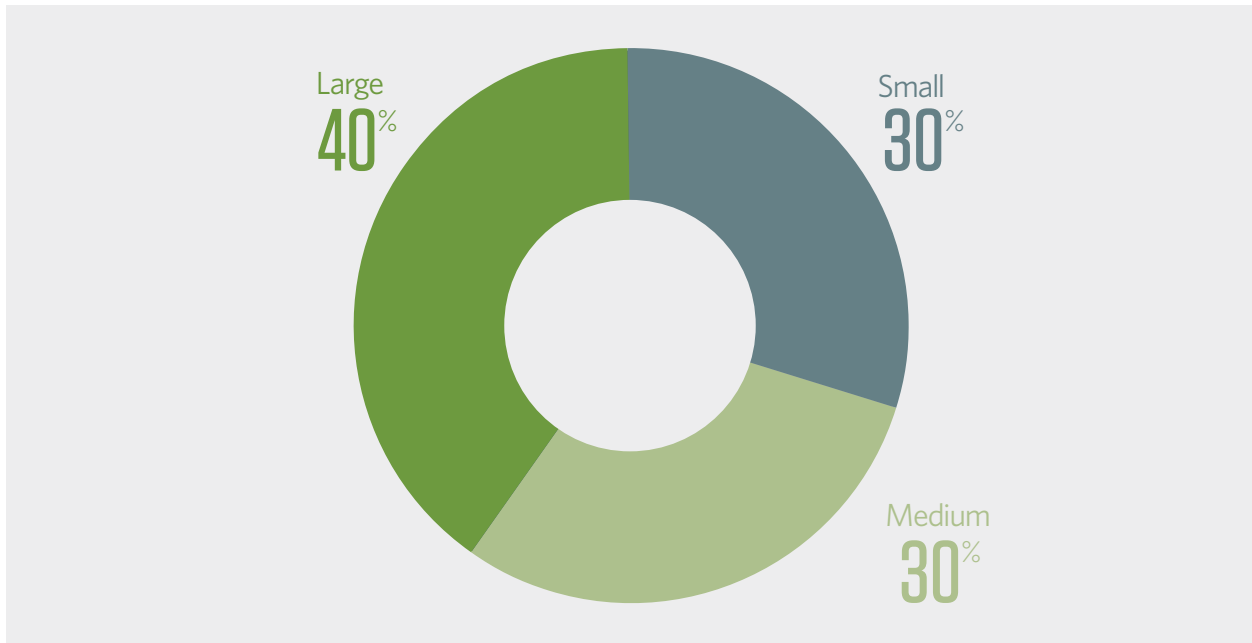
## 5. Appendices

### 5.1 Recruited companies' demographics

The cohort of recruited companies represented a mix of small, medium, and large companies. Figure 6 represents classification by company size based on annual revenue. Companies were defined by three revenue bands: small companies with revenue of less than \$5 billion; medium companies with revenue between \$5 billion and \$20 billion; and large companies with revenue of more than \$20 billion.

Figure 6

#### Cohort Classification by Company Size



Note: Results derived from responses by 10 companies that participated in the survey. When categorized by revenue size, four were large companies, three were medium, and three were small.

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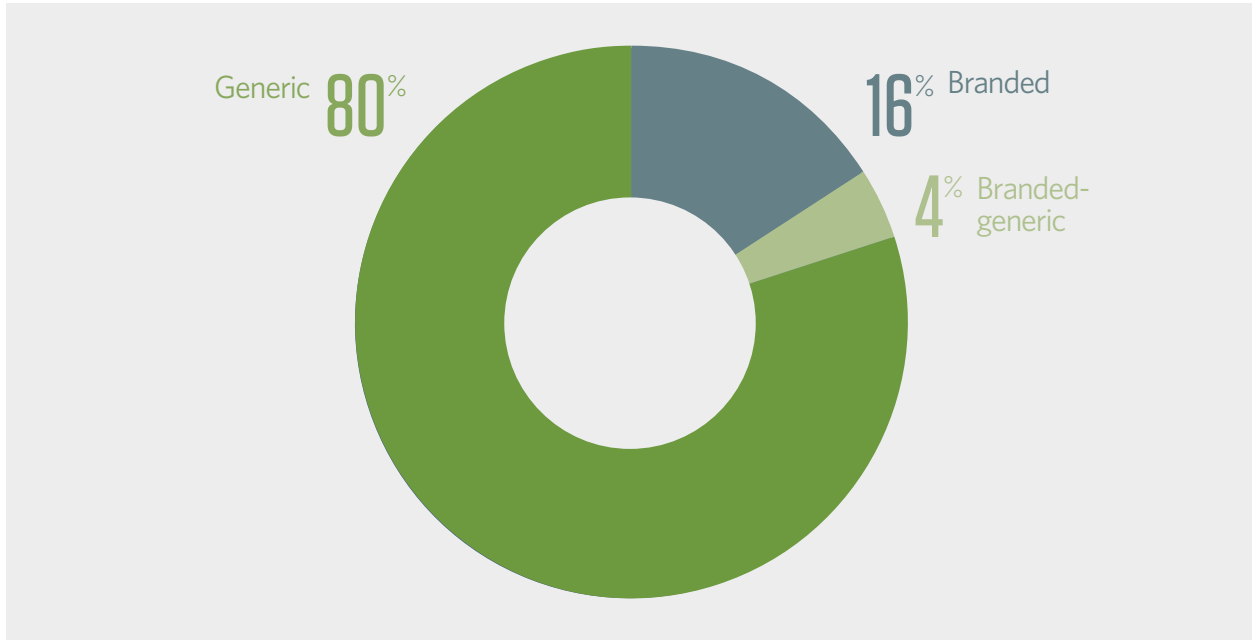
The product portfolios of the participating companies spanned therapeutic areas including cardiology, endocrinology, immunology, infectious diseases, neurology, oncology, and respiratory diseases.

The cohort of participating companies represented a mix of branded, branded-generic, and generic products (Figure 7).

Figure 7

## Cohort's Cumulative Product Sales (Volume) by Branded, Branded-Generic, and Generic Products

Injectable sales



Note: Results derived from responses by 10 companies that participated in the survey. Pie represents total product sales volume of all 10 companies, split by product type.

Source: IMS Health 2015 data

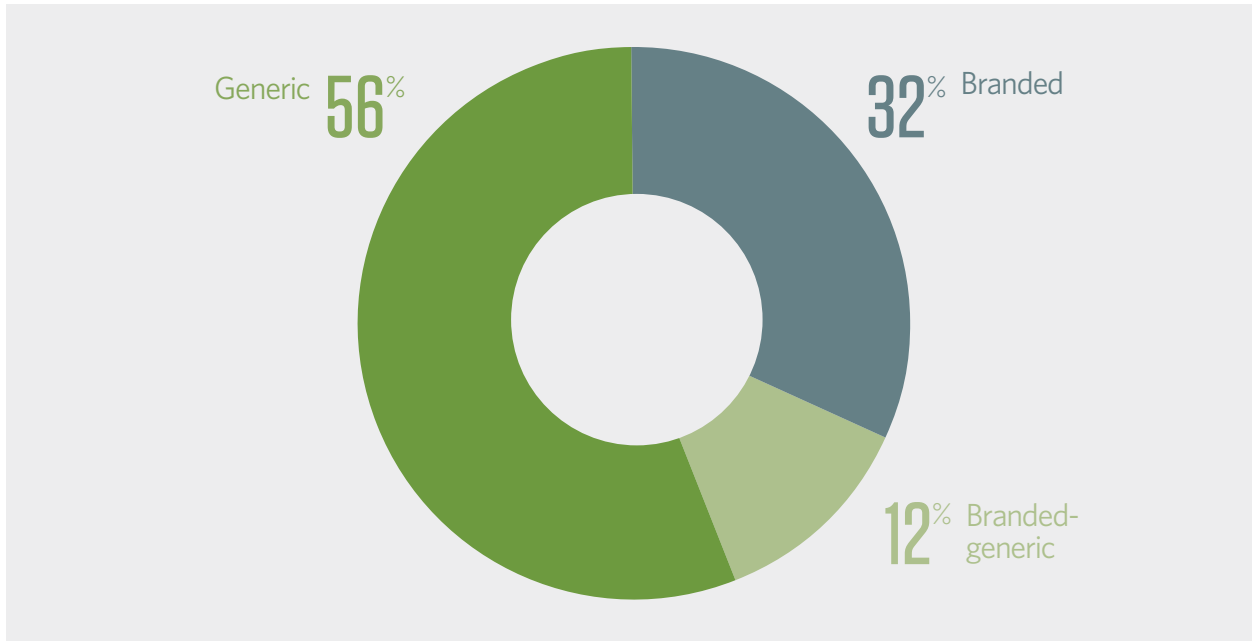
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The cohort of participating companies reflected the overall composition of the U.S. injectable market (Figure 8).

Figure 8

## Cumulative Product Sales (Volume) for U.S. Market by Branded, Branded-Generic, and Generic Products

Injectable sales



Note: Results derived from total industry sterile injectable product U.S. sales volumes for 2015, categorized by product type.

Source: IMS Health 2015 data

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## 5.2 Research scope and methodology

### 5.2.1 Research scope

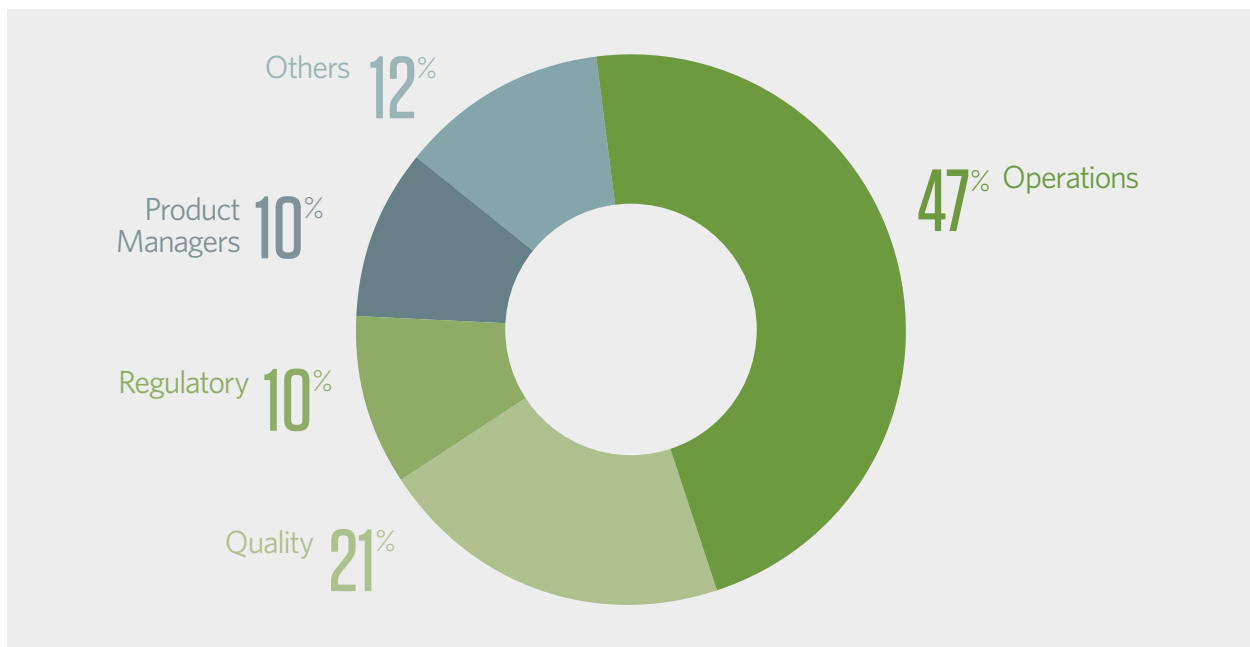
The Pew Charitable Trusts and the International Society for Pharmaceutical Engineering agreed to focus their efforts on the U.S. sterile injectable market because that particular type of product is most commonly cited on the U.S. Food and Drug Administration's Drug Shortages list.<sup>13</sup>

This report relies on FDA's definition of shortage: "A period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug. In general, the [FDA] Drug Shortage Staff focuses on shortages of medically necessary products that have a significant effect on public health."<sup>14</sup>

### 5.2.2 Research methodology

The research consisted of 51 interviews with 10 manufacturers of sterile injectable products sold in the U.S. market. To ensure a cross-functional perspective inside companies, participants interviewed consisted of decision-makers representing supply chain, regulatory, quality, sales, marketing, and manufacturing operations functions. Refer to Figures 9 and 10.

Figure 9  
Participants by Company Function

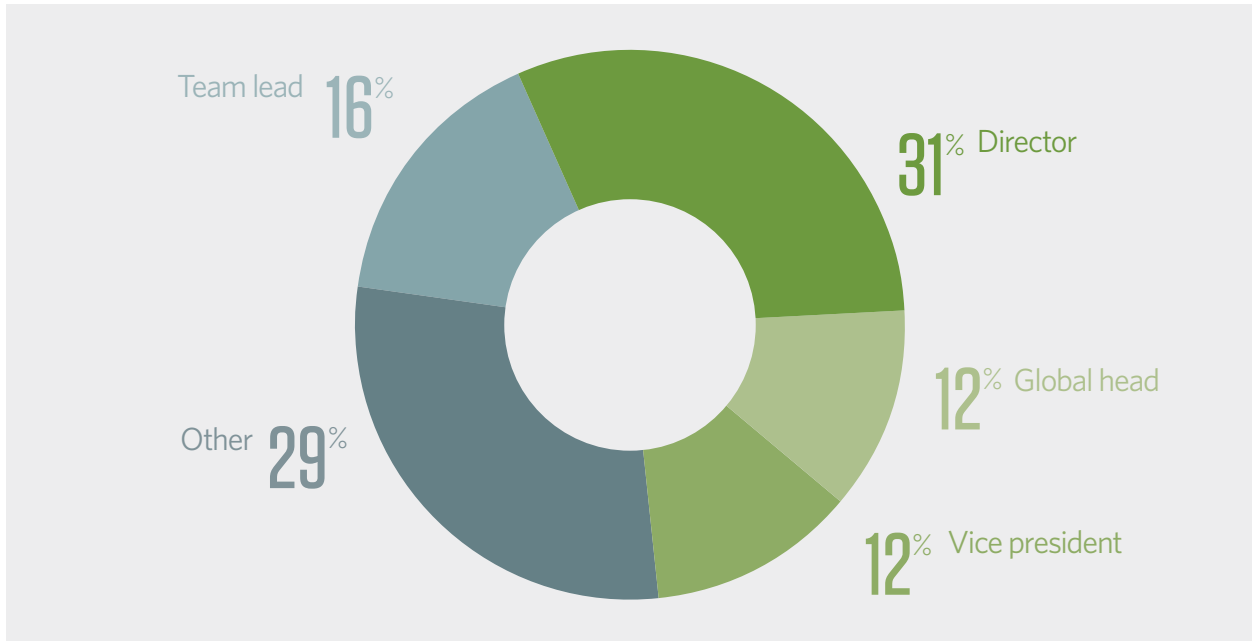


Note: Results derived from 51 participants surveyed, representing 10 companies.

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Figure 10  
Participants by Company Title



Note: Results derived from 51 participants surveyed, representing 10 companies.

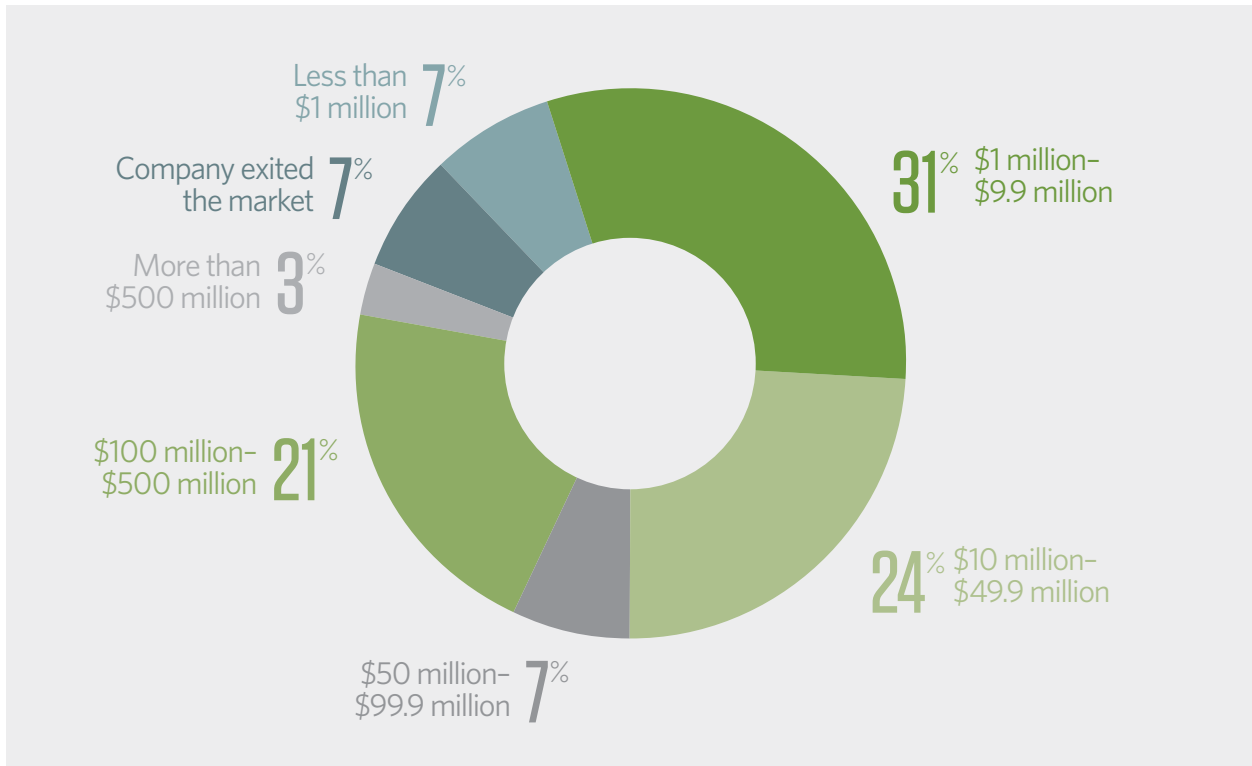
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The companies were also asked to give examples of drug shortages—referred to as products, or reference products, in the report—that they had experienced, and to comment on how market forces influenced supply chain and business continuity decisions. The 10 companies discussed 29 product examples in total, and the information was used to supplement responses from the interviews.

Figures 11 and 12 break down the reference product examples by revenue and product type, respectively.

Figure 11

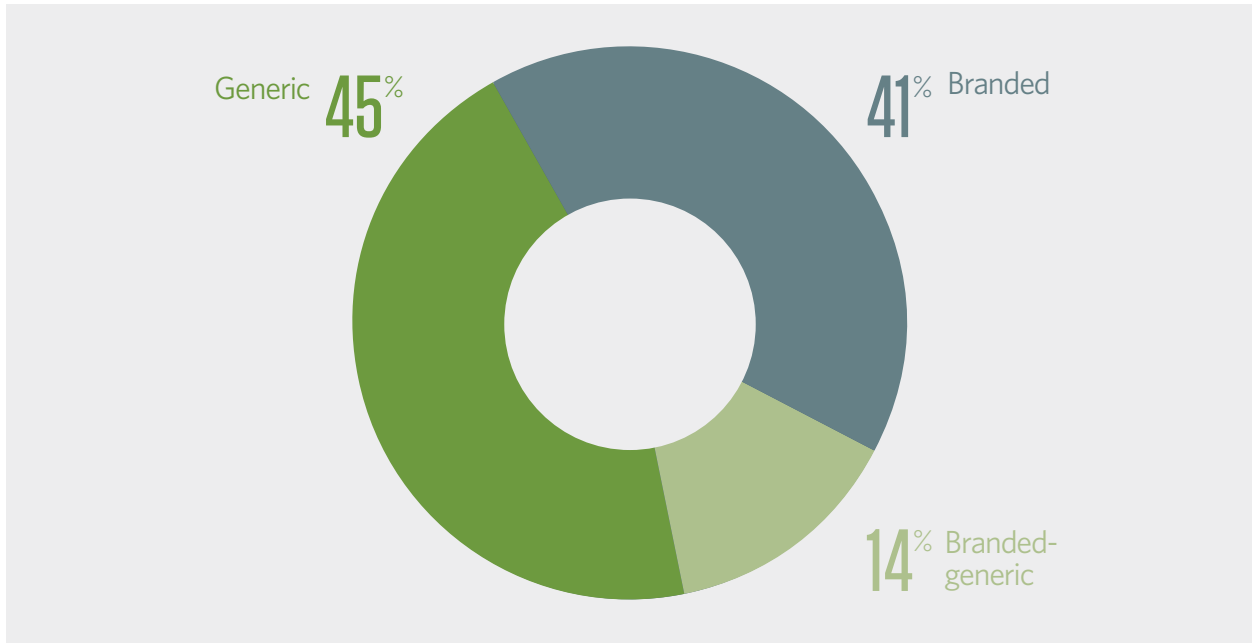
### Distribution of Reference Products Classified as Per-Product Revenue for the Respective Companies



Note: Results derived from 29 products for which shortages occurred.

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Figure 12  
Breakdown of Reference Products by Product Type



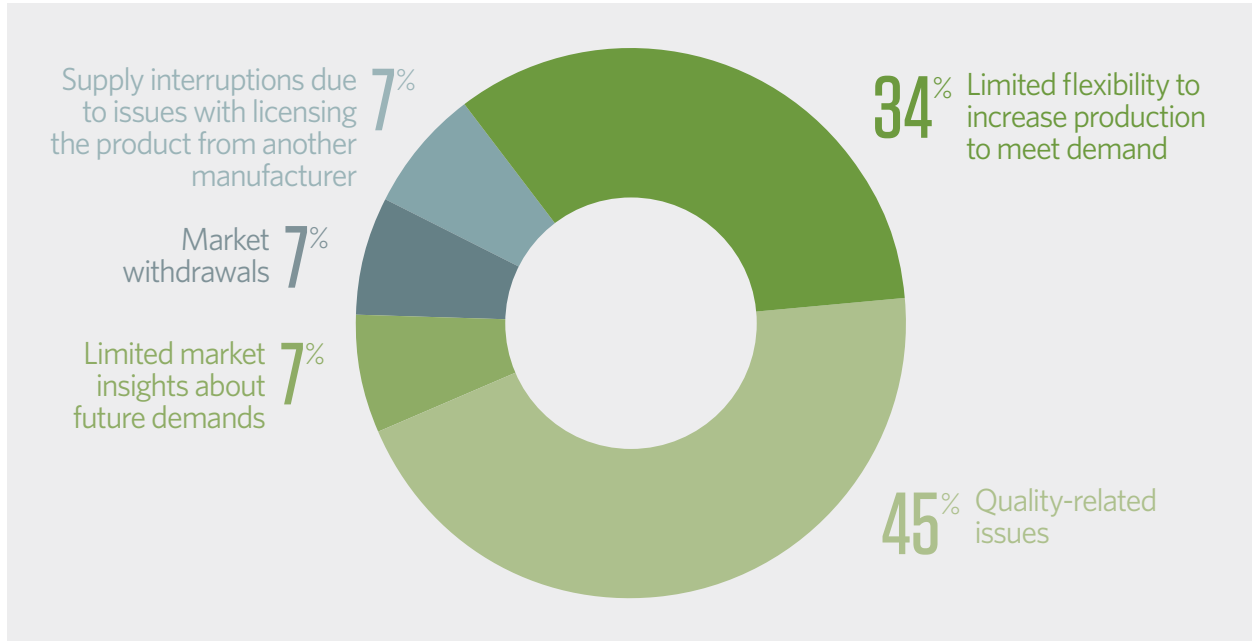
Note: Results derived from 29 products for which shortages occurred.

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Figure 13 breaks down the reference product examples based on the root cause behind the drug shortages.

Figure 13

## Distribution of Reference Products, Broken Down by the Factor That Led to the Shortage



Note: Results derived from 29 products for which shortages occurred.

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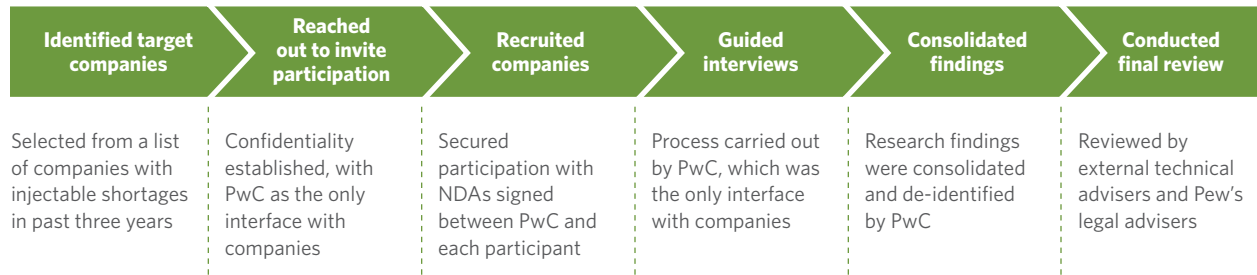
### 5.2.3 Recruitment process and confidentiality

Potential companies were identified through two methods. First, secondary research identified small-, medium-, and large-capitalization pharmaceutical manufacturers of branded and generic sterile injectable products sold in the U.S. market. Second, FDA's Drug Shortages Database identified companies that experienced shortages of small- or large-molecule sterile injectable products in the previous 48 months. The overall process used to identify and recruit the companies is illustrated in Figure 14.

Pew/ISPE secured the services of PricewaterhouseCoopers (PwC), to recruit companies, administer the research, analyze data, and maintain confidentiality. PwC developed a confidentiality framework to maintain the anonymity of participating companies and those companies' responses.

Figure 14

## Steps Followed to Ensure Confidentiality While Engaging With Recruited Companies



### 5.2.4 Research limitations

The collected data were intended to provide a snapshot of the sector's responses to, and handling of, drug shortages. The research, data collection, and analysis in the report focused on economic drivers unique to the sterile-manufacturing business model and did not examine government reimbursement policies, the role of wholesale distributors, or inefficiencies in the downstream distribution network due to external variants. Shortages attributable to unique and uncontrollable causes, such as sudden outbreak of epidemic, resulting in spikes in demand or natural calamities affecting business continuity are referenced when applicable but are not examined for detailed analysis.

### 5.2.5 Technical and legal review

The interview guide was subject to extensive technical review by Pew/ISPE. The report and its conclusions were reviewed by ISPE's technical advisers. The interview guide was reviewed by Pew's legal advisers.

## 5.3 Interview guide

Refer to section 5.1, “Recruited companies’ demographics,” for a description of the type of companies that participated in the study. Refer to section 5.2, “Research scope and methodology,” for a breakdown of the individuals (by title and function) who participated in the interviews.

Area	Questions—Section I
<p><b>Sales &amp; Operations Planning</b></p>	<p>In order to explore the relationship between the <b>incidence of supply interruptions and internal supply chain and business continuity practices</b>, we want to understand the complexity of the supply chain including trends in leveraging external capacity, enhanced flexibility in capacity utilization, and available registered spare capacity. Inventory management and sales &amp; operations planning practices are also a part of this. In terms of the essential demand planning and forecasting processes—</p> <ul style="list-style-type: none"> <li>• Does your company do business continuity planning?               <ul style="list-style-type: none"> <li>· Does your firm require business continuation plans to be in place for all products (Yes/No)?</li> <li>· If no, how do you prioritize which products have business continuity plans?</li> </ul> </li> <li>• If yes, how deep and elaborate/stratified are your BCPs?</li> <li>• Do you consider/include inactive/“cold” BCPs (i.e. just contract in place or capacity in place), or only active/“warm” BCP (i.e. contract plus capacity plus fully registered and operational)?</li> <li>• Which functions are involved in Sales and Operations Planning (S&amp;OP) process? Is it truly a cross-functional process (involves marketing, supply chain, production, finance, etc.)?</li> <li>• What are the key components of your business continuity plan? State a Yes / No for the following statements, if these are applicable to your S&amp;OP process:               <ul style="list-style-type: none"> <li>· Production plan: Estimated production volume is run through manufacturing plants and supply channels</li> <li>· Inventory plan: Inventory volume is planned for raw material (in plant) and finished goods (in distribution network)</li> <li>· Sales plan: Demand for supply is forecasted based on current and projected market factors</li> <li>· Financial plan: Budget is allocated for business operations, new investments, inventory, unplanned activities, etc.</li> <li>· Re-planning: Estimated sales and production are re-planned to respond to changes in market demand</li> </ul> </li> <li>• What are the key factors considered when investing in a new facility or equipment?</li> </ul> <p>Does your Sales and Operations Planning process consider the following factors:</p> <ul style="list-style-type: none"> <li>• Different demand scenarios (seasonal, uncertainty, forecast error). If yes, please respond to the following:               <ul style="list-style-type: none"> <li>· What approaches/methods/tools (e.g. statistical, targeted questionnaire, etc.) are used to forecast demand in your organization?</li> <li>· What factors or constraints are taken into consideration while planning demand?</li> <li>· How is production across different products and product categories prioritized? (Financial objectives, strategic intent, operational constraint—supplier, capacity, etc.)</li> </ul> </li> </ul>

*Continued on next page*

Area	Questions—Section I
<b>Sales &amp; Operations Planning</b> <i>continued</i>	<ul style="list-style-type: none"> <li>▪ Different production scenarios (supply reliability, supplier capacity, cycle time / lead time, capacity, low-cost). If yes, please respond to the following:               <ul style="list-style-type: none"> <li>· What factors are considered for sourcing from dual / multi suppliers (including CMOs)? Critical material, high-volume, risk profile of supplier base, etc.?</li> <li>· Are critical suppliers / CMOs (contract manufacturers, top 80 percent or sole suppliers of raw materials) involved in production planning?</li> </ul> </li> <li>▪ Investment in inventory (overall level, raw material, in-process and finished goods).</li> <li>▪ In terms of overall capacity strategy, does your organization adopt agile or flexible manufacturing? If yes, what levers are used to meet sudden or unexpected increase in demand?</li> <li>▪ Does your organization maintain registered spare capacity or do you maintain strategic inventory of key intermediates or finished products?</li> <li>▪ Does your organization maintain dual capacity for sole source or major market shareholder of medically necessary products?</li> </ul> <p>Company response to demand scenarios and associated challenges--</p> <ul style="list-style-type: none"> <li>▪ How has the overall demand scenario changed in the market over the past five years?               <ul style="list-style-type: none"> <li>· How has your company responded to those changes?</li> <li>· Are these short term responses in order to address immediate market shifts, or are they longer term adjustments and investments?</li> </ul> </li> <li>▪ List key challenges which have been faced by your company in forecasting demand, and how has your company managed those challenges?</li> </ul>
<b>Procurement &amp; Supplier Management</b>	<p>Knowing about S&amp;OP process and BCP of your company was helpful, now, we will briefly focus on the sourcing strategy, management of external capacity (i.e. contract manufacturers) or critical suppliers and practices to manage supply issues caused due to suppliers</p> <ul style="list-style-type: none"> <li>▪ How is the sourcing strategy (single, dual or multi supplier) identified for a particular material or commodity? For an identified manufacturing and production need?</li> <li>▪ Do supplier /CMO contracts in place provide sufficient guidance to suppliers /CMOs on notification of supply issues:               <ul style="list-style-type: none"> <li>· Suppliers / CMO are expected to proactively monitor supplies from the critical tier-2 suppliers</li> <li>· Suppliers / CMO are expected to timely notify you in case supply issues are foreseen</li> <li>· Suppliers / CMO will share risk (or gain) in case of shortage of supplies or coping up with fluctuating demand from the actual plan</li> </ul> </li> <li>▪ What are the typical actions (short-term &amp; long-term) taken in case of an incidence of supply issues from the suppliers / CMOs? What about for manufacturing and production needs</li> </ul>
<b>Inventory Management</b>	<p>We would like to shift the discussion on capabilities of your IT systems in maintaining visibility of inventory from end-to-end in your supply chain</p> <ul style="list-style-type: none"> <li>▪ Are IT systems integrated—purchasing (orders placed), manufacturing (WIP), warehouse &amp; distribution (FG inventory)—to provide real-time visibility in inventory? Do they track real-time status of all orders, shipments and sales?</li> </ul>

Area	Questions—Section I
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<b>Manufacturing Capacity</b>	<p>To understand internal operations at your company better, please throw light on your capacity strategy</p> <ul style="list-style-type: none"> <li>▪ What capacity strategy is being used at your organization – lead capacity, lag capacity and match capacity strategy? <ul style="list-style-type: none"> <li>· Does your facility operate on a single shift / 2-shift / 3-shift basis for the drug product that was short?</li> </ul> </li> <li>▪ Is registered spare capacity available?</li> </ul>
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Area	Questions—Section II
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<b>Purchasers' Behavior/Trends</b>	<p>In order to understand the relationship between the <b>incidence of supply interruptions and external market elements</b>, we want to explore the perceptions that purchasers do not value quality or cannot differentiate products based on production quality. Purchasers are a key step in ensuring that finished drug products are available in the market. We would like to understand the key aspects of dynamics between your company and purchasers / distributors</p> <ul style="list-style-type: none"> <li>▪ Do you have purchasing contracts in place with Group Purchasing Organizations (GPOs)? If yes, please provide the following information on your GPO contracts <ul style="list-style-type: none"> <li>· What is the average duration of the contracts?</li> <li>· Do these contracts establish volume purchase guarantees?</li> <li>· For a particular drug, does your GPO purchase only from you (sole-sourcing contracts) or from multiple companies (multi-sourcing contracts)?</li> <li>· Do these contracts have failure-to-supply clauses/penalties? If yes, can you provide details of the penalties enforceable in case of supply defaults?</li> </ul> </li> <li>▪ Do you receive insights into market trends and developments from your purchasers' i.e., distribution partners / customers?</li> <li>▪ What expectations do distribution/channel partners have with respect to supply chain resiliency and supply reliability? How do you manage those expectations?</li> <li>▪ Is there a minimum performance (i.e., supply chain resiliency and supply reliability) expectations set by your distribution / channel partners? If yes, please answer the following: <ul style="list-style-type: none"> <li>· Percent orders to be delivered on-time and full quantity</li> <li>· Percent rejection</li> </ul> </li> </ul>
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<b>Market Factors</b>	<p>Let's now discuss the significance of external market factors which may impact your market strategy and investment decisions, and the key things your purchasers' value the most</p> <p>Listed below are common market factors which impact companies' investment to increase production and add necessary capacity</p> <ul style="list-style-type: none"> <li>▪ Rank the following based on their importance in making these decisions and securing management approval: <ul style="list-style-type: none"> <li>· Impact on patient population</li> <li>· Timeliness of the regulatory approval process for additional capacity</li> <li>· Regulatory flexibility with changes to process or equipment/line</li> </ul> </li> </ul>
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Area	Questions—Section II
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**Market Factors**  
*continued*

- Short vs. longer term product demand predictability
- Unplanned event in market (sudden increase in demand, drop in supply from competitors)
- Timing of payback of investment, i.e., how important is profitability in making capacity increase investments?
- Others?
- Does your market strategy take the following into account? Please rank the following in importance to your business:
  - Percent market share
  - Change in market composition (new products, new players)
  - Influence of substitute products in the market
  - Strategic business decision due to increasing competition or reducing efficiencies, i.e., significant increase in COGS, price drop by competitor, etc.
- Do you think purchasers of your products value your ability to consistently meet demand and avoid shortages?
- In what way do they express the value they place on your ability to meet demand and avoid shortage?
- In your company’s experience, do purchasers differentiate for the superior supply reliability and supply resiliency of your products? That is, do purchasers put a premium on the enhanced supply reliability and resiliency of your products?
- Are there other mechanisms purchasers can or should employ to recognize and reward supply reliability and supply resiliency?
- Do you see a role for guaranteed-utilization orders for your products in the future, especially for products potentially at risk for short supply?
- Do you think purchasers of your products value quality investments that exceed minimum cGMP compliance requirements? If so, how do purchasers reflect the premium they put on this?
- What is the effect on quality investments in your company if purchasers do not recognize manufacturers that exceed minimum manufacturing practices?

Area	Questions—Section III
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**Margins**

- In order to understand the relationship between **low-margin products and internal supply / BCP practices as well as between high-margin products and internal supply / BCP practices**, we want to examine levels of investment in manufacturing process facilities and equipment, process improvement, appropriate infrastructure vs. routine levels of investment in manufacturing process facilities and equipment, process improvement, appropriate infrastructure. Profit margins are important driver for any company running a business. From a drug manufacturer’s point of view, how do the strategies differ for a low margin product vs. high margin products in terms of investments in quality, capacity utilization, optimizing product mix, etc.?
- What strategies do you implement to achieve or manage lower costs and stay competitive when it comes to low margin or “end of market lifecycle” products? State a Yes / No against each statement:
    - Reliance on single source to consolidate buying or low cost country sourcing
    - Shift manufacturing to low cost countries. Do you have a maximum percent cost of goods? If yes, can you indicate approximately?

*Continued on next page*

Area	Questions—Section III
<b>Margins</b> <i>continued</i>	<ul style="list-style-type: none"> <li>▪ Do you have a minimum gross profit margin as a percent of selling price? If yes, can you indicate approximately? <ul style="list-style-type: none"> <li>· Outsourcing / Contract based manufacturing</li> <li>· Others?</li> </ul> </li> <li>▪ Rank the following practices which are adopted in your company to manage or improve profit margins for low margin or “end of market lifecycle” products based on ease and impact? <ul style="list-style-type: none"> <li>· Optimization of product portfolio mix</li> <li>· Complete withdrawal from a region / market</li> <li>· Reduced investment or disinvestment of equipment / facility leading to improved financial viability</li> <li>· Others?</li> </ul> </li> <li>▪ What strategies do you implement to manage costs and remain competitive when it comes to high margin or high value products in the prime stage of their market or patent lifecycle? State a Yes / No against each statement: <ul style="list-style-type: none"> <li>· Reliance on single source to consolidate buying or low cost country sourcing</li> <li>· Shift manufacturing to low cost countries</li> <li>· Outsourcing / Contract based manufacturing</li> <li>· Others?</li> </ul> </li> <li>▪ Rank the following practices which are adopted in your company to manage profit margins for high margin or high value products in the prime stage of their market or patent lifecycle based on ease and impact? <ul style="list-style-type: none"> <li>· Optimization of product portfolio mix</li> <li>· Rebalancing or shift toward a dedicated region / market</li> <li>· Changes in investment levels of equipment / facility leading to improved financial viability</li> <li>· Others?</li> </ul> </li> <li>▪ What is more likely to dis-incentivize a company from producing a product, low profit margin or lack of predictable demand?</li> <li>▪ How do you distinguish between forecasting strategically and filling a short-term/immediate need?</li> <li>▪ Has the margin for “end of market lifecycle” products declined or improved over the past three years?</li> </ul>

Area	Questions—Section IV
<b>Market Withdrawals</b>	<p>In order to understand the <b>relationship between low-margin products and external market uncertainties</b>, we want to explore the likelihood of market withdrawal when encountering supply interruptions. Please help us understand your point-of-view on the drivers leading to market withdrawals; specifically those which your company may have experienced</p> <ul style="list-style-type: none"> <li>▪ Listed below are reasons that may lead to reduction / ceasing production or withdrawing from the market. Rank the following based on their level of impact on your company’s strategy: <ul style="list-style-type: none"> <li>· The need to address regulatory compliance / manufacturing quality issues at a site to continue production</li> <li>· Realigning of product portfolio because introducing new product (e.g., achieved FDA approval for a new drug), or releasing a new branded-generic drug</li> </ul> </li> </ul>

*Continued on next page*

Area	Questions—Section IV
<b>Market Withdrawals</b> <i>continued</i>	<ul style="list-style-type: none"> <li>· Little or reduced market differentiation—including product differentiation for products with similar profiles - is leading to lower margins</li> <li>▪ Is market concentration an issue for certain drug classes? If yes, what drug classes?</li> <li>▪ How do concentrated markets adjust for the inherent demands of sterile manufacturing production i.e., manufacturing production that requires specialized facilities and dedicated lines? In a concentrated market, has the net amount of production capacity changed, or contracted?</li> </ul>
<b>Facility and Equipment</b>	<p>In order to understand the <b>relationship between market uncertainties and supply chain and business continuity practices</b>, we want to explore levels of investment in manufacturing process facilities and equipment, and integration of supply chain with quality systems. Please educate us on the capabilities of your facility in terms of agility, change-overs, operational efficiency, etc. Also, tell us about the key issues which hinder you to increase agility, operational efficiency etc.</p> <ul style="list-style-type: none"> <li>▪ Is your manufacturing line dedicated for a single product or approved for multiple products?</li> <li>▪ Comment on the ease of change-over in your manufacturing facility. High, med or low.</li> <li>▪ If lines are completely dedicated, does that mean that you have limited agility i.e., ease of change-over.</li> <li>▪ When in a product's life cycle does the emphasis on high supply performance change?</li> <li>▪ Are there processes in place to help identify trends related to specific equipment failures? Or types of equipment categories? Failures that if detected earlier, could have avoided the supply interruption?</li> <li>▪ Do you have flexible production capacity for manufacturing the drug product which is short?</li> </ul> <p>Do you measure Overall Equipment Effectiveness (OEE) for key work stations on a monthly basis and what are the typical OEE levels?</p>
<b>Integration of Supply Chain with Quality Systems</b>	<p>We'd like to ask about the quality systems of your company and how wide a role they play in anticipating or detecting supply interruptions originating from quality / compliance issues</p> <ul style="list-style-type: none"> <li>▪ What are the key systems in place to help communicate compliance risks associated across manufacturing shop floor? (For example: Tools to detect and communicate issues with equipment that historically has had issues)</li> <li>▪ What are the key monitoring systems present in your manufacturing facility? If yes, how could they help in avoiding supply interruption? (For example, would these systems have been able to pick up signals earlier in the process that there were compliance related issues?) <ul style="list-style-type: none"> <li>· Reading early and/or routine signals</li> <li>· Assessing other signals or metrics</li> <li>· Subsequent mitigation strategies/actions based on analysis (i.e., quality metrics)</li> </ul> </li> <li>▪ Describe / identify improvements to the existing processes in place to pick up as well as communicate risks from the "shop floor to executive decision makers."</li> <li>▪ Describe cases where supply interruptions were traced back to issues with either: analytical method transfers, product transfers</li> </ul>

Continued on next page

Area	Questions—Section IV
<b>Integration of Supply Chain with Quality Systems</b> <i>continued</i>	<ul style="list-style-type: none"> <li>▪ Rank the following quality issues in causing supply interruptions based on the occurrence and likely impact:               <ul style="list-style-type: none"> <li>· Rejection due to poor tech transfer process (method)</li> <li>· Rejection due to operator error (man)</li> <li>· Rejection due to machine error (machinery)</li> <li>· Rejection due to outsourced material (material)</li> </ul> </li> </ul>
<b>Investments in New Facilities and/or Equipment</b>	<p>Lastly, we would like to know about what factors which influence decisions to invest in a new facility / upgrade existing one</p> <ul style="list-style-type: none"> <li>▪ Do you have network optimization strategy in place?               <ul style="list-style-type: none"> <li>· If yes, what are the key levers considered while optimizing manufacturing network?</li> <li>· If no, is it challenging for the management to identify capacity constraints early on in the process?</li> <li>· Point out areas where capacity was not utilized to the fullest - perhaps comment on why a product in short supply was not moved to a facility that could have absorbed the demand</li> </ul> </li> <li>▪ Rank the following factors to allow investment in upgrading equipment or facility based on the ease:               <ul style="list-style-type: none"> <li>· Improve productivity</li> <li>· Return on investment (high margin or high selling product)</li> <li>· New requirements (new products, changes, etc.)</li> <li>· Potential risk in meeting market demand</li> <li>· Regulatory compliance issues</li> <li>· Others?</li> </ul> </li> <li>▪ What factors contribute to investing in increased manufacturing capacity to ramp up production? Comment on issues that may have prevented management from identifying new manufacturing sources—whether internal or external due to regulatory expectations (e.g. contract manufacturing partners)</li> </ul>

## 5.4 Reference products database

Reference product number	Case study reference
1	Branded product went into shortage due to issues with the third party and with a component manufacturer. With limited market share, the company had chosen earlier not to dual-source its manufacturing (API or dosage form) or component suppliers. However, post shortage, company decided to invest in building additional in-house backup manufacturing capacity.
2	Competition went out of market because generic product was no longer grandfathered, and company did not want to invest the time and effort needed to get the product up to current standards. Company went into shortage because it was not prepared to absorb the extra demand since at the time it had very limited market share. Company did eventually build two additional lines to pick up demand.
3	Company worked closely with FDA to import product from another country. Although specifications were different, FDA worked with company to demonstrate it was safe for the U.S. market.
4	A relatively low-margin product with multiple competitors. Company had shut down manufacturing line to address quality issues, which in turn caused drug shortages. In this case, the quality team drove the decision that prioritized compliance issues.
5	Company is the only provider, and has a sole supplier and a dedicated manufacturing facility for the branded product. Product demand declined over the course of one year and due to the inability to ramp up operations the drug went into shortage due to manufacturing delays caused by API supply interruptions.
6	Company chose to not create redundancies because (a) there are alternative therapies, (b) company has chosen not to manufacture cytotoxic drugs in-house, and (c) demand for this product is relatively stable and of low volume. However, company has been managing to mitigate shortages by having six months of safety stock.
7	Shortage caused primarily by other manufacturers exiting the market over a one-year period, leaving participating company as the only manufacturer. Company had been running the facility at 100 percent utilization to meet demand, thereby making it susceptible to any manufacturing or supply issues that could cause drug supply interruptions, which it faced when a key supplier exited the market.
8	Company acquired a proprietary delivery system and experienced supply interruptions caused by delays in its tech transfer. In parallel, one of the other manufacturers had manufacturing issues and another chose to exit the market, causing the company to face an increase in product demand.
9	Participating company licensed the product from another manufacturer. Shortages were caused by supply interruptions in sourcing the product from the principal manufacturer. The product has had sharp declines in market volumes (over 80 percent in a two-year period), resulting in significant drops in manufacturing and in turn causing supply interruptions.
10	Generics company had continual issues with its third-party supplier, which was constantly plagued by quality issues, process improvement issues, and FDA warning letters. As a result, company decided to reduce reliance on suppliers and to build internal capabilities to manufacture additional batches.
11	Brief shortages due to labeling issues at multiple plants, with limited impact on patients. Company could not build backup manufacturing for its branded product because the manufacturing process was too complicated. But to help mitigate against shortages, company took steps to invest in building dual source and helping its API manufacturer build up capabilities.
12	Decline in supply from other manufacturers led to increase in demand and, in turn, drug shortages for this generic product. Another manufacturer had supply issues due to inflexible capacity, and another had product recalls due to contamination.
13	Reason for shortage was inaccurate demand forecasting, which had been performed through sales data and couldn't capture the increase in demand.

Continued on next page

Reference product number	Case study reference
14	The company sold the generic product to another manufacturer, resulting in disruption in drug supplies given the time needed to ramp up operations.
15	Company accounted for a major portion (>70 percent) of market share by volume, and it managed production with a dedicated API source and a manufacturing facility for the product. There was an increase in demand caused by exit of one of the other manufacturers and by manufacturing delays on the part of another manufacturer because of regulatory challenges. Company had to increase capacity at its backup manufacturing facility, and shortages were caused by delays associated with getting required regulatory approvals.
16	Shortage was caused primarily by production issues with another manufacturer. The market had three key players. The interviewed company experienced a reduction in market share and accordingly decreased manufacturing capacity.
17	Generic product went into shortage because of quality-related issues with the CMO. Other companies had to pick up demand while quality issues were being addressed. Given the potential loss in market share, company took steps to build up alternate capacity in-house.
18	Only manufacturer for the product. Company had to stop production at one of its sterile injectable sites after regulators observed major violations of good manufacturing practice. Impact was reduced by use of alternative sites, and shortage was soon resolved.
19	Company was in process of developing two additional generic sources of API to reduce dependence on current API manufacturer. Although sales were relatively small, the company took these steps because there were no alternative therapies on the market.
20	One of the manufacturers that had accounted for 25–35 percent market share exited the market due to challenges in sourcing the API. The exit caused an increase in demand and the company had to increase capacity to meet the resulting increase in demand.
21	The product had manufacturing and drug device issues that resulted in product recalls. The manufacturer had to make modifications resulting in drug shortages during that period.
22	Drug shortage resulted from another company's supply interruptions. In response to shortages, FDA requested that participating company build up capacity. However, the competition came back to market earlier than forecasted, leaving the participating company with two lines and not enough demand to meet capacity of even the first line.
23	Supply chain issues with limited API supplier base. Earlier in 2014, another manufacturer that accounted for 20–25 percent market share temporarily exited the market due to supply chain issues, causing an increase in demand, and the participating company had manufacturing delays in meeting that increased demand.
24	A low-margin product with low volumes. The company, with a relatively small market share, exited the market, creating an increase in demand for three other manufacturers.
25	The participating company faced a shortage and started looking for a second source.
26	Shortage was caused by issues with supply and demand. Product has a sole supplier, and supply was interrupted by manufacturing delays from API supply side. In addition, demand for the drug increased over the course of a year.
27	Decline in supply by other generic manufacturers led to increase in product demand and, in turn, drug shortages. One of the other manufacturers faced warning letters, and the other had product recalls due to contamination.
28	Participating company envisaged lower production needs given a drop in product demand over the course of one year and expected entry of another manufacturer the following year. However, an unexpected increase in product demand resulted in drug shortages. The shortages were resolved after the entry of the other manufacturer in second quarter of the next year.
29	Internal site dropped capacity for a branded product because of technical issues and competing resources with another product on the same line. During the same time, the CMO also had a major site failure, dropping backup capacity as well and in turn causing shortages.

## 5.5 Glossary

**Backup manufacturer.** A secondary facility (internal or external to the company) that can manufacture additional product to meet unexpected demand for a product.

**Branded-drug product.** A drug protected by a patent that can be produced and sold only by the company holding the patent.

**Branded-generic product.** A drug that is off patent and bioequivalent to the original product but marketed under a different brand name by another company.

**Business continuity planning.** Strategies a company uses to anticipate and mitigate risks to its supply chain and its ability to deliver product to customers on time.

**Capacity (manufacturing).** Highest sustainable output rate (maximum number of units/volume of drugs per period) that can be achieved with existing resources, maintenance strategies, and drug product specifications.

**Changeover.** Period required to prepare a machine, device, or process so that it can change from producing the last unit or last run of the last batch of a drug to producing the first unit or first run of the new batch of a different drug.

**Cold start.** A company's initiation of a contract with a manufacturer. Before manufacturing can start, a cold start requires a number of steps, including signing the contract, qualifying the labs, training the staff, and transferring the product to the contract manufacturer.

**Compliance issues.** The failure to fulfill the technical, legal, and corporate requirements and the regulations and practices that manufacturers are expected to comply with in order to produce and market products.

**Contract manufacturer.** Provides companies with outsourced pharmaceutical development and manufacturing services.

**Cost of goods sold (COGS).** Direct costs attributable to the production of goods sold by a company. The amount includes the cost of the materials used in the manufacture of a drug along with the direct labor costs of producing it.

**Current good manufacturing practice (cGMP).** Regulations enforced by the U.S. Food and Drug Administration that ensure proper design, monitoring, and control of manufacturing processes and facilities.

**Demand forecasting.** Major process a company puts in place to determine or anticipate future demands for a product. Forecasting methodology can take into account various factors such as age of product, competition, historical demand trends, therapeutic agent type, formulation type, manufacturing arrangements, patent life cycle, and anticipated sales.

**Drug shortages.** FDA defines a drug shortage as a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug. In general, the agency's Drug Shortage Staff focuses on shortages of medically necessary products that have a significant effect on public health.

**Dual-source supplier.** A secondary supplier that a company can use to gain access to excipients, inactive ingredients, or components needed to manufacture a product. Companies use such suppliers to protect against unexpected interruptions experienced by their primary suppliers.

**End-of-market-life-cycle product.** A branded product that is nearing the end of its patent. A generic product enters its end-of-market-life-cycle when an increasing number of products enter the market as competition.

**Excess capacity.** The additional manufacturing capacity a company can use to manufacture product to meet unexpected demand.

**Flexible production facility.** A facility that is better equipped to cope with planned or unplanned changes in volume, capacity, or capability.

**Generic product.** A drug not under patent and not marketed under a specific brand name but comparable to a brand drug in dosage form, strength, route of administration, quality, performance characteristics, and intended use. Such products do not have market exclusivity.

**Group purchasing organization (GPO).** Entity that health care providers such as hospitals, nursing homes, and home health agencies use to purchase products. Such organizations achieve savings and efficiencies by taking advantage of purchasing volume to negotiate discounts with manufacturers, distributors, and other vendors.

**Guaranteed-utilization order.** Supply of certain quantities or units of drugs guaranteed by a drug manufacturer to its purchaser for a specified period of time.

**Inventory management system.** Used to manage the ordering, storage, and use of material in the manufacture of a product.

**Legacy product.** Previously approved and marketed drug, typically developed 10 to 20 years ago. Such products typically have multiple competitors on the market and are low-margin.

**Limited replacement.** A product that has no more than three manufacturers manufacturing an equivalent product at the same time.

**Limited resource.** Typically, a machine or operator or process that is a constraint in the system and directly affects company throughput: output in terms of number of units/volume produced.

**Major market shareholder product.** Drug of which a company holds more than 50 percent of the market.

**Market concentration.** A reduction in number of manufacturers in the market.

**Market exclusivity.** Products for which exclusive marketing rights have been granted by the U.S. Food and Drug Administration to the innovator and that can run concurrently with a patent or not.

**Medically necessary product.** A drug that treats or prevents a serious disease or medical condition for which there is no other adequately available and appropriate substitute or replacement product, as judged by medical staff.

**Network optimization strategies.** Steps companies take to design supply chains that avoid interruptions. Optimization strategies include identifying dual-source suppliers for critical products, identifying backup manufacturers, and putting flexible manufacturing capabilities in place.

**Overall equipment effectiveness (OEE).** A measure of how effectively a machine or equipment is being utilized in a company's manufacturing line or facility—directly related to volume performance, availability, and quality performance of the machine or equipment.



**Patent.** An intellectual property right and a key driver of value for a drug company under whose label the drug is sold. A patented drug is protected against generic competition for a specified period.

**Pricing.** Price set by a company under whose label a drug is sold and that sells the drug in the market. Drug pricing is calculated based on such factors as cost of goods, manufacturing cost, market conditions, competition, brand, and quality.

**Product mix.** The set of all lines and items a company offers for sale.

**Purchaser.** Entity or individual that is a recipient of a drug provided by a drug company. Purchaser could be a drug distributor, group purchasing organization, hospital chain, or end customer with whom the drug company is carrying out a transaction directly.

**Registered spare capacity.** The available amount of a drug manufacturer's excess or spare capacity that is approved for a specified product or products to meet an unplanned increase in market demand.

**Replacements.** Equivalent products supplied by a different manufacturer.

**Safety stock.** Extra inventory maintained to mitigate risk of shortages due to uncertainties in supply and demand.

**Sales and operations planning (S&OP).** A cross-functional process to calculate the overall level of manufacturing output and other activities such as investments, inventory plans, and new-product planning and launch in order to optimize the fulfillment of planned levels of sales. A robust S&OP process is an ongoing process for responding in accordance with changes in market demand, internal factors, and competition.

**Strategic inventory.** Raw material, semifinished products, or finished product held by an organization to ensure continuity of supply. Also referred to as safety stock or business continuity stock.

**Supplier.** An entity that supplies goods or services and commonly adds specialized inputs for manufacturers' products.

**Supply chain resiliency.** Ability of a company's supply chain to continue performing at the same level of performance after a disruption, such as lack of supplies due to floods, shutdown at a supplier, bankruptcy of a distribution partner, or issues with product quality.

**Supply interruption.** A disruption in the availability of a drug in a market.

**Warm start.** Used typically with contract manufacturing organizations to initiate manufacture of the finished dosage form of a product in a short amount of time. The strategy is used to help a company meet unexpected and sudden surges in demand. To accomplish it, manufacturers need to establish (i) contracts in advance and (ii) qualified lines, along with trained staff for the products to be manufactured.

**Wholesalers.** Prescription drug distributors such as manufacturers, repackers, own-label distributors, private-label distributors, jobbers, brokers, warehouses—including manufacturers' and distributors' warehouses, chain drug warehouses, and wholesale drug warehouses; independent wholesale drug traders; and retail pharmacies that conduct wholesale distributions.

## 6. Endnotes

- 1 U.S. Food and Drug Administration, "Manual of Policies and Procedures, Drug Shortage Management, MAPP 4190.1 Rev. 2," <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM079936.pdf>; Federal Food, Drug, and Cosmetic Act, "21 USC 356c(h)(2) as Amended by Title X of FDASIA," Section 506C(h)(2).
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- 10 U.S. Government Accountability Office, *Drug Shortages*, 39-40.
- 11 U.S. Government Accountability Office, *Drug Shortages*, 25.
- 12 International Society for Pharmaceutical Engineering, *ISPE Drug Shortages Prevention Plan* (October 2014), <http://www.ispe.org/drugshortagespreventionplan.pdf>.
- 13 U.S. Food and Drug Administration, "Drug Shortages."
- 14 U.S. Food and Drug Administration, "Manual of Policies and Procedures."

## Additional resources

American Hospital Association, American Society of Anesthesiologists, American Society of Clinical Oncology, American Society of Health-System Pharmacists, Institute for Safe Medication Practices, and The Pew Charitable Trusts, "2014 Drug Shortages Summit" (August 2014), <http://www.ismp.org/pressroom/2014-Drug-Shortages-Summit.pdf>.

U.S. Food and Drug Administration, "Executive Summary: A Review of FDA's Approach to Medical Product Shortages," accessed April 15, 2016, <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm277744.htm>.

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Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, "ASPE Issue Brief: Understanding Recent Trends in Generic Drug Prices" (January 2016), <https://aspe.hhs.gov/sites/default/files/pdf/175071/GenericsDrugpaper.pdf>.

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