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MARSH



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Research Report

A publication from the Supply Chain Risk Management Practice

Building a Safe and Secure Pharmaceutical Supply Chain

Current Protections and Emerging Vulnerabilities
in the Life Sciences Industry

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1. Executive Summary

Among the litany of problems facing life sciences companies, none has garnered as much attention lately as supply chain security. Media focus on the heparin crisis and other supply-related incidents has highlighted the challenge of managing trading networks that span the globe, and the disparity of quality standards and controls across those networks. New sources of raw materials and labor offer cost advantages, but need to be evaluated carefully in terms of risk and reward.

To gauge the strengths and vulnerabilities of the current life sciences supply chain, Marsh Inc., in conjunction with *Pharmaceutical Manufacturing* magazine, conducted a survey of representatives from 66 leading life sciences organizations. The survey results suggest that pharmaceutical manufacturers don't have as much control over supply chain security as they think they have.

Key Findings

Study results show that different segments of the life sciences industry are moving at different paces to fully safeguard their supply chains.

- **Outsourcing is challenging traditional safeguards.** Although the general perception of study participants is that their processes are sufficient, survey results show cracks in the security and product integrity foundation, especially within those enterprises that have adopted an outsourcing-intensive model, in which there is significant third party participation for discovery, clinical trials, and manufacturing processes.

Fully 91% of outsourcing-intensive pharmaceutical participants in the study report having had a "significant incident" (i.e., causing a loss of US\$10,000 or more) due to quality problems or delays with contract partners. Only 59% of their more vertically integrated peers, which have mostly in-house discovery, clinical trial, and manufacturing processes, report having incidents. The study shows that many outsourcing-intensive pharmaceutical companies are lagging behind their more vertically integrated peers in key supply chain safeguards.

- **Contract manufacturers need to beef up Service Level Agreements (SLAs).** Contract manufacturers serving the life sciences industry also have notable differences. They are significantly more likely to include their raw material suppliers in a supplier qualification program and they lead in adoption plans for tamper-resistant packaging and related monitoring technology. But contract manufacturers are the least likely to enforce quality control and related supplier programs through service level agreements (SLAs); only 56% of contract manufacturer respondents report having SLAs.

Study results show that different segments of the life sciences industry are moving at different paces to fully safeguard their supply chains.

- **Protection is greatest where incidents have occurred.** Life sciences organizations that have experienced a supplier quality incident leading to a product recall are three times as likely as their peers to now be auditing and monitoring transportation providers, and they are nearly twice as likely to now be auditing and monitoring their indirect suppliers.
- **Small companies struggle to implement full safety and security capabilities.** Organizations with under US\$100 million in revenue are less likely to have the in-depth policies and procedures of mid-size organizations and large enterprises. They trail their larger counterparts in having a fully documented supplier qualification program and in auditing and monitoring indirect suppliers.

Recommendations

Pharmaceutical safety is both a philosophy and a core value that needs to be built into the process with inspections and monitoring under stringent controls. Standards, policies, procedures, and processes to ensure the safety and security of the supply chain should be agreed to by all participants (no matter how small their role) and should be reinforced by clearly defined SLAs and reporting mechanisms.

Guiding principles to successfully secure and safeguard a pharmaceutical supply chain include:

- **Educate the chain.** It is critical that all supply chain partners are aware of their role in ensuring safety and compliance. SLAs that are part of the legal terms and conditions of procurement and service contracts should be used to help ensure compliance.
- **Demand data collection excellence.** In many cases, the technical capabilities of suppliers—or lack thereof—can create constraints. These should be understood and planned for, capturing required data elements and required information through media in place, and then digitizing this as soon as possible.
- **Institute documentation and communication consistency.** Documentation is critical to ensure that the correct packaging, storage, and handling procedures are consistently applied.
- **Pay full attention to recall and destruction.** It is all-important to ensure that members of the extended supply chain know what to do if the product has been compromised and spoiled. This should be clearly outlined in SLAs between all players in the pharmaceutical supply chain.

- **Be obsessive in continuous monitoring.** Because of margin and market growth pressures, life sciences supply chains are more dynamic than ever before. Best practice companies put in place data analysis processes and “human knowledge” collection procedures to spot specific red flags in their end-to-end supply chains.

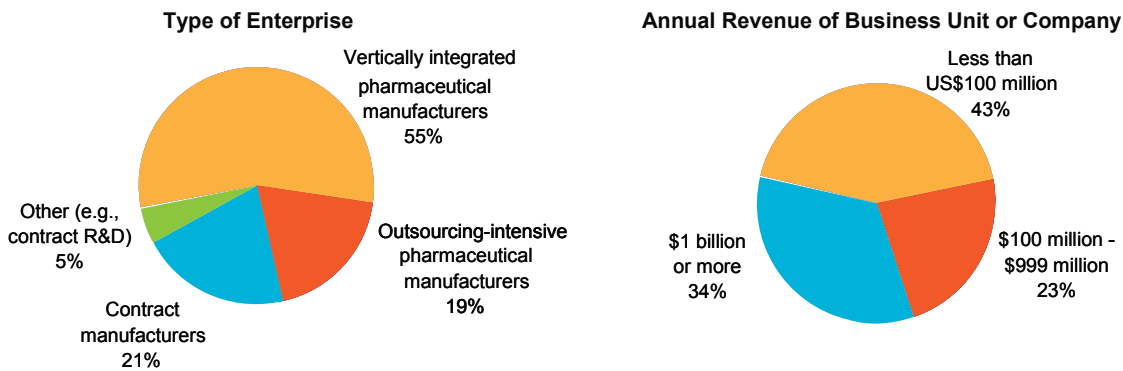
2. Introduction

The global nature of today's life sciences supply chains brings with it inherent risks and rewards. The life sciences industry has recently been experiencing more challenging times as it adapts to increased competition and margin pressures, changing drug discovery trends and regulations, and more geographically dispersed and complex supply chains.

To identify current vulnerabilities, as well as new approaches and solutions to address these issues, Marsh Inc. conducted an on-line survey of 66 North American life sciences organizations, followed by phone interviews with a sampling of the respondents. This research, done with the cooperation of *Pharmaceutical Manufacturing* magazine, was conducted by Marsh in June-August 2008.

Figure 1 describes the key demographics of the study participants. Nearly half of participants were in the quality function of their organization, with most others being in manufacturing, R&D, logistics, planning, or procurement roles.

Figure 1: Demographics of Study Participants



Source: Marsh Inc.

Is the Pharmaceutical Industry Too Complacent?

Overall, responses to questions regarding the selection, management, and monitoring of external entities—suppliers, contract manufacturers, and distribution partners—reflected a perception of “having all the bases covered.” Indeed, 97% of respondents report they have standard operating procedures in place in their organization for product inspection, quality control, storage, and handling. Moreover, 82% say they have documented guidelines for ensuring the physical security of their manufacturing and

distribution facilities, as well as the facilities of their outsource partners that perform these functions on their behalf.

But this complacency may not be justified. With growing evidence of counterfeit drugs and increased potential contamination or reduction in efficacy through inadvertent slips in the chain of custody, even small glitches can contribute to erosion of brand reputation in the minds of doctors and patients.

Moreover, as the results in Chapter 2 show, there are not uniform practices and procedures in the pharmaceutical supply chain today around safety and security, especially as it relates to the extended supply chain. Practices such as outsourcing and offshoring are creating more points of potential vulnerability; and global marketplaces are creating interdependencies that can create cascading damage from an incident.

Changing Business, Evolving Risks

More than 40 years ago, the Food and Drug Administration (FDA), at the instruction of the U.S. Congress, became the overseer of the U.S. pharmaceutical industry with a mandate to ensure that all drugs were produced according to current good manufacturing practices (GMP). This was in response to concerns that sub-standard manufacturing procedures were being employed at the time, jeopardizing the pharmaceutical industry and threatening the lives of patients. Since that time, the combination of modern quality assurance and control principles has resulted in high standards of quality control throughout the entire discovery to dispensing process within the United States.

For years, the high profit margins and vertically integrated nature of large life sciences organizations made this an effective process. However, as evidenced through an ongoing consolidation amongst the large pharmaceutical companies, the life sciences industry has recently been experiencing challenging times as it adapts to more competition, changing drug discovery trends and regulations, as well as more geographically dispersed and complex supply chains.

- **Profit margins are squeezed.** The high profit margins produced by blockbuster drugs in the 1980s and 1990s are fewer and further between. The increasing recall of so-called “miracle drugs” and disappointing clinical trials for some of the most promising products in the pipeline have had a negative impact on balance sheets for several of the large global life sciences manufacturers. Adding to their woes is the proliferation of grey market, diverted, and counterfeit drugs—all of which erode market share and damage consumer confidence.

- **Brand reputation is more important than ever.** The 21st century consumer, armed with information gleaned through the internet, printed media, and television infomercials, no longer takes the product promise at face value. Consultations with medical professionals are now more interactive, with patients expressing concerns about the safety of the medications that are prescribed, and requesting alternatives.
- **Outsourcing and off-shoring introduce new risk factors that need to be controlled.** Cost constraints are compelling enterprises to outsource and off-shore functions once performed within the safe environs of their own FDA-regulated manufacturing facility. Movement of product research, clinical trials, and manufacturing to lower-cost locations—a lure for much of American manufacturing over the past decade—in some cases has resulted in reduced quality controls, re-introducing risk factors that haven't existed for decades. Despite the parity that is possible through automation and controlled environments, the manufacturing facilities in emerging markets are still subject to the challenges of limited infrastructure, varying levels of education, and standards of hygiene.
- **Supply chains are global and so are the risks.** New sources of raw materials and production offer cost advantages, but need to be carefully evaluated in terms of the balance between risk and reward. The recent tragedy related to the processing of pig intestines—a starting ingredient for the production of heparin, a commodity that is used in a high percentage of medical and diagnostic procedures—highlights the dynamics of today's more global and intertwined supply chains. In addition to the products and solutions that include heparin, many medical devices contain or are coated with heparin. Reports indicate that products currently in use within the U.S. medical system may have been contaminated—resulting in further product recalls and implementation of controls to ensure the safety of the medical environment. The heparin saga is just one example of global safety and security events—another recent issue is evidence of paint chips in solid dose tablets, manufactured in a facility in Puerto Rico—and the list goes on.

Outsourcing vs. Offshoring

Outsourcing: A contractual arrangement with a third-party entity to perform the activities that previously took place within a company-owned and -operated facility. A best practice is to establish service level agreements (SLAs) to ensure that quality standards established by the brand owner are adhered to. In practice, SLAs are not always enforced and there is a risk that second, third, and fourth tier providers are not compliant with the brand owner's quality standards.

Offshoring: The establishment of company-owned and -operated facilities in lower-cost locations. A best practice is to establish processes and procedures for the offshore operation to enforce good manufacturing practices (GMP) and adhere to corporate-wide quality and other standards. The operation is treated as an extension of the enterprise, and its suppliers of goods and services are subject to the standards established by the parent company.

Concerns About Potential Supply Chain Vulnerabilities

Despite many companies having the standard pharmaceutical safeguards in place, participants indicated that concerns remain. Not only are consumers and HMOs focused on the cost of pharmaceuticals, but they are increasingly fretful about the risk of negative effects and safety

concerns due to product integrity issues. These worries are not limited to the substitution of generic drugs—brand names are now under scrutiny as well.

Study participants identified a number of areas in which they are concerned about potential supply chain vulnerabilities, including:

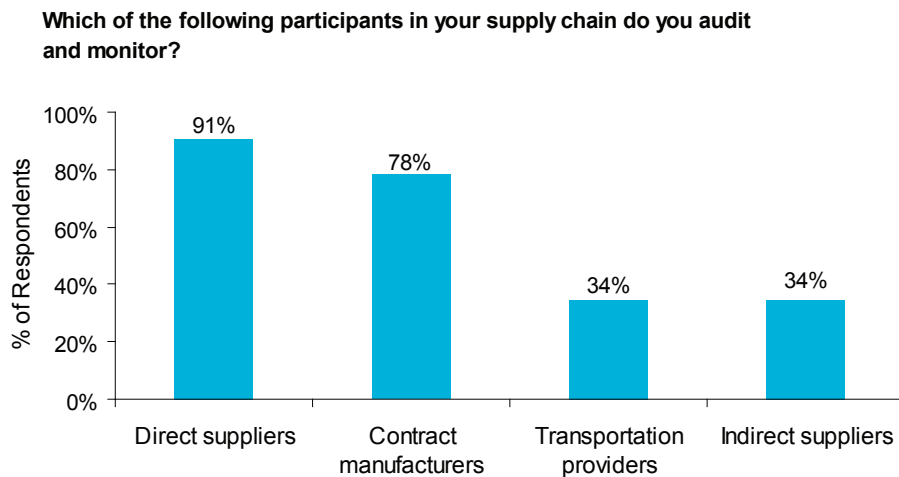
- **Vendor approval and ongoing compliance issues.** Study participants cited such issues as: uncommunicated process changes; vendors making changes to their product without notifying the buyer; vendors having trouble maintaining quality control or yield rates; and unknown impurities in sourced product. One respondent stated, “Vendors [are] making changes to their product without notifying us, or having trouble maintaining quality control (QC).” Another participant said that at a small family-owned vendor, “the owners sometimes do as they feel is best for meeting customer requests for timing rather than following the full steps.”
- **Glitches with continuity of supply.** A number of participants said that sole and single sourcing were of concern, citing a lack of secondary suppliers for every component, having only a single “approved” source of a raw material, raw material shortages, or experiencing issues when vendors unexpectedly got out of the business of selling the product needed.
- **Lack of full supply chain transparency.** A lack of clear visibility to the end-to-end supply chain was also cited, including not knowing the true supplier of a material. Other participants who dealt with temperature-sensitive product cited that shipper integrity and on-time delivery are important concerns for them.
- **Distribution and logistics concerns.** Participants also identified a variety of logistics-related concerns, including cross-mixing and mislabeling at the supplier location; bad storage practices; and labor strikes or weather impacting ports and shipping lines, creating delays that impact production.

3. Inconsistencies in Supply Chain Safety and Security

Different segments of the life sciences industry are moving at different paces to fully safeguard their supply chains, according to the study results. The business model and type of company are a factor in the adoption of supplier and supply chain monitoring and controls. These differences are important, especially in view of the ongoing trend for large pharmaceutical organizations to move toward an outsourced model, with external contract manufacturing, packaging, and distribution.

The study examined the maturity levels of the pharmaceutical manufacturers' quality and risk assessment programs with their supply chain partners. Programs with direct suppliers are the most widespread and mature (see Figure 2). In most cases, the areas of secondary suppliers, storage, third-party logistics, and transportation are not well addressed or have only begun to be addressed in the past two years.

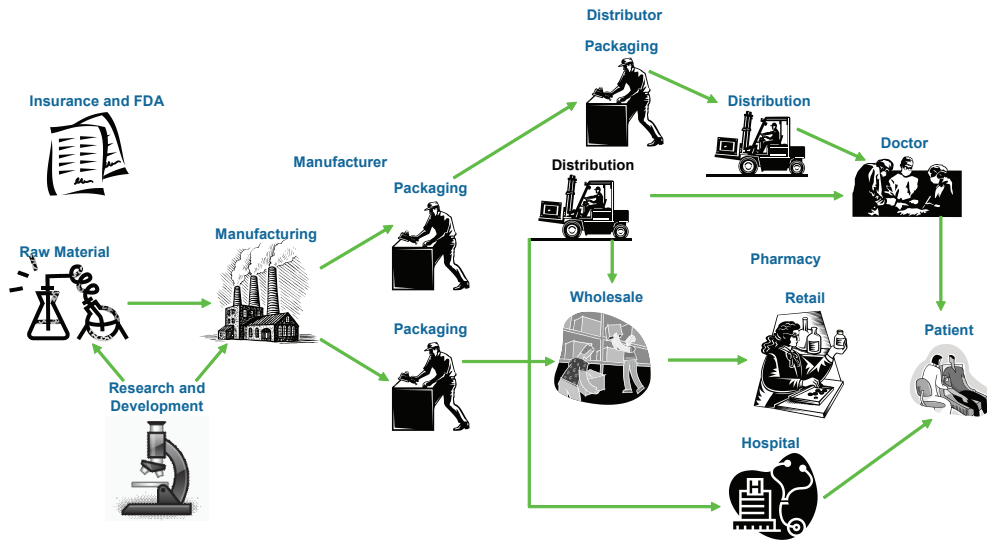
Figure 2: Supply Chain Auditing and Monitoring Trends



Source: Marsh Inc.

Supply chain roles are increasingly played by globally dispersed organizations, thus creating more points of vulnerability that need to be addressed. As the concept of end-to-end supply chain management is embraced, more enterprises are realizing that distribution channels and customers also need to be evaluated to ensure compliance across the complete chain of custody—all the way to the final inch—dispensing or administering the product to the patient.

Figure 3: An Extended Global Network of Inter-related Entities



Source: Marsh Inc.

As reflected in the following comments, this end-to-end supply chain visibility—and control—is not always possible to achieve:

“One of our challenges is that at times our product destined for export finds its way back into the U.S. market. In fact at times our customers end up buying this diverted product at a lower cost.”

“Many of our products are still in clinical trials—we are currently looking at packaging to ensure compliance with the dosing schedule—that is one of the ways we can get some form of control.”

”Due to the nature of the product we are in a position to control our distribution—we only sell to wound clinics and hospitals. This is shipped for immediate use or they freeze when it arrives. However, we have experienced instances where the product is incorrectly handled and damaged.”

Even in the realm of direct supplier management, the picture is not as comprehensive as one might be led to believe. As Figure 4 shows, 26% of respondents say they have a documented supplier qualification program for only their critical direct suppliers, not all of them. A further 9% of participants say they lack a documented program entirely.

Figure 4: Qualification Programs for Direct Suppliers

Does your company have a documented supplier qualification program?



Source: Marsh Inc.

These gaps matter, as Marsh research and client experience have shown that the definition of what is a “critical supplier” varies widely. For many organizations it means the suppliers that one does the most business with (e.g., the most dollars spent). For more mature risk management-oriented companies, a critical supplier is identified as any supplier (regardless of company size or dollars spent) that can cause a critical disruption in business or a meaningful financial or brand reputation problem. And in the case of more exploratory products, supplier maturity is a major issue:

“Our biggest hurdle is moving from general chemistry suppliers to suppliers that make things in a GMP manner—number of these quality suppliers is smaller and they are looking for consistency of demand—in order for that supplier to be viable, we need to be able to project our demand, something that is difficult due to our lack of history.”

“We are concerned that pushing suppliers too hard will create problems. To meet demands at times they make changes and don’t tell us. They may not have the infrastructure in place to notify us about changes. We had that problem recently and that discovery was alarming. This is a problem with a lot of suppliers. It includes packaging, API, and intermediate ingredients.”

“Single source is a risk—if a supplier cannot provide, this impacts production. We are looking for additional sources—biodegradable mesh for example—or items that are not controlled. That is the biggest risk factor to take into account.”

Style of Company Impacts Safeguards

The business model and type of company are also a factor in the adoption of supply chain monitoring and controls. The study looked at three primary types of organizations:

- **Vertically integrated enterprises:** Vertically integrated pharmaceutical manufacturers consider manufacturing to be a core competency, performing key functions in-house. They enforce GMP and controls in their global manufacturing locations, ensuring a consistent environment.
- **Outsourcing-intensive enterprises:** These are organizations that have chosen to outsource a significant amount of discovery, clinical trials, and manufacturing activity. Their core competency is often brand management, including marketing and sales.
- **Contract manufacturers:** Contract manufacturers, with an extended network of suppliers, enforce controls through technology enablers and quality control at each of the nodes. They must follow the quality procedures laid out in the SLAs established by the brand owner.

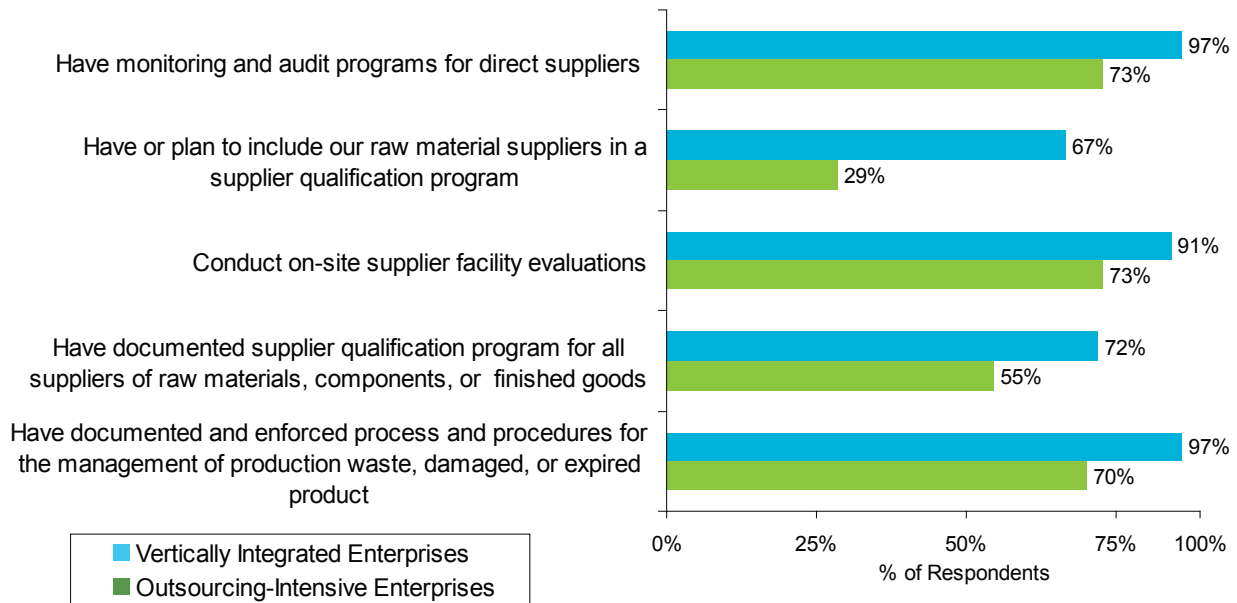
The study results indicate that outsourcing is challenging traditional safeguards. Although the general perception of study participants is that their security and product integrity processes are sufficient, survey results show the contrary, especially within those enterprises that have adopted an outsourcing-intensive model.

Fully 91% of outsourcing-intensive pharmaceutical participants in the study report having experienced a “significant incident” (i.e., causing a loss of US\$10,000 or more) due to quality problems or delays with contract partners. Only 59% of their more vertically integrated peers, which have mostly in-house discovery, clinical trial and manufacturing processes, reported having incidents.

Figure 5 shows the areas in which these outsourcing-intensive pharmaceutical companies are lagging behind their more vertically integrated peers in supply chain safeguards. Because an outsourced business model is more complex to oversee, companies with this model need to be especially vigilant in their safety- and security-related processes.

Fully 91% of outsourcing-intensive pharmaceutical participants in the study report having experienced a “significant incident”.

Figure 5: How Vertically Integrated and Outsourcing-Intensive Pharmaceutical Companies Differ in Safeguarding the Supply Chain



Source: Marsh Inc.

Contract manufacturers serving the life sciences industry have notable differences from other manufacturers. They are significantly more likely to include their raw material suppliers in a supplier qualification program (90%). But they are the least likely to enforce quality control and related supplier programs through SLAs; only 56% of contract manufacturer respondents report having SLAs. In addition, three-quarters of contract manufacturers surveyed say they have or plan to introduce tamper-resistant packaging and related monitoring technology, compared with about one-half of the pharmaceutical manufacturers.

In view of the ongoing trend of outsourcing, these differences in company type are notable. Table 1 compares all three of these manufacturing flavors.

Table 1: Comparing Safety and Security Practices Across Styles of Pharmaceutical Companies

Supply Chain Safety and Security Practices	Outsourcing-Intensive Pharma	Vertically Integrated Pharma	Contract Manufacturing
Monitoring and audit programs for direct suppliers	73%	97%	92%
Have or plan to include their raw material suppliers in a supplier qualification program	29%	67%	90%
Likely to enforce quality control and related supplier programs through SLAs	70%	81%	56%
Report doing on-site supplier facility evaluations	73%	91%	92%
Have documented and enforced process and procedures for the management of production waste, damaged, or expired product	70%	97%	92%
Have had a significant incident	91%	59%	83%
Have had a product recall	55%	47%	75%
Have or plan to introduce tamper-resistant packaging and related monitoring technology	55%	47%	75%

Source: Marsh Inc.

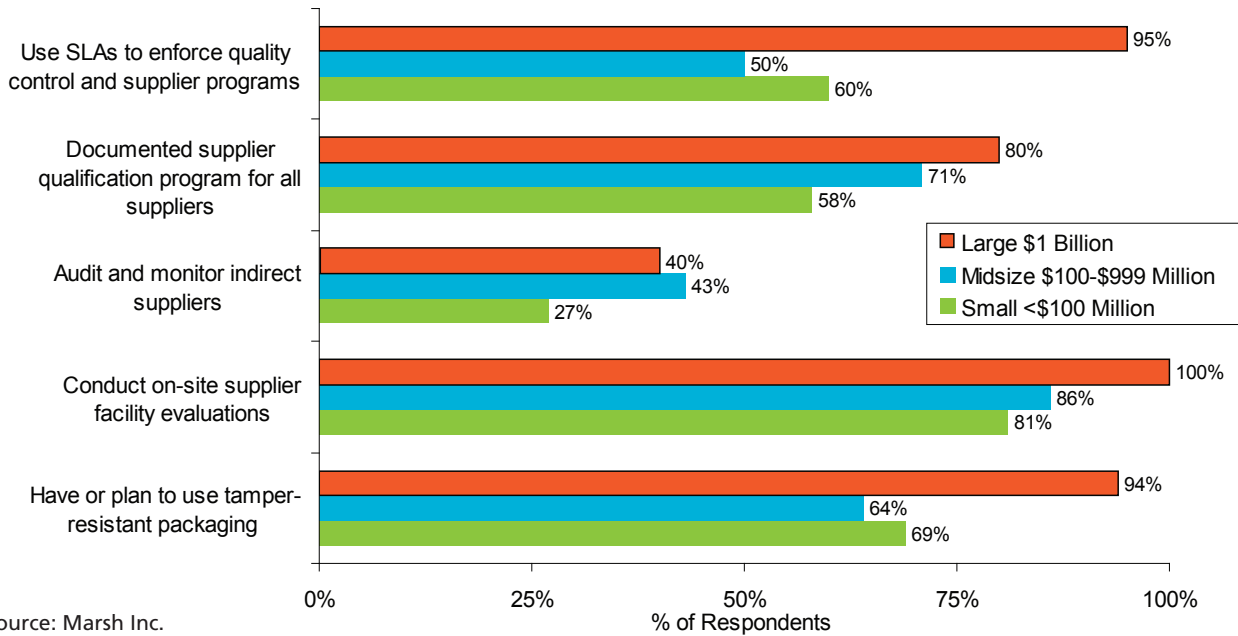
Size Does Matter

Smaller biotech companies struggle with challenges related to scale, single sourcing, and product commercialization. Study results indicate that small companies struggle to implement full safety and security capabilities—and maintain them as they scale. Business units and companies with under US\$100 million in revenue are less likely to have the in-depth policies and procedures of mid-size and large organizations. These smaller entities trail their larger counterparts in having a fully documented supplier qualification program and in auditing and monitoring indirect suppliers.

- By comparison, pharmaceutical organizations with more than US\$1 billion in revenue tend to have more mature supply relationships and more leverage in terms of supplier compliance. For instance, these large enterprises are much more likely to enforce quality control and related supplier programs through service level agreements.

Figure 6 shows key differences among participants, according to their organizational size.

Figure 6: Smaller Companies Trail in Safeguards



Source: Marsh Inc.

Small, start-up organizations are generally staffed with visionary and innovative leaders and teams, and share a closeness and intimacy across functional groups. Exploration and evolution to commercialization are embraced as a journey in which all constituents share the ride. As the company grows, the corporate culture evolves, representing the values of each of the team members, to include a pride in product safety, quality, and efficacy. According to study respondents, this culture is not always easy to sustain as start-ups are absorbed by their incubation partners or mature into commercial entities.

“Our biggest risk is lack of communication internally—sometimes different groups do not communicate and build things in a silo situation. When things are outsourced this gets worse—lots of egos—people are competitive. People are rewarded by what they produce.”

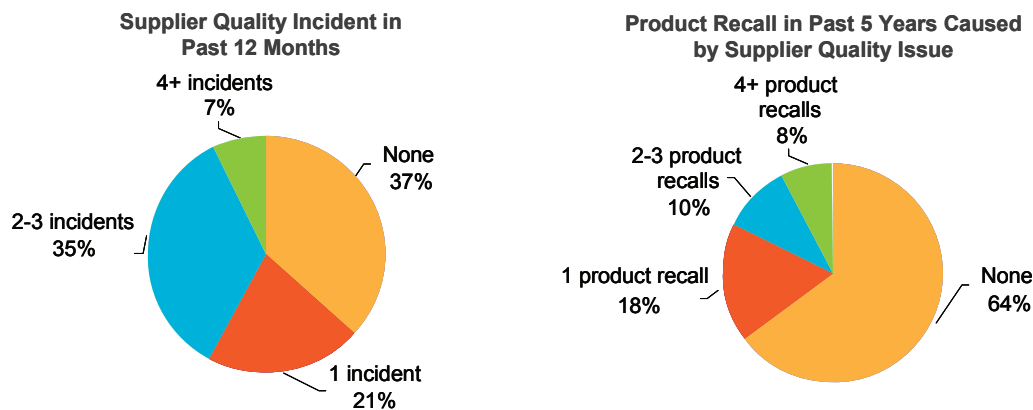
By comparison, large pharmaceutical companies have mature supplier and supply management processes and procedures. Their focus is on reducing the cost of sourcing, manufacturing, and distribution, and increasing corporate profitability. These companies, driven by the cost-containment edicts of management and Wall Street, are facing challenges in the links of the chain closer to patient care—distribution and dispensing. Counterfeit, diversion, and the growing market of illicit drugs is a real threat to the brand promise of the large companies whose

products fill the shelves in the pharmacies—and the medical cabinets of the consumers who rely on the safety of the brands they depend on. As a result, issues such as counterfeit prevention and e-pedigree compliance are important to these organizations. This is demonstrated in their nearly universal focus on implementing tamper-resistant packaging and related monitoring technology.

Protection Is Greatest Where Incidents Have Occurred

Almost two-thirds of respondents report that they have had a supplier quality incident in the past year that caused a delay or interruption in production, or greater than US\$10,000 of product or raw materials that needed to be thrown away. In addition, more than a third say that a supplier quality issue has resulted in a product recall over the past five years (Figure 7).

Figure 7: Number of Supplier Quality Incidents and Recall Events



Source: Marsh Inc.

Organizations that have had a supplier quality issue are much more likely than their peers to have put in place more stringent safeguards and controls. The more serious the issue, the more safeguards have been put in place. Although this is a predictable response, it indicates that those organizations that have not had a recent incident may be leaving key vulnerabilities exposed. Consider the following:

Significant Incident

Companies that have had a “significant incident” (i.e., causing a loss of \$10,000 or more) due to quality problems or delays with contract partners are:

- Much more likely to have documented guidelines for ensuring the physical security of their manufacturing and distribution facilities and those of their outsourcing partners (92% vs. 60%); and
- Nearly twice as likely to have or plan to introduce tamper-resistant packaging and related monitoring technology (90% vs. 50%).

Product Recall

Companies that have experienced a supplier-quality related product recall in the past five years are:

- Three times as likely to now be auditing and monitoring transportation providers (56%) compared with companies that have not had a recall (18%);
- Nearly twice as likely to now be auditing and monitoring indirect suppliers (44% vs. 24%);
- More likely to have a documented supplier qualification program for all suppliers of raw materials, components, or finished goods (78% vs. 58%); and
- More likely to have documented guidelines for ensuring the physical security of their manufacturing and distribution facilities—as well as the facilities of any outsourcing partners that perform these functions on their behalf (94% vs. 69%).

Ultimately it really comes down to thinking about supply chains holistically. As one of the interview respondents put it:

“Risk management is in some cases more of a statement than a practice—people need to talk so that a sense of awareness and sensitivity becomes part of a corporate culture. Quality assurance (QA) needs to become part of the risk management team/working hand in glove so that all factors are taken into consideration.”

4. Changing Environment Requires Changing Controls

What are life sciences enterprises doing to secure the supply chain that supports their brands and reduce the risk of illness and death to the community that they serve?

Custom Packaging and Cost Cutting Require Increased Oversight

One of the key concerns identified in the study is the lack of full transparency of the interrelated links in the supply chain. Conversations with study participants identified areas of growing concern. For example, one emerging trend noted by some participants was for the packaging of inbound ingredients to fall below previously established standards. In one case cited, this resulted in damage to the packaged material, which was a single-sourced and valuable ingredient used in manufacturing

Other conversations reflected some concerns related to the availability and cost of “custom packaging”; the growing trend for single-use packaging adds a level of complexity and cost to an area that played a relatively small role in the past. Another element of the packaging dilemma is the need for chain of custody control, which may require auto-identification and serialization at the unit level to support e-pedigree requirements. And then there was the reported evidence of dust particles—at microscopic levels—in packaging materials for finished product. As these examples illustrate, the devil is still in the detail, and nothing should be taken for granted.

In addition to expressing increased concern over packaging integrity, respondents also identified corporate cost cutting as an area that may threaten the efficacy of finished product. The quest for lower-cost sources of supply has many potential pitfalls—a new supplier offering a lower price should always be questioned to understand how this advantage is possible. Many ingredients share characteristics that imply a sameness (i.e., where the specification allows for interpretation and the potential of substitution for a similar ingredient), but are not an identical compound. Procurement personnel are not normally scientists—their skills include an understanding of dollars and cents versus knowledge of molecular makeup. As such it is always good practice—and should be enforced through policies and procedures—for the evaluation of new or substitute ingredients, products, or packaging to include a team that represents the community that understands the implications of a quality or compound variance.

Time to Get Back to the “Water Cooler” Culture

Another concern of study participants was the perceived increasing isolation between functional groups—not surprising when critical roles are now played out across different continents and within the walls of different companies. Accountability and pride in the creation and safety of the products represented by “the brand” can become lost as enterprises evolve from the exploration and discovery of a start-up organization to the relative maturity of mass commercialization. Increased outsourcing can have a similar impact. Several respondents expressed concern over the increasing isolation of interrelated functions within the discovery to distribution process, even within smaller companies.

Letting the Genie Out of the Beaker

The exploratory nature of some of the compounds being developed in the life sciences industry makes it vital that the minutia of each step in the supply process is well understood and audited throughout the product life cycle.

As products evolve, agents are incorporated into compounds that eventually find their way through the approval process and become commercially viable drugs. However, there is always the chance that one of the critical elements could change—deliberately or inadvertently. The microscopic vigilance of the laboratory environment is not scalable during the product ramp to production and mass commercialization. As one respondent put it:

“As we grew, the decisions in terms of what to buy were made by people in procurement. They were just looking at price reductions and did not realize that they were affecting the product. Subtle differences in ingredients—for example water variations—can create a difference in the compound and the efficacy of the drug.”

Single sourcing of supply was a resounding area of concern for participants, as was the delicate nature of many of the ingredients. Temperature sensitivity, altitude sensitivity, and shortness of product life cycles are among the factors that have to be recorded and communicated across an extended network as enterprises evolve. When this growth pattern includes the outsourcing of critical functions, or the extension of sources of supply to include new players, the levels of risk are elevated.

In addition, the study revealed an evident and underlying concern that some of the flexibility that was possible during a more entrepreneurial stage in corporate evolution would be lost once products were approved. Controls that apply during clinical trials were in most cases not

Know the Red Flags in Sourcing

To identify changes in sources of supply in your end-to-end process, there are specific red flags that should be looked for; these include changing lead time variances, changes in packaging, and changes in country of origin documentation.

One study participant complained that although dealing with a long-term supplier, their company found inconsistencies in lead times, including an extension of up to three weeks in some cases. On questioning this variation, the company found that the primary supplier had started sourcing product from Asia in order to comply with contractual pricing requirements.

Another respondent mentioned noticing changes in the packaging of inbound raw materials, in some cases resulting in damage to the ingredients, a critical component for starting materials. When questioned, the procurement agent admitted having changed suppliers—without including packaging elements in the product specification.

Both cases are examples of the increasing disconnect between constituents in today’s longer and more dynamic supply chains. Diligence on the part of all entities is required to ensure that any changes in source of supply, packaging, labeling, documentation, or mode of transportation are noted and reviewed to establish if an element of risk has been introduced. When a red flag occurs, re-audit this supply line or ask your primary supplier to revalidate the chain of custody and accompanying processes and procedures for this product.

economically viable across a commercial landscape. Additional players would join the game, creating an environment with many hand-offs across the chain of custody.

Attention needs to be given to the documentation, communication, and institutionalization of controls for the receipt, testing, storage, and handling of raw materials and components as they are transformed from delicate biological compounds to life-sustaining products that are widely distributed and dispensed.

Technology enablers should be evaluated for how they can support these processes in a commercial-scale production and distribution environment. These enablers can include mass serialization technology—barcodes, RFID tags, smart packaging, temperature, vibration and other sensors—coupled with related software components to maintain a digital audit trail across the chain of custody. However, the question remains: Who should be responsible for ensuring compliance across a global network of enterprises with potentially different agendas?

Opinions expressed by respondents to the survey and those we spoke to during the interview process varied. Some people felt that the responsibility for ensuring a safe environment rested with “the authorities,” while others felt that the responsibility was on the “brand owners.” However, even with the most stringent controls, there are ancillary factors that need to be taken into account. As one respondent noted:

“Terms of sale can impact the ability to protect the brand—for example, we had a shipment of product that left our manufacturing facility, but was collected by a carrier nominated by our customer—a distributor. The vehicle was involved in an accident and product was spread around the accident site. We were lucky; the driver had the sense to protect the product. If he had not done that, the product could have been stolen and found its way onto the gray market.”

Generic Manufacturers—What Are the Risks?

The “no-name brand” or “store brand” concept that enables the purchase of over the counter (OTC) products at everyday low prices is fueling a sector of the life sciences industry that faces its own challenges. The compounds that comprise the ingredients for “generic equivalent” are very close to those manufactured for the branded product—but as pointed out by one respondent:

“Generics in general, only have to be about 92% the same in terms of ingredients and processes as brand name manufacturing—they don’t have to be 100% identical.”

This is cause for concern. Because generic products have lower margins, companies often are continually searching for cost reductions, some of which could potentially compromise the effectiveness of the finished product. As stated by one frustrated respondent:

“Purchasing folks look at the product description and assume that there is a similarity in compounds—they are always looking for cheaper sources of supply—in many cases this compromises the integrity of the ingredient and the resulting product is not the same.”

Manufacturers of generic substitutes are geographically dispersed, with some having operations in locales that are politically unstable, such as parts of the Middle East. In some cases, these generic supply chains may have more risk factors than branded drugs for supply chain disruption from natural hazards, political strife, bio-terrorism, and so on. To quote a contract manufacturer:

“It is the concern of the era, as a lot of counterfeit cases are there every day, as the borders became more open—this is not concerning only the availability of adulterated/low quality product, but also may extend to cases related to bioterrorism.”

Geographic Risk Factors

Many pharmaceutical manufacturers and biotech companies have moved to a global factory model. Exploratory research and development operations are also finding that the relative ease with which experimentation and clinical trials can take place in distant shores can provide a fast track for the identification of new agents and the development of potential miracle compounds.

One respondent commented:

“American companies make the assumption that everyone uses the same standards as the U.S.—but they don’t!”

Despite the increased need for comprehensive rules and regulations on a global scale to protect the life sciences supply chains, in some regions of the world the policies are loosely written—and in some cases even more loosely interpreted. Regulatory bodies that control manufacturing, storage, and distribution in emerging markets of the world are often in their infancy, especially compared with the regulations of North America, Japan, and the European Union.

Geographic regions that have routinely supported so-called third shift environments, supplying the global market for designer knock-offs, are now home to outsourced life sciences operations. Ethical and other standards do not necessarily apply—factory workers may have no concept

Counting the Counterfeiting

In May 2007, the FDA issued a report warning of counterfeits on the Internet. This followed a 2006 warning about Internet counterfeits of Lipitor, Diovan, Actonel, Nexium, Hyzaar, Ezetrol (known as Zetia in the United States), Crestor, Celebrex, Arimidex, and Propecia. The 2007 report cited Xenical, a weight-loss drug that contained either no active ingredient, or a different active ingredient, sibutramine. Other cases involved Tamifu and Cialis.

These cases fit the typical drug counterfeiting profile: the drugs are relatively expensive, and, in the case of Tamiflu, they may be in short supply. Today, nearly \$39 billion worth of fake drugs are sold each year, roughly 11% of the total annual global. The Center for Medicines in the Public Interest expects this figure to reach \$75 billion by 2010.

The scope of the counterfeiting problem varies widely by country. Pharmacy sales in the United States can be expected to be genuine, and 99% of them are, according to estimates by the World Health Organization (WHO). However, the case is very different for drugs that U.S. citizens buy on the Internet, roughly half of which are likely to be fake.

In Angola and Nigeria, up to 70% of the drug supply is likely counterfeit, according to WHO’s International Medical Products Anti-Counterfeiting Taskforce (IMPACT). In parts of Africa, Asia and Latin America, the figure is over 30%, IMPACT estimates, while in some former Soviet republics, it is higher than 20%; in developing nations it is, on average, over 10%.

of the implications of substituting an inferior ingredient to increase profitability. A further factor is the alarmingly efficient and far-reaching supply chain networks that support the sale and distribution of gray market products. Added to which the penalty for the distribution of counterfeit drugs and medical products is relatively minor compared to the rewards and profits to be made.

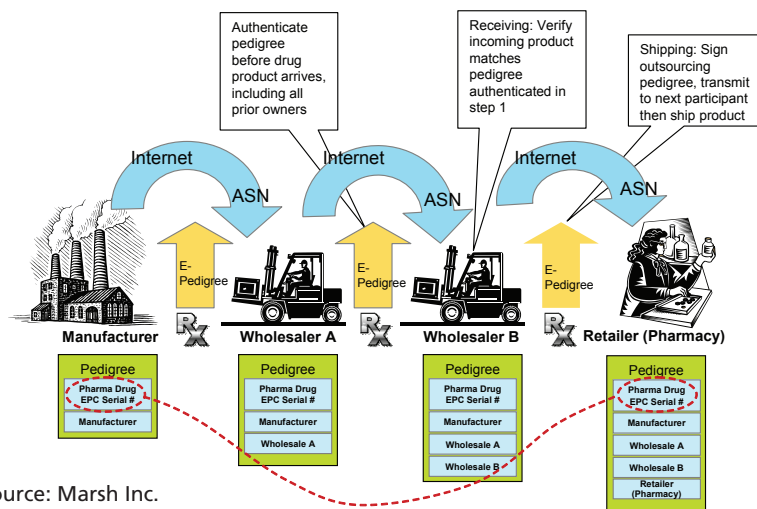
The product integrity problem is evidenced by the growing list of instances of product tampering, contamination, or substitution. An additional factor is the growing trade in pharmaceuticals over the Internet, much of which includes diverted and counterfeit product.

Digital DNA Across the Chain of Custody

In response to the continuing threat of counterfeit, diversion, and other issues within the life sciences industry, the FDA has taken a stronger line with regard to enforcing controls within the manufacturing, storage, and distribution environment.

New regulations are already being enforced in certain states, in support of a secure chain of custody. Effective January 1, 2011, it will be mandatory in the State of California for each participant in the extended supply chain to create an electronic record of manufacturing, shipping, receiving, and storage activities performed. It is proposed that this will be facilitated through the use of auto-identification technologies at the discrete item or shipment level, integrated into shared applications to create a digital record, or e-pedigree. Non-compliance will result in the inability for enterprises to manufacture or distribute product in the State of California. The implications of this regulation are far-reaching and will impact manufacturing, distribution and retail participants in the life sciences supply chain.

Figure 8: Implementing an E-pedigree Program Across the Chain of Custody



Source: Marsh Inc.

China's Growing Regulations

Virtually all the leading pharmaceutical companies now have research and development operations in Asia and/or products “made in China”—even the relatively adolescent biotech industry has followed suit. To ensure a safe and secure supply chain, it is vital to understand the evolving nature of Chinese pharmaceutical oversight.

The primary focus of Chinese regulatory bodies, such as the State Food and Drug Administration (SFDA), is on products administered to the local population. For example: An SFDA surveillance system identified almost 160,000 adverse drug events that had been reported in the first half of 2008, up 50% over the same period in 2007. Wu Zhi'ang, deputy director of the National Adverse Drug Reaction Monitoring Center, affiliated to the SFDA, said the numbers reflect an enhanced and more effective supervision and control system for monitoring existing and potential risks relating to pharmaceuticals.

The spotlight on the safety and security of the pharmaceutical supply chain (and the resultant product recalls that have been much publicized in the global press) has led Chinese authorities to extend their surveillance efforts to drugs destined for export. In an attempt to increase scrutiny over drug exports, the Xinhua News Agency on January 31, 2008, reported that China will adopt a system of licenses and registration. The report cited Commissioner Shao Mingli, the current chief of the SFDA, as stating that “the SFDA would work out an anti-corruption plan that would be in use through 2012.” (In 2007, Zheng Xiaoyu, Shao's predecessor, got the death penalty on bribery charges. Other SFDA officials were sentenced to jail terms.)

These initiatives are positive news for companies and patients dependant on Chinese-manufactured products and ingredients. However, increased vigilance on the part of both industry and the regional regulatory authorities is necessary to ensure that products and raw materials originating in China do not result in adverse drug effects outside Chinese borders.

Regulatory and Advisory Bodies

Many regulatory organizations are regional, and have no jurisdiction or influence across geographic boundaries. Still others are merely consultative, providing guidelines that are not enforceable or monitored. It falls on brand masters—those whose ultimate brand promise is at risk—to understand the areas of risk and to implement and enforce programs to ensure compliance to high levels of product quality and

Panama Tragedy: A Catalyst for Chinese Controls

The deaths of dozens of people in Panama, after taking medicine made in China, motivated the Chinese authorities to extend their investigations into companies manufacturing drugs and medical devices destined for export. Results of the crackdown were outlined in a news report by the Xinhua News Agency on December 4, 2007:

China has shut down 300 drug and medical instrument manufacturers for inferior quality products during a national campaign that has been ongoing since last July, said China's drug watchdog in Beijing on Monday.

“The campaign to correct malpractice in the pharmaceutical industry is showing results,” said Wu Zhen, deputy director of the State Food and Drug Administration (SFDA), at a press conference. By October, about 900 fake drug producers were dug out and 440 cases were handed over to the prosecutors while 279 persons faced criminal charges, he said. During the campaign, inspectors have examined more than 29,000 types of drugs and examined over 148,000 drug registration files and 26,000 files for medical instruments. About 7,300 pharmacy companies withdrew their application for drug approvals during the campaign, Wu said, adding that the quality of drugs, waiting for approval, has greatly improved although the number of applications has dropped. The inspectors also found 1,100 already approved drugs and medical appliances that had been illegally approved.

“Producers of blood products and vaccines were high on the inspection agenda,” Wu said. About 1,300 inspectors were sent to specific pharmaceutical firms to tighten supervision.

integrity. They must also do this in a consistent way across their global operations and those of their manufacturing and packaging partners.

Table 2 outlines some of the global and regional entities that are custodians of the life sciences supply chain.

Table 2: Sample Regulatory and Advisory Bodies

Organization	Operational Perspective	Jurisdiction	Authorities Network
World Health Organization (WHO)	Advisory and consultative	Global authority	No regulatory authority
U.S. Pharmacopoeia	Advisory and consultative	United States	Recommends—once approved, FDA regulates
Medical and Healthcare Products Regulatory Agency (MHRA)	Regulatory	United Kingdom	Power to withdraw products from the market, suspend production, and prosecute a manufacturer
International Conference on Harmonization (ICH)	Advisory and consultative	Global authority	Brings together regulatory authorities of Europe, Japan, and the U.S. to make recommendations
Food and Drug Administration (FDA)	Regulatory and advisory	United States	Responsible for enforcing the Federal Food, Drug, and Cosmetic Act, monitoring products for continued safety, and advising public regarding safety issues
National Association of Pharmacy Regulatory Authorities (NAPRA)	Advisory and consultative	Canada	Association of national pharmacy regulatory organization
European Medicines Agency (EMA)	Regulatory and advisory	European Union	Responsible for scientific evaluation of applications for European marketing authorization for medicinal products
State Food and Drug Administration (SFDA)	Regulatory and advisory	China	The SFDA is directly under the State Council of the People's Republic of China, which is in charge of comprehensive supervision on the safety management of food, health food, and cosmetics and is the competent authority of drug regulation in mainland China

Source: Marsh Inc.

Panama Tragedy: A Catalyst for Chinese Controls (Cont'd)

The administration also verified the companies winning certificates of Good Manufacturing Practice (GMP) and withdrew 150 such certificates, he said. To regulate the medicine distribution, more than 900 drug retailers and wholesalers' sales licenses were withdrawn for selling drugs they should not sell. Meanwhile, around 180 drugs and medical instruments were banned from sale after being advertised illegally.

5. Next Steps and Call to Action

Creating the Right End-to-End Mindset

As identified in the business case for the creation of the International Conference on Harmonization (ICH), establishing a global quality standard through the harmonization of the rules, regulations, and inspection procedures across the global *pharmaceutical manufacturing* process is a most critical element for a safe and secure supply chain. Such consistency is the keystone of quality: quality of raw materials, manufacturing process, and procedures and services that support this critical supply chain.

Safety—like quality—is both a philosophy and a core value that needs to be built into the process and inspected and monitored through stringent controls. Standards, policies, procedures, and processes to ensure the safety and security of the supply chain should be agreed to by all participants (no matter how small their role) and should be reinforced by clearly defined SLAs and reporting mechanisms.

Best Practices for Global Pharmaceutical Supply Chains

Some study participants reported that their organizations' extended supply environment was an unknown factor. Mature supply relationships in some cases masked the changing “country of origin” for raw materials, components, and packaging materials.

For better or worse, the reality is that globalization has changed the rules of manufacturing and distribution forever. It is no longer enough to develop policies, processes, and procedures at an organization or regional level. Programs need to be developed, implemented, and enforced across an end-to-end supply chain, which includes the identification of primary, secondary, and n-tier suppliers of all raw materials, packaging ingredients, components, and the logistics and other service providers that link all these entities in the chain.

A best practice for safeguarding the supply chain is to maintain a clear map of the supply chain religiously updated as supply relationships and product lines evolve. The level of transparency of the end-to-end process is vital to effective monitoring and control.

When establishing “owned and operated” international manufacturing or other operations, best in class enterprises integrate consistent internal standards into these new operations' processes and procedures, ensuring a level of quality and consistency irrespective of geographic location. In some instances, the establishment of operations includes a complex array of desalination, purification, and water treatment facilities as well as the generation of electricity. These offshore locations are able to create a safe and secure manufacturing environment.

Securing the weak links in the global chain also requires that logistics providers follow proper procedures to safeguard the goods. Best practice pharmaceutical companies establish standards for transportation and distribution, and then leverage information technology systems to monitor goods and manage data across this global chain.

How to Protect Your Supply Chain—and Its Patients

Guiding principles to successfully secure and safeguard a pharmaceutical supply chain include:

1. Educate the chain. The key objective is to ensure that all participants in the chain of custody are aware of the risks and possible impact on patients. The concept of “social responsibility” and “patient promise” should be shared across the supply environment, creating a sensitivity in which all participants understand the risks, issues, and impact and become more vigilant as they perform their specific tasks across an extended supply network.

It is critical that all supply chain partners are aware of the expectation related to their role in ensuring safety and compliance. All supply chain participants should be aware of the data that they will need to validate as goods pass into their custody—as well as the digital audit trail required across the product lifecycle. SLAs that are part of the legal terms and conditions of procurement and service contracts should be used to help ensure compliance, a practice used today by about 70% of study respondents.

There are some industry sectors that provide a useful benchmark—the automotive industry, with an extended environment of outsource partners for component manufacturing and final product assembly have instilled “pride of performance” by identifying the final product that each component is destined for. This step has fostered factory workers to have a deep commitment to quality, ensuring consistency across diverse manufacturing locations and populations of factory workers.

Another example comes from the health care industry in Canada. A local health care authority created a “patient awareness” in its distribution environment by posting pictures of infants, children, and elderly patients in the warehouse that supplied the products for the “last inch” in the supply chain.

In the United States, many of life sciences products are distributed by wholesalers. However, it is inherent on the brand owners to ensure that each of the links in the chain is well-versed in the correct process and procedures.

Extending orientation and training to the point of care will continue to be important as well. Sales and marketing personnel need to be diligent in sharing information related to the prescribing and use of the drugs and educating healthcare givers in the correct storage and handling of temperature-sensitive products.

2. Demand data collection excellence. In many cases the technical capabilities of the extended supply chain—or lack thereof—can create constraints. These should be understood and planned for, capturing required data elements and required information through media in place, and digitizing this as soon as possible. A combination of electronic data transfer and auto-identification technology, along with telephone prompts, web-based forms, and even older technologies like facsimile should be evaluated in order to capture information as close to the source as possible and implemented as part of an end-to-end shipment tracking and tracing process.

3. Institute documentation and communication consistency.

Documentation is critical to ensure that the correct packaging, storage, and handling procedures are consistently applied. Ensure that appropriate labels are used to define product receipt, testing, validation, storage, and handling. This should include clearly defined parameters related to hazardous products, temperature control, humidity, and other restrictions that apply. Color codes should also be used to identify hazardous, fragile, and temperature-sensitive items. Although product is usually labeled correctly, instructions may be ignored or else the language in which they are written may be inadequate to support all the players across the extended supply chain.

A best practice is the utilization of RFID and temperature and related sensors to monitor items having special handling requirements—eliminating the human error. However, to date these technologies are not commonly used, in part because of the added expense.

4. Recall and destruction—leave nothing to chance. It is all important to ensure that members of the extended supply chain are well-versed in terms of what to do if the product has been compromised and spoiled. This should be clearly outlined in SLAs between all players in the pharmaceutical supply chain.

Because of margin and market growth pressures, life sciences supply chains are more dynamic than ever before. Best practice companies put in place data analysis processes and “human knowledge” collection procedures to spot red flags in their end-to-end supply chains.

Adhering to these best practices, and ensuring that all participants across the chain of custody are aware of the risks that need to be monitored, will create a safe and secure environment for critical drugs and biotech products.

6. About the Author

Carla Reed is a senior vice president in Marsh Inc.'s Supply Chain Risk Management Practice. Marsh Inc. is the world's leading insurance broker and risk adviser. Ms. Reed has more than 20 years experience in working with a diverse range of organizations in the life sciences industry. Her experience includes management of cross-functional teams to link evolving technologies and concepts to global business issues in existing and emerging markets.

She is the author of a series of white papers on the subject of RFID, sensors, and related technologies in the life sciences industry, with a focus on cold chain (monitoring the state of the product), e-pedigree (ensuring an electronic audit trail across the chain of custody), chain of care (issues and remedies in a clinical environment), and product innovation (discovery, clinical trials, product introduction, and related processes and technology enablers). Ms. Reed can be reached at carla.reed@marsh.com. Additional information about supply chain risk management can be found at www.scrm.marsh.com.

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