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Industry, FDA Still Wary of Supply Chain Security

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Public confidence in pharmaceutical products has waned in recent years based on patient harm caused by adulteration ***(1),*** drug shortages ***(2)*** and poor quality resulting in recalls ***(3).*** Along with concern for patient safety, pharmaceutical professionals at all levels within their organizations have become keenly aware of the potential for damage to the company brand by such incidents.

In response to the risks that threaten the pharmaceutical supply chain, industry mitigation efforts have focused on improving supplier operations with the belief that supplier controls have been deficient. Recognizing that many of the criminal cases have resulted from rogue foreign suppliers who were economically motivated to contaminate the supply base, it is not difficult to appreciate why industry reacted this way. Further supporting industry's preconception that increased supplier controls are needed, the U.S. FDA publicly expressed its expectation that industry audit every supplier in each of their product supply chains as a means to reduce supply chain risk ***(4).*** In order to address FDA expectations and protect the patients they serve, industry ramped up auditor resources, increased metrics used to measure supplier performance, instituted risk-based audit plans, identified "strategic" suppliers, and initiated supplier training.

Despite mitigation efforts employed to date, throughout 2010 and 2011 Xavier University heard consistent concerns from professionals at all levels in both the pharmaceutical and medical device industries regarding the reliability of their supply ***(5).*** These unified concerns led to the launch of the Xavier University Integrity of Supply Initiative in August 2012, which is the basis of the presentation that will be given at the *2014 PDA/FDA Joint Regulatory Conference.*

The mission of the Xavier University Integrity of Supply Initiative is to determine the sources of dysfunction affecting the reliability of supply**,** and to implement sustainable solutions tied to return on investment—such as increased safety, improved quality and enhanced reliability—commensurate with need. Xavier University made a conscious decision to focus on factors affecting the reliability of incoming supply first. Those involved in the Initiative will identify and prove solutions for incoming supply, then these solutions will be assessed for application to the downstream supply chain.

There are 24 organizations engaged in the Initiative, which includes representatives from the FDA, pharmaceutical companies, medical device companies, and suppliers as follows: Abbott, Albemarle Specialty Pharmaceuticals, Amerikam, Baxter, Boston Scientific, Cook, Core Risks, CPKelco, Eli Lilly, FDA Office of the Commissioner, Huber, Johnson & Johnson, Lonza, Merck, Meridian Bioscience, P&G, Patheon, Perrigo, Puritan Products, Roche, Shire, Teleflex, Tornier, and WLS Enterprises.

In an effort to ensure the concern of reliable supply was felt widely across the industry, Xavier University conducted cross-functional interviews of each of the participating organizations involved in the initiative, two organizations from the food industry (Kroger and General Mills), and industry associations (GPhA, IPEC, MDMA, and PhRMA). The result echoed what was heard at the 2010 and 2011 FDA/Xavier conferences, thus verifying concerns expressed regarding supply chain reliability.

The interviews took the pharmaceutical and medical device manufacturers represented in the initiative through a Cause and Effect exercise followed by Pareto analysis, which led to the identification of three main sources of dysfunction related to reliability of supply: (1) incomplete product and process knowledge and development, (2) insufficient supply chain development and management, and (3) inadequate behavior and communication.

Suppliers, through surveys and focus group sessions, corroborated the sources of dysfunction identified by the pharmaceutical and medical device companies. Additionally, *100%* of the input from audiences at the *FDA/Xavier University PharmaLink Conferences* in 2013 and 2014, the *FDA/Xavier University MedCon Conference* in 2013, the *Association of Food and Drug Officials Conference* in 2013, and the *ExcipientFest Americas Conference* in 2014 fell into these same three categories. Xavier University gathered information about these sources of dysfunction through an anonymous survey of suppliers, focus group sessions with suppliers and root cause exercises with manufacturers.

Product and Process Knowledge and Development

Due to common pressures that occur during product and process development (e.g., cuts in time, personnel and funding) manufacturers are often not able to fully understand what is needed from their suppliers to support the finished product. As a result, specifications on incoming materials default to industry standards (such as the U.S. Pharmacopeia) and historical use of the same material in other products, which may not be appropriate for the product in question. The survey found that only 18% of manufacturers ask for supplier technical input on specification setting.

As manufacturers are learning the critical process parameters of their process and critical quality attributes of their product, they do not take into consideration the process variability coming in from their suppliers. When asked, 54% of the suppliers surveyed indicated they would be willing to share process capability with their customers, but the information is requested only 29% of the time. Only 45% of the manufacturers share intended use, despite the fact that 64% of the suppliers expressed that it is critical for them to understand intended use to be able to provide what is truly needed by the manufacturers. A final example is that manufacturers do not gain internal alignment of cross-functional requirements before engaging suppliers. As a result, suppliers are told by their customers that the top priority is high quality, but then are told the cheapest cost is most important, and not to mention they want it faster than is possible. 68% of the suppliers indicated that they receive conflicting information from different members of their customers.

Supply Chain Development and Management

Suppliers were intentionally surveyed that serve industries outside the FDA regulated industries, manufacture many products of various volume and types, and have a large portion of their supply tied to specialty products to ensure the robustness of response. Interestingly, the survey revealed that 91% of pharmaceutical manufacturers employ poor forecasting methodologies, which is vastly different from other industries their suppliers support.

When manufacturers show disregard for the operations of their suppliers, then impossible demands lead to an increase in the potential for error. The survey found that the manufacturers generally have a methodical due diligence process, supplier selection process, and supplier qualification process. Partly due to cuts in time, however, resources and budget for these processes are often disregarded—as reported by the manufacturers themselves. Even suppliers indicated that only 9% of their customers involve cross-functional representatives in the due diligence process, despite manufacturers indicating that their process requires it.

A final example related to this topic comes from a focus group's discussion revealing that contractual terms often conflict with other agreements in place (not to mention that only 14% of the suppliers expressed they have a Quality Agreement in place with their pharmaceutical customers). One story shared concerned a contract that stated than if a laboratory error occurred, the contract laboratory would not get paid for services. In response, the contract laboratory concluded in every investigation that no laboratory error occurred, so all failing data was considered valid. Obviously, an example of unintended consequences, but interesting that it was driven by the manufacturer.

Driving Ideal Behaviors

There is strong recognition that human factors play a large role in how the supply chain operates (as with everything else).

The survey indicated that most manufacturers feel transparency is not possible due to current paradigms of competitive advantage, despite the recognition that transparency increases trust and reliability.

The data also revealed that current metrics used by manufacturers do not trigger action, instead causing distractions that lead to dysfunction on multiple levels. Metrics should include key triggers and associated escalation tied to performance improvement on both sides of the contract. Otherwise, a general lack of understanding of the cultural alignment between the manufacturer and the supplier leads to frustration, performance not meeting expectations, and loss of trust.

Paradigm Shift Leads to Solutions

Perhaps the greatest discovery revealed through the initiative to date is the paradigm shift **(Figure 1)** that every area of dysfunction related to the reliability of incoming supply is caused by and/or can be controlled by the manufacturers themselves, not their suppliers. Instead of increasing controls over supplier operations, this paradigm shift will require manufacturers to assess how their own actions prevent their suppliers from consistently supplying reliable material.

Through this initiative, Good Supply Practices (GSPs) are being developed to improve the practices of the pharmaceutical manufacturers themselves. Each GSP will have components related to product and process knowledge, supply chain development and ideal behaviors in order to address the examples of dysfunction discussed above (and others not included in this article). The GSPs will be pragmatic, will include decision making tools when applicable, and will harmonize practices wherever it makes sense and is possible. Where appropriate, the requirement of critical functions will be stated, but otherwise will provide options for the manufacturers to consider—depending on need. Additional input will be gathered throughout the development stages of the GSPs, and pilot studies will be employed to demonstrate effectiveness.

Figure 1 Major Paradigm Shift Revealed Through the Integrity of Supply Initiative

Through research and interaction with other industries, many of the practices proposed to date have demonstrated real return on investment in those other industries, which is required in order to fulfill the mission of the Integrity of Supply Initiative.

[Editor's Note: Marla Phillips, one of the authors, will present "Increasing Supply Chain Reliability – Shifting Paradigms" in Session A3, "CMO" at the *2014 PDA/FDA Joint Regulatory Conference,* Sept. 9 at 11:15 a.m.**]**

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