Front & Center

Risk Assessments and Sourcing Strategies for Excipients and APIs

Manufacturers are likely very aware of the potential risks associated with the ingredients being used in the manufacturing process of drug products and the importance of mitigating and managing those risks. It is critical for them to have the tools to be aware of what their suppliers are doing, how they are doing it, and ensure the quality of the ingredients they use.

The ability to manage risk and compliance throughout the supply chain is more crucial than ever due to globalization of the supply chain. While globalization potentially increases risks, greater public awareness and more diligent enforcement are raising the quality bar for drug ingredients.[1]

Managing Risk

A poster session presented at the 2017 Annual Meeting of the American Association of Pharmaceutical Scientists (AAPS) by Stephen Andruski, PhD, manager of Verification Programs at USP, illustrated how a drug manufacturer might conduct a risk assessment of the numerous ingredients and components they use. Every ingredient poses its own risk, and Andruski made the point that drug makers would benefit from determining the level of supplier qualification, the type of supplier qualification, and how a third-party verification program can help them address those needs.

"When evaluating the risks associated with an ingredient in your supply chain, you need to stay objective and use a system of tools to come to an objective understanding of the different risks in the ingredients because not every ingredient poses the same risk," Andruski told AAPS poster presentation attendees.

Andruski suggested asking the following questions to determine potential ingredient and supplier risks:

- Is the material coming from a plant or is it being mined? The answer determines the types of potential contaminants and how easy they are to detect. Data shows that even mined material has variations.
- Is there a compendial standard to control those contaminants?
- Does the material change when it is cultivated?
- Is the material complex or simple?
- What are the ingredient's critical quality and performance attributes? Attributes like viscosity, particle size, pH, and surface area can all affect the manufacturing process and performance in the final dosage form.
- Does the product contain a high-value material or one that is potentially subject to economically motivated adulteration or substitution? Andruski said many botanicals are difficult to identify and subject to adulteration or substitution.
- Where is the manufacturer, distributor or supplier located?
- Are you buying directly from the ingredient manufacturer or through a distributor? If purchased from a distributor, do you know who the original manufacturer is? "Some distributors are more transparent than others regarding their ingredient manufacturers," said Andruski.
- Are the manufacturer and the distributor familiar to you? How long have they been in business? In that time, have they changed management? Such changes can affect the company culture, the way they interact with their customers, and the information they are willing to share.

Options for Managing Risk

Managing risk for a variety of ingredients requires supplier qualification. This process can be as simple as sending a questionnaire to the ingredient supplier to obtain information about the ingredient, the company, the firm's business stability, and the markets in which they work. A follow-up on-site audit may be necessary upon reviewing the responses. But, this can be expensive and requires dedicated resources.

Another option is to rely on a third-party audit and certification program. In this case, a contractor performs an on-site audit of the supplier's facility to certify they are following appropriate GMPs.

Andruski suggested that an option to be considered is a third-party verification program like USP's Ingredient Verification Program. The USP Verification Program began in 2001 for dietary supplements, branched out in 2003 to verify dietary ingredients, and in 2006 began verifying pharmaceutical excipients and drug substances.

"USP's third-party verification program helps to ensure the quality of the ingredients going into drug products," said Andruski.

Components of the USP Program

Meeting four key USP Verification Program criteria results in a supplier's ability to use the USP Verified Mark on the ingredients included in the program. First, before conducting the audit, USP looks at the supplier's standard operating procedures (SOPs) to ensure they have a well-developed quality system in place and that they understand that USP will be looking at the quality systems and controls to ensure that they are following good manufacturing practices (GMPs).

Next, a GMP audit provides an overview of the quality system.

"We cite observations of nonconformities during that audit and work with the supplier to take corrective actions and assess those actions to make sure that they've addressed the initial concerns in an adequate fashion," said Andruski. "USP will conduct annual GMP audits and the supplier is required to alert USP of any changes in the manufacturing of the product or the process."

The third component of the USP Verification Program is an audit of the supplier's quality control and manufacturing product documentation. This includes a review of batch records, raw material release documents, and finished product release documentation. Andruski says this provides a detailed view that may not be revealed in a certification audit.

"By digging deep into the documentation, we can see how quality systems are implemented and how quality is controlled on particular products," he said. "We can get a lot of details that are not generally found in typical audit of a facility."

Typically, documentation is sent to USP for review, but in some cases, documentation is reviewed at the supplier's site. Similar to GMP auditing, USP reviews product documentation on a yearly basis.

The fourth component of the USP Ingredient Verification Program is product testing, which also is conducted on a yearly basis. USP samples three lots of the ingredient and tests them. While problems are rare, if any are identified, Andruski said they usually arise because an analytical method is not well verified or validated.

"We believe testing and facility audits are not always sufficient," said Andruski. "Our goal at USP is to know why certain controls and quality systems are in place."

Supplier Usage

At present, most drug ingredient suppliers participating in the USP Ingredient Verification Program are located outside the United States, in locations such as in India and China. Andruski said these companies want to sell products to U.S.-based drug manufacturers and provide assurances that their ingredient is of a high quality.

"The hope is that as recognition for the program grows, we will see more Western Europe and U.S. ingredient manufacturers engaging with us," he said. "We know gaps in quality control may occur with any suppliers, regardless of their geographical origin, if proper monitoring isn't taking place. Companies that will work with us are going to be the quality companies, the better companies. And I think we'll see some companies differentiating themselves as the market continues to grow."

Drug Manufacturers Drive Verification

Drug product manufacturers can use this program as part of their supplier qualification process.

"The goal is for drug product manufacturers to drive the demand for the program by continuing to prioritize indicators of high quality, such as when companies go through the trouble of getting verified," said Andruski. "In theory, drug manufacturers would be more likely to buy the USP-verified materials because they know that USP is looking at the quality of that ingredient and verifying that the specifications are accurate."

He added that having the assurance of USP verification will allow drug makers to focus their resources on the higher risk materials that require close monitoring.

Conclusion

Risk assessment provides a far-reaching view of a supplier's quality system. As part of that risk assessment, the USP Ingredient Verification Program provides an independent assessor's view of quality through a GMP audit, testing, and detailed documentation review. A drug maker buying an ingredient from a supplier that has gone through USP verification can do so with increased confidence that no adulteration or substitution has occurred, said Andruski.

"You really want to ensure the quality of the ingredients going into a product, and that is where good risk assessment, supplier qualification, and supplier verification comes into play," said Andruski. "A product is only as good as the ingredients that make up that product."

Reference

1. Pharma 2020: Supplying the future, PricewaterhouseCoopers, www.pwc.com/gx/en/pharma-life-sciences/pharma-2020/assets/pharma-2020-supplying-the-future.pdf, accessed Nov. 30, 2017.