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Managing Risk in a Complex Excipient Supply Chain

Regulations and industry guidelines focus on ensuring excipient safety by specifying risk assessments and shared responsibility.

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By Cynthia A. Challener [1]
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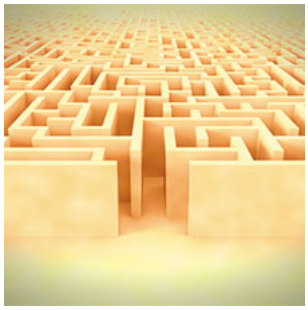

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Excipients are crucial ingredients in final drug formulations with potential impacts on product quality, stability, tolerance, release profiles, local distribution and availability, and thus overall efficacy and safety. Recent regulations have increased the requirements for drug manufacturers and excipient suppliers with respect to ensuring the quality and safety of excipients. The emphasis continues to be on the use of risk assessments and the growing recognition that excipient producers and pharmaceutical companies have shared responsibility for ensuring excipient safety.

Updated guidelines

Excipients are becoming a top priority among regulatory agencies. Regulatory bodies in the United States, European Union (EU), and Japan, as well as those in the 'BRICK' (Brazil, Russia, India, China, and Korea) countries, are modifying existing and/or introducing new regulations for finished pharmaceutical products that specifically address excipients, either directly or indirectly. Many of these regulations have an impact beyond domestic production of drug products, according to Priscilla Zawislak, global regulatory affairs advocacy manager with Dow Pharma Solutions. National pharmacopeias are also placing a greater emphasis on standards for excipients.

Regulations on excipient risk assessment were issued by the European Medicines Agency (EMA) in 2015 (1) with implementation required by March 21, 2016. An update of the annex to the European Commission's guideline on excipient labeling by EMA on Oct. 9, 2017 (2) included the expansion of safety warnings for 10 excipients and the addition of five new excipients to the list, according to Mario DiPaola, senior scientific director at Charles River Labs.

"Recent draft guidance documents issued by FDA, such as the *Abbreviated New Drug Applications* (ANDA), *Refuse to Receive*, and *Controlled Correspondence* guidances, are examples of why drug product manufacturers must have a better understanding of what's needed to comply," adds Zawislak. "Open communication with suppliers about the composition, functionality, and performance of excipients in a drug product is essential. Excipients are no longer regarded as inactive and it is no longer sufficient to simply provide excipient specifications in an investigational new drug application (ANDA). FDA now requires drug product manufacturers to tell the full story about the role and interaction of the excipients with the API in final drug products," she continues.

In China, "Bundling Review" requirements were included within the *Chinese Pharmacopoeia* 2015 standards (3) and will be retained in its future 2020 version.

Industry has also been active in updating voluntary guidelines on ensuring excipient quality and safety. The updated International Pharmaceutical Excipients Council (IPEC) *Quality Agreement Guide* (4) by the IPEC Federation was issued in November 2017. Earlier in the year, the group also published updated guidelines on both excipient good manufacturing practice (GMP) (5) and good distribution practice (GDP) (6), as well as excipient risk assessments (7), according to DiPaola.

Regulatory proliferation driving communication

The proliferation of regulations in many different countries and regions around the world has resulted in different excipient requirements that are often not fully aligned with one another. Global excipient suppliers must work with customers to find ways to meet these challenges across multiple regions, sometimes for one particular type of application, according to Zawislak.

"More diligence is required when excipients fall under drug or API regulations," she says. For example, she notes that Brazil and India have requirements for a specific amount of remaining shelf life for imported drug products, which includes excipients, APIs, and finished drug products. Defining a shelf life in this case is different than for APIs and drug products imported into other countries. "Open communication between raw material suppliers and formulators is particularly important here, because without knowledge of the end use, suppliers cannot help ensure that formulations are in compliance," Zawislak states.

With the proliferation of more regulations for excipients in the BRICK countries and in emerging countries, Dow Pharma Solutions is also initiating dialogue with regulatory agencies as well as customers to address some of these differences. "We see this situation providing a good opportunity, because it opens lines of communication and leads to greater awareness of the key role excipients have in pharmaceutical products," asserts Zawislak.

Contamination concerns

In addition to focusing on excipient quality in recent years, regulatory agencies have strengthened their positions on preventing drug adulteration of both APIs and excipients by enacting a number of new regulations, ultimately requiring tighter control of the manufacturing processes and testing, according to DiPaola.

"A major area of concern in excipient quality is contamination from a number of potential sources, including viruses; microbial and endotoxin/pyrogen contaminants; transmissible spongiform encephalopathy; and impurities resulting from raw materials, byproducts generated during processing, and product degradants. Lack of sterility for excipients deemed sterile is also a potential issue," DiPaola says.

These problems can occur for a number of reasons ranging from the lack of dedicated equipment and/or facilities for the manufacturing of excipients; poor environmental control during manufacturing; and/or inappropriate storage and shipping conditions, among others.

Risk assessment approach

Given this sizeable list of concerns, regulatory bodies have begun to expect excipient users (e.g., drug manufacturers) to perform extensive risk analyses and implement mitigation plans for situations deemed to be high-risk. "Such mitigation strategies may require more testing of excipients for the presence of contaminants or require more control of the manufacturing process and distribution," notes DiPaola.

One example is the EU guideline that became effective in 2016. It requires more formalized risk assessments to be conducted on a regular basis. This approach is not limited to the EU, however, according to Zawislak. "We have seen risk assessments become more of a standard globally as a tool in managing raw material and supplier qualification," she says.

The revised IPEC-PQG GMP Guide, *IPEC-PQG Good Manufacturing Practices (GMP) for Pharmaceutical Excipients 2017* (5), which was published in May 2017, was updated partly in response to the increased requirements for drug manufacturers to perform risk assessments for excipients to determine the appropriate level of GMP that should be used to produce them. It also takes into account third-party standards (EXCiPACT and ANSI) "against which excipient suppliers can be certified to provide assurance that they are operating in conformance with excipient GMP," according to an IPEC news release (8).

Shared responsibility

With increasing regulatory and business demands, the relationships between excipient suppliers and medicinal product manufacturers have never been so important, according to Dominik Odenbach, director, global regulatory and external affairs, Pharma & Human Nutrition, BASF. "A mutual understanding of what is appropriate to ensure the safe and reliable supply of high quality excipients is essential, and it is in the quality agreement that these expectations can be defined," he explains.

The recently revised *IPEC Quality Agreement Guide* (4) reinforces the fact that the business of ensuring excipient safety is a shared responsibility between excipient users and suppliers, according to DiPaola. "The quality agreement enables the drug manufacturer and the excipient supplier to establish a partnership through which all quality requirements and responsibilities are clearly delineated. This legally binding agreement provides a process by which costly product quality issues can be minimized and ensures that the drug manufacturer can meet its regulatory expectations and requirements," he explains.

"We have found that use of the IPEC QA templates published in 2009 significantly facilitate and accelerate the negotiations between excipient suppliers and customers and, hence, reduce the workload related to the review and discussion of quality agreements for all parties involved," adds Odenbach. "BASF strongly promotes the use and further optimization of standard templates."

The major change incorporated in this latest version of the *IPEC Quality Agreement Guide* is the addition of the Manufacturer's Statement. The original version of the guide addressed the need to have a quality agreement between the excipient manufacturer and its direct customer (e.g., the drug product manufacturer or distributor) and between the distributor and its customer.

In recent years, customers who buy from distributors have been requesting quality agreements with excipient manufacturers as well. However, because there is no direct business relationship between the excipient manufacturer and the distributor's customer, formalizing a three-way company agreement would be necessary—and complicated, according to Zawislak.

The Manufacturer's Statement addresses this gap. It is written by the excipient manufacturer to define its quality responsibilities for manufacturing the excipient through its lifecycle (e.g., maintenance of a quality management system, adherence to GMPs, change notification, etc.). The Manufacturer's Statement is signed and dated by the manufacturer and can then be attached to agreements between distributors and their customers.

"It is important to note that the Manufacturer's Statement is not a full quality agreement between three companies or a stand-alone document. It is, however, a signed statement from the excipient manufacturer regarding its quality responsibilities, which are generally the same regardless of the end-use customer. As a result, the need for a three-way quality agreement is eliminated, yet each party is protected with respect to quality assurance," Zawislak observes.

Variability is an issue

Aside from variations in the regional regulations designed to ensure excipient safety, a key challenge for the pharmaceutical industry is the lack of integrity and transparency within the excipient supply chain and variability in the quality of excipients, according to DiPaola.

Significant test method variability is another issue for Ann Gulau, a quality assurance scientist at Dow Pharma Solutions. “This variability should be considered when setting monograph and specification limits. Currently, there are many tests that have much higher variability than the monograph specification limits. As a result, significant amounts of material are discarded as unsuitable for pharmaceutical use, despite no real safety or quality concerns,” she explains.

Further issues for DiPaola are the limited amount of testing currently performed for excipient release and the lack of robust stability data.

Updated and harmonized monographs needed

Most current excipient testing is conducted according to pharmacopeia methods, which like excipient regulations, vary on a regional basis.

“It is not value-added to measure essentially the same properties with different methods to satisfy all regional requirements. There are frequently minor regional test differences in various pharmacopeia that require additional testing or studies to prove equivalency. This additional testing does not improve product quality or patient safety,” asserts Barbara Serr, business analytical leader for Dow Pharma Solutions.

For instance, despite the global pharmacopoeial harmonization efforts in the US, Europe, and Japan, the *Chinese Pharmacopoeia* (*CP*) develops individual excipient monographs with separate requirements, according to Odenbach. “For an excipient manufacturer, higher analytical efforts and costs to release globally used materials are necessary to introduce products to the Chinese market, if possible at all. These stringent Chinese requirements create new hurdles to trade, restricting choice, and raising costs, also for pharma manufacturers or consumers,” he says.

Complicating this particular issue is the lack of timely availability of an official—and therewith binding—English translation of the *Chinese Pharmacopoeia*. “In preparation for *CP* compliance, analytical method set up and validation work must be performed in the release labs of the excipients manufacturers, for non-Chinese speaking lab personnel an impossible task. In addition, from a technical and testing point of view, several excipient monographs require technically non-achievable limits and/or demand the performance of technically non-feasible methods. Furthermore, scientific cooperation with the Chinese Pharmacopoeia experts in advance is difficult and protracted,” Odenbach states.

Many of these methods also are in need of modernization. “Current methods tend to be highly time consuming, frequently lack appropriate sensitivity, and generally rely on older analytical technologies,” observes DiPaola. Adds Serr: “Continuation of old limit tests to satisfy some regional pharmacopeia is unwarranted and unnecessary testing. Additionally, some test items may simply be historic without any real relationship to patient safety. Monographs should be updated with a focus on items that are real safety concerns instead of simply continuing historical practices without real purpose.

One recent example of an improvement is the conversion from old wet chemical methods to the use of inductively coupled plasma-mass spectrometry for elemental impurity determinations. “Using this advanced analytical technique has revealed that many excipients do not contain any of the elements of concern,” Serr notes.

DiPaola would like to see more use of mass spectrometry for the detection and characterization of impurities/contaminants and newer ultra-high-performance liquid chromatography technology with high-resolution columns.

Dynamic situation

Ultimately, according to DiPaola, pharmaceutical manufacturers are held accountable for the overall quality and safety of pharmaceutical products. They are thus applying more pressure on excipient suppliers for greater control of the quality and safety of their excipients, as well as tighter control of excipient distribution.

At the same time, regulation in the pharmaceutical industry is a dynamic situation, according to Zawislak. “Patient safety is the ultimate goal and often requires development of regulations and standards to achieve that goal in an ever-changing world. Regulations also need to keep pace with emerging technologies and innovations in drug development,” she observes.

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