



Excipients: A Blind Spot in Ensuring Medicine Quality and Supply Chain Resilience

USP Global Public Policy Position





ISSUE

Excipients play an important role in drug development, delivery, effectiveness, and stability and are critical to pharmaceutical quality and supply chain resiliency and reliability. Excipient quality issues and shortages have contributed to supply chain disruptions, drug shortages, and adverse patient health outcomes. For example, excipients and raw materials have been the source of contamination and adulteration of pharmaceutical products despite the responsibility of manufacturers to assure the quality of the materials produced or used.¹ However, the totality of supply chain risks posed by excipients is unknown, as no single entity has a complete picture of where critical excipients are made, and at what volume.

Without additional visibility into excipients supply chains, public policy interventions to prevent or mitigate drug shortages cannot adequately consider or address the potentially significant downstream risks excipients pose to the overall medicines supply chain. A risk-benefit based regulatory scheme can help maintain the quality of excipients and raw materials through medicine supply chains and bolster supply chain resiliency. Additional regulatory oversight and guidance are needed to ensure that high-risk excipients or components are more rigorously evaluated to safeguard medicines quality and medicine supply chains.

POSITION

Policies and initiatives to identify and respond to risks and vulnerabilities within the upstream medicines supply chain need to recognize the inextricable link between excipient quality and supply chain resiliency, and overall medicines quality and supply chain resilience. U.S. Pharmacopeia (USP) supports policies that:

1. Recognize excipients as a critical component of drug shortage policy solutions

Considering potentially significant downstream impacts of excipient shortages and supply chain disruptions, USP underscores the need for excipients to be considered and included in policy solutions to mitigate or prevent drug shortages, which may include stockpiling decisions, geographic diversification initiatives, the development of essential or vulnerable medicines lists, and the use of alternative excipients in drug manufacturing due to impurity and safety concerns for existing excipients.

2. Encourage mapping and assessing vulnerabilities within excipients supply chains

USP calls for additional investments in and support of efforts and initiatives to:

- Conduct ongoing surveillance of the pharmaceutical supply chain, including excipients;
- Provide alerts on risks, vulnerabilities, and anticipated drug ingredient and product shortages; and
- Conduct research to fill the gaps in the mapping of the pharmaceutical supply chain, including excipients.

3. Promote adopting a risk-benefit based regulatory approach for excipients

USP supports the adoption and use of a risk-benefit based regulatory approach for excipients, which will identify excipients that are vulnerable to quality and sourcing issues and that could subsequently contribute to supply chain disruptions. Such a risk-benefit based regulatory approach should be informed by a list of contributing risk factors, ranging from volume, sourcing, and manufacturing complexity, to excipient stability and the potential for adulteration or contamination.

Enhancing visibility into excipients supply chains is essential to properly focus efforts to prevent or mitigate drug shortages



DISCUSSION

Background

In medicines, excipients include everything except the active pharmaceutical ingredients (APIs) and play a critical role in drug development, delivery, effectiveness, and stability. Excipients comprise up to 90 percent of a medicine's total ingredients and serve important functions as binders, disintegrants, coatings, preservatives, colors, and flavorings.² Excipients are essential for delivering a medicine's APIs and affect how well a drug performs in the body. They play a crucial role in the pharmaceutical industry, streamlining the processing of the drug delivery system during manufacturing, boosting the performance, effectiveness, and/or delivery of the drug, and helping to maintain the integrity of the drug during storage. Excipients are important to the overall formulation of a drug, they must be quality-assured.

Like APIs, some excipients are chemicals that have complex manufacturing processes and the potential for stability issues. Excipients can be a source of contamination and adulteration of pharmaceutical products. Documented excipient quality issues have caused true and significant patient harm, including deaths.¹ Drug products contaminated with diethylene glycol (DEG) have led to hundreds of deaths over the past 85 years.³ In 1937, more than 100 people, many of them children, died in the United States after ingesting diethylene glycol-tainted "Elixir of Sulfanilamide."³ The 1937 incident in the U.S. led to the enactment of the Federal Food, Drug, and Cosmetic Act requiring drug manufacturers to prove the safety of their products before they can be marketed in the United States. Congress also required that drugs must generally meet standards for identity, strength, quality, and purity found in the *United States Pharmacopoeia–National Formulary* published by USP. More recently, in 2022

and 2023, confirmed or suspected contamination of over-the-counter children's cough syrups with DEG and ethylene glycol (EG) led to the deaths of more than 300 children in Africa and Asia.⁴ While these excipient quality concerns and impacts were publicized and reported, the source of drug product contamination is not always known. A lack of awareness remains regarding which excipients are most vulnerable to quality issues and supply chain disruptions and are essential to supply chain security. In addition, it is unclear which drug shortages—and how many—have been caused by quality issues associated with excipients.

While the location of finished dosage form (FDF) and API manufacturing facilities is known, there is limited understanding within governments or in the private sector about where many of the key ingredients used in the manufacturing of pharmaceuticals—including excipients—are made, and at what volume. When quality issues associated with excipients arise, finding the source of contamination or adulteration remains difficult, as current visibility into the origin of the excipient and tracking of the excipient supply chain are insufficient. Greater visibility of the origin of excipients is critical to identify the original manufacturer of an excipient, and the original Certificate of Analysis (COA) and assess the impact of excipient suppliers and distributors on excipient products ultimately used in drug manufacturing. Challenges to improving the visibility of the excipients supply chains, as well as to quality and regulatory oversight of excipients, are compounded by certain realities:

- 1) excipients may not be specifically made for use in specific drug products;
- 2) excipients are often available from multiple global suppliers;
- 3) excipients are used for products and industries beyond pharmaceuticals, including the food, cosmetic, or personal care industries;

- 4) excipients manufactured specifically for pharmaceutical use sometimes have special grades available; and
- 5) multisource suppliers of the same grade of excipient can result in batch-to-batch or supplier-to-supplier variability, including potentially performance differences.⁵

A lack of traceability of the excipient supply chain also persists.⁶ From the excipient manufacturer to the excipient user (the drug manufacturer), excipients can potentially pass through many intermediaries. This creates a blind spot in the visibility of this supply chain and in excipient quality since sources of contamination or adulteration and threats to product effectiveness and stability can occur at any point of the supply chain.

USP General Chapter <1080> *Bulk Pharmaceutical Excipients—Certificate of Analysis* can serve as a guide for the preparation and appropriate use of a COA for pharmaceutical excipients.⁷ The goals of the chapter are to standardize the content and suggest a format for COAs for excipients, and to clearly define the roles and responsibilities of excipient manufacturers and distributors. By providing this foundation for mutual understanding, the COA will serve as an important element of the overall supply chain controls needed to provide the user with assurance of excipient conformance to specification and its suitability for use in pharmaceuticals.

Excipients must be recognized as a critical component of drug shortage policy solutions

Geographic concentration of excipient suppliers has significant downstream impacts. Even if there is geographic diversification of API and FDF manufacturing, such resilience efforts could be undermined if drug manufacturers rely on the same excipient supplier facing a supply chain issue. As excipients are essential to ensuring a medicine will work as intended to achieve its therapeutic effect, breakdowns of critical excipient supply chains can have significant implications. For example, magnesium stearate is included in 32,060 drug products according to NIH DailyMed, including medicines to treat high cholesterol, high blood

pressure, diabetes, and bacterial infections.⁸ Accordingly, shortages of or supply chain disruptions associated with widely used excipients such as magnesium stearate could impact millions of patients.⁹ **Considering the potentially significant downstream impacts of excipient shortages and supply chain disruptions, USP underscores the need for excipients to be considered and included in policy solutions to mitigate or prevent drug shortages, which may include stockpiling decisions, geographic diversification initiatives, the development of essential or vulnerable medicines lists, and the use of alternative excipients in drug manufacturing due to impurity and safety concerns for existing excipients.**

Vulnerabilities within excipients supply chains need to be mapped and assessed

Foundational mapping of the entirety of the pharmaceutical supply chain to identify vulnerabilities and threats along its segments—including excipients—is lacking. There is a need to identify, characterize, and quantify risks and vulnerabilities throughout the medicine supply chain—including excipients—in a way that yields actionable and timely insights and informs effective decisions and solutions to improve medicine supply chain resiliency and help mitigate or prevent drug shortages. **USP calls for additional investments in and support of efforts and initiatives to conduct ongoing surveillance of the pharmaceutical excipients supply chains; provide alerts on risks, vulnerabilities, and anticipated drug ingredient and product shortages; and conduct research to fill the gaps in the mapping of the pharmaceutical supply chain, including excipients.**

Improving the quality of excipients is critical to ensure supply chain resiliency

To help ensure medicine quality, which is inextricably linked to supply chain resiliency, it is important for manufacturers and regulators to confirm the consistent quality of drug product ingredients, including excipients, regardless of where they are made. An excipient ultimately needs to be safe in the amount it will be used, perform its intended



function in the product, not adversely affect the bioavailability or performance of the active drug, and be manufactured according to appropriate good manufacturing practices.

Adherence to public standards supports excipient quality

Public quality standards, including validated test procedures, acceptance criteria, other requirements, and reference materials, can help manufacturers and regulators verify the identity, strength, and purity of excipients used in medicines, which increases the availability of quality medicines and builds confidence that medicines will perform as expected. Such quality standards are included as documentary standards in the *United States Pharmacopeia–National Formulary (USP–NF)*, and USP Reference Standards for excipients have been tested and approved as suitable for use as comparison standards in *USP–NF* tests and assays. *USP General Chapter <1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients* provides guidelines for methods, facilities, and manufacturing controls to be used in the production of pharmaceutical excipients to ensure that excipients possess the quality, purity, safety, and suitability for their claimed use.¹⁰ Recognizing the importance of evaluating and qualifying current and new excipient suppliers, *USP General Chapter <1083> Supplier Qualification*, which includes excipients, provides a quality risk-based approach on how to select, assess, approve, and monitor suppliers of ingredients (including excipients), packaging materials, and other components and services.¹¹ In addition to standards, USP offers resources such as the [DEG toolkit](#)¹² and educational programs to promote pharmaceutical and excipient quality and safety and prevent patient harm.

Excipient quality can be enhanced using a risk-benefit based regulatory approach

Building upon the adherence to public standards to improve the quality of excipients, additional regulatory oversight and guidance are needed in the area of risk assessment. Excipient risk can be assessed based on the physical, chemical, and biological hazards present, including microbiological contamination. The risk posed by excipients can vary based on the route of administration of the affected drug product and the function of the excipient. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) quality guideline Q9, *Quality Risk Management*, provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality, including excipients.¹³ The two primary principles of quality risk management included in ICH Q9 are: 1) the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and 2) the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.¹³

To date, countries and regions have taken a variety of approaches to excipients regulation. Overall, regulatory oversight of excipient manufacturing and distribution practices in many regions and countries, including the United States places regulatory burden on the drug manufacturer. This paradigm causes a significant risk to the supply chain and to drug manufacturers who rely on COA and reduced testing without appropriate data verification.



In the United States, excipients can be qualified once they are included in an approved new drug application, serving a defined function within an approved drug product.¹⁴ After three or more drugs containing an excipient appear in a U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER)-approved drug product, excipients are listed on FDA's CDER Inactive Ingredient Database (IID).¹⁵ According to the FDA, “[f]or new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and may require a less extensive review the next time it is included in a new drug product reflecting the same maximum daily exposure and maximum potency per unit dose as outlined in IID. For example, if a particular inactive ingredient has been approved in a certain dosage form at a certain potency, a sponsor could consider it safe for use in a similar manner for a similar type of product.”¹⁶ Based on findings from a survey USP developed and launched in March 2019, the current regulatory approval pathway for excipients creates a challenge for the use of novel excipients.¹⁶ As such, novel excipients are addressed in a separate USP public policy position document.

Europe has taken a more direct, risk-based approach to excipients regulation. Since March 2016, pharmaceutical manufacturers in the European Union have been required to implement good manufacturing practice (GMP) requirements, including completed risk assessments, for each excipient used.¹⁷ Leading up to this requirement, the European Commission (EC) released *Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use*,¹⁸ which state “quality risk management principles should be used to assess the risks presented to the quality, safety and function of each excipient and to classify the excipient in question, e.g., as low risk,

medium risk or high risk.” The guidelines then state “for each excipient from each manufacturer used, the manufacturing authorisation holder should identify the risks presented to the quality, safety, and function of each excipient from its source – be that animal, mineral, vegetable, synthetic, etc. – through to its incorporation in the finished pharmaceutical dose form. Areas for consideration should include, but are not limited to:

- (i) transmissible spongiform encephalopathy;
- (ii) potential for viral contamination;
- (iii) potential for microbiological or endotoxin/pyrogen contamination;
- (iv) potential, in general, for any impurity originating from the raw materials, e.g., aflatoxins or pesticides, or generated as part of the process and carried over, e.g., residual solvents and catalysts;
- (v) sterility assurance for excipients claimed to be sterile;
- (vi) potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities;
- (vii) environmental control and storage/transportation conditions including cold chain management, if appropriate;
- (viii) supply chain complexity;
- (ix) stability of excipient;
- (x) packaging integrity evidence.”

Countries can leverage existing frameworks for assessing and managing excipient risk, including that outlined in ICH Q9, to establish and improve regulatory oversight of excipients. Using a risk-benefit based approach to excipient regulation, tools and resources can be allocated more efficiently, and higher-risk excipients can be more rigorously evaluated to safeguard the quality of the final drug product. **As such, USP supports the adoption and use of a risk-benefit based**

regulatory approach for excipients, which will identify excipients that are vulnerable to quality and sourcing issues and that could subsequently contribute to supply chain disruptions. Such a risk-benefit based regulatory approach should be informed by a list of contributing risk factors, ranging from volume, sourcing, and manufacturing complexity, to excipient stability and the potential for adulteration or contamination.

ABOUT USP

USP is an independent, scientific, global non-profit organization founded in 1820 when eleven physicians took action to protect patients from poor-quality medicines. Convening in the old U.S. Senate Chamber, they published a national, uniform set of guidelines for medicines called the U.S. Pharmacopeia. A core pillar of USP's work is to help strengthen the global supply chain so that the medicines, dietary supplements, and foods that people rely on for their health are available when needed and meet quality standards as expected and required. USP is governed by more than 500 organizations, including scientific, healthcare practitioner, consumer, and industry organizations, as well as dozens of government agencies, who together comprise the USP Convention.

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