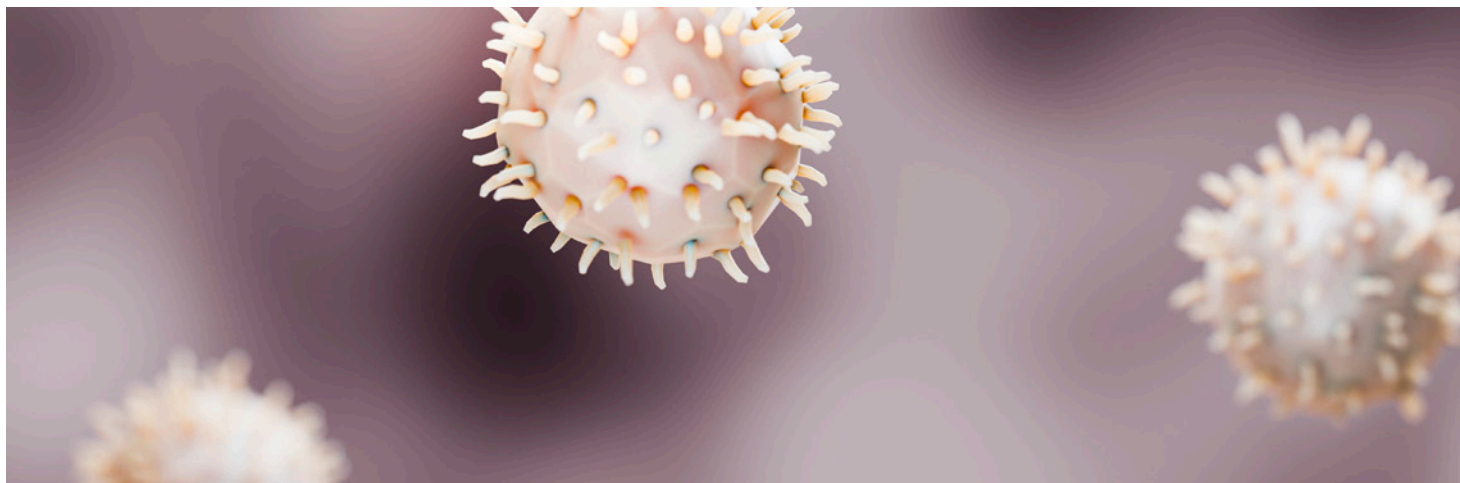


Fostering the Use of Novel Excipients in Drug Products

USP Public Policy Position





ISSUE

Excipients are essential to the global supply of safe and efficacious medicines. Traditionally, excipient specifications were established with a primary focus on their intended use in the drug product, and a secondary focus on excipient composition. However, this is changing; the current formulary of excipients does not address formulation challenges or issues experienced by excipient makers and drug makers, especially for new and emerging therapies and modalities. Along with continuous advancements in novel and therapeutic biological drugs, complex generic drugs increasingly use new, complex excipients such as complex polymers, and novel excipients are frequently introduced as part of a new drug product's development.

Excipients with novel properties can have a significant impact on drug development and, as a result, the number and types of treatments available to patients. To address the advancements in the arena of novel excipients, augmented collaboration, communication, and coordination are needed between public and private stakeholders to facilitate the provision of scientific input and the exchange of information, and to remove current barriers in using novel excipients for new therapeutics and advanced formulations. Additional regulatory clarity is needed to provide a regulatory approval pathway for excipients that supports the use of novel excipients.

POSITION


Policies and initiatives to facilitate the introduction and use of novel excipients should rely not only on increased cooperation and coordination between stakeholders, but on regulatory developments to support their use in new therapies and modalities. U.S. Pharmacopeia (USP) supports:

1. Convening stakeholders to share information, scientific input, and lessons learned

USP supports efforts to convene public and private stakeholders in order to foster dialogue and provide scientific input to help build a path forward for developing novel excipients in an environment of regulatory uncertainty.

2. Building a transparent, independent pathway for novel excipients

USP supports the development of a transparent, independent approval pathway for novel excipients. Unlike drug products, there is no U.S. Food and Drug Administration (FDA) regulatory pathway outside of its drug application and approval process to review and evaluate the safety and toxicity of an excipient for introduction into a new drug, abbreviated new drug, or non-prescription drug – all excipients are reviewed and approved as part of the drug application process. This may create reluctance on the part of new drug developers to use a novel excipient in a drug application



Increased public-private collaboration is needed to help remove barriers to novel excipient introduction, innovation, and use

since there may be a risk of the FDA determining that the excipient-related data provided in the application is not sufficient for the proposed level of exposure, route of administration, duration of exposure, and patient population. An entire drug application using a novel excipient could be rejected due to uncertainty surrounding acceptance of the excipient by the FDA.

DISCUSSION

Background

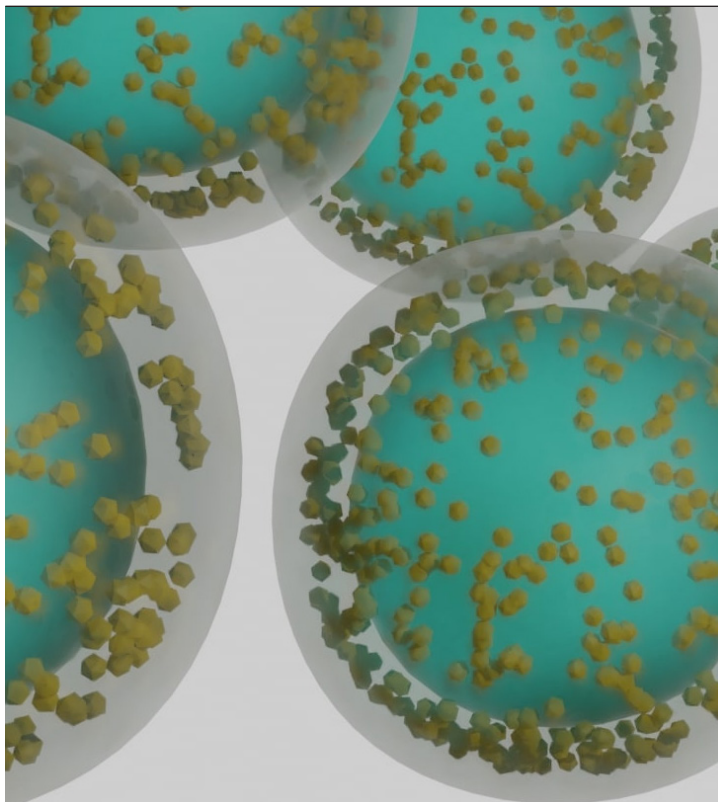
A novel excipient is defined by the FDA as any excipient that has not been previously used in FDA-approved drugs and does not have an established use in food.¹ In medicines, excipients include everything except the active pharmaceutical ingredients (APIs) and play a critical role in drug development, delivery, effectiveness, and stability. Excipients comprise up to 90 percent of a medicine's total ingredients and serve important functions, acting 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.

Novel excipients are critical to the development of new drug modalities and therapies. However, there are a limited number of novel excipients to choose from, which creates challenges and limitations to drug development and innovation. Understandably, pharmaceutical manufacturers may be reluctant to introduce a novel excipient into a

new drug application, as there is a high level of risk and uncertainty surrounding the regulatory acceptance of novel excipients. As a result, a second-best formulation that uses established excipients is often pursued, or a drug development project is halted.

USP developed and launched a novel excipients survey in March 2019, the goal of which was to better understand the impact of the current drug approval pathway on novel excipient innovation. The purpose and objectives of the survey were to identify any challenges impacting stakeholders related to novel excipients and to better understand stakeholders' views on the current state of innovation in excipients development. The survey, the results of which were published in 2020, showed that more than three-quarters of users faced challenges in using novel excipients.³ Challenges faced by survey respondents ranged from inability to maintain the stability of final drug products and overcome bioavailability and solubility issues, to excipient limitations resulting in drug reformulations, delays, or discontinuation of drug formulations.

Increased communication, collaboration, and coordination is needed between public and private stakeholders to remove the current barriers to using novel excipients for new therapeutics and advanced formulations. Building a community that encompasses excipient formulators and manufacturers, pharmaceutical manufacturers, research and development scientists, academia, quality assurance and regulatory affairs professionals, regulators and other government officials, and non-profit organizations could enable the sharing of feedback and contributions toward proposed and actual methods to ensure the quality of novel excipients. The formation of such a community could help support innovation, reduce the risk associated with novel excipient use, and bring new therapeutics to market. USP has



created a Novel Excipients Knowledge Hub (<https://go.usp.org/novel-excipients>) to share information and resources that will include updates on USP's work to develop standards for novel excipients. Such information sharing needs to be augmented by improved and increased stakeholder interactions and communication. **USP supports efforts to convene public and private stakeholders in order to foster dialogue and provide scientific input to help build a path forward for developing novel excipients in an environment of regulatory uncertainty.**

Developing a transparent, independent pathway for novel excipients is critical to foster and support their use in drug products

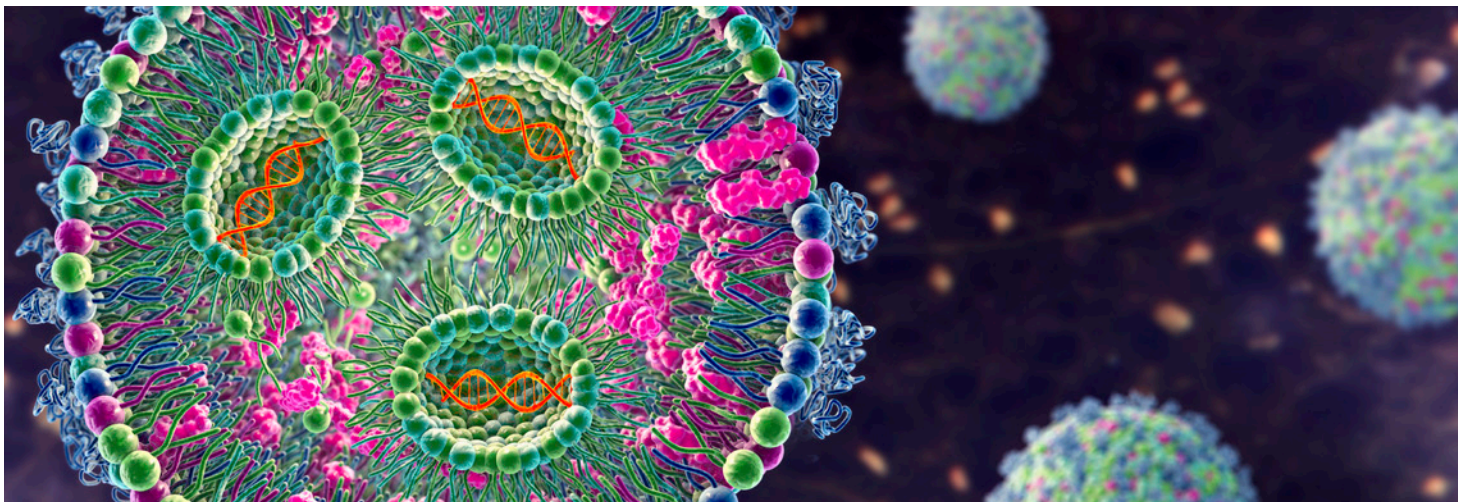
The development, updating, and use of quality standards can serve as a mechanism to better support the introduction, innovation, and use of novel excipients, and to address the challenges faced by stakeholders. Ultimately, the development and use of novel excipients are inextricably linked to the release of clear regulatory guidance and the implementation of an independent approval pathway for novel excipients.

Development of public standards can support novel excipient quality

Public quality standards can help manufacturers and regulators advance efforts to remove barriers to using novel excipients in drug products. USP has convened a Novel Excipients Expert Panel (NEEP) of toxicologists from around the world, formed by the Excipients Test Methods Expert Committee chair, to revise and update *USP General Chapter <1074> Excipient Biological Safety Evaluation Guidelines*. The purpose of this chapter is to provide a mechanism for excipient manufacturers to help build a set of current and up-to-date toxicity data tests for the safety assessment of novel excipients dependent on intended use, duration of use, and dosing.⁴ In addition, USP is applying the "emerging standards" concept to support industry on guidelines pertaining to quality aspects of novel excipients. An emerging standard is a standard under development made available at an earlier stage for stakeholder input and contributions. Emerging standards are intended to improve USP's official standards elaboration process by increasing transparency and allowing for broader stakeholder participation prior to formal notice and comment through publication in the Pharmacopeial Forum. The application of the "emerging standards" concept to novel excipients therefore can provide a framework to convene stakeholders, as well as enable stakeholders to engage with USP on novel excipients at the exploratory stage of development (non-compendial). Ultimately, emerging standards can provide a mechanism to better support the development of quality novel excipients, address the challenges faced by stakeholders, and create a path forward for developing novel excipients in an environment of regulatory uncertainty.

Independent evaluation of novel excipients can promote their development and use

The results of USP's 2019 survey on novel excipients also indicated that the lack of both clear regulatory guidance and an independent regulatory approval pathway for novel excipients in the United States is impeding their development and use. Excipients are not independently evaluated; evaluation occurs only through an excipient's inclusion in



a drug application. In the United States, excipients can be qualified once they are included in an approved new drug application and serve a defined function within an approved drug product.⁵ After three or more drugs containing an excipient appear in an FDA Center for Drug Evaluation and Research (CDER)-approved drug product, excipients are listed on FDA's CDER Inactive Ingredient Database (IID). 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."⁶

In the United States in 2021, following industry requests and USP stakeholder engagement, the FDA created an independent pilot review program for novel excipients, Pilot Program for the Review of Innovation and Modernization of Excipients (PRIME), to review toxicity and quality data. The pilot launched in September 2021, with applications accepted for possible inclusion until December 2021. The aim of PRIME is to allow excipient manufacturers to obtain FDA review of certain novel excipients prior to their use in drug formulations.¹ During the initial proposal stage, applicants submitted summaries to the FDA describing the proposed use, the drug development need, and the public health benefit of a novel excipient (e.g., new route of administration,

enhanced drug bioavailability, facilitating introduction of new technologies for serious and life-threatening diseases). Applicants selected for participation in the pilot program—limited to approximately four total during the first two years of the pilot program—are required to have a full data package and a timeline for its submission. The FDA has indicated that the completion of this phase will allow excipient manufacturers to obtain FDA review of certain novel excipients prior to their use in new drug formulations.

While the FDA PRIME program represents a step in a new regulatory direction for excipients, drug developers are currently reluctant to use novel excipients as there is no independent FDA regulatory pathway outside of its drug application and approval process to review and evaluate the safety and toxicity of an excipient for introduction into a new drug, abbreviated new drug, or non-prescription drug. FDA may determine that novel excipients are not fully supported by the submitted safety data such as for the proposed level of exposure, route of administration, duration of exposure, and patient population. An entire drug application using a novel excipient could be rejected due to uncertainty surrounding acceptance of the excipient by FDA. Considering the barriers to using novel excipients that exist in the normal application process for drug products, **USP supports the development of a transparent, independent approval pathway for novel excipients.**



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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