This article discusses the recent increase in FDA warning letters citing cGMP violations related to excipients and describes USP’s analysis of the excipient-related warning letters issued from 2013 through 2018. It also explains how USP’s programs and resources can help drug companies comply with FDA regulations.

In 2017 and 2018, the FDA’s Center for Drug Evaluation and Research (CDER) issued 38 warning letters to pharmaceutical firms in the US and 12 other countries for failing to test for identity of incoming excipients, failing to verify the information on excipient suppliers’ certificates of analysis (COAs) at regular intervals, or both. This compares with three warning letters in the four years from 2013 to 2016 that specifically cited excipients or inactive ingredients, according to an analysis by the US Pharmacopeia (USP) of FDA warning letters.
issued between 2013 and 2018. This increase represents a significant uptick in warning letters that expressly identify excipients or inactive ingredients in current good manufacturing practice (cGMP) violations.

We note that a majority of the 38 warning letters issued in 2017 and 2018 were sent to firms that manufacture over-the-counter (OTC) medicines. FDA has stated that in the past several years it has been working to inspect all facilities that had not been previously inspected [1]. The agency also noted that this work has contributed to an increase in basic cGMP problems identified in facilities making lower-risk OTC medicines.

According to the FDA’s Regulatory Procedures Manual, the agency issues warning letters for violations of regulatory significance. The FDA warning letters analyzed by USP are written notifications that the FDA has found manufacturers to have violated cGMP regulations such that their drug products are adulterated within the meaning of the Federal Food, Drug, and Cosmetic (FD&C) Act. The letters also inform the companies that they are responsible for correcting the problems cited and informing the FDA of their plans for correction. Warning letters give firms an opportunity to take voluntary and prompt corrective action before the agency initiates an enforcement action, if warranted.

According to the warning letters:

- Pharmaceutical manufacturers must perform at least one test to verify the identity of each drug component; and
- If relying on COAs from suppliers for conformity with other appropriate written specifications, manufacturers must validate and establish the reliability of the suppliers’ test analyses at appropriate intervals.

### Analysis of excipient-related FDA warning letters

USP staff reviewed the FDA warning letters posted on fda.gov for cGMP violations issued by CDER’s Office of Manufacturing Quality and the Office of Regulatory Affairs (ORA) district offices from 2013 through 2018 to pharmaceutical manufacturers that marketed drugs in the US. USP staff searched the letters for keywords that indicated excipient testing issues, such as excipient (or a specific excipient), inactive ingredient, drug components, or raw materials, separate from active pharmaceutical ingredients and noted the specific Code of Federal Regulations (CFR) violations cited in the warning letters. Table 1 shows the number of FDA warning letters issued to drug product manufacturers each year that mention excipients or inactive ingredients for the years analyzed.

Highlights of USP’s analysis of the 2017–2018 FDA warning letters include the following:

Failure to test component samples or validate supplier COA. Thirty-eight companies were cited between January 2017 and November 2018 for failing to conduct at least one identity test of incoming components of the drug product prior to release to production and/or failing to test for conformity to appropriate specifications for purity, strength, and quality of each component (or in lieu of such testing, failing to establish the reliability of their supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals).

Warning letter recipients were instructed to provide the FDA with the procedures they would use in the future to test incoming components, including excipients, for conformity with all appropriate written specifications for identity, purity, strength, and quality. If the recipients accept their suppliers’ COAs in lieu of testing the components for purity, strength, and quality, the warning letters direct the recipients to specify how they plan to establish the reliability of their suppliers’ test results through periodic validation.

**Import alerts.** Twenty-eight of the 38 companies that received FDA warning letters in 2017 and 2018 citing excipient testing deficiencies were located outside the US, including facilities in Australia, Austria, Canada, China, France, Hong Kong, India, Ireland, Mexico, South Korea, Spain, Taiwan, and the United Kingdom. The warning letters cited all of these facilities for multiple cGMP violations, and the FDA placed all but three of them on import alert.

According to the FDA’s website, placing a facility on import alert means that the agency has enough evidence to allow for the detention without physical examination (DWPE) of products from that facility that appear to be in violation of FDA laws and regulations. Furthermore, the FDA warning letters notified these companies that the FDA may withhold approval of any new applications or supplements listing their firm as a drug manufacturer and may continue to refuse admission of the companies’ products until all violations are corrected and the FDA has confirmed their compliance with cGMP.

Testing for diethylene glycol (DEG) in glycerin. FDA warning letters to six companies in 2017–2018 cited their failure to analyze lots of glycerin raw material from their suppliers for the presence of DEG and ethylene glycol.

DEG contamination in glycerin-containing pharmaceuticals was first recognized as a problem in 1937 and has resulted in numerous lethal poisoning incidents in

### Table 1

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<tr>
<th>Year</th>
<th>Excipient-related warning letters</th>
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<tr>
<td>2018</td>
<td>21</td>
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<td>2017</td>
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humans worldwide. Both the FDA and industry have tried to educate manufacturers to help ensure that they are using quality materials. USP has updated the glycerin monograph to include this adulterant as part of the required identification test, and the FDA issued a guidance on the testing of glycerin for DEG [2].

Five firms cited in 2017–2018 FDA warning letters that failed to follow USP’s established testing procedure for DEG contamination in glycerin raw material from their suppliers were instructed to provide a detailed risk assessment for their drug products containing glycerin that were within expiry in the US market. If the firms found that they had released any batch for which results were out of specification, they were instructed to indicate the corrective actions they would take, such as customer notifications and product recalls. One additional firm had already initiated a recall of all their drug products from the US market because of cGMP violations, including failure to test for DEG contamination in glycerin, prior to being issued an FDA warning letter.

**Contract manufacturers.** Several of the warning letters in 2017–2018 notified drug manufacturers that, as contract facilities, they are responsible for the quality of the drug products they produce regardless of the quality agreements they may have with their suppliers or product owners. In other words, they are required to ensure that drug products are made in accordance with the cGMP requirements for safety, identity, strength, quality, and purity. The FDA has issued a guidance on contract manufacturing and quality agreements [3].

**cGMP consultants.** In 36 of the 38 excipient-related warning letters from 2017–2018 that USP analyzed, the FDA strongly recommended that companies engage a qualified consultant to assist their firm in meeting cGMP requirements. In one of the remaining cases, the FDA acknowledged that the company had already hired a cGMP consultant.

**USP standards and resources**

USP’s science-based public standards and resources can help with drug component testing and supplier COA validation. For example, USP monographs and quality standards for excipients provide the appropriate, validated test procedures to establish the identity, purity, and limits of contaminants in an excipient. Currently, the United States Pharmacopeia and the National Formulary (USP–NF) includes more than 530 excipient monographs. In addition, USP is continually developing new monographs and public standards for materials that are not currently contained in USP–NF.

USP also maintains extensively characterized physical reference standards that help pharmaceutical manufacturers verify the quality of their excipient supply. These specimens have well-defined physical and chemical properties and when used in conjunction with the monograph help ensure the identity, strength, quality, and purity of materials.

USP encourages manufacturers to provide information for the development of new monographs or to donate reference standard candidate materials.

**Proposed general chapter on supplier qualification.**
To help further support managing complex supplier networks and their effect on quality, USP is working with stakeholders to develop an informational general chapter on supplier qualification throughout the pharmaceutical supply chain. This proposal, if approved by the expert committee, will provide standardized, robust solutions for supply chain partner management and development. USP is also developing a toolkit of solutions to provide guidance and help minimize risk to product quality caused by insufficient supply chain development and management.

USP and other stakeholders recognized the need for this general chapter due to research that suggested supply chain failures are not solely caused by suppliers but may be related to risks either induced by the drug product manufacturers or that the manufacturers could have avoided. The direct impact of this paradigm shift is that it refocuses resources from micromanaging suppliers to improving internal processes that can affect relationships and supplier performance. It should enable firms to take ownership of the failure modes impacting supply chain integrity and develop solutions that will help to reduce product quality risks. It will also promote understanding of critical root causes that affect supply chain integrity and, therefore, could create risks to product quality.

The proposed general chapter is now proceeding through USP’s public standards-setting process, with participation drawn from industry and regulatory professionals, and opportunities for public comment through USP’s Pharmacopeial Forum (PF). USP will announce when the proposed chapter appears in PF. Publication in USP–NF is expected by early 2021.

**Excipient verification program.** The USP Ingredient Verification Program for Excipients (USP IVP-E) provides independent third-party verification of the quality of ingredients and is designed to help drug product manufacturers qualify their excipient suppliers and verify COAs. The program includes annual GMP facility audits, annual random lot testing to help ensure that materials comply with their specifications, and quality control and manufacturing documentation reviews that help manufacturers routinely verify the information on excipient suppliers’ COAs.

The program goes beyond a paper or on-site GMP audit, evaluating not only what the supplier is doing to control quality and how those controls are being implemented, but also why those are the correct controls to help ensure product quality. The USP IVP-E GMP quality control and manufacturing product documentation review evaluates the quality of the excipient and the manufacturing process from start to finish, providing drug product manufacturers with a more standardized means of qualifying their suppliers on an annual basis. It is important to note that, according to FDA regulatory
requirements, regardless of whatever supplier validation program is in place, drug manufacturers are still required to conduct at least one test to verify the identity of each component of a drug product, including excipients.

Although drug manufacturers can use USP’s resources to help with excipient supply and testing issues, it is ultimately the responsibility of all drug manufacturers to confirm that their products comply with appropriate cGMP requirements to safeguard patient health.

References
3. www.fda.gov/media/86193/download.

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