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USP Statement on Third Party Laboratory Benzene Findings

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Rockville, MD—As a public standards-setting organization committed to safeguarding public health, the U.S. Pharmacopeia (USP) reviewed the recent Citizen Petition to the U.S. FDA by a third-party laboratory testing company. Its study described in the Citizen Petition found high levels of benzene, a known carcinogen, in commonly used topical acne treatments that contain benzoyl peroxide. USP issued the following statement in response to the Citizen's Petition:

"The petition referenced USP and indicated that modified USP methods and procedures were used in the study. The presence of unsafe levels of benzene should be taken seriously. Full transparency around the testing methods is also needed to understand the accuracy of these results. Only results from validated methods applied appropriately should be used to judge the quality of a medicine. As noted in USP's recent white paper, results from non-validated tests may be misleading, have negative impacts on the behavior of health plans and patients, and can result in drug shortages and reduced patient adherence to their treatment regimens.

"If changes are made to a USP method, complete validation data is necessary to demonstrate that a product meets USP standards. Alternate methods must produce results comparable to the relevant USP method (see USP *General Notices and Requirements* section *6.30 Alternative and Harmonized Methods and Procedures*). The petition does not provide critical details of method validation that would be necessary to understand whether the results are accurate.

"Entities can test products for benzene content utilizing validated USP standards used for pharmaceutical product testing worldwide. The standards include monographs for benzoyl peroxide and its dosage forms and General Notice *5.60.20 Residual Solvents in* USP *and* NF *Articles*, which states that the requirements of the *USP* General Chapter <467> *Residual Solvents* are applicable to all *United States Pharmacopeia and the National Formulary* articles. General Chapter <467> states that no more than (NMT) 2 parts per million (ppm) of benzene may be present. It is important to note that USP standards are applicable during the entire shelf life of the product, not just at the time of release.

"The third-party laboratory used a practice known as accelerated thermal degradation in its study, which is when the storage temperature of the product is increased to greater than label-indicated conditions to simulate degradation over a longer period. Accelerated thermal degradation may be an acceptable study. However, we cannot confirm that the elevated temperatures chosen in the study design (50 to 70° Celsius for a period of up to 18 days) reflect the changes expected to occur in the drug products under conditions of use and storage per the label.

“If excessive temperatures are used, the degradation may differ from what occurs under the recommended conditions of the label. The third-party laboratory demonstrated that stressed storage conditions outside the labeled recommendations can prompt product degradation, which is well-known and why manufacturers indicate storage conditions for products. Limited stability studies under labeled conditions should be used to confirm the validity of temperatures chosen for accelerated degradation and determine if benzene would still appear in the drug products above the USP pharmacopeial limit of NMT 2 ppm. The petition does not provide details of such study.”

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