November 1, 2022

Ms. Jessica Simpson
Senior Manager, Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 11-22-001-PN

Dear Ms. Simpson:

This letter reiterates FDA's recommendation to omit the USP-NF monographs for carbomers that are manufactured with benzene as the polymerization solvent and summarizes previous communications on the topic. The monographs recommended for deletion include Carbomer 934P, Carbomer 940, Carbomer 934, Carbomer 1342, and Carbomer 941. Benzene is a Class 1 solvent, known carcinogen and hematotoxin, and as such should not be used in manufacturing of drug products or ingredients used in drug products.

Solvents in Class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified.[1] Furthermore, even when use of a Class 1 is justified, these Carbomer monographs allow residual benzene levels that are significantly higher than the 2 ppm permitted by Table 1 of ICH Q3C and USP ⟨467⟩ RESIDUAL SOLVENTS.

During a meeting on February 11, 2020, FDA requested that USP omit the above Carbomer monographs from USP-NF. This was followed up by an email from FDA to USP on January 11, 2021 concurring the proposal to revise the monographs with updated Identification tests to be in effect during the omission implementation period. On June 9, 2022, FDA released a communication titled: "FDA alerts drug manufacturers to the risk of benzene contamination in certain drugs."[2] The statement stated that *"manufacturers should not use benzene in the manufacture of drugs."* Furthermore, the statement included: *"We note that certain United States Pharmacopeia – National Formulary (USP-NF) carbomer monographs allow for levels of benzene of 100 ppm or greater. To eliminate confusion and because of the safety concerns associated with these unacceptable levels of benzene, FDA has asked USP to remove (or "omit") these monographs from their compendium."*

[1] Q3C(R8) Impurities: Guidance for Residual Solvents Guidance for Industry
[2] https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs

Given the known health risks associated with benzene exposure and existing policy that its use should be avoided in the manufacturing of drug products and ingredients, the FDA would like to reiterate its prior request that Carbomer 934P, Carbomer 940, Carbomer 934, Carbomer 1342, and Carbomer 941 be removed from USP-NF.

We are requesting that this safety issue be addressed in a timely manner so that the monograph omissions are implemented by 2025. We hope this letter will be helpful to USP and the **Complex Excipients** Expert Committee. Please feel free to contact me at Pallavi.Nithyanandan@fda.hhs.gov if there are any questions. Please use the reference number provided above on any ensuing correspondence.

Sincerely yours,

Pallavi Nithyanandan -S

Digitally signed by Pallavi Nithyanandan -S
Date: 2022.11.01 14:34:39 -04'00'

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