Risk Factors for Benzene Contamination

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Outline

- Background
- Interpretation of ICH Q3C
- USP Carbomer monographs
- Recommendations to USP on Carbomers
- USP Notices of Intent to Revise

Background

- Benzene is a known human carcinogen that causes leukemia and other blood disorders.
- Recent product recalls due to benzene contamination may be related to inactive ingredients such as carbomers (thickening agents), isobutane (a spray propellant), or other drug components made from hydrocarbons.
- Drug manufacturers are required to:
  - Establish scientifically sound and appropriate specifications and test procedures to assure drug components (active and inactive ingredients) and finished drug products conform to appropriate quality specifications (21 CFR 211.84, 21 CFR 211.160).
  - Test raw materials and finished product batches (21 CFR 211.165) prior to release to ensure they meet appropriate specifications for identity, strength, quality, and purity.

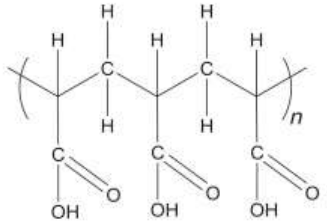
Please see: https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs

Risk Assessments

- FDA recommends risk assessments as a tool to:
  - determine if manufacturers have appropriate specifications, test methods, and controls to ensure drugs are free from contamination.
  - evaluate the possible presence of benzene in their drug products and components, including active ingredients and inactive ingredients.

USP Carbomer Monographs (current)

USP-NF Monographs	Benzene limits
Manufactured without benzene	
Carbomer Homopolymer	2 µg/g (2 ppm)
Carbomer Copolymer	2 µg/g (2 ppm)
Carbomer Interpolymer	2 µg/g (2 ppm)
Manufactured with benzene	
Carbomer 934 (homopolymer)	0.5% (5,000 ppm)
Carbomer 934P (homopolymer)	0.01% (100 ppm)
Carbomer 940 (homopolymer)	0.5% (5,000 ppm)
Carbomer 941 (homopolymer)	0.5% (5,000 ppm)
Carbomer 1342 (copolymer)	0.2% (2,000 ppm)



Typical structure for carbomers.

Benzene limit per USP <467> and ICHQ3C for Residual Solvents: **<2 ppm**

Interpretation of ICH Q3C

- Class 1 solvents **should not be employed in the manufacture** of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect.
- Exception for drugs considered a “significant therapeutic advance”:
  - If Class 1 solvent use is unavoidable in order to produce a drug product with a significant therapeutic advance, levels should be restricted as shown in Table 1, unless otherwise justified (2 ppm listed for benzene)
    - Note: sunscreens and hand sanitizers, the subject of many recent recalls due to benzene, are **not** drugs considered “significant therapeutic advance”, nor is the use of benzene as a solvent unavoidable in their manufacture.

Interpretation of ICH Q3C- continued

- Even when use of a Class 1 is justified, these **Carbomer monographs (Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, Carbomer 1342) allow residual benzene levels that are significantly higher than the 2 ppm** permitted by Table 1 of ICH Q3C and USP ⟨467⟩ Residual Solvents.
- The ICH Q3C guideline and USP <467> is **not to be interpreted** as recommending that controlling benzene at nmt 2 ppm in the drug product alone is sufficient in the absence of significant therapeutic advance.

FDA Correspondence with USP on Carbomers

- FDA recommended that USP delete monographs for Carbomer 934P, Carbomer 940, Carbomer 934, Carbomer 1342, and Carbomer 941
- History:
  - Feb 2020 meeting
  - Email on Jan 2021
  - Letter sent November 2022
- Reiterated the known health and safety risks associated with benzene.
- Recommended making monograph omissions effective no later than 2025.

USP Notice of Intent to revise

- Posted Notice of Intent to Revise on November 18, 2022.
- USP intends to omit monographs for:
  - Carbomer 934,
  - Carbomer 934P,
  - Carbomer 940,
  - Carbomer 941,
  - Carbomer 1342
- Targeted official date of August 1, 2025

Recommendations for Industry

- Upcoming CDER Guidance for Industry on *Products With Benzene-Containing Carbomers: Recommendations for Reformulation* will advise on
  - Reporting categories for various dosage forms based on risk considerations for switching to another carbomer with similar physicochemical properties.

- FDA encourages early implementation of reformulation if using Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, Carbomer 1342 prior to the proposed monograph omission date of August 1, 2025.

Thank you!