Reformulating Drug Products That Contain Carbomers Manufactured With Benzene

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2023
Pharmaceutical Quality/CMC

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TABLE OF CONTENTS

I. INTRODUCTION....1
II. BACKGROUND....2
III. RECOMMENDATIONS AND REQUIREMENTS....3
REFERENCES....9
APPENDIX....10

Contains Nonbinding Recommendations

Reformulating Drug Products That Contain Carbomers Manufactured With Benzene Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations for applicants and manufacturers[2] on what tests should be performed and what documentation should be submitted or available to FDA to support the reformulation of drug products that use carbomers manufactured with benzene. Certain United States Pharmacopeia (USP) carbomer monographs currently allow for unacceptable levels of benzene, which raises safety concerns. FDA has requested that the USP omit (or remove) these monographs,[3] and applicants and manufacturers may need to reformulate their drug products to avoid using these carbomers. This guidance provides recommendations for testing and documentation related to reformulation, taking into consideration the various routes of administration and dosage forms of affected drug products. For application holders, this guidance also recommends appropriate submission types to notify the Agency of such changes.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For purposes of this guidance, the term *applicants and manufacturers* refers collectively to applicants and application holders, owners of marketed drug products that are not the subject of approved applications (such as OTC monograph drug products), and drug product manufacturers.

[3] See FDA's request to USP at https://www.fda.gov/media/174455/download?attachment. A link to this letter can also be found on the following FDA web page: FDA alerts drug manufacturers to the risk of benzene contamination in certain drugs (https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs). On November 18, 2022, in response to FDA's request, the USP issued a Notice of Intent to Revise, stating that it intends to omit the Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, and Carbomer 1342 monographs, with a targeted official date of August 1, 2025. See https://www.uspnf.com/notices-carbomer-omissions-20221118.

The recommendations in this guidance are consistent with the International Council for Harmonisation (ICH) guidance for industry *Q3C Impurities: Residual Solvents* (December 1997) and the companion ICH guidance for industry *Q3C — Tables and List* (August 2018) (2018 ICH Q3C guidance),[4] as well as applicable scale-up and post-approval changes (SUPAC) guidances.[5] The recommendations in this guidance apply to drug products subject to both new drug applications (NDAs) and abbreviated new drug applications (ANDAs) (hereafter *application products*), as well as other marketed drugs, including nonprescription drugs without an approved application governed by the provisions of section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h) (i.e., OTC monograph drugs). This guidance applies to topically applied liquid and semisolid dosage forms (e.g., creams, gels, lotions, ointments), immediate-release solid oral dosage forms, modified-release solid oral dosage forms, and oral suspensions.

This guidance does not address toxicological considerations related to the unavoidable use of benzene in drug products, drug substances, or inactive ingredients.

FDA is implementing this guidance without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (see 21 CFR 10.115(g)(2) and (g)(3)). FDA made this determination because benzene is a known human carcinogen. By providing recommendations on how applicants and manufacturers can reformulate certain drug products, the Agency seeks to facilitate the transition away from using carbomers manufactured with high levels of benzene. Publishing this guidance without prior public comment addresses the immediate public health need to expedite the discontinuation of the use of these carbomers and provides a less burdensome risk-based approach to applicant submissions, relative to existing guidances on SUPAC.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Carbomers are a group of polymers composed of acrylic acid. They are widely used as inactive ingredients in drug products as fillers, emulsifiers, gelling agents, and binding agents. There are carbomers currently used as inactive ingredients that are manufactured using benzene as a polymerization solvent. Benzene is a known human carcinogen. As such, both the 2018 ICH Q3C guidance and USP General Chapter <467> *Residual Solvents* designate benzene as a Class 1 solvent (i.e., Solvents That Should Be Avoided) and recommend that it not be employed in the manufacture of drug substances, excipients, and drug products. However, there are still

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] See the SUPAC guidances listed in the References section of this guidance.

several grades of carbomers manufactured using benzene as a solvent that are used in pharmaceutical products even though alternative grades of carbomers manufactured without the use of benzene are available.

At the time of publication of this guidance, carbomers manufactured with benzene that are used in FDA-regulated drug products may fall under the United States Pharmacopeia-National Formulary (USP-NF) monographs Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, or Carbomer 1342. These monographs permit benzene levels as high as 5,000 parts per million (ppm). In comparison, the USP-NF Carbomer Homopolymer, Carbomer Copolymer, and Carbomer Interpolymer monographs cover carbomers that are manufactured without benzene and limit benzene as an impurity to no more than 2 ppm. To avoid confusion, and because of the safety concerns associated with these unacceptable levels of benzene permitted by these monographs, FDA has asked the USP to remove (or "omit") the Carbomer 934P, Carbomer 940, Carbomer 934, Carbomer 1342, and Carbomer 941 monographs from the USP-NF compendium. FDA is issuing this guidance to help facilitate and expedite the reformulation of drug products that use carbomers manufactured with benzene.

III. RECOMMENDATIONS AND REQUIREMENTS

Under section 501(a)(2)(b) of the FD&C Act (21 U.S.C. 351(a)(2)(B)), a drug that is not manufactured, processed, packed, or held in conformity with current good manufacturing practice to assure that the drug meets requirements for safety, and quality and purity characteristics, which it purports or is represented to possess, is considered adulterated.[6] Manufacturers should not use benzene in the manufacture of drugs. The 2018 ICH Q3C guidance states that Class 1 solvents, such as benzene, generally should not be employed in the manufacture of drug substances, excipients, or drug products because of their unacceptable toxicity.[7]

The 2018 ICH Q3C guidance and USP General Chapter <467> provide guidance on limited cases where the presence of benzene may be tolerated. Specifically, both sources note that if benzene use is unavoidable to produce a drug product with a significant therapeutic advance, then its level should be restricted to the level recommended in the 2018 ICH Q3C guidance and USP General Chapter <467>, unless otherwise justified.

[6] Entities that manufacture drug products that may be at risk for benzene contamination should test their drugs accordingly and should not release any drug product batch that contains benzene at levels above 2 ppm, consistent with the recommendations described in the 2018 ICH Q3C guidance. If any drug product batches with benzene levels above 2 ppm are already in distribution, the manufacturer should contact FDA to discuss the voluntary initiation of a recall. See https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs.

[7] See the 2018 ICH Q3C guidance at p. 5.

For drugs that are recognized in an official compendium, manufacturers that use Carbomer 934P, Carbomer 940, Carbomer 934, Carbomer 1342, and Carbomer 941 as solvents will be required to reformulate to avoid use of these carbomers in their drug products once the USP monographs have been removed.[8] However, pending the USP's removal of the monographs for these carbomers that contain unacceptable levels of benzene, FDA recommends that manufacturers select an alternative grade of carbomer that is manufactured without the use of benzene and has similar chemical composition (e.g., carbomer homopolymer) and physical properties (e.g., viscosity, rheology).

When switching to non-benzene-containing grades of carbomers, applicants and manufacturers should consider the following information regarding chemistry, manufacturing, and controls; in vitro release or dissolution testing; and in vivo bioequivalence documentation.

- Applicants are responsible for evaluating the effects of any postapproval compositional change on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product before distribution of the drug product made with the change.[9] Applicants must submit proposed formulation changes through supplements to their applications.[10]

- For applicants and manufacturers (including manufacturers of OTC monograph drugs) making such a formulation change, information to support compliance with current good manufacturing practice requirements[11] must be documented and made available for FDA to review during an inspection under section 704(a)(1) of the FD&C Act (21 U.S.C. 374(a)(1)) or when requested by FDA in advance or in lieu of an inspection as described in section 704(a)(4) of the FD&C Act (21 U.S.C. 374(a)(4)).

- The studies that should be conducted following reformulation of drug products with alternative carbomers include tests for critical quality attributes for drug products (e.g., applicable comparative physicochemical and structural characterizations), and in some cases, additional bioequivalence studies depending on the dosage form, route of administration, intended use, and the scope/level of the proposed change as determined by the principles described in the applicable SUPAC guidances. Below is an outline of

[8] Although section 501(b) of the FD&C Act (21 U.S.C. 351(b)) provides in part that a drug, including an inactive ingredient, is adulterated if it is a drug the name of which is recognized in an official compendium and its quality falls below the standard set forth in the compendium, unless that difference in quality is plainly stated on its label, the drug must also meet the safety standard as stated in section 501(a)(2)(B) of the FD&C Act.

[9] See section 506A of the FD&C Act (21 U.S.C. 356a), 21 CFR 314.70, and 21 CFR 314.97. A holder of an approved application under section 505 of the FD&C Act (21 U.S.C. 355) must assess the effects of the change before distributing a drug product made with a manufacturing change (see 21 CFR 314.70(a)(2) and 21 CFR 314.97(a)). In addition, information to support compliance with current good manufacturing practice requirements must be documented (see, for example, 21 CFR 211.100(a), 21 CFR 211.160(b), 21 CFR 211.180(e), and 21 CFR 211.194(a)).

[10] Applicants must notify FDA of a change to the conditions established in an approved application. See 21 CFR 314.70 and 21 CFR 314.97.

[11] See, for example, 21 CFR 211.100(a), 21 CFR 211.160(b), 211.180(e), and 211.194(a).

the relevant dosage forms and the respective SUPAC guidances, if one is available for that dosage form. The recommended test documentation and submission type[12] for different dosage forms are summarized in the Appendix. Release testing (based on approved specifications for application products), batch records, stability data, and dissolution/in vitro release testing (IVRT) data (as applicable) should be documented for all dosage forms.

- **Semisolid dosage forms.** Applicants and manufacturers should follow the recommendations in the guidance for industry *Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997) (SUPAC-SS guidance) for the appropriate tests and studies to be conducted and documented, as well as for the recommended submission type, if applicable.

  - When substituting a carbomer manufactured with benzene with an alternative carbomer that has similar chemical composition and physical properties and in a similar quantity,[13] applicants and manufacturers should follow the recommendations for level 2 changes (see the SUPAC-SS guidance, section III.B.). Additional chemistry documentation can include physicochemical and structural characterization data (e.g., evaluation of pH and rheology for one batch of the pre- and post-change products). An IVRT study to compare the pre- and post-change batches should be generated, and applicants should include this information in their submission. For application products, a changes being effected in 30 days (CBE-30) supplement should be submitted.

  - When substituting with ingredient(s) that do not meet the above parameters (including non-carbomer ingredients), recommendations for level 3 changes should be followed (see the SUPAC-SS guidance, section III.C.). For application products, a prior approval supplement (PAS) should be submitted.

- **Immediate-release solid oral dosage forms.** Applicants and manufacturers should follow the recommendations in the guidance for industry *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995) (SUPAC-IR guidance) for the appropriate tests and studies to be conducted and documented, as well as for the recommended submission type, if applicable, except as otherwise noted in this guidance.

  - When substituting a carbomer manufactured with benzene with an alternative carbomer that has similar chemical composition and physical properties and in a

[12] SUPAC guidances use the term *filing documentation* to describe recommended application submission types and filing categories associated with a change in the chemistry, manufacturing, and controls of a drug.

[13] Not exceeding the range noted in the SUPAC-SS guidance, section III.B.1.

similar quantity,[14] applicants and manufacturers should follow the recommendations for level 2 changes (see the SUPAC-IR guidance, section III.B.). However, for application products, a CBE-30 supplement should be submitted rather than a PAS.[15] Applicants and manufacturers should use risk assessment approaches to assess the potential effect of the change on drug quality and manage the risk appropriately.[16] The change from a carbomer manufactured with benzene to one manufactured without benzene is not expected to significantly alter quality or performance for an immediate-release dosage form because the new carbomer should provide similar structural characteristics and performance for the drug, presuming the applicant or manufacturer is using carbomers that meet established quality requirements.

- When substituting with ingredient(s) that do not meet the above parameters, recommendations for level 3 changes should be followed (see the SUPAC-IR guidance, section III.C.). For application products, a PAS should be submitted.

– **Modified-release solid oral dosage forms.** Applicants and manufacturers should follow the recommendations in the guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (September 1997) (SUPAC-MR guidance) for the appropriate tests and studies to be conducted and documented, as well as for the recommended submission type, if applicable, except as otherwise noted in this guidance.

- When substituting a carbomer manufactured with benzene with an alternative carbomer that has similar chemical composition and physical properties and in a similar quantity,[17] applicants and manufacturers should follow the recommendations for level 2 changes (see the SUPAC-MR guidance, sections III.B. and IV.B.). For application products, when the carbomer is a release-controlling excipient, a PAS should be submitted. However, when the carbomer is a non-release-controlling excipient, a CBE-30 supplement should be submitted rather than a PAS.[18] Applicants and manufacturers should use risk assessment

[14] Not exceeding the range noted in the SUPAC-IR guidance, section III.B.1.b.

[15] Section 506A of the FD&C Act addresses manufacturing changes made postapproval and defines some types of changes as major changes. Generally, major manufacturing changes require applicants to file a PAS. However, FDA may change the reporting category for changes to specifications and reformulation. See section 506A(c)(2)(A) of the FD&C Act.

[16] See the ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023).

[17] Not exceeding the range noted in the SUPAC-MR guidance, section III.B.1.b.

[18] Section 506A of the FD&C Act addresses manufacturing changes made postapproval and defines some types of changes as major changes. Generally, major manufacturing changes require applicants to file a PAS. However, FDA may change the reporting category for changes to specifications and reformulation. See section 506A(c)(2)(A) of the FD&C Act.

approaches to assess the potential effect of the change on drug quality and manage the risk appropriately.[19] Provided the carbomer is a non-release-controlling excipient, the change from a carbomer manufactured with benzene to one manufactured without benzene is not expected to significantly alter quality or performance for a modified-release dosage form, because the new carbomer should provide similar structural characteristics and performance for the drug, presuming the applicant or manufacturer is using carbomers that meet established quality requirements.

- When substituting with ingredient(s) that do not meet the above parameters (including non-carbomer ingredients), recommendations for level 3 changes should be followed (see the SUPAC-MR guidance, sections III.C. and IV.C.). For application products, a PAS should be submitted.

– **Oral suspensions**.

- Oral suspensions are not addressed in current SUPAC guidances.

- Testing to demonstrate that the reformulated product meets specifications and executed batch records should be documented and, for application products, provided. Applicants and manufacturers should perform stability testing according to an established stability protocol. For application products, the supplement supporting reformulation should include 3 months of accelerated stability data for 1 batch, and 1 batch should be placed on long-term stability studies. Before marketing, manufacturers of marketed drug products without an application should also compile 3 months of accelerated stability data for 1 batch and place 1 batch on long-term stability studies.

- When substituting a carbomer manufactured with benzene with the same quantity[20] of an alternative carbomer that has similar chemical composition and physical properties, a CBE-30 supplement should be submitted rather than a PAS for application products.

- When substituting with ingredient(s) that do not meet the above parameters (including non-carbomer ingredients or a change in quantity), a PAS should be submitted for application products.

- Applicants and manufacturers should use risk assessment approaches to assess the potential effect of the change on drug quality and manage the risk appropriately.[21]

[19] See ICH Q9(R1).

[20] Applicants should provide a rationale to justify any potential changes in quantity.

[21] See ICH Q9(R1).

- For dosage forms and/or routes of administration (e.g., ophthalmic, buccal) that are not covered in this guidance, applicants should contact FDA for recommendations. For NDA products, the applicant should contact the specific product's review division. For ANDA products, the applicant should contact FDA through a controlled correspondence for recommendations.

- The above recommendations generally apply to premarketing changes as well as postmarketing changes. However, in the event of premarketing changes, applicants should contact FDA for recommendations. For pending NDAs, the applicant should contact the specific product's review division. For pending ANDAs, the applicant should contact the project manager specified for the ANDA. For communications before submitting an ANDA, applicants should refer to the guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020) and the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022) for additional information describing the procedures on how to clarify regulatory expectations regarding individual drug development programs.

REFERENCES[22]

Abbreviated New Drug Application-Related Guidances

Guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020)

Guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)

ICH Guidances

ICH guidance for industry *Q3C — Tables and List* (August 2018)

ICH guidance for industry *Q3C Impurities: Residual Solvents* (December 1997)

ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023)

ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009)

Pharmaceutical Quality System/Quality System Guidances

Guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006)

Scale-Up and Post-Approval Changes Guidances

Guidance for industry *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)

Guidance for industry *Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)

Guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (September 1997)

[22] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

APPENDIX

This table summarizes the recommended test documentation and filing documentation (for application products) for different dosage forms.

Dosage Form	Test Documentation	Filing Documentation
Semisolid Dosage Forms	• Chemistry documentation • In vitro release documentation • Physicochemical and structural characterization data • In vivo bioequivalence documentation as appropriate	• CBE-30* supplement • PAS* (level 3 change only)
Immediate-Release Solid Oral Dosage Forms	• Chemistry documentation • Dissolution documentation • In vivo bioequivalence documentation as appropriate	• CBE-30 supplement • PAS (level 3 change only)
Modified-Release Solid Oral Dosage Forms	• Chemistry documentation • Dissolution documentation • In vivo bioequivalence documentation as appropriate	• CBE-30 supplement • PAS (when level 3 change and/or when carbomer is release-controlling excipient)
Oral Suspensions	• Chemistry documentation • Dissolution documentation • In vivo bioequivalence documentation as appropriate	• CBE-30 supplement • PAS (when substituting with alternative excipients that do not have similar chemical composition and physical properties)

* CBE-30 = changes being effected in 30 days; PAS = prior approval supplement