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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA-2025-D-0507]**

# Replacing Color Additives in Approved or Marketed Drug Products; Draft Guidance for Industry; Availability

**AGENCY**: Food and Drug Administration, HHS.

**ACTION:** Notice of availability.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Replacing Color Additives in Approved or Marketed Drug Products." This draft guidance provides recommendations for replacing color additives in approved or marketed drug products. If a color additive is replaced in a drug product, information to support the change should be retained and available at the manufacturing facility. Additionally, this draft guidance recommends that new drug application (NDA) and abbreviated new drug application (ANDA) holders submit information to support color additive replacements in changes being effected in 30 days (CBE-30) supplements. Although a qualitative or quantitative change to an inactive ingredient is generally considered a major change, in many cases, replacing a color additive with one that is listed in the color additive regulations is unlikely to adversely affect the identity, strength, quality, purity, or potency of the drug product. Therefore, this draft guidance recommends a CBE-30 for such a change.

**DATES:** Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

**ADDRESSES:** You may submit comments on any guidance at any time as follows:

*Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

*Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions*: All submissions received must include the Docket No. FDA-2025-D-0507 for "Replacing Color Additives in Approved or Marketed Drug Products." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions,"

publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

*Docket*: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001

New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance.

**FOR FURTHER INFORMATION CONTACT:** Ashley Boam, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 4192, Silver Spring, MD 20993-0002, 301-796-6341, cder-quality-policy@fda.hhs.gov.

**SUPPLEMENTARY INFORMATION:**

## I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Replacing Color Additives in Approved or Marketed Drug Products." This draft guidance provides recommendations for replacing color additives in approved or marketed drug products. If a color additive is used in a drug product, the color additive must conform to FDA's color additive regulations. If FDA deems the color additive unsafe and repeals the color additive regulation, the color additive must be removed or replaced. Color additives can also be replaced for other reasons (e.g., as a business decision).

This draft guidance describes considerations for replacing a color additive, regardless of the reason for the change, including:

- Ensuring that the selected color additive conforms with the color additive requirements (see section 721(a)-(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379e(a)-(b)) and parts 70-71, 73-74, and 80-82 (21 CFR parts 70-71, 73-74, and 80-82))
- Updating information, including labeling, composition statements, master batch records, and drug product specifications (as applicable)
- Documenting information to support the change, including maintaining appropriate records at the manufacturing site (see 21 CFR 211.180)
- Submitting information to support the change in a supplement (for application products)

Although a qualitative or quantitative change in inactive ingredients is generally considered a major change, in many cases, replacing a color additive with one that is listed in the color additive regulations (parts 73, 74 and 82) is unlikely to adversely affect the identity, strength, quality, purity, or potency of the drug product. Therefore, replacing a color additive can generally be considered a moderate change that applicants can submit in a CBE-30.

The recommendations in this draft guidance apply to two groups: *applicants* and *manufacturers*. In this draft guidance, the term *applicants* refers to holders of approved NDAs or ANDAs for drug products that are regulated by CDER. In this draft guidance, the term *manufacturers* refers to manufacturers of:

- Drug products marketed under an NDA or ANDA (including contract manufacturers)
- Drug products that are not marketed under a drug application, including nonprescription drugs subject to section 505G of the FD&C Act (21 U.S.C. 355h) (i.e., over-the-counter monograph drug products)
- Compounded drug products subject to section 503B of the FD&C Act (21 U.S.C. 353b)
- Other drug products that are subject to current good manufacturing practice (CGMP) requirements

Some entities may be both *applicants* and *manufacturers*. These entities should follow the appropriate recommendations for their roles in each specific situation.

The recommendations in this draft guidance do not apply to drug products in which a color additive is the active pharmaceutical ingredient (e.g., methylene blue). The recommendations also do not apply to drugs approved under section 505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)) for which replacing a color additive would create a *different drug* (see also 21 CFR 314.70(h)). Additionally, because biological products rarely include color additives, the recommendations in this draft guidance do not apply to products that have an approved biologics license application. However, if a color additive is used as an inactive ingredient in a biological product, the additive must be listed in the color additive regulations and its use must conform to

the regulation (see section 721(a)-(b) of the FD&C Act and parts 70, 71, 73, 74, and 80 through 82).

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Replacing Color Additives in Approved or Marketed Drug Products." 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. As we develop any final guidance on this topic, FDA will consider comments on the applicability of Executive Order 14192, per OMB guidance M-25-20, and in particular, on any costs or cost savings.

## II. Paperwork Reduction Act of 1995

While this draft guidance contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521). The collections of information in §§ 70.25 and 71.1 relating to the submission of color additive petitions including labeling have been approved under OMB control number 0910-0016. The collections of information in 21 CFR 201.56 and 201.57 relating to the submission of labeling for prescription drug products and biological products have been approved under OMB control number 0910-0572. The collections of information in 21 CFR parts 210 and 211 relating to CGMP requirements, including manufacturing records, have been approved under OMB control number 0910-0139. The collections of information in 21 CFR part 314 relating to the submission of NDAs and ANDAs, as well as related post approval submissions (including annual reports) and drug master files, have been approved under OMB control number 0910-0001. The collections of information

relating to labeling for certain over-the-counter products have been approved under OMB control number 0910-0340.

## III. Electronic Access

Persons with access to the internet may obtain the draft guidance at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

Dated: May 27, 2025.

**Grace R. Graham,**

*Deputy Commissioner for Policy, Legislation, and International Affairs.*

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