Replacing Color Additives in Approved or Marketed Drug Products

Guidance for Industry

DRAFT GUIDANCE

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

May 2025
Pharmaceutical Quality/Chemistry, Manufacturing, and Controls (CMC)

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Replacing Color Additives in Approved or Marketed Drug Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance provides recommendations for replacing color additives[2] 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.[3] If FDA deems the color additive unsafe[4] and repeals[5] 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 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[6]
- Updating information, including labeling, composition statements, master batch records,[7] and drug product specifications (as applicable)

[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] The terms *color additive* and *colorant* are sometimes used interchangeably. This guidance uses the term *color additive* consistent with the regulation at 21 CFR 70.3(f).

[3] The color additive regulations are in 21 CFR parts 70-71, 73-74, and 80-82. Parts 73, 74, and 82 list permitted color additives and their chemical specifications, uses, restrictions, labeling requirements, and certification requirements.

[4] See section 721(a) and 721(b)(5)(B) of the FD&C Act (21 U.S.C. 379e(a) and 379e(b)(5)(B)).

[5] See section 721(d) of the FD&C Act.

[6] See section 721(a)-(b) of the FD&C Act and 21 CFR parts 70-71, 73-74, and 80-82.

[7] For the purpose of this guidance, the term *master batch records* refers to the *master production and control records* (see 21 CFR 211.186).

- Documenting information to support the change, including maintaining appropriate records at the manufacturing site[8]

- Submitting information to support the change in a supplement (for application products)

For application products, this guidance also explains why replacing a color additive with one that conforms to FDA's color additive regulations can generally be considered a moderate change for which a changes being effected in 30 days (CBE-30) supplement is appropriate. This recommendation supersedes Component and Composition Changes Questions 1 and 2 in the guidance for industry *SUPAC-IR Questions and Answers about SUPAC-IR Guidance* (February 1997).[9]

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. SCOPE

These recommendations apply to two groups: *applicants* and *manufacturers*. In this guidance, the term *applicants* refers to holders of approved new drug applications (NDAs) and approved abbreviated new drug applications (ANDAs) for drug products that are regulated by the Center for Drug Evaluation and Research.[10] In this guidance, the term *manufacturers* refers to manufacturers of:

- Drug products marketed under an NDA or ANDA (including contract manufacturers)[11]

- Drug products that are not marketed under a drug application, including nonprescription drugs subject to section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (i.e., over-the-counter monograph drug products)[12]

- Compounded drug products subject to section 503B of the FD&C Act[13]

- Other drug products that are subject to current good manufacturing practice (CGMP) requirements

[8] See 21 CFR 211.180.

[9] 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.

[10] This guidance does not apply to products regulated by other centers (e.g., medical devices, foods, dietary supplements, cosmetics).

[11] See the guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016).

[12] See 21 U.S.C. 355h.

[13] See 21 U.S.C. 353b.

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 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[14] for which replacing a color additive would create a different drug.[15] Additionally, because biological products rarely include color additives, the recommendations in this guidance do not apply to products that have an approved biologics license application (BLA). 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 regulations.[16]

III. BACKGROUND

The FD&C Act defines a *color additive* as any dye, pigment, or other substance that can impart color to a food, drug, cosmetic, or the human body.[17] Color additives used in a drug are deemed unsafe and prohibited except to the extent that FDA approves their use.[18] Color additives used in approved or marketed drugs must be listed in the color additive regulations.[19] If FDA changes the color additive regulations (e.g., removing a color additive), drug products that no longer comply with the regulations must be updated to conform with the regulations.[20] If FDA removes a color additive from the regulations, any drug product containing that additive will be considered adulterated and cannot be marketed.[21] The introduction or delivery for introduction of an adulterated drug into interstate commerce is a prohibited act.[22] Furthermore, FDA may refuse entry of a drug if it is or appears to be adulterated, unapproved, or otherwise fails to meet applicable requirements.[23]

A drug product is also considered adulterated if the drug product contains a color additive that is not listed for such use (e.g., use of a color additive in an oral formulation when the color additive is only authorized for use in topical drugs) or if the drug product fails to comply with the statutory and regulatory requirements.[24] The manufacturing of drug products, including changes

[14] See 21 U.S.C. 355(b)(2).

[15] Applicants may not submit supplements to 505(b)(2) applications for changes that create a different drug as described in 21 CFR 314.70(h). For the purposes of § 314.70(h), in reference to a 505(b)(2) application, "a drug is considered a different drug if it has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence."

[16] See footnote 6.

[17] See § 70.3(f) and section 201(t)(1) of the FD&C Act (21 U.S.C. 321(t)(1)).

[18] See section 721(a) of the FD&C Act.

[19] See footnote 6.

[20] See section 721(d) of the FD&C Act and footnote 6.

[21] See section 501(a)(4) of the FD&C Act (21 U.S.C. 351(a)).

[22] See section 301(a) of the FD&C Act (21 U.S.C. 331(a)).

[23] See section 801(a) of the FD&C Act (21 U.S.C. 381(a)).

[24] See section 501(a)(2)(B) and (a)(4) of the FD&C Act.

to production and process control procedures to replace a color additive, must comply with CGMP requirements.[25] The firm's change control procedures should include, but are not limited to, the activities described in Sections V and VI to evaluate the effects of the color additive change and the associated implementation activities.

IV. DISCUSSION

Although changes to the "qualitative or quantitative formulation of the drug product, including inactive ingredients," are generally considered major changes,[26] in many cases, replacing a color additive with one that is listed in the color additive regulations is unlikely to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. Therefore, for a drug product marketed under an NDA or ANDA, replacing a color additive can generally be considered a moderate change that applicants can submit in a CBE-30.[27,28] However, if changes are made other than replacing a color additive and making the associated adjustments in excipient levels described in this section, a CBE-30 may not be appropriate and a prior approval supplement may be warranted.[29] A CBE-30 must be submitted at least 30 days before distribution of the postchange drug product.[30] To submit a CBE-30 for a color additive replacement, the change should not include:

- Changes in the levels of other inactive ingredients that exceed 5 percent of the target unit dose weight.[31]

- A major change that would require FDA approval before the change is implemented and the product is distributed.[32] This includes changes that FDA determines to have the

[25] See e.g., 21 CFR 211.100(a). Additionally, see the guidances for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006) and *Process Validation: General Principles and Practices* (January 2011) and the International Council for Harmonisation (ICH) guidance for industry *Q10 Pharmaceutical Quality System* (April 2009) for additional recommendations on change control.

[26] See § 314.70(b)(2)(i) and 21 CFR 314.97(a).

[27] Section 506A of the FD&C Act (21 U.S.C. 356a) addresses postapproval manufacturing changes and defines major changes. Generally, major manufacturing changes (e.g., changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients) require applicants to file a prior approval supplement (§ 314.70(b)). However, FDA may change the reporting category for changes to specifications and reformulation (see section 506A(c)(2)(C), 506A(d)(1)(C), and 506A(d)(3)(B)(ii) of the FD&C Act).

[28] This recommendation supersedes Component and Composition Changes Questions 1 and 2 in the guidance for industry *SUPAC-IR Questions and Answers about SUPAC-IR Guidance*.

[29] To determine the appropriate filing category, applicants should refer to § 314.70 in addition to the *Changes to an Approved NDA or ANDA* (April 2004) guidance for industry and the SUPAC guidances for industry. The SUPAC guidances for industry are *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), *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), and *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).

[30] See § 314.70(c).

[31] See footnote 29.

[32] See § 314.70(b).

potential to adversely affect the safety or effectiveness of the drug product.[33,34] This could occur when factors associated with the change (e.g., diluents in the color mixture) necessitate a more extensive assessment because a specific population uses the drug product (e.g., neonates).

If a color additive is removed rather than replaced, it is considered a minor change that applicants must describe in an annual report.[35]

Manufacturers should retain the supporting information at the manufacturing facility. To comply with CGMP requirements, manufacturers and applicants must confirm that drug products continue to meet specifications[36] through the expiry date. Relevant records and other information that demonstrates compliance with CGMP requirements must be made available to FDA during inspections or when FDA requests the information in advance of or in lieu of an inspection.[37]

V. SELECTING A REPLACEMENT COLOR ADDITIVE

When selecting a replacement color additive, manufacturers and applicants should review the color additive regulations. They must ensure that the color additive regulations list the proposed color for use in drugs and that the proposed level and use conform to the regulations.[38] Certain color additive regulations restrict the allowable levels of color additives. For example, 21 CFR 73.1200(c) restricts the total amount of elemental iron per day. Manufacturers and applicants that remove or replace a color additive should also ensure that drug product strengths remain distinguishable to help prevent medication errors (e.g., when drug products such as tablets are marketed in multiple strengths).

Manufacturers and applicants can check the Inactive Ingredient Database (IID)[39] for additional information, including the levels of color additives that have been used in FDA-approved drug products. Although this information can be useful, color additives and levels of color additives that are not listed in the IID can be acceptable if the color additive is listed in the regulations and is used within the regulation's restrictions.

If a manufacturer or an applicant intends to use a color additive that is not already listed in FDA's color additive regulations for the particular use, a petition must be sent to the Human Foods Program.[40] If FDA finds the color additive safe and suitable for such use, the additive will

[33] See section 506A(c)(2)(C) of the FD&C Act.
[34] See level 3 changes in the SUPAC guidances. The SUPAC guidances are listed in footnote 29.
[35] See § 314.70(d)(2)(ii). If a color additive is removed rather than replaced, the updates of composition statements, manufacturing records, and labeling as described in Section VI apply, and such updates should be documented in the annual report. See SUPAC level 1 changes for test documentation (see SUPAC guidances in footnote 29).
[36] See 21 CFR 211.160(b)(3).
[37] These inspections are conducted under section 704(a)(1) of the FD&C Act (21 U.S.C. 374(a)(1)). Requests for records in advance of or in lieu of inspections are described in section 704(a)(4) of the FD&C Act. See also § 211.180 for general records requirements.
[38] See footnote 6.
[39] The IID can be accessed on FDA's web page at https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.
[40] See 21 CFR part 71.

be listed in the color additive regulations.[41] A new color additive cannot be used in a drug product until it is added to the color additive regulations.[42]

VI. ASSESSING AND DOCUMENTING THE CHANGE

Manufacturers and applicants are expected to prepare accurate manufacturing records.[43] The information described in the following sections, including stability data, should be retained at the manufacturing facility. The recommendations below describe the documentation that should be generated to support a color additive replacement, including in vitro data. Manufacturers and applicants should also update labeling[44] to accurately reflect the color additive replacement, as applicable. Applicants must evaluate the effects of the change on their approved drug product,[45] and they should submit this information in a CBE-30, as appropriate.

A. Conducting Studies to Assess the Change

Manufacturers and applicants should follow the recommendations below to ensure that the postchange drug product continues to meet established specifications through the drug product's expiry date. As part of evaluating the change, manufacturers and applicants should do the following:

- Manufacture one or more batches, which should be pilot scale or larger, as recommended for an exhibit batch in scale-up and postapproval changes (SUPAC) level 2 changes.[46]

- Document release testing (based on approved or updated specifications), batch records, and stability data.

- Perform pharmaceutical development studies and dissolution or in vitro release testing studies (as applicable).[47]

- Obtain stability data from one or more batches of postchange drug product. Both applicants and manufacturers should ensure that the postchange product placed on stability continues to meet established specifications before implementing the change. At

[41] See section 721(b)(1) of the FD&C Act.
[42] See section 721(a)(1)(A) of the FD&C Act.
[43] See § 211.186(b)(3) through (4) and 21 CFR 211.188(a) and (b)(3) through (4).
[44] See 21 CFR 201.100(b)(5)(ii) for label requirements for drug products that are not for oral use. Although § 201.100(b) does not require the names of inactive ingredients for oral drug products, from a safety perspective, listing the inactive ingredients allows for identification of ingredients that may cause sensitivities or allergic reactions in some patients. Therefore, FDA recommends including the names of inactive ingredients, including color additives, in the labeling of oral drug products. Certain color additives must be disclosed on labels (see 21 CFR 201.20 for disclosure of FD&C Yellow No. 5 and/or FD&C Yellow No. 6).
[45] See §§ 314.70(a)(2) and 314.97(a). For ANDAs, see 21 CFR 314.94(a)(9)(ii) concerning differences in inactive ingredients. See also the recommendations in the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021).
[46] See the SUPAC guidances in footnote 29.
[47] Ibid.

the time of supplement filing, applicants should provide at least 3 months of stability data at accelerated and long-term stability conditions[48] to confirm the previously established shelf life.

- Update and validate analytical methods, as appropriate.

The in vitro data recommendations above assume that no other changes are made that would necessitate in vivo bioequivalence studies.[49] If the previous color additive provided additional functions, the assessment of the change should include pharmaceutical development studies. These studies should be done to ensure that the replacement color additive provides the same functions and that the drug product meets applicable quality standards. For example, if the color additive's opacity protects the active pharmaceutical ingredient or drug product from light degradation, appropriate test methods to assess the stability of the formulation would include tests to ensure that the replacement color additive provides similar protection.[50] Manufacturers of over-the-counter monograph drug products must ensure that the replacement of the color additive does not interfere with analytical methods routinely used to ensure consistent drug product quality, such as release or stability tests.[51] Similarly, other manufacturers and applicants should also ensure that the color additive does not interfere with the analytical methods.

B. Updating the Composition Statement, Drug Product Specifications, and Labeling

Manufacturers and applicants should update manufacturing records and retain this information at the manufacturing facility. They should update the following:

- The replacement color additive's name (using the name listed in its color additive regulation), its level, and the regulation or regulations with which it complies.[52]

- Any additional adjustments that are made if the level of the replacement color additive differs from the level of the previous color additive. This can include changes to the levels of other ingredients, the total weight, and the percentages of inactive ingredients.

- The information in the master batch record to match the revised composition statement.

[48] See the ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003) for definitions of accelerated and long-term study conditions.

[49] See the level 3 changes described in the SUPAC guidances. The SUPAC guidances are listed in footnote 29.

[50] See § 211.166(a)(3). See also the ICH guidance for industry *Q1B Photostability Testing of New Drug Substances and Products* (November 1996).

[51] See 21 CFR 330.1(e). In over-the-counter monograph drug products, inactive ingredients, including color additives, must not interfere with tests or assays to determine if the product meets its standards of identity, strength, quality, and purity.

[52] See the draft guidance for industry *Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs* (April 2024). When final, this guidance will represent FDA's current thinking on this topic.

- The statement of ingredients in the drug product labeling including the DESCRIPTION section of the Prescribing Information and the container label or labels (e.g., carton labeling, patient labeling), if applicable.[53]

- The specifications for drug product release and stability if the replacement color additive changes the description of the drug product (e.g., the replacement color additive changes the drug product appearance from red to pink).

Applicants should submit an updated composition statement and drug product description in section 3.2.P.1 of the common technical document (CTD).[54] The updates should include a list of all of the ingredients in the drug product and their amounts on a per unit basis. Applicants should also ensure that the drug product composition is qualitatively and quantitatively consistent throughout the submission.

C. Documenting the Change

Table 1. Summary of Recommended Documentation for Replacing a Color Additive

This table summarizes the recommended documentation for replacing a color additive. Both applicants and manufacturers should retain this information at the manufacturing site, and applicants should submit this information in a CBE-30, as appropriate.[55] For detailed discussion refer to sections VI.A-B.

Category	Recommended Documentation
Composition statement, drug product specifications, and labeling	Update the description and composition statement (in 3.2.P.1 for applicants) to include: • The name of the replacement color additive (as stated in the regulations) • The level of the replacement color additive • The relevant color additive regulations • Any adjustments to the levels, total weight, and percentages of other inactive ingredients

Continued

[53] See footnote 44.

[54] See the ICH guidance for industry *M4Q: The CTD — Quality* (August 2001).

[55] Manufacturers must maintain all records necessary to demonstrate compliance with CGMP requirements. See § 211.180.

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Category	Recommended Documentation
Composition statement, drug product specifications, and labeling	Update the master batch record to match the information above. Update the statement of ingredients in the drug product labeling including the DESCRIPTION section of the Prescribing Information and the container label or labels (e.g., carton labeling, patient labeling), if applicable. If the replacement color additive changes the description of the drug product, update the drug product release and stability specifications.
Studies to assess the change	Manufacturers and applicants should manufacture one or more batches and place the batches on stability. Manufacturers and applicants should retain the data below at the manufacturing site, and applicants should submit this data: <u>Batch Release Data</u> Based on updated specifications or the specifications that were approved in the application <u>In Vitro Data</u> Dissolution or in vitro release testing (if applicable) <u>Stability Data</u> At least three months of stability data at accelerated and long-term conditions to confirm the previously established shelf life. Applicants should provide this data at the time of filing. FDA may request additional stability information to assess the effects of the change. <u>Pharmaceutical Development Studies</u> If the previous color additive had a function beyond imparting color, submit data to show that the replacement color additive serves a similar function and the same quality standards are met.

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REFERENCES

Draft Guidances for Industry

Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs (April 2024)[1]

Guidances for Industry

Changes to an Approved NDA or ANDA (April 2004)

Contract Manufacturing Arrangements for Drugs: Quality Agreements (November 2016)

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)

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

Process Validation: General Principles and Practices (January 2011)

Quality Systems Approach to Pharmaceutical CGMP Regulations (September 2006)

SUPAC-IR Questions and Answers about SUPAC-IR Guidance (February 1997)

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)

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M4Q: The CTD — Quality (August 2001)

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Q1B Photostability Testing of New Drug Substances and Products (November 1996)

Q10 Pharmaceutical Quality System (April 2009)

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (May 2021)

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