POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Evaluating Color Additives and Flavors Intended for Oral Drug Products Submitted or Referenced in INDs and NDAs

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PURPOSE

This MAPP describes the policies, procedures, and responsibilities in the Office of Pharmaceutical Quality (OPQ), in collaboration with the Office of New Drugs (OND), for assessing a color additive[1] or a flavor present as an excipient in an oral drug product submitted as part of an investigational new drug application (IND), new drug application (NDA), NDA supplement, or an amendment to one of these submissions, or referenced in a Type IV drug master file (DMF).[2,3]

Specifically, this MAPP is intended to: (1) identify the information on color additives and flavors to be documented by product quality assessors for Type IV DMFs, INDs, NDAs, and NDA supplements; and (2) delineate when a request for an OND evaluation of a flavor would become necessary during a quality assessment.

[1] 21 CFR 70.3(f)

[2] See the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005) for additional information on this topic. 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.

[3] The principles in this MAPP may be applied to topical drug products that include a color additive.

This MAPP does not apply to the assessment of color additives and flavors that are part of original abbreviated new drug applications or their supplements because the Office of Generic Drugs evaluates the acceptability of color additives and flavors for drug products submitted in an abbreviated new drug application.

BACKGROUND

Color Additives

Color additives are subject to the requirements of section 721 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379e). Under section 721(a) of the FD&C Act, a color additive is deemed unsafe for use in food, drugs, cosmetics, and medical devices unless such use conforms to a color additive listing regulation issued by FDA. The Center for Food Safety and Applied Nutrition (CFSAN) reviews color additive petitions and issues responsive regulations authorizing the use of color additives in food, drugs, cosmetics, and medical devices. The established regulations for color additives can be found in Title 21 of the Code of Federal Regulations (CFR), parts 70 through 82. The regulations in 21 CFR parts 73, 74, and 82 identify each color additive, provide chemical specifications for the color additives, and identify uses and restrictions, labeling requirements, and the requirement for batch certification. A firm may petition FDA to list a new color additive or modify an existing regulation.[4,5] The regulations in 21 CFR part 71 describe the petition process for new color additives or new uses for listed color additives.

Color additives used in marketed drugs must comply with FDA's color additive requirements.[6] For marketed drugs, the use of a color additive not in the regulations, the improper use of a color additive in the regulations, or the use of a color additive that does not conform to the purity and identity specifications of the listing regulation may cause a drug product to be adulterated.[7]

Section 721(c) of the FD&C Act and FDA's color additive regulations (21 CFR parts 70 and 80) separate cleared color additives into two main categories: those subject to batch certification (sometimes called *certifiable*) and those exempt from batch certification.

[4] Section 721(b)(5)(C) of the FD&C Act

[5] See the Color Additive Petitions web page (https://www.fda.gov/industry/color-additives/color-additive-petitions) and the guidance for industry *Color Additive Petitions – FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, Cosmetics, or Medical Devices* (July 2009).

[6] See the Color Additives Listed for Use in Drugs (From the Code of Federal Regulations) web page, which includes sublinks to colors exempt from and subject to certification (https://www.fda.gov/industry/drugs/color-additives-listed-use-drugs-code-federal-regulations). Note that these regulations are subject to change. Refer to the CFR for current information.

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

FDA conducts the certification program for batches of color additives that are required to be certified.

- Batch certification is required for color additives listed in 21 CFR parts 74 and 82 before the use of each batch of the color additive in a marketed drug product.

  – Color additive certification,[8] for marketed products, is the process by which FDA ensures that newly manufactured batches of color additives meet the identity and specification requirements of their listing regulations. The decision to require batch certification is based on the nature of the impurities in the additive and variability in the manufacturing process. In some cases, color additives that require batch certification may contain impurities of toxicological concern.

- Under the certification process, firms send a sample from each manufactured batch of a certifiable color additive to FDA, and the sample is evaluated by FDA's Color Certification Laboratory.[9] FDA personnel evaluate its physical appearance and chemically analyze it. Results are reviewed for compliance with the identity and specifications in the color additive listing regulation.

Of note, color additive clearances or certifications from foreign countries cannot satisfy the requirement that color additives used in drug products marketed in the United States be used in conformance with a color additive regulation issued by FDA and, where applicable, be batch certified by FDA.

Flavors

Flavors used in drug products are usually complex, proprietary chemical mixtures and may contain natural and/or artificial ingredients that may be identified in the CFR as cleared food additives (e.g., 21 CFR part 172, subpart F) or as generally recognized as safe (GRAS) for use in food (21 CFR parts 182 and 184). Additionally, some flavor substances may be used in food on the basis of *self-determined* GRAS status (i.e., a GRAS determination made by industry and not reviewed by FDA) or on the basis of a successful GRAS notification reviewed by CFSAN.[10] OND considers — but is not bound by — food additive status, GRAS determinations, history of safe use in food, and other relevant safety information as it reviews the safety of flavor preparations (that may include, for example, diluents or preservatives) and individual flavoring substances in accordance with the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005).

[8] 21 CFR part 80

[9] Ibid.

[10] https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices

POLICY

Color Additives

- OPQ will confirm that the color additive is listed in 21 CFR 73, 74, or 82, and its use complies with the conditions set forth in the individual listing regulation (see Attachments 1 and 2 and refer to the CFR for updates).

- OPQ will communicate options (see procedures for color additives) to the applicant if the proposed use of the color additive does not conform to an applicable color additive regulation.

- OPQ will ensure that, when applicable, a statement on batch certification is included under the specifications for color additives used in the manufacture of the drug product.

- OPQ will confirm that the color used in the drug product does not exceed limitations on levels of use for the color additive in drug products stated in the individual listing regulation (under use and restrictions) (see Attachment 1). When a color additive regulation states permissible levels of use in terms of current good manufacturing practice, the Inactive Ingredient Database (IID) may provide information on levels of use approved for other drug products.

- OPQ will refer to 21 CFR 73.1200(c), which allows for the use of synthetic iron oxide in drug products if the amount consumed in accordance with labeled or prescribed dosages does not exceed 5 milligrams, calculated as elemental iron, per day. This applies to the total iron oxide present in the drug product from all sources (e.g., coatings and imprinting inks). OPQ will consult OND regarding the determination of maximum daily exposure (MDE)[11] of the drug product.

Flavors

- OPQ will determine whether the flavor preparation (i.e., the flavor substances and other constituents of the flavor preparation) has been previously reviewed by FDA for use in food or drug products (referring to the food additive regulations, the GRAS regulations, successful GRAS notifications, and the IID)

[11] See the draft guidance for industry *Using the Inactive Ingredient Database* (July 2019; when final, this guidance will represent the FDA's current thinking on this topic), which defines MDE as the total amount of the excipient that would be taken or used in a day based on the maximum daily dose (MDD) of the drug product in which it is used. MDE is calculated as the dosage unit level of the excipient multiplied by the maximum number of dosage units recommended per day (excipient (milligram) x number of units). MDE may also be referred to as maximum daily intake for oral drug products. When an MDD is not provided in the product labeling, FDA will consider the applicant's rationale for an MDD when calculating excipient MDE.

- If the flavor preparation has been reviewed by FDA for use in food or drug products, OPQ will determine whether proposed use of the flavor preparation in the drug product exceeds any previously reviewed limits on levels of use, for any constituent part

- If the flavor preparation is new to FDA or the newly proposed use exceeds levels of use previously reviewed by FDA, the flavor preparation will be assessed for safety by the OND pharmacology/toxicology reviewer

RESPONSIBILITIES

Color Additives

Office of New Drug Products and Office of Lifecycle Drug Products (Division of Post-Marketing Activities I) Product Quality Assessors will:[12]

- Confirm the color additive is listed in 21 CFR part 73, 74, or 82, and its use complies with the conditions set forth in the individual listing regulation (see Attachments 1 and 2 and refer to the CFR for updates)

- For INDs and original NDAs and NDA supplements, document and assess the quality-related information (as provided under the Procedures section) for a color additive proposed for use in an oral drug product in the quality assessment (QA)[13]

- If a numerical limit is provided in terms of concentration of a color additive in drug products in the individual listing regulation, determine that the numerical limit (e.g., stated as a percentage or parts per million) has not been exceeded for the finished drug product, focusing on the dye molecule or color additive substance itself

- Contact the OND clinical and nonclinical[14] reviewers on the review team for the determination of MDE of the color based on maximum daily dose to determine that it meets the regulatory limit when the regulatory limit is stated in terms of daily exposure (as is the case for iron oxide)

- Send information requests where appropriate

[12] Product quality assessors in the Office of New Drug Products are responsible for reviewing original NDAs and product quality assessors in the Office of Lifecycle Drug Products (Division of Post-Marketing Activities I) are responsible for reviewing NDA supplements.

[13] The OPQ assessment should be documented and archived in the appropriate platform for the submission type.

[14] For the purposes of this MAPP, *nonclinical* refers to pharmacology/toxicology.

Flavors

Office of New Drug Products and Office of Lifecycle Drug Products (Division of Post-Marketing Activities I) Product Quality Assessors will:[15]

- For INDs and original NDAs and NDA supplements, document and assess quality-related information (as provided under the Procedures section) in the QA[16] for a flavor proposed for use in an oral drug product

  – For INDs and original NDAs, the MDE for flavors is assessed as part of the clinical and nonclinical review so no action related to MDE is needed

  – For NDA supplements, the product quality assessor will follow existing procedures for calculating the MDE

- Determine whether the flavor preparation (i.e., the flavor substances and other constituents of the flavor preparation) has already been reviewed by FDA for use in food or drug products (referring to the food additive regulations, the GRAS regulations, successful GRAS notifications, and the IID)

  – If so, also determine whether the proposed use of the flavor preparation in the drug product exceeds any previously reviewed limits on levels of use, for any constituent part

  – If not, or if the newly proposed use exceeds levels of use previously reviewed by FDA, refer such use to OND for safety evaluation by the pharmacology/toxicology reviewer

- Determine whether the flavor or its components are listed in the IID[17]

  – If the proposed use of the flavor or its components exceeds the levels in the IID, and the MDE is not supported by use in previously approved NDAs or abbreviated new drug applications, a safety evaluation from the OND nonclinical reviewer will be needed. The suitability of an excipient should not be based solely on the IID. Product quality assessors should consider the patient population and duration of use. If the flavor or its components have not

[15] Product quality assessors in the Office of New Drug Products are responsible for reviewing original NDAs and product quality assessors in the Office of Lifecycle Drug Products (Division of Post-Marketing Activities I) are responsible for reviewing NDA supplements.

[16] The OPQ assessment should be documented and archived in the appropriate platform for the submission type.

[17] https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

been used in the same context as the drug product under assessment, OND clinical and nonclinical safety evaluation should be requested.

- Ensure that the Type IV DMF contains appropriate information so the nonclinical reviewer can make a safety assessment, if needed

OPQ/Office of Program and Regulatory Operations Regulatory Business Project Manager will:

- Send out all communications for INDs, original NDAs and NDA supplements, and Type IV DMFs, including information requests or deficiencies

- Manage any meeting requests with the Type IV DMF holder

OND Nonclinical and Clinical Reviewers will:

- Review the nonclinical toxicity and clinical information, respectively, in the relevant submission. Nonclinical toxicity information includes in vitro genetic toxicology assays and studies in animals, but not analytical assays to determine the quality of any constituents in the flavor. Clinical teams review data generated in humans.

PROCEDURES

Color Additives

- The product quality assessor should confirm that the quality-related color additive information in the electronic common technical document (eCTD) section 3.2.P.1, Description and Composition of the Drug Product, of the application includes the amount used on a per-unit basis, the function of the color additive, and a reference for the listing within the color additive regulations (21 CFR part 73, subpart B; part 74, subpart B; or part 82, subparts C and D for drugs).[18] The product quality assessor should confirm that the color additive is listed in 21 CFR 73, 74, or 82 and its use complies with the conditions set forth in the individual listing regulation (i.e., verify compliance with uses, restrictions, and batch certification; see Attachments 1 and 2 and refer to the CFR for updates). If this information is missing, an information request should be sent to the applicant requesting this information.

- If the proposed quantity of the color additive in the drug product exceeds an applicable limit in the regulations, the product quality assessor should send an

[18] For an IND, relevant quality information is typically provided within the submission itself and not the eCTD. This applies to the other eCTD references in this MAPP.

information request to the applicant with the following recommendations: (1) reduce (to allowable limits, where provided) the amount of color additive used in the manufacture of the drug; or (2) replace the color additive with one that can be used in desired quantities without exceeding a limit in the regulation.

- The product quality assessor should ensure that the applicant has included a statement confirming batch certification in the specifications for the color additive, when applicable.[19] If information about batch certification is missing from the color additive specifications, an information request should be sent to the applicant.

- If the color additive is not listed in the CFR, the product quality assessor should recommend that the applicant replace the color additive with one that is used in accordance with an FDA color additive regulation.

Flavors

The quality information relevant to the flavor composition could be provided in an application, supplement, or amendment to an application, or a Type IV DMF.

- The product quality assessor should confirm that the flavor used in the drug product is identified in eCTD section 3.2.P.1 of the submission. The product quality assessor should confirm that the composition table includes the amount of flavor used on a per-unit basis, its function, and a reference to the relevant quality standards (e.g., compendial monographs or manufacturers' specifications).

- The quality information for the composition of the flavor can be found in a separate table in eCTD section 3.2.P.1 of the submission or the Type IV DMF. The product quality assessor should confirm that the composition table includes the components of the flavor, the Chemical Abstracts Service (CAS) Registry Number or Unique Ingredient Identifier (UNII) for each component, amount on a per-unit basis, the function of the component, quality standard, and any available reference to the CFR.

- Flavor information provided in the submission should be documented as part of the Type IV DMF assessment or in the quality assessment, respectively. If this information is not included in the Type IV DMF or submission, the product quality assessor should request that it be included. Because of the proprietary nature of some flavor information, the applicant should be contacted to provide information on the flavor only if the application does not reference a Type IV DMF for the flavor. If the application references a Type IV DMF for the flavor,

[19] See the FDA's Batch Certification Process section on the Color Certification FAQs web page, available at https://www.fda.gov/industry/color-certification/color-certification-faqs#cert.

the request should be directed to the DMF holder. For information on Type IV DMF content expectations, see available guidance.[20]

- If the components of a flavor preparation have not been previously reviewed and found acceptable by FDA for use in food at an unspecified maximum level of use, the product quality assessor should determine the MDE of the flavor or its individual components based on information in the submission or the DMF if one is referenced using the existing procedures for MDE calculation. If the MDE of the flavor or its components cannot be justified by levels listed in the IID,[21,22] a safety evaluation from an OND nonclinical review team member should be requested.

- If OPQ determines that an OND nonclinical and/or clinical assessment is needed, the OPQ product quality assessor should notify the assigned review team members where the safety justification or toxicology data on flavor components are located (i.e., in the Type IV DMF or in the chemistry, manufacturing, and controls section of the NDA).

- The product quality assessor should verify that the IND, NDA, or NDA supplement includes the amount of flavor in the final drug product composition, and document it in the quality assessment to assist the nonclinical and/or clinical reviewers in calculating the MDE and performing the safety evaluation, where needed.

EFFECTIVE DATE

This MAPP is effective on June 18, 2021.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
6/18/2021	Initial	N/A

[20] See the guidance for industry *Drug Master Files: Guidelines* (September 1989) and the draft guidance for industry *Drug Master Files* (October 2019; when final, this guidance will represent the FDA's current thinking on this topic).

[21] https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

[22] If the flavor is listed in the IID, the product quality assessor should cross-check the application under review with the referenced Type IV DMF for the flavor to confirm that the same flavor mixture is being identified in both.

Attachment 1: Listing of Color Additives Subject to Certification (21 CFR Part 74, Subpart B, Drugs)

The following list provides the color additives subject to certification found in 21 CFR part 74, subpart B, including their common names and corresponding CFR section numbers.[23] Note that most permitted color additive lakes are listed in 21 CFR part 82.

Color Additive	Common Name	Drug Regulations 21 CFR part 74
FD&C Blue No. 1	Brilliant Blue FCF	74.1101
FD&C Blue No. 1 Lake	(eye area use)	74.1101
FD&C Blue No. 2	Indigotine	74.1102
D&C Blue No. 4	Alphazurine FG	74.1104
D&C Blue No. 9	Indanthrene Blue	74.1109
FD&C Green No. 3	Fast Green FCF	74.1203
D&C Green No. 5	Alizarin Cyanine Green F	74.1205
D&C Green No. 6	Quinizarine Green SS	74.1206
D&C Green No. 8	Pyranine Concentrated	74.1208
D&C Orange No. 4	Orange II	74.1254
D&C Orange No. 5	Dibromofluorescein	74.1255
D&C Orange No. 10	Diiodofluorescein	74.1260
D&C Orange No. 11	Erythrosine Yellowish Na	74.1261
FD&C Red No. 3	Erythrosine	74.1303
FD&C Red No. 4	Ponceau SX	74.1304
D&C Red No. 6	Lithol Rubin B	74.1306
D&C Red No. 7	Lithol Rubin B Ca	74.1307
D&C Red No. 17	Toney Red	74.1317
D&C Red No. 21	Tetrabromofluorescein	74.1321
D&C Red No. 22	Eosine	74.1322
D&C Red No. 27	Tetrachlorotetra-bromofluorescein	74.1327
D&C Red No. 28	Phloxine B	74.1328
D&C Red No. 30	Helindone Pink CN	74.1330
D&C Red No. 31	Brilliant Lake Red R	74.1331
D&C Red No. 33	Acid Fuchsine	74.1333
D&C Red No. 34	Lake Bordeaux B	74.1334
D&C Red No. 36	Flaming Red	74.1336
D&C Red No. 39	Alba Red	74.1339
FD&C Red No. 40	Allura Red AC	74.1340
FD&C Red No. 40 Lake	Allura Red AC	74.1340
D&C Violet No. 2	Alizurol Purple SS	74.1602

continued

[23] See the CFR for the most up-to-date information.

Table, continued

Color Additive	**Common Name**	**Drug Regulations 21 CFR part 74**
FD&C Yellow No. 5	Tartrazine	74.1705
FD&C Yellow No. 5 Lake	(eye area use)	74.1705
FD&C Yellow No. 6	Sunset Yellow FCF	74.1706
D&C Yellow No. 7	Fluorescein	74.1707
Ext. D&C Yellow No. 7	Napthol Yellow S	74.1707a
D&C Yellow No. 8	Uranine	74.1708
D&C Yellow No. 10	Quinoline Yellow WS	74.1710
D&C Yellow No. 11	Quinoline Yellow SS	74.1711

Attachment 2: Listing of Color Additives Exempt From Certification (Subpart B, Drugs)

The following list provides the color additives exempt from certification found in 21 CFR part 73, subpart B, including their corresponding CFR section numbers.[24]

Color Additive	**Drug Regulations 21 CFR part 73**
Diluents in color additive mixtures for drug use exempt from certification	73.1001
Alumina (dried aluminum hydroxide)	73.1010
Chromium-cobalt-aluminum oxide	73.1015
Ferric ammonium citrate	73.1025
Annatto extract	73.1030
Calcium carbonate	73.1070
Canthaxanthin	73.1075
Caramel	73.1085
β-Carotene	73.1095
Cochineal extract; carmine	73.1100
Potassium sodium copper chloropyhllin (chlorophyllin-copper complex)	73.1125
Dihydroxyacetone	73.1150
Bismuth oxychloride	73.1162
Synthetic iron oxide	73.1200
Ferric ammonium ferrocyanide	73.1298
Ferric ferrocyanide	73.1299
Chromium hydroxide green	73.1326
Chromium oxide greens	73.1327
Guanine	73.1329
Mica-based pearlescent pigments	73.1350
Pyrogallol	73.1375
Pyrophyllite	73.1400
Logwood extract	73.1410
Mica	73.1496
Spirulina extract	73.1530
Talc	73.1550
Titanium dioxide	73.1575
Aluminum powder	73.1645
Bronze powder	73.1646
Copper powder	73.1647
Zinc oxide	73.1991

[24] See the CFR for the most up-to-date information.