Guidance for Industry: Preparing a Color Additive Petition for Submission to the Center for Food Safety and Applied Nutrition for Color Additives Used in or on Contact Lenses

Contains Nonbinding Recommendations

May 2006

Comments and suggestions regarding this document may be submitted at any time. Submit comments to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition (CFSAN)
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Guidance for Industry[1]
Preparing a Color Additive Petition for Submission to the Center for Food Safety and Applied Nutrition for Color Additives Used in or on Contact Lenses

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does

not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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I. Introduction

This document is intended to assist industry in preparing a petition for a color additive to be used in or on contact lenses. The guidance outlines the data requirements for a color additive petition and provides recommendations to address these requirements so that FDA can properly assess the safety of the proposed use of the color additive in contact lenses. This guidance represents an update to an earlier document published in 1996, “Guidelines for Approval of Color Additives in Contact Lenses Intended as Colors” and supplements a more general document entitled, **"Color Additive Petitions: FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, or Cosmetics." (ssLINK/ucm091779.htm)*** The 1996 guidance included recommendations for estimating exposure for the types of contact lenses that were prominent in the market at the time (i.e., lenses worn for a 1-year period). Since 1996 there has been an increase in the use of daily-wear lenses. The current guidance contains recommendations for estimating exposure based on current product availability (e.g., daily-wear disposable lenses; daily-wear lenses worn for 14 days, or one year; continuous-wear lenses; extended-wear lenses, etc.). The current guidance also reduces the number of toxicology tests recommended for establishing the safety of the color additive. While the earlier guidance document included a discussion of only safety and chemistry data requirements, the current guidance has been expanded to include recommendations for environmental data requirements and an explanation of the fees associated with submitting a color additive petition for use of a color additive in contact lenses.

FDA's guidance documents, including this guidance, 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

A color additive is defined in subsection 201(t)(1) of the Federal Food, Drug, and Cosmetic Act (FFDCA) as a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral or other source that is capable of imparting color when added or applied to a food, drug, cosmetic, or to the human body. Any substance that otherwise meets the definition of a color additive may be exempt from the definition if it is used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability or consumer acceptability is concerned (21 CFR 70.3(g))[2].

Under section 721(a) of the FFDCA, the use of a color additive in or on a medical device in direct contact with the body for a significant period of time is deemed unsafe unless it either conforms to the terms of a regulation prescribing its use or to an exemption for investigational use. A color additive for use in or on contact lenses is subject to the requirements of section 721 (previously 706) of the FFDCA.

A color additive petition (CAP) is submitted to request issuance of a regulation allowing new uses of color additives. A CAP must contain data and information to establish that a color additive is safe for use in or on foods, drugs, cosmetics, or medical devices. FDA's regulations that implement the CAP process are found in 21 CFR part 71. Data requirements for CAPs are described in 21 CFR 71.1(c).

Under the FFDCA, FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for processing all CAPs, including those for color additives to be used in medical devices; however, the FDA's Center for Devices and Radiological Health (CDRH) is responsible for evaluating the safety and effectiveness of the medical device itself. To market a daily wear contact lens, a premarket notification (510(k)) must be submitted to CDRH at least 90 days prior to introduction of the lens into interstate commerce. Extended wear lenses require a Premarket Approval (PMA) application. Guidance for submitting a 510(k) or PMA for colored contact lenses is available at the **CDRH website (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)**.

To assist you in developing an appropriate strategy for obtaining approval of a color additive to be used in contact lenses, we recommend that you consider the following:

- The CAP review period can take up to, and may extend beyond, 180 days.
- A CAP will be processed according to the procedures and fee schedules in 21 CFR 70 and 71.
- You should submit the CAP directly to CFSAN. Do not include the CAP in your 510(k) submission to CDRH as this will cause delays in processing the CAP and your 510(k) submission.
- A CAP included with a 510(k)/PMA submission is subject to the confidentiality provisions of 21 CFR Part 71 rather than those in 21 CFR Part 814.

III. Recommendations for Addressing Chemistry Data Requirements in 21 CFR 71.1(c).

A. Identity, Composition, Properties, and Specifications of Color Additive:

1. **Chemical Name:** Chemical names should conform where possible to the nomenclature adopted by

Chemical Abstracts, and, if already regulated by FDA for other uses, the name used in current regulations. You should submit the Chemical Abstracts Registry number (CAS No.) for each color additive. If a CAS No. is not available, you should request one from the Chemical Abstracts Service. For assistance, contact Chemical Abstracts Service, Customer Service, 2540 Olentangy River Road, PO Box 3012, Columbus, Ohio, 43210 or telephone (1-800) 753-4227. Email: **help@cas.org (mailto:help@cas.org)**.

2. Common and Trade Names: You should include common and/or trade names in a CAP; however, they should not be the only means of identification of color additive materials. For example, if the color additive is listed in the Colour Index (CI), you should include the identifying number. If you are unsure of the identity of the color additive, you should contact the manufacturer as to the name and identity of the material being provided.

3. Structural Information: For each color additive, you should present the molecular formula, molecular weight and chemical structure.

4. Method of Manufacture and Chemical Composition: You should provide a full description of the manufacturing process of the color additive. This description should include:

a. A list of all substances and amounts used in the synthesis.

b. Reaction conditions for the synthesis (e.g., time, temperature, pH, etc., as appropriate).

c. Equations for principal reactions, as well as known or likely side reactions.

The chemical composition of the color additive should include the identity of its components, including the coloring principle, by-products, and other impurities. Typical amounts of the components should be determined either by analysis or calculation (i.e., theoretical amounts based on the amounts of starting materials and stoichiometry of the reactions).

5. Properties of Color Additive: To identify and characterize the additive and differentiate it from other color additives, you should provide information on the chemical, physical and/or spectral properties of the color additive. Data that may be of use include, but are not restricted to, melting point, refractive index, solubilities, spectral curves, saponification value, acid value, etc.

6. Specifications: In proposing specifications for the color additive, you should provide detailed analytical methods for enforcing these specifications, as well as validation data supporting their accuracy, precision, and specificity. Recommendations concerning proposed specifications for petitioned color additives are as follows:

a. You should propose chemical specifications for the color additive that, together with the identity, define the article of commerce and reflect the composition of the proposed color additive. Specifications in the Food Chemicals Codex, US Pharmacopeia or National Formulary may be incorporated by reference. Examples of specifications for listed color additives are available in existing regulations in 21 CFR Parts 73 and 74. You should identify any individually-specified component (e.g. using common name, IUPAC or Chemical Abstract name, and CAS No., where possible).

   Specifications generally consist of the following (as appropriate):

   - Volatile matter (specify conditions, maximum percentage).
   - Soluble, extractable or insoluble matter (specify solvent or conditions, percentage) and soluble impurities (identity, specify solvent or conditions, maximum ppm).
   - Residual salts (identity, maximum percentage).
   - Unreacted intermediates and related compounds (identity, maximum percentage, ppm or ppb).
   - Subsidiary colors (identity, maximum percentage).

- Individual components that are included in the identity of the color additive (identity, minimum or maximum percentage).
- Pesticide residues (maximum ppm).
- Solvent residues (identity, maximum percentage or ppm).
- Ash (maximum percentage).
- Heavy metals (identity, maximum ppm).
- Total color content (assay, minimum percentage). This may include contributions from the identified color components and subsidiary colors.

b. You should consider that impurities of specific toxicological concern (e.g., chemical carcinogens) may be present in the proposed color additive. You should review the manufacturing process, the chemical literature on the proposed color additive and related compounds, and the specifications of listed related color additives. If carcinogens, compounds that may degrade to carcinogens, or compounds that may be metabolized to carcinogens are likely to be present, then you should contact FDA for guidance.

B. Amount of Color Additive Proposed for Use in Contact Lenses:

1. You should report typical as well as maximum likely use levels of the color additive in the lens.
2. You should estimate the maximum weight of a typical lens.
3. From (1) and (2), you should estimate the typical and maximum weight of the color additive in the lens.

C. Enforcement Methods:

You should provide practicable analytical methods to determine that the color additive in lenses is a permitted color additive and is being used at appropriate levels if a tolerance is required.

D. Estimation of Color Additive Exposure:

Potential exposure to a color additive in or on contact lenses generally is determined based on the results from a migration study in which the color additive is extracted from the lens. Migration data developed using the procedures outlined in this section are intended to provide estimates of the highest level of migration of the color additive that might result from the anticipated use of the color additive in contact lenses.

You can use this general test design in developing an appropriate migration study, However, since there are many types of contact lenses currently available (e.g., daily-wear single-use disposable lenses; daily-wear lenses used for 14 days to 1 month, or longer; extended-wear lenses worn overnight for up to 7 days or continuously for up to 30 days), we recommend that a migration study protocol be submitted to FDA for comment prior to initiating the study to ensure that the extraction conditions are appropriate for the type of contact lens in which the color additive will be used. Note that this protocol does not take into account any possible leaching of the color additive during rinsing and storage of contact lenses in a sterile saline solution prior to wear.

In general, the migration studies should be performed at 37 ^{o}C for an appropriate time period that represents the maximum intended lifetime of the contact lens. An extraction time of 14 days is usually sufficient for lenses such as daily-wear and for extended-wear lenses used for up to 14 days. If a color additive is to be used in lenses that are worn for longer than 14 days, an accelerated migration study may be performed to reduce the extraction time. Assuming first order kinetics, every 10 ^{o}C increase in the

accelerated test temperature above the normal test temperature (37°C) will enhance the rate of migration exponentially by a factor of two. For example, an accelerated migration study at 67 °C for 6.5 weeks would be suitable for predicting 1-year use at 37 °C, assuming the lenses are worn 24 hours per day. A more reasonable estimate is to assume that the lenses would be worn for 14 hours per day for 1 year. In this case, the accelerated conditions would be 67 °C for 3.8 weeks. In the case of rigid gas permeable (RGP) lenses, because of the thermal instability of the polymer used in the lenses, an accelerated migration study should be performed below 55 °C.

Extractions should be carried out using 0.9% (by weight) saline solution or phosphate-buffered saline (pH 7.4) and a surface area to volume ratio of 120 cm^2 lens to 20 ml extract[3]. The extraction container should be closed using a screw cap with a suitable elastomeric liner or an equivalent extraction device, to prevent saline loss during extraction.

Perform the extractions on five sets of colored lenses and five sets of uncolored lenses (i.e., to serve as a blank). Analyze the extract from each set of colored and uncolored lenses in triplicate at the end of the extraction period. Subtract any contribution from the blank extract from that of the colored lenses.

Describe the analytical method for quantifying the color additive. We recommend that the limit of detection (LOD) be determined from triplicate analyses of the five blank extracts described above. Measure the signal from each blank extract at the end of the extraction period, and calculate the average signal and standard deviation. The LOD (m+3s) is located three standard deviations (3s) above the average blank signal (m). Validate the analytical method by spiking the blank extracts with the color additive at levels of approximately one-half of, equal to, and twice the LOD (or amount of color additive extracted) and analyze each spiked sample in triplicate. Calculate the percent recovery from each spiked sample. Color additives may be dissolved in appropriate media (i.e., a saline solution with organic modifier added[4]) for the validation.

Provide a calibration curve for determining the level of the color additive. Include the correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares to evaluate the degree of linearity. Select concentrations of color additive standards for constructing the calibration curve on the basis of the concentration range expected for the color additive in a contact lens. Provide a data summary, sample calculations, raw data and sample chromatograms for all analyses. You can find further elaboration on validation methods and data requirements in ***Recommendations for Submission of Chemical and Technological Data for Direct Food Additive and GRAS Food Ingredient Petitions*** **(/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm124917.htm)**.

Calculate potential exposure to the color additive based on the results of the migration study. If the color additive was detected in the extracts, use the amount detected. If the color additive was not detected, use the LOD value. Assuming that a pair of contact lenses will be worn for a maximum of 14 days, for example, the exposure to the color additive is calculated as follows[5]:

$$\frac{\text{X mg color additive}}{\text{kg extract}} \times \frac{\text{20 ml extract}}{\text{120 cm}^2} \times \frac{\text{2.99 cm}^2}{\text{lens}} \times \frac{\text{kg}}{10^3\text{g}} \times \frac{\text{g}}{\text{ml}} = \frac{\text{mg color additive}}{\text{lens}}$$

$$\text{And} \quad \left[\left(\frac{\text{mg color additive}}{\text{lens}}\right) \text{ X } \left(\frac{\text{2 lens}}{\text{person}}\right)\right] /14 \text{ days}$$

Where: mg color additive/kg extract is the amount of color additive (in ppm) detected in the extracts, or if not detected, the LOD of the method; 20 mL/120 cm^2 is the volume to lens surface area ratio for the extraction; and 2.99 cm^2/lens is the estimated surface area of a contact lens with a 1.38 cm diameter[6].

In the case when a migration study with the color additive cannot be performed, you may calculate a conservative estimate of exposure to the color additive for the lifetime of one pair of lenses based on the assumption that: (i) the color additive is used in the contact lens at the maximum intended use level; and (ii) 100% of the color additive in the contact lens migrates. Assuming, for example, that a pair of contact lenses will be worn for a maximum of 14 days:

$$\left[\left(\frac{\text{X µg color additive}}{\text{lens}}\right) \text{ X } \left(\frac{\text{2 lens}}{\text{person}}\right)\right] /14 \text{ days}$$

Where µg color additive/lens is the maximum intended use level of the additive in the contact lens.

It should be noted that a “worst case” scenario for exposure to the color additive assumes that there is 100% migration of the color additive from the contact lens at the practical maximum use level of 50 µg/lens[7], resulting in a maximum exposure of

$$\left[\left(\frac{\text{50 µg color additive}}{\text{lens}}\right) \text{ X } \left(\frac{\text{2 lens}}{\text{person}}\right)\right] /14 \text{ days} = 7 \text{ µg/p/d}$$

over the lifetime of one pair of contact lenses (assuming that the lenses are worn for 14 days).

E. Tolerance

If you believe that the color additive should have limitations on the conditions of use to ensure safety, we recommend that you provide the basis for such limitations and include proposed codified text for the final rule.

F. Batch Certification.

If an exemption from batch certification is requested, you should provide the rationale that explains why certification is unnecessary to ensure the safety of the intended use of the color additive. If the color additive may contain impurities of toxicological concern, batch certification may be required to ensure their presence at safe levels.

IV. Recommendations for Addressing Safety Data Requirements in 21 CFR 71.1(c):

For FDA to approve a color additive, the CAP must contain safety information that establishes that the color additive will be safe for its intended use. However, no additional toxicological testing is needed for color additives to be used in contact lenses if the color additive is already approved for eye area use in cosmetics.

Toxicological testing of color additives not approved for eye area use and non-listed or provisionally-listed color additives will depend on exposure levels and degree of concern for potential toxicity of the color additive *and its impurities*. We will consider chemistry and available toxicology information in the safety determination. The

following are recommended tests for safety assessment of colored contact lenses, as well as other factors to be taken into account when submitting safety data:

- FDA recommends an *in vivo* Three Week Ocular Irritation Test in Rabbits (Draize test) using both colored and uncolored lenses, described in the "**Toxicology" section of Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses (/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080960.pdf)**.
- FDA also recommends the Guinea Pig Maximization Test (using extracts of colored and uncolored lenses[8]) to test for contact sensitization, as described in the "Toxicology" section of **Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses ()**.
- FDA cannot list a color additive for use in contact lenses if it has been demonstrated to induce cancer in a test appropriate for the evaluation of safety for such use.
- FDA will conduct risk assessments for color additives that are not known or suspected carcinogens, but that contain minor amounts of carcinogenic impurities. If we consider the estimated upper-bound lifetime cancer risk to be negligible for the carcinogenic impurities, we may list the use of the color additive.

V. Recommendations for Addressing Environmental Data Requirements in 21 CFR 71.1(c)

In 21 CFR 25.15(a), all petitions requesting agency action must contain either a claim of categorical exclusion or an environmental assessment (EA). Approval of a petition for color additives used in contact lenses, sutures, filaments used as supporting haptics in intraocular lenses, bone cement, and in other FDA-regulated products having similarly low levels of use is a class of actions that is normally categorically excluded, under 21 CFR 25.32(l), from the requirement to prepare an EA or an environmental impact statement (EIS). The reason for this exclusion is because the agency believes that, based on experience with CAPs, this class of actions is not likely to have a significant impact on the environment due to the small expected introductions of substances into the environment as a result of use and disposal. However, if extraordinary circumstances exist that there may be significant environmental effects due to use and/or disposal from the proposed use of the color additive in or on contact lenses, the exclusion in § 25.32(l) would not apply, and the petition would require an EA as defined under 21 CFR 25.40. An extraordinary circumstance may be shown by data available to either the agency or industry sponsor and may be based on production, use, or disposal from use of a substance. Data available to the agency include public information, information in the submission, and information the agency has received in other submissions for the same or similar substances. For information on extraordinary circumstances, please see 21 CFR 25.21.

If you believe that the petitioned use of a color additive in contact lenses qualifies for categorical exclusion under § 25.32(l), then your petition must include a claim of categorical exclusion as required by § 25.15; an adequate claim of categorical exclusion must (1) cite the section of the CFR under which the categorical exclusion is claimed (i.e., § 25.32(l)), (2) include a statement of compliance with the categorical exclusion criteria (small annual market volume), and (3) include a statement that, to your knowledge, no extraordinary circumstances exist that require submission of an EA. Guidance for preparing a claim of categorical exclusion or an EA is available at **http://www.cfsan.fda.gov/~dms/opa-eg.htm (/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081153.htm)**.

VI. Prescribed Fees

A color additive petition must be accompanied by an appropriate deposit for listing the color additive (Sec. 721(e) of the FFDCA). The fee for listing a new color additive to be used only in or on contact lenses is $2600. The fee to extend the use of a listed color additive to include contact lenses is $1600. Checks should be made payable to the Food and Drug Administration.
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[1]This guidance has been prepared by the Division of Petition Review, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition (CFSAN) at the US Food and Drug Administration.

[2] For example, the Center for Devices and Radiological Health (CDRH) generally does not require a CAP for a color used as an ultraviolet blocker/absorber in contact lenses or intraocular lenses, because the color is not added to the lens for the purpose of imparting color and the resulting color only minimally affects the color of the eye.

[3] USP biological reactivity test (USP 28-NF 23, 2005 USPC, Inc.) at **http://www.uspnf.com/uspnf/login (http://www.uspnf.com/uspnf/login)**.

[4] Organic modifier may be needed to solubilize the color additive in the spiking/recovery experiments. Thus, it is necessary to include the organic modifier in the blank samples to account for any interference or matrix effects.

[5] The time period used in the calculations should be the typical lifetime of the subject lenses.

[6] If a contact lens with a different diameter is used, the surface area should be adjusted accordingly.

[7] Chemistry memorandum regarding color additives in contact lenses dated February 19, 1985. P. Schwartz to A. Lipman.

[8] Extracts of the lens material should be prepared in a polar solvent. Extracts also should be analyzed for concentration of color additive and other lens components and the results included in the toxicology section of the CAP. For extract procedures, see **Premarket Notification (510(k)) Guidance for Daily Wear Contact Lenses (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080928.htm)**.

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* This document was revised in July 2009. See **"Color Additive Petitions: FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, Cosmetics, or Medical Devices." (/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/ucm171631.htm)**

More in Laws, Regulations, and Guidance (/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/default.htm)

Color Additive Guidance

(/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/ucm153033.htm)

Color Additive Regulations
(/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/ColorAdditiveListingRegulations/default.htm)