



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 74

[Docket No. FDA-2017-C-0935]

Listing of Color Additives Subject to Certification; D&C Black No. 4

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending the color additive regulations to provide for the safe use of D&C Black No. 4 for coloring ultra-high molecular weight polyethylene (UHMWPE) non-absorbable sutures for use in general surgery. This action is in response to a color additive petition (CAP) submitted by DSM Biomedical.

DATES: This rule is effective July 10, 2018. See section VIII for further information on the filing of objections. Submit either electronic or written objections and requests for a hearing on the final rule by July 9, 2018.

ADDRESSES: You may submit objections and requests for a hearing as follows. Please note that late, untimely filed objections will not be considered. Electronic objections must be submitted on or before July 9, 2018. The <https://www.regulations.gov> electronic filing system will accept comments until midnight Eastern Time at the end of July 9, 2018. Objections received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

*Electronic Submissions*

Submit electronic objections in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Objections submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your objection will be made public, you are solely responsible for ensuring that your objection 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 objection, that information will be posted on <https://www.regulations.gov>.
- If you want to submit an objection with confidential information that you do not wish to be made available to the public, submit the objection 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 objections submitted to the Dockets Management Staff, FDA will post your objection, 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-2017-C-0935 for "Listing of Color Additives Subject to Certification; D&C Black No. 4." Received

objections, those filed in a timely manner (see ADDRESSES), 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.

- Confidential Submissions--To submit an objection with confidential information that you do not wish to be made publicly available, submit your objections 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." We will review this copy, including the claimed confidential information, in our 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.gpo.gov/fdsys/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.

FOR FURTHER INFORMATION CONTACT: Joseph M. Thomas, Center for Food Safety and Applied Nutrition (HFS-265), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740-3835, 301-796-9465.

SUPPLEMENTARY INFORMATION:

### I. Introduction

In the *Federal Register* on March 6, 2017 (82 FR 12531), we announced that we filed a color additive petition (CAP 7C0310) submitted by DSM Biomedical (petitioner), 735 Pennsylvania Dr., Exton, PA 19341. The petition proposed to amend the color additive regulations in part 73 (21 CFR part 73), *Listing of Color Additives Exempt from Certification*, to provide for the safe use of high-purity carbon black for coloring UHMWPE non-absorbable sutures for use in general surgery.<sup>1</sup> After the petition was filed and during our review, we determined that the color additive will require batch certification by FDA. We intend to give each certified batch of the subject color additive the name D&C Black No. 4. Therefore, this color additive will be identified as D&C Black No. 4 and will be listed in part 74 (21 CFR part 74), *Listing of Color Additives Subject to Certification*.

### II. Identity and Specifications

D&C Black No. 4 is a high-purity carbon black prepared by the oil furnace process. It is manufactured by injecting a heated aromatic petroleum feedstock into the combustion zone of a natural gas-fired furnace to produce carbon black. The reaction is quenched with water and the

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<sup>1</sup> The original petition did not specify that the color additive is to be used in sutures that are non-absorbable. Therefore, our March 6, 2017, notice of filing did not specify that the color additive is intended for use in non-absorbable sutures. However, petitioner's subsequent submissions to FDA indicated that the intended use of the additive is for sutures that are non-absorbable.

carbon particles are further cooled and separated by a filter. The recovered high-purity carbon black is dried and pelletized to produce the final D&C Black No. 4 commercial product, consisting of aggregated particles with a surface area ranging from 50 to 260 meters squared per gram ( $m^2/g$ ). D&C Black No. 4 is mechanically mixed at a maximum level of 1 percent by weight with the UHMWPE suture raw materials to form a homogenous suspension, absent of chemical reaction between components, and extruded to form black colored sutures.

As explained in section III, the color additive D&C Black No. 4 may contain low levels of potentially carcinogenic polycyclic aromatic hydrocarbon (PAH) contaminants. To limit the amounts of these contaminants in the color additive, FDA is setting specifications for total PAHs, as well as for the individual PAH species benzo[*a*]pyrene (B[*a*]P) and dibenz[*a,h*]anthracene. These specifications are consistent with specifications for other high-purity carbon blacks approved by FDA, including the color additive D&C Black No. 2 (§ 74.2052 (21 CFR 74.2052)), which is approved for use in certain cosmetics, including cosmetics for use in the area of the eye (i.e., eyeliner, brush-on-brow, eye shadow, mascara), and high-purity furnace black, which is approved for use in food-contact polymers (§ 178.3297 (21 CFR 178.3297)). These specifications are also supported by the safety information reviewed as a part of this petition (see section III). In addition, to ensure compliance with these specifications, FDA is requiring that D&C Black No. 4 for use in UHMWPE non-absorbable sutures be from a batch of the color additive certified by FDA.

The identity for D&C Black No. 4 is the same as D&C Black No. 2, except for the surface area. For D&C Black No. 2, we set specifications for arsenic, lead, and mercury, total color (as carbon), total sulfur, ash content, surface area, and weight loss on heating, in addition to the specifications for total PAHs, benzo[*a*]pyrene (B[*a*]P), and dibenz[*a,h*]anthracene. We are

setting the same specifications that were established for D&C Black No. 2 for D&C Black No. 4 for these parameters with the exception of surface area specification, which is broader for D&C Black No. 4.

### III. Safety Evaluation

#### A. *Determination of Safety*

Under section 721(b)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379e(b)(4)), a color additive cannot be listed for a particular use unless a fair evaluation of the data and information available to FDA establish that the color additive is safe under the intended conditions of use. Furthermore, under 21 CFR 70.5(c), a color additive intended for use in a surgical suture must have a listing specifically providing for this use. FDA's color additive regulations in 21 CFR 70.3(i) define "safe" to mean that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive.

Section 721(b)(5)(B)(ii) of the FD&C Act provides that for any use of a color additive that will not result in ingestion of any part of such additive, the color additive shall be deemed to be unsafe and shall not be listed if, after tests that are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found to induce cancer in man or animal. Importantly, however, section 721(b)(5)(B) of the FD&C Act applies to the additive itself and not to impurities in the additive. That is, where an additive itself has not been shown to cause cancer, but contains a carcinogenic impurity, the additive is properly evaluated under the general safety standard using risk assessment procedures to determine whether there is a reasonable certainty that no harm will result from the intended use of the additive (*Scott v. FDA*, 728 F.2d 322 (6th Cir. 1984)).

*B. Safety of the Petitioned Use of D&C Black No. 4*

In evaluating the safety of a color additive, FDA customarily reviews the available data on each relevant chemical impurity to determine whether the chemical induces tumors in animals or humans. If FDA concludes that the chemical impurity causes cancer in animals or humans, the Agency calculates the unit cancer risk for the chemical and the upper bound limit of lifetime human cancer risk from the chemical's presence in the additive. To establish with reasonable certainty that D&C Black No. 4 intended to color UHMWPE non-absorbable sutures is not harmful under the intended conditions of use, we have considered the exposure to the color additive and its impurities, the additive's toxicological data, and other relevant information (such as published literature) available to us.

The petitioner incorporated safety information that was previously submitted to FDA on behalf of Cabot Corp. in Food Additive Petition 5B4464 by reference to support the safety of high-purity furnace black as a colorant for polymers in food-contact applications. D&C Black No. 4 is manufactured in the same manner as the referenced high-purity furnace black.

The petitioner also submitted data from an extraction study testing the migration of D&C Black No. 4 from UHMWPE sutures and provided data from two studies demonstrating biocompatibility of UHMWPE sutures along with other information. The petitioner's data from the extraction study indicated that D&C Black No. 4, when added to UHMWPE non-absorbable sutures at the maximum level of 1 percent, remains physically embedded in the suture matrix resulting in the color additive not being detected in the extracts at the limit of quantitation. This study evaluated the amount of non-volatile residue (NVR) and any extractables that could migrate from the suture. The study was performed with water, hexane, and ethanol at 50 °C for 24 hours and demonstrated that D&C Black No. 4 does not migrate from the suture following

exposure to solvents with varying polarities and exposure to heat. The study also yielded NVRs not able to be analyzed. To estimate potential exposure from D&C Black No. 4, the petitioner used data from the extraction study and the conservative assumption that all of the NVR that was extracted and not able to be analyzed was D&C Black No. 4. The petitioner derived an estimate for the mass amount of D&C Black No. 4 expected to migrate over a lifetime, expressed as the mean daily exposure, based on its proposed use level in surgical sutures, and using data for the maximum NVR extracted and the surface area of the tested sutures.

While FDA agrees with using the conservative assumption that all NVR extracted was D&C Black No. 4, the petitioner's exposure estimate represents the scenario where D&C Black No. 4 would migrate from the sutures 1 day post-implantation. However, since non-absorbable sutures are intended to be left in the body indefinitely post-implantation, it is necessary to average the petitioner's exposure estimate over an individual's lifetime post-implantation (assumed to be 70 years) to estimate the lifetime average exposure to D&C Black No. 4. In this manner, we estimated the lifetime average exposure to D&C Black No. 4 to be 15.3 nanograms per person per day (ng/p/d). However, as carbon black is known to be thermally stable, inert, and insoluble in water and common solvents, we agree with the petitioner's conclusion that D&C Black No. 4 is firmly embedded and does not migrate from the suture matrix, resulting in no potential exposure to D&C Black No. 4 from sutures that are in contact with the body (Ref. 1).

As discussed in section II, D&C Black No. 4 has been shown to contain low levels of PAH impurities, some of which are carcinogenic. We have previously considered the safe use of high-purity carbon black as a color additive in cosmetics (D&C Black No. 2; § 74.2052) and as a colorant in food-contact polymers (high-purity furnace black; § 178.3297) and set limits for PAHs in these high-purity carbon blacks to minimize exposure. We are setting similar limits for

PAHs in D&C Black No. 4 as those established for D&C Black No. 2: total PAHs (not more than 0.5 milligrams per kilogram (mg/kg) (500 parts per billion)); B[a]P (not more than 0.005 mg/kg (5 parts per billion)); and dibenz[*a,h*]anthracene (not more than 0.005 mg/kg (5 parts per billion)).

There were no detectable PAHs at the limit of quantitation resulting from the petitioner's extraction study. The petitioner stated that the trace levels of PAHs in the color additive, as limited by specifications, are strongly bound to the surface of D&C Black No. 4 carbon particles due to the powerful adsorption capabilities of the color additive. FDA concurs that any PAH impurities are not expected to migrate under the proposed specifications and conditions of use (Ref. 1). In calculating the lifetime average exposure to PAHs from the use of D&C Black No. 4 in sutures, we used the conservative assumption that total PAHs, B[a]P, and dibenz[*a,h*]anthracene are present in the color additive at their specification limits. These assumptions, along with the assumption that all NVR extracted from the sutures is D&C Black No. 4, calculated over a 70-year lifespan, results in a conservative estimated lifetime average exposure of total PAHs of  $7.7 \times 10^{-6}$  ng/p/d, B[a]P of  $7.7 \times 10^{-8}$  ng/p/d, and dibenz[*a,h*]anthracene of  $7.7 \times 10^{-8}$  ng/p/d (Ref. 1).

Current data have shown B[a]P to be a high contributor to the total carcinogenic potential for the PAH family (Ref. 2). To assess the risk from exposure to PAHs, FDA has used a worst-case assumption that all PAHs are present in D&C Black No. 4 as B[a]P. We used data from a carcinogenesis bioassay on B[a]P, conducted by H. Brune, et al., to estimate the upper-bound limit of lifetime human risk from exposure to B[a]P equivalents resulting from the petitioned use of the color additive (Ref. 3). The authors reported treatment-related benign forestomach tumors or esophageal tumors in male rats exposed to B[a]P. Using a linear-at-low-dose extrapolation

method and tumor incidence data from the H. Brune, et al. study, we estimated the unit cancer risk (UCR) for B[a]P to be 1.75 (milligrams per kilogram bodyweight per day (mg/kg bw/day))<sup>-1</sup> (Ref. 4). The UCR represents the derived cancer risk calculated per unit dose of the additive. This same UCR was used to assess the risk from exposure to PAHs for D&C Black No. 2 (69 FR 44927, July 28, 2004) and high-purity furnace black (Ref. 5). The lifetime cancer risk (LCR) was calculated by multiplying the UCR for B[a]P by the estimated lifetime average exposures. This results in LCRs of  $2.24 \times 10^{-15}$  and  $2.24 \times 10^{-13}$  for B[a]P and total PAHs, respectively. Because of the conservative assumptions we used to calculate the exposure estimate and the carcinogenic potency of PAHs in the color additive, and the fact that PAHs bind tightly to carbon black and are not expected to migrate, the lifetime-averaged individual exposure to PAHs is likely to be substantially less than our worst-case exposure estimate. Thus, the probable lifetime human risk would be less than the estimated LCR. Therefore, we conclude that there is reasonable certainty that no harm from exposure to PAHs will result from the petitioned use of the additive (Refs. 1 and 3).

#### IV. Conclusion

Based on the data and information in the petition and other available relevant material, FDA concludes that the petitioned use of D&C Black No. 4 for coloring UHMWPE non-absorbable sutures for use in general surgery is safe. We further conclude that the additive will achieve its intended technical effect and is suitable for the petitioned uses. Based on the available information, we are amending the color additive regulations in part 74 as set forth in this document. In addition, in accordance with 21 CFR 71.20(b), we conclude that batch certification of D&C Black No. 4 is necessary for the protection of public health because of the

need to limit the levels of PAHs, some of which have been shown to be carcinogenic. Therefore, part 74 should be amended as set forth in this document.

#### V. Public Disclosure

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that we considered and relied upon in reaching our decision to approve the petition will be made available for public disclosure (see FOR FURTHER INFORMATION CONTACT). As provided in § 71.15, we will delete from the documents any materials that are not available for public disclosure.

#### VI. Analysis of Environmental Impact

We previously considered the environmental effects of this rule, as stated in the notice of petition published in the *Federal Register* of March 6, 2017. We stated that we had determined, under 21 CFR 25.32(l), that this action "is of a type that does not individually or cumulatively have a significant effect on the human environment" such that neither an environmental assessment nor an environmental impact statement is required. We have not received any new information or comments that would affect our previous determination.

#### VII. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### VIII. Objections

This rule is effective as shown in the DATES section, except as to any provisions that may be stayed by the filing of proper objections. If you will be adversely affected by one or more provisions of this regulation, you may file with the Dockets Management Staff (see ADDRESSES) either electronic or written objections. You must separately number each

objection, and within each numbered objection you must specify with particularity the provision(s) to which you object, and the grounds for your objection. Within each numbered objection, you must specifically state whether you are requesting a hearing on the particular provision that you specify in that numbered objection. If you do not request a hearing for any particular objection, you waive the right to a hearing on that objection. If you request a hearing, your objection must include a detailed description and analysis of the specific factual information you intend to present in support of the objection in the event that a hearing is held. If you do not include such a description and analysis for any particular objection, you waive the right to a hearing on the objection.

Any objections received in response to the regulation may be seen in the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <https://www.regulations.gov>. We will publish notice of the objections that we have received or lack thereof in the *Federal Register*.

#### IX. References

The following references are on display with the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References that are published articles and books are not on display.

1. Memorandum from H. Lee, Division of Petition Review, Office of Food Additive Safety (OFAS), CFSAN, FDA to J. Thomas, Division of Petition Review, OFAS, CFSAN, FDA, dated April 27, 2018.

2. Choi H, R. Harrison, H. Komulainen, et al., "Polycyclic Aromatic Hydrocarbons." *WHO Guidelines for Indoor Air Quality: Selected Pollutants*. Geneva: World Health Organization; 2010.

3. Brune H., R. P. Deutsch-Wenzel, M. Habs, et al., "Investigation of the Tumorigenic Response to Benzo(a)pyrene in Aqueous Caffeine Solution Applied Orally to Sprague-Dawley Rats," *Journal of Cancer Research and Clinical Oncology*, 102(2):153-157, 1981.

4. Memorandum from N. Anyangwe, Division of Petition Review, OFAS, CFSAN, FDA to J. Thomas, Division of Petition Review, OFAS, CFSAN, FDA, dated April 27, 2018.

5. Memorandum from the Indirect Additives Branch, FDA, to the Executive Secretary, Quantitative Risk Assessment Committee, FDA, concerning "Estimation of the Upper-bound Lifetime Risk from Polynuclear Aromatic Hydrocarbons (PAH's) in High-Purity Furnace Black (HPFB): subject of Food Additive Petition No. 5B4464 (Cabot Corp.)," dated May 9, 1996.

#### List of Subjects in 21 CFR Part 74

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 74 is amended as follows:

#### PART 74--LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

1. The authority citation for part 74 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

2. Section 74.3054 is added to subpart D to read as follows:

§ 74.3054 D&C Black No. 4.

(a) *Identity*. The color additive D&C Black No. 4 is a high-purity carbon black prepared by the oil furnace process. It is manufactured by the combustion of aromatic petroleum oil feedstock and consists essentially of pure carbon, formed as aggregated fine particles with a surface area range of 50 to 260 meters (m)<sup>2</sup>/gram.

(b) *Specifications*. D&C Black No. 4 must conform to the following specifications and must be free from impurities other than those named to the extent that such other impurities may be avoided by good manufacturing practice:

(1) Surface area by nitrogen BET (Brunauer, Emmett, Teller) method, 50 to 260 m<sup>2</sup>/gram.

(2) Weight loss on heating at 950 °C for 7 minutes (predried for 1 hour at 125 °C), not more than 2 percent.

(3) Ash content, not more than 0.15 percent.

(4) Arsenic (total), not more than 3 milligrams per kilogram (mg/kg) (3 parts per million).

(5) Lead (total), not more than 10 mg/kg (10 parts per million).

(6) Mercury (total), not more than 1 mg/kg (1 part per million).

(7) Total sulfur, not more than 0.65 percent.

(8) Total polycyclic aromatic hydrocarbons (PAHs), not more than 0.5 mg/kg (500 parts per billion).

(9) Benzo[*a*]pyrene, not more than 0.005 mg/kg (5 parts per billion).

(10) Dibenz[*a,h*]anthracene, not more than 0.005 mg/kg (5 parts per billion).

(11) Total color (as carbon), not less than 95 percent.

(c) *Uses and restrictions.* (1) D&C Black No. 4 may be safely used at a level not to exceed 1.0 percent by weight of the suture material for coloring ultra-high molecular weight polyethylene non-absorbable sutures for general surgical use.

(2) Authorization and compliance with this use must not be construed as waiving any of the requirements of sections 510(k), 515, and 520(g) of the Federal Food, Drug, and Cosmetic Act with respect to the ultra-high molecular weight polyethylene surgical sutures in which D&C Black No. 4 is used.

(d) *Labeling.* The label of the color additive must conform to the requirements of § 70.25 of this chapter.

(e) *Certification.* All batches of D&C Black No. 4 must be certified in accordance with regulations in part 80 of this chapter.

Dated: June 1, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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