4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket Nos. FDA-2011-C-0344 and FDA-2011-C-0463]

Listing of Color Additives Exempt From Certification; Reactive Blue 246 and Reactive Blue 247 Copolymers

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 additional copolymers of 1,4-bis[4-(2-methacryloxyethyl)phenylamino]anthraquinone (C.I. Reactive Blue 246) and copolymers of 1,4-bis[(2-hydroxyethyl)amino]-9,10-anthracenedione bis(2-methyl-2-propenoic)ester (C.I. Reactive Blue 247) as color additives in contact lenses. This action is in response to two color additive petitions (CAPs) filed by CooperVision, Inc.

DATES: This rule is effective May 2, 2013. See section VII for related information on the filing of objections. Submit either electronic or written objections and requests for a hearing by May 1, 2013.

ADDRESSES: You may submit either electronic or written objections and requests for a hearing, identified by Docket No. FDA-2011-C-0344 (C.I. Reactive Blue 246) or FDA-2011-C-0463 (C.I. Reactive Blue 247), by any of the following methods:

Electronic Submissions

Submit electronic objections in the following ways:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments.

Written Submissions

Submit written objections in the following ways:

- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and the appropriate docket number (FDA-2011-C-0344 for C.I. Reactive Blue 246 or FDA-2011-C-0463 for C.I. Reactive Blue 247) for this rulemaking. All objections received will be posted without change to http://www.regulations.gov, including any personal information provided. For detailed instructions on submitting objections, see the "Objections" heading of the SUPPLEMENTARY INFORMATION section.

Docket: For access to the dockets to read background documents or objections received, go to http://www.regulations.gov and insert the docket numbers, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Regarding CAP 1C0291 (C.I. Reactive Blue 246):

Judith Kidwell,

Center for Food Safety and Applied Nutrition (HFS-265),

Food and Drug Administration,

5100 Paint Branch Pkwy.,

College Park, MD 20740-3835,

240-402-1071.

Regarding CAP 1C0292 (C.I. Reactive Blue 247):

Teresa Croce,

Center for Food Safety and Applied Nutrition (HFS-265),

Food and Drug Administration,

5100 Paint Branch Pkwy.,

College Park, MD 20740-3835,

240-402-1281.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a notice published in the Federal Register of June 28, 2011 (76 FR 37690), we announced that CooperVision, Inc., 6150 Stoneridge Mall Rd., suite 370, Pleasanton, CA 94588 (petitioner) had filed two color additive petitions (CAP 1C0291 and CAP 1C0292). The petitions proposed to amend the color additive regulations in 21 CFR part 73, subpart D, Medical Devices, to provide for the safe use of additional copolymers of 1,4-bis[(2-hydroxyethyl)amino]-9,10-anthracenedione bis(2-methyl-2-propenoic)ester (C.I. Reactive Blue 247) and additional copolymers of 1,4-bis[4-(2-methacryloxyethyl)phenylamino]anthraquinone (C.I. Reactive Blue 246) as color additives in contact lenses. The color additives are produced by copolymerizing the reactive dyes with various vinyl and/or acrylic monomers such that the dyes are bound covalently and cross-linked in the resulting polymer matrix.[1]

[1] According to the International Union of Pure and Applied Chemistry (IUPAC), a vinyl polymer is prepared from a monomer containing the vinyl group $–CH=CH_2$. Acrylic polymers are one subclass of vinyl polymers; however, not all acrylic polymers (e.g., methacrylic polymers) are vinyl polymers using the IUPAC definition (Ref. 1). The term

Current regulations for C.I. Reactive Blue 246 and C.I. Reactive Blue 247 copolymers (21 CFR 73.3106 and 73.3100, respectively) list the reaction products of these reactive dyes with specific vinyl and/or acrylic monomers for use in coloring contact lenses.[2] The petitions sought to expand the list of permitted monomers to include any suitable vinyl and/or acrylic monomer capable of forming a contact lens. The petitions were filed under section 721 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 379e). In § 73.3100, Reactive Blue 247 is identified as 1,4-bis[(2-hydroxyethyl)amino]-9,10-anthracenedione bis(2-propenoic)ester. As part of this final rule, we are correcting the nomenclature for Reactive Blue 247 by inserting "2-methyl" before "2-propenoic."

II. Safety Evaluation

Under section 721(b)(4) of the FD&C Act, a color additive may not be listed for a particular use unless the data available to FDA establishes that the color additive is safe for that use. Our color additive regulations at 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."

"vinyl and/or acrylic monomers" includes monomers that form vinyl polymers, monomers that form acrylic polymers (e.g., acrylate, methacylate, acrylamide, etc.), or any combination thereof.

[2] 21 CFR 73.3106 originally allowed for the safe use of 1,4–bis[4–(2–methacryloxyethyl) phenylamino]anthraquinone (C.I. Reactive Blue 246) copolymerized with hydroxyethyl methacrylate monomer or a blend of hydroxyethyl methacrylate and N-vinyl pyrrolidone monomers (58 FR 17506, April 5, 1993). The regulation was later amended to also allow for the safe use of C.I. Reactive Blue 246 copolymerized with a blend of 3–[tris(trimethylsiloxy)silyl]propyl vinyl carbamate and N-vinyl pyrrolidone monomers (60 FR 10495, February 27, 1995).

21 CFR 73.3100 allows for the safe use of 1,4–bis[(2–hydroxyethyl)amino]–9,10–anthracenedione bis(2–propenoic)ester (C.I. Reactive Blue 247) copolymerized either with glyceryl methacrylate, methyl methacrylate, and ethylene glycol dimethacrylate monomers, or with N,N–dimethyl acrylamide, methyl methacrylate, and ethylene glycol dimethacrylate monomers (61 FR 51584, October 3, 1996).

As part of our safety evaluation of the color additives, we considered exposure to unreacted C.I. Reactive Blue 246 and 247 and any impurities (e.g., reaction byproducts) from the petitioned use of the color additives. We also considered results from skin sensitization, ocular irritation, and cytotoxicity studies with either representative lens materials or extracts from the lens materials (i.e., the color additives that are the subjects of the petitions).[3]

A. C.I. Reactive Blue 246

We calculated an exposure estimate for C.I. Reactive Blue 246 from its proposed use in three representative contact lens formulations using vinyl and/or acrylic monomers based on results from a leachability study that was conducted by the petitioner. This study demonstrated that there was no detectable migration of C.I. Reactive Blue 246 at the limit of detection (LOD) of an appropriate analytical method for any of the lens formulations evaluated. We estimated the potential exposure to any one impurity using the maximum amount of total impurities determined in C.I. Reactive Blue 246.

The average daily exposure to C.I. Reactive Blue 246 from its proposed use would be no greater than 13 nanograms (ng)/person/day (p/d) and the maximum exposure to any one impurity will not exceed 0.6 ng/p/d. These estimates represent worst-case exposure, and the actual exposure to C.I. Reactive Blue 246 and its impurities from the use of the color additive in contact lenses is expected to be significantly lower. Based on data submitted in the petitions, as well as other relevant information, we note that it is highly unlikely that either C.I. Reactive Blue 246 or its components would migrate from the contact lens into the aqueous environment of the eye because the reactive dye is covalently bound and cross-linked during polymerization such that any migration from the resulting copolymer matrix as a result of the proposed uses will be

[3] Both the petitioner's representative formulations and currently regulated formulations consist of either C.I.

negligible. Therefore, we conclude that the exposure to the color additive, including any impurities that may be present in it, from the petitioned use would be negligible (Ref. 2).

The petitioner submitted data from 24 toxicology studies on either representative lens materials or extracts from representative lens materials with and without C.I. Reactive Blue 246 to establish the safety of the copolymerized color additives of C.I. Reactive Blue 246. Studies included guinea pig maximization studies, in vivo ocular irritation studies in rabbits, and cytotoxicity studies. Based on our review of these studies, we conclude that there is no evidence of toxicity (Ref. 3).

B. C.I. Reactive Blue 247

We calculated an exposure estimate for C.I. Reactive Blue 247 from its proposed use in three representative contact lens formulations using vinyl and/or acrylic monomers based on results from a leachability study that was conducted by the petitioner. This study demonstrated that there was no detectable migration of C.I. Reactive Blue 247 at the LOD of an appropriate analytical method for any of the lens formulations evaluated. We estimated the potential exposure to any one impurity using the maximum amount of total impurities determined in C.I. Reactive Blue 247.

The average daily exposure to C.I. Reactive Blue 247 from its proposed use would be no greater than 10 ng/p/d and the maximum exposure to any one impurity will not exceed 0.5 ng/p/d. These estimates represent worst-case exposure, and the actual exposure to C.I. Reactive Blue 247 and its impurities from the use of the color additive in contact lenses is expected to be significantly lower. Based on data submitted in the petitions, as well as other relevant information, we note that it is highly unlikely that either C.I. Reactive Blue 247 or its

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Reactive Blue 246 or C.I. Reactive Blue 247 copolymerized with various vinyl and/or acrylic monomers.

components would migrate from the contact lens into the aqueous environment of the eye because the reactive dye is covalently bound and cross-linked during polymerization such that any migration from the resulting copolymer matrix as a result of the proposed uses will be negligible. Therefore, we conclude that the exposure to the color additive, including any impurities that may be present in it, from the petitioned use would be negligible (Ref. 4).

The petitioner submitted data from 24 toxicology studies on either representative lens materials or extracts from representative lens materials with and without C.I. Reactive Blue 247 to establish the safety of the copolymerized color additives of C. I. Reactive Blue 247. Studies included guinea pig maximization studies, in vivo ocular irritation studies in rabbits, and cytotoxicity studies. Based on our review of these studies, we conclude that there is no evidence of toxicity (Ref. 5).

III. Conclusion

Based on the data contained in the two petitions and other available relevant material, we conclude that the petitioned use of the reaction products formed by copolymerizing either C.I. Reactive Blue 246 or C.I. Reactive Blue 247 with vinyl and/or acrylic-monomers to form colored contact lenses is safe and that the color additives will achieve their intended technical effect. We further conclude that there is no need for imposing a limitation on the amount of color additive to be used, beyond the limitation that reactants may be used in amounts not to exceed the minimum reasonably required to accomplish the intended technical effect. Therefore, we are amending the regulations in part 73 (21 CFR part 73) as set forth in this document. In addition, based upon the factors listed in § 71.20(b) (21 CFR 71.20(b)), we have determined that batch certification of these color additives is not necessary for the protection of the public health.

IV. Public Availability of Documents

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.

V. Environmental Impact

We previously considered the environmental effect of this rule, as stated in the June 28, 2011, Federal Register notice of petitions for CAP 1C0291 and CAP 1C0292 (76 FR 37690). 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.

VI. 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.

VII. 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. Any person who will be adversely affected by this regulation may file with the Division of Dockets Management (see ADDRESSES) either electronic or written objections regarding this document. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered

objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. It is only necessary to send one set of documents. Identify documents with the appropriate docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. FDA will publish notice of the objections that we have received or lack thereof in the Federal Register.

VIII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at http://www.regulations.gov.

1. Barón, M., K.-H. Hellwich, M. Hess, K. Horie, et al, "Glossary of Class Names of Polymers Based on Chemical Structure and Molecular Architecture (IUPAC Recommendations 2009)", Pure and Applied Chemistry, 81(6), pp. 1131-1186, 2009.
2. Memorandum from H. Lee, Division of Petition Review, Chemistry Review Team, to J. Kidwell, Division of Petition Review, Regulatory Group I, FDA, July 26, 2011.
3. Memorandum from S. Park, Division of Petition Review, Toxicology Review Team, to M.Harry, Division of Petition Review, Regulatory Group I, FDA, November 30, 2011.

4. Memorandum from H. Lee, Division of Petition Review, Chemistry Review Team, to T.Croce, Division of Petition Review, Regulatory Group II, FDA, August 16, 2011.
5. Memorandum from T.Walker, Division of Petition Review, Toxicology Review Team, to T.Croce, Division of Petition Review, FDA, January 13, 2012.

List of Subjects in 21 CFR Part 73

Color additives, Cosmetics, Drugs, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 73 is amended as follows:

PART 73--LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

1. The authority citation for part 73 continues to read as follows:

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

2. Amend § 73.3100 by revising the section heading and paragraph (a) to read as follows:

§ 73.3100 1,4-Bis[(2-hydroxyethyl)amino]-9,10-anthracenedione bis(2-methyl-2-propenoic)ester copolymers.

(a) Identity. The color additives are the copolymers formed as the reaction product of 1,4-bis[(2-hydroxyethyl)amino]-9,10-anthracenedione bis(2-methyl-2-propenoic)ester (C.I. Reactive Blue 247) (CAS Reg. No. 109561-07-1) with one or more vinyl and/or acrylic monomers to form the contact lens material.

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3. Amend § 73.3106 by revising paragraph (a) to read as follows:

§ 73.3106 1,4-Bis[4-(2-methacryloxyethyl) phenylamino]anthraquinone copolymers.

(a) Identity. The color additives are the copolymers formed as the reaction product of 1,4-bis[4-(2-methacryloxyethyl)phenylamino]anthraquinone (C.I. Reactive Blue 246) (CAS Reg. No. 121888-69-5) with one or more vinyl and/or acrylic monomers to form the contact lens material.

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Dated: March 25, 2013.

Susan M. Bernard,

Director,

Office of Regulations, Policy and Social Sciences,

Center for Food Safety and Applied Nutrition.

[FR Doc. 2013-07294 Filed 03/29/2013 at 8:45 am; Publication Date: 04/01/2013]