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Via Federal Express

Division of Dockets Management (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 1998C-0431; Response to Gatewood Organization's Objection and Request for a Hearing on 21 C.F.R. Part 73 Listing of Color Additives Exempt from Certification; Mica-Based Pearlescent Pigments

Dear FDA:

On behalf of our client, EMD Chemicals, Inc., the purpose of this letter is to respond to the objections set forth in the August 22, 2005 electronic-mail message sent by Gatewood Organization, LLC (the "Gatewood Objection") to the Food and Drug Administration (FDA) regarding the July 22, 2005 *Federal Register* notice of the final rule for mica-based pearlescent pigments.¹ This rule was issued in response to a color additive petition (CAP 8C0257) from EMD Chemicals, Inc. (formerly EM Industries) filed on June 22, 1998. Gatewood has objected to the final rule for mica-based pearlescent pigments "on behalf of persons adversely affected by or particularly sensitive to the presence of added iron oxides and iron salts in any form." Gatewood Objection at 1. Accordingly, Gatewood has requested that FDA further consider a number of assertions regarding the safety of the pigments and, in particular, the safety of iron oxide as a component of the pigments.

Gatewood's request for a hearing has no merit and must be denied for two reasons. First, Gatewood has failed to comply with FDA's procedural requirements. Second, Gatewood's request fails to provide reliable evidence showing that there are genuine and substantial issues of fact requiring a hearing to resolve. FDA has, in fact, considered the potential health and safety concerns regarding the use of up to 3% mica-based pearlescent pigments in ingestible drugs, with a maximum iron oxide content no greater than 55% in those pigments containing iron oxide. Through FDA's review of the extensive data submitted in support of the color additive petition, and based on the Agency's independent review of the potential effects associated with the intended use of the mica-based pearlescent pigments, FDA has determined that the proposed use of the pigments will not pose a health or safety concern with respect to the entire population. As a result, there is no basis on which to hold a hearing.

¹ 70 *Fed. Reg.* 42271 (July 22, 2005).

I. FDA Must Deny The Hearing Request Because Gatewood Has Not Complied With The Procedural Requirements Stated In Applicable Regulations And The Notice Promulgating The Final Regulation

Under 21 C.F.R. § 12.24(b)(6), the party requesting a hearing must meet the requirements in applicable regulations and in the notice promulgating the final regulation or the notice of opportunity for hearing. Gatewood has failed to meet two applicable requirements: (1) the requirement in the *Federal Register* notice and 21 C.F.R. § 12.22 for objecting to the final rule and requesting a hearing; and (2) the requirement in 21 C.F.R. § 71.30(b) with respect to the fee that is required to accompany an objection. We address these issues, in turn, below.

A. Gatewood Did Not “Specify With Particularity” the Grounds for Its Objections

As stated in the preamble to the final regulation and 21 C.F.R. § 12.22(a)(2) and (3), “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.” 70 *Fed. Reg.* at 42272 (“VII. Objections”). Furthermore, an objection is required to include “a detailed description and analysis of the factual information to be presented in support of the objection,” including “any report, article, survey, or other written document relied upon” (with certain exceptions). 21 C.F.R. § 12.22(a)(5).

Gatewood failed to separately number each objection to the final rule on mica-based pearlescent pigments, and Gatewood failed to specify with particularity the provisions of the regulation to which the objection is made and the grounds for the objection. Rather, Gatewood’s objections are a series of hypotheses, speculation, and general “what if” scenarios. None of these “issues” is described in sufficient detail to warrant further consideration. Moreover, Gatewood did not include any documents or other materials to support its claims.

The *Federal Register* notice clearly states that failure to include a detailed description and analysis of the specific factual information intended to be presented in support of any particular objection shall constitute a waiver of the right to a hearing on the objection. Accordingly, since Gatewood’s objections were not numbered and did not include a detailed description and analysis of the specific information intended to be presented (*i.e.*, the evidence), Gatewood has waived the right to a hearing on the objections.

B. Gatewood’s Objection Did Not Include the Required Fee

Under FDA’s regulations, “objections and [requests for] hearings relating to color additives shall be accompanied by a filing fee of \$250.00.” 21 C.F.R. §§ 70.19(k) and 71.30(b). Nothing in Gatewood’s Objection suggests that the required filing fee of \$250.00 was submitted. Section 70.19(q) permits the Commissioner of FDA to waive or refund the fee in whole or in part when the action “will promote the public interest.” Here, it is questionable whether Gatewood (a self-described “small consulting company”) is acting more to protect the commercial interests of one or more of its clients than the public interest as a whole. Thus, FDA should not waive the required fee. Similarly, there is no indication that Gatewood petitioned FDA to waive the fee on

the grounds that the fee presents a hardship. 21 C.F.R. § 70.19(r). As Gatewood appears to be a for-profit organization, it is highly doubtful that a \$250 fee would present a hardship. Assuming that Gatewood did not submit the required fee, FDA must deny the request for a hearing.

II. FDA Must Deny The Hearing Request Because Gatewood Has Not Shown That A Hearing Is Justified

Even if Gatewood's request for a hearing is not denied on procedural grounds, the request is substantively insufficient to warrant a hearing. A party seeking a hearing is required to meet a threshold burden of producing evidence that supports the need for a hearing.² In particular, a hearing request must present sufficient reliable evidence to raise a "genuine and substantial issue of fact," and the evidence must be adequate to resolve the issue as requested and to justify the action requested.³ Gatewood's Objection does not show that a hearing is justified. Specifically, Gatewood has failed to present sufficient reliable evidence to raise a genuine and substantial issue of fact. Indeed, Gatewood's complaints are entirely "mere allegations or denials or general descriptions of positions and contentions," which cannot be the basis for granting a hearing. 21 C.F.R. § 12.24(b)(2). Even assuming that the evidence is sufficient and reliable, it is not adequate to resolve the issue as requested and justify the action requested. Although Gatewood did not clearly state its objections, the following discussion addresses what appear to be the primary concerns.

- A. "FDA has not considered aspects for use in orally ingested drug products in the review of the affect [sic] of this rule permitting iron salts for color additive components." (Gatewood Objection at 1)

It is not clear what is meant by this vague assertion. It appears to suggest that FDA's review of this petition did not account for individuals who are particularly sensitive to iron; accordingly, those individuals' added exposure to iron salts allegedly may result in adverse effects that were not accounted for in FDA's review. Gatewood has failed to raise a genuine and substantial issue of fact and presented no reliable evidence to support the claim that FDA failed to account for this class of individuals. In addition, Gatewood presents no reliable evidence to support the assumption that iron salts would be present from the iron oxide component of the pigments.

FDA performed an extensive review of the safety of the use of the mica-based pearlescent pigments and, in particular, the use of iron oxide at the intended use levels. Iron oxide is widely known from the scientific literature to be a very poor source of iron for

² See 21 C.F.R. § 12.24(b) ("Ruling on objections and requests for hearing"); *Douglas M. Costle v. Pacific Legal Foundation*, 445 U.S. 198, 214-215 (1980), *reh. den.*, 445 U.S. 947 (1980), *citing Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 620-621 (1973).

³ See 21 C.F.R. § 12.24(b).

fortification purposes due to its extremely low and almost nonexistent solubility/bioavailability.⁴ Indeed, a review of the memoranda cited as references in the final rule makes clear that the solubility and bioavailability of iron from the iron oxide component of pearlescent pigments are expected to be low, even when in contact with artificial gastric and intestinal juices.⁵ There is no evidence to suggest that the solubility and bioavailability profile of the iron from iron oxide would be different when consumed by people who are particularly sensitive to additional iron exposure. Furthermore, there is no evidence to suggest that iron salts would be potential byproducts or impurities of the iron oxide, particularly given the known stability of iron oxide. For all of these reasons, FDA must deny the request for a hearing on this point.

- B. “With this rule pertaining to drugs, synthetic rust in pearlescent color additive for orally ingested drug products is expected to limit availability of medications for the persons who must monitor iron intake. This risk, albeit for the minority, does not appear to have been considered in the drug use petition. There is no offset benefit provided in the review for the majority related to the use of the pearlescent rust color additive.” (Gatewood Objection at 2)

Gatewood has failed to raise a genuine and substantial issue of fact and presented no evidence to support the general allegation that iron oxide (derisively termed “synthetic rust”) in pearlescent color additives used in drugs would limit the availability of medications for persons who must monitor iron intake. As noted above, iron oxide is widely known to be an extremely poor source of iron for fortification purposes due to its extremely low and almost nonexistent solubility/bioavailability, even in the acidic environment of the stomach. Thus, individuals who ingest drugs containing iron oxide pigments would not be exposed to any significant level of absorbable iron.

Moreover, given the composite nature of the finished color additive and its method of manufacture, it is even less likely that iron would be absorbed from ingestion of the pearlescent pigments than from ingestion of iron oxide, *per se*. In the pearlescent pigments, iron oxide is deposited on the surface of the mica platelet by a wet precipitation process. The layer of iron oxide that covers the mica substrate has been stabilized by calcination. For this reason, it cannot be easily dissolved by weak media such as are found in the human GI system. Accordingly, there is no evidence to suggest that individuals who consume drugs made with the pearlescent pigments will be exposed to iron in any absorbable form or, consequently, that sensitive individuals will need to avoid such products. For all of these reasons, FDA must deny the request for a hearing on this point.

⁴ See World Health Organization, 571. *Iron (WHO Food Additive Series 18)*, at <http://www.inchem.org/documents/jecfa/jecmono/v18je18.htm>.

⁵ Division of Petition Review (DPR), Toxicology Review Group (HFS-265), *Comprehensive Final Toxicology Evaluation Memorandum: CAP 8C0257*, to A. Orstan, Ph.D., Consumer Safety Officer, DPR, December 20, 2004, at p. 7.

C. “Contaminants, if present from this single color component source, can reasonably be expected to exceed a 0.1% threshold.” (Gatewood Objection at 2)

Gatewood has not raised a genuine and substantial issue of fact and provided no reliable evidence to support the general allegation that contaminants from the color additive will exceed the stated 0.1% threshold. Similarly, Gatewood has not provided any information to suggest that such a contaminant level would present any health or safety concerns, either to the general public or to sensitive individuals. The calculations offered by Gatewood in this context rest on the questionable assumption that a single ingestible drug tablet is 5 grams or 5000 mg. Gatewood has not provided any evidence to support this tablet size, which is substantially different than FDA’s unchallenged assumption that a single tablet is 600 mg, as discussed at length in the review memoranda.⁶ Further, Gatewood does not provide any basis to conclude that 0.1% is a relevant threshold level for drug impurities or contaminants in finished drug products.⁷

A review of FDA’s memoranda in the docket makes clear that FDA performed a “worst-case” dietary exposure calculation for iron oxide and elemental iron. In particular, FDA assumed that the entire population uses the intended pharmaceutical products, that all pharmaceutical products contain the pigments at the maximum specified level, and that each component (namely, iron oxide) of the pigment is present at the maximum level within the pigment (*i.e.*, 55%). Taking into account these worst-case assumptions, FDA still determined that the maximum potential dietary exposures to iron oxide and elemental iron are safe.

The mica-based pearlescent pigments do not contain any compounds that can be referred to as “iron contaminants.” When the pigment is analyzed by state-of-the-art methodology, iron is detected only in the form of iron oxide because of the calcination step. However, even in the unlikely event that potentially absorbable iron species were to be present in the pigment on the order of 0.1%, as apparently suggested by Gatewood, the corresponding level of such species in the tablet would be in the sub- or low- microgram range. Gatewood has not provided any evidence to suggest that such low levels of exposure would present any toxicological concerns. For all of these reasons, FDA must deny the request for a hearing on this point.

⁶ Division of Product Manufacture and Use (HFS-246), *CAP 8C0257 (MATS M2.0 & 2.1): EM Industries, Inc. (submission of 21 April, 1998 and 27 May, 1998). Use of pearlescent pigments as a color additive in tablets and other pharmaceutical preparations*, to Color Additive Special Project Team, Attn.: Aydin Orstan, Ph.D., Division of Petition Control, HFS-215, Jan. 21, 1999, at 001489/p. 4.

⁷ FDA’s drug guidance documents indicate that acceptance criteria should be established for organic impurities in drug substances (active ingredients) that may exceed 0.1%. *See generally*, Draft FDA “Guidance for Industry - Drug Substance: Chemistry, Manufacturing, and Controls Information” (January 2004) (<http://www.fda.gov/cder/guidance/3969DFT.pdf>). However, iron and iron oxide are inorganic compounds expected to be used in finished drug products. Thus, there is no indication that Gatewood’s expressed concerns are relevant to the intended use of the pigments.

- D. “The docket documents provide no evidence that FDA has fully evaluated and stipulated the manufacturing and controls conditions appropriate for safe increased use of iron oxides and salts in the additive pigment.” (Gatewood Objection at 1)

This argument presents a mere allegation without support from specifically identified reliable evidence. Although a detailed discussion of manufacturing controls may not be included in the public docket, in our experience FDA routinely considers the available information on potential manufacturing byproducts and impurities, and places appropriate regulatory controls on such compounds when the available information warrants it. The information included in CAP 8C0257 demonstrates that the manufacturing process for the pearlescent pigments is well established and has been shown to produce consistent pigment products that are tightly controlled and tested for quality and purity. The pigments and their constituent ingredients are thoroughly screened for impurities as part of ongoing quality control, and the specifications in the petition are intended to control all impurities of concern that may potentially be present in the finished pigment.⁸ The fact that FDA did not find it necessary to include any manufacturing controls or limits on impurities beyond those specified in the final rule is a further indication that the pigments are not reasonably expected to contain additional impurities at levels that could give rise to any concern. For all of these reasons, FDA must deny the request for a hearing on this point.

- E. “The specifications itemized in the rule permitting such proposed use fail to identify limits of free iron and ferrous oxides or other iron salts in the final color product or the methods of detecting and differentiating the color additive from other potential ferrous iron contaminants.” (Gatewood Objection at 1)

Gatewood’s comment is simply a statement of disagreement with FDA’s action. Even assuming that the specifications itemized in the final rule do not identify limits on free iron, it is not necessary to do so. As discussed in depth in the review memoranda included in the docket, iron oxide is an inorganic, stable compound, which is deposited on the surface of the mica platelet by vapor deposition and held there via the manufacturing process described previously.⁹ In addition, ferrous ions and other compounds which Gatewood describes are not stable under high temperature calcination conditions, which the pigments undergo during processing.

Furthermore, EMD Chemicals produces its pigments in accordance with good manufacturing practice (GMP) and the current International Pharmaceutical Excipients Council guidelines. Each raw material used in the production of the pigments has a strict specification

⁸ See CAP 8C0257 at 28-29 (dated April 6, 1998) (copy released under the Freedom of Information Act, at 000032-000033).

⁹ Division of Petition Review (DPR), Toxicology Review Group (HFS-265), *Comprehensive Final Toxicology Evaluation Memorandum: CAP 8C0257*, to A. Orstan, Ph.D., Consumer Safety Officer, DPR, December 20, 2004, at p. 7.

that is aimed at limiting the amount of trace materials. Therefore, even if the final rule does not identify limits of free iron, it is not necessary to do so since the evidence shows that there will be no free iron, ferrous oxides, or other iron salts in the final color product. For all of these reasons, FDA must deny the request for a hearing on this point.

- F. “Such iron contaminants [free iron, ferrous oxides, or other iron salts], as historically established in numerous cases, regardless of source, are expected to cause drug interference with increased risk. We would present such cases.” (Gatewood Objection at 1) “Synthesis chemistry has long established that any iron contaminants cause stability issues for many API. In multiple cases, virtually undetectable ferrous ion contaminants induced API failures, which are not detectable by HPLC or other routine drug release testing. (Gatewood Objection at 2)

Gatewood has provided no reliable evidence to support the general allegation that iron contaminants are expected to cause drug interference by causing stability issues for many active pharmaceutical ingredients (APIs). Even if Gatewood did, this assertion does not raise a genuine and substantial issue of fact.¹⁰ It is the responsibility of the drug company to determine whether a possible interaction could exist between pigments containing iron oxide and the active drug substance. EMD Chemicals anticipates that the primary dosage forms (*i.e.*, tablet, caplet, capsules) will be ones in which the active drug ingredient does not come into contact with the pigment by virtue of where the pigment is found (*i.e.*, in film coating for tablets and caplets and in gelatin mass for capsules). Moreover, the API and the coating containing the pigment likely will have different dissolution kinetics. For all of these reasons, FDA must deny the request for a hearing on this point.

- G. “However, that use [iron salts’ presence in pigments used in contact lenses] where the color is bound in resin and used in a pH neutral environment should not be compared with use in drug products ingested into the acidic environment of the stomach. Therefore, the FDA inclusion of all iron salts in this Final Rule simply to make the two divergent uses consistent in terminology is chemically and physiologically incorrect and should not be considered valid.” (Gatewood Objection at 1-2)

Gatewood’s claims are simply general allegations and statements of disagreement with FDA’s action. The reference to the final rule for color additives containing iron salts for use in contact lenses is relevant to the color additive at issue here because it sets forth FDA’s rationale for using the name “mica-based pearlescent pigments” to describe EMD Chemicals’ product. The materials in the docket make it evident that, in clearing the pigments for use in ingested

¹⁰ Gatewood’s statements inappropriately try to recast an issue of current good manufacturing practices (cGMP) compliance for the finished drug product as a safety issue with a color additive.

drugs, FDA did not rely on its safety assessment for the pigments for use in contact lenses. Rather, the Agency conducted a separate, thorough safety assessment for the use of the pigments in ingested applications. The fact that iron salts may be used in the manufacture of the pigments does not adversely impact the safety of the pigments for sensitive consumers, because the iron salts will not be present in the finished pigments. As indicated by the information in the petition, and as discussed in the notice of the final rule, in the manufacture of the pigments, the iron salts are converted to iron hydroxide and ultimately to iron oxide. For the foregoing reasons, FDA must deny the request for a hearing on this point.

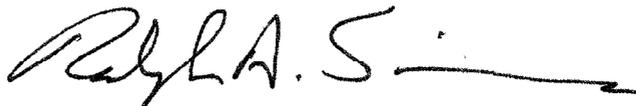
III. Conclusion

Gatewood's request fails to justify a hearing, both on procedural and substantive grounds. The request does not provide any information which raises a "genuine and substantial issue of fact" supported by reliable evidence. Instead, Gatewood presents "mere allegations" and "general descriptions of positions and contentions." A hearing cannot be granted on these bases. For the reasons set forth above, FDA must deny Gatewood's request for a hearing.

* * *

Thank you for your attention. If you should have any questions or concerns with respect to the issues presented in this letter, please do not hesitate to contact us.

Respectfully submitted,



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