Ref. 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

ıte: November 24, 2004

om: Division of Petition Review
Chemistry Review Group

ıbject: CAP 8C0257 (MATS#971 M2.4.1.1): EM Industries, Inc. Use of pearlescent pigments in pharmaceutical preparations. Update of intake estimates.

ɔ: Division of Petition Review, HFS-265
Regulatory Group II
Attention: Aydin Örstan, Ph.D.

This memorandum addresses the request by the Toxicology Review Group (HFS-265), in a meeting held 10/29/2004, that we provide a separate intake estimate for pearlescent pigments used in pharmaceuticals, as well as for lead, mercury, arsenic, iron oxide, mica, and titanium dioxide that result from this use. We were also requested to comment on the intake of pseudobrookite from the use of pearlescent pigments in pharmaceuticals.

In the previous chemistry memorandum dated 4/16/2003, we provided eaters-only intake estimates of the pearlescent pigments and their components from all of the proposed and regulated uses. The 4/16/2003 memorandum provided the details of our intake estimates for both food and pharmaceutical uses. Therefore, the eaters-only intake of the pearlescent pigments and their components from their intended use in pharmaceuticals presented here is taken from the tables of our 4/16/2003 memorandum, except for arsenic and mercury, which are calculated here for the first time. We have also revised intake of lead from that in our 4/16/2003 memorandum. We have estimated intakes for children (2-4 years) and adults (20-70 years) based on age groups identified previously for the intake of pharmaceuticals.[1]

1. Pearlescent pigments

In a previous memorandum,[2] we provided the eaters-only intake of pearlescent pigments from their use in pharmaceuticals. We used the upper limit of the typical use level range (3%) to estimate exposure. Our previous estimate used the worst-case assumption that the pharmaceutical products (including tablets, liquid preparations, and dentifrices) would be consumed by the entire population (i.e., 100% eaters).

The petitioner did not provide further data on the relative percentages of the population consuming pharmaceutical products formulated with pearlescent pigments. Therefore, we shall continue to assume 100% consumers of these pharmaceuticals.[2] We shall rely on the worst-case scenario, in which: (1) all tablets (solid or gelatin) are formulated with 3% pearlescent pigments; and (2) 100% of the population consumes pharmaceuticals formulated with pearlescent pigments.

The eaters-only intake of the pearlescent pigments from their intended use in pharmaceuticals is reproduced in the Table 1, below.

[1] Chemistry memorandum, CAP 8C0257, dated January 21, 1999, E. Jensen to A. Orstan.
[2] Chemistry memorandum, CAPs 8C0257 & 8C0262, dated January 30, 2003, H. Lee to A. Orstan.

Table 1. Eaters-only intake of pearlescent pigments from pharmaceuticals (g/p/d)

Age group	% Eaters	Mean	90th percentile
Adults (20-70 years)	100	0.05	0.1
Children (2-4 years)	100	0.04	0.08

II. Heavy metals (Lead, arsenic, and mercury)

In a previous memorandum,[3] we provided the intake of lead from the use of pearlescent pigments in pharmaceuticals assuming a maximum lead limit of 5 mg/kg based on data provided in the petition. However, at the meeting on 7/9/2003, the petitioner proposed a new lead limit of 4 mg/kg. The OCAC chemist has determined that this newly proposed specification is acceptable.[4] Therefore, we shall recalculate the intake of lead from the intended use of the pearlescent pigments in pharmaceuticals using the proposed specification limit of 4 mg/kg. We shall also calculate the corresponding intakes of arsenic and mercury based on the petitioner's proposed a specification limit of 3 mg/kg for arsenic and 1 mg/kg for mercury.

We have estimated the eaters-only intake of each of the heavy metals by multiplying by the eaters-only intake of the pearlescent pigments from pharmaceuticals uses (Table 1) by the proposed specification limit for each of the heavy metals (lead: 4 mg/kg; arsenic: 3 mg/kg; mercury: 1 mg/kg). Table 2, below, summarizes the intakes of the individual heavy metals from the pharmaceutical uses of pearlescent pigments. The intakes for lead in Table 2, below, supersedes those in our previous memoranda.

Table 2. Eaters-only intakes of individual heavy metals from pharmaceuticals (μg/p/d)

		% Eaters	Mean	90th Percentile
Lead	Adults (20-70 years)	100	0.20	0.40
	Children (2-4 years)	100	0.16	0.32
Arsenic	Adults (20-70 years)	100	0.15	0.3
	Children (2-4 years)	100	0.12	0.24
Mercury	Adults (20-70 years)	100	0.05	0.1
	Children (2-4 years)	100	0.04	0.08

III. Iron oxide

In the submission dated 2/11/2003, the petitioner stated that the maximum level of iron oxide

[3] Chemistry memorandum, CAPs 8C0257 & 8C0262, dated 4/16/2003. H. Lee to A. Orstan.
[4] Memorandum dated 7/14/2003, N.Hepp to A. Orstan.

(Fe_2O_3) in the pigments will be 55%. This is reduced from the level of 60% stated in the original submission. We have conservatively calculated the eaters-only intake of iron oxide from the use of pearlescent pigments in pharmaceuticals by multiplying the eaters-only intake of pigments from pharmaceutical uses (Table 1) by the maximum level of iron oxide in the pigments (55%). The eaters-only intake of elemental iron was calculated by multiplying the corresponding intake of iron oxide by 0.7.[5] These results are summarized below.

Table 3. Eaters-only intake of iron oxide and elemental iron from pharmaceuticals (g/p/d)

		Iron oxide		Elemental Iron	
Age group	% Eaters	Mean	90th percentile	Mean	90th percentile
Adults (20-70 years)	100	0.03	0.06	0.02	0.04
Children (2-4 years)	100	0.02	0.04	0.01	0.03

Iron oxide is currently regulated for use as a color additive in several applications, including ingested or topically applied drugs such that the intake of elemental iron shall not exceed 5 mg/p/d (equivalent to 7 mg/p/d iron oxide; synthetic iron oxide, §73.1200). The exposure to iron oxide from its regulated use in drugs (maximum 7 mg/p/d) would be subsumed under the petitioned use of pearlescent pigments containing iron oxide (30 mg/p/d and 20 mg/p/d at the mean for adults and children, respectively; Table 3).

IV. Mica

As a conservative approach, we have assumed that maximum level of mica [$(K_2Al_6Si_6O_{20})(OH)_4$] in the pigments is 88%, as described in a previous chemistry memorandum.[1] The eaters-only intake of mica from the use of pearlescent pigments in pharmaceuticals is calculated by multiplying the eaters-only intake of pigments from pharmaceutical uses (Table 1) by the level of mica in the pigments (88%). The results are summarized below.

Table 4. Eaters-only intake of mica from pharmaceuticals (g/p/d)

Age group	% Eaters	Mean	90th percentile
Adults (20-70 years)	100	0.05	0.1
Children (2-4 years)	100	0.04	0.08

Mica is currently regulated for use as a color additive in several applications, including dentifrices and externally applied drugs in accordance with GMP (§73.1496). The intake of mica from its currently-regulated use in dentifrices is likely to be substitutional for that from a similar petitioned use of pearlescent pigments.

V. Titanium dioxide

As a conservative approach, the eaters-only intake of titanium dioxide (TiO_2) from the use of

[5] That is : [(2 x 56 g Fe)/(160 g Fe_2O_3)]=0.7

pearlescent pigments in pharmaceuticals is calculated by multiplying the eaters-only intake of pharmaceuticals (Table 1) by the maximum level of titanium dioxide in the pigments (52%).[1] The results are summarized below.

Table 5. Eaters-only intake of titanium dioxide from pharmaceuticals (g/p/d)

Age group	% Eaters	Mean	90th percentile
Adults (20-70 years)	100	0.03	0.06
Children (2 -4 years)	100	0.02	0.04

Titanium dioxide is currently regulated for use as a color additive in several applications, including ingested and externally applied drugs in accordance with GMP (§73.1575). The petitioned use of titanium dioxide in pearlescent pigments in pharmaceuticals may substitute for some of the currently-regulated uses in pharmaceuticals.

VI. Pseudobrookite

In the previous chemistry memorandum dated 5/5/2000,[6] the mean *per capita* daily intake of pseudobrookite (Fe_2TiO_5) from the proposed use of pearlescent pigments in pharmaceuticals was estimated to be 15 mg/p/d (adults) and 12 mg/p/d (children). We note that the estimate is based on the assumptions that: (1) the intake of pearlescent pigments from the proposed use in pharmaceuticals is 87 mg/p/d for adults and 70 mg/p/d for children; and (2) all of the pigment ingested is Candurin® Honeygold, which contains a theoretical maximum of 18% by weight of pseudobrookite.

This intake scenario for pseudobrookite from the petitioned use of pearlescent pigments in ph armaceuticals is highly conservative, as it assumes that all of the pearlescent pigments contain pseudobrookite at the theoretical maximum level. In reality, only those pigments formulated wi th titanium dioxide, iron oxide and mica could potentially contain pseudobrookite, and it is not likely that pseudobrookite would be present at the theoretical maximum level in all of the pig ments. Therefore, we would expect that the probable intake of pseudobrookite from the propo sed use of the pearlescent pigments in pharmaceuticals would be negligible.

Information presented by the petitioner in the meeting held 12/5/2001 indicate that pseudobrookite is an inert, orthorhombic, dense oxide mineral found in nature, that would be indigestible under most gastric and intestinal conditions. Based on its composition, we concur that pseudobrookite would be very insoluble when ingested.

VII. Conclusions

The intake of pearlescent pigments and their components from the proposed use in pharmaceuticals have been estimated for adults and children. These are conservative estimates, as they based on the assumptions that the entire population uses the intended pharmaceutical products, all pharmaceuticals products contain the pigments at the maximum specified level, and that each component (i.e., iron oxide, mica, titanium dioxide, and individual heavy metals) of the pigment is present at the maximum level within the pigment.

[6] Chemistry memorandum, CAPs 8C0262 & 8C0257, dated 5/5/2000. E. Jensen to A. Orstan.

Consequently, we note that our intake estimates for iron oxide, elemental iron, mica and titanium dioxide subsume the intake from currently-regulated uses in drugs.

We have no further questions regarding the chemistry information in the subject petition. The petition is suitable for regulation with respect to the chemistry information.

Hyoung S. Lee, Ph.D.

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HFS-265: HSLee: 436-1316:CAP257 final memo.doc
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