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KFDA Drug Safety Policy Division
#643
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RE: Proposed limitations on use of color additives in pharmaceutical products

Dear Ms. Jong-pil, Lee:

The International Association of Color Manufacturers (IACM) is the trade association that represents the manufacturers and end-users of coloring substances that are used in foods, including natural and artificial colors. We are writing to you to offer further information and to express our concerns related to the draft proposal related to a limitation of 0.1% on the use of a number of specific color additives in pharmaceutical and supplement products.

In pharmaceutical and supplement products, added colorants perform important functions. Most critically, surveys of doctors, nurses, and pharmacists have shown that color is the main identification factor to prevent prescribing, dispensing, and administration errors. For many pharmaceutical and supplement applications, artificial color additives are preferred over natural colors due to their specific coloring ability, uniformity, stability, and intensity of color. Currently, there are some pharmaceutical and supplement applications for which there are not suitable natural color alternatives to artificial colors. Restricting or reducing the maximum permitted levels of this important class of color additives would have a detrimental effect upon the pharmaceutical and supplement industries, and more importantly for the consumers that rely on these drug or supplement products.

IACM takes the continuing demonstration of the safety of color additives as its top mission, and we believe that the regulation of these additives that is of most benefit to consumers relies on sound, thorough science and risk assessment and management practices that utilize this science and consider input from all stakeholders.

In considering the draft proposal to limit the use of color additives to no more than 0.1% of the final product, IACM has concerns that no risk assessment has been carried out. As IACM understands it, such risk assessments are required by the World Trade Organization Sanitary and Phytosanitary (SPS) Measures Agreement.[1] Such a risk assessment would also be consistent with international harmonization practices through the Codex Alimentarius.

[1] The SPS Agreement requires members to "base their sanitary or phytosanitary measures on international standards…where they exist." (WTO SPS Measures Agreement, Article 3).

IACM would like to offer our assistance in providing data to the KFDA should a safety evaluation of color additives be planned. IACM or its predecessor organization, the Certified Color Manufacturers of America (CCMA), has sponsored a large number of metabolism, toxicology, carcinogenicity, genotoxicity, and reproductive/developmental toxicity studies on many of these color additives, and stands ready to provide the KFDA with appropriate data should the required risk assessment be planned.

Much of this data has formed the robust datasets that were the basis of the evaluations of these color additives by the US FDA and by the World Health Organization/United Nations Food and Agriculture Organization Joint Expert Committee on Food Additives (JECFA), which acts as the risk assessment body for the Codex Alimentarius. As a result of the US FDA evaluations, 7 of these color additives and their aluminum lakes are allowed for use at levels consistent with Good Manufacturing Practices (GMP) within the United States. As a result of the JECFA evaluations, full specifications for each of the food colorants listed within the draft notifications referenced above have been established and, where appropriate, acceptable daily intake (ADI) levels have been established. The JECFA evaluations have also led to the development of food additive provisions within the Codex General Standard for Food Additives for many of the cited food colorants and in several different food categories. We have attached a table to this document that indicates the acceptable daily intake for synthetic colors that have been evaluated at JECFA.

As mentioned above, IACM is unaware at this time of any specific, new risk assessments that have been conducted that have formed the basis for the proposed use restrictions of the cited color additves. However, IACM would like to briefly comment on a matter of potential significance to the use of color additives: the publication of a study (McCann et al., 2007) that implies a link between the intake of mixtures of color additives and a small increase in hyperactive behavior in two groups of children.[2]

Regarding the McCann et al. study, two groups of young children were administered two different mixtures of artificial color additives and sodium benzoate (a commonly used food preservative) and their hyperactive behavior was evaluated using observational and testing methods. One of the mixtures contained the colorants Sunset Yellow FCF, Carmoisine, Tartrazine, Ponceau 4r, and the preservative sodium benzoate. The other mixture contained Sunset Yellow FCF, Carmoisine, Quinoline Yellow, Allura Red AC, and sodium benzoate. The authors reported that statistical analysis of the results indicated that one of the mixtures appeared to increase hyperactive behavior in a group of 3-year old children, but not in a group of 8-9-year old children. The other mixture was not reported to increase hyperactive behavior in the group of 3-year old children, but was reported to produce a small increase in hyperactive behavior in the group of 8-9-year old children. The statistical analysis suggested that, if taken collectively, hyperactive behavior in children taking the test mixture increased roughly 8% relative to children not administered the mixtures. Additionally, the authors noted that even within those groups of children that were administered the test mixtures of artificial color additives, there were “substantial individual differences in the response of the children to the additives.”

[2] McCann D, Barrett A, Cooper A et al. (2007) Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomized, double-blinded, placebo-controlled trial. Lancet, 370, 1560-1567.

The United Kingdom Food Safety Authority requested that the European Food Safety Authority (EFSA), the chief regulatory authority for food products in the EU, review the McCann et al., study. In their evaluation, they found that the study provides only limited evidence that the two different mixtures of artificial color additives and sodium benzoate tested in the study had a small and statistically significant effect on children selected from the general population. They further indicated that the effects were not statistically significant for the two mixtures in both age groups, and that since mixtures and not individual additives were tested, it was not possible to ascribe the observed effects to any individual compounds. Finally, they indicated that the clinical significance of any reported effects remains unclear. As a result, EFSA concluded that the study was not of sufficient significance to warrant a re-evaluation of the regulatory status of the colors tested.

More recently, in March 2011 the US Food and Drug Administration convened a two-day meeting of an independent Food Advisory Committee (FAC) to review not only the Southampton Study, but all earlier studies that asserted a link between consumption of artificial color additives and hyperactive behavior in children. After two days of scientific discussion, presentations by researchers, and public comment by parents and stakeholders, the FAC voted 11-3 that there was no causal relationship between the intake of artificial color additives and hyperactive behavior.[3]

IACM strongly asserts that the results of the McCann et al., study and previous studies do not provide support for restrictions on the use of artificial color additives within pharmaceutical and supplement products. As the authors of the Southampton study have already stated, much additional work remains to be done to establish whether the results can be reproduced and to understand the significance of any validated results. This important work must be carried out prior to any further consideration as to whether there are risk assessment or risk management implications.

We remain at your disposal to provide any additional information concerning the strong safety record of all of the artificial color additives that are produced or used by our member companies, including the scientific evidence that our colors are safe. In the interim, we strongly urge that the scientific evidence that colors are safe be considered in a manner consistent with harmonized international standards.

IACM thanks you for considering these comments.

Sincerely,

Sean Taylor
Scientific Director
International Association of Color Manufacturers

[3] The full FDA response and transcripts of this meeting are not yet available. In the interim, preliminary minutes are now available at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/ucm250901.htm

SYNTHETIC COLOR ADDITIVES

Name of Color Additive	JECFA Acceptable Daily Intake (mg/kg bw/d)
Brilliant Blue (FD&C Blue No. 1)	0-12.5
Indigo Carmine (FD&C Blue No. 2)	0-17
Fast Green FD&C Green No. 3	0-25
Erythrosine FD&C Red No. 3	0-25
Allura Red FD&C Red No. 40	0-7
Tartrazine FD&C Yellow No. 5	0-7.5
Sunset Yellow FD&C Yellow No. 6	0-2.5
Amaranth FD&C Red No. 2	0-0.5
Carmosine	0-4.
Brown HT	0-1.5
Green S	Temporary ADI withdrawn
Patent Blue V	ADI not allocated
Orange B	No information available
Black PN	0-1
Ponceau 4R	0-4
Rose Bengal	Not permitted