From: Joseph Cranston [Joseph_Cranston@ama-assn.org]
Sent: Monday, February 07, 2005 11:24 AM
To: FDADockets@oc.fda.gov
Cc: grossm@cder.fda.gov
Subject: "Use of Color on Drug Product Packaging Hearing"

The purpose of this email is to formally request the opportunity to participate and present at the FDA's Part 15 Hearing on the "Use of Color on Pharmaceutical Product Labels, Labeling, and Packaging," to be held on March 7, 2005 in Bethesda, MD.

Presenter will be Joseph Cranston, PhD, Director, Science, Research and Technology, American Medical Association (AMA), 515 North State Street, Chicago, IL, 60610 (312-464-4554). Dr. Cranston will be presenting on behalf of the American Medical Association (AMA) and the AMA will be paying all of his expenses to this meeting.

Dr. Cranston is on the staff of the AMA and, in that capacity, was the staff author of the AMA Council on Scientific Affairs' Report 5, "The Role of Color Coding in Medication Error Reduction" (A-04) [attached]. This report is cited by the FDA in its Federal Register Notice on February 3, 2005 as a resource for citations regarding the role of color coding and medication error reduction.

Dr. Cranston would like to briefly discuss: 1) why the Council report was written; 2) what were the report's major findings; and 3) what is the key recommendation of the report. The AMA would also like to publicly commend the FDA for focusing on this issue.

Dr. Cranston needs a maximum of 10 minutes to present the AMA's comments, but can do so in 5 minutes if the FDA desires to keep the presentations as brief as possible.

The FDA's consideration of this request is appreciated. We look forward to receiving the Agency's reply.

REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS

CSA Report 5-A-04

Subject: The Role of Color Coding in Medication Error Reduction

Presented by: J. Chris Hawk, III, MD, Chair

Referred to: Reference Committee E
(,MD, Chair)

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At the 2003 Annual Meeting of the American Medical Association's (AMA) House of Delegates, Report 8 of the Council on Scientific Affairs (CSA), "CSA's Sunset Review of 1992 and 1993 House Policies," recommended that AMA Policy H-115.976 (AMA Policy Database) be rescinded. Policy H-115.976 states:

> The AMA encourages the pharmaceutical industry to adopt standards developed by the American Society of Anesthesiology and endorsed by the American Society for Testing and Materials for the color coding of all vials and ampules in hospital operating suites.

The CSA recommended that this policy be rescinded because experts in the field of medication errors do not believe color coding – with a few exceptions – is the correct approach to reduce medication errors. Rather, bar coding will likely be the better approach. Furthermore, the CSA believed Policy H-115.976 was actually a "directive" that is now more than ten years old.

The House of Delegates referred this matter back to the CSA for an evaluation of the merits of color coding in reducing medication errors. The purpose of the current report is to determine the role of color coding in medication error reduction.

## Methods

Literature searches were conducted in the MEDLINE database for English-language articles published between 1966 and January 2004 using the search terms "color," "colour," or "color coding," in combination with "medication or medication errors," "drug [and injectable]," "anesthesia or anaesthesia," "ophthalmic or ophthalmology or eye," and "injectable or ampule." A total of 696 citations were identified; 530 of these were unrelated to the issue of color coding and medication errors, leaving 136 citations for further analysis.

Literature searches also were conducted in the International Pharmaceutical Abstracts database for English-language articles published between 1970 and January 2004 using the search terms "color or coding or code," in combination with "drug or medication or injectable." A total of 744 citations were identified; 721 of these were unrelated to the issue of color coding and medication errors, leaving 23 citations for further analysis.

Additional references were identified from the bibliographies of articles obtained via the above literature searches.

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Action of the AMA House of Delegates 2004 Annual Meeting: Council on Scientific Affairs Report 5 Recommendations Adopted, and Remainder of Report Filed.

In addition to literature searches, information on the role of color coding in medication error reduction was obtained by direct communication with experts in the field at the Institute for Safe Medication Practices (ISMP), the American Society of Health-System Pharmacists (ASHP), the United States Pharmacopeia (USP), and the Food and Drug Administration (FDA).

## Results

Terminology. Color has been used in three distinct ways to reduce errors in medicine. *Color matching* is used to match one item to another. For example, a medical device may have a blue plug that inserts into a blue receptacle, a yellow plug that inserts into a yellow receptacle, and so forth. Color matching is rarely used to match pharmaceutical products and there is no evidence to prove its value for this purpose.[1] Color matching will not be considered further in this report.

*Color differentiation* involves the use of color to distinguish one product from another. For example, color differentiation has been used on drug product labels to prevent confusion among products within a manufacturer's product line (e.g., so pharmacists can efficiently find and select medications from storage areas). Color differentiation also is used to draw attention to specific portions of a drug product label (e.g., to highlight a warning or the concentration of a drug). While color differentiation has not been scientifically proven to prevent medication errors, there are a number of anecdotal examples where this has been used successfully to reduce medication errors.[2] Color differentiation will not be considered further in this report.

*Color coding* is the systematic, standard application of a color system to aid in the classification and identification of drug products. A color coding system allows people to memorize a color and match it to its function.[1,2]

Color coding systems. Based on the CSA's review of the literature, there currently are three widely used color coding systems for pharmaceutical products that are intended to reduce medication errors. Perhaps the simplest and most widely known color coding system is the USP's black-cap packaging requirements for *Potassium Chloride for Injection Concentrate*. In response to reports of deaths due to accidental injection of concentrated potassium chloride injections, in 1993 the USP mandated that the cap of the container vial and the overseal be colored in black and bear the words, "Must be Diluted." Product containers also must carry the following boxed warning: CONCENTRATE MUST BE DILUTED BEFORE USE. The use of a black closure system on a vial is prohibited, except for *Potassium Chloride for Injection Concentrate*.[3]

In response to reports of serious adverse events resulting from patient difficulty in distinguishing between various ocular medications,[4,5] the American Academy of Ophthalmology (AAO) endorsed the uniform use of a color coding system for the caps and labels of topical ocular medications.[6] The AAO worked with the FDA and the pharmaceutical industry to establish a uniform color coding system for the caps and labels of all topical ocular medications. Specific Pantone colors were assigned to defined classes of ocular drugs according to the nature of the disease being treated, the product's side effect profile, and the risk of serious sequelae if a product is inadvertently switched with another. No other topical medications should carry the same color. The proper color codes are as follows:[6]

| Class | Color | Pantone Number |
|---|---|---|
| Anti-infectives | Tan | 467 |
| Anti-inflammatories/steroids | Pink | 197 |
| Mydriatics and cycloplegics | Red | 1797 |
| Nonsteroidal anti-inflammatories | Gray | 4 |
| Miotics | Dark Green | 348 |
| Beta-blockers | Yellow | Yellow C |
| Beta-blocker combinations | Dark Blue | 281 |
| Adrenergic agonists | Purple | 2583 |
| Carbonic anhydrase inhibitors | Orange | 1585 |
| Prostaglandin analogues | Turquoise | 326 |

The FDA supports the AAO-recommended uniform color coding system for the caps and labels of all topical ocular medications. In its Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics, the FDA states: "An applicant [manufacturer] should either follow this system or provide adequate justification for any deviations from the system."[7]

A third color coding system is designed to reduce medication errors in anesthesiology. The American Society for Testing and Materials (ASTM) has developed a standard (Standard D 4774-94) for "user applied" syringe drug labels in anesthesiology.[8] The ASTM standard assigns a specific color to each class of anesthetic drug (e.g., opioids). The standard background colors for user applied syringe drug labels are as follows:[8]

| Drug Class* | Examples | Pantone Color, All Uncoated |
|---|---|---|
| 1. Induction agents | thiopental, methohexital, thiamylal, etomidate, ketamine | yellow |
| 2. Tranquilizers | diazepam, midazolam | orange 151 |
| 3. Muscle relaxants | succinylcholine,** curare, mivacurium, vecuronium, pancuronium, atracurium | fluorescent red 805 |
| 3a.Relaxant antagonists | neostigmine, edrophonium, pyridostigmine | fluorescent red 805 or warm red*** and white diagonal stripes |
| 4. Narcotics | morphine, fentanyl, meperidine | blue 297 |
| 4a.Narcotic antagonists | levallorphan, naloxone | blue 297 and white diagonal stripes |
| 5. Major tranquilizers | droperidol, chlorpromazine | salmon 156 |
| 5b. Combinations of narcotics and major tranquilizers | Innovar®, fentanyl-droperidol combination | blue 297 and salmon 156 longitudinal stripes |
| 6. Vasopressors | epinephrine,** ephedrine, phenylephrine | violet 256 |
| 6a.Hyptotensive agents | trimethaphan, nitroprusside, nitroglycerin, phentolamine | violet 256 and white diagonal stripes |
| 7. Local anesthetics | bupivacaine, lidocaine | gray 401 |
| 8. Anticholinergic agents | atropine, glycopyrrolate | green 367 |

*Drugs that do not fit into the above classes should be labeled with black printing on a white background.
**All printing is to be in black boldtype, with the exception that "succinylcholine" and "epinephrine" shall be printed against the background color as reversed plate letters within a black bar running from edge to edge of the label.
***Warm red may be used if the printing of 805 fluorescent red stripes presents insurmountable difficulties.

Under this color coding system, anesthesiologists (or nurses) apply the appropriate colored labels to syringes containing the appropriate medication prior to surgery. The colored labels are intended to provide visual cues during surgery so there will be a reduced risk of interclass drug error; i.e., to reduce the problem of accidental syringe swapping. This standardized color coding system has been adopted by anesthesiologists in the United States, Australia, New Zealand, Canada,[9] and, most recently, Great Britain.[10]

Policy H-115.976 directed our AMA to seek support of the pharmaceutical industry and the FDA to adopt ASTM Standard D 4774-94 for commercially produced vials and ampules. For example, all manufacturers of vials and ampules containing induction agents would be required to use a yellow background on their labels. However, neither the pharmaceutical industry nor the FDA has adopted this color coding system for commercial products.[2]

Does color coding reduce medication errors? Evidence in the scientific literature that proves color coding reduces medication errors is extremely limited. Moreover, the use of color coding of pharmaceutical products for the purpose of reducing medication errors is controversial among experts.

Prior to requiring black caps on vials of potassium chloride for injection concentrate, a number of deaths were reported to the USP-ISMP Medication Errors Reporting Program due to mix-ups with sodium chloride 0.9% injection. These fatalities were eliminated, based on reports to this database, after the color coding and labeling changes went into effect. However, deaths due to accidental concentrated potassium chloride injection still occur. Restricting the availability of these products in clinical areas is proposed by experts as the best way to eliminate this problem.[2,11]

Published scientific evidence that evaluates whether the AAO's color coding system reduces medication errors is nonexistent. It is widely accepted that many ophthalmology patients have compromised vision. Also, prior to the implementation of the color coding system, there were documented cases of serious adverse events resulting from patient difficulty in distinguishing between various ocular medications.[4-6] Given that the AAO, the FDA, and the pharmaceutical industry continue to support the color coding system for topical ocular medications, it is assumed there is some anecdotal evidence that color coding has reduced the number of reports of adverse events due to failure to distinguish among ocular medications. Moreover, there now are a number of case reports in the literature that describe inadvertent instillation of nonophthalmic substances into the eye because of similarities in packaging and labeling with topical ocular medications.[12-15] This has led many ophthalmologists to call for manufacturers of nonophthalmic substances to better distinguish their packaging and labeling to prevent these errors.

On the other hand, the USP-ISMP Medication Errors Reporting Program has received reports of "intraclass" medication errors with topical ocular medications. For example, reports of mix-ups between cyclopentolate hydrochloride 1% and tropicamide 1% solutions have been received. Both products were from the same manufacturer and had the same colored labels.[1] The ISMP believes that, while the AAO's color coding system may work well in physician offices and in patients' homes, the potential for error could increase in pharmacies and on nursing units where product packages with similar colors, logos, fonts, and sizes are placed next to one another. The ISMP has recommended that pharmacies purchase topical ophthalmic products within the same class from different manufacturers in order to reduce similarities and prevent errors.[2]

One well-designed scientific study has been conducted in an attempt to determine whether the color coding system for user applied syringe drug labels in anesthesiology actually reduces

medication errors. Fasting and Gisvold analyzed intraoperative problems related to anesthesia, including medication errors, that were prospectively recorded for 55,426 procedures over a 36-month period in a 970-bed hospital in Norway. After the first 18 months, the anesthesiology department implemented color coded syringe labels, according to ASTM Standard D 4774-94, and also had educational meetings and audits focusing on medication errors. About 15% of cases experienced intraoperative problems with no difference between the first 18 months (Period 1) and the second 18 months (Period 2) of the study. However, only 63 total drug errors (0.11%) were recorded during the 36 months, 40 drug errors during Period 1 and 23 drug errors in Period 2, after color coding and education were implemented. While this represented a 37% decrease in drug errors after the intervention, it was not statistically significant ($P = 0.07$) due to a high beta error. Forty-five of the 63 drug errors were "wrong drug" errors and, of these, 12 patients were erroneously given a muscle relaxant while awake. In Period 1 there were 16 syringe swaps, and in Period 2 there were 12 syringe swaps; again, this difference was not statistically significant. None of the syringe swaps in Period 2 were between syringes with different colors, however. Also, no syringe swaps occurred between drugs in syringes of different sizes throughout the entire study. Interestingly, ampule swaps were decreased from eight in Period 1 to only one in Period 2, and this was statistically significant ($P = 0.04$). The authors concluded that syringe swaps were not eliminated by color coding and suggested color alone may not be sufficiently strong as a visual cue to eliminate errors. They also concluded that syringe swaps occur most often between syringes of the same size.[16] This latter finding was consistent with a 1993 Australian Incident Monitoring Study that also found syringe swap errors usually occurred between syringes of the same size.[17]

Disadvantages of color coding systems for pharmaceutical products. In addition to the lack of scientific evidence that proves color coding reduces medication errors, experts in the field of medication errors also cite other reasons why the widespread adoption of color coding systems for pharmaceutical products should be done with great caution. Potential problems include:

- There is a limit to the number of discernable colors available for commercial use.
- Subtle distinctions in color are poorly discernable unless products are adjacent to one another.
- Color coding of drug classes can increase the chance of "intraclass" medication errors (see above).
- Colors may fade when exposed to light.
- It is not always possible to exactly reproduce Pantone colors from batch to batch.
- Approximately 8% of men and less than 1% of women have some difficulty with color vision (colorblindness).
- Color coding can be error-prone if it is not applied consistently across the industry, or within a single manufacturer's product line.
- Physicians and other health professionals may be unable to remember large or multiple-color coding systems.
- Color coding may offer a false sense of security and, in some instances, result in failure of the physician or other health professional to "Read the label."[1,2,18,19]

The ASHP, a professional association of institutional pharmacists that focuses on medication error prevention, "opposes reliance on color by health professionals and others to identify drug products, and opposes actions by manufacturers of drug products to promulgate reliance on color to identify drug products." Rather, the ASHP supports the reading of drug product labels as the most important means of identifying drug products in order to prevent errors.[20] The ISMP also has concerns about widespread adoption of color coding and believes it should be used with

extreme caution.[1,2] Other than the AAO color coding system for topical ocular medications, neither the FDA nor the pharmaceutical industry has embraced color coding systems for pharmaceutical products.[18] In fact, the FDA is contemplating a guidance for industry that would generally oppose color coding for pharmaceutical products (Jerry Phillips, RPh, personal communication). Also, the USP has not supported widespread adoption of color coding (Diane Cousins, RPh, personal communication). Recently, in response to serious medication errors related to neuromuscular blocking agents, the USP is recommending that the ferrules and overseals of vials containing neuromuscular blocking agents contain the words, "Warning-Paralyzing Agent." However, based on the advice of the FDA and three USP Expert Committees, the USP rejected color coding the vials with Pantone Red.[21]

## Conclusion

Currently, there are three widely used color coding systems for pharmaceutical products that are intended to reduce medication errors:

- USP's black-cap packaging requirements for *Potassium Chloride for Injection Concentrate*;
- AAO's uniform color coding system for caps and labels of topical ocular medications; and
- ASTM's Standard D 4774-94 for color coding of user applied syringe labels in anesthesiology.

Each of these color coding systems enjoys strong support from health professionals (e.g., ophthalmologists, anesthesiologists) who use them.

However, evidence in the scientific literature that proves color coding reduces medication errors is extremely limited. Moreover, the use of color coding of pharmaceutical products for the purpose of reducing medication errors is controversial among experts. A variety of potential problems with color coding of pharmaceutical products argue against its widespread adoption. A number of organizations involved in medication error prevention, including the ASHP, ISMP, USP, FDA, and the pharmaceutical industry either oppose color coding or recommend caution in its application.

## RECOMMENDATIONS

The Council on Scientific Affairs recommends that the following recommendations be adopted and the remainder of this report be filed:

1. That our AMA recommends to the Food and Drug Administration, the United States Pharmacopeia, and the pharmaceutical industry that color coding of pharmaceutical products for the purpose of preventing medication errors be considered cautiously on a case-by-case basis. **(Directive to Take Action)**

2. That our AMA encourages further research on the effectiveness of color coding of pharmaceutical products in reducing medication errors. **(New HOD Policy)**

3. That current AMA Policy H-115.976 be rescinded. **(Rescind HOD Policy)**

No fiscal impact.

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