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ISMP
An ECRI Affiliate

Community/Ambulatory Care

ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

Identifying color additives in regulated drug products

PROBLEM: Some patients are sensitive to the color additives approved by the US Food and Drug Administration (FDA) for use in medications. Even though allergies or intolerances to these approved color additives are relatively infrequent, a subset of patients do experience reactions to:

- Red dyes, particularly FD&C red #4 (carmine, only approved for use in externally applied drugs) and FD&C red #40 (Allura Red)
- Yellow dyes, particularly FD&C yellow #5 (tartrazine) and FD&C yellow #6 (Sunset Yellow)
- Blue dyes, particularly FD&C blue #1 (Brilliant Blue)

FD&C (short for Federal Food, Drug, and Cosmetic Act) in front of the colorant name and number (e.g., FD&C yellow #6) indicates that it has been approved for use in food, drugs, and cosmetics, and D&C (e.g., D&C red #33) indicates it has been approved for use in drugs and cosmetics. These approved colorants can be found in many medications. Patients who are allergic to these approved color additives and unknowingly take or apply medications that contain them may experience hypersensitivity reactions that range from mild (e.g., stomach cramps, skin reactions, and rashes), to moderate (e.g., facial swelling, hives, skin lesions, wheezing), to severe (e.g., anaphylactic reactions).

ISMP recently received a report about a medication that contained D&C red #33 that, due to labeling confusion, was almost dispensed for a patient with a red dye allergy. While the product's principal display panel on the immediate container clearly listed FD&C yellow #6, the D&C red #33 color additive was only listed in the package insert.

The Event

Ibuprofen oral suspension was prescribed for a 7-year-old child with a known red dye allergy. Pharmacy staff discovered that the package insert for a prescription-

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ISMP names a new medical director, Kelley Shultz, MD

Kelley Shultz, MD, has been appointed as the Medical Director of ISMP. Kelley has considerable experience in many aspects of healthcare, including pediatric hospital medicine, and has served as a consultant for ISMP since 2012. She also has served as a patient safety officer for a large health system as well as the Director of Clinical Informatics, Director of Simulation and Teamwork Training, and Medical Director and founder of the Perinatal Outreach Simulation Program for Cincinnati Children's Hospital. In these roles, she has created many programs to improve the safety culture, standardize best practices, and help organizations move toward high reliability. She has extensive electronic health record experience and has helped with the implementation of different systems at nearly a dozen hospitals. She also currently serves on the General Pediatrics Exam Committee of the American Board of Pediatrics and is actively involved in the education of residents and fellow practitioners. We look forward to working with Kelley in the years ahead.

SAFETY briefs

Chlorhexidine product needs improved packaging. An oral surgeon prescribed chlorhexidine gluconate 0.12% oral rinse for post-surgical site care. The patient's directions said to swish 15 mL around in her mouth for 30 seconds, then to spit it out. An ambulatory care pharmacy dispensed a 473 mL bottle (Xttrium Laboratories). This product has a white-ridged opaque plastic, squeeze-off child safety cap that doubles as a dosing cup (**Figure 1**). However, the bottle may be difficult to open (cap must be squeezed) and the instructions for opening the bottle are hard to find on the label. After opening the bottle, the cap is intended to be used as the product's dosing device, measuring 15 mL doses. However, the tiny, raised letters/numbers and 15 mL fill line are difficult to visualize (**Figure 2**, page 2), even with the cap tilted and under direct light. Even more concerning is that some patients who do not see the markings on the cap might assume that the dose would be a capful (as it is for many over-the-counter mouthwashes and rinses).

Figure 1. Chlorhexidine gluconate 0.12% oral rinse (Xttrium Laboratories) is topped with a plastic safety cap that measures 15 mL doses.

We contacted the manufacturer about these issues and suggested improving the packaging and instructions. Meanwhile, you may want to consider stocking the product in a bottle with a regular child-

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only 473 mL bottle of ibuprofen oral suspension (100 mg/5 mL) from Perrigo specified that the product contained D&C red #33, but this inactive ingredient was not listed on the bottle's principal display panel. However, another color additive, FD&C yellow #6, was listed there (**Figure 1**), leading the pharmacy technician and pharmacist to initially and incorrectly assume that this was the only color additive in the product. Fortunately, a pharmacy staff member read the package insert and noticed that the product also contained D&C red #33 before the product was dispensed for the child.

It is easy to see how pharmacy staff and other clinicians might be misled and incorrectly assume that all color additives are listed on the principal display panel since the FD&C yellow #6 is listed there. The reason for the confusion is muddled in a myriad of labeling regulations for both prescription and over-the-counter (OTC) medications.

Figure 1. The principal display panel on a large bottle of ibuprofen oral suspension from Perrigo indicates that it "Contains FD&C yellow #6," but the product also contains D&C red #33, which is only listed in the package insert.

Labeling Regulations

Why was the inactive ingredient, D&C red #33, missing from the bottle label?

According to the Code of Federal Regulations Title 21–Food and Drugs (www.ismp.org/ext/716), prescription drugs for **other than oral use** are required to include the names of all inactive ingredients in the product labeling, with the exception that color additives may be designated as coloring without naming specific color components, unless required by other regulations [21 CFR 201.100(a)(5)]. Prescription medications **for oral use** are not required to list all of the inactive ingredients in the product labeling; not on the immediate container label, not on the outside wrapper (e.g., carton label, if present), nor in the package insert. Since the event described above involved a prescription-only bulk bottle of ibuprofen oral suspension, the inactive ingredient D&C red #33 was not required on the container label.

For over-the-counter medications, including varying strengths, concentrations, and volumes of ibuprofen, the regulations require the listing of each inactive ingredient in the *Drug Facts* section on the outside container or wrapper of the retail package, or on the immediate container label. Thus, OTC ibuprofen oral suspensions available to consumers include information about all the color additives in the product in the "Inactive Ingredients" section of the *Drug Facts* label.

Why did the inactive ingredient, D&C red #33, appear in the package insert?

Even though companies are not required to include all the inactive ingredients on oral prescription medication labeling, most companies voluntarily list these ingredients, including specific color additives, in the "Description" section of the package insert.

Why was the inactive ingredient, FD&C yellow #6, listed on the principal display panel on the ibuprofen bottle?

The Code of Federal Regulations Title 21–Food and Drugs also establishes specific labeling requirements for certain inactive ingredients, particularly those that are

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resistant cap (or the 15 mL unit dose containers). When dispensing the multi-dose bottle, provide patients with an easy-to-read and appropriately sized metric-only dosing cup or oral syringe for safe dose measurement and administration. Using the teach-back method, educate patients how to open the bottle and measure the appropriate dose.

Figure 2. The tiny, raised numbers/letters and 15 mL dose line are difficult to see on the inside of the safety cap.

Look-alike ophthalmic containers a long-standing problem. Ophthalmic ointment tubes of Bausch + Lomb neomycin and polymyxin B sulfates and bacitracin zinc are nearly indistinguishable from the company's erythromycin 0.5% ophthalmic ointment; even their outer cartons look similar (**Figure 1**, page 3). These products may be stored near one another in a pharmacy's segregated ophthalmic section. Both products are used to treat superficial ocular infections, but erythromycin 0.5% ointment is also the *only* available drug approved by the US Food and Drug Administration (FDA) for the prevention of gonococcal ophthalmia neonatorum. A dispensing error—for example, the triple antibiotic ointment dispensed instead of the erythromycin ointment—may not be easily recognized given the small container size along with tiny, hard-to-read print.

We have previously published our concern with the ophthalmic product color-coding system approved for manufacturer use by the American Academy of Ophthalmology (www.ismp.org/ext/674) and tacitly approved by the FDA (www.ismp.org/ext/673) because it contributes to similarities in packaging and labeling, and thus,

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likely to be allergens. According to Section 201.20, the label for OTC products administered orally, nasally, rectally, or vaginally that contain FD&C yellow #6 must declare its presence using the name "FD&C Yellow #6." Also, the labeling of both OTC and prescription drug products containing FD&C yellow #6 must declare its presence. Thus, the statement, "Contains FD&C yellow #6," appears on the label of the bulk bottle of ibuprofen oral suspension.

Interestingly, the regulation associated with declaring FD&C yellow #6 use on the label and/or labeling of both OTC and prescription products was suspended in 1988 pending further agency action (Department of Health and Human Services, Food and Drug Administration. 21 CFR Parts 74 and 201. FD&C Yellow No. 6 Label Declaration. *Federal Register*. December 6, 1988:49138, www.ismp.org/ext/720). At this time, it appears that companies would not be required to comply with declaring the use of the FD&C yellow #6 color additive. However, as required elsewhere in the regulations, OTC products should list all specific color additives as inactive ingredients on the *Drug Facts* label, and prescription products would be expected to continue the voluntary listing of inactive ingredients, including color additives, in the "Description" section of the package insert.

Are there regulations associated with FD&C yellow #5?

According to Section 201.20, the labeling for both OTC and prescription drug products administered orally, nasally, rectally, vaginally, or for use in the area of the eye that contain FD&C yellow #5 also must declare its presence using the names "FD&C Yellow No. 5 and tartrazine." Additionally, for prescription drugs administered orally, nasally, rectally, vaginally, or for use in the area of the eye that contain FD&C yellow #5, a warning statement in the "Precautions" section of the package insert is required: "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

Safe Practice Recommendations: Query patients upon admission or at each encounter about any food, medication, over-the-counter product, dietary supplement, and environmental intolerances or allergies they may have, asking a scripted question or using a prompt to help identify a color additive intolerance or allergy. If the patient has experienced an adverse reaction to a color additive or food dye, obtain and document information about the specific reaction so it can be distinguished as either an allergy or an intolerance. If a patient has a known color additive or food dye intolerance or allergy, be sure it is listed in a standardized, clearly visible location on all drug-related pages or screens of the electronic health record (EHR) and pharmacy computer system. All allergies to color additives or food dyes also should be properly coded to allow for clinical decision support, when possible, during allergy screening.

If a patient has a known allergy to a food dye or color additive, an allergen in a medication's inactive ingredients may not be readily apparent, as even the product's appearance might not serve as a clue regarding color additives. Practitioners will need to become label detectives, reading the "Description" and "Precautions" sections of the package insert as well as the *Drug Facts* label to determine all the inactive ingredients of a product, including color additives. After you have read the package insert or *Drug Facts* label, if you are not sure whether a certain medication contains the color additive, call the manufacturer for more drug information. If a patient cannot take a medication critical to their recovery or health due to the color additive in the medication, compounding pharmacies might be able to provide the medication without the allergen.

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results in mix-ups between ophthalmic products. The color blue is supposed to be reserved for use with beta blockers, while the color tan should be used for antibiotics. However, these Bausch + Lomb antibiotics prominently use the color blue in horizontal bands on both the tube and outer carton, but only display a narrow, tan vertical band on the cartons and tubes.

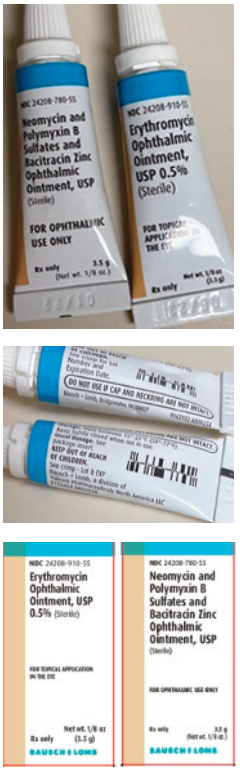

Figure 1. Bausch + Lomb ophthalmic ointment tubes of neomycin, polymyxin B, and bacitracin zinc and erythromycin (top: front of tubes; middle: back of tubes) look very similar, as do their outer cartons (bottom).

Look-alike ophthalmic products have been a long-standing problem, generating a steady stream of complaints sent to ISMP over the past 20 years. Just within the past few months, along with the above report, we also received reports of look-alike phenylephrine hydrochloride, atropine sulfate, and tropicamide ophthalmic solutions from Akorn Pharmaceuticals. All of these drugs fall into the red color-code category used to differentiate mydriatics and cycloplegics from other ophthalmic products. The red and white box, with a black band across the top, and the product concentration highlighted in red (**Figure 2**) contribute to the similar appearance of these containers.

Figure 2. Cartons of phenylephrine hydrochloride, atropine sulfate, and tropicamide ophthalmic solutions from Akorn Pharmaceuticals appear nearly identical.

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Confusion with InPen insulin pen systems

ISMP received a report from an outpatient pharmacy regarding a close call with a product called **INPEN** (**Figure 1**). This is a Bluetooth-connected "smart" insulin pen system for mealtime insulins that is prescribed with either insulin aspart (**NOVOLOG** or **FIASP**) or insulin lispro (**HUMALOG**) U-100 cartridges. Once the pen is loaded with the cartridge, InPen is used along with a smart phone app to interact with continuous glucose monitoring systems, remind patients to use their insulin, and log and track insulin doses. It can also administer half-unit doses.

The report sent to us mentioned that an electronic prescription was received for "InPen (for Novolog or Fiasp) subcutaneous." Shortly afterwards, a prescription for the same patient was received for three Novo**LOG** U-100 3 mL cartridges. When a pharmacy technician went to the pharmacy's wholesaler website, there were six different InPen devices listed, each with a description of their color (blue, gray, or pink). The technician incorrectly assumed that the pens differed by color. The pen labeled "InPen/blue/Lilly" was ordered, along with Novo**LOG** cartridges. However, when the InPen arrived, pharmacists noticed a label on the product that stated, "For use with Humalog 3 mL U-100 insulin cartridges."

Figure 1. InPen devices are insulin specific and connect with a smart phone app via Bluetooth to help manage diabetes.

Upon further investigation, it was found that of the six pens available, there are only two different models of the InPen, and each model is available in three colors. One model is used with Huma**LOG** while the other model is for Novo**LOG** or Fiasp. The models are not interchangeable due to the size differences between the respective insulin cartridges. The choice in colors appears to be for patient-preference and does not indicate which type of insulin is being used. Upon discovery of the error, the correct InPen device was ordered and replaced prior to dispensing the pen and insulin cartridges to the patient. It was noted by the reporter that the wholesaler's information online regarding the InPen device was confusing and contributed to the ordering error. It is not clear why three different color pens are needed. This type of error would be less likely to occur if each model was one unique color.

Mitigation strategies include educating pharmacy staff on the availability and details of these new products, the packaging differences between Novo**LOG** and Fiasp cartridges and Huma**LOG** cartridges; adding warnings in the computer system to alert pharmacy staff to verify that the InPen device selected is compatible with the patient's insulin cartridges; and clearly naming each InPen in the computer system with the name of the insulin with which it is compatible. At the pharmacy counter, show the InPen and insulin cartridges to the patient and have both the patient and pharmacy staff person independently verify that the device and cartridge are compatible. For more information on dispensing InPen devices and their specific national drug codes (NDCs) and compatibilities, visit: www.ismp.org/ext/724.

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One strategy to prevent mix-ups is to purchase products from different manufacturers to reduce the number of look-alike containers. Storing ophthalmic products intermingled with the rest of the pharmacy inventory, rather than segregating them in their own section, might be of benefit. When dispensing these products, careful visual product verification will be key in preventing mix-ups, and barcode scanning prior to dispensing is a must. FDA should work with manufacturers to focus more on reducing similarity among look-alike containers.

Special Announcements

Nominations for Cheers Awards

Each year, ISMP honors individuals, organizations, and groups from various healthcare disciplines that have demonstrated an exemplary commitment to medication safety through innovative projects with an **ISMP Cheers Award**. Nominations for this year's **Cheers Awards** will be accepted through **September 10, 2021**. Please refer to page 5 for a checklist of DOs and DON'Ts when submitting a nomination for a **Cheers Award**. To submit a nomination, visit: www.ismp.org/node/1036.

FREE ISMP webinar

Join us on **July 20, 2021**, from **8:00-9:15 a.m. ET** for a **FREE** webinar on ***The Inside Track on Drug Naming Safety Standards***. Hear first-hand from our panel of experts about the problems that created a need to improve drug naming safety, the steps in the development of a drug name, and the benefits of drug name testing. For more information and to register, visit: www.ismp.org/node/25216.

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DOs and DON'Ts for submitting an ISMP CHEERS AWARD Nomination

Do you know an Individual or an Organization/Group Collaborative that you want to nominate for an **ISMP CHEERS AWARD**? Here are some helpful tips to make sure your nomination meets the criteria. Nominations that are incomplete or do not meet the criteria outlined below will not be considered.

DO

Nominate an Individual or Organization/Group Collaborative that:

- ✓ Clearly identifies a high-risk, error-prone medication safety initiative
- ✓ Demonstrates successful implementation of the initiative
- ✓ Provides measurable outcomes
- ✓ Utilizes innovative, proactive medication error-reduction strategies based on ISMP's philosophy and/or recommendations in ISMP newsletters, ISMP Action Agendas, ISMP guidelines, or other ISMP resources
- ✓ Participates in medication safety committees, teams, and/or does advocacy work
- ✓ Will share the initiative with others (at no cost)

Complete the nomination form:

- ✓ Ensure all fields are filled in accurately and completely
- ✓ Provide your information as the submitter
- ✓ Provide information about the nominee
- ✓ Provide a short paragraph describing why you believe this nominee should receive an award
- ✓ If nominating an **Organization/Group Collaborative**, also provide a paragraph describing the initiative and the impact it made, state whether the initiative has been shared outside the organization, and if the nominee is willing to share the initiative results with a broader audience
- ✓ After clicking NEXT, upload documentation to support the nomination (e.g., a full description of the nomination, slides, data tables, diagrams, figures, meeting minutes, pamphlets)
- ✓ If nominating an **Organization**, submit the additional required forms (Interdisciplinary Commitment Declaration, Leadership Declaration) and information (proof of accreditation by a professional body)

Submit your nomination, along with all supporting documents and forms, by September 10, 2021

DON'T

- Submit a nomination that does not clearly identify a high-risk, error-prone medication safety initiative
- Submit only a few sentences about the nominee with no supporting documentation
- Forget to complete all the information on the nomination form before clicking NEXT
- Copy and paste pages of information into the text boxes on the nomination form
- Forget to upload a full description of the nomination and additional documentation to support your nomination after completing the initial form (after you click NEXT)
- Forget to submit all your information by **September 10, 2021**

For a list of past **ISMP CHEERS AWARD** winners, visit: www.ismp.org/node/124