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ISMP An ECRI Affiliate

Acute 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 to these approved color additives are relatively infrequent, a few in particular have been linked to intolerances and allergic reactions:

- 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-only 473 mL bottle of ibuprofen oral suspension (100 mg/5 mL) from Perrigo specified that the product

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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

HIGH-ALERT

Unreadable expiration dates and barcodes. A pharmacy technician was checking an automated dispensing cabinet (ADC) for medications that were about to expire. One product checked was testosterone gel, 50 mg per packet, from Upsher-Smith Laboratories. The technician was unable to read the expiration date embossed along the side of the packet (**Figure 1**) and could not confirm whether the product was expired. The technician removed the medication from the ADC and returned it to the pharmacy, where others also were unable to read the expiration date. Thus, pharmacy staff could not determine whether any patients had received a medication that had potentially expired.

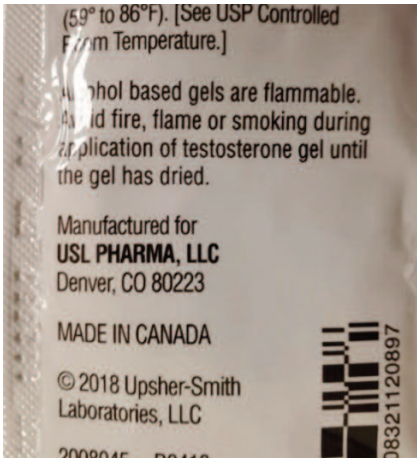

Figure 1. Expiration date (and lot number) embossed along the left edge of the testosterone gel packet (50 mg) from Upsher-Smith Laboratories is not readable.

Manufacturers should utilize robust quality checks in their manufacturing, packaging, and labeling operations to ensure their products are safe and that all necessary information is legible. USP (General Chapter <7> *Labeling*) requires that "all products display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background, or it shall be

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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 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.

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sharply embossed, and easily understood." For this product, that requirement is not met.

In addition to not being fully readable, the expiration date on the packet appears to display a 2-digit year and a 2-digit month, each separated by a slash mark. A new USP requirement that will become official in 2023 will require a 4-digit year. Also, although we cannot tell if the 2-digit month is numeric or alpha characters, the 2023 requirement also calls for a 3-digit alpha character display (or a 2-digit numeric display) for the month to avoid the need to guess if JN is January or June, JU is June or July, and MA is March or May. ISMP has spoken to Upsher-Smith about the unreadable expiration date.

Additionally, we have received several reports in the past 2 weeks about unreadable barcodes—this time unreadable by a scanner, not by the human eye. First, the light blue barcode, shiny reflective label paper, and the placement of the barcode horizontally along the bottle curvature of SPS (sodium polystyrene sulfonate) Suspension from CMP Pharma can lead to scanning complications at the bedside (**Figure 2**). As a result, some nurses have bypassed the barcode scanning process during medication administration, thus limiting their chances of catching an error.

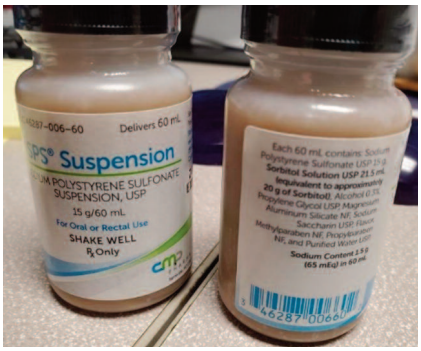

Figure 2. Scanning difficulties caused by the light blue barcode, shiny reflective label paper, and horizontal placement of the barcode along the bottle curvature of SPS (sodium polystyrene sulfonate) Suspension from CMP Pharma.

ISMP has also received a different type of complaint about the barcode on Mallinckrodt Pharmaceuticals transdermal fenta**NYL** 12 mcg/hour patches. When individual patch pouches are scanned, the electronic system indicates that the pouch contains 5 patches (the total number of patches in the carton) instead of just one patch. It appears that the

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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, drug, 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) or medical record. 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.

How will PCA be administered to patients during an MRI?

Problem: A hospital reported two events involving patients receiving patient-controlled analgesia (PCA) who were in radiology for magnetic resonance imaging (MRI). Because the PCA pumps used in the hospital were not compatible with an MRI (would be attracted to the MRI magnet), a procedure was in place for the MRI professional staff to add several feet of extension sets to the PCA tubing so the pump could be left outside of the room.

For one patient, morphine in the PCA pump drug reservoir was used to prime the PCA extension tubing. After the PCA setup was verified by a nurse and another practitioner,

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barcode is missing part of the national drug code (NDC). Mallinckrodt Pharmaceuticals has been alerted to the problematic barcode. Other dosage strengths of fenta**NYL** patches from this manufacturer do not share this problem.

For expiration date readability and barcode scanning problems, ISMP interacts regularly with the US Food and Drug Administration (FDA), which provides follow up with manufacturers as necessary to assure compliance with standards and regulatory requirements. We encourage readers to submit reports of unreadable expiration dates or barcodes to ISMP so we can continue to advocate for product improvements.

HIGH-ALERT **"What happens if you give potassium chloride IV push?"** ISMP recently asked a senior pharmacy student, "What happens if you give undiluted potassium chloride by intravenous (IV) push?" The question was posed during a review of our June 3, 2021, newsletter article about a death that occurred when a vial of potassium chloride concentrate injection was dispensed by the pharmacy and administered undiluted to a patient during a code (Administration of concentrated potassium chloride for injection during a code: still deadly! *ISMP Medication Safety Alert! Acute Care.* 2021;26[11]:1-5, www.ismp.org/node/25027). The student's answer: "Vein sclerosis." That surprised us and gave us pause. What do you think? Practitioners must understand that undiluted potassium chloride given IV push will stop the heart, causing death.

In the event mentioned above and examined in our recent newsletter article, the potassium chloride concentrate was administered IV push rather than diluted and infused due to a misunderstanding of the prescriber's intent. In the process of ordering, dispensing, and administering the drug, checks by pharmacy technicians, pharmacists, and nurses did not stop the error from occurring, which resulted in the patient's death. Sadly, healthcare students may not be learning about these issues in the classroom. Hopefully, those who precept students and residents take the time to address safety issues like those with potassium chloride concentrate injection. Consider saving and sharing applicable lessons learned from the June 3, 2021, newsletter article.

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the intravenous (IV) tubing (with the extension tubing) was connected to the patient's IV site and the patient's maintenance IV infusion was initiated at an undisclosed rate. While a nurse was still in the MRI room, and before any PCA doses had been initiated, the patient's oxygen saturation dropped below 90 percent and the patient became somnolent. The nurse suspected that the patient had just received a bolus of morphine that was in the extension sets. The patient was given supplemental oxygen, attempts were made to arouse the patient, and the charge nurse and anesthesia resident were immediately notified. One dose of IV naloxone was administered to the patient. The patient's mentation remained labile, and his respiratory rate varied from 4 to 8 breaths per minute; he eventually required additional doses of naloxone and became more responsive but still sleepy after each dose. Based on the morphine concentration and the volume of drug-containing fluid used to prime the tubing, it was discovered that the patient had received a bolus of approximately 56 mg of morphine.

A second hospitalized patient who had been receiving **HYDRO**morphone PCA experienced a similar event. The patient had been awake, alert, and oriented when assessed on the nursing unit prior to transfer to the MRI suite. Once in radiology, extension tubing was attached to the patient's PCA and primed with **HYDRO**morphone. During the MRI, the patient was placed on 3 liters of oxygen and was reported to be sleeping throughout the scan. When the patient was brought back to the nursing unit, his respirations were minimal and shallow, and the patient was barely conscious. The patient required multiple doses of IV naloxone before returning to his baseline status. Upon investigation, it was determined that the patient, as with the first patient, had received an inadvertent bolus of the opioid related to how the PCA and extension tubing had been set up.

Safe Practice Recommendations: Both patients received a large, unintended bolus of an opioid, resulting in respiratory depression that required use of a reversal agent. As a result, the hospital reported they are now removing PCA pumps from patients before going to radiology for an MRI. However, this requires coordination with providers to ensure adequate pain management while the PCA is disconnected. In addition to the time required to transport the patient to radiology, an MRI might take anywhere from 15 to 90 minutes to complete, depending on the area of the body examined. So, if the PCA pump is disconnected, a process is needed to ensure that patients with pain are adequately treated and monitored during the procedure and until they return to their room.

In some cases, this may mean that it will be necessary to infuse an opioid at a basal rate during an MRI. There are MRI-compatible infusion pumps, such as the IRadimed MRidium pump (www.ismp.org/ext/717), as well as a shielded PCA pump system from B. Braun, the SpaceStation MRI Perfusor PCA syringe pump (www.ismp.org/ext/718), which is compatible with their infusion pumps. Or the hospital may elect to send the PCA pump with the patient and utilize extension sets for a basal rate, supplemented by a nurse injecting the patient with a prescribed bolus dose of pain medication, as necessary.

In any event, ensure that a process exists to address the pain control needs of patients receiving PCA when they undergo an MRI. This entails managing ongoing medication therapy during an MRI, training staff, providing alternative pain management therapy, using MRI-compatible equipment, and determining where to connect the PCA line if the patient has a primary line for infusions, and/or if bolus doses of contrast media during the MRI are needed. Also, develop guidelines for monitoring MRI patients who are receiving an IV opioid. The challenges and potential risks involved with the use of extension tubing, priming, and line tracing in the MRI setting are not unique to PCA therapy. These risks pose a safety concern for all IV drug therapy, such as an anticoagulant, insulin, or a vasopressor, during an MRI.

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. The Awards will be presented in December—more to follow on the celebration! Nominations for this year's Cheers Awards will be accepted through **September 10, 2021**. ISMP accepts external nominations, including self-nominations. Please refer to **page 5** for a checklist of **DOs and DON'Ts** when submitting a nomination for a Cheers Award. For more information and to submit a nomination, visit: www.ismp.org/node/1036.

Free FDA webinar series

The US Food and Drug Administration's (FDA) Division of Drug Information is presenting a FREE webinar, ***FDA Drug Topics: Overview of Risk Evaluation and Mitigation Strategies (REMS) for Health Care Providers***, on **June 22**, 2021. For details, visit: www.ismp.org/ext/30, and to register for the program, visit: www.ismp.org/ext/31.

Please take our survey!

We have extended the deadline to **July 30, 2021**, for responding to the ***ISMP Survey on the 2020-2021 Targeted Medication Safety Best Practices for Hospitals.*** Please take a few minutes to respond to this important survey by visiting: www.ismp.org/ext/702.

To subscribe: www.ismp.org/node/10

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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