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ISMP

Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

FDA guidance needed to assure safe labeling practices by 503A and 503B compounders

Problem: Increasingly, ISMP has been receiving complaints and reports of errors, some serious, about prefilled compounded syringes that look alike. Drug shortages may be worsening the situation, as hospitals may be relying more on compounders they have not previously used to fulfill their needs. The US Food and Drug Administration (FDA) does not hold the labeling of drugs compounded or repackaged by pharmacies or outsourcing facilities to all of the same standards as FDA-approved products. For example, if certain conditions are met, federal law exempts compounded drugs from the requirement for labeling with adequate directions for use. Further, ISMP has become aware that some compounders deviate from USP <7> labeling standards. Specifically, under USP <7>, the *strength per total volume* should be the primary and prominent expression on the principal display panel of the label, followed by the amount per mL enclosed by parentheses (a USP requirement since 2009). However, ISMP has observed that the *strength per mL* has often been used as the primary expression on compounders' labels, leading to inconsistencies between products in the hospital, thus creating unsafe conditions. Errors have occurred when the more prominent per mL strength is mistaken as the total amount of drug in the syringe. Such errors were the impetus for the USP <7> requirement for prominence of the strength per total volume on labels.

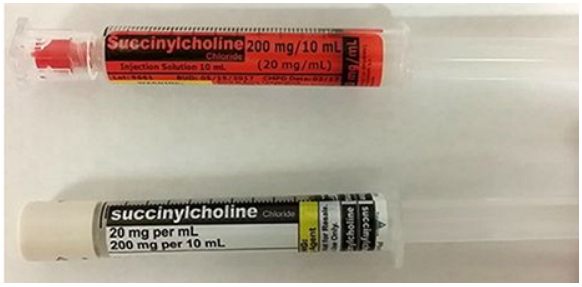

Figure 1. Both syringes contain the same drug, strength, and volume, but the primary display of strength is expressed per total volume (top) on the syringe from Cantrell Drug Company and per mL on the PharMEDium syringe label (bottom).

Our March 23, 2017, newsletter described a case in which a pharmacist and an anesthesiologist reported finding two syringes of succinylcholine with the strength displayed differently, both in the same pocket of the anesthesia cart in the operating room (OR) suite. Each syringe contained the same amount of drug, but one, from Cantrell Drug Company, was labeled using the USP <7> standard of strength per total volume, while the other one, from PharMEDium, listed the amount per mL as the primary display of concentration (**Figure 1**). Both practitioners thought a significant medication error could occur if the succinylcholine strength was misidentified. Apparently, syringes from the two compounders had been purchased and stocked without noticing and addressing the labeling inconsistency.

Figure 2. Look-alike outsourced **EPINEPH**rine syringes from PharMEDium.

ISMP has also received reports of high-dose, 1 mg per 10 mL (100 mcg/mL) **EPINEPH**rine syringes that were placed in OR syringe bundles that normally contained 100 mcg per

continued on page 2—Compounders >

SAFETY briefs

HIGH-ALERT **FentaNYL-SUFentanil mix-ups during shortages.** Once again, a fenta**NYL** shortage is creating unsafe conditions for patients who may require analgesia and sedation. As happened during fenta**NYL** shortages in 2001 and 2011, some hospitals have temporarily switched to **SUF**entanil. In our February 7, 2001, and November 17, 2011 newsletters, we mentioned several dosing errors that occurred with **SUF**entanil during a fenta**NYL** shortage. In one case, an anesthesiologist administered 50 mcg of **SUF**entanil intravenously (IV) instead of fenta**NYL**. The patient developed respiratory arrest and required intubation. In another event, a pharmacist made a patient-controlled analgesia (PCA) solution with **SUF**entanil instead of fenta**NYL**, using the same concentration. In a case related to the way mnemonics were assigned to these drugs, a nurse selected **SUFENTA** (**SUF**entanil) 50 mcg per mL instead of **SUBLIMAZE** (fenta**NYL**) 50 mcg per mL after typing "su" and choosing the wrong drug. All of the involved patients became unresponsive and required supportive care but recovered.

Hospitals may now be susceptible to similar errors because of the current fenta**NYL** shortage. Since **SUF**entanil is approximately 5 to 10 times more potent than fenta**NYL**, educate staff about the potency differences and include visual reminders wherever the drugs are stored. Design mnemonics for these products carefully, and avoid the use of "su" alone to select either medication. Where possible, eliminate the brand name Sublimaze. Hospitals may also want to develop guidelines for converting between fenta**NYL** and **SUF**entanil (e.g., fenta**NYL** 50 mcg IV equals **SUF**entanil 10 mcg IV) that are readily available to prescribers, pharmacists, and nurses. An independent double check should be required prior to administering such potent IV narcotics on nursing units. Also, have pharmacy prepare doses of **SUF**entanil whenever possible.

continued on page 2—SAFETY briefs >

> Compounders—continued from page 1

10 mL (10 mcg/mL) **EPINEPH**rine syringes (**Figure 2**, page 1). To prevent look-alike product mix-ups, pharmacy staff had affixed auxiliary labels to the syringes to differentiate between the high- and low-dose **EPINEPH**rine. However, a technician misapplied a 10 mcg per mL auxiliary label to a high-dose syringe.

There has also been confusion reported between **HYDRO**morphone and fenta**NYL** syringes from QuVa Pharma, a 503B compounder. While the two syringes clearly communicate their respective drug names, there are other similarities that may draw attention away from reading and discerning the drug name. These similarities include using the same ASTM International standard blue color code for opioid analgesics on the label, a flagged white section of the label common to both syringes, the same syringe sizes, and the same red color for the tamper-evident caps (**Figure 3**).

Another look-alike compounded syringe error reported recently involved a patient in a hypotensive state during surgery. FDA received an expedited manufacturer report from Nephron Pharmaceuticals about a patient given the neuromuscular blocking agent succinylcholine instead of the intended vasoconstrictor medication, phenylephrine. The patient's hypotensive state was prolonged due to the medication error. Fortunately, the event resolved without further medical intervention as the patient was already intubated and under anesthesia at the time of the inadvertent administration of succinylcholine. The person reporting the incident mentioned that both syringes were "placed backwards" (drug name down) in the tray, with the Nephron logo facing up, making the syringes look similar. **Figures 4a** and **4b** show the Nephron succinylcholine and phenylephrine syringes, with labels showing the drug names in one orientation (**Figure 4a**) but looking identical when placed drug name down in the tray (**Figure 4b**). The company recently revised these labels (**Figure 4c**, page 3).

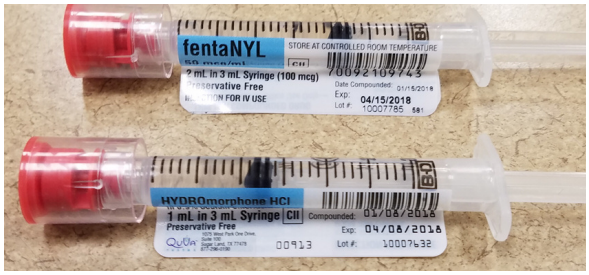

Figure 3. Look-alike fenta**NYL** and **HYDRO**morphone syringes from QuVa Pharma with the same ASTM International blue color on the label, a flagged white section of the label common to both syringes, and the same color tamper-evident caps.

Figure 4a. Nephron phenylephrine and succinylcholine syringes differentiated by ASTM International standard color coding.

Figure 4b. Same two syringes shown in Figure 4a look identical when placed drug name down in the tray.

Based on reports sent to ISMP and FDA, 503A pharmacies and 503B outsourcing facilities inconsistently follow label guidelines required of manufacturers under FDA and USP standards. Look-alike labeling is also a problem, and there are other serious issues that have contributed to errors. For example, some compounders package highly concentrated, high-alert medications in a single syringe, with the expectation that the entire contents or aliquots will be used to make diluted drug

continued on page 3—Compounders >

> SAFETY briefs cont'd from page 1

HIGH-ALERT

StabilOx canister removed from Simplist opioid packages. Fresenius Kabi recently informed customers that it is removing the StabilOx canister from its **DILAUDID** (**HYDRO**morphone) and morphine prefilled syringe blister packs (**SIMPLIST**) to help increase production of these products. The removal of the canister, which contains iron oxide and is ferromagnetic, is unrelated to our February 22, 2018, article about the canister's attraction to a magnetic resonance imaging scanner (MRI). Product NDC numbers, package dimensions, carton configuration, and shelf life will remain the same. The new packaging is expected next month.

CycloSPORINE dispensing errors. Almost 20 years ago, we published an article about **SANDIMMUNE** (cyclo**SPORINE** capsules and oral solution) and how this non-modified form of the drug has decreased bioavailability compared to **NEORAL** or **GENGRAF** (cyclo**SPORINE** [MODIFIED] capsules and oral solution). At the time, a survey by Novartis identified that 24% of prescriptions failed to specify which form of the drug should be dispensed, and only 22% of these prescriptions were clarified. We mention this because, 20 years later, we are still receiving reports of patients receiving Sand**IMMUNE** when the prescriber's preference was for a cyclo**SPORINE** modified oral formulation. Three patients recently received Sand**IMMUNE** instead of the more appropriate form of the drug, Neoral or Gengraf. In another case, during medication reconciliation, a nurse documented that a hospitalized patient was taking cyclo**SPORINE** but did not verify the brand name to determine if it was the modified or regular form of the drug. The patient's physician prescribed Sand**IMMUNE**, and the patient received a dose before a pharmacy technician discovered that the patient had recently filled a prescription for Gengraf.

Because of the difference in formulation, these products are not interchangeable. Blood levels must be monitored to prevent serious consequences if a transplant patient receives the wrong formulation. Prescribers should indicate the brand name, and pharmacists should clarify prescriptions for cyclo**SPORINE**. Order entry systems should clearly display these different forms of the drug, and a hard stop should force verification of the correct drug form during prescribing.

> Compounders—continued from page 2

infusions. However, mishaps may occur that result in the administration of the entire syringe contents, undiluted.

Safe Practice Recommendations: FDA should not allow products from compounders to follow different container labeling standards than commercial manufacturers, thus creating unsafe conditions. Unfortunately, sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act exempt compounded drugs from some of the labeling required of commercial drug manufacturers. FDA should convene a Pharmacy Compounding Advisory Committee meeting to review relevant error reports received since implementation of the Compounding Quality Act and sections 503A and 503B. The goal should be to publish a guidance that calls upon compounders to follow the same safety standards required of commercial manufacturers, including a requirement for 503B compounders, which are regulated by FDA under the Act, to submit their labels to FDA for review. While regulatory changes are considered, compounders should voluntarily comply with the same labeling standards currently required for commercial manufacturers.

When syringes prefilled by compounders are needed in healthcare organizations, we strongly advise using only compounders that follow USP <7> labeling practices, which requires the total amount of drug per total volume in the syringe to be the primary display of strength, followed by the per mL amount in parentheses. Syringes with color-coded labels based on the ASTM International standard also should not be accepted from compounders for use outside the OR. Color-coded syringe labels used outside the OR could lead to mix-ups in differentiating individual drugs within a class. Organizations should also employ barcode scanning technology when possible to verify that the correct medication has been selected prior to dispensing and/or administration, although a number of the medications provided by compounders are used in the OR or during resuscitation–settings in which barcode scanning technology is not common.

Figure 4c. Nephron succinylcholine and phenylephrine labels have recently been revised and improved.

National Poison Prevention Week: March 18-24

Unintentional poisoning is the leading cause of accidental injury deaths for people ages 25-64, even more than motor vehicle accidents. The third week in March each year is designated as **National Poison Prevention Week**, a week dedicated to raising awareness about the burden of poisoning and highlighting specific ways to prevent it. Join ISMP in celebrating this week by visiting www.ismp.org/sc?id=3114 and planning activities to support poison prevention, such as posting and distributing general facts about poisonings and how to prevent them.

If you would like to subscribe to this newsletter, visit: www.ismp.org/sc?id=382

ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES

Report medication and vaccine errors to ISMP: Please call 1-800-FAIL-SAF(E), or visit our website at: www.ismp.org/MERP or www.ismp.org/VERP. ISMP guarantees the confidentiality of information received and respects the reporters' wishes regarding the level of detail included in publications.

Special Announcements

New free ISMP CE opportunities

ISMP has two new on-demand programs that address **subcutaneous insulin use** in adults and **sterile compounding safety**. These programs offer a convenient way for nurses, pharmacists, and pharmacy technicians to earn medication safety continuing education (CE) credit at no cost. For details, visit: www.ismp.org/sc?id=3111 and www.ismp.org/sc?id=3112.

"Intensive" training in medication safety

Don't miss our next **Medication Safety Intensive (MSI) Workshop** on **April 5-6** in **Philadelphia**. The workshop will arm you with the knowledge and tools needed to establish a focused medication safety program and infrastructure for continued safety improvements. For details, visit: www.ismp.org/sc?id=637.

Apply for a Fellowship

You have until **March 31** to submit an application to become an **ISMP Safe Medication Management Fellow** or an **FDA/ISMP Safe Medication Management Fellow**. Fellows will spend a year working with the nation's top leaders in error prevention and safe medication use. All candidates must have at least 1 year of postgraduate clinical experience and relocate to the area. For details, visit: www.ismp.org/sc?id=3064.

Free FDA webinar series

The US Food and Drug Administration's (FDA) Division of Drug Information is presenting a series of free educational webinars for healthcare professionals to learn more about the FDA and drug regulation. The next webinar, **FDA Drug Topics: An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System**, is scheduled for **April 10**. This webinar will introduce the many phases of drug safety surveillance, from drug development through post approval, and will focus on how FDA's Division of Pharmacovigilance (DPV) conducts pharmacovigilance, develops safety signals, and communicates its findings. Continuing education (CE) credit is available. For details, visit: www.ismp.org/sc?id=3113, and to register for the program, visit: www.ismp.org/sc?id=3110.