February 26, 2026 | Volume 31 ■ Issue 4

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

Warning: For IM use only! Penicillin G benzathine administered via potentially fatal IV route

Problem: Penicillin G (parenteral/aqueous) solution is highly water-soluble and, when administered intravenously (IV), leads to high but short-lived serum levels. It is approved for IV or intramuscular (IM) use. On the other hand, penicillin G benzathine is insoluble, so practitioners can only give it IM, which provides a longer duration of action by slowly releasing penicillin over several days or weeks. Penicillin G benzathine has a *Boxed Warning* stating that it is not for IV use because this route has been associated with cardiorespiratory arrest and death. Errors related to confusion between the penicillin formulations have been reported to ISMP over the years, including the following:

Recent Event Reported

*A prescriber ordered **BICILLIN L-A** (penicillin G benzathine) 2.4 million units/4 mL suspension IM for a patient with syphilis. This medication was not frequently prescribed in this patient care unit (and not stocked in the automated dispensing cabinet [ADC]), so a pharmacy technician delivered it to the medication room. The nurse obtained the syringe, scanned the barcode, and administered the medication IV to the patient. After administration, the nurse went to document on the medication administration record (MAR), which prompted her to select the site of IM administration, and she identified that she had administered the drug via the wrong route.*

The nurse contacted a pharmacist to learn about the potential adverse effects of IV administration. The pharmacist communicated that there was a Boxed Warning for this risk, notified the prescriber, and recommended monitoring the patient for potential lethal arrhythmias, respiratory arrest, and worsening renal function. The patient was transferred to a higher acuity unit for close monitoring and placed on telemetry.

The patient experienced one critical diastolic blood pressure (36 mm Hg) approximately 2 hours after administration of penicillin G benzathine, which quickly normalized. Two days prior to the administration of penicillin G benzathine, the patient had received doses of meloxicam 15 mg and ketorolac 10 mg IV, nonsteroidal anti-inflammatory drugs (NSAIDs) that are also associated with a risk of renal side effects. The patient's serum creatinine nearly doubled during the next 2 days. The prescriber documented "likely crystalline nephropathy from IV administration of penicillin G benzathine in the setting of NSAID administration" in the electronic health record (EHR) and ordered Lactated Ringer's to infuse at 150 mL/hr. The patient's serum creatinine returned to baseline, and no further adverse changes in urine output were identified. The patient did not experience any chest pain, electrocardiogram changes, shortness of breath, oxygen desaturation, or other significant alterations in vital signs.

Penicillin G benzathine was not often used in this organization. The nurse was unaware that it must be given IM and that it could be fatal if given IV. During the investigation, the nurse stated that she felt rushed because the patient was preparing for a bath, and there were multiple visitors in the patient's room, interrupting her workflow. The patient had a saline lock in place, and most parenteral medications were administered IV rather than IM. There was a product note on the order in the MAR that stated, "For IM use ONLY," but this could be easily overlooked. The organization plans to build an alert upon scanning of penicillin G benzathine that indicates, **WARNING: For IM use only!**

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SAFETY briefs

Calcium chloride or calcium gluconate? A nurse's good catch prevented harm. A prescriber ordered 1 g/10 mL of calcium chloride (undiluted 100 mg/mL) intravenously (IV) every 8 hours for a patient with hypocalcemia. A pharmacist verified the order and dispensed the first dose. When the nurse scanned the barcode to administer the dose, she received an alert: "Administration via a CENTRAL line ONLY; Severe necrosis and sloughing may occur when administered peripherally; contact pharmacy when central line unavailable." Since the patient did not have a central line, the nurse called the pharmacy and spoke to a different pharmacist who advised them not to administer this peripherally. The pharmacist contacted the prescriber and recommended changing the order to calcium gluconate. The prescriber told the pharmacist that they had thought they had ordered calcium gluconate, not calcium chloride, from their preference list in the electronic health record (EHR). The prescriber changed the order to calcium gluconate, and the nurse administered this to the patient via a peripheral IV line.

When discussing the good catch during a team meeting, the pharmacist who verified the order said they were not aware of the danger of dispensing or administering undiluted calcium chloride in a care setting that does not have continuous cardiac monitoring/telemetry. Through safety huddles, the entire pharmacy staff was educated about the risks of administering calcium chloride IV push peripherally, including severe skin necrosis/sloughing and cardiac arrhythmia. In this hospital, undiluted calcium chloride is reserved for patients in cardiac arrest and administered as a rapid bolus via a central line or intraosseous route.

Organizations should develop a standard IV calcium administration protocol,

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Denver Case: Infant Death

This recent incident is similar to a case we wrote about in our February 11, 1998 article, A Case Riddled with Latent and Active Failures. This case, which was widely covered in the news media at the time, involved three Denver, Colorado, area nurses who were indicted for criminally negligent homicide and faced a possible 5-year jail term for their role in the death of a newborn. The newborn received a large dose of penicillin G benzathine IV. Two of the nurses accepted a deferred guilty plea prior to trial, but one of the nurses went to trial. In support of this nurse, ISMP conducted a root cause analysis of this event and found more than 50 deficiencies in the medication-use process that contributed to the error. Had even one of these latent failures been addressed before the incident, the error either would not have happened or would not have reached the infant. The nurse who stood trial was eventually acquitted of the charges.

In brief, an infant was born to a mother with a prior history of syphilis. Despite having incomplete patient information about the mother's prior treatment for syphilis and the current status of both the mother and child, a decision was made to treat the infant for congenital syphilis. After phone consultation with infectious disease specialists and the health department, an order was written for one dose of "Benzathine penicillin G 150,000U IM."

The physicians, nurses, and pharmacists, unfamiliar with the treatment of congenital syphilis, also had limited knowledge about this nonformulary drug. The pharmacist consulted both the infant's progress notes and Drug Facts and Comparisons to determine the usual dose of penicillin G benzathine for an infant. However, she misread the dose in both sources as 500,000 units/kg, instead of 50,000 units/kg. Consequently, the pharmacist incorrectly prepared the order as 1,500,000 units. The pharmacy dispensed the tenfold overdose in a plastic bag. The bag contained two full syringes of 1.2 million units/2 mL each, with green stickers on the plungers to "note dosage strength." A pharmacy label on the bag indicated that 2.5 mL of medication was to be administered IM to equal a dose of 1,500,000 units.

After glancing at the medication sent from the pharmacy, the infant's primary care nurse expressed concern to her colleagues about the number of injections required. Hospital policy limited IM injections in infants to a maximum of 0.5 mL, meaning this dose would require five injections. Anxious to prevent any unnecessary pain to the infant, two colleagues, an advanced-level nursery nurse and a neonatal nurse practitioner, decided to investigate the possibility of administering the medication IV instead of IM.

At the time, Neofax '95 was one of the medication resources relied upon by the two nurses to determine if penicillin G benzathine could be administered IV. The Neofax monograph on penicillin G did not specifically mention penicillin G benzathine; instead, it noted the treatment for congenital syphilis with aqueous crystalline penicillin G IV slow push or penicillin G procaine IM. Nowhere in the two-page monograph was penicillin G benzathine mentioned, and no specific warnings were present regarding "IM use only" for penicillin G procaine and penicillin G benzathine.*

*Although penicillin G procaine is no longer available in the United States, it is available as a combination product with penicillin G benzathine, **BICILLIN C-R**, which carries the same *Boxed Warning* that it is not for IV use.

Unfamiliar with the various forms of penicillin G, the nurse practitioner believed that "benzathine" was a brand name for penicillin G. Because she believed that aqueous crystalline penicillin G and penicillin G benzathine were the same drug, the nurse practitioner concluded that it could be safely administered IV. The primary care nurse, who was not certified to administer IV medications to infants, transferred care of the infant to the advanced-level nursery nurse and the nurse practitioner.

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including monitoring parameters (e.g., laboratory levels, electrocardiogram, patient assessment for pain/discomfort). Optimize systems (e.g., EHR, IV workflow management systems, smart pump drug library dose error-reduction systems) and build clinical decision support to guide prescribers to select the appropriate calcium product (e.g., calcium chloride, calcium gluconate), dose, concentration, rate, and route of administration based on the indication and IV access (i.e., peripheral versus central). Educate practitioners about the appropriate use of calcium chloride, the importance of escalating concerns about the safety of an order, and to report close calls and errors for shared learning.

Work needed to improve investigational drug labeling. A pharmacist reported a close call due to confusion about the medication strength when dispensing an investigational drug for a patient. The pharmacy staff had not been informed that the investigational drug sponsor had made a change to the size of the sachet, a packet that contains the drug as granules for oral solution. The investigational drug was previously packaged as 3 g and 9 g sachets, but the sponsor had phased out the 3 g sachets, and only 9 g and 12 g sachets were available. Assuming the product sizes were still 3 g and 9 g, the pharmacist almost dispensed 2 different size sachets, thinking they were needed to provide a 12 g dose. This would have resulted in a 21 g dose based on the new sachet sizes. Besides not knowing about the modification to the sachet size, the package label uses confusing Roman numerals to list key product information. For example, Roman numeral III indicates the dose (**Figure 1**, page 3). The protocol documentation sheet describes what the Roman numerals mean but adds to the confusion by stating, "III. g" which can be misinterpreted as a 3 g dose (**Figure 2**, page 3). The pharmacist caught the error prior to dispensing the dose to the patient.

The hospital that reported this event has since updated the available sachet sizes in their dispensing system and has provided staff with additional training about the study

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While preparing for drug administration, neither nurse noticed the tenfold overdose, nor did they see that the syringe was labeled by the manufacturer stating, "IM use only." The manufacturer's warning was very difficult to see because the syringe had to be rotated 180 degrees away from the drug name to view it. The nurses began to administer the first syringe of penicillin G benzathine IV push. After about 1.8 mL was administered, the infant became unresponsive, and resuscitation efforts were unsuccessful.

This tragic event occurred more than 25 years ago! Despite many technological advancements since then, this recent case highlights that there is still a risk for practitioners to administer penicillin G benzathine by the potentially fatal IV route. The Denver case received significant attention at the time; however, it is unclear if newer practitioners are aware of it or if its lessons learned are still being shared. If you queried your practitioners, do you feel confident that 100% of them would know that penicillin G benzathine is for IM use only?

Safe Practice Recommendations: To prevent these types of errors from occurring, manufacturers should provide IM medications in prefilled syringes with attached needles and safety guards to facilitate the correct route of administration. Also, organizations should consider the following recommendations to safeguard penicillin G benzathine, including Bicillin C-R, the combination product with penicillin G procaine.

Evaluate storage practices. Review the storage location of penicillin G benzathine products. Physically separate these products from other parenteral penicillin formulations.

Standardize prescribing. Ensure orders and order sets for penicillin products include indication-based doses with dose range checking. Default penicillin G benzathine orders to the IM route and test that users cannot modify the route.

Safeguard dispensing. Pharmacy should prepare and dispense patient-specific doses for neonatal and pediatric patients. Barcode scan each product separately when stocking in the pharmacy and filling the ADC.

Limit overrides. Do not allow penicillin G benzathine products to be removed via override from the ADC.

Optimize BCMA. Barcode medication administration (BCMA) is a crucial step to prevent errors from reaching patients. Build an alert upon scanning penicillin G benzathine barcodes to remind practitioners, such as "**FOR DEEP INTRAMUSCULAR INJECTION ONLY. WARNING: FATAL IF GIVEN BY OTHER ROUTES!**" Monitor compliance data and regularly observe BCMA practices within your organization to help identify potential workflow issues leading to workarounds.

Review drug libraries. If your organization has IV penicillin G (parenteral/aqueous) on formulary, review the entry in the smart pump drug library. Ensure the description is clear and not vague (e.g., penicillin, penicillin G).

Read the label. Educate staff to carefully review medication labels after removing the medication from the storage location, when programming the pump (when applicable, for example, for penicillin G [parenteral/aqueous] infusions), and prior to administration.

Evaluate additional warnings. Consider the use of ADC alerts, signage in storage locations, or other warnings, such as adding an auxiliary label on penicillin G benzathine syringes to specify "**FOR DEEP INTRAMUSCULAR INJECTION ONLY. WARNING: FATAL IF GIVEN BY OTHER ROUTES!**"

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protocol. They have also created a sticker that specifies the amount of granules per sachet (e.g., 9 g, 12 g) that staff apply when the medication is received from the sponsor. This strategy relies on staff remembering to apply the sticker, which is also not ideal.

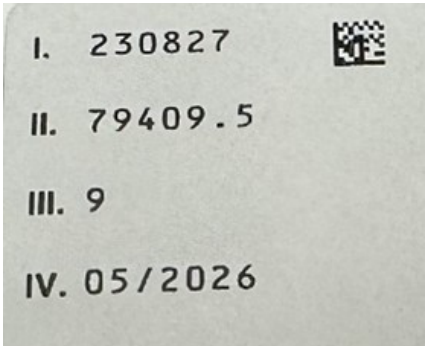

Figure 1. The sponsor uses Roman numerals to list key information on the package label. Roman numeral III lists the investigational drug sachet size as "9," referring to 9 g.

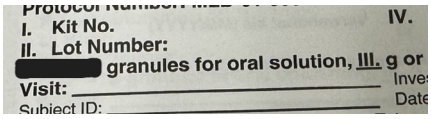

Figure 2. The protocol documentation sheet lists the dose as "III. g" referring to Roman numeral III on the package label where you will find the dose ("9" [9 g] in Figure 1). However, this could be confusing, and someone could misinterpret this to mean 3 g is the dose required.

The lack of robust guidelines and inconsistent practices for investigational drugs leads to suboptimal labeling, which can result in inaccurate preparation, dispensing, and/or administration of the drug. This may lead to medication errors and patient harm. Despite recommendations from ISMP (for additional information, review our April 19, 2018 article, Investigational Drugs: Product-Related Issues Pose Significant Challenges [Part I], and our May 3, 2018 article, Investigational Drugs: Strategies for Sponsors, FDA, and Clinical Sites To Prevent Product-Related Errors [Part II]), investigational drug sponsors continue to provide packaging with unsafe dose expressions on their labels, and more action needs to be done to enhance safety.

In November 2025, the US Food and Drug Administration (FDA) and the National Institutes of Health (NIH) co-authored an article, Investigational Drug Container and

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Promote optimal conditions. Ensure the physical environment offers adequate space and lighting and allows practitioners to remain focused on the medication-use process without distractions. For additional information, review our October 5, 2023 article, Minimizing Distractions and Interruptions During Medication Safety Tasks.

Educate practitioners. Educate staff on the differences between parenteral penicillin products, emphasizing why penicillin G benzathine products (with or without penicillin G procaine) are for IM use only. If an infrequently used medication is prescribed, pharmacists should communicate with the nurse to inform them of any special administration instructions. Encourage staff to speak up if they are unfamiliar with or uncertain about the safety of a medication order.

Learn from errors. Report medication errors and close calls to ISMP, including those involving penicillin products. Review internally reported errors as well as published external events, such as these cases.Rum dolorum quis et repta est, volupientio esequament quidem deri officim amus utas estrunt aturerovit laboriate voluptate etur? Quis moluptatem. Nam, velis adic torrores dolum

Special Announcements

Doctor and nurse participants needed for study

Practitioners sometimes confuse drug names that look and sound alike. Researchers at Northwestern University invite you to participate in an online experiment studying drug name confusion errors. **The experiment takes about an hour and pays $100 upon completion.** To participate, you must be a physician or nurse who has prescribed or administered at least one medication in the United States in the past year (no more pharmacists are needed to sign up for this study at this time). If interested, email drugname.study@northwestern.edu.

Virtual MSI workshop

Join us for one of our ***ISMP Medication Safety Intensive (MSI)*** workshops in 2026. This unique 2-day virtual program is designed to help you address current medication safety challenges that impact patient safety. Program faculty will provide you with the knowledge, as well as specific tools and resources, needed to establish and sustain an aggressive, yet focused medication safety program.

- **Acute care** focused program: **March 12 and 13, 2026**
- **Community and Specialty pharmacy** focused program: **May 1 and 8, 2026**

For more information and to register, please click here.

Webinar on RTA product safety in the OR

Join us for our webinar, ***Advancing Anesthesia Safety: The Impact of Ready-to-Administer (RTA) Injectable Solutions in the OR***, which will be held on **March 25, 2026, at 2:00 pm**. Faculty will describe risks with preparing and administering medications that are manipulated in the perioperative and procedural settings, and compare the safety profiles of traditional presentations to RTA products that can impact patient outcomes. For more information and to register, click here.

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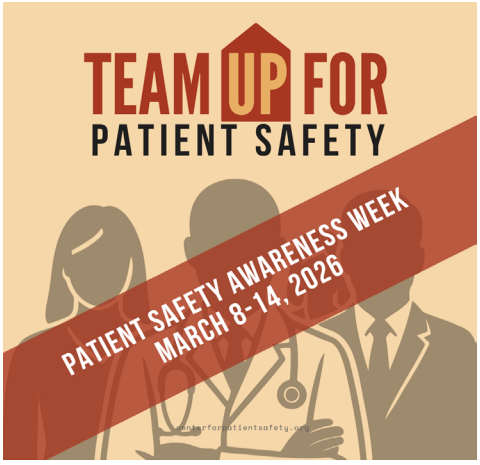
Carton Labelling: Yearning for Improvement,[1] which emphasizes the following:

- There is limited regulatory oversight to standardize and govern labeling for container label and carton labeling of investigational drugs that are administered during the drug development phase.
- Missing and poorly organized information on the container label and carton labeling of investigational drugs can lead to medication errors, harm to the study participants, and inaccurate study outcomes.
- There is a need to increase awareness about the pitfalls of deficient container label and carton labeling of investigational drugs. Stakeholders must collaborate to improve investigational drug labeling, which will help improve patient safety and preserve the integrity of study outcomes.

We encourage organizations to continue to send ISMP and FDA reports and pictures of investigational drug labels/labeling that have or may contribute to errors as well as any actual medication errors.

Reference

1) Won KS, Tassone J, Jin H. Investigational drug container and carton labelling: yearning for improvement. *Int Pharm J.* November 2025.



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