Additional strategies to improve complete delivery of small-volume intermittent infusions

In the December 3, 2020 newsletter, ISMP published an article to remind practitioners that up to half of the medication in a 50 mL small-volume intermittent infusion (medication diluted in a small bag) could remain in the tubing after intravenous (IV) administration when using a longer macrobore primary administration set connected to a patient’s vascular access device. Without adequate flushing of the tubing, the residual volume of the medication remaining in the tubing may not be administered to the patient, leading to a significant underdose. Furthermore, if the tubing is used later for medication or fluid administration, the residual volume left in the tubing from the previous infusion could result in an inadvertent bolus of the medication.

Oftentimes, the administration of a small-volume intermittent infusion through a primary administration set is due to the absence of a primary infusion or carrier fluid, which nurses cannot hang without an order. A primary administration set may also be used to address delayed doses caused by failing to open the roller clamp on a secondary infusion. Lack of practitioner awareness regarding the potentially significant loss of medication in the tubing coupled with scarce details in organizational policies and procedures about how to administer small-volume intermittent infusions and/or flush the tubing afterwards also contribute to the problem.

Results of a recent study suggest that the best practice to minimize medication loss in the tubing is to administer small-volume intermittent infusions as secondary infusions using a shorter secondary administration set with a compatible primary infusion. To promote this practice, one of several key recommendations we published in our previous article was to embed an order for an appropriate carrier fluid in order sets used to prescribe common small-volume intermittent infusions. This would enable nurses to administer the small bag as a secondary infusion as well as flush the residual volume through the tubing with the carrier fluid to deliver the full dose.

Since we published the article in December 2020, several US smart infusion pump vendors, including Ivenix, B. Braun, Baxter, BD, and ICU Medical, have communicated with ISMP to confirm the prevalence of this problem and to suggest other ways that the residual medication lost or retained in the tubing can be managed so that patients receive the full prescribed dose and/or do not receive an unintended bolus dose from any residual medication left in the tubing. In fact, one smart pump vendor sent ISMP a link to a recent news report about a series of events in the United Kingdom (UK) in which more than a dozen patients stopped breathing, and 40 additional patients experienced serious adverse effects, after a residual amount of a neuromuscular blocking agent used during anesthesia remained in the patients’ IV lines and was then inadvertently administered by unsuspecting practitioners who used the same IV lines postoperatively. One patient described ongoing nightmares associated with the horrifying error that left him fully conscious but unable to breathe. Within a 3-year period, 58 similar events were uncovered in the UK during a follow-up investigation.

Based on the feedback we received from US smart infusion pump vendors, the following additional strategies should be considered to reduce the risk of underdoses and continued on page 2 — Intermittent infusions >
inadvertent bolus doses due to the residual volume of medication that may remain in the tubing after administration of small-volume intermittent infusions. Some of these recommendations can help you maximize options that might be available with your smart infusion pumps. Talk to your vendor's clinical staff if you are uncertain regarding your pump's functionality or for help with best practices specific to the vendor's technology.

Administer as a Secondary Infusion
As previously recommended, most small-volume intermittent infusions should be administered as secondary infusions, not primary infusions. Some pumps will allow organizations to specify that all small-volume intermittent infusions must be delivered as a secondary infusion ONLY, including in a smart pump interoperability environment and regardless of whether the electronic health record allows such specifications. Some smart pumps will even allow each concentration of a medication delivered in a small bag to be configured as either a primary or secondary infusion. If the small-volume intermittent infusion is specified to be infused strictly as a secondary infusion, the clinician will either be alerted if they attempt to program it as a primary infusion, or they will only be provided with a secondary programming screen upon selection of the drug—they will not be able to program it as a primary infusion.

As an alternative, some smart pumps allow the use of short primary administration sets, which can be used to administer small-volume intermittent infusions. Using a short primary administration set avoids concerns with unopened roller clamps, head-height differentials, and limitations in concurrent flow rates, while significantly limiting the potential for significant residual volume remaining in the tubing.

Use Microbore Tubing
Consider using microbore (small bore) administration sets for the primary infusion or carrier fluid to minimize the residual volume left in the tubing. Microbore tubing has a lower priming volume compared to macrobore (regular bore) tubing. Thus, there will be less residual volume left in the tubing when using microbore tubing. For the small-volume intermittent infusion, use a secondary administration set with the smallest priming volume that can be used with the pump.

Provide an Accurate VTBI
When you combine the overfill volume that manufacturers add to each small bag with the volume of all the additives (e.g., antibiotic) injected into each pharmacy-prepared small-volume intermittent infusion, the bag contains more volume than the manufacturers' labeled amount (e.g., 50 mL, 100 mL). If the clinician administering the small-volume intermittent infusion programs the pump to deliver only the manufacturer's labeled volume, which is less than the actual volume in the small bag, it may cause the pump to stop the infusion at the programmed volume to be infused (VTBI), potentially leaving a clinically significant volume of the infusion in the small bag (and tubing). The patient may not receive the residual medication left in the small-volume intermittent infusion unless the clinician decides to estimate the remaining volume in the small bag and then reprogram the pump to deliver the full prescribed dose. Still, underestimating the residual volume left in the bag will result in underdosing or repeated, time-consuming attempts to administer the full dose. Overestimating the residual volume will result in an alarm and, in some pumps, may require air removal from the tubing. It may also cancel any "automatic secondary flushing" functionality available with the pump (see Flush the Line). Also, if there is a primary infusion or carrier fluid available, the pump might prematurely switch to this infusion at the predefined primary infusion or carrier fluid infusion rate (see Flush the Line for problems associated with this action).

If an accurate total VTBI was determined upfront, provided on the pharmacy label, and used to program the pump, most of these issues could be eliminated. Thus, continued on page 3 — Intermittent infusions >
ISMP has long recommended that the pharmacy label on the bag explicitly states how to deliver the entire dose, including all overfill and additive amounts. The pharmacy should include the actual total VTBI on the label, combining an estimate of the manufacturer’s overfill, the exact volume of all additives, and the stated volume in the bag (e.g., 50 mL). Vendors of small-volume intermittent infusions can provide hospitals with a targeted amount and range of overfill in each of their products. For infusions in which the dose remaining in the tubing must also be infused to deliver the entire dose, the label and the medication administration record (or a standard procedure for intermittent infusions) should specify that the tubing should be flushed with a particular diluent and volume. When the rate of administration is critical, as for some medications given intermittently by an infusion pump, ensure that information about the rate of administration and flush is built into relevant protocols and smart infusion pumps.

If the pharmacy admixture label cannot display the total VTBI (including overfill and additives) or if the small-volume intermittent infusion will be assembled by clinicians in patient care units right before administration (e.g., two-part, ready-to-mix delivery systems), organizations should consider prepopulating the total VTBI in the infusion pump’s drug library by estimating the manufacturer’s overfill and determining the volume of additives used for common small-volume intermittent infusions. Another viable option is to weigh a sampling of commonly used small-volume intermittent infusion bags after preparation (using gravimetrics) to determine the total volume, and to use this amount for subsequent VTBI labeling, programming, and/or prepopulation in the infusion pump’s drug library. A third option is to use commercially available premixed small-volume intermittent infusions. While each premixed bag contains a small amount of overfill, the additional volume in each bag also includes full-concentration drug solution, meaning that programming the pump to deliver the labeled volume (e.g., 50 mL, 100 mL) typically results in the patient receiving the full dose of medication, as long as the medication remaining in the tubing has been administered to the patient.

Most organizations realize that an accurate VTBI is critical for chemotherapy infusions and might weigh each of these prepared infusion bags to get an accurate total volume; still, the primary way to ensure patients receive the full dose of medication at the required time and at the intended rate of infusion is to provide an accurate VTBI for all small-volume intermittent infusions. If your facility uses smart pumps which allow the clinician to automatically infuse the entire contents of the secondary container via an “infuse to empty” function, encourage clinicians to not alter this default setting which allows the entire dose to be administered to the patient.

**Use Pump Alarms to Detect Unopened Clamps**

Historically, closed roller clamps on small-volume intermittent infusions have happened more frequently than reported, leading to delays in administration and/or omissions. There is no easy remedy for this human failure mode; however, some infusion pumps can sense an upstream occlusion if the roller clamp leading to the intermittent infusion is closed, thereby alerting the clinician to check and release any clamps. Also, some pumps require the clinician to confirm that the roller clamp is open when starting the infusion, even calling the clinician back to the pump if this verification does not occur. Please be aware that this functionality might not exist when the pump is operating in “anesthesia mode.”

**Flush the Line**

Most pumps can be programmed to automatically switch to the primary infusion or carrier fluid when the small-volume intermittent infusion is complete. However, even though the bag might be empty, the medication from the intermittent infusion that remains in the tubing will often be delivered at the primary infusion or carrier fluid; still, the primary way to ensure patients receive the full dose of medication, as long as the medication remaining in the tubing has been administered to the patient. The vaccination site identified several contributing factors. The two light-protecting bags were close to each other and within arm’s reach of the vaccinating nurse. Both bags had the appropriate labels affixed, but the nurse thought the syringes all contained the vaccine. It is easy to see how that can occur since all the prefilled syringes looked similar. After the erroneous EPINEPHrine injection, one patient reported feeling tachycardic (which, at first, was attributed to the stress of vaccination). Neither patient suffered any lasting or serious adverse effects.

We recommend that COVID-19 vaccination sites stock only EPINEPHrine autoinjectors rather than using prefilled syringes of EPINEPHrine. The EPINEPHrine autoinjector looks visually different than prefilled vaccine syringes and, with training, is very easy to use in an emergency. Doses of EPINEPHrine and vaccine should be kept in different storage locations but close enough to the vaccinators so they can be easily and rapidly retrieved as needed. Consider storing the EPINEPHrine autoinjectors in an anaphylaxis kit with a tear-off lock.
Intravenous drug errors are a significant patient safety concern. For example, a recent study reported substantial errors in the administration of medication via intravenous tubing.

To address these issues, we recommend implementing a comprehensive strategy that includes:

1. **Patient Safety Policies:** Develop and implement clear policies on medication administration, including the use of prefilled syringes.
2. **Staff Training:** Conduct regular training sessions for all healthcare staff involved in medication administration.
3. **Technological Solutions:** Utilize smart pumps and electronic medication administration systems that can alert healthcare providers to potential errors.
4. **Labeling and Packaging:** Implement clear and consistent labeling practices to reduce the risk of medication mix-ups.
5. **Feedback Mechanisms:** Establish mechanisms for regular feedback and review of medication administration practices.

By adopting these strategies, healthcare organizations can significantly reduce the risk of intravenous drug errors and improve patient safety.
Dr. Reddy’s glass naloxone syringe is relatively new to the market, first approved last year. These syringes had recently been purchased due to a backorder with the hospital’s usual naloxone supply from International Medication Systems (IMS), an Amphastar Pharmaceuticals company, which was provided with a Luer-Jet glass vial and plastic injector (Figure 2). The hospital had not experienced a problem with the Amphastar/IMS product.

A pharmacist investigated the problem, spoke to the ED nurses, and recreated the problem using an ICU Medical pressure infusion extension set with a Clave/MicroClave connector. The line flushed normally with saline, but after connecting a Dr. Reddy’s naloxone syringe, the pharmacist was unable to push the solution through, just as the nurses had reported.

Glass syringes used with MicroClave needlefree connectors have presented problems in the past. In a 2011 Safety Communication about adenosine and amiodarone in glass syringes (www.ismp.org/ext/663), the US Food and Drug Administration (FDA) noted that the action of inserting the glass syringe tip can cause the pin in the MicroClave access system to break off in the syringe tip, preventing delivery of the medication. There have been similar international reports involving EPINEPHrine injection (www.ismp.org/ext/671), and the package insert for at least one product in a glass syringe has identified an incompatibility problem with multiple needlefree connectors (www.ismp.org/ext/672). In the recently reported events, a piece of plastic had lodged inside the Dr. Reddy’s naloxone syringe nozzle (Figure 3), effectively blocking the flow of medication. This compromised the MicroClave port, which increased the risk of IV line contamination and infection.

The reporting hospital and ISMP notified Dr. Reddy’s about this problem. The company did not provide either of us with a satisfactory response, only mentioning that the problem occurred because the needle contained in the syringe carton was not used (of course not, since a needlefree IV injection was intended). In the US, BD, B. Braun, and Vygon all market similar needlefree connector products that have internal cannulas or pins, but we are not aware of similar reports of problems during administration. To address glass syringe incompatibility, ICU Medical has developed a syringe adapter, CS-25, which enables the use of glass syringes with needlefree connectors when prefilled plastic syringes are not available. However, it is unlikely that these will be routinely used by all who administer an IV injection. If used, these should be provided in a kit along with the prefilled syringe.

The hospital will be using other naloxone products or, if using the Dr. Reddy’s syringe, will administer the medication intramuscularly or via the nasal route using an atomizer, not IV through a MicroClave connector. If incompatible prefilled glass syringes remain on the market, FDA and device/drug manufacturers need to clearly communicate this potential problem, and perhaps include prominent warnings on the packaging itself.

> SAFETY briefs cont’d from page 4

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.

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 and administration is a must. FDA should also work with ophthalmic product manufacturers to focus more on reducing similarity among look-alike containers.

Figure 2. No administration problems occurred when using the Amphastar/IMS naloxone syringe with a plastic injector.

Figure 3. Silicone core appears in nozzle of Dr. Reddy’s naloxone prefilled syringe.

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

To register, visit: www.ismp.org/node/127.
One of the most important ways to prevent medication errors is to learn about problems that have occurred in other organizations and to use that information to prevent similar problems at your practice site. To promote such a process, the following selected items from the January – March 2021 issues of the ISMP Medication Safety Alert! have been prepared for leadership to use with an interdisciplinary committee or with frontline staff to stimulate discussion and action to reduce the risk of medication errors. Each item includes a brief description of the medication safety problem, a few recommendations to reduce the risk of errors, and the issue number to locate additional information. Look for our high-alert medication icon under the issue number if the agenda item involves one or more medications on the ISMP List of High-Alert Medications in Acute Care Settings (www.ismp.org/node/103). The Action Agenda is also available for download in a Microsoft Word and Excel format (www.ismp.org/node/24070) that allows expansion of the columns in the table designated for organizational documentation of an assessment, actions required, and assignments for each agenda item. Continuing education credit is available for nurses at: www.ismp.org/nursing-ce.

Key: ⚠ — ISMP high-alert medication

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<td>(2)</td>
<td>ISMP’s top 10 errors/hazards from 2020 include: 1) inappropriate use of extended-release opioids; 2) not using smart infusion pumps with dose error-reduction systems in perioperative settings; 3) oxytocin errors; 4) hazards with infusion pumps outside coronavirus disease 2019 (COVID-19) patients’ rooms; 5) COVID-19 vaccine errors; 6) using the “syringe pull-back” method during sterile compounding; 7) sterile admixture outside the pharmacy; 8) medication loss from residual volume left in the tubing; 9) tranexamic acid wrong route errors; and 10) use of error-prone abbreviations, symbols, or dose designations.</td>
<td>These issues warrant your attention and priority given the serious consequences of a related error. Review the list of errors and hazards in detail and implement the recommended actions to mitigate these risks (<a href="http://www.ismp.org/node/22438">www.ismp.org/node/22438</a>). Include strategies to prevent these errors and hazards in your 2021 strategic medication safety improvement plan.</td>
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<td>Medication errors remain a significant contributor to preventable patient harm. Thus, healthcare executives face the daunting task of making sustainable medication safety improvements in their organization—yet they cannot do it alone. In 2018, less than half of US hospitals had created an MSO position to address this ongoing challenge. While medication safety is a shared responsibility, the MSO position cannot be covered by other practitioners simply by adding “medication safety” to their job descriptions.</td>
<td>Healthcare executives should hire a qualified, dedicated MSO; empower them to act on medication safety concerns; and position them on the organizational chart where it will best enhance their ability to affect change, ensure that the organization identifies and learns from medication risks and errors (both internal and external), and implement high-leverage strategies to reduce medication errors.</td>
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<td>(1, 2)</td>
<td>Numerous Moderna and Pfizer-BioNTech vaccine errors have been reported since December 2020. Examples include accidental administration of casirivimab instead of the Moderna vaccine due to labeling issues, waste of leftover vaccine doses, administration to the wrong age group, errors with scheduling, and dilution errors with the Pfizer vaccine. Recent errors involved “dilution” of the Pfizer vaccine with air after empty syringes were pulled back in preparation to withdraw diluent and were thought to contain 0.9% sodium chloride.</td>
<td>Establish an efficient procedure for scheduling patients and ensure vaccination sites have adequate space for the administration and monitoring processes. Verify the competency of vaccinators and have the pharmacy prepare and label vaccine doses when possible. Create an action plan for leftover vaccine doses to prevent waste. Be prepared to immediately treat any allergic reactions. Do not preopen syringe packages to draw up air in advance. Have a single practitioner dilute each vial of vaccine and withdraw all doses from that vaccine vial.</td>
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<td>We continue to receive reports of COVID-19 vaccine-related SIRVA, which presents as persistent shoulder pain and weakness after intramuscular (IM) injection into the shoulder capsule instead of the deltoid muscle. For one patient, an x-ray revealed a ligament tear and capsule involvement which might require surgical repair.</td>
<td>Vaccinators must understand the proper technique for IM injection into the deltoid muscle: expose the upper arm/shoulder area, measure 2 to 3 finger widths from the acromion process (bony prominence above the deltoid), and locate the armpit as the lower border. Outline the deltoid muscle and inject the needle at a 90-degree angle.</td>
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<td>Current Vaccination Record Cards provided by the US federal government specify the two doses that are required for the Moderna and Pfizer-BioNTech COVID-19 vaccines. A hospital received these two-dose vaccination cards with the first shipment of the Janssen single-dose COVID-19 vaccine, which could cause confusion.</td>
<td>An update to the federal Vaccination Record Card for the single-dose COVID-19 vaccine is NOT currently being considered. For now, single-dose COVID-19 vaccine providers should cover all references to a second dose (front and back of the card) with a note that the Janssen product is a single-dose vaccine.</td>
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<td>Online retailers are selling authentic, empty COVID-19 vaccine vials and cartons as souvenirs. This is risky because the vials may be refilled with unknown substances and marketed as real COVID-19 vaccines.</td>
<td>Be cautious of how you dispose of your empty COVID-19 vaccine vials and cartons. Remind consumers and colleagues that COVID-19 vaccines are distributed only by the federal government and are free.</td>
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January - March 2021

ISM P M edication Safety A lert!

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IN USE

PROBLEM

RECOMMENDATION

ORGANIZATION ASSESSMENT

ACTION REQUIRED/ASSIGNMENT

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<td>A long-term care (LTC) nurse called an off-site pharmacy with orders for IV bamlanivimab to treat mild to moderate coronavirus disease 2019 (COVID-19) in four residents. The pharmacist misheard the nurse and dispensed belimumab, which is used to treat active systemic lupus. Nurses were not familiar with bamlanivimab and did not recognize the error before administering the wrong medication.</td>
<td>When drug orders are verbally communicated to the pharmacy, enunciate the order clearly, spell the drug name, include the indication, and expect the recipient to read it back. Immediately follow up the verbal communication by sending an electronic or faxed order to the pharmacy. Prescribers should communicate the purpose of the medication during the ordering process.</td>
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<td>When a child is discharged, some hospital computer systems convert oral ibuprofen suspension doses to a metric volume to help parents measure each dose. However, the concentration that the parents use may not be known. Parents who were told to give their child the mL amount for the children's formulation (100 mg/5 mL) instead used the infant's formulation (50 mg/1.25 mL), which led to 2-fold overdoses.</td>
<td>Prior to discharge, counsel parents about the availability of the two liquid ibuprofen strengths. Refer to the two strengths as “children’s ibuprofen” (100 mg/5 mL) and “concentrated infant drops” (50 mg/1.25 mL). Ensure parents understand that the dose in mL (volume) is based on which concentration they use.</td>
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<td>△ Common themes identified during an analysis of transdermal patch errors include the following: mistakes in the frequency of patch application or removal; lack of awareness of patches on the patient's skin upon admission; dose confusion due to scopolamine patch labeling; inappropriate prescribing of fentanyl patches for opioid-naïve patients with acute pain; and clonidine patch covers applied without the medication patches.</td>
<td>Collect a medication history, including opioid status (naïve versus tolerant), and perform a skin assessment looking for patches upon admission. Build order sets with appropriate application frequencies. Dispense clonidine patches and adhesive covers in a ziplock bag with a label explaining the two components. Employ barcode scanning to ensure correct product selection. Verify the patch's indication prior to dispensing and application.</td>
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<td>△ The barcode on the AbbVie Nimbex vial is printed horizontally, curving around the circumference of the vial, making it difficult or impossible to scan.</td>
<td>When possible, only purchase vials with a barcode printed perpendicular to the curve of the vial.</td>
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<td>A pharmacist received a prescription for Entresto 100 mg twice daily, which did not match any available strengths. The pharmacist dispensed Entresto 97 mg/103 mg, believing it was closest to the prescribed dose (100 mg). However, the physician had added the two component strengths together (which is how clinical trial data in the product labeling is reported) and intended the patient to take the 49 mg/51 mg strength. The patient suffered adverse effects.</td>
<td>Entresto should be prescribed according to the strengths of each respective drug, not the total strength of all active ingredients. If a prescribed dose clearly does not match the strength of available products, the pharmacist should clarify the dose with the prescriber. Consider including an alert in prescribing and dispensing software.</td>
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<td>The oral syringe that accompanies a 15 mL bottle of concentrated oral morphine solution (20 mg/mL) has dose markings starting at 5 mg. Needing a 2 mg dose for a patient, a nurse used a 1 mL parenteral syringe to accurately draw up the dose. However, the oral morphine was then accidentally administered intravenously to an opioid-naïve patient.</td>
<td>Oral morphine solution is available in various concentrations. For lower doses, a 2 mg/mL (10 mg/5 mL) concentration is available with a dosing cup. Concentrated oral morphine should be reserved for opioid-tolerant patients. Furthermore, the pharmacy should dispense ready-to-administer doses in labeled oral or ENFit syringes rather than dispensing a 15 mL bottle that contains 150 doses.</td>
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<td>ValGANCiclovir powder for oral solution was inadvertently prepared using 70% isopropyl alcohol instead of water. The alcohol bottle had previously contained distilled water, and both “alcohol” and “water” were on the label. Similar events have been reported, including antibiotics reconstituted with formalin, which sent several children to the hospital. NxN isopropyl alcohol is also available in bottles that look just like drinking water.</td>
<td>Discard any chemicals not regularly used. Do not reuse containers that previously held another substance. For chemicals that must remain in the pharmacy, determine if the chemical(s) might be confused with another product (i.e., similar name, container size or shape). Place prominent warning labels on chemicals and store them away from drug products. Do not store or supply chemicals for others (e.g., laboratories, surgical centers) to use.</td>
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