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DEA Publishes New Version of Pharmacist's Manual

The latest version of the *Pharmacist's Manual: An Informational Outline of the Controlled Substances Act* has been released by Drug Enforcement Administration's (DEA's) Diversion Control Division. The guide is provided to assist pharmacists in understanding the Federal Controlled Substances Act and its regulations as they pertain to the pharmacy profession. This edition has been updated to include information on the Secure and Responsible Drug Disposal Act of 2010, the Comprehensive Addiction and Recovery Act of 2016, and the SUPPORT for Patients and Communities Act of 2018, and replaces all versions of the guidance previously issued by the agency. The new *Pharmacist's Manual* can be accessed by visiting the DEA website.

Time to End VinCRIStine Syringe Administration

This column was prepared by the Institute for Safe Medication Practices (ISMP), an ECRI affiliate. Have you experienced a medication error or close call? Report such incidents in confidence to ISMP's National Medication Errors Reporting Program online at www.ismp.org or by email to ismpinfo@ismp.org to activate an alert system that reaches manufacturers, the medical community, and Food and Drug Administration (FDA). To read more about the risk reduction strategies that you can put into practice today, subscribe to the ISMP Medication Safety Alert!® newsletters at www.ismp.org.

At the request of FDA, Pfizer has revised the prescribing information and product packaging for vin**CRIS**tine sulfate injection. Importantly, they have removed wording from the vin**CRIS**tine package insert that described direct intravenous (IV) injection of vin**CRIS**tine via a syringe. FDA recommended this revision at the request of ISMP, the National Comprehensive Cancer Network, and The Joint Commission.

The WARNINGS section of the package insert now states, "To reduce the potential for fatal medication errors due to incorrect route of administration, vin**CRIS**tine sulfate injection should be diluted in a flexible plastic container and prominently labeled as indicated 'FOR INTRAVENOUS USE ONLY—FATAL IF GIVEN BY OTHER ROUTES.'" More than 140 deaths are known to have occurred in the United States and globally due to accidental intrathecal injection of the drug via syringe, often when it was mixed up with, or wrongly assumed it was supposed to be given with, another drug meant for intrathecal administration, such as methotrexate. No such cases have been reported with dilution of vin**CRIS**tine in a minibag, due to physical differences in the packaging and the need for an administration set.

Unfortunately, some practice sites are still using syringes to administer IV vin**CRIS**tine. Based on data collected in response to the *ISMP Medication Safety Self Assessment for High Alert Medications* between September 2017 and March 2018 from 442 US hospitals, nearly 20% of respondents still used syringes at least part of the time, including 13% who always used syringes to administer IV vin**CRIS**tine. Thus, the risk of accidental intrathecal injection still exists in the US and globally.

Dispensing vin**CRIS**tine and other vinca alkaloids in a minibag of compatible solution, and not in a syringe, was among the very first *ISMP Targeted Medication Safety Best Practices for Hospitals,* which were launched in 2014[1]. Then, in March 2019, ISMP called on the FDA to eliminate all mention of syringe administration from official vin**CRIS**tine labeling.[2]

ISMP has frequently referred to wrong route administration of vin**CRIS**tine and vinca alkaloids as the "most serious of all medication errors." Patients experience tremendous pain and are often aware of their impending death, which typically occurs within days or weeks. There is no effective reversal once the mistake is made. Even with the labeling change, there is nothing to stop health care practitioners from administering vin**CRIS**tine via syringe (except if they can only get the drug dispensed in a minibag). We hope that every hospital and health system will investigate exactly how vin**CRIS**tine is being administered at any site that uses the drug. It is time to end the practice of syringe administration by making it a requirement for all vin**CRIS**tine doses to be diluted in a minibag.

References

1. *www.ismp.org/guidelines/best-practices-hospitals*
2. *www.ismp.org/resources/ismp-calls-fda-no-more-syringes-vinca-alkaloids*

What Pharmacists Need to Know About Biosimilar and Interchangeable Biological Products

This column was prepared by FDA, an agency within the US Department of Health and Human Services, that protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines, and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Biological products are a diverse category of products and are generally large, complex molecules. These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biological products approved for use in the US, including therapeutic proteins (eg, filgrastim), monoclonal

antibodies (eg, adalimumab), and vaccines (eg, influenza and tetanus).

Section 351(k) of the Public Health Service Act (PHS Act) provides an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product, which can help provide more affordable treatment options for patients. For example, on March 23, 2020, FDA-approved insulin products were transitioned to regulation as biological products under the PHS Act, which means that transitioned insulin products are open to competition from future biosimilars, including interchangeable biosimilars.

Key Terms for Biosimilar and Interchangeable Products

- **Biosimilar Product:** A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an FDA-approved reference product.
- **Interchangeable Product:** An interchangeable product is a biosimilar that meets additional approval requirements and may be substituted for the reference product without the intervention of the prescribing health care provider.
- **Reference Product:** A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar or interchangeable product is compared.

Are Biosimilars the Same as Generic Drugs?

Biosimilars and generic drugs are versions of brand name drugs and may offer more affordable treatment options to patients. Biosimilars and generics are approved through different abbreviated pathways that avoid duplicating costly clinical trials. But biosimilars are not generics, and there are important differences between them.

For example, the manufacturer of a generic drug must demonstrate, among other things, that the generic contains the same active ingredient as the brand name drug and that the generic is bioequivalent to the brand name drug. By contrast, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the reference product, except for minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness.

Unlike generics, biosimilars are generally prescribed by brand name by a health care provider, while interchangeables, like generics, may be substituted without the involvement of the prescribing health care provider, depending on state laws.

What is the Purple Book?

The Purple Book database contains information on FDA-licensed (approved) biological products regulated by the Center for Drug Evaluation and Research, including licensed biosimilar and interchangeable products, and their reference products. It also contains information about all FDA-licensed allergenic, cellular, and gene therapy, hematologic, and vaccine products regulated by the Center for Biologics Evaluation and Research .

The Purple Book has simple and advanced search capabilities and some information that you can find includes the proprietary (brand) name and nonproprietary (proper) name of biological products, applicant (company), dosage form, product presentation (eg, autoinjector, vial), route of administration, and strength. The Purple Book also will display FDA-approved interchangeable products and note with which brand product each interchangeable product may be substituted.

Are Therapeutic Equivalence Codes Assigned to Biological Products?

FDA does not assign therapeutic equivalence codes to biological products listed in the Purple Book like it does for small molecule drugs listed in the "Orange Book." The Purple Book provides information about whether a biological product has been determined by FDA to be biosimilar to or interchangeable with a reference product.

Can Interchangeable Products Be Substituted at the Pharmacy?

Many states have laws that address pharmacy-level substitution, including permitting substitution of interchangeable products, and the specific laws vary from state to state.

There are currently no FDA-approved interchangeable products. Once there are, interchangeables, by definition, can be expected to produce the same clinical result as the reference product in any given patient.

Biosimilar and interchangeable products meet FDA's rigorous standards for approval, and patients and health care providers can be assured of the safety and effectiveness of these products, just as they would for the reference product.

Where Can I Find Additional Resources?

- *fda.gov/biosimilars*
- *purplebooksearch.fda.gov*
- *fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act*
- *fda.gov/media/135340/download*

Final Insanitary Conditions at Compounding Facilities Guidance Released by FDA

Continuing efforts to protect patients from exposure to poor quality compounded drugs, FDA has published final guidance for compounding facilities regarding insanitary conditions. The final guidance, *Insanitary Conditions at Compounding Facilities Guidance for Industry,* provides recent examples of insanitary conditions that FDA has observed at compounding facilities and details corrective actions that facilities should take when they identify these conditions. The guidance is intended to help compounders identify and prevent such issues at their facilities.

While some compounders work hard to meet quality standards, FDA says its investigators continue to observe poor conditions that impact drug quality and that have the potential to harm patients. These include the presence of dirt, mold, insects, trash, peeling paint, unclean exhaust vents, and dirty high-efficiency particulate air filters.

In response to the draft guidance, FDA states that it has also added recommendations for compounders to use risk management tools to develop appropriate controls to prevent insanitary conditions at facilities. The guidance also addresses the regulatory actions that FDA may take in response to these conditions.

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The amendment to the regulation allowing for pharmacists to order and administer vaccines to children three years and older was prompted by a report from CDC in which it found a significant decrease in rates of routine childhood vaccinations due to social distancing and other COVID-19 mitigation strategies, including "[p]arental concerns about potentially exposing their children to COVID-19 during well child visits." The CDC report concluded that the decrease in childhood vaccination rates is a public health threat and a collateral harm caused by COVID-19, and that rapidly expanded access to vaccinations is needed to respond to the pandemic. According to the HHS secretary, given the prevalence of community pharmacies across the country and their significant role in annual influenza vaccination, allowing more qualified pharmacists to administer the influenza vaccine to children will make vaccinations more accessible.

Pharmacists and pharmacy interns must meet strict requirements before administering vaccines to children between the ages of three and 18 including:

- The vaccine must be Food and Drug Administration approved and authorized.
- The vaccination must be ordered and administered according to the ACIP standard immunization schedule.
- The licensed pharmacist (and intern, if administering) must complete a practical training program of at least 20 hours that is approved by the Accreditation Council for Pharmacy Education (ACPE). The program must include hands-on injection technique, clinical evaluation of indications and contraindications of vaccines, and the recognition and treatment of emergency reactions to vaccines. It is the Board's opinion that this could be done via the training obtained as part of the PharmD education at an ACPE-accredited college of pharmacy, or by completing an immunization continuing education course from an ACPE-accredited provider that matches these criteria.
- The licensed pharmacist must complete a minimum of two hours of ACPE-accredited immunization-related continuing pharmacy education during each state licensing period.
- The licensed pharmacist and intern must have a current cardiopulmonary resuscitation (CPR) certificate.
- The licensed pharmacist must comply with record-keeping and reporting requirements of Kentucky. This should include informing the patient's primary care physician, when available; submitting the required immunization information to the state or local immunization information system (vaccine registry); complying with requirements with respect to reporting adverse events; and complying with the requirement whereby the person administering the vaccine must review the vaccine registry or other vaccination records prior to administering the vaccine.
- The licensed pharmacist must inform childhood -vaccination patients and their adult caregivers of the importance of a well-child visit with a pediatrician or other licensed primary care physician and refer patients as appropriate.

This regulation is only in effect during the federal government's declaration of a public health emergency, as declared in the *Federal Register*. Once the Declaration expires, Kentucky law will once again govern the ordering and administering of childhood vaccines by pharmacists.

This regulation is coupled with broad-sweeping immunity for ordering and administering the vaccines permitted under this regulation if done so pursuant to the requirements listed above. This includes immunity under both federal and state law with respect to all claims for loss caused by, arising out of, relating to, or resulting from the administration or use of the vaccine.

Child Fatalities and Near Fatalities From Accidental Ingestion of Prescription Medications

In 1970, to reduce the unintentional or accidental poisonings of children, Congress passed the Poison Prevention and Packaging Act (PPPA), which required the use of child-resistant packaging on different household substances, including medications. The overall incidence of unintentional poisonings decreased after passage of the PPPA. Starting in the early 2000s, accidental poisonings from medications have accounted for the majority of pediatric poisonings.[1] From 2001 to 2008, there was an increase in emergency room visits, injuries, and hospital admissions resulting from pediatric self-ingestion of medications, with the greatest increase in self-ingestion of prescription medications.[2]

CDC reports almost 50,000 young children a year are taken to the emergency room after unsupervised access to medications.[3] Opioids, benzodiazepines, sulfonylureas, beta blockers, centrally acting antiadrenergics, and calcium channel blockers are the drug classes most associated with hospitalization of children under six years following accidental poisonings.[4] Twelve active ingredients were involved in 45% of hospitalizations following accidental ingestions. Buprenorphine and clonidine accounted for 15% of hospitalizations.[4] In comparing hospitalization after unsupervised opioid ingestion, one child was hospitalized per 500 unique buprenorphine patients, versus one child per 48,500 oxycodone patients, and one child per 119,000 hydrocodone patients.[4]

The 2019 Annual Report of the Kentucky Child Fatality and Near Fatality External Review Panel listed overdose or ingestion cases as one of the top three categories for child fatality or near fatality in Kentucky for the last four years.[5] In 2018, buprenorphine-containing products and clonidine

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accounted for 17 of the 31 overdoses or ingestions that the panel reviewed. In 2018, the Kentucky Poison Control Center received almost 5,000 inquiries about pharmaceutical exposures in young children, and 897 children under the age of 12 were treated in Kentucky emergency rooms for drug overdose.[5]

Unsafe medication storage and removal of prescription medication from original child-resistant packaging are common findings in unsupervised ingestions of medication.[6,7]

CDC recommends storing all medications, including over-the-counter and dietary supplements, in a location that is out of children's reach and out of sight.[3] Medications should be put away after every use, with the safety cap locked after each use. Visitors should store any purses, bags, or coats with medication inside in secure locations out of children's reach and sight. In the majority of unsupervised ingestions of prescription medications by young children, the medication was removed from the original dispensing container, placed in an alternative container such as a weekly pill container or a plastic sealed bag, or the prescription medication was not in a container.[7] Alternative containers are often used as reminders for patients to take medication and do not meet the PPPA's requirements for child-resistant packaging. Young children most often accessed medications prescribed to parents, grandparents, and siblings.

When counseling on proper medication storage, pharmacists should encourage parents and grandparents to follow the recommendations in CDC's Up and Away campaign[3] and counsel on how to model safe medication behavior. Pharmacists should counsel patients receiving medication in non-child-resistant packaging, or who use alternative containers such as pillboxes, on the risks of unintentional pediatric ingestion of medications. Pharmacists should consider ordering and dispensing medication, specifically those medications at a high risk of pediatric poisoning, in child-resistant unit-dose packaging. The availability of manufacturer unit-dose packaged buprenorphine-naloxone strips in 2010 and tablets in 2013 resulted in a decrease in the incidences of accidental pediatric poisonings from buprenorphine.[8,9]

The pharmacy and drug inspectors will be providing an information sheet regarding child fatalities and near fatalities with the inspection report following routine inspections.

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Official Method of Notification

The *Kentucky Board of Pharmacy Newsletter* is considered an official method of notification to pharmacists, pharmacist interns, pharmacies, wholesalers, and manufacturers credentialed by the Board. **These *Newsletters* will be used in administrative hearings as proof of notification.** Please read carefully. The Board encourages you to store them electronically in a folder or keep them in the back of the *Kentucky Pharmacy Law Book* for future reference.

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