The Safety of Intravenous Drug Delivery Systems: Update on Current Issues Since the 2009 Consensus Development Conference

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Abstract

This review was prepared in advance of the Third Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems that was held at the W Hotel in Chicago, Illinois, from November 1 through 3, 2018. The purpose of this conference was to evaluate the safety of intravenous (IV) infusion systems used for medication administration. The expert panel of pharmacists, physicians, and nurses updated the findings of the Second Consensus Development Conference in 2009 that reviewed 5 IV drug delivery systems (manufacturer ready to use, outsourced ready to use, point-of-care activated, pharmacy compounded, and nonpharmacy compounded at point of care) with regard to applicability, ease of use, regulatory compliance, cost, safety, and implementation. The Third Consensus Development Conference expanded on previous findings by reviewing proceedings related to new standards, legislation, technologies, and shortage-related challenges related to IV medication administration that have been published since 2009. Invited faculty and audience members participated in revising a preliminary report summarizing these changes during the meeting.

Keywords

drug delivery, safety, Drug Quality and Security Act, USP, IV workflow management systems

Introduction

Medication errors have long been a focus of health care safety initiatives and received mainstream attention with the 1998 report by the Institute of Medicine *To Err is Human*.¹ Drug administration is the stage in the medication use process most vulnerable to error, and intravenous (IV) drug administration often results in the most severe error-related outcomes because of its high-risk nature and sterility requirements.² The safety of IV drug delivery systems continues to be an area of focus for clinical, regulatory, and accrediting bodies.

Since 1999, interdisciplinary expert panels have periodically convened to evaluate the safety of available IV drug delivery systems.^{3–5} These panels of pharmacists, physicians, and nurses have identified issues related to these systems, including clinician perspectives, potential problems, and characteristics influencing preferences.

The first Consensus Development Conference on the Safety of IV Drug Delivery Systems in 1999 evaluated the relative safety of nonelectronic IV drug delivery systems then available.⁶ A decision-analysis methodology ranked 6 available systems based on domains of safety, cost, simplicity of use, and training required for operation. The systems

scoring highest were manufacturer-prepared products, point-of-care activated products, and pharmacy-based admixture systems, which the panel considered safest, easiest, and most flexible, respectively. However, the need for a combination of delivery systems was noted because of the limited availability of manufacturer-prepared and point-of-care activated products.

The Second Consensus Development Conference noted few developments in the availability of IV drug delivery systems, but significant changes in guidelines and standards governing their use.³ These changes included revisions to the United States Pharmacopeia (USP) chapter <797> on compounded sterile preparations (CSPs), The Joint Commission (TJC) medication management standards, and Centers for Medicare and Medicaid Services (CMS) rules on hospital-acquired conditions. Other significant nonregulatory changes included standardization versus customization of parenteral

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nutrition, outsourcing of parenteral products, and incorporation of robotics and smart pump technologies.

The 2009 panel ranked 5 systems on domains of applicability, ease of use, regulatory compliance, cost, safety, and resources required for implementation, using a decision tool that can be used by clinicians when determining the most appropriate system to implement at a specific facility.⁵ From highest to lowest total score, the ranked systems were manufacturer ready-to-use, outsourced ready-to-use, point-of-care activated, pharmacy compounded, and nonpharmacy compounded at point of care. Similar to the first Conference, manufacturer ready to use systems were rated highest in all domains except for applicability. Although considered most applicable, pharmacy-compounded products scored low in “ease of use” and “regulatory compliance” domains because of their cost and complexities in adhering with new USP <797> standards. Nonpharmacy compounded point-of-care activated delivery was considered least safe and least compliant. Overall, the panel noted that the complexity of IV medication delivery has increased, and that no single delivery system meets the needs of all patient populations and patient care environments.

Since the 2009 Consensus Development Conference, many important regulatory changes have again occurred. These include proposed revisions to USP Chapter <797>, the creation of USP <800> for handling of hazardous drugs, and revision of TJC National Patient Safety Goals (NPSGs).⁷⁻¹¹ Perhaps the most notable change is the creation of the 2013 Drug Quality and Security Act (DQSA) triggered by the New England Compounding Center (NECC) meningitis outbreak, representing the largest outbreak of health care-associated infections in the United States.¹⁰⁻¹³ The DQSA presents challenges for pharmacies in meeting standards related to drug compounding and drug supply chain security.¹² Other recent events that may influence utilization of IV drug delivery systems include the Standardize for Safety Initiative, an effort led by the American Society of Health-Systems Pharmacy (ASHP) through funding from the Food and Drug Administration (FDA) to reduce errors and improve transitions of care.¹⁴ Overall, pharmacies’ response to achieve compliance with these changes may require significant resource investment and support from executive organizational leadership.¹⁵

Changes related to IV drug delivery systems include expansion of the availability and adoption of IV workflow automation technologies, including IV workflow management systems (WMSs) and robotic compounding. These offer automation in the preparation, verification, tracking, and documentation of CSPs.^{16,17} Integrating these processes electronically offers the potential to improve safety and electronic traceability of CSPs. However, selecting an IV WMS that best suits an organization’s needs may prove challenging and may face barriers in funding and adoption.¹⁷

Last, clinical challenges related to drug shortages continue to influence IV drug delivery. This has been highlighted

by recent shortages of small volume parenteral (SVP) solutions, which led many facilities to transition from IV infusion to IV push administration of some drugs. Guidelines have been produced on both drug shortage management and IV push administration.¹⁸⁻²⁰

Revised Guidelines and Standards

USP <797>

The introduction of USP Chapter <797> in January 2004 was intended to improve patient safety by establishing standards for the preparation of CSPs.³ In achieving this goal, the chapter established requirements for competence of compounding personnel, equipment and facilities, and the categorization of CSPs into immediate use preparations and low-, medium-, and high-risk levels, based on their potential for microbial, chemical, and physical contamination.²¹ Implementation of standards in Chapter <797> and its revisions has required significant resource investment for many organizations, and prompted some to move from pharmacy-compounded preparations toward other IV drug delivery systems. These alternatives include manufacturer-prepared, point-of-care activated, or outsourced compounding systems.

Proposed revisions to Chapter <797> were introduced in September 2015.²² Major revisions include changes to beyond-use dates (BUDs) of CSPs, facility design, environmental monitoring, documentation, and compounding personnel training.^{21,22} Previously, a CSP’s risk level and storage conditions determined its BUD. Proposed revisions to Chapter <797> will usher in a new paradigm for BUDs, which is rooted in the determination by USP that no sterile compounding is inherently “low risk.” The 3 categories of low, medium, and high risk will be collapsed to Category 1 and Category 2, which are distinguished primarily by the conditions of CSP preparation and the time within which the CSP will be used. Category 1 CSPs, which may be prepared in a segregated compounding area, will have shorter BUDs based on storage conditions. Category 2 CSPs, which must be prepared in a cleanroom environment, may be given longer BUDs. In addition, assigning BUDs to Category 2 CSPs will also consider additional variables including the method of achieving sterility (ie, compounding from only sterile products or performing terminal sterilization), performance of sterility testing, and addition of preservatives. Beyond-use dates assigned to CSPs under the new paradigm will differ from those long used by compounding personnel. Some facilities may require redesign to achieve longer BUDs within the new USP <797> BUD paradigm. For example, when compounding Category 2 CSPs, the ISO (International Organization for Standardization) Class 8 anteroom and the ISO Class 7 buffer room must be separated by walls and doors.

The revised Chapter <797> will also introduce the term “in-use time,” which refers to the time before which a

conventionally manufactured product or a CSP must be used after it has been opened or punctured.²¹ In-use times will be determined based on the type of product or CSP and the environment within which it is manipulated, and may not exceed the expiration date of the manufactured product or the BUD of a CSP. This may add an additional consideration during administration of IV medications.

The frequency of environmental monitoring will also be increased with proposed <797> revisions.²¹ Currently, the Chapter requires testing every 6 months for viable and non-viable air sampling, and periodically for surface sampling; the revised Chapter would require these tests monthly for viable air and surface sampling and every 6 months for non-viable air sampling. This may encourage hospital pharmacies to purchase volumetric air samplers or other equipment to insource this testing rather than outsourcing this responsibility to contracted outside entities.

New requirements have also been proposed for documentation and training qualifications of compounding personnel.²¹ The Chapter will require a master formulation record for CSPs prepared in batches for multiple patients or prepared from nonsterile ingredients, as well as standard operating procedures on all aspects of the compounding operation. Training and evaluation of compounding personnel on a list of core competencies in sterile compounding must also be performed and documented initially and in annual refresher training. Reevaluation and requalification of compounding personnel will be required at least quarterly for visual observation, gloved fingertip sampling, and media-fill testing. Adherence to these requirements may demand significant initial and ongoing labor related to documentation and training initiatives.

Following the receipt of over 8000 public comments from more than 2500 stakeholders in response to the initial proposed Chapter <797> revision, USP plans to post a second revision for public comment in fall 2018.²³ The final revised Chapter is anticipated to become official on December 1, 2019, at the same time as USP Chapter <800>.²¹

USP <800>

The new USP Chapter <800> will set standards for appropriate handling of hazardous drugs, and has far-reaching implications for many health care personnel and settings.^{8,24} Chapter <800> was developed after several reports of adverse effects of hazardous drugs on exposed health care personnel.²⁵ The Chapter is intended to establish practice and quality standards for handling hazardous drugs to promote safety for patients, health care workers, and the occupational environment. The scope of USP <800> spans the time from when hazardous drugs are received up to and including their administration and disposal of waste. Therefore, health care personnel handling hazardous drugs in any setting (including pharmacies, physician offices, clinics, and home health care settings) are affected by USP

<800>. Although USP has no enforcement authority, some states have opted to enforce compliance with standards in Chapter <797>, and these and other states may do the same with USP Chapter <800>.^{24,26}

The hazardous drugs governed by Chapter <800> include those in the National Institute for Occupational Safety and Health (NIOSH) list of antineoplastic and other hazardous drugs.⁸ Health care entities must maintain a list of hazardous drugs, which may include drugs on the NIOSH list, in addition to other drugs. Additions to the entity's custom list of hazardous drugs may originate from newly approved drugs or investigational drugs used by the entity, which should be evaluated based on criteria considered by NIOSH in identifying hazardous drugs. The entity's list of hazardous drugs must be reviewed annually and with the use of a new agent or dosage form of a hazardous drug.

New in USP <800> is the requirement that sterile compounding of hazardous drugs be in a room that is separate from compounding of nonhazardous drugs.^{8,25} Previously, USP <797> provided the "low use" exemption, whereby entities performing only low volumes of hazardous drug compounding could place a biological safety cabinet (BSC) or a compounding aseptic containment isolator in a positive pressure room. This low use exemption will no longer be permitted under USP <800>. Rooms dedicated to compounding of hazardous drugs must have negative pressure, fixed walls, outside venting, and the appropriate number of air changes per hour. Containment primary engineering controls must be externally vented Class II or III BSCs. Laminar airflow hoods, containment ventilated enclosure, and Class I BSCs are not permitted.

Elimination of the low use exemption may present difficulties for compounders of very low volume antineoplastics, as any compounding will require the proper facilities per USP <800>.⁸ The potential for significant capital investment and facility upgrades was acknowledged by USP and influenced the extended period between publication of USP <800> in February 2016 and its effective date in 2019, allowing pharmacies and other facilities to obtain budget approvals.²⁷ Some foresee the potential for organizations with multiple campuses to consolidate compounding of hazardous drugs to fewer locations, and the potential for smaller pharmacies to begin outsourcing hazardous drug compounding because of high costs or limited space for facility redesign and upgrading. This is likely to have broad impact, as noted by a survey of hospital pharmacies published in 2018 that found 80% of facilities prepare hazardous drugs, yet fewer than 10% were compliant with USP <800>.²⁸

Because Chapter <800> governs all steps of hazardous drug handling, areas outside compounding spaces are also affected.⁸ Designated areas are also required for receipt, unpacking, and storage of hazardous drugs. Receipt and unpacking must occur in an area that is neutral/normal or negative pressure, rather than the positive pressure ante-rooms leading into negative pressure cleanrooms where

unpacking may have previously occurred.^{8,15} In addition, antineoplastic hazardous drugs must be stored in negative pressure rooms, and if necessary, in a dedicated refrigerator. Administration of hazardous drugs will now require supplemental engineering control with a closed system drug-transfer device (CSTD) when the dosage form allows their use. A CSTD is also recommended for use when compounding. Similar to requirements in <797>, Chapter <800> will also require documentation of training and assessment of competencies at least annually for all personnel who handle hazardous drugs.

TJC and CMS Standards

Accrediting bodies have also revised standards related to IV drug delivery. The Joint Commission has issued revised NPSGs effective in 2018.⁷ Among these is the recommendation that continuous infusion heparin should be administered via programmable pumps to provide consistent and accurate dosing.⁷ Another goal involves the prevention of central line-associated bloodstream infections, which would require risk assessments and quality improvement initiatives related to underlying sterile compounding processes. In October 2015, CMS announced that as part of their Conditions of Participation, hospital pharmacies must comply with USP Chapter <797>, which will influence accrediting bodies to inspect for <797> compliance.²²

New Legislation

As mentioned previously, the NECC tragedy triggered the introduction of the DQSA through amendments to the Federal Food, Drug, and Cosmetic Act (FDCA). The DQSA consists of two titles related to drug compounding (Title 1) and drug supply chain security (Title 2).¹⁰⁻¹²

Title 1 of the DQSA formalized the distinction between traditional compounding (ie, that performed pursuant to a prescription or medication order within a prescriber-patient-pharmacist relationship) and compounding performed by outsourcing facilities (ie, that performed in anticipation of customer orders).²⁹ Pharmacies continuing the practice of traditional compounding would fall under a “safe harbor” of Section 503A of the amended FDCA. A 503A compounding facility is regulated by state boards of pharmacy and is exempted from requirements of the FDCA applicable to outsourcing facilities.

Pharmacies may elect to outsource compounding to external entities, and these outsourcing facilities may provide benefits in improving operational efficiency, staffing, quality assurance, and cost control.²⁹ Outsourcing facilities are federally regulated by FDA within the framework of the new Section 503B of the amended FDCA.^{10,12} Outsourcing facilities are not required to be licensed pharmacies or obtain prescriptions for specific patients, and must comply with current good manufacturing practices (cGMP). Facilities governed

by Section 503B voluntarily register with FDA and submit to regular inspections on a risk-based schedule to ensure greater patient safety.

Title 2 of the DQSA, the Drug Supply Chain Security Act (DSCSA), has the goal of protecting consumers from potentially harmful drug products and requires the availability of an electronic system for tracking the pedigree of prescription medications by documenting information pertaining to each change in ownership of a drug.^{12,30} This “track and trace” provision of the DSCSA will allow FDA to improve detection and removal of potentially unsafe products from the distribution supply chain.³¹ Although not specifically intended to impact IV medications, its provisions will nonetheless be applicable to IV products and is intended to improve their safety along the supply chain.

Recommended Best Practices

Several organizations have recently proposed best practices to improve the safety of IV drug delivery. In 2014, the Institute for Safe Medication Practices (ISMP) launched the Targeted Medication Safety Best Practices for Hospitals initiative.³² This initiative intended to identify and encourage national adoption of best practices for serious medication safety issues, some of which apply to safety of IV drug delivery. In its 2018-2019 revision, ISMP recommends that the process of verifying the accuracy of CSPs be assisted by the use of technology (eg, barcode and gravimetric verification of ingredients); use of the “syringe pull-back method” is discouraged.³³

Similarly, the ASHP proposed the Standardize for Safety (S4S) initiative.¹⁴ This initiative is rooted in the problem that no national consensus exists for standard concentrations of IV medications, which presents potential for error upon transitions in care. Specific to IV drug delivery, the S4S initiative offers recommendations for concentrations and dosing units for intermittent and continuous IV medications in adult and pediatric patients, as well as for patient-controlled analgesia and epidural medications. Notably, one of the guiding principles in the S4S panel deliberations was a decision matrix tool that placed high priority on the use of commercially available products whenever possible to take advantage of the greater safety provided by cGMP conditions of manufacturing facilities.

Last, the Board of Pharmacy Specialties in 2018 announced it will begin offering specialist credentialing for CSP pharmacists to validate their knowledge and skills in this practice area.³⁴ The goal of specialist credentialing is to ensure patient safety and improve therapeutic outcomes. The introduction of the CSP Pharmacy Specialty reflects the Board’s commitment to accountability for the care delivered to patients, given the risk of improperly prepared CSPs. In the future, specialist credentialing may place greater emphasis on board certification of compounding pharmacists.

IV Workflow Automation Technologies

Traditionally, verification of CSPs has relied on highly manual processes, including calculations, visual inspection of source ingredients and their quantities (eg, via the syringe pull-back method), and manual inspection of final products.^{17,35} Potential for human error in these safety gaps could be addressed by IV automation technologies of fully robotic compounding or IV WMSs.¹⁷ These technologies offer automated calculations, image capturing, barcode scanning, and gravimetric analysis of CSPs. In addition to improving safety, these features may also help decrease waste and improve operational efficiency.

Automation technologies offer the potential to meet some requirements of new regulations discussed above.^{17,35} For example, the ability of IV WMSs to document all steps in the compounding process may help pharmacies meet provisions of DSCSA regarding traceability. Furthermore, robotic compounding may help reduce employee exposure to hazardous drugs, thereby facilitating compliance with provisions of USP <800>. Best practice recommendations from ISMP to utilize technology in CSP verification could also be met through replacement of the syringe pull-back method with image capture and barcode and gravimetric verification.

A 2017 survey on the state of pharmacy automation identified a trend toward increasing adoption of IV automation technologies, particularly among larger institutions.¹⁶ Nonetheless, adoption of these technologies faces barriers related to cost, integration into current workflows, and interoperability with electronic health records.¹⁷ Recommended considerations for evaluating these technologies have been proposed by ASHP, which may serve as a guide to pharmacies considering their adoption.¹⁷ In addition, an international panel of pharmacy and technology leaders in IV robotics prepared consensus recommendations to better understand the role and implementation of automated IV compounding in health-systems and for their implementation.³⁶

Drug Shortages

Drug shortages are an ever-present clinical threat influencing drug therapy and safety, and their effects on IV drug delivery have recently been highlighted. In 2017, a hurricane led to interrupted supply of SVPs from a major manufacturer and a nationwide shortage of saline and dextrose SVPs ensued.³⁷ Without the ability to dilute IV drugs in larger volumes for infusion, many turned to IV push administration of some drugs to conserve SVPs.^{37,38} This presented risk for adverse outcomes because IV push administration is associated with a higher error rate than other routes of IV administration.³⁹

In recent years, at least 9 organizations provided recommendations for IV push drug administration.⁴⁰ Most notable among these may be 2015 guidances from ISMP.¹⁹ In addition, guidances for management of the SVP shortage were

published in 2017 by ASHP.²⁰ Both ISMP and ASHP recommended providing IV push medications in a ready-to-administer form whenever possible to minimize need for manipulation outside of sterile compounding areas. The ASHP guidance also recommended availability of policies, guidelines, and staff training related to IV push administration, and ISMP recommended barcode scanning prior to administration. The ASHP also released a 2018 revision of its guideline on managing drug shortages, which recommends considering administration processes when making decisions in managing a shortage.¹⁸

Summary

Since the most recent Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems in 2009, important changes continue to occur. Regulatory changes include the revision of USP Chapter <797> and the introduction of Chapter <800>, both of which will require significant investments in sterile compounding workflow, personnel training, documentation, and potentially facility design in the preparation of CSPs and handling of hazardous drugs. In addition, the DQSA introduced 503B outsourcing facilities that prepare CSPs under cGMP conditions, and may influence pharmacies' decisions regarding outsourcing and insourcing CSP preparation. Other efforts to promote best practices include revisions to TJC NPSGs, CMS conditions for participation, recognition of CSP Pharmacy as a board-certified specialty practice area, and initiatives from ISMP and ASHP to improve accuracy of CSPs and streamline standard concentrations of IV medications. Shortages of IV drugs will continue to influence aspects of IV drug delivery, especially those drugs that are amenable to IV push administration. Expanding availability and adoption of IV workflow automation technologies presents opportunity to achieve compliance with new recommendations while improving patient safety and operational efficiency.

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