Third Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems—2018

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Purpose. The Third Consensus Conference on the Safety of Intravenous Drug Delivery Systems was convened to evaluate the benefits and risks of available systems and assess ongoing threats to the safety of intravenous drug delivery.

Summary. The Third Consensus Conference on the Safety of Intravenous Drug Delivery Systems convened in Chicago, Illinois in November 2018. An expert panel of healthcare providers with experience in medication quality and safety, pharmacy and nursing operations, information technology, and/or sterile compounding led the conference. An experienced audience of approximately 30 healthcare leaders provided feedback to the panel via preconference survey and during the conference. Additionally, expert speakers presented on a range of issues, including the effects of drug shortages, the impact of standards and guidelines, and patient and administrator perspectives on the importance of intravenous drug delivery safety.

Conclusion. At the end of the conference, the expert panel concluded that manufacturer ready-to-use products remain the safest intravenous drug delivery system due to their many benefits and low overall risk profile. The panel identified various ongoing threats to the safety of intravenous drug delivery, with major concerns including the impact of drug shortages and lack of intravenous product standardization. Finally, the panel agreed upon a series of statements designed to advance the safety of intravenous drug delivery in healthcare institutions.

Keywords: drug administration, drug compounding, drug safety, intravenous infusion, pharmacy administration

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In November 2018, the Third Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems convened in Chicago, Illinois (https://ivconference.uic.edu/). This conference brought together experts to review current standards, guidelines, and regulations; discuss the impact of medication errors and drug shortages; and update best practices with regard to the safety of intravenous (i.v.) drug delivery. The inaugural Consensus Development Conference convened in 1999 and evaluated the relative safety and cost of 6 i.v. drug delivery systems.[1] These systems included manufacturer-prepared, pharmacy-based i.v. admixture, point-of-care-activated, direct i.v. administration (i.e., i.v. push), augmented i.v. push, and volume control chambers. Conference participants used a decision-analysis methodology to rank the systems based on the following 4 domains: safety, cost, simplicity of use, and education or training requirements. Based on this ranking, manufacturer-prepared, point-of-care-activated, and pharmacy-based i.v. admixture systems received higher overall scores, with manufacturer-prepared products determined to be the safest option due to continuous quality assurance during the production process. However, the experts noted the need to have a variety of drug delivery systems due to the lack of consistent availability of preferred systems.

The Second Consensus Development Conference occurred approximately 10 years later in 2008.[2] Since the initial conference, conference attendees noted few advances in i.v. drug delivery system availability; however, significant changes in guidelines and standards governing their use were developed and implemented. These included revisions to *United States Pharmacopeia (USP)* chapter 797 on compounded sterile preparations (CSPs), Joint Commission medication management standards, and Centers for Medicare and Medicaid Services rules on hospital-acquired conditions. The Second Consensus Conference had a 2-fold purpose, as follows: to reassess and prioritize the safety and cost of 5 i.v. drug delivery systems (i.e., manufacturer ready to use, outsourced ready to use, point-of-care activated, pharmacy compounded, and nonpharmacy compounded at point of care) and to review changes in the practical use of these systems in light of changing market and operational forces.

An expert panel developed a decision matrix that scored the 5 i.v. drug delivery systems within the following 6 separate domains: applicability, ease of use, regulatory compliance, cost, safety, and implementation.[2] Similar to results from the initial conference, manufacturer ready-to-use products received the best scores across all domains, with the exception of applicability, as conference participants felt that manufacturer offerings were not nearly broad enough and were especially lacking for special populations, such as pediatrics and neonates. The expert panel also scored outsourced ready-to-use products high in most domains, and these products were the second most favorable type of i.v. drug delivery system. This was followed by point-of-care-activated, pharmacy-compounded, and nonpharmacy-compounded at point-of-care systems. The nonpharmacy-compounded at point-of-care system received the lowest overall scores due to concerns regarding safety and regulatory compliance. The expert panel also remarked that the complexity of i.v. medication delivery had increased, and no currently available single system met all needs and situations.

Since the 2008 Second Consensus Development Conference, the landscape related to i.v. drug delivery continued to evolve significantly, highlighting the need to organize a third conference. Perhaps the most significant regulatory change was enactment of the Drug Quality and Security Act following the 2012 multistate outbreak of fungal meningitis and other infections due to contaminated steroid injections produced by the New England Compounding Center (NECC).[3] The passage of the Drug Quality and Security Act reflected a new national emphasis on safety with regard to CSPs and stressed the critical nature of ensuring the integrity of the drug supply chain.[3,4] Other notable changes included proposed revisions to *USP* chapter 797 and modifications to the Joint Commission National Patient Safety Goals, as well as the creation of *USP* chapter 800 on handling hazardous drugs in healthcare settings.[5–7] Additionally, the American Society of Health-System Pharmacists (ASHP), through funding provided by the Food and Drug Administration, initiated the first national, interprofessional effort to standardize i.v. medication concentrations through the Standardize 4 Safety initiative in order to reduce i.v. medication errors and improve transitions of care.[8] Beyond these regulatory and standardization initiatives, the expansion of the availability and adoption of i.v. workflow automation technologies in the last decade, including i.v. workflow management systems and robotic compounding, offer institutions the potential to further improve the safety and electronic traceability of CSPs although barriers in funding and adoption have been challenging.[9] Last, clinical challenges related to drug shortages expanded significantly since the Second Consensus Development Conference, as highlighted by recent shortages of small-volume parenteral (SVP) solutions, which resulted in many institutions switching to the delivery of medications via i.v. push.[10]

Conference format

Similarly to the first and second conferences, the Third Consensus Development Conference used the National Institutes of Health consensus development process.[11] This process is intended to build consensus on a controversial healthcare-related issue through an evaluation of the scientific literature resulting in the development of a consensus statement that advances the understanding of the topic. For the Third Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems, the planning committee from the University of Illinois at Chicago College of Pharmacy initially met with the Chair of the expert panel in May 2018 in order to determine appropriate topics for the conference agenda. In the following month, the Chair and planning committee identified and invited potential expert panel members and conference speakers, including representatives from The Joint Commission, ASHP, and the Institute for Safe Medication Practices (ISMP). Expert panel members were chosen based on their experience with medication quality and safety, pharmacy and nursing operations, information technology, and/or sterile compounding. Additionally, the planning committee, with input from expert panel members, assembled an experienced audience of approximately 30 healthcare leaders to provide feedback to the panel during the conference. These practitioners represented a variety of practice settings (e.g., urban and rural hospitals, major health systems, and pediatric hospitals) and primarily practiced in areas related to medication quality and safety, medication use policy, or healthcare administration. A white paper, "The Safety of Intravenous Drug Delivery Systems: Update on Current Issues Since the 2009 Consensus Development Conference," was published and distributed to the expert panel in September 2018 as an assessment of the current issues related to

i.v. drug delivery systems.[9] The panel members reviewed the paper and subsequently developed a 20-question premeeting survey, which was sent to all registered conference attendees on September 25, 2018. In the survey, conference attendees were asked to note the level of agreement with a wide range of statements related to current issues associated with i.v. drug delivery. Twelve of the statements presented in this preconference survey were adapted from a survey of audience members in the Second Consensus Development Conference, affording the opportunity to compare results between 2008 and 2018. The remaining 12 statements were original to the 2018 conference. The consensus conference was supported by an unrestricted educational grant from Fresenius Kabi LLC; however, the company was not involved in planning or executing the conference.

Conference summary

The Chairperson commenced the conference by reviewing the results from the preconference survey. Table 1 summarizes the statements presented and the responses submitted, comparing participants in the 2008 and 2018 conferences. Table 2 summarizes conference participant responses to original statements that were developed by the expert panel specifically for the 2018 conference. Overall, preconference survey respondents suggested that i.v. admixture use is safer today than it was 5 years ago. This may be due to a variety of factors, including an ongoing uptake in technology (e.g., barcoding and smart pumps), the increasing use of premixed, ready-to-use products, and the implementation of safety standards with regard to manually compounded admixtures (e.g., *USP* chapter 797). Since the 2008 conference, attendees also identified 2 major issues, outsourcing and drug shortages, that have significantly impacted the safety of i.v. drug delivery systems. Following the NECC tragedy, many healthcare institutions reassessed their use of outsourced compounding facilities with some institutions building their own facilities and others expending resources to perform comprehensive site visits in order to determine an appropriate outsourcing vendor.[12] In addition, the impact of drug shortages could not be understated by attendees, with numerous respondents (25 of 31 [81%]) reporting a patient safety event related to a supply disruption. This percentage was much higher than the 21% of respondents who were aware of the occurrence of at least one medication error related to a drug shortage in the 2017 ISMP national survey on drug shortages.[13]

Following review of the preconference survey results, expert speakers presented on a range of issues that influence the safety of i.v. drug delivery systems. Topics included the impact of an i.v. medication-related error from the perspective of a patient affected by NECC, a viewpoint on the importance of medication safety from the hospital administrator perspective, infection control and contamination considerations, and the substantial effect drug shortages have on using safe i.v. drug delivery systems in healthcare institutions. Additionally, the expert panel and conference attendees listened to presentations on relevant pharmacy standards and guidelines since 2008 and their effect on current i.v. drug delivery systems from the Joint Commission, ASHP, and ISMP, as well as an updated overview of *USP* chapter 797 and results from the 2018 *USP* chapter 797 hospital compliance study. Finally, the Chief Pharmacy Officer (CPO) from Massachusetts General Hospital gave a presentation on the various i.v. drug delivery systems (manufacturer ready to use, outsourced ready to use, point-of-care activated, pharmacy compounded, and nonpharmacy compounded at point-of-care) and a perspective on their regulatory, quality, safety, operational, and staffing benefits and concerns (Appendix A). Prior to being the CPO at Massachusetts General, the speaker was the Assistant Director of Pharmacy for Support and Operating Room Services at the Medical University of South Carolina (MUSC) Medical Center. He also participated extensively in national pharmacy initiatives and organizations, including the ASHP/ASHP Foundation's Pharmacy Practice Model Initiative Summit, the ASHP Council on Public Policy, and the Vizient AMC Pharmacy Network Executive Committee. Specific comments were made regarding the need for institutions to work towards a better understanding of the various factors that contribute to the cost-effectiveness of safe i.v. drug delivery. After the presentations, a facilitated discussion session occurred where conference attendees provided comments to the expert panel and then the panel was sequestered to write the consensus conference draft statements.

Findings from the panel

During the sequestration, panel members originally scored the 5 i.v. drug delivery systems within the 6 separate domains, similar to the Second Consensus Development Conference. This ranking reaffirmed the overall superiority of manufacturer ready-to-use products as the safest i.v. drug delivery systems, followed by outsourced ready-to-use, pharmacy compounded, point-of-care activated, and nonpharmacy compounded at point of care. However, the panel then discussed a different approach to evaluating these systems based on the presentations and comments received during the conference. Since the majority of the conference discussion appeared to focus on threats to the safety of i.v. drug delivery systems, the panel identified 8 "threats" and then ranked their severity from 1 (highest threat) to 8 (lowest threat) (Appendix B). Overall, the expert panel scored drug shortages and lack of standardization as being the 2 most significant threats. These were followed by a lack of uptake of automation and technology proven to improve safety and the absence of appropriate education and training for pharmacists, pharmacy technicians, and other healthcare providers involved in i.v. drug delivery. Less impactful threats included the lack of taking appropriate

Table 1. Comparison of the 2018 Preconference Survey and 2008 Conference Survey Results[a]

Statement	No. (%) Who Agree in: 2008[a]	2018 (*n* = 31)
Intravenous admixture use in health systems is safer today than it was 5 yr ago.	38/50 (76)	28 (90)
USP Chapter <797> has improved the safety of manually compounded admixtures.	29/50 (58)	27 (87)
The majority of US hospitals have standardized all possible i.v. admixture concentrations.	10/50 (20)	8 (26)
Health systems today maximize their use of premixed, point-of-care-activated, and ready-to-use products.	24/49 (49)	16 (52)
Smart pumps have improved the safety of i.v. drug administration at my facility.	38/50 (76)	30 (97)
Outsourcing i.v. admixtures is a safe practice.	29/51 (57)	20 (65)
Outsourcing i.v. admixtures is cost-effective.	29/49 (59)	14 (45)
My hospital uses barcode patient verification technology for the administration of i.v. products.	19/50 (38)	31 (100)

[a]For the 2008 Consensus Development Conference, the survey was conducted on site at the initiation of the conference using an audience response polling system; therefore, the number of respondents for each statement was not consistent. These are shown along with the number of those who agreed with each statement.

Table 2. Results from Preconference Survey Statements Specific to the 2018 Conference

Statement	No. (%) Who Agree in 2018 (*n* = 31)
My hospital has experienced a disruption of supply from manufacturers or outsourced (503B) compounding entities.	30 (97)
My hospital is preparing for the updated revisions of USP scheduled to be released in December 2019.	29 (94)
Although i.v. infusion pumps are consistently used, transitions of care may result in the use of alternative pumps. This transition can result in medication errors.	25 (81)
My hospital has experienced a patient safety event related to a supply disruption.	25 (81)
In the past 5 yr, my hospital administrators have been more willing to provide financial support for cleanroom changes.	23 (74)
My hospital has shifted to using more i.v. push and less i.v. piggyback for intermittent i.v. medications.	22 (71)
My hospital evaluates error reduction alerts regularly and determines if staff are responding to them appropriately.	21 (68)
My hospital does a comprehensive review and site visit of an outsourcing company as part of our due diligence when choosing a vendor.	20 (65)
My hospital has a proactive system in place to identify and mitigate diversion of i.v. products.	11 (35)
My hospital uses an automated i.v. workflow management system to improve the safety and efficiency of the medication use process.	11 (35)
My institution consistently uses electronic health record operability to interface between the i.v. pump and the electronic health record.	6 (19)
The majority of US hospitals have a complete understanding of the various factors that contribute to the cost-effectiveness of delivering safe i.v. admixtures to patients (i.e., product and staffing waste).	0 (0)

actions on data collected regarding i.v. drug delivery through various information technologies (e.g., computerized physician order entry and i.v. medication workflow systems), the evolving and complicated CSP regulatory landscape, the financial costs associated with improving safety, and the lack of information technology

interoperability (i.e., various systems within an institution may not "work" together effectively to improve safety).

The panel concluded that drug shortages in particular are not only a highly significant threat to patient safety, but they are also a threat to the consistent use of the safest i.v. drug delivery system. Of all reported shortages through September 30, 2018 (n = 137), 56% involved injectable medications.[14] The rate of new shortages continues to increase and involves many essential medications (e.g., bupivacaine, lidocaine, morphine, saline, and sterile water) that severely impact patient care as well as pharmacy operations. The inability to acquire manufacturer ready-to-use products due to shortages may result in medication errors and patient harm,[13] as healthcare institutions are required to use less-safe i.v. drug delivery systems. The lack of standardization was also highly ranked by the panel as a threat to the safety of i.v. drug delivery systems. Variations in i.v. medication concentrations during transitions of care within the same institution or between different facilities can increase the likelihood of a medication error.[15] Additionally, a requirement to compound patient-specific preparations leading to the calculation of custom infusion rates may also lead to harm. The lack of agreement regarding standard concentrations for widely used i.v. medications may result in healthcare institutions increasing the amount of pharmacy-compounded products and thereby increase quality and safety concerns.

Within this context, the panel developed a series of overarching statements regarding i.v. drug delivery safety. These statements include the following: (1) Healthcare institutions should promote a culture of i.v. drug delivery safety across all sites of care that is patient-centric and proactive. (2) Organizational leadership is accountable for ensuring the highest level of safety regarding i.v. drug delivery systems. (3) Manufacturer-prepared products are the safest i.v. drug delivery system, and manufacturer-prepared, ready-to-administer products are preferred for patient use whenever possible. (4) Compounding sterile preparations is a high-risk practice, and incorporating established standards, such as *USP* chapter 797, is essential to ensure benefit while reducing risks to the patient. (5) All nonpharmacy compounding should be restricted to only immediate-use, urgent situations. (6) Specialized education, training, certification, and competency with regard to compounding of sterile preparations should be required for pharmacists, pharmacy technicians, and other involved healthcare providers. (7) Automation and technology that have been validated to improve the safety of CSPs should be implemented. (8) The profession of pharmacy must take the lead in interdisciplinary efforts for the safety of i.v. drug delivery systems. (9) A legislative and regulatory framework that supports and encourages i.v. medication safety in all settings (e.g., physician offices) should be developed. Finally, (10) the organizational costs of inaction, or of pursuing the minimum action necessary with regard to the safety of i.v. drug delivery, far exceed an institutional financial investment in the safest systems for the patient and staff.

Conclusion

The purpose of the Third Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems was to assess the benefits and concerns of the available i.v. drug delivery systems and to examine ongoing threats to the safety of i.v. drug delivery. After reviewing relevant presentations and receiving input from conference invitees, the panel reaffirmed that manufacturer ready-to-use products remain the safest i.v. drug delivery system. Additionally, the panel concluded that drug shortages and lack of standardization are the 2 most significant threats to patient safety. Finally, the expert panel developed a series of statements designed to advance i.v. drug delivery safety in healthcare institutions.

Disclosures

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Appendix A—Benefits and concerns of available i.v. drug delivery systems

I. Manufacturer ready to use
   a. Benefits
      i. Low risk for contamination
      ii. Provides a dose-specific, ready-to-administer form for rapid operational and patient use
      iii. Consistently of high quality and produced using current good manufacturing practices
      iv. Meets regulatory requirements
      v. Maximizes available expiration dating
      vi. May enable an institution to reallocate workload and resources
   b. Concerns
      i. Shortages can impact use
      ii. Products not necessarily available for special populations (e.g., pediatrics)
      iii. Acquisition costs
      iv. Ready-to-use frozen products may require thawing/storage space

II. Outsourced ready to use
   a. Benefits
      i. Provides a customized, ready-to-administer dose for each patient
      ii. Potential alternative in manufacturer drug shortage situations
      iii. Generally low risk for contamination, with consistent sterile compounding services, including extended beyond-use dating
      iv. May enable an institution to reallocate workload and resources
   b. Concerns
      i. Although there is a low risk of contamination with these products, healthcare institutions should inspect outsourcing facilities with regard to appropriate sterile compounding processes
      ii. Financial costs
      iii. Requires advanced planning to effectively integrate into the medication use process (e.g., ordering, stocking, and distribution)

III. Point-of-care activated
   a. Benefits
      i. Integrates well with automated cabinets
      ii. Maximizes available expiration dating
      iii. Ease of use
   b. Concerns
      i. Risk of inactivation errors
      ii. Products not necessarily available for special populations (e.g., pediatrics)

IV. Pharmacy compounded
   a. Benefits
      i. Can customize dose for each patient
      ii. Doses are labeled in accordance with institutional standards
      iii. Direct control over quality assurance to minimize contamination risk and personnel hiring to safeguard staff competence
   b. Concerns
      i. Complexity of compounded preparations and continued use of syringe pull-back method
      ii. Inconsistent/nonexistent standard operating procedures for workforce training
      iii. Staffing shortages
      iv. Space limitations
      v. Need to meet regulatory requirements/competencies

V. Nonpharmacy-compounded point of care
   a. Benefits
      i. Immediate availability of a customized dose for each patient
   b. Concerns
      i. High potential for error
      ii. Low compliance with regulatory requirements
      iii. Inadequate or absent labeling
      iv. Contamination risk

Appendix B—Ranking of threats to the safety of i.v. drug delivery systems from high to low

I. Drug shortages
II. Absence of standardization (e.g., lack of standard i.v. medication concentrations)
III. Lack of uptake of automation and technology proven to improve the safety of i.v. medications
IV. Absence of appropriate education and training for pharmacists, technicians, and other healthcare providers involved in i.v. drug delivery
V. Lack of appropriate action on data collected regarding i.v. drug delivery
VI. Complex regulatory landscape
VII. Financial costs
VIII. Lack of information technology interoperability