How the selection of an IV dose form can impact medication safety at your institution

Part 3 of a multi-article series as we explore how premixed IV products can positively impact your pharmacy operations.

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Introduction

Medication safety for intravenous (IV) products has been under extreme scrutiny primarily due to numerous reports of tainted products from large pharmacy compounders, such as contaminated steroids from the New England Compounding Center (NECC)[1], which caused significant patient harm. Other large 503B companies have closed operations in recent years, presumably due to increased oversight by regulatory agencies and high potential for litigation. In the hospital setting, IV compounding remains one of the highest risk processes for pharmacy leaders to oversee, due to its complexity as well as the strict regulatory guidelines that must be routinely measured and achieved to continue operations. In this article, we will discuss how the decision to utilize a specific IV dose form will impact medication safety throughout your healthcare system.

Expert and Regulatory Guidance

Before we review the specifics around IV compounding safety, let's review the guidance from our medication expert groups and regulatory agencies.

The Institute for Safe Medication Practices (ISMP) represents the global gold standard for medication safety information. Their multi-disciplinary team of experts often work with leaders across the nation to develop consensus guidelines for a variety of medication safety related topics. One of their medication safety summits focused on compounded sterile products where a guidance document named, ISMP Guidelines for Safe Preparation of Compounded Sterile Preparations (2016)[2] was developed. In this guidance document, the expert team has recommended the following:

> **To the maximum extent possible, COMMERCIALLY-PREPARED, premixed parenteral products and unit dose syringes are used versus manually compounded sterile products.**

To summarize this statement, ISMP recommends that organizations use IV products prepared by FDA-approved pharmaceutical companies which follow current good manufacturing practice (cGMP) whenever possible, rather than organizations compounding products themselves and/or outsourcing production to a compounding pharmacy.

The American Society of Health-System Pharmacists (ASHP) is the largest group of health-system pharmacists in the United States and they often create policies and guidelines on recommended best practices. In 2018, they created the document titled, ASHP Guidelines on Preventing Medication Errors in Hospitals[3]. In this document, the following statements were made in regards to IV products:

> **Standardization may help avoid error-prone calculations, reduce waste, streamline inventory, and facilitate the use of premixed i.v. solutions.**
>
> **Whenever possible, medications should be available for inpatient use in unit-of-use and ready-to-administer packaging without further manipulation by the person administering the medication.**

While the ASHP document is focused on both non-sterile and sterile dosage forms, the guidance is clear that premixed IV solutions are preferred as well as products that are ready-to-administer without any additional manipulation.

The Centers for Medicare and Medicaid Services (CMS) is the largest healthcare payer in the United States. CMS publishes a State Operations Manual (SOM) which provides regulations and interpretive guidance for hospitals[4]. In the current SOM, CMS recommends that "whenever possible, medications are dispensed in the most ready to administer form available from the manufacturer…"

CMS allows for several agencies to perform accreditation for hospital facilities. One of the most well-known accreditation agency is The Joint Commission (TJC). TJC standards are often aligned with the standards set forth in the CMS SOM. In a sentinel event about high-alert medications published by TJC in 1999, TJC recommends using commercially available premixed IV formulations of high-alert medications (e.g., heparin, dopamine etc.) to prevent errors[5].

ISMP, ASHP, CMS, and TJC are consistent in their recommendation for the use of commercially-prepared, premixed IV products to decrease medication errors. The rationale for the preference of premixed products is due to the complexity of the IV compounding process, thereby mitigating error potential and improving medication safety.

IV Compounding in the Pharmacy

Table 1 outlines various dosage forms that are available for IV medications, including ready-to-administer (RTA), various ready-to-use (RTU) products as well as compounded sterile products (CSPs).

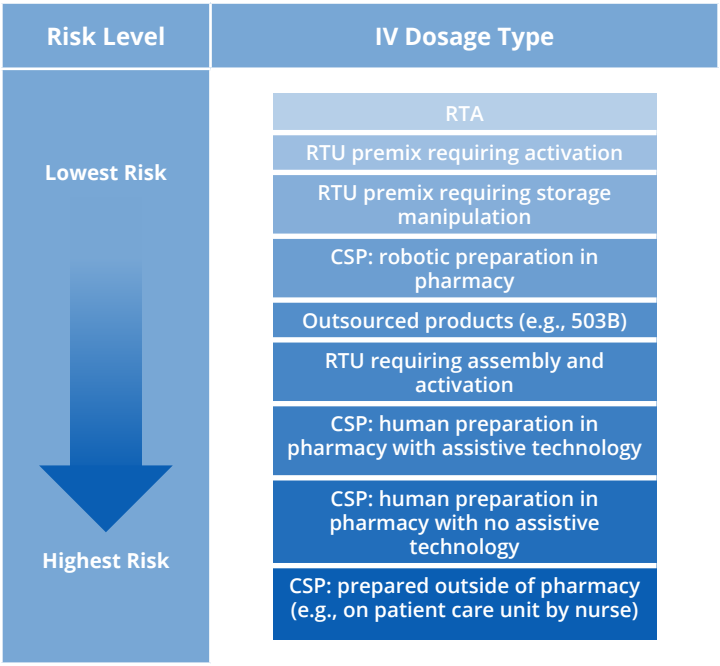
Table 1.

Dose Type	Meaning	Description
RTA	ready-to-administer	Premixed from manufacturer and can be administered without any further manipulation
RTU	ready-to-use	Premixed product requires activation prior to use or Premixed product requires thawing or some type of storage manipulation prior to use or Product requires both assembly and activation prior to use
CSP	compounded sterile product	Sterile product that is prepared using component ingredients by a qualified individual or device in a sterile environment Preparation options include: – Robotic preparation – Human preparation with assistive technology – Human preparation without assistive technology

IV Compounding in the Pharmacy (cont.)

The risk stratification that the author has estimated for various IV products and compounding procedures, which takes into account potential for error is shown in Image 1. The stratification is based on the number of steps involved in the process as well as the incorporation of automation to mitigate error. The lowest risk process is the commercially-prepared ready-to-administer (RTA) product that does not need to be compounded or manipulated prior to administration. Whenever compounding is required, in any fashion, the potential for error increases significantly due to the complexity of the process.

Image 1. Risk stratification for various IV products, which takes into account potential for error (e.g., contamination, preparation error etc.)



RTA: ready-to administer
RTU: ready-to-use
CSP: compounded sterile product

For manual IV compounding, Flynn et al.[6] performed an observational study which reviewed compounding accuracy at 5 different hospitals. The results showed the mean error rate for the combined hospitals was 9% (145 errors from 1679 doses). The study also indicated that 2 errors for each 100 errors were judged to be clinically significant, which would represent 0.18% of the doses. These estimates are in-line with other studies that estimate error rates for manual IV compounding ranging from 5% to 15%[7,8,9,10]. While these percentages may seem small, keep in mind that large institutions routinely compound > 1,000 doses in one day, making the number of clinically significant errors each day substantial. In contrast, the same study indicated the error rate for premixed IV products was < 1% (2 errors from 746 doses)[7], which provides objective evidence that premixed products are inherently safer than products prepared using a complex manual compounding process.

By incorporating technology into the IV compounding process, such as an IV workflow system which leverages automation in the form of bar code scanning, image capture, and standardized work flow, the identification of errors becomes more apparent during the compounding process, thus making the process safer than a corresponding manual process. The author's experience with a commonly used IV workflow system has identified errors for ~4.7% of doses, which is consistent with the nationwide average with the same IV workflow system. While an IV workflow system is not foolproof, it greatly enhances the safety as compared to a manual compounding process by making errors more visible[11,12].

Contemporary robotic solutions take IV workflow automation one-step further by removing human intervention during the complex compounding process. Robotics continue to improve their throughput and become smaller in size, often allowing for devices to be retrofitted into existing IV cleanrooms. Manual efforts are still required to both load and unload the device, however the robot performs the critical compounding steps and often uses bar code scanning, image capture, and gravimetrics as additional safeguards. Robotics has potential to revolutionize IV compounding as the technology continues to improve and evolve.

IV Compounding outside the Pharmacy

In the United States, the majority of IV compounding occurs in the pharmacy, and a small amount of compounding occurs outside the pharmacy by other healthcare personnel, such as a nurse or anesthesia providers. TJC expects that compounding outside of the pharmacy "is reserved for situations where an immediate/urgent need for medications is present and a delay in waiting for the pharmacy to compound items could delay care and for items with limited stability once compounded."[13]

IV compounding outside of the pharmacy falls under the immediate-use provision in the United States Pharmacopoeia (USP) Chapter 797 (rev. 2008). Immediate-use requires the following criteria to be met:

- compounding to involve the simple transfer of not more than three manufactured packages and not more than two entries into any one container (e.g., 2 vials and 1 IV bag)
- administration begins in 1 hour or less following the start of compounding

In addition, TJC recommends that immediate-use compounding occur in a segregrated compounding area, which can often be difficult to achieve on the nursing unit.

For additional information around IV medication safety, you can check out the THRIV Coalition for IV Accuracy at thrivcoalition.org.

IV Administration

Similar to IV compounding, the process for the administration of IV products is also complex with many opportunities for error to occur. In addition, administration occurs at the end of the medication use process and generally has limited safeguards in place to detect and intercept errors. Common errors include wrong infusion rate, inappropriate timing (too early or late), incompatibility, wrong patient etc. A comprehensive failure mode effects analysis (FMEA) is a tool that can be used to identify the potential for risk at each of the critical steps during IV medication administration[14]. Westbrook et al.[15] identified administration errors occurred 69.7% of the time, with 25.5% of the errors classified as significant. Wrong infusion rate was the most common occurrence.

Many IV administration errors can occur regardless of IV dosage form. However, one differentiating feature that should be highlighted is whether additional action by the nurse, or other healthcare professional, is required prior to administration. Some RTU products require assembly and/or activation prior to being administered. From the author's experience, the activation step can be forgotten, which results in the administration of the diluent alone, without the active medication. Surprisingly, there is limited data in the literature related to the frequency for this type of error.

The time needed for the administration of a first dose is an important factor to consider in certain situations, such as the first antibiotic dose in a patient with sepsis. Typically, urgent medications will be stored in automated dispensing cabinets (ADCs) to expedite the time required from provider order to the time it takes for a nurse to start administering the product. IV dose forms with room temperature stability and longer expiration dates, such as commercially prepared RTA products, are often preferred for ADC storage, thereby making them prime candidates for urgent use.

Expiration Error

Additional pharmacy technician resources may be required to manage product dating in central pharmacy storage locations, but especially for any decentralized inventory located in ADCs. Products stored in ADCs, especially with short dating such as CSPs and certain RTUs, have potential to be administered after their beyond-use date (BUD) if not managed appropriately by pharmacy personnel.

In many healthcare facilities, IV bags are kept in a supply or medication room on the nursing unit. IV bags in a multi-pack (i.e., more than one IV bag in an overwrap) require applying a BUD to each IV bag when the overwrap is removed. Achieving 100% compliance with this practice is often challenging and improper IV bag dating is often scrutinized by accrediting agencies such as TJC. Utilizing single-wrapped RTA products do not require the application of a BUD when removed from an overwrap if they are administered immediately.

503B Pharmacy Compounders

The FDA keeps an up-to-date listing of registered 503B pharmacy compounding facilities in its database[16]. After an FDA inspection occurs, a Form-483 is issued for inspection observations or warnings when quality practices are not in compliance with regulatory standards.

The following data represents information from the FDA 503B compounding registry[16].

Registered 503B compounders:	**69**
Intend to compound from bulk substances:	**58 (84%)**
Were issued a FDA-483:	**53 (77%)**
Not inspected yet:	**12 (17%)**
Inspected and not issued a FDA-483	**4 (6%)**

Even though 77% of 503B compounders had an FDA-483 issued, there were 12 compounders listed that have not been inspected yet, leaving the number of inspected pharmacies with no findings at 4.

The vast majority of 503B compounders (84%) perform high risk compounding by using bulk drug substances, otherwise known as active pharmaceutical ingredients (API), to reduce cost. High risk compounding requires a critical sterilization step, usually in a terminal process, to prevent contamination. Inability to conduct proper sterilization, like what occurred with the New England Compounding Center's (NECC) contaminated steroids, has potential to be disastrous for any downstream patients.

The combination of FDA-483 findings and the widespread use of high-risk compounding makes using a 503B pharmacy compounder a risky proposition for any organization. Appropriate vetting, which includes an on-site visit and completing a comprehensive risk assessment, is generally recommended by organizations to ensure proper 503B compounder selection occurs.

Conclusion

Compounding IV products involves a complex process and has high potential for error, especially when manual efforts are used. Technologies such as IV workflow and robotics are aimed directly at reducing compounding errors, but do not eliminate them completely. However, the use of RTA products will help to minimize compounding errors, help to eliminate administration errors associated with assembly and/or activation and greatly reduce errors associated with product usage past it's compounded beyond use date (BUD). Multiple expert and regulatory groups have clearly prioritized the use of commercially-prepared RTA IV products to improve medication safety. The guidance and data are clear that RTA products have an improved medication safety profile as compared to other IV dosage types.

References

1. https://www.pewtrusts.org/-/media/assets/2019/02/compoundingoutbreaks_chart-feb2019_v1.pdf
2. ISMP Guidelines for Safe Preparation of Compounded Sterile Products, Revised 2016.
3. Molly Billstein-Leber, Pharm.D., BCPS, COL Jorge D. Carrillo, Pharm.D., M.S., M.P.H., BCPS, Angela T. Cassano, Pharm.D., BCPS, FASHP, Kym Moline, Pharm.D., M.S.A., Jennifer J. Robertson, Pharm.D., BCPS, ASHP Guidelines on Preventing Medication Errors in Hospitals, American Journal of Health-System Pharmacy, Volume 75, Issue 19, 1 October 2018, Pages 1493–1517, https://doi.org/10.2146/ajhp170811
4. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_a_hospitals.pdf (Accessed: April 13, 2021)
5. https://www.jointcommission.org/-/media/tjc/documents/resources/patient-safety-topics/sentinel-event/sea_11.pdf (Accessed: April 13, 2021)
6. Fynn EA, Pearson RE, Barker K. Observational study of accuracy in compounding i.v. admixtures at five hospitals. Am J Health-Syst Pharm. 1997;54(8):904-12.
7. Parshuram CS, Dupuis LL, To T, et al. Occurrence and impact of unanticipated variation in intravenous methotrexate dosing. Ann Pharmacother. 2006;40(5):805-811.
8. Anton C, Ferner RE. Medication errors detected in infusions. Arch Intern Med. 2003;163(8):982.
9. Parshuram CS, Ng GY, Ho TK, et al. Discrepancies between ordered and delivered concentrations of opiate infusions in critical care. Crit Care Med. 2003;31(10):2483-2487.
10. Seger AC, Churchill WW, Keohane CA, et al. Impact of robotic antineoplastic preparation on safety, workflow and costs. J Oncol Pract. 2012;8(6):344-349.
11. Yihong Deng, B.S, Alex C. Lin, Ph.D, John Hingl, B.S.Pharm., M.B.A, Guixia Huang, M.S, Mekibib Altaye, Ph.D, Heather Maynard, Pharm.D, Dave Mayhaus, M.S., Pharm.D, Jonathan Penm, Ph.D, Risk factors for i.v. compounding errors when using an automated workflow management system, American Journal of Health-System Pharmacy, Volume 73, Issue 12, 15 June 2016, Pages 887–893, https://doi.org/10.2146/ajhp150278
12. Stephen F Eckel, Pharm.D., MHA, BCPS, Jordyn P Higgins, Pharm.D, Elizabeth Hess, Pharm.D., M.S., FISMP, Thomas Cerbone, B.S.Pharm, Jennifer B Civiello, Pharm.D, Christian Conley, Pharm.D., M.S, Nilofar Jafari, Pharm.D., M.P.H, Shailly Shah, Pharm.D., M.S., BCPS, Stephen L Speth, M.S, Lynn Thornton, Pharm.D., BCPPS, BCPS, CPPS, Multicenter study to evaluate the benefits of technology-assisted workflow on i.v. room efficiency, costs, and safety, American Journal of Health-System Pharmacy, Volume 76, Issue 12, 15 June 2019, Pages 895–901, https://doi.org/10.1093/ajhp/zxz067
13. https://www.jointcommission.org/standards/standard-faqs/critical-access-hospital/medication-management-mm/000002176/ Accessed: 17-May-2021
14. Wayne Adachi, Pharm.D., Amy E. Lodolce, Pharm.D., BCPS, Use of failure mode and effects analysis in improving the safety of i.v. drug administration, American Journal of Health-System Pharmacy, Volume 62, Issue 9, 1 May 2005, Pages 917–920, https://doi.org/10.1093/ajhp/62.9.917
15. Westbrook JI, Rob MI, Woods A, Parry D. Errors in the administration of intravenous medications in hospital and the role of correct procedures and nurse experience. BMJ Qual Saf. 2011 Dec;20(12):1027-34. doi: 10.1136/bmjqs-2011-000089. Epub 2011 Jun 20. PMID: 21690248; PMCID: PMC3228265.
16. https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities Accessed: 17-May-2021