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IV Insulin Infusions: Is Variation the Enemy Of Quality and Safety?

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Situation

A recent discussion in the ASHP listserve about the storage of IV insulin infusions revealed practice variations for the preparation and storage of insulin infusions in US hospitals (ASHP Inpatient Practitioner Community. Refrigerated regular insulin drips. Posted June 6, 2019). Much has been written about IV insulin therapy guidelines, effectiveness, and the risks for patient harm. Do we fully appreciate the operational effect on both pharmacy and nursing? Are there implications for USP General Chapter <797> compliance? Is there a clinical impact associated with turnaround time? What safety measures are used to mitigate the risks for patient harm from this high-alert medication?

We conducted a survey of US hospitals to more fully describe the current state and present the insights in the SBAR (situation, background, assessment, and recommendation) format, which is a familiar model of communication in health care settings.

Background

Intravenous insulin therapy is indicated for many clinical conditions (Table 1).[1] The benefits of the infusion route include the rapid onset of action, the ability to titrate the dose, and the relatively short duration of action. Insulin infusions are accepted as the preferred route of insulin administration in critical care, obstetrics, and perioperative patients, as well as patients receiving total parenteral nutrition. Adding clinical services to the hospital scope of care affects pharmacy services when additional insulin infusions are part of the standard of care.

Table 1. Potential Indications for IV Insulin Therapy

Diabetic ketoacidosis
Hyperglycemic, hyperosmolar state
Critical care illness (medical/surgical)
Post-cardiac surgery
Myocardial infarction or cardiogenic shock
Prolonged NPO status in insulin-deficient patients
Labor and delivery
Uncontrolled hyperglycemia during high-dose glucocorticoid therapy
Perioperative period
Post-organ transplant
Stroke
Total parenteral nutrition therapy
Dose-finding strategy before converting patient to subcutaneous insulin

NPO, nothing by mouth

Source: *Diabetes Spectr.* 2014;27(3):218-223.

Assessment

A 14-question survey was designed to gather information from hospitals across the United States about the volume of insulin infusions and how they are prepared; beyond-use dating (BUD); and how they are dispensed, stored, and wasted. Additional information was requested about the safety measures used to mitigate harm, because insulin is a high-alert medication. The survey invitation was sent to 1,750 pharmacists on a proprietary mailing list.

Responses were received from 79 pharmacists, with 71% reporting as directors of pharmacy. Most (70%) of the hospitals were general acute care facilities. Because the scope of care in a hospital can affect the number of insulin infusions, information was requested about the number of services per hospital. The most common services at the hospitals are critical care and obstetrics, followed by stroke, cardiac surgery, and solid-organ transplantation (Table 2).

Table 2. Respondent Characteristics

Roles	**Hospitals**	**%**
Director of pharmacy	56	71
Pharmacy manager	10	13
Chief pharmacy officer	5	6
Clinical specialist	5	6
Medication safety officer	2	3
Staff pharmacist	1	1
Hospital Size, Beds	**Hospitals**	**%**
≤25	24	30
26-250	23	29
251-500	17	22
>500	15	19
Insulin Infusions Dispensed/Day	**Hospitals**	**%**
0-10	57	74
11-50	20	26

Preparation

The majority of hospitals dispense 0 to 10 insulin infusions per day (74%). The number of insulin infusions per day increases by both the size of the facility and the number of services. Most hospital pharmacies compounded 100% of the insulin infusions. In 17 hospitals the preparation is split between pharmacy and nursing, and all insulin infusions were made by nursing in 3 hospitals. The standard concentration is 1 unit/mL, with a few hospitals reporting a range of concentrations from 0.5 to 10 units/mL, and 1 hospital reported no standard concentrations.

Storage, Dispensing, and BUD

A resounding majority of hospitals prepare and dispense insulin infusions on demand (Figure 1), followed by a mix of both on-demand and batch preparation. Very few facilities store insulin infusions at the point of care (POC)/nursing unit; when stored on the unit, the insulin infusions are refrigerated. Many references are cited for determining the BUD for compounded insulin infusions (Figure 2), and hospitals cited more than 1 reference. USP <797> appears to be the preferred source of truth (75%), given the current emphasis by

Centers for Medicare & Medicaid Services–approved accrediting bodies and enforcement by state boards of pharmacy for the expected FDA compliance on compounding safety and sterility.[2]

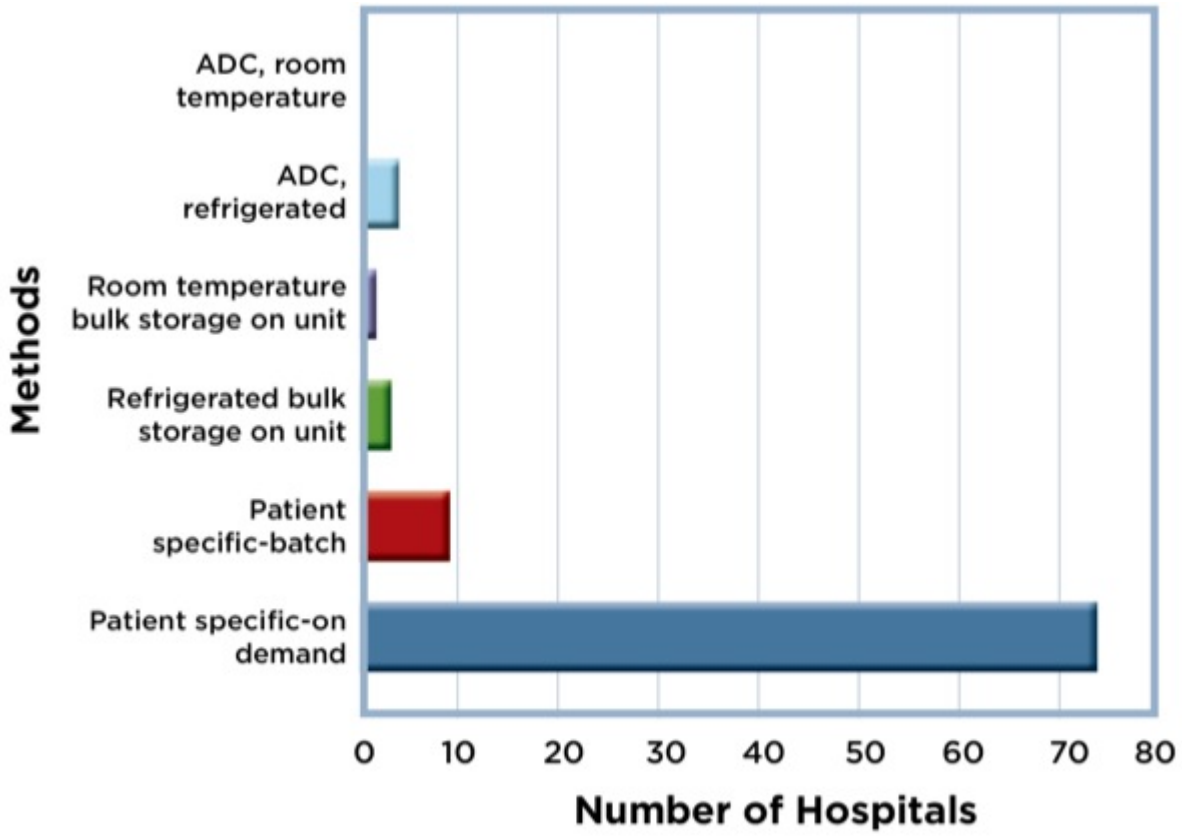

Figure 1. Storage and dispensing.
ADC, automated dispensing cabinet

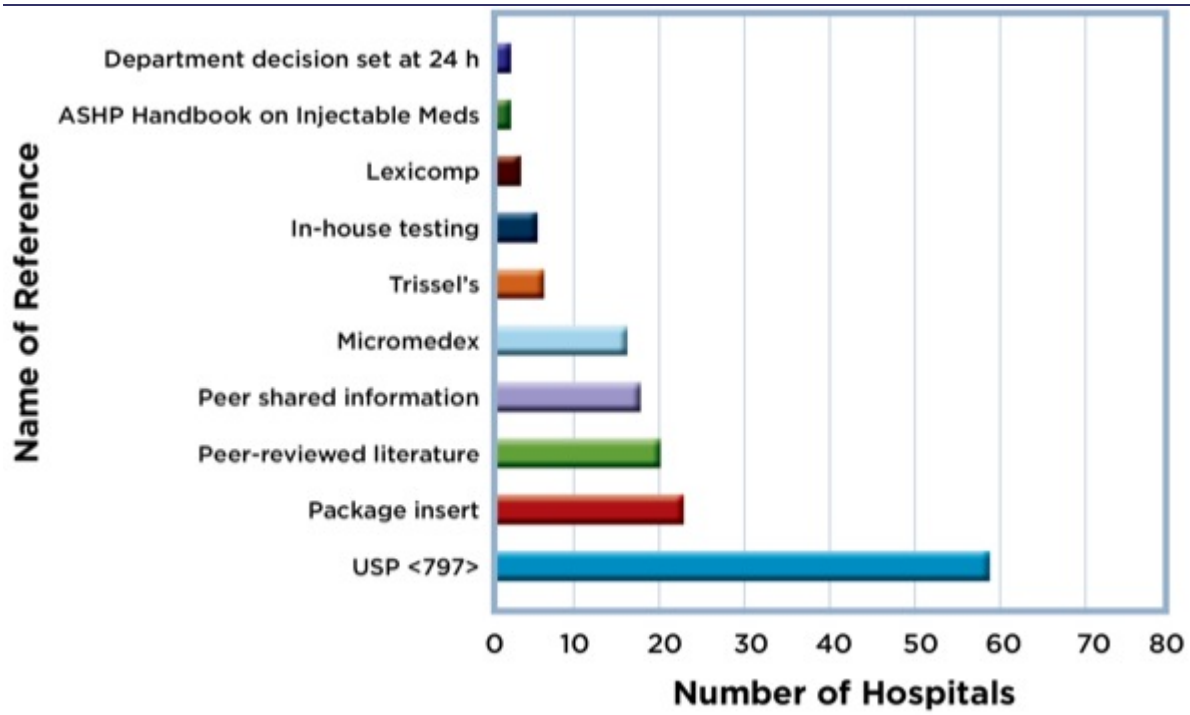

Figure 2. References for BUD.
BUD, beyond-use dating

A wide range of BUDs are assigned that vary by preparation and storage (Figure 3). Room temperature and refrigerated were the two most common storage methods. Most respondents gave a 24-hour BUD (range, 24 hours to 14 days) for room temperature storage. When insulin infusions were refrigerated, respondents cited 24 hours BUD (range, 24 hours to 30 days). Of note, when insulin infusions were prepared as *immediate use*, the responses ranged from 4 hours to 30 days. Very few hospitals freeze insulin infusions, and 1 respondent suggested that "insulin cannot be frozen."

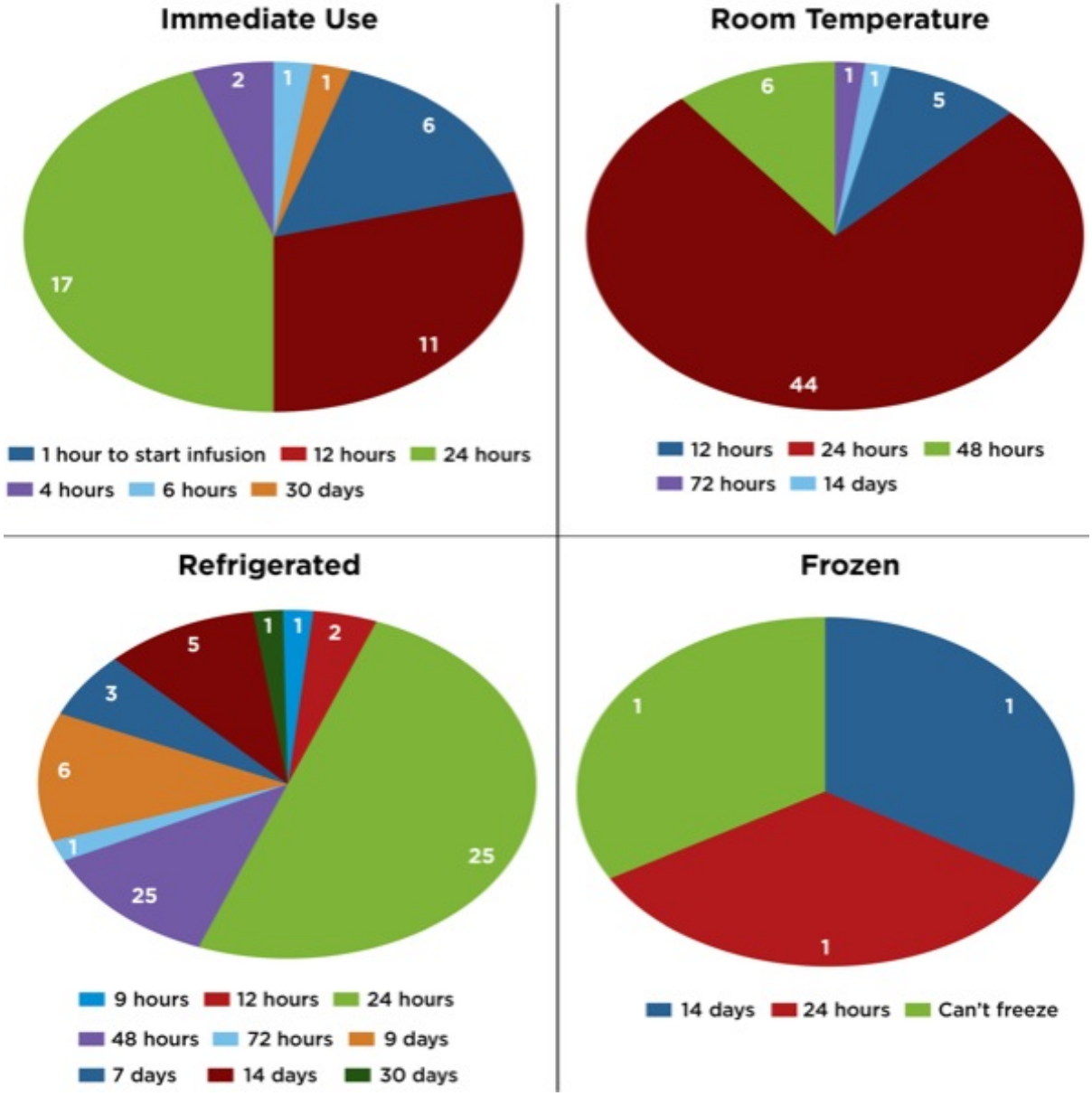

Figure 3. BUD by storage type.

Patient Safety

As defined by the Institute for Safe Medication Practices (ISMP), high-alert medications are drugs that bear a heightened risk for causing significant patient harm when they are used in error.[3] Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients. Intravenous insulin is generally considered a high-alert medication, and several tactics are employed to mitigate

the risk for error and patient harm. Respondents were asked to select all applicable options used by their hospital to improve safety (Table 3). Only 1 standard insulin concentration, use of IV smart pumps, independent nurse double check at the bedside before starting an infusion, patient label applied in the pharmacy, and the use of preestablished order sets were the top 5 tactics reported to mitigate risk. Three other options were offered by the respondents: having another nurse double-check the compounding nurse, the use of a buretrol to limit the risk for overdose, and having the pharmacist verify the IV pump with the nurse.

Table 3. Insulin Safety Measures

Safety Measures	**Hospitals, n**	**%**
Only 1 standard insulin drip concentration product	66	84
Insulin drip must be placed on a smart IV pump for administration	66	84
Independent nurse double check at bedside before starting infusion	56	71
Patient ID label applied in pharmacy	52	66
All insulin drips ordered from preestablished order sets	47	59
Pharmacist must visually verify dose of insulin before injection into IV piggyback	39	49
High-alert medication label applied in pharmacy to bag	39	49
Compounded using IV workflow program using barcode scanning and documentation	20	25
Segregated storage in the pharmacy	20	25
IV-line label placed for insulin drips	20	25
Not available on override from ADC	19	24
Patient ID label applied on nursing unit	10	13
Segregated storage on unit	7	9
Pharmacist verifies smart pump changes before initiation through smart pump to eMAR bidirectional interface	2	3
Other		
Have a second nurse verify when compounding	1	1
Have a buretrol in place	1	1
Pharmacist compounds, labels, dispenses, and verifies pump with nurse	1	1

ADC, automated dispensing cabinet; **eMAR,** electronic medication administration record; **ID,** identification

Waste and Disposal

Respondents were asked to estimate the number of compounded insulin infusion bags that are wasted every day. Hospitals that do anticipatory compounding for insulin infusions may be particularly affected by the need to dispose of expired doses. Nineteen hospitals (25%) replied that they are wasting more than 10 doses per day; 19% said they are wasting none; and 23% of hospitals had no idea how many doses are wasted.

The insulin that is used for compounded infusions contains the preservative m-cresol (meta-cresol).[4,5] M-cresol is on the Environmental Protection Agency's (EPA's) Resource Conservation and Recovery Act (RCRA) list of hazardous chemicals that are classified as toxic hazardous waste (EPA Waste Code D024) if it exceeds the regulatory limit of 200 ppm.[6] Insulin infusions prepared at a standard concentration of 1 unit per 1 mL will exceed the 200-ppm concentration level; therefore, used IV bags that contain some amount of insulin must be part of the hospital's RCRA waste management program. Empty bags and tubing can be disposed of as solid waste.

Recommendations

Based on the survey data, hospitals across the United States may be dispensing anywhere from 3,650 to 18,250 insulin infusions per year. Insulin infusions are used in both critical access hospitals and general acute care facilities. The number of insulin infusions dispensed per day is directly affected by the bed size and the scope of service at the hospital. Insulin by IV infusion is the standard of care for hyperglycemia in critically ill patients, especially those who have undergone cardiac surgery. Patients who have undergone organ transplantation and those with acute stroke may benefit from close management of hyperglycemia, and IV insulin infusion is the preferred route of administration for perinatal mothers. Factors that influence the incidence of hyperglycemia in these patient populations, such as the increasing rate of obesity in the United States, will cause a continued and increasing demand for insulin infusions.

As the demand increases for insulin infusions, so will the demand on pharmacy resources. Regardless of the size and scope of a hospital, most insulin infusions are prepared and dispensed on demand. Very few hospitals are using batch compounding for insulin infusions, and even fewer are using refrigeration to extend BUD. Benchmarks are not available to calculate the time to prepare, label, and dispense 1 insulin infusion, but the gradual increase in demand is a direct increase on the pharmacy and pharmacy technician workload. The safety of on-demand preparation and dispensing can be affected by competing priorities, interruptions, and distractions in the pharmacy environment. Long turnaround times when insulin is compounded on demand can lead to a delay in initiation of therapy and stabilization of blood sugar, which can contribute to negative patient outcomes.[7,8]

All insulin infusions are not created equal. The survey indicates that it is still common for nurses to prepare insulin infusions at the POC, without the benefit of a segregated compounding area (at a minimum). There are many reasons for this, such as non–24-hour pharmacy services, an urgent need to initiate therapy, or an ongoing insulin infusion bag running dry while on the pump. Insulin infusions that are prepared outside the pharmacy have a short BUD and must be discarded if not started within 4 hours (USP <797>; 2019 USP 42-NF37).[2] The BUD for insulin infusions compounded using aseptic techniques outside a cleanroom or segregated compounding area recently was increased from 1 to 4 hours to accommodate nonhospital practitioners and settings.

Insulin infusions made at the POC most likely do not include a product-specific label for barcode medication administration due to the absence of such printers outside the pharmacy. An independent nurse double check before initiating the infusion is a common safety practice, but survey respondents did not mention an independent nurse double check to ensure the correct amount of insulin is added to the bag during preparation at the POC. Products compounded at the POC are noted to have a high risk for error and low reliance on regulatory compliance.[9]

Beyond-use dating for sterile compounded products will vary based on the preparation environment and storage (room temperature vs refrigerated vs frozen). Within each storage category, respondents also reported a wide range of BUDs. The degree of variation may be related to the variety of references noted by the respondents. The range of BUDs and preparation and storage methods are a cause for concern. Just as standardizing the concentration of insulin in the infusion is important to reduce errors, the lack of standardization of BUDs may create a risk for patient harm.

It is reassuring to see that many of the safety measures established by the ISMP have been widely adopted. Compounding safety measures were used less often, with only 25% responding that they are using some type of IV workflow system. Only two respondents are using the relatively newer systems with bidirectional information to improve safety especially for infusion rate changes. Many of the safety measures depend on education, training, time, and attention that can be undermined by workload, lack of time, interruptions, distractions, and turnover of compounding technical staff.

Wasted products and EPA RCRA disposal waste streams comprise the hidden costs of IV insulin therapy. Decreasing waste will decrease workload on the pharmacy and the associated costs. Reducing waste could reduce the costs and compliance concerns associated with disposal of insulin infusions.

How can hospitals reduce the variability in practice to ensure the safety of insulin infusions? Initial recommendations for process improvements might include batch preparation and extended BUD based on moving to refrigerated storage. The turnaround time to initiate therapy and maintain the infusion could be shortened by batch production and storage at the POC. This can be facilitated by an extended BUD and segregated room temperature storage in an automated dispensing cabinet (ADC). Extended BUD also may help reduce waste.

Will storing insulin infusions at the POC increase the risk for errors? On-demand dispensing from the pharmacy may be a safety measure to ensure order verification before initiation, preventing a wrong medication error with a high-alert medication. Risks may be mitigated at the POC by prohibiting removal from the ADC on override and storing in segregated sections of the ADC—not in open bulk storage. Storage at the POC with access controls could eliminate the need for on-demand preparation and dispensing.

The value proposition for manufactured, ready-to-use infusions and other sterile products has been well established (Table 4).[7-14] Experts agree that nonpharmacy compounded sterile products are the least favored method for preparing infusions, followed closely by pharmacy compounded products. Many risks associated with high-alert medications have been mitigated by the use of manufactured, ready-to-use products (eg, heparin and potassium chloride). The recent approval of a ready-to-use insulin infusion is another option for hospitals.

Table 4. Safety Hierarchy of Sterile Preparations

2018: "Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry"[10]	Although compounded drugs can serve an important need, they can also pose a higher risk to patients than FDA-approved drugs. Compounded drug products are not FDA approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality.

2017: "An Assessment of Currently Available I.V. Push Medication Delivery Systems"[11]	Manufacturer-prepared RTA ranked higher over manufacturer-prepared not-RTA, repackaged or outsourced injectables, pharmacy-prepared single-dose injectables, HCP-prepared multidose injectables, and HCP-prepared single-dose injectables: based on procurement, dispensing, safety, usability, efficiency, and compliance.
2016: ISMP Guidelines for Safe Preparation of Compounded Sterile Preparations[14] 2017: "An Assessment of Currently Available I.V. Push Medication Delivery Systems"[11]	To the maximum extent possible, commercially prepared, premixed parenteral products and unit-dose syringes are used versus manually compounded sterile products.
2016: FDA Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act Guidance for Industry[13]	Because compounded drugs have not undergone premarket review for safety, effectiveness, and quality, they should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient.
2011: "Guidelines for the Safe Preparation of Sterile Compounds: Results of the ISMP Sterile Preparation Compounding Safety Summit of October 2011"[15]	Level 1 Recommendation: When available, commercially prepared, premixed IV products that meet the patient's needs are used over manually compounded sterile products. Where; Level 1 (Recommendation)=best practice that is strongly encouraged but that may not be applicable to all institutions or in all circumstances.
2008: "Second Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems—2008"[9]	Manufacturer RTU: ranked higher over outsourced RTU, point of activated, pharmacy compounded, nonpharmacy compounded at POC: based on applicability, ease of use, regulatory compliance, safety, and implementation.

2000: "Consensus Development Conference Statement on the Safety of Intravenous Drug Delivery Systems: Balancing Safety and Cost"[16]	Manufacturer prepared: ranked higher over POC activated, and pharmacy prepared: based on safety, costs, simplicity, and training.

HCP, health care provider; **ISMP,** Institute for Safe Medication Practices; **POC,** point of care; **RTA,** ready to administer; **RTU,** ready to use

In conclusion, IV insulin infusion therapy is indicated for many types of patients, with future growth in demand anticipated. The degree of variation in preparation, BUD, and safety measures raises concerns for patient injury. How is your hospital pharmacy meeting the needs of patients and caregivers?

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