

Latiolais Leadership Program Consensus Development Conference on the Safety of Intravenous Drug Delivery Systems

White Paper

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Adverse drug events have captured the attention of the public and the safety of the medication use process has become a public policy issue. The overall frequency, clinical significance, proximal causes and costs have been well documented. The exact frequency of adverse drug events associated with intravenous drug delivery is known, but given the percentage of drug therapy that is given by this route in the acute care setting is likely to be high.

At the same time that concerns about safety in health care are being raised, there is also concern about the cost of care. Providers are under extreme pressure to reduce costs to remain competitive in the market. No element of health care is immune from scrutiny in the effort to reduce costs. IV drug delivery systems are no exception.

For health care providers and health care systems managers to make good decisions about the cost drivers of care, like IV drug delivery systems, they need information about the relative value of the technology. Cost considerations need to be balanced against quality and safety considerations to maximize overall provider performance. While much is known about the problems that can arise with IV drug delivery, not much is known about the relative balance of cost vs. quality and safety for the currently available drug delivery systems.

The gold standard for evaluation is the double blind, randomized controlled study. While ultimately, any question should be answered through research, sometimes decisions must be made before the results of well-designed studies can be completed. One method for evaluating new treatments and technologies that has been developed by the National Institutes of Health is the Consensus Development Conference. This method provides preliminary guidance in making decisions where a division of opinion exists.

One of the important elements to the Consensus Development Conference methodology is the review of current knowledge in the area in question and listing the strategic questions that need to be answered. The purpose of this White Paper is to do both of these things.

Currently available IV drug delivery systems

Since the introduction of intravenous therapy in the 18th century, several systems have been delivered to administer drugs via this route. For purposes of this White Paper, the scope of intravenous drug delivery systems that will be reviewed includes non electronic systems that are used in non-critical care patients to administer small volume drug doses. They include:

- IV push. With this system, sterile drugs are prepared and placed in a syringe for direct injection into a vein or venous access device. The syringes can be purchased commercially in a ready-to-administer form, be prepared for use in a pharmacy or by a nurse at the point of care.

- Volume control chambers. With this system a cylindrical chamber is added to the IV site into which drugs can be placed for infusion into the patient. Drugs are diluted and infused by fluids that run through the chamber from a distal large volume parenteral solution.
- Pharmacy-prepared minibags/glass bottles. With this system, drugs are added to small volumes (50-100 ml.) of 5% dextrose or 0.9% saline contained in plastic bags or glass bottles (an "IV admixture"). The contents of these containers are infused by connecting the container to an existing IV line ("piggyback"). The rate of infusion is controlled by adjusting a clamp on the IV set.
- Gravity-fed vented syringe system. With this system, a syringe is prepared containing a drug which is then placed in a plastic bag, hung on an IV pole and the drug infused through a vented secondary set that is attached to an IV line.
- Spring-loaded syringe-based system. With this system, a syringe is prepared containing a drug which is placed in a device with a spring that exerts constant positive pressure on the plunger of the syringes. The drug is infused from the syringe as pressure forces the fluid through tubing that is attached to the main IV line.
- Manufacturers' container. With this system, the drug is provided in a ready-to-hang container without diluent. The drug is reconstituted and infused from the original drug container by attaching the container a secondary set which is attached to an IV line.
- Point-of-care activated mini bag system. These systems enable a vial of the drug to be attached to a mini bag (ADD-VantageR, Minibag PlusR) or primary IV line (CRISR) so that it can be reconstituted and mixed with the fluid. After the mixing has taken place, the drug can be infused through the primary IV line or a secondary set that is attached to the main IV line.
- Premix mini bags. With this system, the drug is mixed with diluent by a manufacturer and provided as a ready-to-administer dose. The drug is infused through a secondary set that is attached to the main IV line.
- Frozen mini bags. With this system, the unstable drugs are mixed with diluent by a manufacturer and frozen for delivery to the customer. The product must be thawed before administration through a secondary set that is attached to the main IV line.

The characteristics of different intravenous drug delivery systems have been reviewed by Rapp¹ and are summarized in tables 1 through 8.

The scope does not include electronic intravenous drug delivery systems.

Studies of IV drug delivery safety

Concerns about the safety of drugs administered by the intravenous route began to be expressed in the late 1960's. Patterson and Nordstrom reported that 60 percent of IV solutions being used at a hospital contained more than one drug, some of which contained five drugs. More than half of the IV solution were prepared over one hour before actual administration. Concerns about incompatibilities between drugs and the length of time between preparation and administration of the drugs prompted the authors to recommend a pharmacy-based intravenous admixture program².

The medication errors associated with IV drug preparation and administration proposed by Patterson and Nordstrom were studied by Thur, Miller and Latiolais. They reported a total error rate of 21% in a system where nurses prepared and administered parenteral admixtures. The wrong dose was prepared or administered in 9% of the observations, incompatible drugs were mixed in 6% of the cases, the wrong drug or solution was used in 3% of the observations, and drugs that were not ordered were prepared or administered 3% of the time. Furthermore, deviations from recommended sterile technique procedures were observed. In 100 observations, the work counter was not cleaned in 99 cases, hands were not washed in 97 cases, the sterile

areas of the IV container were touched in 47 cases, and vial or bottle tops were not cleaned in 31 cases³.

O'Hare et al. performed an audit to identify the type, rate and potential severity of errors associated with medical and nursing staff administering intravenous drugs over a four week period. A disguised observer technique was used whereby the observer accompanied the person involved with preparing and giving each doses. A total of 291 errors were detected in 168 of the observed doses. Error types included incorrect time, rate, volume diluent, preparation method, duplication or dose omission. Of 132 doses given by senior house officers 129 (98%) had at least one error, and 39 of the 47 doses (83%) were given in error by the nurses⁴.

Thomson and Feer studied the uniformity of drug concentrations in IV admixtures prepared by nurses and pharmacists. Significant differences were found in the concentrations of admixed drugs delivered over time due to incomplete mixing. Fewer differences in uniformity were found in admixtures prepared by pharmacists than those prepared by nurses⁵.

A report of errors in drug computations by physicians, nurses and pharmacists was reported by Perlstein et al. Medical personnel were tested for their ability to correctly compute drug doses for sick newborns. One of every 12 doses computed by registered nurses contained an error that would have resulted in the administration of an amount that was ten times higher or lower than the dose ordered. Pediatricians give the same test made errors at the rate of one of 26 computations attempted. Pharmacists were shown to have better computational skills than either nurses or physicians⁶.

While much of the literature about the safety of IV drug delivery was published in the pharmacy literature and has advocated pharmacy-based, centralized IV admixture programs, it has been found that pharmacists too make errors. Sanders et al studied the compounding accuracy and aseptic techniques in three hospital pharmacies with IV admixture programs. They found that when pharmacists did not know they were being watched, they had a higher mean percent error (8.21 vs. 7.24) and contamination (7 vs. 1) rate than pharmacy technicians. With monitoring, pharmacists had a lower mean percent error (5.84 vs. 6.29) and contamination (0 vs. 4) rate. The authors conclude that compounding accuracy and maintenance of aseptic control improve with monitoring⁷.

Flynn, et al reported the results of an observational study of accuracy in IV admixtures prepared in the pharmacy departments at five hospitals, representing each geographic region of the US. The medication, dose, base solution and other details were observed and compared to the IV labels used to prepare the dose. The mean error rate for the five hospitals combined was 9% (145 errors for 1679 dosages) excluding ready to use doses. Errors were highest in nutritional solutions prepared manually (37%) and lowest in premixed minibags (2%). Error rates for syringes were 12% and small volume injectables were 8%. Mean error rates for individual pharmacies ranged from 6% to 10%. Wrong dose errors were the most common type of error. Of every 100 errors, two were judged to be potentially clinically important⁸.

Sterility is another concern about the preparation and administration of drugs via the intravenous route. Miller, Smith and Latiolais discovered significant differences in contamination rates comparing an "open" system where the IV solution could be exposed to room air to a "closed" system where room air does not enter the system. They also found that the probability of a dependence between the admixture compounding in the nursing unit compared to a laminar flow hood was not different, prompting the authors to conclude that sterile technique is more important than environment in assuring product sterility⁹.

The impact of laminar air flow and clean room dress on contamination rates of intravenous admixtures was studied by Brier, Latiolais and Schneider. Intravenous admixtures were prepared

by one investigator using aseptic technique under four environmental conditions: laminar airflow with clean dress, laminar airflow without clean room dress, clean table top with clean room dress, and clean table top without clean room dress. The incidence of contamination of admixtures compounded in laminar airflow conditions was significantly less than those compounded on a clean table top, regardless of operators' dress. The authors concluded that when one adheres to aseptic technique, the environment in which admixtures are prepared is the most important variable affecting the microbial contamination rate¹⁰.

The introduction of flexible plastic IV fluid containers was shown to decrease the frequency of in use contamination at the patient care level by Letcher et al. They found that of 366 flexible plastic containers collected at the bedside that 4.9% were contaminated and of 365 administration sets, 5.5 % were contaminated. The predominance of *S. Epidermidis* found as contaminants suggest that touch contamination was the primary cause¹¹.

More recent studies of costs and contamination rates have not demonstrated differences between IV solutions from different manufacturers or types of iv drug delivery systems. Allinson et al compared IV solutions from three different manufacturers all of which used plastic containers, but had different features. No differences were found in contamination rates between solutions in these three systems¹². Paxinos et al studied contamination rates and costs in four intermitted intravenous infusion systems including volume control chambers, piggyback with minibag, tandem minibag with volume control chamber and manufacturers drug container. They too found no difference in contaminations among these four systems¹³.

The rate of drug delivery is an important characteristic of IV drug delivery systems. Most of the work investigating the impact of different methods for intravenous drug administration has been done in pediatric patients. Because of the small size of pediatric patients, accurate and uniform drug dose delivery is critical. Leff and Roberts studied different methods of intravenous drug administration in pediatric patients and found that syringe infusion pump or manual retrograde injection techniques were both practical, safe, dependable and effective as a means to deliver both IV fluids and medications as a desired or known rate¹⁴. The manual retrograde injection technique is accomplished by occluding the tubing at a point between the patient and the injection site during a bolus injection. The IV fluid flow subsequently delivers the dosage volume to the patient. Nahata, et al found significant differences in the serum concentrations of tobramycin when it was infused using different intravenous drug infusion systems or ports of entry into the system. A syringe infusion pump was compared to two different infusion control devices attached to IV sets at different places¹⁵. Specific gravity of drugs has also been found to influence the amount and rate of drug delivery at slow infusion rates. Rajchgot et al found that drugs with higher specific gravity settle in reservoirs in the infusion system such as filters, chambers and loops in the tubing¹⁶. The impact of the choice of IV tubing also has an impact on drug delivery rates to infants¹⁷. Issues related to the rate of intravenous drug delivery in adults has not been studied.

Problems with the preparation of intravenous admixtures, both at the bedside and centrally in the pharmacy prompted the industry to market premixed intravenous admixtures in the early 1980's. Early response to this development was cautious. A commentary by Loeb, Fishman and Kochis subtitled "a critical challenge for hospital pharmacy" highlighted the advantages of premixed admixtures. These include preparation time savings, assurance of properly reconstituted drugs, proper labeling, and lengthy expiration dating which in turn reduces waste. Disadvantages cited included potential for confusion among different manufacturers' products, space considerations for storage, availability of information about the products and cost¹⁸. A more positive conclusion was drawn by Lee who stated that the use of premixed IV admixtures is a positive technological advance in drug packaging, that the advantages outweigh the disadvantages and predicted that it will soon become the universally accepted form of IV drug packaging¹⁹.

An alternative method for preparing drugs for intravenous administration was use of manufacturers' containers that were configured for reconstitution, attaching to piggyback IV tubing and hanging from an IV pole to be administered as a piggyback infusion. In 1985, Rapp described this system as a preferred method for administering IV drugs during a cost conscious era and noted that as many as 60% of drugs were available in this package. In addition to cost, an additional advantage cited was the capacity to select diluents that would allow most IV solutions to be isotonic²⁰.

One of the problems with pharmacy prepared IV admixtures is waste resulting from products that are made but never used. Salberg et al report loss from IV product waste in one hospital of \$28,000 per year²¹. Adachi et al reported annual material cost waste of \$38,000²². Vogel, et al tested a method to calculate the product waste in IV admixture programs in six hospitals and found the percentage of wasted IV admixtures to range from 2.2 % to 15.6% (mean 8.4%). The annualized cost of this waste ranged from \$3,341 to \$145,928 (mean \$74,932)²³.

Because of the relative expense of premixed intravenous admixtures, several authors have attempted to develop objective methods for making decisions about their purchase. Witte et al described the use of decision analysis as a tool for formalizing the process of selecting an IV drug delivery system from among various alternatives. Decision analysis involved listing the criteria used to make the decision followed by the assignment of a number for each criterion based on its relative importance to the overall decision. Each system considered was rated in order of preference, with the preferred system given the highest number within each criterion. The system with the most overall points was selected. On the basis of this analysis considering product acceptability, compatibility, inventory control, minimal space, accurate product, avoidance of contamination, stability, minimal waste and minimal personnel time, a frozen, premixed admixture system was selected over batch preparation or manufacturers' container systems²⁴.

Smith and Kitrenos investigated the time and costs of preparing and administering cefazolin sodium small volume injections using automated and manual systems. They compared manual piggyback, manual 24-hour piggyback, manual syringes, spring loaded syringe pump, electronic compounding device, manufacturers' container and point of care activated systems. They found that the manual 24-hour piggyback system (IV admixture) was the most cost effective method for preparing and administering cefazolin small volume injections²⁵.

A similar study was performed by Smith and Amen in which seven methods for preparing and administering small volume injections was compared in 13 hospitals. The systems that were compared were minibag, frozen ready to use, manufacturers' container, syringe pump, and two point of care activated systems. When labor time and material costs associated with the preparation and administration of initial and subsequent doses of small volume injections, the point of care activated systems where the drug is placed in the primary IV line (CRISR) was found to be less expensive²⁶.

Aside from cost issues, the accuracy and variability of a manufacturer premade IV solutions have been compared to those prepared by a hospital pharmacy IV room. Dasta et al studied the concentration of theophylline in a commercially available, premixed product to a dose prepared in the hospital pharmacy. It was found that the mean theophylline concentration for the pharmacy prepared product was different and more variable than the premixed. For a lower concentration admixture, the pharmacy mixed solution was less concentrated than the premixed, and for a higher concentration admixture, the pharmacy mixed solution was more concentrated²⁷.

Strategic questions

Based on the work that has been published during the past 30 years on the subject of intravenous drug delivery systems, several strategic questions still remain. Despite the

publication of recommendations by the National Coordinating Committee on Large Volume Parenterals in 1980^{28,29,30} and the ASHP Technical Assistance Bulletin on Quality Assurance for Pharmacy Prepared Sterile Products in 1993³¹, there is evidence to support or refute different intravenous drug delivery systems. While evidence of errors in the preparation and administration of drugs for intravenous use can easily be found, the clinical significance of these errors has not been proven. As a result, clinicians and health care systems managers do not have an economic or scientific basis to make decisions about the selection of the safest cost-effective decision. Studies are needed to answer these questions. Until the definitive research is done, experts will need to make judgements based on the weight of evidence that currently exists. The questions that need to be answered to make these judgements are:

- *Are drug preparation errors really less frequent when doses are prepared by a pharmacist compared to nurses or physicians?* This question remains despite early evidence that nurses and physicians make errors when calculating doses and preparing the final product. Recent evidence suggests that pharmacists and pharmacy can be lax in these tasks too. The availability of commercially available pre mixed doses has reduced the potential need to prepare intravenous drug doses at the site of care.
- *How important is drug sterility as an important strategic issue in selecting an intravenous drug delivery system?* This question remains despite efforts to upgrade the environments in which sterile doses are prepared and improving the consistency and quality of aseptic technique. Research has shown that the most important determinant of sterility is technique, not the environment. Furthermore, commercially available products have reduced concerns about drug product sterility.
- *How important is the accuracy of intravenous drug delivery systems?* This question remains because of evidence that pharmacists make errors when they prepare sterile doses and the products themselves are variable in concentration when compared to commercially available doses. Doses prepared in patient care areas at the point of care are often not properly mixed. Drug accuracy in pediatric care is even more critical because of the more narrow therapeutic range of safety.
- *What are the overall total in use costs of the different intravenous drug delivery systems?* This question remains because information about the cost of wastage and adverse drug events has not been adequately characterized or factored into the overall costs of the systems. While there are individual estimates of the cost of waste, these estimates are highly variable and cannot be easily generalized. The cost of adverse drug events has not been studied at all.

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Table 1
 Characteristics of manufacturers' piggyback bottles

- Usually not expensive
 - Prepared by single step process in the pharmacy (diluent added)
 - Can adjust osmolality by selecting different diluents
 - Can adjust fluid volume if necessary in fluid restricted patients
 - Stability data are readily available
 - Compatible with current minibag systems, providing a vented secondary set is used
 - Requires more freezer space than minibags
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Table 2
Characteristics of battery operated syringe pumps

- Relatively inexpensive because the syringe is the drug storage and administration container
 - Requires a two-step dilution process in the pharmacy since both drug and diluent must be added to the syringe
 - Poses a maintenance problem because someone must replace batteries and perform maintenance and cleaning
 - Usually can be used in all patient care areas, including the ICU because volume and osmolality can be controlled
 - Stability data on drugs in frozen syringes are becoming available
 - Uses positive pressure, which may increase the severity of i.v. infiltration
 - Not necessary to interrupt the primary i.v. infusion
 - Requires a special secondary set
 - Requires a capital equipment purchase or some type of lease program to acquire pumps
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Table 3
Characteristics of spring operated syringe pumps

- Relatively inexpensive (depends on price of sets)
 - Requires a two-step dilution process in pharmacy
 - Requires a special set for each flow rate and syringe size
 - Pumps require virtually no maintenance
 - Changes in specific gravity and surface tension can affect flow rate
 - Can be used in all areas of the hospital, including the ICU because volume and osmolality can be controlled
 - Stability data on drugs frozen in syringes are becoming available
 - Uses positive pressure which may increase the severity of i.v. infiltration
 - Not necessary to interrupt the primary i.v. infusion
 - An implementation guide is available from the manufacturer
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Table 4
Characteristics of gravity feed vented syringe systems

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- Relatively inexpensive (depends on price of secondary sets)
 - Requires a two-step dilution process in pharmacy
 - No electric equipment is required
 - Can probably be used in all areas of the hospital, including the ICU because volume and osmolality can be controlled
 - Stability data on drugs frozen in syringes are becoming available
 - Completely compatible with current gravity feed minibag systems (with special set)
 - A useful implementation guide is available from the manufacturer
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Table 5
Characteristics of multiple dose programmable pumps (using syringes, minibags or minibottles)

- Programming scares some nurses because of the fear of making mistakes
 - A small risk of inadvertently administering the entire daily dose at one time
 - Very expensive (\$2000- \$5000)
 - After reconstitution, many drugs are not stable at room temperature for 24 hours
 - When properly used, pumps reduce nursing and pharmacy time
 - The system becomes more cost effective as the number of daily doses increases
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Table 6
Characteristics of the controlled release infusion system (CRIS)

- Cost depends on the cost of primary sets and empty vials
 - Diameter of drug vial top must be 20 mm to fit the spike holder on the primary i.v. set
 - Unless the drug is colored, it is difficult to tell if the drug has been administered since the fluid stays in the vial throughout infusion
 - Drug administration rate varies with the flow rate of the primary i.v. infusion
 - Drug must be in liquid form (reconstituted) before the vial is spiked
 - Specific gravity of the drug may affect drug delivery rate
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Table 7
Characteristics of the frozen or premixed minibag system

- Cost effectiveness varies depending on upcharge negotiation with each hospital or buying group
- Reduces pharmacy labor
- Probably reduces waste
- Loss of flexibility in controlling osmolality and volume

- Requires additional freezer space
 - Will generally be the most expensive system unless labor costs are factored into the cost estimate
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Table 8
Characteristics of the ADD-Vantage system

- May be cost effective when both the waste in the admixture system and the cost of labor are considered
- To a certain extent, control of the admixture program reverts to the nursing staff
- Requires all drugs to be in a special vial. Therefore, availability of many drugs in this form will be limited for some time
- The tip of the vial can be left in the minibag, which may increase particulate matter and may bother some patients who observe this
- There is a possibility that the nurse could forget to reconstitute the drug