

ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures

Purpose

Automated compounding devices are frequently used by pharmacists for the extemporaneous preparation of parenteral nutrition admixtures. This continuing shift from manual compounding procedures comes as a result of significant advances in automated technology, as well as in response to changing health care demands to provide admixture compounding in a safer, more efficient, and more accurate manner. Approximately 65% of the hospitals in the United States currently use automated compounding devices for parenteral nutrition admixtures on a daily basis.^a Compounders are also used for other types of intravenous admixtures and in other settings, including home care and long-term-care facilities; therefore, the overall magnitude of their use may be substantial. As with other automated systems or devices, the benefits can be realized only when the technology is used appropriately. Significant patient harm may occur when safety and quality assurance measures are overlooked or circumvented.¹

The purpose of these guidelines is to outline the key issues that should be considered to safely and cost-effectively incorporate this technology into the pharmacy operations of health care organizations. The guidelines focus on parenteral nutrition admixtures, but the safety issues are also applicable to the use of compounders for other types of i.v. admixtures. The term “health care organization” is used throughout the guidelines as a general descriptor and is intended to be inclusive of any of the practice settings and types of facilities in which compounders are used, including, for example, home infusion companies. These guidelines should be used in conjunction with the ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products and device manufacturers’ instruction manuals and training materials. Pharmacists should use professional judgment in assessing their health care organization’s needs for automated compounding devices and in adapting these guidelines to meet those needs.

Background

The act of extemporaneously compounding any parenteral formulation is complex and not without inherent risks; therefore, compounding tasks are best performed by personnel most qualified to do so. An incompatible, unstable, or contaminated i.v. infusion may induce significant patient morbidity and even mortality.¹ Pharmacists are specifically educated and legally responsible for performing these tasks safely. Pharmacists are also responsible for training other personnel to perform relatively simple tasks with the least risk possible.

The extemporaneous preparation of multiadditive products, such as parenteral nutrition admixture compounding, should be performed under the direct supervision of a

pharmacist and in the appropriate environment.² The historical method of compounding these multicomponent admixtures has been to manually use gravity-driven transfers for large-volume additives, such as amino acids, dextrose, lipids, and sterile water. Small-volume additives, such as electrolytes, trace minerals, multivitamins, and drugs, have often been added manually and separately with a syringe. Thus, this compounding method is limited by the visual inspection of volumes transferred between stock containers, as well as by the precision of the calibrations marked on the stock containers or transfer devices.

The manual method of parenteral nutrition admixture compounding is labor-intensive and requires multiple manipulations of infusion containers, sets, syringes, needles, and so forth, which can lead to the extrinsic contamination of the final admixture with sterile and nonsterile contaminants. A sterile contaminant can be particulate matter from elastomeric vial enclosures (needle cores), and nonsterile contaminants can be bacteria and other infectious materials. Minimizing the number of extemporaneous manipulations of the parenteral infusion containers and supplies improves compounding efficiency and reduces the risk of extrinsic contamination and associated sequelae.³

The emergence of automated technology as an alternative approach to parenteral nutrition admixture compounding has led to potentially improved compounding accuracy with the use of fluid pump technology and software that controls the compounder pump. Fluid can be delivered from the source container to the final container by using either a volumetric or a gravimetric fluid pumping system. Volumetric systems transfer a specified volume of fluid from a source container to a final container via a rotary peristaltic pump. The tubing is stretched around a rotor and, as the rotor turns, solution is pulled from the source container and pushed toward the final container. Measurements are based on the theory that each rotor movement advances a constant amount of fluid through the system. The total volume delivered is calculated by the volume pulled into the tubing by each rotor movement multiplied by the number of movements. These systems usually incorporate a final check of the *actual* total bag weight by comparing it with a calculated *expected* weight.

In gravimetric systems, measurement of fluid volume delivered from the source container to the final container is determined by weighing the fluid transferred and dividing the weight by the solution’s known specific gravity, thereby converting weight to volume. Two types of gravimetric pumps are available: additive and subtractive. With an additive pump, a single load cell is positioned to measure each fluid as it is delivered to the final container. With a subtractive pump, load cells are positioned beneath the source containers to measure each fluid as it is being pumped from its source container. Weight is determined by subtracting the posttransfer weight from the pretransfer weight of the container for each source solution. When all transfers are

completed, the system compares the *actual* total bag weight with a calculated *expected* weight.

In addition to the compounder, dedicated software may be used to electronically transfer information to the compounding device. Automated compounding software has additional features that can enhance the management of the parenteral nutrition program. Software issues and their integrity are additional critical components unique to compounder methods and require continuous monitoring to ensure that the operations are correct.⁴

Justification for the Use of Automated Compounding Devices

When is it appropriate to use compounders, and how will decisions affect others within and outside the pharmacy department? It is incumbent upon the pharmacist to ensure that the department is fully knowledgeable about the operation of the compounder and that a minimum acceptable standard of pharmacy practice is met. First, internal decisions need to be made to justify the expenses associated with this technology. Second, policies and procedures should be in place to assess workflow, establish training programs, and standardize compounder use in the specific pharmacy practice setting. Third, changing current compounder contracts may result in more cost than the savings that might appear in the new contracts. Specifically, the initial incorporation of an automated compounder into daily pharmacy practice is a labor-intensive effort, and such transitions can be disruptive and can even increase the risk of errors. This may be particularly true during staff orientation to new devices. Such changes must be carefully reviewed; if they are determined to be worthwhile, a well-coordinated transition plan should be devised beforehand. Whether transition costs (including the potential for unused sets and supplies) can be deferred to the new contract is another factor for consideration.

The principal emphasis associated with using automated compounding devices in health care organizations should be improving patient care and enhancing efficiency while remaining cost-effective. "Cost-effectiveness" is, therefore, a relative term with respect to personnel, as the labor saved is often redirected to other aspects of pharmaceutical care that could also improve patient safety. Time that was previously spent on operations associated with parenteral nutrition admixture compounding can now be aimed at other issues, such as optimization of drug and nutritional therapies, reorganization of product utilization, quality assurance programs, and augmentation of other core pharmaceutical services. Specific objectives related to cost justification of automated compounding devices may include the following:

1. Enhanced efficiency and worker safety during the parenteral nutrition compounding process and patient safety with parenteral use.
2. Reduction in labor associated with manually compounded parenteral nutrition admixtures. Assessment of the overall labor and material costs associated with the current manual compounding methods should include hidden costs such as pharmacists' time to perform calculations, quality assurance checks, and compounder set-up, as well as staff training (initial and on-going).
3. Reduction in waste through more efficient use of base solutions and additives. Inventory can often be

reduced by consolidating source solutions to a few high-concentration, large-volume additives.

In some cases in which the cost of implementing automated compounding technology in one facility is prohibitive, health care organizations have opted to explore regional compounding centers or outsourcing to contractors.

Performance Requirements and Responsibilities

The use of automated devices for compounding parenteral nutrition admixtures should be clearly defined by the health care organization and the manufacturer. This includes the ongoing responsibilities of the pharmacy department and those of the manufacturer during and after implementation of the compounder in the pharmacy practice setting.

Three areas need to be clearly defined before choosing an automated compounding system: (1) the system's performance requirements, (2) the manufacturer's responsibilities, and (3) the pharmacy department's responsibilities. The performance requirements of the automated compounding system should ensure that

1. The compounder exceeds the level of accuracy achieved with manual compounding. The automated compounding device should be accurate to within 5% of the amount programmed, with verification of the amount pumped versus the programmed amount for each ingredient.
2. The automated compounding device has inherent safeguards, including the ability to detect inadvertent source-solution mixups; the ability to detect situations that could result in inaccurate deliveries, such as occluded transfer-set tubing and empty source containers; and the ability to keep incompatible source solutions separate.
3. The automated compounding software alerts the user when formulation issues arise.
4. The automated compounding software meets the standards of the American Society for Parenteral and Enteral Nutrition for parenteral nutrition label formats.⁵
5. The automated compounding software assists the pharmacist in producing physicochemically compatible parenteral nutrition formulations.
6. The automated compounding software provides useful clinical information.
7. The automated compounding software integrates with existing pharmacy programs wherever possible to optimize patient care and avoid therapeutic duplications.

The contractual agreement with the manufacturer should provide continuous support of the compounder and software, including information updates, problem solving, and emergency coverage. FDA considers all automated compounding devices class II devices,⁶ and as such they must comply with federal regulations. The manufacturer's responsibilities are as follows:

1. The manufacturer should supply, and the pharmacist should verify, that the device is 510K cleared as evidence of compliance with regulatory requirements; that the device meets the fire and safety standards established by Underwriters Laboratories (i.e., is

- UL-approved); that the operator's manual and other documentation support recommendations for use; and that accuracy statements and manufacturer claims are valid.
2. The manufacturer should provide 24-hour support for the compounder and its software throughout the life of the contract.
 3. The manufacturer should routinely provide the latest version of the compounder software in a timely manner.
 4. The manufacturer should ensure adequate availability of compounding supplies.
 5. The manufacturer should provide detailed information and instructions on the appropriate use of the compounder and its software. References should be provided when appropriate.
 6. The manufacturer should comply with FDA requirements for reporting adverse events.

Within the pharmacy department, specific policies and procedures should be developed that address responsibilities for compounder operations and maintenance, staff training, and monitoring compounder performance at all times. Before selecting and implementing an automated compounder, the pharmacy department should

1. Define and agree on automated compounding system needs and performance requirements.
2. Develop an implementation team with a lead person.
3. Develop a set of policies and procedures.

Control of the Automated Compounding Device in Daily Operations

The pharmacy department is responsible for the use, maintenance, and performance of the automated compounding device, including decisions about who has access to the compounder and its operations. Specific consideration should be given to the following:

1. Only designated pharmacy department personnel should have access to the compounder and its software. The level of access should correspond to the level of authority and expertise of the personnel.
2. Before being granted access to a compounder, pharmacy personnel should pass established competency-standard testing.
3. Access to and use of the compounder by pharmacy support personnel (i.e., pharmacy technicians, students, and other designated support staff) should be directly supervised by an authorized pharmacist.
4. The additive configuration or sequence of the compounder for compounding parenteral nutrition admixtures should not be altered from the established format without the authorization of a designated pharmacist.
5. The compounder should not be used for any purpose other than parenteral nutrition admixture compounding without authorization from a designated pharmacist. If the compounder is used for other extemporaneous drug preparation, this should be done separately from the schedule for parenteral nutrition admixtures. The use of the compounder in this manner will likely require the use of new compounding sets and admixture configurations.

Safety and Efficacy Features

The complexity of automated compounding device functions makes it imperative that the pharmacy department develop a specific plan for ensuring safe and efficacious use at all times. The safety and efficacy features should outline the core principles necessary for carrying out the complex tasks of parenteral nutrition compounding. The plan should identify the minimum standards that are routinely assessed through an established monitoring and surveillance program. Automated compounding devices on the market differ in hardware design, mechanisms of fluid transfer, and software applications. Consequently, sterility and quality assurance testing procedures and measures are also different, including routine assessments of accuracy in the delivery of correct amounts of nutrients. Consideration should be given to the following in accordance with the device manufacturer's specific instructions:

1. Establishing minimum competency standards for all personnel who have access to and operate the compounder. Competency standards should ensure that the compounder user has sufficient expertise to identify errors that may inadvertently bypass quality assurance systems. The competency standards should be reviewed and validated on a routine basis for all personnel operating the compounder.
2. Establishing specific procedures for the operation of the compounder that standardize its use, irrespective of the individual operator. Changes in compounder operations should occur only when authorized and should be communicated to all staff involved in compounding.
3. Including sterility and quality assurance measures to avoid extrinsic contamination and to ensure accurate delivery of parenteral nutrition additives.
4. Ensuring that compounder tubing changes occur at appropriate specified time intervals in accordance with the manufacturer's recommendations.
5. Devising methods for assessing and calibrating the accuracy of the compounder in delivering precise levels of substrates and additives.
6. Developing a contingency plan and a readily available backup system or method for providing uninterrupted parenteral nutrition therapy to patients in the event of compounder failure.
7. Ensuring that adequate amounts of solutions and supplies for automated compounding are on hand.

Quality Assurance Monitoring and Documentation

Automated compounding devices are intended to provide a higher margin of accuracy and to streamline the labor-intensive tasks associated with the manual extemporaneous preparation of large-volume, multiadditive parenteral nutrition admixtures and other admixtures. The compounders are not designed to replace oversight functions, which require the expertise of a pharmacist.

In theory, automated compounding devices provide compounding accuracy superior to that of traditional methods of manual compounding. However, the performance of compounders must be critically challenged by the pharmacist to ensure that their manufacturing specifications are

equal to the task. In the pharmaceutical industry, that process is called validation. Ongoing quality assurance measures specified by the device manufacturer for assessing the performance of the compounder, as well as corrective actions, should be clearly delineated in policies separate from those dedicated to operational tasks. “Ongoing” means daily, and whatever measures are determined to be essential should be performed each day because random checks may not detect a more insidious, intermittent flaw that could assume major clinical significance.^{7,8}

The pharmacy department may work with other departments to assess the compounder’s performance if such expertise is not available within the pharmacy department. For example, portions of parenteral nutrition admixtures may be sent to the health care organization’s laboratory to determine dextrose content. However, laboratory methods are usually designed for biological rather than pharmaceutical systems and should be validated to meet USP requirements for the components being tested. If outside departments participate in the quality assurance program, their methods should be appropriately validated in accordance with USP specifications and the results documented within the pharmacy department records on the compounder’s performance.

The pharmacy department should develop a monitoring and surveillance plan with output reports that encompasses the principles outlined under the section on safety and efficacy features. The plan should detail specific policies and procedures that will ensure the continuing operation of the automated compounding device at optimum performance levels at all times. The data generated by the monitoring procedures should be reported to the pharmacy director and other appropriate oversight personnel and kept as a permanent record of the compounder’s operations. These reports should be regularly reviewed in the assessment of trends and other long-term measures of performance. Specific consideration should be given to

1. Establishing performance standards and continuous quality assurance measures for assessing the compounder’s performance and product quality during setup and in-process (during compounding) and end-process testing.
2. Establishing quality assurance testing of user-defined software variables validating that the correct responses to user commands occur.
3. Validating all quality assurance testing before implementation.
4. Establishing a minimum performance standard for each quality assurance test. For example, deviations in the accuracy of delivering a single additive cannot exceed a predetermined percent error without immediate corrective actions.
5. Documenting all quality assurance data on a daily basis. A comprehensive review of the data and documentation of performance trends should be performed at scheduled intervals as necessitated by aseptic conditions. The compounder should have scheduled, routine cleaning and maintenance according to the manufacturer’s recommendations to ensure proper operation.

Storage and Inventory

The pharmacy department is responsible for housing the automated compounding device, related disposable supplies,

and admixture ingredients. Other departments, such as materials management, may order and store additional supplies for the compounder yet defer to the pharmacy for the selection of the components necessary for proper compounder operation. Specific consideration should be given to

1. Maintaining an adequate inventory of supplies necessary for compounder operation and patient needs.
2. Procuring all large-volume parenteral nutrition components (amino acids, dextrose, and lipids) from one manufacturer unless such combinations have adequate physicochemical data that ensure the stability, compatibility, and safety of the final formulations commensurate with the data for single-source products.⁵ Any proposed substitute products should be assessed for compatibility and approved by designated pharmacy personnel qualified to do so and possibly by the pharmacy and therapeutics committee if clinical issues are identified.
3. If a health care organization’s contract requires a change in the brand of parenteral products, designated pharmacy personnel should verify that the new products are compatible. If a new product is approved, designated pharmacy personnel should verify that the new product is compatible, add it to the compounder formulary, and revise the admixture requirements and instructions relevant to the compounder’s operations.

Education and Training

Pharmacists, by education and training, are competent to safely compound pharmaceuticals, including parenteral nutrition admixtures. Nevertheless, the introduction of automated compounding devices requires specific training of pharmacists as well as other pharmacy personnel in the operation, maintenance, and quality assurance of compounders. Specific consideration should be given to ensuring that

1. Pharmacy administration determines the individuals who will be responsible for education and training in the use of the compounders.
2. All education and training are documented in a permanent record maintained in the pharmacy department and in personnel files.
3. All pharmacy personnel using or supervising compounder operations are tested at regular intervals to ensure that individuals meet the department’s minimum competency standards.
4. Retraining, competency assessment, and appropriate documentation accompany upgrades and new versions of the compounder to ensure the continued proficiency of personnel, safety of compounder operations, and adequacy of oversight.

Device Variability

Automated compounding devices are marketed by several manufacturers. Even though there are similarities among compounders, there may be significant differences in the design, accuracy, operation, maintenance, software, and manufacturing support, among other things. The safe operation and supervision of any given compounder depend on adherence to the manufacturer’s specific instructions and

continuous quality assurance monitoring of compounding performance. The safe and efficient operation of an automated compounding system depends on defined responsibilities for the pharmacy and manufacturer, as well as on strict adherence to policies, procedures, and quality assurance programs.

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Approved by the ASHP Board of Directors on April 27, 2000. Developed through the ASHP Council on Professional Affairs.

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The bibliographic citation for this document is as follows: American Society of Health-System Pharmacists. ASHP guidelines on the safe use of automated compounding devices for the preparation of parenteral nutrition admixtures. *Am J Health-Syst Pharm.* 2000; 57:1343–8.