



## Centralized Pharmacy Filling: Overview, Needs and the Impact of Automation

## INTRODUCTION

The history of the preparation of IV admixtures represents a continuing centralization of function and process with attendant improvements in accuracy, sterility and patient safety.

Initially, IV admixtures were prepared by nurses and physicians in patient care areas as they were needed. While there was little documentation of errors at that time, studies have shown that error rates could reach as high as 20% with this mode of preparation.

Even before pharmacies prepared such doses, nurses in certain areas would pre-draw medication doses they thought they might need in anticipation of such need. This practice was most notable in emergency care areas such as emergency rooms and operating rooms. Indeed, significant medication errors have been associated with this practice when it did not include careful labeling and storage to ensure that other providers who might encounter those doses knew what was in the syringes. The Joint Commission's 2006 National Patient Safety Goals<sup>1</sup> include a goal to label all medications, medication containers (i.e., syringes, medicine cups and basins) or other solutions on and off the sterile field in perioperative and other procedural settings.

In the early 1970s pharmacies began taking over the function of preparing IV admixtures, predicated on their ability to provide this service with improved economies, cleanliness and labeling (often in conjunction with standardization), with the aim of reducing error rates. It became demonstrable that the application of batch filling processes (with batch filling controls), dose preparation within controlled environments (such as laminar air flow hoods) and complete and appropriate labeling improved patient safety, cut costs and permitted redeployment of scarce nursing resources to tasks more suited to their education and training.

This process often started with moving complex preparations (such as intravenous nutrition) to the pharmacy, followed by other products that required exacting preparation (such as chemotherapy and vasoactive drips), and finally, virtually all infusion preparations. In some hospitals, even infusions that come commercially prepared are issued as patient-specific doses in keeping with definitions of dispensing that often include the placement of a medication in final association with a patient's name.

By the early 1980s some of these more complex preparations had already been outsourced to such organizations as B-Braun's Central IV Admixture Service (CAPS), leaving pharmacies to prepare the more common preparations.

Health-system pharmacy IV preparation has been more extensively studied than nursing preparation and it has documented error rates as high as 9% (considerably less than that of nursing, but appreciable).

The introduction of USP Chapter <797> has created increased pressure for centralized filling because many hospitals that would otherwise consider continuing to prepare IV admixtures locally now find themselves facing significant personnel, procedural and facilities changes in order to continue to provide that function. Health systems can therefore address this issue by further centralizing IV admixtures for several of their hospitals into a location that meets or exceeds regulatory requirements. Such centralization provides the benefits of excellence in facilities and procedures and consistency of preparation and labeling across multiple sites that are difficult to achieve using disparate preparation facilities.

Thus, the profession now finds itself confronting a set of issues that has arisen from the centralization of IV admixtures that began in the early 1970s.

## MEETING IMMEDIATE NEED

Such centralization creates logistical challenges. Even hospitals with pharmacies that have centralized IV production within their own walls sometimes have difficulty getting needed doses into patient care areas in a timely fashion, and have created floor stock systems in order to allow primary care providers to render immediately needed medication therapy. These ‘floor stock’ systems, mechanized or not, place the primary care providers in the role of preparing doses that are needed for immediate use, removing the safety checks and preparation guidelines in the heat of the moment, when they are most urgently needed to prevent therapeutic misadventures. Recent headlines have provided graphic detail on this issue.

Centralizing IV preparation outside the hospital, in a facility that serves multiple hospitals, increases the magnitude of this problem. Some centralized facilities estimate that they can fill 65 - 70% of doses as patient-specific doses with the remainder having to be prepared for immediate use on site “in the heat of battle.”

Another logistical issue is order volatility; a dose prepared for a specific patient at a centralized IV admixture facility may arrive at the treating hospital only to discover that the therapy for that patient has been changed or discontinued.

One solution to this conundrum is to have the centralized facility prepare non-patient-specific doses *in anticipation of use* in a ready-to-use format, mitigating the most likely sources of preparation error (i.e., selecting the wrong source container, drawing up the wrong amount of drug or contaminating the preparation). Given adequate controls, these doses are better prepared, better labeled and better managed than doses prepared *ad hoc* by primary care providers yielding more consistent and effective, as well as safer, medication use.

Indeed, the late Paul Parker once referred to the provision of doses in any form other than ready-to-use as “pseudo-pharmacy.”

## MANUFACTURING, COMPOUNDING OR SOMETHING ELSE?

The central variables to this question seem to be the location of dose preparation relative to the location of the patient, the timing of dose preparation relative to the timing of dose administration, whether or not the doses are labeled with specific patients' names and the manner (environment and technique) of preparation.

Preparation of medication doses that are labeled for specific patient use, even at a remote location, is generally considered within the purview of the practice of pharmacy, although some State Boards of Pharmacy do not permit this practice. Thus, if a pharmacy prepares a dose for a specific patient in response to a valid medication order in a healthcare facility, that is clearly the practice of pharmacy. If that same pharmacy prepares such doses a day in advance and then issues them (presuming there are no sterility or stability concerns with this practice) with patient-specific labeling, this is also generally considered to be within the scope of practice. In addition, if a centralized pharmacy prepares doses labeled for individual patients (where permitted), such doses are generally recognized as being within the practice of pharmacy.

On the other hand, preparation of non-patient-specific doses in anticipation of use represents a regulatory issue. If a centralized pharmacy prepares doses not labeled for individual patients, the question arises as to whether that pharmacy is really compounding in anticipation of use (which is generally recognized as valid pharmacy practice) or is manufacturing doses without having specific patient use in mind.

Thus, the debate has been framed as a compounding vs. manufacturing debate, with the FDA contending that all compounded preparations are new, unregulated drugs by definition, for which they choose not to enforce the Food Drug and Cosmetic Act (FDCA), as long as such drugs are compounded in response to a physician's prescription and do not constitute replication of a commercially available product. By this definition, a medication dose compounded in anticipation of need is manufacturing.

*Arguably, the preparation of IV admixtures is neither manufacturing nor compounding.*

Manufacturing involves the commercial preparation of medication doses without any consideration of individual use. In the case of injectable products, it represents acquiring raw (perhaps non-sterile) drug, preparing sterile, non-pyrogenic containers to hold that drug, sterilizing the drug, metering the drug into the container and labeling the container for general use. This process is described in detail in standard operating procedures for the preparations involved, which are then subjected to lot and batch controls. Those procedures and controls must be verified to ensure they will reliably produce medication packages that contain consistent, safe and effective medication.

Compounding involves the non-commercial preparation of a customized medication dose by combining ingredients in a prescribed formula based on a specific physician's prescription or order. Either the prescription order or the pharmacist's knowledge and skill (or both) specify what ingredients are to be used, the quantities to be used, the order in which those ingredients are to be combined and the techniques used to prepare them.

IV admixture doses conform to neither of these definitions. Irrespective of whether a nurse prepares a dose in a patient care area, a pharmacist prepares a dose in a hospital pharmacy (or satellite IV room) or a pharmacist prepares a dose in a central fill pharmacy, they all prepare the dose by acquiring a commercially available product, preparing it according to the manufacturer's instructions (or comparable literature from refereed journals and texts), storing it according to those same instructions and then administering it.

Indeed, the Fifth Circuit Court of Appeals ruled in *Medical Center Pharmacy et al v. Mukasey, Leavitt, and von Eschenbach (No 06-51583)* that "if one considers 'compounding' to include creating specialized dosage forms consistent with the instruction on a drug's label, that would be a kind of compounding that would not result in a 'new drug' under the FDCA's definition." The pharmaceutical manufacturer has already guaranteed the potency and sterility of the ingredients and has provided instructions (in the form of labeling), which, if followed, will result in a preparation of known potency for a known period of time, as long as the dose is stored as described in the appropriate literature. The resulting solution implements the intended use of the product as described in FDA-approved labeling.

If diluents are required, the pharmacist acquires them from another commercially available container whose manufacturer has already stipulated that they are sterile and pyrogen-free when used according to their instructions. The dose prepared is not a "new product" but is simply the implementation of the intended use for a commercially available product as described in the manufacturer's FDA-approved labeling.

The pharmacist performs exactly the same *dose preparation* function that the nurse performs on the floor but brings added value to the preparation process by applying batch control processes, cleaner and more controlled preparation environments and economies of scale.

The process of sterile dose preparation in the pharmacy is therefore substantially different both from compounding and manufacturing. As such, the question becomes, "at what point may sterile dose preparation become compounding, or even manufacturing?"

Clearly, preparation of a sterile dose from a commercially available drug product according to the manufacturer's instructions by any authorized healthcare professional, pursuant to a valid physician's order, is neither compounding nor manufacturing.

Preparing a dose that involves combining a drug with a diluent according to the manufacturer's instructions is clearly not compounding.

Preparing a dose that contains a number of medications (such as a TPN, a cardioplegia solution or a mixture of two antibiotics to be given together) is probably compounding.

The question that remains to be answered therefore becomes, is a sterile dose prepared from a manufacturer's container according to its labeling (or other authoritative source) in anticipation of use *prepared, compounded or manufactured?*

Baxa asserts that such a dose is *prepared*, just as a dose drawn up in preparation of an order is prepared by a nurse, only with better controls, better labeling, under cleaner conditions and with better storage. As such, it falls under the purview of routine pharmacy practice. Reasonable assurance of safety, sterility and stability therefore arises from the normal pharmacy processes of:

- Verifying that the correct drug was selected
- Verifying that the correct diluent (if any) was applied
- Verifying that the correct amount of diluent (if any) was applied
- Verifying that the correct amount of the prepared drug solution was placed in the dose container
- Verifying that the dose container is properly and completely labeled

Indeed, even if the activity were deemed to be manufacturing, verifying proper drug selection, verifying proper diluent selection, verifying the addition of the proper amount of diluent and verifying that the final dose contains the correct amount of fluid could meet the requirement for verifying that the manufactured product meets specifications, since the “manufacturing” involves using FDA-approved commercial products that have already been demonstrated to contain the correct amounts of the correct ingredients.

Activities that would support preparation in reasonable anticipation of use would include documented traceability of individual doses to the patient-specific orders for which they were ultimately used, and demonstration that production of the non-patient-specific doses was driven by historical patient-specific usage over relatively short periods of time.

Activities that would cause such preparation to fall into the realm of manufacturing include preparation of quantities in advance of reasonably anticipated need, or sale of such prepared doses to facilities outside the administrative boundaries of the healthcare system within which doses were centralized.

## AUTOMATION AND CENTRALIZED DOSE PREPARATION

Meeting the requirements for adequate control of the production process becomes easier when those processes are automated. Automation of dose preparation processes can, and should, include intermediate process-control steps that help ensure the quality of the final product. Considering the production of sterile medication doses, those steps might include:

- Automated, self-documenting checklists to prompt users to complete all required tasks
- Programs for environmental assessment to regularly demonstrate maintenance of the aseptic environment
- Programs for media-challenging the production process
- Verification of all source ingredient containers, preferably using a system such as scanning the bar codes applied by the manufacturer when those packages were prepared
- Verification of all dose labeling, using a system such as bar code application and scanning
- Weight verification that the correct amount of diluent (if needed) was used
- In-process checks to verify the dose container was properly closed

Pharmacy automation can address the requirements for production control and quality required for a successful central fill pharmacy operation. One product, IntelliFill® i.v., offers these checks including:

- Device-level and batch-level automated checklists to prompt the user to perform necessary tasks
- A program for air- and contact-sampling to verify maintenance of the aseptic environment
- A program for regular certification of the HEPA filter
- A program for regular production of media-challenge doses
- Barcode verification of proper loading of all drug vials
- Barcode verification of proper loading of diluents and reservoir with traceability back to the original manufacturer's lot numbers and expiration dates for each source ingredient
- Barcode verification of injection vials as they are used
- Required re-verification of vials if their identity has become questionable
- Photographic tracking of vials for each dose
- Barcode verification that the proper label has been applied
- Load cell verification that the proper amount of fluid has been injected into a vial
- Final weight check of each syringe with the final weight
- Automated in-process checks to verify:
  - Continuous and proper function of the HEPA filter unit
  - Proper loading of each syringe
  - Proper loading of each vial
  - De-capping and re-capping of syringes occurs as planned
  - Vial de-capping occurs as planned
  - Automated component movement is complete and accurate
  - Completed dose is dropped from the device and delivered to its output location
  - The load cell is within calibration
  - The analytical balance that weighs the syringes is within calibration
- If user interventions are required, the software automatically marks any uncapped syringes at risk and requires the user to dispose of those syringes based on the type and degree of intervention required

Additionally, since each dose produced by IntelliFill i.v. has a unique identifier that can be used to access the records of that unique syringe, this logging supports a mapping process by which non-patient-specific doses can be mapped to patient orders, creating complete traceability from source products to the dose finally administered to a specific patient. Indeed, one can envision a software product that uses barcode scanning to automate dispensing of non-patient-specific doses to patient orders while simultaneously checking that the assigned doses are within date and contain the correct drug and correct amount of drug.

## CONCLUSION

Beginning in the 1970s, health systems moved to centralize pharmacy filling operations to take advantage of economies of scale in labor and inventory management and better control the cleanliness and labeling of ordered doses. The introduction of USP <797> increased the pressure on health systems to move to a centralized model to ensure compliance. Some systems took the model a step further by centralizing filling for multiple hospitals to a single, compliant preparation facility.

Centralization created challenges for health systems in terms of dose delivery logistics and waste. "Immediate use" needs complicated the model by requiring decentralized preparation areas to support therapeutic changes, first doses and stat orders.

In addition, significant challenges arose in terms of quality control, training, documentation and verification for central fill doses.

Pharmacy automation can enable health systems to meet the documentation and regulatory challenges for successful central fill operations. Specifically IntelliFill i.v. provides levels of control currently unavailable to manual pharmacy practice and provides demonstration of product quality that could meet the FDA mandate for verifying that a manufactured product meets its specifications.

*IntelliFill i.v. is manufactured for Baxa Corporation by FHT, Inc.*

1 The Joint Commission. [www.jointcommission.org](http://www.jointcommission.org).