Automating the Sterile Compounding Process

Traditionally, the process of creating compounded sterile preparations (CSPs) is one of the least automated in hospital pharmacy practice. Given the required resources, detailed preparation process, and overall cost related to CSP production, many pharmacies choose to outsource the task. However, pharmacies that outsource must consider the impact of relinquishing control over a process that has the potential to cause significant patient injury. Fortunately, compounding automation has matured in recent years, introducing sophisticated solutions for various stages in the CSP process and providing pharmacies an opportunity to review their approaches to compounding sterile preparations.

In recent years, the University of Rochester Medical Center (URMC) has faced a steadily increasing demand for complex CSPs, prompting the pharmacy to seek automated solutions to reduce or eliminate the potential for human error and system failures in our manual compounding process. Following an analysis of internal workflows and available solutions during 2011 and 2012, URMC determined that adopting a more centralized, technology-assisted compounding model would be the best choice for optimizing patient safety, protecting staff interests, and lowering costs.

**Manual Compounding Risks**

Manual sterile compounding requires detailed procedures executed by highly trained staff and must incorporate multiple check and verification steps. Unfortunately, these complex processes often occur under time pressures and within constrained spaces; such conditions foster the potential for human error, and the probability of detecting an error once the compounding process is complete is relatively low.

Like most hospital pharmacies, the patient-specific compounding process at URMC begins with a provider order for an IV product that requires compounding. A final product label and compounding recipe is generated, indicating the product to be compounded, including the ingredients and amounts. These printed labels often go through a sorting routine based on when the product is needed (patient acuity), the time or conditions required to produce the preparation, or patient location. Critical information, including lot number and expiration dates for ingredients, is recorded manually. Each preparation then passes through a pre-check process. Admixing takes place in the cleanroom, and syringes are drawn back to indicate the volume of each ingredient added. The finished product and materials are sent to the pharmacist for a final check and labeling.

The well-known challenge to this process is truly validating CSP accuracy. To address this, many facilities have eliminated the syringe drawback method of checking for some high-risk products. Nonetheless, pharmacists checking the final product often do not have all of the information necessary to confirm that every step in the process was completed fully and accurately.

**URMC’s Compounding Solutions**

URMC chose an automated robotic strategy (left) supported by a human assistive device (right) for those products that cannot be compounded by the robot.

**Ensuring Quality Control**

Many pharmacy practitioners view the primary advantage of in-house sterile compounding as the ability to exercise total control over the process and, thereby, help to ensure patient safety. The devastating results of CSP errors—wherever they occur—are sobering, as more than 25 pharmacy compounding errors were associated with 1,049 adverse drug events and 89 deaths in the United States between 2001 and 2013, and these numbers are based on limited reporting. Contamination of sterile products is the most common error, followed by pharmacist and technician miscalculations. In what is probably the most publicized case, a multi-state fungal meningitis outbreak in 2012 that caused illness in over 700 patients and 64 deaths was traced to the use of expired ingredients and unsterile conditions at the New England Compounding Center in Massachusetts. In the case of outsourced products, the risk from contaminated CSPs is exponentially related to the breadth of distribution.

Nevertheless, it is important to acknowledge the fact that human error is a risk factor in even the most well-organized, <797>-compliant, in-house operations. Although many changes to state and federal oversight of compounding operations have occurred since those incidents, URMC became convinced that an automated, in-house system that employs bar codes, digital imagery, and gravimetric verification was necessary to facilitate comprehensive control over the compounding process with attendant quality assurance measures to optimize patient safety.
Likewise, the quality control capabilities of automation extend to staff protection. The precise controls and image capture mechanisms create a fully documented trail for each CSP produced, and this helps reduce the risk of errors accidentally slipping through the cracks. No pharmacist or techni-
cian wants to make a mistake, but the pressures of a busy workload can create a fissure in even the most solid manual processes. Partnering staff expertise with powerful automation technology is key to the provision of safe medications.

A Technology-Enabled Approach
URMC began analyzing its sterile compounding process by accessing data from the hospital’s error reporting system and conducting a thorough gap analysis. Through a failure modes and effects analysis, staff also evaluated near misses and potential errors to further characterize weaker compounding practices. The primary focus was to identify the points in the process where mistakes were most likely to occur and determine how best to protect the integrity of the process. The weak points identified included incorrect product selection, incorrect concentration of the selected product, incorrect volume of additives, and application of the wrong label to a product.

Ultimately, this process led to the decision to incorporate technology in the sterile compounding process. After reviewing the available technology-assisted and fully automated options, URMC chose a fully automated robotic strategy supported by human assistive devices for those products that cannot be compounded by the robot. The robotic system was installed and began producing CSPs in April 2014, and the human assist devices are going live this month. Coming from a manual compounding background, the human risk factors inherent in CSP production were simply too significant to be ignored. Given the increases

**Indication**
Neulasta® (pegfilgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive antineumor drugs associated with a clinically significant incidence of febrile neutropenia. Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

**Special Healthcare Provider Instructions for the On-body Injector for Neulasta**
A healthcare provider must fill the On-body Injector with Neulasta using the co-packaged prefilled syringe and then apply the On-body Injector for Neulasta to the patient’s skin (abdomen or back of arm). The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector for Neulasta. Approximately 27 hours after the On-body Injector for Neulasta is applied to the patient’s skin, Neulasta will be delivered over approximately 45 minutes. A healthcare provider may initiate administration with the On-body Injector for Neulasta on the same day as the administration of cytotoxic chemotherapy, as long as the On-body Injector for Neulasta delivers Neulasta no less than 24 hours after the administration of cytotoxic chemotherapy.

The prefilled syringe co-packaged in the Neulasta Delivery Kit contains additional solution to compensate for liquid loss during delivery through the On-body Injector for Neulasta. If this syringe is used for manual subcutaneous injection, the patient will receive an overdose. If the prefilled syringe for manual use is used with the On-body Injector for Neulasta, the patient may receive less than the recommended dose. Do not use the On-body Injector for Neulasta to deliver any other drug product except the Neulasta prefilled syringe co-packaged with the On-body Injector for Neulasta.

The On-body Injector for Neulasta should be applied to intact, non-irritated skin on the arm or abdomen.

A missed dose could occur due to an On-body Injector for Neulasta failure or leakage. If the patient misses a dose, a new dose should be administered by single prefilled syringe for manual use as soon as possible after detection.

Review the Patient Information and Patient Instructions for Use with the patient and provide the instructions to the patient.

Refer to the Healthcare Provider Instructions for Use for the On-body Injector for Neulasta for full administration information.

For any On-body Injector for Neulasta problems, call Amgen at 1-800-772-6436 or 1-844-MYNEULASTA (1-844-696-3852).

**Advice to Give to Patients Regarding Administration via the On-body Injector for Neulasta**
Advis patients to avoid activities such as traveling, driving, or operating heavy machinery during hours 24-29 following application of the On-body Injector for Neulasta (this includes the 45-minute delivery period plus an hour post-delivery). Patients should have a caregiver nearby for the first use.
in volume demand and the ever-tightening regulatory restrictions, we felt an automated compounding robot needed to be part of the solution. When the compounding process is fully automated within the enclosed, secure environment of a robot, human error is essentially eliminated, and the potential for contamination is drastically reduced. To date, URMC robots have produced over 13,000 preparations without any known errors or contamination concerns, and the number of robot-produced doses likely will grow dramatically over the next few months, as the pharmacy approaches full implementation.

Although a fully robotic sterile compounding operation can offer unparalleled levels of containment and precision, it also requires a significant investment; many facilities simply cannot justify these costs. Fortunately, human-assisted automation models exist that can apply process checks similar to those offered by fully automated systems. Pharmacists and technicians involved in compounding must adhere to the tenets of USP <797> and practice aseptic technique regardless of the containment levels, so using digital image capture during manual mixing stages can be a valuable addition. Likewise, the addition of bar coding and software tracking of products used in each CSP enables recalls through lot identification and offers a sound audit trail. Regardless of the size of an in-house sterile compounding operation, automated checks and balances are a wise investment.

The time required to introduce technological processes into CSP workflow and to maintain systems initially may seem onerous, but improved efficiency and accuracy offset those concerns for many pharmacies. Technology can save time by eliminating manual documentation, sorting of labels, and pre-check processes. When errors occur in manual compounding, the rework involved in reproducing products is time-consuming and wasteful.
Valuable Workflow Tools

Given the pace of technology advancements and changes in hospital pharmacy practice models, CSP production workflow requires constant review. One of the main reasons URMC chose an automated robotic solution with human assist technology was its incorporation of three precise workflow tools—bar code scanning, digital imagery, and gravimetric checking. These tools combine to provide enhanced safety to the sterile compounding process.

Bar Code Confirmation: Bar code scanning is incorporated into the sterile compounding process to identify the ingredients to be used and confirm that they match the patient order or batch requirement. Bar codes are helpful because they verify each specific compounding product at the outset of the process and replace or enhance manual check processes that are otherwise time-consuming, error-prone, and riddled with confirmation bias. However, bar codes do not assist in confirming the accuracy of the compounding process beyond the selection of ingredients.

Digital Imagery: Digital imagery provides visual confirmation of the steps taken to produce a CSP, along with a visual log for reference and documentation. Instead of manually attempting to confirm the steps a technician or pharmacist has taken via vial checks and drawn back syringes, pharmacists now have real-time access to images for reference. This functionality serves as an effective auditing tool to continually improve the compounding process and as a record in the event a particular compound requires detailed review.

Digital imagery also presents its own challenges; adequate data storage and network bandwidth can be problematic, and the technology is limited by what the human eye can view and by the inherent error in visual measuring devices, such as syringe gradations. Furthermore, although digital imagery can confirm that the correct volume was drawn, it does not guarantee that the correct solution was added to the final container. This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 6,924,784; 5,923,623; 5,805,755; and other patents of applicants pending.
Gravimetric Checking: Gravimetric checking assesses the specific gravity of a solution to help ensure the right amount of the correct ingredient is added to the compounded mixture. This process is considerably more accurate than analyzing a drawn back syringe or reviewing a visual image of a syringe filled with fluid.

Although these tools can help optimize the safety and efficiency of CSP production, pharmacy must invest the necessary time and training in order to properly ingrain them in the compounding workflow. Supporting these technologies introduces challenges that require additional focus, including:

- Maintaining an active product database to support bar code scanning
- Acquiring specific gravities of various solutions for gravimetric checking
- Reprogramming technology when alternative drugs are introduced is a particular concern, as medication shortages have become the norm

Prioritizing new workflows to support these technologies is key to process adoption and success. With these tools in place, URMC will augment its patient safety measures, allowing its pharmacy staff to focus time and resources on critical tasks. These benefits outweigh any concerns about the time required to maintain the system and incorporate advancements.

The Future of Sterile Compounding
As the regulatory environment for sterile compounding continues to tighten its control and demand more in terms of accountability and traceability, hospital pharmacists need to remain abreast of the latest developments, become fluent in USP standards related to compounding (including Chapters <797> and the forthcoming <800>), as well as the federal Drug Quality and Security Act, and any state reforms that may be underway.

Hospitals and health systems constantly are positioning themselves to provide the highest quality, most cost-effective, and safest patient care. No stone should remain unturned when it comes to quality and process improvements in the pharmacy, and sterile compounding should rank as a high priority, given the potential for error leading to injury. Forward-looking organizations acknowledge automation’s potential role in a comprehensive solution to the complexities and accountability associated with compounding sterile preparations.

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References