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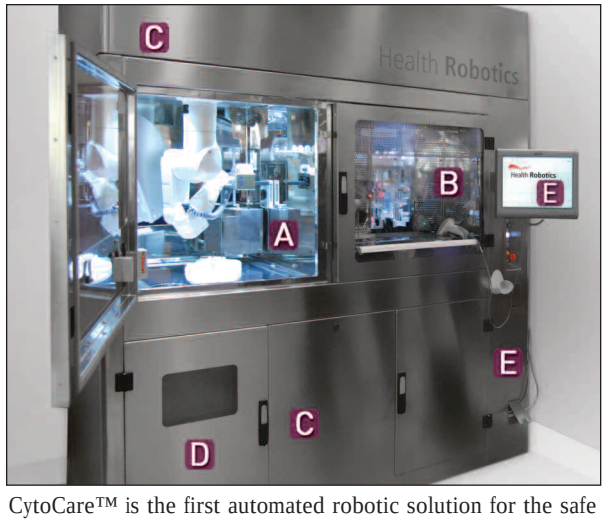
PRODUCT INFORMATION GUIDE

The Future of Hazardous IV Drug Preparation Is Here

By their nature, the hazardous drugs used to treat certain diagnoses carry intrinsic risk to patients and health care workers if they are not dosed, compounded, handled, and administered with accuracy and appropriate safeguards. Patients may be put at risk due to errors in product identification, dose calculation, dose measurement, and labeling. In addition, health care workers are at risk of accidental exposure when handling, compounding, and administering hazardous drugs.

The Danger to Patients

While all medication errors have the potential to do harm, errors involving IV admixtures, particularly those containing hazardous drugs, can have especially catastrophic results. Patients' lives can be negatively and permanently impacted and loss of life is quite possible. In one study, compounding and labeling errors were found to occur in 3% to 7% of inpatient cases, suggesting that medication errors harm more than 90,000 U.S. hospital patients annually.[1] For these reasons, health care facilities continue to seek the best combination of people, practices, equipment, and technology to improve safety and decrease the potential for iatrogenic morbidity and mortality.



CytoCare™ is the first automated robotic solution for the safe preparation of patient-specific, hazardous drugs. **A**: drug-compounding area. **B**: loading/unloading/temporary storage area. **C**: air-treatment unit with HEPA filters. **D**: automatic waste management area. **E**: electronics compartment.

The Danger for Health Care Workers

As they prepare the very drug products that will save lives and improve quality of life, pharmacists, pharmacy technicians, and other health care workers are at considerable risk for exposure to hazardous drugs. Accidental inhalation, ingestion, injection, and percutaneous absorption are all possible when compounding and/or administering hazardous IV medications. The results of such exposure may have the potential to do significant harm. A number of products, for example, are known carcinogens. Dangers to the unborn are also an issue, as studies show that adverse reproductive outcomes, including miscarriage, possible infertility, and congenital malformations, can result when female health care workers come in contact with dangerous drug products.[2-5]

Today's Safety Strategies

While many, if not all, facilities have taken steps to promote safe practices, there remains the potential for error and accidental exposure. Historically, the best options for improving patient safety have been combinations of additional in-process checking/validation by staff members, software-based ordering and compounding aids, improved compounding environments, and additional staff training. The options for protecting staff members from accidental exposure have been limited to the adoption of personal protective attire, compounding devices, and specialized training. Each of these strategies may produce incremental improvements, yet reports of errors and exposures persist.

The Regulatory Response

Drugs are classified as hazardous by the Occupational Safety and Health Administration (OSHA) if studies in animals or humans indicate that exposure to them has the potential for causing cancer, developmental or reproductive

toxicity, or harm to organs. The National Institute for Occupational Safety & Health (NIOSH), an advisory panel to OSHA, recommends instituting workplace safety procedures to minimize hazardous drug exposure. In particular, a landmark NIOSH Alert, released in 2004, calls for closed-system transfer devices (CSTDs), which limit the potential for generating dangerous aerosols and reduce health care worker exposure to hazardous drugs.[6]

Another seminal document addressing the subject of hazardous drug preparation and patient/health care worker safety is *United States Pharmacopeia* (*USP*) *Chapter 797*, which sought to "prevent patient harm and fatality from microbial contamination (nonsterility), excessive bacterial endotoxins, large content errors in the strength of correct ingredients, and incorrect ingredients in CSPs." However, *USP 797* focused on manual compounding, with contamination rates as high as 6%. In addition, *USP 797* only briefly addresses the issue of hazardous drugs and offers little concrete guidance on protecting health care workers from harmful exposure.

What Is the Scope of the Environmental Contamination Problem?

Studies since the early 1990s reveal a high level of contamination, even when health care workers implement a Class II biological-safety cabinet (BSC), which has an open front and vertical-laminar-airflow through a high-efficiency particulate air (HEPA) filter. In a 1993 study in the U.S. involving a limited number of wipe samples collected from pharmacy and clinic areas, contamination with antineoplastic agents was found in 18% of the pharmacy samples and 14% of the clinic samples tested.[7]

Further studies have found detectable concentrations of one to five hazardous drugs in places such as BSC surfaces, floors, countertops, storage areas, tables, and chairs in patient-treatment areas and locations near drug-preparation areas. A six-site study conducted in 1999 found cyclophosphamide and ifosfamide, drugs used to treat several types of cancers, on work surfaces and floors of a drug-preparation area even though Class II BSCs were in place.[8] In a 2001 study, 13 of 20 investigations found six drugs (cyclophosphamide, methotrexate, ifosfamide, epirubicin, and cisplatin/carboplatin) in health care workers' urine samples.[9] Hazardous surface contamination was containable, study results showed, with the addition of CSTDs.[10] The concentration of cyclophosphamide or ifosfamide in the urine of heath care workers and the percentage of samples with these drugs was reduced. *These findings may invite the question as to whether or not CSTDs (or other containment strategies) will, at some point, be mandatory.*

Why Are Humans Involved in Compounding At All?

Unfortunately, no matter how many steps are taken to prevent errors and accidental exposure, questions about the safety of manual compounding environments persist. Can health care workers be certain that current equipment is even used correctly? Are workers properly trained? Is the compounding environment and are workload expectations conducive to safety?

In traditional compounding and drug handling, hospitals rely on human checks and balances to prevent errors. Still, mistakes are made, no matter how closely hospital personnel try to adhere to accepted safe drug-handling protocols.

Simply touching containers of hazardous drugs can expose workers to residual drug that may be present on those containers. Further, active drug may "escape" containment during the compounding process in the form of drips, aerosols, powder dispersion, and/or vapor generation. While proper technique may afford some measure of protection, the studies mentioned above seem to indicate that technique alone is not sufficient to produce a safe environment for staff members.

Patients may also continue to be at unnecessary risk, even when rules and precautions are put into place. Failures to execute properly with respect to rules and precautions certainly exist. In some cases, staff members report being "distracted" or "too busy" when questioned about errors. Errors may occur at multiple points in the medication preparation cycle, including, but not limited to dose calculation, measurement, and labeling. Especially in cancer treatment, dose-calculation errors, prescription errors, and drug-exchange errors have extremely high potential for adverse consequences to patients.

Why Not Automate the Drug-Preparation Process?

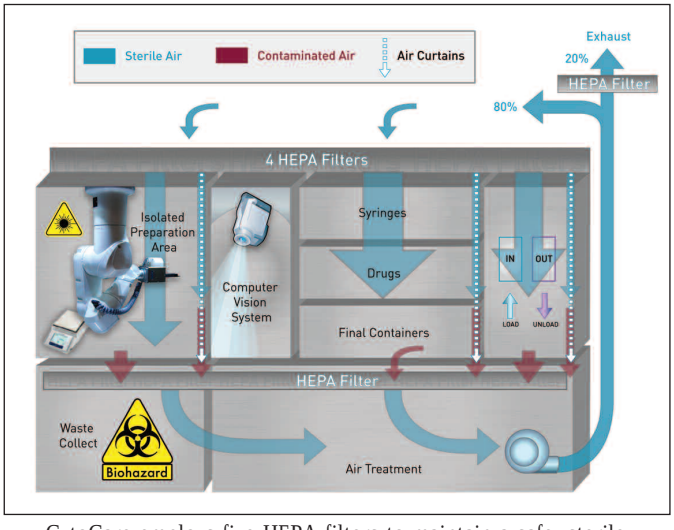
In essence, we have tried to "check" errors and exposures out of the compounding process and we have tried to "train" them out as well. Both approaches seem to fall short of the desired level of safety. In the end, it may only be possible to "engineer" errors and accidental exposure out of these processes. Robotic drug-preparation and handling processes afforded by automation mitigate drug-handling dangers in several ways. For one thing, robotics systems, unlike humans, are not subject to distractions or to the negative impact of peak workload situations on performance. Robots follow the same, correct procedures every time, without fail. In addition, automated systems are not prone to potentially catastrophic errors involving misplaced decimal points, mistakes that can lead to dangerous, even potentially fatal, tenfold (or worse) inaccuracies.

In contrast to manual compounding, robotic systems afford quality control, safety, and efficiency unattainable by humans. CytoCare™, by Health Robotics, is the world's first and only robotic solution for the safe preparation of patient-specific IV doses of hazardous drugs. CytoCare is designed to meet the challenges of safe drug preparation.

In an automated process, CytoCare produces sterile, accurate, ready-to-administer IVs. The CytoCare system features an ISO Class-5-certified air quality environment, employing negative-pressure, externally vented airflow, and a process for eliminating the potential for cross-contamination of substances. In fact, no part of the machine ever contacts medications.

Is the Best CSTD a Robot?

The CytoCare drug-preparation process begins with a trained pharmacist planning the preparation cycle. He or she validates the prescription and manages incoming preparation requests with CytoCare's onboard computer system, featuring interfaced integration with hospital pharmacy systems. He or she prelabels the final dose container then inserts the proper drugs, compounding supplies, and final containers into the robot's loading area. A variety of final containers from various manufacturers may be used, including multiple syringe sizes, multiple bag sizes, and elastomeric containers. CytoCare's sophisticated technology identifies drugs, diluents, and containers using a combination of bar code scanning and digital imaging. Product identification and preparation instructions are "known" to the robot through its onboard formulary, further ensuring accurate results.



CytoCare employs five HEPA filters to maintain a safe, sterile environment during each phase of the drug-preparation process.

Employing a six-axis robotic arm, CytoCare begins the actual compounding process. Powdered drugs are reconstituted as specified in the formulary. Doses are then measured using three independent systems: encoders on the syringe driving mechanism, laser-guided syringe plunger positioning, and pre- and postweight comparison on a precision scale (using density, sometimes referred to as "specific gravity") to ensure dose accuracy. In this way, CytoCare also automatically finds deficits or excesses of drug products in containers, should they occur. It is important to note that cross-contamination is avoided through the use of new consumables for each product (syringes and needles). No tubing sets are required during compounding. The robot also uses a commercially available needle that is designed to minimize coring and a visual guidance system to effect a near-perfect septum penetration.

CytoCare's measurement technology represents a vast improvement over traditional measurement methods. The ISO standard 7886, which governs syringe calibration tolerances in manual compounding, permits low precision levels; a more than 4% error rate is acceptable! The calibration scale on the syringes used in manual compounding therefore suffers from variability, so the resulting drug product quantities are also subject to inaccuracy. CytoCare employs a laser eye to measure travel distance during the drug-measuring process, a fail-safe method that overcomes the problem of dead space at the end of the plunger's route.

At the conclusion of the compounding process, finished doses are presented to the operator in the loading/unloading chamber. A final, patient-specific label verifying the drug product's preparation is then generated, and every step of the product's preparation is documented. This feature affords hospitals a seamless record of all steps for complete searchability and accountability.

CytoCare also manages partial vials that may remain after doses are compounded. It tracks beyond-use dating according to hospital-selected guidelines. If a subsequent dose is requested and can be compounded from an existing partial vial, the robot will do so without asking for additional product. This may significantly reduce waste that is inherent in a human-based compounding scenario.

To further protect staff members and the compounding environment, CytoCare collects used supplies and remaining, unusable containers in an onboard waste container. It is constantly monitored (by weight) and alerts the operator when it is filled to a certain percentage of its capacity. When it hits a threshold, CytoCare automatically seals the container with a glue-on lid. A manifest of the waste container's contents is generated and the container is ready for proper disposition.

To maintain a sterile environment, CytoCare employs five HEPA filters, arranged such that air is filtered as it enters and exits the chambers. In addition, strategically placed "air curtains" between the chambers preclude the passage of contamination from one area to the next. This is important for the operator as it protects him/her from contaminants that may be present in the compounding chamber while he/she works in the loading/unloading area. It also shields products from contamination in different areas of the compounding chamber to avoid such problems as aerosolized drug being deposited on the external

surface of a final container. The chambers, which are made of stainless steel, are cleanable with antimicrobial solutions and typical decontamination solutions used in cleaning BSC's. During off hours, when CytoCare is not in use, ultraviolet lamps are used to further disinfect the robot's internal environment.

How Much Can Be Saved by Switching to a Robotic System?

Robotic IV admixture production has the potential to reduce operating expenses substantially, often in excess of the cost of the technology. Categories of savings include, but are not necessarily limited to, supply, waste, and staffing expense. This is especially true in oncology where, for example, compounding and/or protocol management errors may result in wasted doses. This becomes very expensive in an environment where wasting a single dose of drug may, on average, cost a facility over $600. In total, oncology medication waste could cost a hospital thousands of dollars. This will become increasingly important if, as estimated by the World Health Organization, we see a 50% increase in cancer cases between now and 2020.

CytoCare assists in decreasing waste in at least two ways. First, by eliminating the "oops" factor when doses are either made when they should not be or when they are made at the right time, but are made in error. CytoCare helps with these errors through both software and robotic controls. The software can be used to effectively manage protocols, such that doses are only made after all prerequisites are satisfied in the protocol. In traditional systems, a few doses are made prematurely due to unnoticed "holes" in protocol management. CytoCare takes care of the rest of the errors by calculating, selecting products, measuring, and labeling accurately and with robotic precision.

The second type of waste reduction strategy is related to waste that is inherent in the compounding process, primarily in discarding unused portions of drug vials. These may be discarded in manual compounding systems due to lack of processes by which to maintain control over them. For example, what can you do with a partial vial of a hazardous drug while you are awaiting another order for that drug? In most cases, there is no safe, effective way to store it and to track its beyond-use dating parameters. CytoCare offers a strategy that will help with this. First, the robot has "parking spaces" for partial vials located in the compounding chamber. It tracks every partial vial from the time that it is first reconstituted/used. CytoCare places vials in the parking lot and "remembers" each location where a vial is stored. Each vial's beyond-use dating is continually monitored to ensure that no drug is used beyond an acceptable time limit. As subsequent orders are placed, CytoCare first "looks" at the inventory in the parking lot and uses partial vials when it can, before requesting new vials.

Supplies used in compounding, especially CSTDs, also add significant cost to drug compounding and administration processes. In some cases, CSTDs may add costs of $10 to $15 per dose to the compounding process and an additional $10 per dose to drug administration expenses. CytoCare can eliminate much, if not all, of this additional cost.

Hospitals and cancer centers that install CytoCare can potentially realize tremendous ROI very quickly from waste savings, elimination of CSTDs, and efficiency upgrades. Take, for example, a hospital that produces 30 chemotherapy doses per day or 7,800 doses per year. Assuming that the average drug expense is $600 per dose, waste from partial vials is 3% of purchases (and CytoCare can reduce this by 50%) and doses are made in error (or at the wrong time) 0.4% of the time. The estimated annual savings are shown in **TABLE 1.**

Table 1: Estimated Operational Cost Elimination With CytoCare

Expense/Source of Waste	Resulting Costs	Annual Savings
CSTD	7,800 doses x $15/dose (Rx & nursing)	$117,000
Partial vials	$4,680,000 (total spend) x 1.5%	$70,000
Medication errors	7,800 x 0.4% x $600/dose	$18,720
Total savings		$205,720

CSTD: closed-system transfer device.

CytoCare's software features interface integration, enabling hospitals to maximize the efficiency of communication systems. This will further enhance the efficiency of the drug-preparation process and, ultimately, save hospitals money. In addition, the machine allows for the precise calculation of single-drug preparation based on the amount of medication actually used. It is also possible to retrieve information from a single preparation or extract aggregated data for reporting purposes. This facilitates easy cost-tracking, which translates into added cost efficiencies for hospitals. ■

References

1. Bond CA et al. Clinical pharmacy services, hospital pharmacy staffing, and medication errors in United States hospitals. *Pharmacotherapy.* 2002;22(2):134-147.
2. Selevan SG et al. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. *N Engl J Med.* 1985;313(19):1173-1178.
3. Stücker I et al. Risk of spontaneous abortion among nurses handling antineoplastic drugs. *Scand J Work Environ Health.* 1990;16(2):102-107.
4. Hemminki K et al. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. *J Epidemiol Community Health.* 1985;39(2):141-147.
5. Valanis B et al. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med.* 1999; 41(8):632-638.
6. NIOSH Alert. Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings. September 2004.
7. McDevitt JJ et al. Exposure of hospital pharmacists and nurses to antineoplastic agents. *J Occup Med.* 1993;35:57-60.
8. Connor et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health Syst Pharm.* 1999;56(14):1427-1432.
9. Harrison BR. Risks of handling cytotoxic drugs. In: Perry MC, ed. *The Chemotherapy Source Book.* 3rd ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2001:566-582.
10. Wick C et al. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. *Am J Health Syst Pharm.* 2003;60(22):2314-2320.