In-Depth Survey Report

Engineering Control Evaluation at Veterinary Hospital F

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Abstract

NIOSH researchers conducted a field survey at Veterinary Hospital F in August 2018. The purpose of the site visit was to identify and evaluate hazardous drug engineering controls as well as to sample for potential surface contamination at the hospital. NIOSH researchers also observed and interacted with the hospital's veterinarians and staff to obtain information about the hazardous drug work practices, daily activities, and oncology treatment processes.

A TSI® Accubalance® Plus Air Capture Hood Model 8373 was used to measure mechanically generated supply and exhaust airflows in the pharmacy's main room and cleanroom areas. Air measurements were taken using the instrument's backpressure compensation to ensure accurate readings. The pharmacy area had more supply air (0.52 m^3/s or 1098 cfm) than was mechanically exhausted (0.16 m^3/s or 329 cfm) which aligned with the positive pressure observation earlier in the qualitative test with the Wizard Stick handheld smoke generator.

The positive pressure non-hazardous drug sterile compounding cleanroom calculated air changes per hour (ACH) was 104, thus exceeding the minimum ACH requirements [USP 2019]. The anteroom's calculated ACH was 63, also exceeding the minimum ACH requirements [USP 2019]. The negative pressure hazardous drug sterile compounding cleanroom calculated ACH was 69, also exceeding the minimum ACH requirements [USP 2019]. The pressure differential from the anteroom to the general pharmacy area was 0.07 inches of water, from the anteroom to the negative pressure hazardous drug sterile compounding cleanroom was 0.04 inches of water; and from the anteroom to the positive pressure non-hazardous drug sterile compounding cleanroom was 0.03 inches of water. Recently-conducted certification records indicated the negative pressure hazardous drug cleanroom supply was 0.20 m^3/s (434 cfm) and it had a negative pressure of -0.017 inches of water, which meets the USP <800> requirement of -0.01 to -0.03 inches of water [USP 2019]. During the NIOSH site visit, the Magnehelic® pressure differential gauge read -0.04 inches of water. The room remained very negative despite on-site maintenance staff efforts to correct the problem. Since both biological safety cabinets (BSCs), one-each within the positive pressure and negative pressure cleanrooms, were recently certified prior to the NIOSH visit, these were not quantitatively evaluated during the field survey.

The presence of potential surface contamination was evaluated with wipe samples. These were collected in areas where the staff handled chemotherapy drugs, such as the oncology department. Wipe samples were also collected in less obvious places (i.e., telephone, door handles) to determine if current workplace safety practices at the hospital were adequate to prevent inadvertent contamination of these surfaces. In some cases, a single sample could be evaluated for more than one analyte simultaneously. Vinblastine and cyclophosphamide were the drugs handled during the NIOSH visit. NIOSH staff did not see chemotherapy administration to patients during the visit. Sample results revealed that 1 out of 9 wipe samples submitted for carboplatin was positive (6.75 ng/sample). The 2 samples submitted for vinblastine

were non-detectable (ND). The ND determination means that contamination was either not present, or was present at levels below the detectable limit of the analytical method. Two of 19 samples submitted were positive for cyclophosphamide (3.6 ng/sample) and doxorubicin (1.0 ng/sample) while simultaneously being ND for vincristine, epirubicin, and methotrexate. The doxorubicin wipe sample was between the limit of detection (LOD) and limit of quantification (LOQ). Five out of 5 wipe samples submitted for N-methyldiethanolamine (MDEA) were positive (5.2 to 48.6 ng). All of the 5 wipe samples submitted for toceranib, chlorambucil, and lomustine were ND. MDEA was monitored as a potential stable marker for the highly unstable antineoplastic drug mustargen as explained in the text.

Although some of the wipe sample analytical results were ND, there is no safe level of exposure when handling hazardous drugs. The carboplatin, cyclophosphamide, doxorubicin, and MDEA presence serves as a reminder that hazardous drug contamination can sometimes linger despite cleaning efforts. Therefore, it is important to continue to use engineering controls (e.g., biological safety cabinets), supplementary controls (e.g., closed system drug-transfer devices), protective work practices (e.g., surface cleaning after every oncology patient, regardless of whether I.V. chemotherapy was administered), and personal protective equipment (e.g., gloves and gowns rated for chemotherapy protection, respirators, shoe covers, eye protection) to reduce unintentional exposures to the staff or pet owners.

Introduction

Background for Control Technology Studies

The National Institute for Occupational Safety and Health (NIOSH) is the primary Federal agency engaged in occupational Safety and health research. Located in the Department of Health and Human Services, it was established by the Occupational Safety and Health Act of 1970. This legislation mandated NIOSH to conduct a number of research and education programs separate from the standard setting and enforcement functions carried out by the Occupational Safety and Health Administration (OSHA) in the Department of Labor. An important area of NIOSH research deals with methods for controlling occupational exposure to potential chemical and physical hazards. The Engineering and Physical Hazards Branch (EPHB) of the Division of Field Studies and Engineering has been given the lead within NIOSH to study the engineering aspects of health hazard prevention and control.

Since 1976, EPHB has conducted a number of assessments of health hazard control technology on the basis of industry, common industrial process, or specific control techniques. Examples of these completed studies include the foundry industry; various chemical manufacturing or processing operations; spray painting; and the recirculation of exhaust air. The objective of each of these studies has been to document and evaluate effective control techniques for potential health hazards in the industry or process of interest, and to create a more general awareness of the need for or availability of an effective system of hazard control measures.

These studies involve a number of steps or phases. Initially, a series of walk-through surveys is conducted to select plants or processes with effective and potentially transferable control concept techniques. Next, in-depth surveys are conducted to determine both the control parameters and the effectiveness of these controls. The reports from these in-depth surveys are then used as a basis for preparing technical reports and journal articles on effective hazard control measures. Ultimately, the information from these research activities builds the data base of publicly available information on hazard control techniques for use by health professionals who are responsible for preventing occupational illness and injury.

Background for this Study

The 2004 *NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings* introduced a standard of universal precautions for handling hazardous drugs safely [NIOSH 2004]. The health effects due to occupational exposure to these drugs are extensive and can include chromosomal and other types of genetic damage, reproductive damage [NIOSH 2004], and exposure can cause adverse pregnancy outcomes [Albin 2010]. The NIOSH Alert states that its guidance applies to any worker who handles hazardous

drugs, including veterinary medicine and animal care (VM/AC) workers [NIOSH 2004]. Cancer is a leading cause of death among cats and dogs and attributes to 50 percent of pet deaths each year [Crump 2013]. In addition, chemotherapy is widely used to treat animals with cancer and other ailments as owners wish to prolong the lives of their beloved pets [Fielding and Lacroix 2009]. As chemotherapy drug (most are identified as hazardous drugs) use increases and lower-cost generic drugs become available, many veterinarians are administering chemotherapy drugs on their own or through a veterinary oncologist [MacDonald 2009].

In the U.S., there are an estimated 500,000 VM/AC workers, not including young adults who work part-time or during school breaks [Mobo et. al 2010]. This project specifically benefits special population/priority population groups as 95% of veterinary technicians are women of reproductive age with a mean age of 38 [Technicians 2008]. Veterinary medicine is similar to human healthcare in that the professional objective is to provide medical, surgical, and preventive healthcare to a patient. Both veterinary medicine and human healthcare personnel are vulnerable to needlestick injuries, radiation exposure, and hazardous drugs [Hall et. al 2013]. However, VM/AC workers are more likely to have accidents and occupational diseases, as they are susceptible to animal bites, zoonoses, animal-related respiratory hazards, physical injury, and veterinary-related reproductive hazards [Epp and Waldner 2012; Hall et. al 2013]. Although both professions handle hazardous drugs, there are differences in how veterinary clinics obtain, prepare, and administer the drugs, house the dosed patient, and handle a dosed patient's excreta or vomitus [Seibert 2013]. A recent study showed that VM/AC workers were exposed to hazardous drug concentrations 15 times higher than human healthcare personnel, partly due to how chemotherapy is administered in animals versus humans [Klahn 2014]. Cost, time, inconvenience, and discomfort are just some of the reported barriers for VM/AC workers not using safety measures in their practices [Klahn 2014].

Also unlike human health care, veterinary medicine's job duties are not compartmentalized. It is common for administrative personnel to conduct day-to-day animal-care activities, especially in small clinics [Seibert 2013]. Administrative personnel may restrain animals for hazardous drug administration, clean cages, feed the animals, and assist the veterinarian. When they occur, tasks involving unsafe work practices not only affect the primary task worker, they put other VM/AC workers, such as veterinary assistants, kennel attendants, or animal care workers, at risk for occupational exposure to chemotherapy drugs. This work-task diversity emphasizes the need for a thorough evaluation (and cross-training) of safety practices in the handling of hazardous drugs (and the patients the drugs are administered to) in veterinary medicine. VM/AC workers need to be educated in: 1) the risk of the drugs they are handling; 2) how to handle the drugs safely through proper use of engineering controls and personal protective equipment (PPE); and 3) how to avoid exposure to hazardous drugs and their metabolites through carefully delineated safe work procedures.

Conversations with veterinary stakeholders revealed that the warnings and guidance in the NIOSH Alert are not effectively reaching VM/AC workers. Animal oncology clinics are staffed with general practitioners and clinic staff without awareness of chemotherapy safety [Klahn 2014]. In one reported case study, a veterinarian admitted pouring hazardous drugs down the sink at his clinic. He then developed thyroid cancer at the age of 35, reportedly as a result of handling hazardous drugs. It was further estimated that over 4,000 veterinary practices administer chemotherapy without any safety measures [Smith 2010]. While the NIOSH Alert has had a significant impact upon hazard awareness and exposure prevention within human healthcare, there are significant differences (real and perceived) between the practices of human and veterinary medicine. These differences have reportedly been a roadblock in the NIOSH Alert's positive impact upon veterinary medicine. Controlling exposures to occupational hazards is the fundamental method of protecting workers. Traditionally, a hierarchy of controls establishes preferences in determining how to implement feasible and effective controls. The most preferred control, the elimination or substitution away from the use of hazardous drugs, is not realistic for this industry. The use of personal protective equipment is considered to be the least effective exposure control on a consistent basis [Mobo et. al 2010]. Therefore, engineering controls and work practice guidelines together form the first lines of defense for VM/AC worker protection against hazardous drug exposure.

Hospital Description

The veterinary hospital, which is the subject of the report, is referred to as Veterinary Hospital "F" in order to preserve its anonymity. Veterinary Hospital F provides primary, specialty, and emergency care to small and large animal patients. The hospital offers various services including oncology. The oncology department administers chemotherapy to patients four to five days a week. Chemotherapy drugs are compounded in the hospital's on-site pharmacy and administered to patients in the oncology department. In 2015, a cleanroom was added to the pharmacy for compounding chemotherapy drugs. The cleanroom configuration utilized a single positive-pressure anteroom that served both a negative pressure hazardous drug sterile compounding cleanroom and a positive pressure non-hazardous drug sterile compounding cleanroom. A Labconco horizontal flow bench (4 foot, Laminar Air Flow Work Station, Model 3888420, Labconco, Kansas City, MO) is located in the positive pressure non-hazardous drug sterile compounding cleanroom (Figure 1). A Labconco biological safety cabinet (BSC) (Class II, Type A2, model 302481100, Labconco, Kansas City, MO) is located in the negative pressure hazardous drug sterile compounding cleanroom (Figure 2). Both hoods were certified on August 1, 2018.

Chemotherapy Preparation and Administration

Closed System Drug-Transfer Devices (CSTDs)

For non-sterile drugs, Veterinary Hospital F uses the ICU Medical closed system drug-transfer device (CSTD) system (ICU Medical, Inc., San Clemente, CA) to prepare various drugs. For sterile-drugs, particularly drugs administered to chemotherapy patients, the hospital uses the Equashield CSTD (Equashield LLC, Port Washington, NY) to prepare and administer liquid forms of chemotherapy (Figure 3). By definition, a CSTD mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system [NIOSH 2004]. CSTDs limit the potential for aerosolizing drug contamination and can reduce worker exposure to sharps, thus reducing the likelihood of occupational exposure to hazardous drugs [NIOSH 2004]. Each CSTD system traditionally consists of a syringe adapter (i.e., CSTD syringe connector) plus three component adapters: vial adapter, intravenous (I.V.) port adapter or Y-site adapter, and a bag adapter or infusion adapter. Each of these adapters mates with the syringe adapter.

Occupational Exposure Limits and Health Effects

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH investigators use mandatory and recommended occupational exposure limits (OELs) when evaluating chemical, physical, and biological agents in the workplace. Generally, OELs suggest levels of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects even though their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a pre-existing medical condition, and/or hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects even if the occupational exposures are controlled at the level set by the exposure limit. Combined effects are often not considered in the OEL. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus can increase the overall exposure. Finally, OELs may change over the years as new information on the toxic effects of an agent become available.

Most OELs are expressed as a time weighted average (TWA) exposure. A TWA exposure refers to the average airborne concentration of a substance during a normal 8- to 10-hour workday. Some substances have recommended short-term exposure limit (STEL) or ceiling values which are intended to supplement the TWA where there are recognized toxic effects from higher exposures over the short-term.

In the U.S., OELs have been established by Federal agencies, professional organizations, state and local governments, and other entities. The U.S. Department of Labor OSHA permissible exposure limits (PELs) [CFR 2003] are occupational exposure limits that are legally enforceable in covered workplaces under the Occupational Safety and Health Act. NIOSH recommendations are based on a critical review of the scientific and technical information available on the prevalence of health effects, the existence of safety and health risks, and the adequacy of methods to identify and control hazards [NIOSH 1992]. They have been developed using a weight of evidence approach and formal peer review process. Other OELs that are commonly used and cited in the U.S. include the threshold limit values (TLVs) recommended by ACGIH®, a professional organization [ACGIH 2010]. ACGIH TLVs are considered voluntary guidelines for use by industrial hygienists and others trained in this discipline "to assist in the control of health hazards." Workplace environmental exposure levels (WEELs) are recommended OELs developed by AIHA, another professional organization. WEELs have been established for some chemicals "when no other legal or authoritative limits exist" [AIHA 2007].

OSHA requires an employer to furnish employees a place of employment that is free from recognized hazards that are causing or are likely to cause death or serious physical harm [Occupational Safety and Health Act of 1970, Public Law 91–596, sec. 5(a)(1)]. Thus, employers are required to comply with OSHA PELs. Some hazardous agents do not have PELs, however, and for others, the PELs do not reflect the most current health-based information. Thus, NIOSH investigators encourage employers to consider the other OELs in making risk assessment and risk management decisions to best protect the health of their employees. NIOSH investigators also encourage the use of the traditional hierarchy of controls approach to eliminating or minimizing identified workplace hazards. This includes, in preferential order, the use of: (1) substitution or elimination of the hazardous agent, (2) engineering controls (e.g., local exhaust ventilation, process enclosure, dilution ventilation), (3) administrative controls (e.g., limiting time of exposure, employee training, work practice changes, medical surveillance), and (4) PPE (e.g., respiratory protection, gloves, eye protection, hearing protection).

Occupational Exposure Limits and Hazardous Drugs

Currently there are no PELs, RELS, or TLVs® for hazardous drugs [NIOSH 2004]. However, a PEL, REL, and TLV® have been established for inorganic arsenic compounds, such as arsenic trioxide, an antineoplastic drug [NIOSH 2004]. A WEEL has been established for some antibiotics. Some pharmaceutical manufacturers develop risk-based OELs and that information may be listed on the safety data sheets (SDSs) [NIOSH 2004].

Methodology

BSC and Oncology Department Performance Evaluations

Equipment: BSC Qualitative Smoke Test

A Wizard Stick (Zero Toys, Inc., Concord, MA) handheld “smoke” generator was used to visualize air movement inside and around the periphery of the pharmacy drop off window (Figure 4). The wizard stick produces a stream of safe, condensed vapor droplets and contains no actual solid 'smoke' particles, however the vapor droplets float in the air, appearing similar to smoke, and their flow path is indicative of the flowpath of the air in which they are suspended.

Procedure

The “smoke” was released around the periphery of the pharmacy’s drop off window to qualitatively evaluate whether the pharmacy was under positive or negative pressure. If the smoke moved inwards toward the pharmacy, then the room was under negative pressure. If the smoke moved outwards away from the pharmacy window, then the room was under positive pressure.

Equipment: Measurement of Supply and Exhaust Airflow Rates in the Pharmacy and Cleanroom

A TSI Accubalance® Plus Air Capture Hood Model 8373 (TSI Incorporated, St. Paul, MN) was used to measure airflow for the supply and return ventilation in the pharmacy and cleanroom (Figure 5).

Procedure

The instrument was setup according to the manual using the appropriate flow hood 0.6 m x 0.6 m (2 ft x 2 ft) or 0.6 m x 1.2 m (2 ft x 4 ft) to match the corresponding sized supply and exhaust louvers. The instrument was turned on and the hood was placed over the supply or exhaust vent. The measured airflow was displayed in cubic feet per minute (cfm) on the instrument’s screen during measurement. Air measurements were taken using the instrument’s backpressure compensation to ensure accurate readings.

Wipe Sampling Method

Surface wipe samples were collected throughout Veterinary Hospital F using different sampling methods. Samples were collected in areas where drugs were handled by the workers, such as the pharmacy, cleanroom areas, intensive care unit (ICU), oncology department, and in places similar to those where traces of drugs have been found in human studies, such as door handles [Connor et. al 2010; Hon et. al 2013]. Wipe samples were also taken in less obvious places to determine if the hospital’s current workplace safety practices were successful in

preventing secondary contamination. NIOSH researchers were careful not to collect two samples from the same surface area. It should be noted that each of these wipe sampling methods are internal methods created specifically for this research study. There is limited data on recovery studies from various surfaces.

Wipe Sampling Method 1: Bureau Veritas North America Analytical Methods

The Bureau Veritas North America wipe sample collection method uses Texwipe™ Alpha™ Polyester Series Swabs (TX715, ITW Texwipe, Kernersville, NC) and a 50:50 mixture of methanol and water (both high-performance liquid chromatography grade) solvent to collect surface wipe samples. Although the subsequent analytical methods may vary by analyte, this wipe sample collection method is applicable for analysis of carboplatin, vincristine, methotrexate, cyclophosphamide, epirubicin, doxorubicin, and vinblastine (sulfate). Carboplatin is analyzed using Bureau Veritas North America's internal method, BV-2017-30843 (Bureau Veritas North America, Novi, MI), which uses high performance liquid chromatography/mass spectrometry (HPLC/MS) to find platinum. Vinblastine (sulfate) is analyzed using MAXAAM's internal method NAT 2006-14763, which uses HPLC. Vincristine, methotrexate, cyclophosphamide, epirubicin, and doxorubicin are analyzed using MAXAAM's internal method BV-2016-29599, which also uses HPLC/MS. Table I shows the analytical limit of detection (LOD), limit of quantification (LOQ), and analytical range for each of the analytes.

Prior to the visit to Veterinary Hospital F, several 16 mL amber vials with screw caps were filled with 1 mL of a 50:50 mixture of methanol and water. During the site visits, once a sampling location was identified, a surface wipe sample was collected using the Texwipe™ Alpha™ Polyester Series Swabs and solvent. First, the cap of the amber vial was removed and one of the swabs was inserted. After the swab was wetted with the solvent, the swab was pressed against the sample location and moved back and forth, progressing over an approximate 10 centimeter (cm) x 10 cm surface. The swab was then turned over and the same back and forth movement was repeated in a perpendicular direction to that first taken over the same 10 cm x 10 cm surface area. The excess solvent in the vial was poured onto an absorbent pad in a closable plastic bag for later disposal. The swab was placed head first partially into the vial opening and lateral pressure was applied to the swab stick to snap the head off and deposit it in the vial without touching. The cap and a label were placed on the vial. This surface wipe sampling collection method was repeated throughout the hospital. The samples were placed on ice packs until they were delivered to the NIOSH contract laboratory and stored frozen until analysis. Results are reported in nanogram of drug per sample (ng/sample). Vinblastine results are reported in microgram of drug per sample (µg/sample).

Wipe Sampling Method 2: NIOSH Internal Analytical Method

NIOSH developed a solvent system for surface wipe sampling and analysis using one of two wipe sampling media:Texwipe™ Alpha™ Polyester Series Swabs and Whatman™ filter papers (number 1442-055, 55-mm ashless circles, GE Healthcare, Chicago, IL).This sampling method applies to chemical analyses for lomustine (or

CCNU), toceranib, N-methyldiethanolamine (MDEA), and chlorambucil. MDEA was the actual analyte tested for in the sample analysis, as an indicator for mustargen. Table II shows the analytical LD), LOQ, and analytical range for each of the analytes.

The solvent used to moisten sampling media for collection of this set of analytes was 83% acetonitrile/17% dimethylsulfoxide/0.20% hydrochloric acid. This blend resulted from extensive experiments conducted in the lead-in to the first site survey performed for this research project and subsequent modifications. The blend provided stability in solution and adequate recoveries from quality control samples for all four of the antineoplastic drug analytes in this group via control of pH, solubility and other factors. The same solvent was used for preparation of calibration standards and in-house quality control samples to ensure compatibility with field samples during analysis.
After the swab/filter paper was wetted with the solvent, the wipe sample procedure was the same as that described in Wipe Sampling Method 1. Upon collection, the sampling media was placed over the 125 mL translucent polypropylene jar (Nalgene™ Wide-Mouth Straight-Sided Polypropylene copolymer [2118-0004], Thermo Scientific™, Rochester, NY) opening. If the swab was used for wipe sampling, then the swab (head first) was placed over the jar's opening and a lateral pressure applied to the swab stick to snap the head off and into the jar without touching. A second swab was wetted and the surface wipe sample collection was repeated for the same area using the same technique. The two wetted swabs made up one sample.

If the filter paper was used for wipe sampling, then a petri dish, separated into its top and bottom halves, was used for preparing the sample. First one Whatman™ filter paper was placed into each half of the petri dish. A pipettor and pipette were used to measure 250 microliters (µL) of the solvent onto each filter paper. An area of approximately 10 cm x 10 cm was sampled with one wetted filter paper and placed into a polypropylene jar. The same 10 cm x 10 cm area was then re-sampled, in a wiping progression perpendicular to the first filter using the second wetted filter paper. The second wetted filter paper was placed into the same jar. The two wetted filter papers made up one sample.

Upon sample collection, the lid and a sample label were placed on the jar. The samples were placed on ice packs and transported to a NIOSH laboratory freezer for cold storage until analysis. For processing the samples were brought to room temperature and extracted by 1 hour of agitation on an orbital shaker (180 rpm) after the addition of 9.5 mL of the aforementioned solvent, for a total of 10 mL sample volume. Extracts were filtered (0.22 µm polyvinylfluoridene syringe filters) and transferred to 2 mL capped glass autosampler vials. Analysis was performed using liquid chromatography–mass spectrometry (HPLC-MS). Results are reported in mass of drug (ng).

The analysis utilized controlled parent ion fragmentation (MS/MS) to yield multiple product ions for each compound. Two ions were monitored for each analyte and the

more intense response was used for quantification. Positive responses for an analyte were indicated by peak responses in the chromatograph above calculated limits of detection (q.v.) and by the presence of both expected fragment ions as previously exhibited by the calibration standards. Additionally, the intensity ratio of fragment ion responses for samples was compared to the average ratio observed for pure analyte standards, as an additional parameter for identifying reliable positive responses in the field samples. No isotopically labeled analyte standards were available for use in the HPLC/MS analysis, but all samples and calibration standards were fortified with a low concentration of hexamethylphosphoramide, a compound strongly responsive in HPLC/MS. The response of this compound was monitored throughout the analysis to indicate any significant changes in instrument response or chromatographic performance.

Results

BSC Face Velocity Measurements

Both biological safety cabinets (BSCs), one-each within the positive pressure non-hazardous drug and the negative pressure hazardous drug compounding cleanrooms, were recently certified prior to the NIOSH visit so the NIOSH researchers did not perform quantitative BSC evaluations. The performance of the hazardous drug BSC was verified qualitatively using the handheld smoke generator.

Qualitative Smoke Test

The Wizard Stick smoke generator was used to qualitatively test if the pharmacy was under negative or positive pressure. Smoke was released directly outside the pharmacy drop-off and pickup window. The smoke moved away from the pharmacy window, which indicated the pharmacy was under positive pressure.

Measurement of Supply and Exhaust Airflow Rates in the Oncology Department

The TSI Accubalance® Plus Air Capture Hood was used to measure mechanically generated supply and exhaust airflows in the pharmacy's main room and cleanroom areas. The pharmacy area was under positive pressure and had more supply air (0.52 m^3/s or 1098 cfm) than was mechanically exhausted (0.16 m^3/s or 329 cfm). The positive pressure non-hazardous drug sterile compounding cleanroom's volume (10.2 m^3 [360 ft^3]) and supply airflow (0.29 m^3/s [622 cfm]) were used to calculate the ventilation rate in air changes per hour (ACH) for the room to be 104 (Equation 1). The anteroom's volume (17.2 m^3 [680 ft^3]) and supply airflow (0.30 m^3/s [640 cfm]) were used to calculate the ventilation rate in ACH for the room to be 63. The negative pressure hazardous drug sterile compounding cleanroom's BSC exhaust (0.23 m^3/s or 482 cfm) and room volume (11.8 m^3 [418 ft^3]) were used to calculate an ACH of 69.

Equation 1:

$$ACH = \frac{Airflow\ (^{m^3}/_{s}) \times 3600\ sec}{Room\ Volume\ (m^3)}$$

$$ACH = \frac{Airflow\ (^{ft^3}/_{min}) \times 60\ min}{Room\ Volume\ (ft^3)}$$

Wipe Sampling

Surface wipe samples were collected throughout Veterinary Hospital F's pharmacy, cleanroom areas, oncology department, and ICU. Tables III through V report the analytical chemistry results from these samples. Sample results revealed that 1 out of 9 wipe samples submitted for carboplatin was positive (6.75 ng/sample). The 2 samples submitted for vinblastine were non-detectable (ND). The ND determination means that contamination was either not present, or was present at levels below the detectable limit of the analytical method. Two of 19 samples submitted were positive, one for cyclophosphamide (3.6 ng/sample) and one for doxorubicin (1.0 ng/sample) while simultaneously being ND for vincristine, epirubicin, and methotrexate. The doxorubicin wipe sample was between the LOD and LOQ. Five out of 5 wipe samples submitted for MDEA were positive (5.2 to 48.6 ng). All of the 5 wipe samples submitted for toceranib, chlorambucil, and lomustine were ND.

General Observations

NIOSH researchers observed and interacted with hospital's pharmacists, veterinarians, and staff to obtain information about the day-to-day activities along with oncology treatment processes. General observations are listed below:

- A refrigerator in the pharmacy had a "No Human Food" sticker; however, an employee was observed placing lunch in the refrigerator.
- A staff member weighed a powdered drug at her desk and the same scapula used to transfer the powder was placed on the unprotected desk surface.
- The hospital does not separate the chemotherapy laundry from the rest of the facility.
- Chemotherapy patients are placed in kennels that are properly labeled.

- Chemotherapy treatment signs are posted on the door of the oncology department (Figure 6).

- The negative pressure hazardous drug cleanroom was overly negative partially due to a non-functioning heating, ventilating, and air conditioning (HVAC) supply.

- Although changed after each chemotherapy patient, a cloth blanket is used on the examination table (Figure 7).

- Chemotherapy drugs are on shelves in the open pharmacy area (Figure 8).

- 3M healthcare particulate respirators and surgical masks (item number 1860S, 3M, St. Paul, MN) are used during hazardous drug compounding; however, staff are not fit-tested on the specific respirator in use.

Discussion

The hospital recently certified both BSCs, one-each within the positive pressure and negative pressure cleanrooms, prior to the NIOSH visit, therefore the BSCs were not quantitatively evaluated during the field survey. Given that this certification was just 14 days prior to the NIOSH visit, NIOSH researchers used the reported airflow values in our evaluation and did not conduct additional BSC airflow measurements. The certification records indicated the negative pressure hazardous drug sterile compounding cleanroom supply was 0.20 m^3/s (434 cfm) and it had a negative pressure of -0.017 inches of water, which meets the USP <800> requirement of -0.01 to -0.03 inches of water [USP 2019]. Exhaust from the negative pressure hazardous drug cleanroom was provided by the BSC (0.23 m^3/s [482 cfm]). The room's volume was 11.8 m^3 (418 ft^3) and the calculated ACH based on the certifier's measured exhaust for the BSC was 69. During the NIOSH site visit, the Magnehelic® pressure differential gauge read -0.04 inches of water (Figure 9). Indications were that the supply air to the negative pressure hazardous drug sterile compounding cleanroom was not functioning correctly. The room remained very negative despite on-site maintenance staff efforts to correct the problem during the site visit.

While the pharmacy was determined to be under positive pressure, one of the supply vents was found to have a negative airflow measurement. After removing adjacent ceiling tiles, it was noted that the flexible supply duct was disconnected from the supply vent, thus the positive pressure in the pharmacy was forcing room air up and out through the supply louver and into the plenum above the ceiling tiles.

The NIOSH researchers' strategy was to collect surface wipe samples after each chemotherapy treatment and randomly throughout the hospital. During the site visit, no chemotherapy was administered to patients; however, surface wipe

samples were still collected throughout the pharmacy and treatment areas. Surface wipe samples were analyzed by the contract lab, Bureau Veritas North America. Vinblastine and cyclophosphamide were the drugs handled during the NIOSH visit. NIOSH staff did not see chemotherapy administration to patients during the visit.

The analytical results from all of the Bureau Veritas North America's field samples were ND except for three, which were positive for either carboplatin, cyclophosphamide, or doxorubicin. The doxorubicin result was between the LOD and LOQ and was collected from the BSC in the open pharmacy that was once used for preparing chemotherapy. The positive carboplatin wipe sample was collected from the door handle leading to the adjacent hallway in the Oncology Department. The positive cyclophosphamide wipe sample was collected from the cleanroom's floor by the BSC in the Pharmacy. MDEA was found on the BSC that pharmacy formerly used for preparing chemotherapy, the pill counting counter, the pharmacy sink and counter, the drug area counter by the anteroom, and the desk in the hazardous drug sterile compounding cleanroom.

It is common to have a wipe sample analysis for hazardous drug contamination result in a ND finding, even in the presence of a hazardous drug manipulation [NIOSH 2012]. Some of the hazardous drugs, such as doxorubicin, are not stable and can decay rapidly [NIOSH 2012]. Instability due to several factors has been anecdotally observed for lomustine and chlorambucil in the course of development of the NIOSH analytical method for these drugs, and degradation is expected to be especially rapid in open workplace environments without controlled parameters. Thus, a number of the drugs under study are less likely to be detected from surface wipe samples.

Particular note should be made regarding the compound MDEA, which was the indicator analyte for mustargen contamination. Mustargen is especially reactive in uncontrolled environments (e.g., when local pH does not promote stability) which contributes to its particularly hazardous nature. Typically, mustargen rapidly decays to degradation products of which MDEA is the most important in environments with typical humidity levels. Since it was very unlikely that intact mustargen would be detected at a workplace site if sampling and/or analysis occurred outside of a spill event, and since safety issues prevented the development of a direct mustargen detection method in the NIOSH laboratory, the decision was made to focus instead on MDEA, as a potential marker for the original compound. However, positive sample results for MDEA may not be indicative of actual mustargen contamination, since ethanolamine compounds (of which MDEA is one) are often used in modern manufacturing techniques and cleaning media. For purposes of this investigation, MDEA presence in workplace samples should only serve as a potential warning and cannot be conclusively linked to a particular source. Thus, it may not indicate actual mustargen contamination.

In earlier surveys conducted under this umbrella project, an effort was made to qualify the link between MDEA detected in samples with mustargen at the work sites by using an alternate HPLC/MS method to screen for the presence of other

ethanolamine compounds such as diethanolamine (DEA) and triethanolamine (TEA). If these other widely used compounds were present in field samples along with MDEA, it might indicate general ethanolamine contamination rather than the prior presence of mustargen as a specific source for the observed MDEA. In these screening tests DEA and TEA were always observed along with MDEA, and indeed were also present in some samples for which MDEA levels were ND, illustrating the ubiquity of ethanolamines in workplace environments. However, no meaningful quantitative correlations were found between levels of MDEA and DEA or TEA, suggesting that when MDEA was present it was not necessarily just a contaminant or intentional component of whatever sources had contributed the other ethanolamines. In summary, it is not possible to guarantee or dismiss that when MDEA is detected in a workplace sample that it definitely signals the presence of a prior mustargen contamination event. This caveat should be kept in mind when considering the positive MDEA responses listed in this report.

The hospital also used CSTDs to prepare and administer chemotherapy, which studies have shown can reduce surface contamination [Sessink and Bos 1999; Nygren et al. 2002; NIOSH 2004; Harrison et al. 2006; Nyman et al. 2007; Yoshida et al. 2009; Sessink et al. 2010; Vyas 2013]. Another possible reason most of the samples did not detect any drug is that the level of hazardous drugs on surfaces may vary over time. This variation is influenced by drug amounts handled, patient load, and work practices [NIOSH 2012].

One limitation of the study is there are currently only a handful of analytical methods covering a small fraction of the 218 hazardous drugs on the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* [NIOSH 2016]. The hospital uses several hazardous drugs for which the NIOSH researchers were not able to sample due to the absence of an analytical method. An additional limitation is the time between sample collection and analysis. Although surface wipe samples are shipped on ice within 24-hours of their collection, it may be much longer before the analytical laboratories can analyze the samples. This delay in sample analysis could decrease the chances of detecting a positive wipe sample.

Conclusions and Recommendations

The carboplatin, cyclophosphamide, doxorubicin, and MDEA presence serves as a reminder: that hazardous drug contamination can sometimes linger despite cleaning efforts. Therefore, it is important to continue to use engineering controls (e.g., biological safety cabinets), supplementary controls (e.g., closed system drug-transfer devices), protective work practices (e.g., surface cleaning after every oncology patient, regardless of whether I.V. chemotherapy was administered), and personal protective equipment (e.g., gloves and gowns rated for chemotherapy protection, respirators, eye protection) to reduce unintentional exposures to the staff or pet owners.

NIOSH researchers observed proper work practices that Hospital F had in place during the visit. The hospital is encouraged to:

- Continue using the hospital's standard operating procedures (SOPs) for administering of drugs, spills, post administration of drug cleaning, and patient management [USP 2019].

- Continue to use the BSC to prepare chemotherapy treatments for patients [NIOSH 2004; USP 2019].

- Continue to clean exposed compounding surfaces within the BSC each time a hazardous drug is compounded inside the cabinet even if there is no noticeable spill or leak. United States Pharmacopeia (USP) <797>, Pharmaceutical Compounding: Sterile Preparations, has a section on cleaning and disinfecting compounding areas [USP 2019].

- Continue to use PPE for handling hazardous drugs [NIOSH 2004; NIOSH 2010; USP 2019].

- Continue to use gloves during all tasks involving a chemotherapy patient [USP 2019]. Staff should wear American Society for Testing and Materials (ASTM)-tested chemotherapy gloves [USP 2019]. Continue to change gloves every 30 minutes unless otherwise recommended by the glove manufacturer or if contaminated, torn, or punctured [USP 2019].

- Continue to use CSTDs during compounding and administering of hazardous drugs [NIOSH 2004; USP 2019]. Although CSTDs may reduce worker exposure to hazardous drugs, they may not entirely eliminate exposure [Sessink and Bos 1999; Nygren et al. 2002; NIOSH 2004; Harrison et al. 2006; Nyman et al. 2007; Yoshida et al. 2009; Sessink et al. 2010; Vyas 2013]. The NIOSH Alert identifies CSTDs as supplemental controls that should only be used in combination with ventilated primary engineering controls (i.e., biological safety cabinets and containment isolators) to further protect against worker exposures to hazardous drugs [NIOSH 2004]. Therefore, it is important to continue to use the BSC and proper PPE to protect the staff, even when CSTDs are used.

- Continue the practice of washing hands after compounding, administering, or handling hazardous drugs [USP 2019].

- Continue to use the *Chemotherapy Treatment in Process* sign [NIOSH 2010; USP 2019].

Below are a few recommendations for consideration within the hospital's work practices as well as towards the facility design that could reduce unintentional exposures to hazardous drugs:

- Ensure that all employees expected to wear respiratory protection are trained and fit-tested on the specific respirator in use. The respirator must be used as part of a comprehensive respiratory protection program and the user must be enrolled into a Respiratory Protection Program in accordance with the requirements of OSHA 1910.134 [OSHA 2011].

  Respirators should be used in a proper respirator program under the supervision of a properly trained respirator program administrator. Respirators used without such a program, with all its essential elements, cannot be relied upon to protect workers.

  Each worker required to wear a respirator must be medically evaluated and cleared by a physician to wear the specific respirator before performing assigned tasks. For respirators to be effective and protect workers from harmful exposures, they must be selected, inspected, and maintained properly. Respirators should be inspected by the worker prior to each use for any defects. Reuseable respiratory protective equipment should also be cleaned, disinfected, and re-inspected after each use. Respiratory protective devices should never be worn when a satisfactory face seal cannot be obtained. Many conditions may prevent a good seal between the worker's face and the respirator. Some of these conditions include facial hair, glasses, or an unusually structured face. All workers required to wear a respirator must be properly trained on the selection, use, limitations, and maintenance of the respirator. They also must be fit–tested to assure a proper seal between the workers face and the specific make/model of respirator assigned for their use, prior to performing work tasks in a contaminated area.

  All workers should receive annual fit–testing with a quantitative testing device. When not in use, respirators must be stored in a clean environment located away from any source of contamination.

- Develop an SOP for receiving a hazardous drug shipment [USP 2019].

- Ensure that the BSC used for preparation of chemotherapy drugs is externally vented (preferred) or has redundant–high efficiency particulate air (HEPA) filters in series [USP 2019].

- Ensure that the BSC is certified on a yearly basis and after it has been repaired or relocated [CDC 2009]. Ensure that the hood certification process includes the most recent edition of the National Sanitation Foundation (NSF) Standard 49, Biosafety Cabinetry Certification [NSF/ANSI 2016].

- Do not reuse disposable gowns. Use gowns once and throw them away in chemotherapy waste [USP 2019].

- Gloves and other PPE worn while handling hazardous drugs should be removed before leaving the oncology department [USP 2019].

- Gloves should also be worn when unpacking hazardous drug shipment [USP 2019].

- Clean area after each chemotherapy administration [USP 2019].

- Clean scissors and other tools after each use with chemotherapy patients [NIOSH 2010; USP 2019].

- Wash clothing and blankets that could be contaminated with drug separately from items with no anticipated drug contamination [USP 2019].
    - **UPDATE:** The hospital stopped using reusable bedding for patients treated with chemotherapy drugs.

- Ensure dedicated cleaning supplies (mops, rags, buckets, etc.) used within chemotherapy treatment areas are not used in other areas of the hospital [NIOSH 2004].

- Prevent other staff from entering the room unprotected during chemotherapy administration [NIOSH 2010; USP 2019].

- Place color-coded neckbands on patients recently treated with chemotherapy drugs [NIOSH 2012].
    - **UPDATE:** The hospital started using color-coded collars on patients recently treated with chemotherapy drugs.

- Do not allow food or drinks (caps and no caps) to be in areas where chemotherapy is prepared or administered.

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Appendixes

Table I. LOD[1]/LOQ[2] and analytical ranges of analyte for BVNA Methods

Analyte	LOD (ng)[3]	LOQ (ng)	Analytical Range (ng)
Carboplatin	0.8	2.7	0.4 to 100
Cyclophosphamide	0.8	2.7	0.4 to 100
Doxorubicin	0.8	2.7	0.4 to 100
Epirubicin	0.8	2.7	0.4 to 100
Methotrexate	0.8	2.7	0.4 to 100
Vincristine	0.5	1.7	0.5 to 75

Table II. LOD[1]/LOQ[2] and analytical ranges of analyte for NIOSH Method

Analyte	LOD (ng[3])	LOQ (ng)	Analytical Range (ng)
Methyldiethanolamine (MDEA: marker for mustargen)	3.8	12	5.0 – 1000
Lomustine	38	127	25 – 5000
Chlorambucil	0.35	1.1	5.0 – 1000
Toceranib	0.13	0.42	5.0 - 100

*Limits of detection for an analyte in the NIOSH method were determined by running injections of blank sample solvent prior to analysis and collecting peak height values covering the elution period of the analyte in HPLC/MS (typically about 0.40 min). The standard deviation of these peak height values is determined and Sigma is defined as 2(SD). The slope of the peak height calibration plot (m) is also determined. LOD is then calculated as [3(Sigma)]/m and LOQ as [10(Sigma)]/m.

[1] LOD = limit of detection
[2] LOQ = limit of quantification
[3] ng = nanogram of drug

Table III. Chemotherapy Drugs in Surface Wipe Samples, Day 1

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng/sample)[4]
Oncology Department	Front edge of stainless steel tray	BV-2017-30843[5] (Carboplatin)	ND[6]
Oncology Department	Door handle leading to adjacent hallway (no picture)	BV-2017-30843	6.75
Oncology Department	Kennel area	BV-2017-30843	ND
Oncology Department	Door handle to kennel area	BV-2017-30843	ND
Oncology Department	Edge of examination table	BV-2016-29599 (vincristine, methotrexate, cyclophosphamide, epirubicin, doxorubicin)	ND
Oncology Department	Infusion pole	BV-2016-29599	ND
Oncology Department	Front jars' lids on desk area	BV-2016-29599	ND
Oncology Department	Saliva marks on examination table	BV-2016-29599	ND
Oncology Department	Plastic pad in kennel	BV-2016-29599	ND
Oncology Department	Kennel handle and clipboard (patient was on vincristine)	BV-2016-29599	ND
Intensive Care Unit	Surface of scale	BV-2016-29599	ND
Intensive Care Unit	Table surface in front of scale	BV-2016-29599	ND
Intensive Care Unit	Keyboard and mouse by scale	BV-2016-29599	ND

[4] ng/sample = nanogram of drug per sample
[5] Bureau Veritas North America's Internal Method
[6] ND = results are not detected at the LOD

Table IV. Chemotherapy Drugs in Surface Wipe Samples, Day 2

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng/sample)[7]
Pharmacy	Anteroom tray	BV-2017-30843[8] (Carboplatin)	ND[9]
Pharmacy	Table in cleanroom	BV-2017-30843	ND
Pharmacy	Hood in pharmacy area (was used for chemotherapy drugs in the past) (Figure 10)	BV-2016-29599 (vincristine, methotrexate, cyclophosphamide, epirubicin, doxorubicin)	(1.0)[10] for doxorubicin; ND for the other drugs
Pharmacy	Random spots on hood in pharmacy area	BV-2016-29599	ND
Pharmacy	Counting counter	BV-2016-29599	ND
Pharmacy	Door handle to anteroom to cleanroom	BV-2016-29599	ND
Pharmacy	Sink area before the anteroom	BV-2016-29599	ND
Pharmacy	Cleanroom's floor below BSC (Figure 11)	BV-2016-29599	3.6 for cyclophosphamide; ND for the other drugs
Pharmacy	Chemotherapy bin in anteroom	NAT 2006-14763 (Vinblastine)	ND

[7] ng/sample = nanogram of drug per sample
[8] Bureau Veritas North America's Internal Method
[9] ND = results are not detected at the LOD
[10] ( ) = Result between the limit of detection (LOD) and limit of quantification (LOQ)

Table V. NIOSH Lab Results: Chemotherapy Drugs in Surface Wipe Samples, Day 2[11]

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng)[12]
Pharmacy	Former BSC used for preparing chemotherapy[15]	NIOSH Method (filter paper)	48.1 and 48.6 (MDEA[13]); ND[14] (toceranib, chlorambucil, and lomustine)
Pharmacy	Pill counting counter[15]	NIOSH Method (filter paper)	12.3 and 13.3 (MDEA); ND (toceranib, chlorambucil, and lomustine)
Pharmacy	Pharmacy sink and counter[16]	NIOSH Method (filter paper)	(6.1) (MDEA); ND (toceranib, chlorambucil, and lomustine)
Pharmacy	Drug area counter by anteroom[16]	NIOSH Method (filter paper)	(6.3) (MDEA); ND (toceranib, chlorambucil, and lomustine)
Pharmacy	Hazardous drug sterile compounding cleanroom's desk[16]	NIOSH Method (filter paper)	(5.2) (MDEA); ND (toceranib, chlorambucil, and lomustine)

[11] Wipe samples for this method were not collected on Day 1
[12] ng = mass of drug
[13] MDEA = N-methyldiethanolamine
[14] ND = results are not detected at the LOD
[15] Presence of two numerical values for a sample indicates that the sample was selected for rerun and the second value was obtained for the second analysis
[16] ( ) = Result between the limit of detection (LOD) and limit of quantification (LOQ)

Figure 1. Labconco Laminar Air Flow Work Station (Photo Credit: NIOSH)

Figure 2. Labconco BSC, Class II, Type A2 (pharmacist shown preparing chemotherapy drug for administration) (Photo Credit: NIOSH)

Figure 3. Equashield CSTD, syringe adapter shown (Photo Credit: NIOSH)

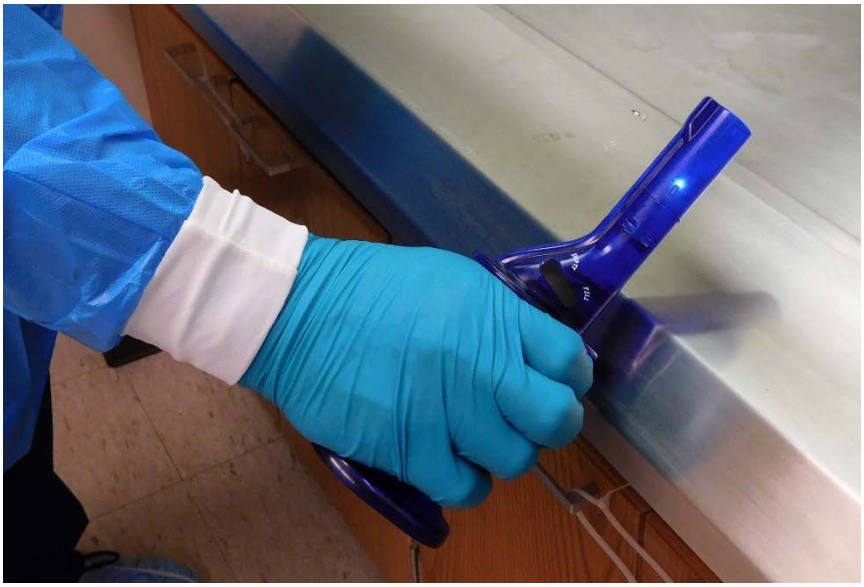

Figure 4. Example of a qualitative smoke test with Wizard Stick Smoke Generator (Photo Credit: NIOSH)

Figure 5. TSI Accubalance® Plus Air Capture Hood (Photo Credit: NIOSH)

Figure 6. Oncology Department's treatment sign (Photo Credit: NIOSH)

Figure 7. Oncology Department's administration room with blanket shown (Photo Credit: NIOSH)

Figure 8. Open shelf area with chemotherapy drugs in Pharmacy (Photo Credit: NIOSH)

Figure 9. Magnehelic® pressure differential gauge read -0.04 inches of water for cleanroom (Photo credit: NIOSH)

Figure 10. Hood in pharmacy area (was used for chemotherapy drugs in the past) (Photo Credit: NIOSH)

Figure 11. Cleanroom's floor below BSC (Photo Credit: NIOSH)

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