In-Depth Survey Report

Engineering Control Evaluation at Veterinary Hospital B

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Abstract

NIOSH researchers conducted a field survey at Veterinary Hospital B in May 2017. 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 and daily activities along with the oncology treatment processes.

A TSI® VelociCalc™ Plus Model 9565-P thermal anemometer was used to measure air velocities at the face of the fume hood, while a Wizard Stick handheld smoke generator was used to visualize air movement inside and around the periphery of the hood. Both the qualitative and quantitative tests showed that the chemical fume hood was operating appropriately. The fume hood's face velocity (0.44 m/s [86.5 fpm]) was within the range of operation of 0.41 to 0.51 m/s (80 to 100 fpm) that is considered adequate for most hoods. A TSI Accubalance® Plus Air Capture Hood Model 8373 was used to measure the supply (0.33 m^3/s or 704 cfm) and exhaust (0.345 m^3/s or 737 cfm) ventilation in the oncology department. The air changes per hour (ACH) of the oncology department was calculated from the exhaust rate to be 11, which is less than the required ACH (minimum 12 ACH) for unclassified containment secondary engineering control. The room static pressure was measured using the manometer function of the TSI® VelociCalc™ and found to be under negative pressure, which is preferred when administering chemotherapy.

The presence of potential surface contamination was evaluated through the use of wipe samples. These were collected in areas where chemotherapy drugs were handled by the workers, such as the pharmacy, oncology, intensive care unit, and research departments. Wipe samples were also collected in less obvious places (i.e., telephone, door handles) to determine if the hospital's current workplace safety practices were adequate to prevent inadvertent contamination of these surfaces. Sampling and analytical procedures varied by the hazardous drug for which they would be evaluated (i.e., the analyte). In some cases, a single sample could be evaluated for more than one analyte simultaneously. These sampling methods are internal and were created specifically for this research study. There is limited data on recovery studies from various surfaces. Carboplatin and cyclophosphamide were the only hazardous drugs actually in use during the NIOSH visit. Sample analyses results revealed that 7 of 7 wipe samples submitted for toceranib analysis (an observed patient was on toceranib) came back positive (0.063 to 4.4 ng). Seven of 7 of the samples submitted for N-methyldiethanolamine (MDEA) analyses were also positive (1.6 to 15 ng) while simultaneously being non-detectable for lomustine and chlorambucil. Two samples submitted for vinblastine, 8 samples submitted for carboplatin and 21 samples submitted for simultaneous vincristine, methotrexate, cyclophosphamide, epirubicin, and doxorubicin analyses all resulted in a non-detectable (ND) determination, meaning that contamination was either not present, or was present at levels below the detectable limit of the analytical method. MDEA was monitored as a potential stable marker for the highly unstable antineoplastic drug mustargen as explained in the text.

Although many of the wipe sample analytical results were ND, there is no safe level of exposure when handling hazardous drugs. The presence of toceranib and MDEA contamination serves as two reminders: (1) that the patients themselves can be a source of exposure, even when the drugs are not being directly handled and (2) that hazardous drug contamination can sometimes linger despite cleaning efforts. This emphasizes the importance of proper work practices regarding the use of gloves and shoe covers, hand washing, and food/drink prohibitions within the hazardous drug handling environments. 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 life 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 PPE is considered to be the least effective exposure control on a consistent basis [Mobo et. al 2010]. Therefore, engineering controls and work practice guidelines are 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 "B" in order to preserve its anonymity. The Veterinary Hospital B provides primary, specialty, and emergency care to small animal patients. The hospital offers nine referral services including oncology, as well as pharmacy and diagnostic services. The oncology department has five staff members, which include veterinarians, residents, interns, and a technician. The oncology department has been in the hospital for four years with chemotherapy administration to patients two to six times per day, 4 days a week. Veterinary Hospital B gives chemotherapy drug handling safety training to dedicated oncology technicians and only in-house trained personnel can administer chemotherapy to patients.

The oncology department uses one treatment area to discuss the patient's treatment with the owner. The oncology department's exam room is used to draw blood, conduct physical examinations, and administer chemotherapy. This room consists of a large desk area (Figure 1), kennels for large dogs (Figure 2), and a kennel area for cats and small dogs (Figure 3). There is also an examination table in the room (Figure 4). The hospital is in the process of renovating the pharmacy and adding a hazardous drug compounding clean room with a Class II Type C biological safety cabinet (BSC) [Labconco 2017]. Until the renovation is completed, the pharmacist has to prepare the patients' doses in an isolated, semi-adjacent department's laboratory fume hood (Hamilton Laboratory Solutions, last certification on February 22, 2017) (Figure 5) which is currently dedicated to the drug compounding activities.

Chemotherapy Preparation and Administration

Closed System Drug-Transfer Devices (CSTDs)

Veterinary Hospital B uses the PhaSeal closed system drug-transfer device (CSTD) system (Becton, Dickinson and Company, Franklin Lakes, NJ) to prepare and administer I.V. liquid forms of chemotherapy (Figure 6). 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.

Oral Chemotherapy

For oral chemotherapy, the patient is given the pill in either in a flavored pill pocket or a pill gun (or piller) (Figure 7). After the technician verifies the patient swallowed the pills, the patient is placed within a holding kennel until discharged to go home.

Chemotherapy Injection

For chemotherapy injection, the patient is given the liquid drug by subcutaneous or intramuscular route. The liquid drug is delivered through a CSTD, which is attached to a butterfly catheter.

I.V. Chemotherapy

Sometimes a patient needs to receive chemotherapy through I.V. via catheter (Figure 8). Although technique varies among technicians administering the dose, the overall process is similar. First, the patient is prepped by shaving the injection site and cleaning it with alcohol. Veterinary Hospital B uses a cleaning technique that involves alcohol followed by betadine. After the injection area is prepped, the indwelling intravenous catheter and the T-port are inserted. Next, the catheter and T-port are wrapped with bandage to keep the catheter in place. The CSTD Y-site adapter is connected to the catheter and the catheter is flushed with saline. The cap is removed from the I.V. line and the syringe adapter is attached to the end of the I.V. line. Next, the syringe adapter is connected to the Y-site adapter, which is attached to the catheter. The chemotherapy is given until the I.V. bag is empty. Once the bag is empty, saline is pushed into the I.V. bag through the bag adapter. This process is used to ensure all the drug is cleared from the I.V. line. Next, an additional amount of saline is pushed into the catheter to flush the line. The T-port line is closed and the catheter is removed from the patient's vein. The patient is bandaged and placed within a holding kennel until discharged to go home.

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. 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 (PELs) [CFR 2003] are occupational exposure limits that are legally enforceable in covered workplaces under the Occupational Safety and Health Act. NIOSH *recommended exposure limits* (RELs) 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]. 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 the American Industrial Hygiene Association (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 product's safety data sheets (SDSs) [NIOSH 2004].

Methodology

Compounding Hood and Compounding Lab Performance Evaluations

Equipment: Compounding Hood Face Velocity Measurements

A TSI® VelociCalc™ Plus Model 9565-P thermal anemometer (TSI Incorporated, St. Paul, MN) was used to measure air velocities at the face of the Compounding Hood, a Hamilton Laboratory Solutions chemical fume hood located in the research department (Figure 9).

Procedure

To determine the Compounding Hood's average face velocity, the open face of the hood was divided into an equal-area grid of eight squares measuring approximately 0.09 square meters (m^2) (1 square foot [ft^2]) each. A 5-second average velocity measurement was taken at the center of each square, while holding the anemometer perpendicular to the inward airflow direction. The average face velocity across the entire hood face was then determined by calculating the average of the equal-area square velocity measurements.

Equipment: Hood 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 chemical fume hood in the research laboratory (Figure 10). 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 fume hood's open face and in the interior of the hood to qualitatively evaluate the capture efficiency and evaluate potential areas of concern. If the smoke was captured quickly and directly by the hood at the point where compounding operations are performed, it was a good indication of acceptable control design and performance. If the smoke was slow to be captured or took a circuitous route to the hood exhaust intake, this would indicate a potential problem. In addition, the adverse effect of cross drafts upon hood capture was evaluated by releasing smoke near the periphery of the hood face. Lack of direct capture or evidence of reverse-flow turbulence would be indicative of poor hood performance.

Equipment: Compounding Lab Static Pressure Measurements

The manometer function of the TSI® VelociCalc™ Plus Model 9565-P thermal anemometer was used to measure room static pressure in the Compounding Lab,

relative to that in the adjacent corridor. This served as an indication of whether the room was under positive or negative pressure.

Procedure

Initially, the manometer was zeroed by attaching opposite ends of the same manometer sampling tube to the high-pressure and low-pressure manometer sampling ports. Next, with the manometer positioned outside of the compounding lab, one end of a manometer sampling tube was attached to the low-pressure port on the anemometer while the free end of the tube was routed through the air gap under the lab entry door and several inches into the compounding lab. The high-pressure port was left open to the corridor and the differential pressure across the entry door threshold was recorded in inches of water gauge (in. w.g.) pressure.

Equipment: Measurement of Supply and Exhaust Airflow Rates in the Oncology Department

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 oncology department (Figure 11).

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 Methods

Surface wipe samples were collected throughout Veterinary Hospital B using different sampling methods. Samples were collected in areas where drugs were handled by the workers, such as the pharmacy, oncology, intensive care unit, and research departments, and in places similar to those where traces of drugs have been found in human studies, such as door handles and telephones [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 Method

The Bureau Veritas North America wipe sample collection method uses Texwipe™ Alpha™ Polyester Series Swabs (TX715, ITW Texwipe, Kernersville, NC) and a 50:50 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 Bureau Veritas North America's internal method NAT 2006-14763, which uses HPLC. Vincristine, methotrexate, cyclophosphamide, epirubicin, and doxorubicin are analyzed using Bureau Veritas North America'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 B, several 16 mL amber vials with screw caps were filled with 1 mL of 50:50 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 sealable plastic bag for later disposal. The swab (head first) was placed partially into the vial opening and lateral pressure was applied to the swab stick to snap the head off and into 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) except for vinblastine results, which 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 of lomustine (or CCNU), toceranib, N-methyldiethanolamine (MDEA), and chlorambucil sampling using two different wipe sampling media: Texwipe™ Alpha™ Polyester Series Swabs and Whatman™ filter papers (number 1442-055, 55-mm ashless circles, GE Healthcare, Chicago, IL). MDEA was analyzed as a potential indicator for mustargen contamination that remained after the rapid degradation expected for the compound in typical open environments (see Discussion). Table II lists the LOD, LOQ, and calibration plot concentration range for each of the analytes. Sampling media used to collect this set of analytes was moistened with a solvent blend of 50% acetonitrile/50% dimethylsulfoxide/0.20% hydrochloric acid, selected through extensive experiments conducted during method development for the survey. It provided stability in solution and resulted in adequate recoveries from in-house spiked quality control samples for all four of the antineoplastic drugs in this set via

control of pH, solubility, and other factors. The same solvent was used to prepare calibration standards and quality control samples to ensure compatibility with field samples during analysis.

For wipe sample collection, a swab was wetted with the solvent and the wipe sample procedure was the same as that described in Wipe Sampling Method 1. Upon collection, the swab was placed (head first) over the opening of a 125 mL translucent polypropylene jar (Nalgene™ Wide-Mouth Straight-Sided Polypropylene copolymer [2118-0004], Thermo Scientific™, Rochester, NY). Lateral pressure was 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 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 disposable pipet tip were used to measure 250 microliters (µL) of the solvent onto each filter paper. An area of approximately 10 cm x 10 cm was wiped with one wetted filter paper and placed into a 125 mL 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 jar was capped and a sample label affixed. Samples were placed on ice packs and transported to a NIOSH laboratory freezer for storage at approximately -10ºC until analysis. Samples were returned to room temperature and were processed by extraction via orbital shaker using a total of 10 mL of the aforementioned solvent blend. The supernatant was filtered and 2 mL was transferred to autosampler vials and fortified with internal standard (see Discussion) for analysis via HPLC/MS. Results are reported as mass of drug (ng).

Results

Compounding Hood and Compounding Lab Performance Evaluations

Compounding Hood Face Velocity Measurements

Hood velocity measurements were collected on a Hamilton Laboratory Solutions chemical fume hood, located in a temporary Compounding Lab. The average face velocity of the hood was 0.44 meters per second (m/s) (86.5 feet per minute [fpm]) as measured by the anemometer. The maximum face velocity was 1.32 m/s (259 fpm) with a minimum face velocity of 0.13 m/s (25.0 fpm).

Hood Qualitative Smoke Test

The Wizard Stick smoke generator was used to qualitatively test the capture efficiency of the lab hood. Smoke was released inside the hood at the center compounding position, inside the hood along the perimeter of the open hood face, outside of the hood along the perimeter of the open hood face, and outside of the hood directly in front of the hood face opening. In each case, the smoke was captured quickly, pulled further into the hood, and removed via the exhaust system. This showed the fume hood had acceptable performance.

Compounding Lab Static Pressure Measurements

The manometer function of the anemometer was used to measure the Compounding Lab's room static pressure. The instrument's pressure specification has an accuracy of ±0.005 inches of water gauge (in. w.g.) of the reading [TSI 2016]. The room pressure was negative, however, the magnitude of the negative pressure was too small to quantify.

Measurement of Supply and Exhaust Airflow Rates in the Oncology Department

The TSI Accubalance® Plus Air Capture Hood was used to measure the supply and exhaust airflows in the oncology department. The total measured supply air was 0.332 cubic meter per second (m^3/s, or 704 cfm). The total measured exhaust airflow was 0.348 m^3/s (737 cfm). The measured exhaust airflow and the room volume (111 m^3 [3909 ft^3]) were used to calculate the ventilation rate in air changes per hour (ACH) for the room (Equation 1). The ACH was calculated to be 11.

Equation 1:

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

Or

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

Wipe Sampling

Surface wipe samples were collected throughout Veterinary Hospital B's oncology department, ICU department, pharmacy department, and the research department, which housed the chemical fume hood. Tables III and IV report the analytical chemistry results from these samples. Sample analyses results revealed that 7 of 7 wipe samples submitted for toceranib analysis came back positive (0.063 to 4.4 ng). Seven of 7 of the samples submitted for N-methyldiethanolamine (MDEA) analyses were also positive (1.6 to 15 ng) while simultaneously being non-detectable (ND) for lomustine and chlorambucil. Two samples submitted for

Vinblastine, 8 samples submitted for carboplatin and 21 samples submitted for simultaneous vincristine, methotrexate, cyclophosphamide, epirubicin, and doxorubicin analyses all resulted in a ND determination, meaning that contamination was either not present, or was present at levels below the LOD of the analytical method.

General Observations

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

- One of the technicians performed a blood draw with no gloves.
- Employees administering hazardous drugs were observed wearing N95 respirators during drug administration tasks; however, there was reported uncertainty among the employees regarding respirator selection and fit testing policies.
- During the intravenous chemotherapy treatment with carboplatin, when the technician removed the cap on the I.V. line, clear liquid dropped onto her gloves. The technician then followed good workplace practice and changed her outer layer of gloves because she did not know if the liquid was simply saline or if it contained carboplatin.
- Some of the antineoplastics are stored in a cabinet above the kennels in the oncology department. There are no labels or signs on the cabinet door to indicate the presence of hazardous drugs.
- Drinks (with caps) were in areas where hazardous drugs were handled.
- The refrigerator that was used to store antineoplastics was appropriately labeled, "No Food Or Beverage May Be Placed In This Unit."
- Pharmacy staff use chemotherapy transport bags for drug transfers.

Discussion

The engineering assessment showed that the chemical fume hood utilized as a compounding hood was operating effectively. The hood's face velocity (0.44 m/s [86.5 fpm]) was within the range of operation of 0.41 to 0.51 m/s (80 to 100 fpm) that is considered adequate for most laboratory hoods [ANSI/ISEA 2012]. Engineering evaluations also measured the oncology department's room to be under negative pressure, which is ideal when administering chemotherapy (negative pressure between 0.01 to 0.03 in. w.g.) [USP 2019]. However, the room

did not meet the required minimum ventilation rate (12 ACH) for an unclassified containment secondary engineering control [USP 2019].

The NIOSH researchers' strategy was to collect surface wipe samples after each chemotherapy treatment and randomly throughout the hospital. Carboplatin and cyclophosphamide were the only drugs used during the NIOSH visit. Some drugs, such as vincristine, were analyzed for even if the drug was not used during the visit. Field wipe samples were analyzed by either the NIOSH lab or a contract lab, Bureau Veritas North America. Several of the NIOSH-analyzed samples were positive for drug contamination, others were determined to be ND. It is not uncommon to have a wipe sample for hazardous drug result in a ND [NIOSH 2012]. Some of the hazardous drugs, such as doxorubicin, are not stable and can decay rapidly [NIOSH 2012]. These drugs are less likely to be positive for a surface wipe sample. 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 the level of hazardous drugs on surfaces varies over time. This variation is influenced by drug amounts handled, patient load, cleaning, and work practices [NIOSH 2012].

All the field samples analyzed for MDEA and toceranib were positive, although at low concentrations. The toceranib results are not surprising since the patient (dog) was on the oral medication and NIOSH researchers were able to sample a wet spot (saliva) and other areas that the dog touched. (The patient was not given toceranib while at the hospital; it is a drug that is given orally at home by the patient's owner.) Although MDEA was not used during the NIOSH visit, this marker of potential mustargen contamination was present on the samples. The MDEA contamination potentially originated from the prior therapeutic use of the drug mustargen within the oncology lab. Its lingering contamination serves as a warning in regards to the potential exposures to veterinary staff, long after the actual drug administration.

In-house NIOSH HPLC/MS analyses employed controlled fragmentation (MS/MS) of the parent ion of each analyte. Two fragment ions were monitored for each, with the more intense ion used for quantification and the other for confirmation. Positive response for an analyte was indicated by quantification ion response above the calculated LOD (q.v.) and by the presence of both expected fragment ions. Additionally, the ratio of intensities of the two fragment ion responses observed for field samples was compared to the average ratio observed for pure analyte (i.e., the calibration standards) as an additional metric for assessing positive analyte response in samples. If both ions were present but their ratio differed significantly from the expected value, it suggested that the quantitative value determined for the analyte might be affected by an unresolved interference and could thus be suspect. These results are designated appropriately in Table IV (q.v.).

No isotopically labeled standards for the analytes of interest were available for the HPLC/MS analysis. To monitor instrument stability during quantification, samples were fortified with 10 ng/mL levels of hexamethylphosphamide, a compound which responds strongly in LC-MS under the conditions of analysis, as an internal standard. However, this compound did not coelute with any of the analytes. Therefore its response could not be used directly to correct for analyte signal drift, but did provide some indication of instrument stability over the course of analysis. Additionally, low-level calibration standards were periodically interspersed with field samples and responses were compared to expected levels. Quality controls were prepared in triplicate by spiking three levels of analytes onto applicable wiping media, which were processed and run with field samples to demonstrate extraction procedure efficacy and instrument performance. Finally, several field samples were rerun to determine whether reanalysis produced analyte values similar to initial values; in these cases both separate results are listed in Table IV.

Instability has been anecdotally observed for lomustine and chlorambucil in the course of NIOSH analytical method development, and documented for doxorubicin and other drugs elsewhere [NIOSH 2012]. Degradation of unstable compounds is expected to be especially rapid in open workplace environments absent controlled parameters. Mustargen is also very reactive in uncontrolled environments and rapidly decays to several products, of which the ethanolamine MDEA is the most important in environments with typical humidity levels. Since it was unlikely that intact mustargen would be detected at a workplace site if sampling and/or analysis took place long after a contamination event, the decision was made to quantify MDEA, which was readily detectable via HPLC/MS, 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. In a prior survey measuring antineoplastic drugs via the NIOSH method in a veterinary oncology setting, the field samples were subsequently screened for other ethanolamine compounds, which were widely found to be present. However, no meaningful quantitative correlations existed between these compounds and MDEA, suggesting that when MDEA was present it could not be automatically regarded as a contaminant or intentional component of whatever sources had contributed the other ethanolamines. The same reasoning applies to the current survey by extension. It is therefore not possible to guarantee or to dismiss the determination that detection of MDEA in a field sample, as occurred in the present survey, signals the presence of a prior mustargen contamination event.

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 that NIOSH researchers were not able to

sample for because of the lack of analytical methods. Another limitation is analysis time. 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 due to analyte instability as discussed above.

Conclusions and Recommendations

Although many of the surface wipe samples were ND except for MDEA and toceranib, there is no safe level of exposure when handling hazardous drugs. The presence of toceranib contamination is a reminder that the patients themselves can be a source of exposure. The MDEA presence serves as two reminders: (1) that hazardous drug contamination can sometimes linger despite cleaning efforts and (2) the detected contamination of desk and cabinet surfaces one might ordinarily think of as "safe," emphasizes the importance of proper work practices regarding the use of gloves and shoe covers, hand washing, and food/drink prohibitions within the hazardous drug handling environments. Therefore, it is important to continue to use engineering controls (biological safety cabinets), supplementary controls (CSTDs), protective work practices (surface cleaning after every oncology patient, regardless of whether I.V. chemotherapy was administered) and personal protective equipment (PPE) [gloves and gowns rated for chemotherapy protection, respirators, shoe covers, eye protection] to reduce unintentional exposures to the staff and other patients.

NIOSH researchers observed proper work practices that Hospital B utilized during the visit. The hospital is encouraged to:

- Continue to 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 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 and after each use for any defects. Reuseable respiratory protective equipment should also be cleaned and disinfected 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 and also be fit–tested to assure a proper seal between the workers face and the respirator 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.

- Upon installation and initial certification of the new BSC, continue to get the BSC recertified on a yearly basis and after it has been repaired or relocated [CDC 2009].

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

- Continue to clean the BSC each time a hazardous drug is used 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] (Figure 12).

- Continue to use CSTDs while compounding and administering 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 primary engineering controls (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 PEC and proper PPE to protect the staff, even when CSTDs are used.

- Continue to use the *chemotherapy treatment in process* sign (Figure 13). This deters other staff from entering the room unprotected when hazardous drugs are in use [USP 2019].

- Continue washing hands after compounding, administering, or handling hazardous drugs [NIOSH 2010].

- Continue using the hospital oncology department's standard operating procedures (SOPs) for administering of drugs, spills, post administration cleaning, and patient management.

- Continue to use dedicated cleaning supplies (mops, rags, buckets, etc.) used within the oncology department are not used in other areas of the hospital [NIOSH 2004].

- Continue to use disposable, non-porous bedding for patients [NIOSH 2010].

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

- Since the Veterinary Hospital B remodelling plans have chosen to use a BSC as its primary engineering control (PEC), select a BSC that has been certified in accordance with the most recent edition of the National Sanitation Foundation (NSF) Standard 49, Biosafety Cabinetry Certification [NSF/ANSI 2016].

- Dispose of PPE after each use, or whenever it becomes contaminated [NIOSH 2004].

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

- Label all cabinets and refrigerators used to store antineoplastics.

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Appendixes

Table I. LOD[1]/LOQ[2] and analytical ranges of analyte for Bureau Veritas North America's Internal Methods

Analyte	LOD (ng)[3]	LOQ (ng)	Analytical Range (ng)
Carboplatin	5	NA[4]	5 to 200
Vinblastine[5]	1	3.3	1 to 75
Cyclophosphamide	5	17	5 to 200
Doxorubicin	5	17	5 to 200
Epirubicin	5	17	5 to 200
Methotrexate	5	17	5 to 200
Vincristine	5	17	5 to 200

Table II. LOD/LOQ and analytical ranges of analyte for NIOSH Method

Analyte	LOD (ng)	LOQ (ng)	Analytical Range (ng)
Methyldiethanolamine (MDEA: marker for mustargen)	1.4	4.6	10 to 2500
Toceranib	0.040	0.14	10 to 350
Lomustine	8.2	27	100 to 7500
Chlorambucil	0.66	2.2	10 to 2500

[1] LOD = limit of detection
[2] LOQ = limit of quantification
[3] ng = nanogram of drug
[4] NA = 75% recovery was not achieved
[5] Results for this method were reported in micrograms/sample (µg/sample)

Table III. Bureau Veritas North America Results: Chemotherapy Drugs in Surface Wipe Samples

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng/sample)[6]
Oncology Department	Floor by examination table and small animal cages	NAT 2006-14763 (Vinblastine)	ND[7]
Oncology Department	Floor in large animal cages	NAT 2006-14763	ND
Oncology Department	Corner of mat where carboplatin was administered; PhaSeal CSTD was used during drug administration	BV-2017-30843 (Carboplatin)	ND
Pharmacy Department	Desk in pharmacist's office (non-counting area)	BV-2017-30843	ND
Pharmacy Department	Telephone in pharmacist's office	BV-2017-30843	ND
Pharmacy Department	Door handle pharmacist's office	BV-2017-30843	ND
ICU Department	Infusion pump buttons and pole base	BV-2017-30843	ND
Research Department	Front lip of fume hood	BV-2017-30843	ND
Research Department	Inside fume hood; PhaSeal CSTD was used during drug compounding	BV-2017-30843	ND
Research Department	Work surface where prepared drug is stored until transport to Oncology Department	BV-2017-30843	ND
Oncology Department	Exhaust grill corner (dust covered)	BV-2016-29599 (vincristine, methotrexate, cyclophosphamide, epirubicin, doxorubicin)	ND
Oncology Department	Supply cart handle (by sharps container)	BV-2016-29599	ND
Oncology Department	Supply cart tray at base	BV-2016-29599	ND
Oncology Department	Corner of mat on examination table (cyclophosphamide pills)	BV-2016-29599	ND
Oncology Department	Chemotherapy patient flow sheet book	BV-2016-29599	ND
Pharmacy Department	Receiving desktop	BV-2016-29599	ND

[6] ng/sample = nanogram of drug per sample
[7] ND = results are not detected at the LOD

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng/sample)[6]
Pharmacy Department	Receiving desktop keyboard and mouse	BV-2016-29599	ND
Pharmacy Department	Old compounding room floor where hood used to be	BV-2016-29599	ND
Pharmacy Department	Old compounding room door handle	BV-2016-29599	ND
Pharmacy Department	Desk in pharmacist's office (counting area)	BV-2016-29599	ND
Pharmacy Department	Glass tray in pharmacist's office (counting area)	BV-2016-29599	ND
Pharmacy Department	Chair in pharmacist's office (counting area)	BV-2016-29599	ND
Pharmacy Department	Keyboard and mouse in pharmacist's office	BV-2016-29599	ND
Pharmacy Department	Desk chair in pharmacist's office	BV-2016-29599	ND
Pharmacy Department	Pill storage bin in pharmacist's office	BV-2016-29599	ND
Pharmacy Department	Floor in front of pill counting area in pharmacist's office	BV-2016-29599	ND
ICU Department	Under I.V. pole	BV-2016-29599	ND
ICU Department	Floor of empty kennel where chemotherapy patients are housed	BV-2016-29599	ND
Research Department	Chemotherapy drug cart	BV-2016-29599	ND
Research Department	Outside of chemotherapy drug refrigerator	BV-2016-29599	ND
Research Department	Surface wipe sample of floor in front of fume hood in Research Department	BV-2016-29599	ND

Table IV. NIOSH Lab Results: Chemotherapy Drugs in Surface Wipe Samples

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng)[8]
Oncology Department	Examination table's pad—saliva from patient (dog) (Figure 14)	NIOSH Method (swab)	(3.8)[9] and (4.4)[10] for toceranib
Oncology Department	Floor outside of kennel—dog on toceranib (Figure 15)	NIOSH Method (swab)	(6.3) for MDEA[11]; (0.56) for toceranib; ND for lomustine and chlorambucil
Oncology Department	Floor near examination table (Figure 16)	NIOSH Method (filter paper)	9.3 and (9.8) for MDEA; (0.28) and (0.29) for toceranib; ND for lomustine and chlorambucil
Oncology Department	Floor near examination table (Figure 16)	NIOSH Method (filter paper)	(8.0) for MDEA; (0.35) for toceranib; ND for lomustine and chlorambucil
Oncology Department	Floor of empty kennel (Figure 15)	NIOSH Method (filter paper)	(1.6) for MDEA; 0.15 for toceranib; ND for lomustine and chlorambucil
Oncology Department	Desktop surface in front of keyboard (Figure 1)	NIOSH Method (filter paper)	9.8 for MDEA; (*0.063*)[12] for toceranib; ND for lomustine and chlorambucil
Oncology Department	Cabinet with chemotherapy drug bin storage (Figure 17)	NIOSH Method (filter paper)	(14.7) and (15.0) for MDEA; (0.019) for toceranib; ND for toceranib[13], lomustine and chlorambucil
Oncology Department	Chemotherapy drug bins (Figure 17)	NIOSH Method (filter paper)	(6.8) for MDEA; ND for toceranib, lomustine, and chlorambucil

[8] ng = mass of drug
[9] ( ) = indicate that quantitative values are uncertain due to nonconformance of fragment ion ratios with expected ratio range for the analyte
[10] 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
[11] MDEA = N-methyldiethanolamine
[12] *Italics* = Result between the limit of detection (LOD) and limit of quantification (LOQ)
[13] Toceranib was ND for the first analysis and (0.019) for the rerun

Figure 1. Oncology department's desk area (Photo Credit: NIOSH)

Figure 2. Oncology department's kennels for large dogs (Photo Credit: NIOSH)

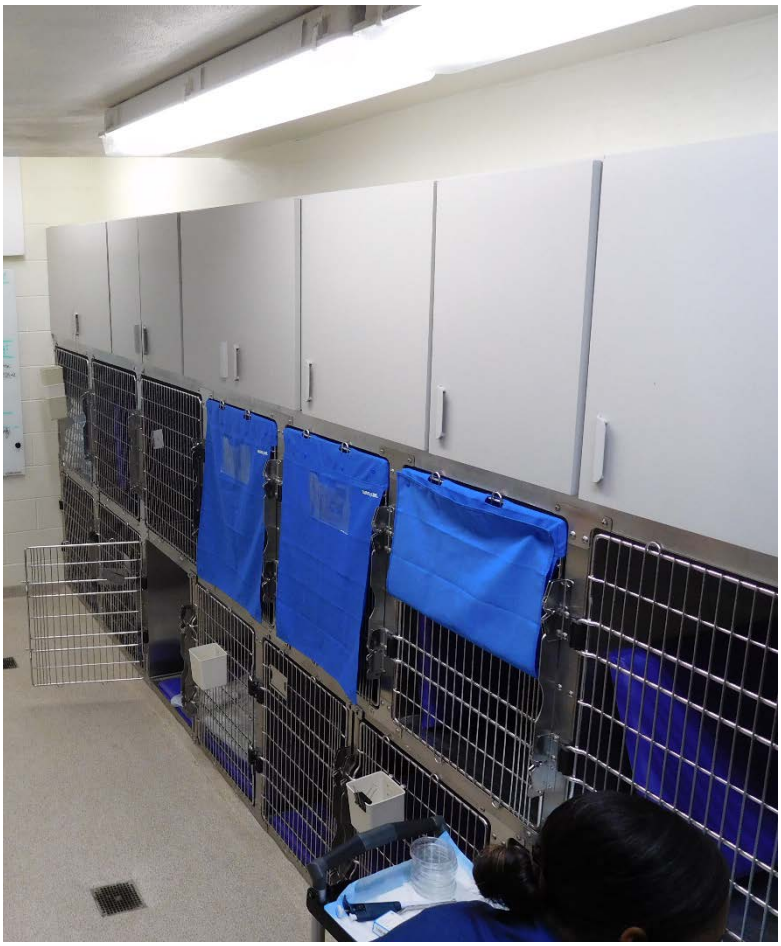

Figure 3. Oncology department's kennels for cats and small dogs (Photo Credit: NIOSH)

Figure 4. Oncology department's examination table (Photo Credit: NIOSH)

Figure 5. Chemical fume hood where chemotherapy drugs are compounded (Photo Credit: NIOSH)

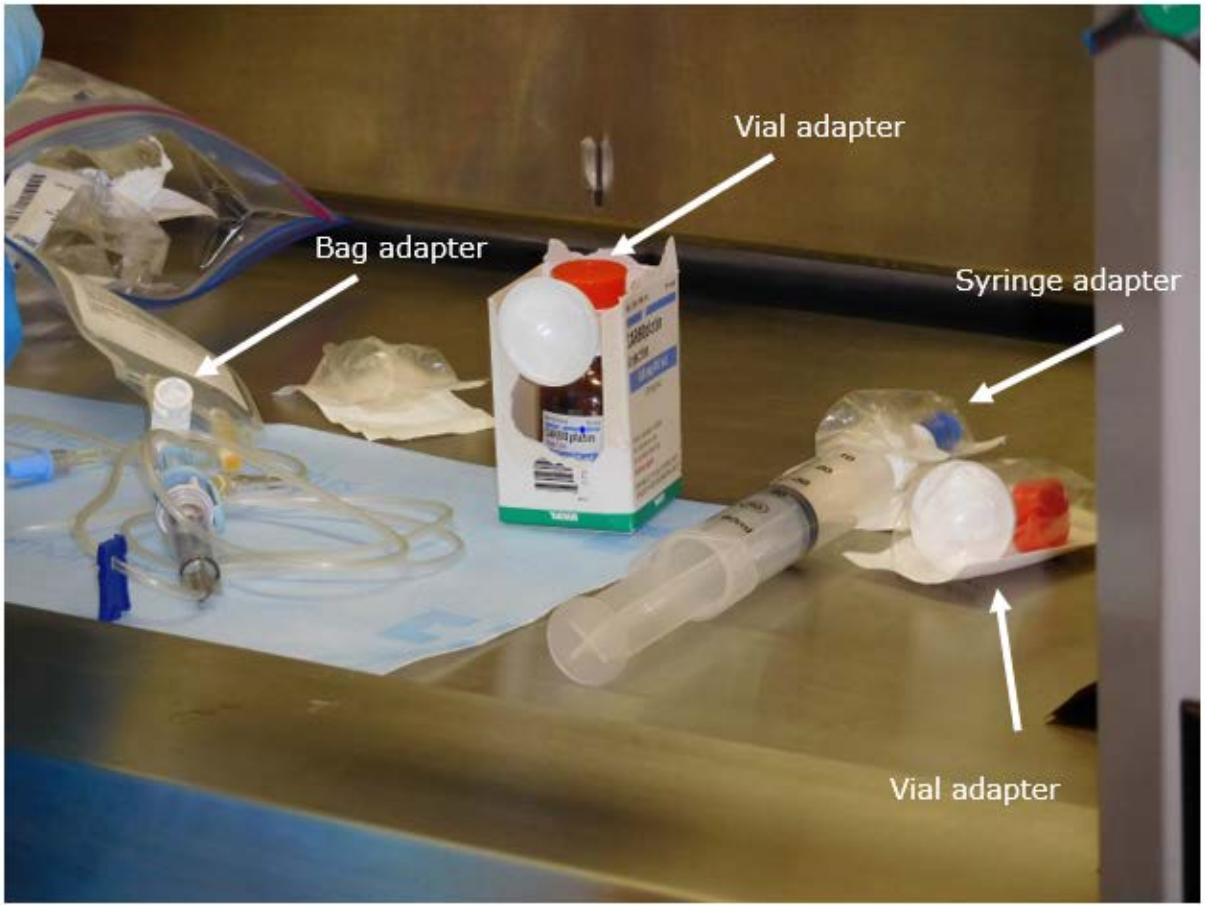

Figure 6. PhaSeal closed system drug-transfer device (CSTD) system (Photo Credit: NIOSH)

Figure 7. Pill pocket (Photo Credit: NIOSH)

Figure 8. Saline syringe with PhaSeal syringe adapter on the disposable underpad (Photo Credit: NIOSH)

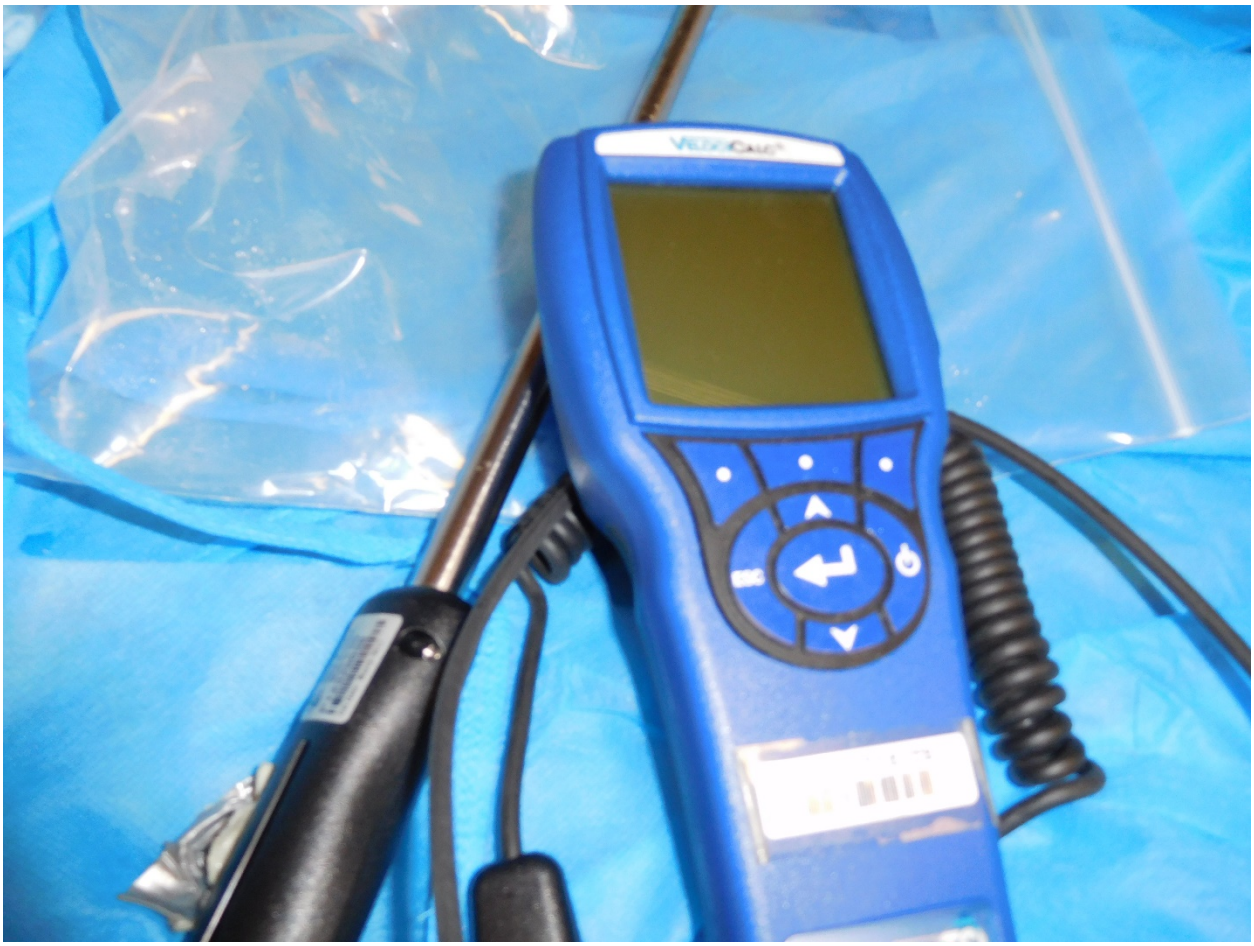

Figure 9. TSI® VelociCalc™ Plus Model 9555-P thermal anemometer (Photo Credit: NIOSH)

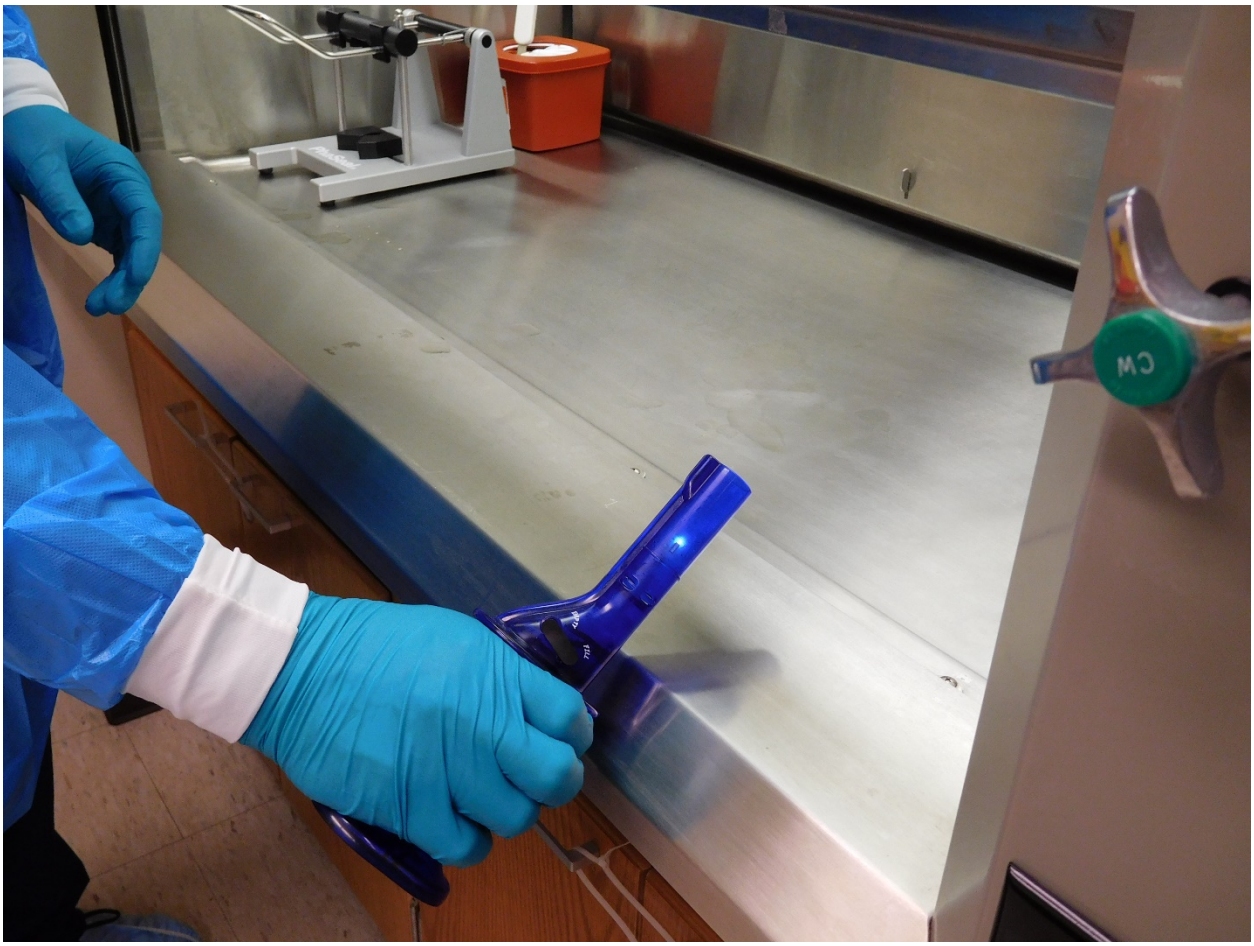

Figure 10. Wizard Stick Smoke Generator (Photo Credit: NIOSH)

Figure 11. TSI Accubalance® Plus Air Capture Hood (Photo Credit: NIOSH)

Figure 12. PPE for chemotherapy treatment (Photo Credit: NIOSH)

Figure 13. Chemotherapy in progress sign (Photo Credit: NIOSH)

Figure 14. Examination table's pad—saliva from patient on toceranib (**note:** wet spot is from cleaning solution, not patient) (Photo credit: NIOSH)

Figure 15. Floor outside of kennel—dog on toceranib (Photo credit: NIOSH)

Figure 16. Floor near examination table (Photo credit: NIOSH)

Figure 17. Chemotherapy drug bins in Oncology Department (Photo Credit: NIOSH)

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