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Environmental Monitoring for Sterile Hazardous Drug Compounding

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Compounding safe sterile preparations requires harmonization of people, processes and engineering controls. With hazardous drugs, the additional element of healthcare provider safety must be included. Often when environmental monitoring is discussed in the context of hazardous drugs, the lens is narrowly focused on hazardous drug residues on surfaces. In the context of USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings, the lens is broadened to not only consider monitoring hazardous drug residues but also all the required holistic environmental monitoring criteria listed in USP <797> Pharmaceutical Compounding—Sterile Preparations.

Section 6 of USP <797>, Microbiological Air and Surface Monitoring, outlines the baseline requirements for air quality and viable sampling processes. USP <797> has additional requirements for monitoring and documenting the compounding environment, including temperature, humidity and room pressures. Preceding any discussion of hazardous drug environmental monitoring of hazardous drug residues, the baseline requirements of the noted environmental monitoring quality program as outlined in USP <797> must first be addressed.

An environmental monitoring program must be dynamic enough to provide adequate information on personnel and processes to guide decisions on the safety of products compounded for patients. USP clearly defines the ISO classifications, temperatures, humidity, room pressures and microbial status for compounding to ensure compounding areas are operating in the optimal "State of Control." Incorporating the additional monitoring of hazardous drug residues in the environmental monitoring program adds to a comprehensive program. Optimal environmental monitoring should confirm consistent, high-quality environmental conditions at all times.[1]

USP <797> sets the minimal criteria for an environmental monitoring program and is highlighted and summarized in Table 1.[2]

Table 1. Minimum Criteria for an Environmental Monitoring Program

Element	Frequency
Site requirements	
Temperature (should be <20° C)	Document daily
Relative humidity (should be <60%)	Document daily
Pressure differentials (continuous monitoring) Cleanroom suite • Anteroom >0.02 inches of W.C. • (+) Pressure buffer room >0.02 inches of W.C. • (-) Pressure buffer room –0.01 to –0.03 inches of W.C. • SCA • C-SCA –0.01 to -0.03 inches W.C.[b]	 Document daily Document daily Document daily Not required Document daily
Certification requirements: classified areas	
Airflow test	6 months[a]
HEPA filter integrity test **Note**: PECs and ceiling HEPAs	6 months[a]
Dynamic smoke pattern test	6 months[a]
Total airborne particle sampling	6 months[a]
Microbiological monitoring: classified areas	
Volumetric active viable air sampling in each classified area[c]	6 months (Category 1 and 2) 3 months (Category 3)
Viable surface sampling	Monthly (Category 1 and 2) Weekly[d] (Category 3)

C-SCA, containment segregated compounding area; PECs, primary engineering controls; W.C., water column.

[a] Recertification of classified areas must take place for the following: redesign and construction of the compounding area; replacement or movement of a PEC; change or addition of equipment in the compounding area that may alter air movement; and major facility service changes that may affect compounding area.

[b] C-SCAs were introduced in the final version of USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings (2019).

[c] Some state boards of pharmacy require more frequent viable air sampling versus USP <797>.

[d] Refer to *USP <797> Section 6.3.2 Surface Sampling Procedures* for further guidance

Sites that compound sterile drugs managed by pharmacy personnel have traditionally established environmental monitoring programs through outsourced certifying companies. These companies provide certification of classified areas and may include the addition of air and surface microbiological monitoring.[3] Certification of the classified areas should be performed by the Controlled Environment Testing Association's National Board of Testing qualified individual(s), with additional accreditation by the National Sanitation Foundation for biological safety cabinets used in the compounding of hazardous drugs.[4]

Resourceful sites have fully optimized their experiences with personnel microbiological assessments (media fills and glove-fingertip and thumb sampling) to conduct the viable air and surface environmental monitoring requirements. Sites opting to manage the microbiological requirements of USP should engage the assistance of their infection control and microbiology departments in addition to the outsourcing certification contractors to formalize and validate the insourcing program. Of note, there may be an additional requirement of the microbiology laboratory to have an accreditation or certificate to manage, read and interpret the results of viable environmental samples.

Identifying Viable Sampling Locations

Viable sampling must occur during normal operations (dynamic conditions) for the collection to be meaningful and process-related. Caution must be taken to ensure the sampling process does not contaminate or interfere with defined operations for

patient care. Sites that have historically used an outsourcing certifying company to conduct viable sampling can gather a good amount of information on the number of samples and general locations of sampling. Most certifying companies create sampling maps that can be used to assist sites with establishing their insourcing sampling locations.

Sampling sites are best selected with thought to human activity during product movement and compounding. Pay close attention to high-touch areas within the workspace such as staging carts/work surfaces, possible areas where airflow may be poor and areas where dust may accumulate.

Viable Sampling in the Primary Engineering Controls and Containment Engineering Controls

The highest risk point for the contamination of compounding sterile preparations is the direct compounding area located within the primary engineering control (PEC) and containment primary engineering control (C-PEC). USP <797> has defined prescribed limits for microorganisms located in and around the PEC and C-PECs (Table 2).

Regardless of the compounding room type (cleanroom suite, segregated compounding area, containment segregated compounding area), viable air sampling must take place within the workspace of the PECs at least every six months for air samples and at least monthly for surface samples, or sooner if the PEC/C-PEC is significantly moved or has repairs that may alter the airflow pattern.

To help identify sampling locations, observe the processes within the PEC/C-PEC, and select surfaces that could pose a risk to the integrity of the products being made and that can provide important information on the applicable standard operating procedures. USP <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments provides guidance and references to assist sites.

After Viable Surface Sampling

Surfaces where growth media have come into direct contact must be cleaned with a sterile germicidal cleaning agent followed by a sterile disinfectant to remove any residual growth media. Any residue could promote the growth of microorganisms. All cleaning of the compounding environment must be documented, which would include any cleaning performed by certifying companies after viable sampling.

Incorporating Hazardous Drug Residue Sampling Into Environmental Monitoring

Lingering residue of hazardous drugs can create a risk. The link between low-dose continuous exposure to hazardous drugs and negative health outcomes in exposed healthcare workers continues to strengthen. There are now hundreds of published studies worldwide suggesting a link between exposure and genetic damage, reproductive issues, teratogenesis, end-organ damage, and cancer. The National Institute for Occupational Safety and Health (NIOSH) website (www.cdc.gov/niosh; see Hazardous Drug Exposures in Healthcare: Antineoplastic Agents) is an excellent resource library for many of these studies.[5]

As a result of this growing body of evidence, there has been a continued evolution of standards and guidelines around hazardous drug exposure and worker safety from organizations such as NIOSH, the Occupational Safety and Health Administration, the Environmental Protection Agency, USP, the FDA, ASHP, the Oncology Nursing Society, the American Society of Clinical Oncology, the Hematology/Oncology Pharmacy Association, the International Society of Oncology Pharmacy Practitioners, and others as well as the continued evolution of technology to support safer compounding and administration of these drugs. Although there are no established minimum levels of exposure for these drugs, the goal, according to the latest guidance from NIOSH (bit.ly/3AFBeNv), is to create a work environment with as low a level as reasonably achievable (ALARA) in terms of exposure, with the ideal goal being zero exposure.

Despite the best safety efforts, hazardous drug residue can be present on a variety of surfaces in the work environment, and once present can easily "migrate" to other areas of the workplace. This creates the potential for human uptake through avenues such as touch contamination, inhalation and ingestion. Wick et al, in an early 1999 study and repeated by others, demonstrated the presence of hazardous drugs in the workplace as well as in the bloodstream and tissues of nurses, pharmacists and technicians working in the affected areas.[6-9]

Data to Support Hazardous Drug Safety Program Investments

Although organizations have invested significant resources in safety measures such as primary, secondary and supplemental engineering controls, personal protective equipment (PPE), and process controls, the demonstrated effectiveness of these measures remains in question. Unlike other hazardous exposure situations such as radiation, where workers can wear a radiation dosimeter badge to clearly see their exposure over time, there are a wide

Table 2. USP <797> Prescribed Limits To Viable Air and Surface Samples

ISO classification	Actionable sample limits in colony-forming units (CFUs)
Viable air sample[a]	
ISO 5	>1 CFU
ISO 7	>10 CFUs
ISO 8	>100 CFUs
Viable surface sample[b]	
ISO 5	>3 CFUs
ISO 7	>5 CFUs
ISO 8	>50 CFUs

[a] CFU/cubic meter (1,000 L) of air/media device.

[b] CFU/media device.

variety of hazardous drugs, and no such easy visualization of exposure is available. Running a safety program without any objective measures to determine whether the program is indeed achieving the desired outcome of ALARA in terms of exposure is not a feasible approach. A process verification methodology is required. The FDA defines process verification as "confirmation by examination and provision of objective evidence that specified requirements have been fulfilled."[10] The keywords in this definition are "objective evidence." Process verification requires some sort of quantitative proof that specifications have been met and seeks to answer the question, "Are we doing things right?" The obvious outcome marker for a hazardous drug safety process verification is surface contamination; is there evidence of the presence of hazardous drugs in the workplace? This is opposed to process validation, which seeks to answer the question, "Are we doing the right thing?"

However, this is not as simple as it may sound. There are a wide variety of drugs on the NIOSH list of hazardous drugs, and sampling for these drugs in the work environment requires specialized testing processes and equipment. A national consensus group was convened in 2020 to generate guidelines around surface testing and monitoring, and this group produced 11 national consensus statements.[11] However, the group did not provide definitive guidance on key elements, such as frequency of testing and results interpretation.

USP <800> introduced the concept of actively using environmental sampling (surface wipe sampling) of hazardous drug residues.[12] Although surface wipe sampling may be the method of choice to evaluate workplace contamination with hazardous drugs, currently, there are a considerable number of published studies that have documented variations in the methodologies used for surface wipe sampling and reporting of results for hazardous drug residues. One consistency among the published studies, however, is the identification of hazardous drug residue in numerous locations throughout the compounding spaces, drug administration locations and throughout facilities.

USP <800>'s perspective for the use of surface wipe sampling is a recommendation that the practice "should" be considered within a hazardous drug safety program.[12] Sampling should be considered on a routine basis (i.e., every six months) or more often if spills or concerns over risky processes exist. Sites should perform a tracer (follow the drugs from receipt to disposal) to identify all touch points by personnel and equipment to set a map for sampling.

Environmental wipe sampling for hazardous drug residue does not define the overall efficacy of a program. It merely gives a point in time and the residue that is or is not present and/or measurable at that time. Sites should consider sampling for the most common drugs handled, and may want to consider one or two representative hazardous drugs, that is, cyclophosphamide (acidic) and fluorouracil (basic).

Table 3. Sampling Locations

Within the pharmacy/compounding space
C-PEC work surface
Front air vent cover of a C-PEC (i.e., biological safety cabinet)
Transfer antechamber of a containment aseptic compounding isolator
Automated compounding devices (i.e., repeater pumps), keypads used for compounding hazardous drugs
Bins used for storing hazardous drugs
Floor directly in front of the C-PEC
Countertops used for staging hazardous drug preparations
Computer keyboards/mouse devices used within the C-SEC
Drug administration areas (outside of compounding environment monitoring)
Delivery and storage location countertop or bins for hazardous drugs
Infusion pump keyboards
Computer keyboard/mouse

C-PEC, Containment primary engineering control; C-SEC, Containment secondary engineering control.

Sampling Locations and Frequency For Hazardous Drug Residues

USP does not give any specific requirements for the number of samples; sites should choose the number of samples based on what they consider to be at risk. Sampling locations should be identified by observing the hazardous drug handling processes, from receipt of the drug to the point of use and disposal. Many published papers have provided guidance for areas to consider including the locations as noted.

The frequency of sampling remains a major question. Understanding that surface sampling is simply a snapshot in time, the noted interval suggested in USP <800> would seem to be of limited value.

The process of sampling for hazardous drug residues is itself a hazardous process. Sites should have personnel don the appropriate PPE that would be worn for compounding. All materials not sent back to the sampling laboratory must be disposed of as hazardous waste. Personnel may be tempted to keep pens and stickers that are left over; however, this should be highly discouraged due to their potential contamination with hazardous drug residue.

Quantitative Hazardous Drug Residue Sampling Tests

There are two primary testing approaches. One method involves the application of a solvent to the work surfaces with the sample then shipped to a laboratory, where specialized testing methods are used, such as high-performance liquid chromatography in combination with mass

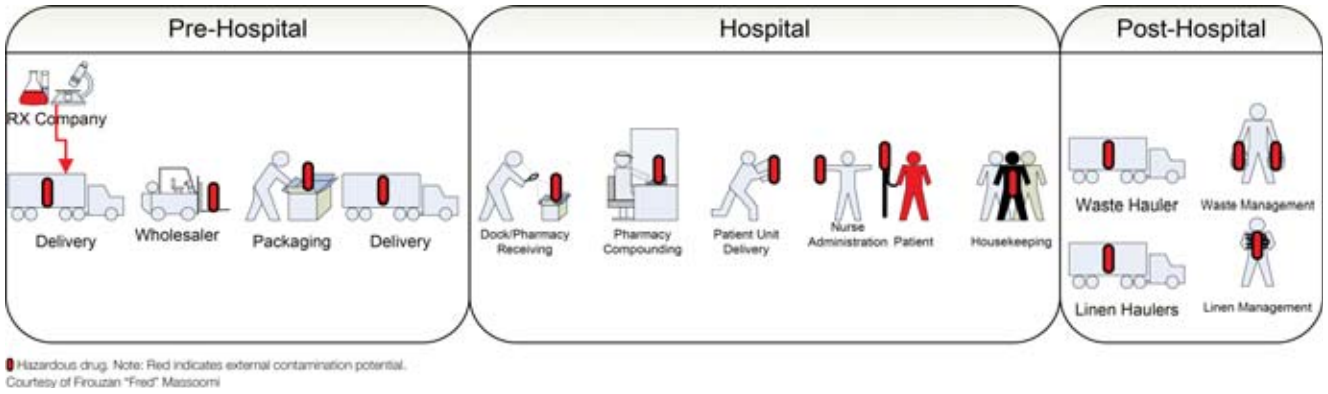

Figure 1. Hazardous drug handling process.

spectrometry (MS). Other methods used in combination with MS or tandem MS include gas chromatography and ultra-high-performance liquid chromatography; inductively coupled plasma MS has been used to detect platinum compounds.[13-15] Results for the samples from kit vendors may take anywhere from two weeks up to one month.

Of note, commercial kits only test for a handful of specific hazardous drugs, and the results do not represent all drugs. As such, non-detectable results from a specific analysis do not guarantee that no hazardous drug residue is present only the residues of drugs tested. The value of these tests is as a surrogate, noting their limitations.

Qualitative Hazardous Drug Residue Sampling Tests

In addition to the traditional wipe analysis kits that quantify defined hazardous drugs, there also is a qualitative quick test system that can detect the presence of defined residues without quantifying. In 2018, BD released the HD Check Analyzer as a system to provide qualitative results in as little as 10 minutes for hazardous drug residues.[16]

The system requires minimal training for results. The HD Check Analyzer is designed to be an intuitive and easy process, with just eight steps:

1. Assemble supplies and don PPE.
2. Identify test surface using the HD Check template.
3. Swab the test surface.
4. Transfer the swab to the sampling tube and invert five times.
5. Squeeze four drops from the sampling tube onto the methotrexate or doxorubicin drug assay cartridge.
6. Allow five minutes for the drug assay cartridge to develop.
7. Turn on the analyzer and place the developed cartridge in the system when prompted.
8. Read the positive or negative result.

At the time of writing, the system was limited to methotrexate, doxorubicin and cyclophosphamide, which are used at most facilities in the United States. (BD is developing a catalog of the most frequently handled hazardous drugs in the United States to determine which additional drugs might be added to the HD Check product offering.) Unlike the commercially available wipe analysis kits, the HD Check Analyzer checks for the presence of the drug without quantifying the results. The system leverages concentration thresholds to determine positive or negative: methotrexate and doxorubicin at 0.1 ng/cm^2 and cyclophosphamide at 0.5 ng/cm.^{2} The mere presence of residue should result in the same response to a quantified sample: recleaning and reassessment to baseline.

Sites should consider the continuum of the hazardous drug handling process (Figure 1) and assign routine sampling intervals for assessing for residue.

Due to the immediacy of the results, the HD Check Analyzer can be used:

- daily to verify cleaning processes;
- whenever primary engineering controls and surfaces where hazardous drugs are used are cleaned; and
- whenever a spill occurs to verify the spill has been fully cleaned.

Conducting real-time wipe analysis to identify any hazardous drug residue serves as a tool that can assist sites with verifying the effectiveness of their hazardous drug handling practices.

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Collaboration of Quantitative and Qualitative Testing

A best-practice approach to these two testing methodologies may be to deploy a combination of both. The rapid qualitative test can be used daily for key areas/processes with one or two drugs as surrogate outcome markers for verification of the overall safe handling program performance. The quantitative kits, which test for more drugs, can be used to establish baseline levels and periodically at six months or, if consistent positives from the rapid tests are observed, to quantify the amount of drug present or after a major spill to verify cleaning efforts (noting limitations of hazardous drug testing capacities).

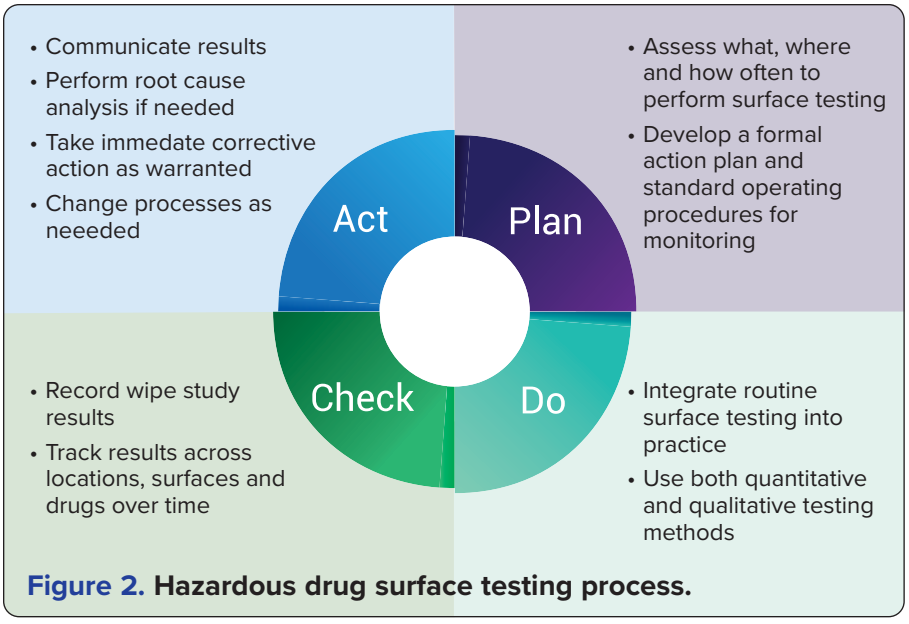

Figure 2. Hazardous drug surface testing process.

Interpreting Results

All results from environmental sampling should be reviewed and assessed by the designated person who is responsible for managing the sterile compounding program and the administrator in charge. Together, a decision on what to do with the results should be formulated. As noted previously, USP does not give acceptable limits for measurable residue; the best practice is to have no measurable residue. If the test(s) demonstrates an excursion (i.e., a positive sample for the presence of drug residue), a review of the processes surrounding the location of the positive sample should take place. Personnel also should be informed of the results, and a thorough deactivation, decontamination, cleaning and disinfection of the area must take place, followed by repeat sampling.

Sampling of the area should continue until results return to a baseline of no residue. If continuous positive samples occur, the site may warrant the use of an outside agency to assist with addressing the cleaning processes and operating procedures. Using the root cause assessment process to review sampling results, processes, personnel and facilities will aid in an effective corrective and/or preventive action plan to mitigate their recurrence, with the goal of enhanced safety.

Documentation of the Environmental Monitoring Program

USP clearly states that a formal environmental monitoring program be developed, written into standard operating procedures and implemented as part of a quality control program. The documentation of viable air and surface sample results, hazardous drug residue sampling results, temperatures, humidity, and room pressures can help guide any subsequent investigative processes. Sites should develop written or electronic sampling forms that provide data that can be trended and referenced if an action level is exceeded for the investigation. Sampling forms should have the names of each individual involved with sampling: the date of sampling, sample type (air, surface, hazardous drug residue), sample location, sampling devices, expiration date/lot number of sampling devices, calibration date of equipment if used, period of sampling, number of personnel in sampling area and temperature/humidity of the sampling area. The information must be legible and complete, and staff should be instructed to not erase, blot out or scribble out any information but instead use a line through the unwanted documentation with a date/personnel initial notation. All information must be stored in a manner for quick access while preventing deterioration and/or loss. The documentation must comply with state and federal laws and must be stored for at least three years or longer, if directed by licensing agencies. Pharmacy compounding compliance software automates the documentation requirements and allows for a easily retrievable , consistent, systematic process for the accurate documentation requirements.

Creating a Continuous Improvement Plan for Environmental Monitoring of Hazardous Drugs

Overall, a hazardous drug surface sampling program integrated into the formality of the required environmental monitoring program validates and verifies the performance of safe handling processes for hazardous drugs could follow the continuous improvement project planning tool Plan-Do-Check-Act methodology (Figure 2).

With the availability of rapid testing tools, a better approach would be to identify an organization's highest-risk processes and to test at least daily in those areas to verify safe handling and cleaning. This approach also establishes a testing history to trend performance over time to identify any areas or processes that consistently show evidence of surface contamination.

The best practice for a hazardous drug environmental monitoring safety program would be for surface wipe analysis to go beyond defining a historical issue and concurrently verify processes within the hazardous drug continuum. For example, staff at each compounding location (sterile and non-sterile) could conduct an immediate wipe test to confirm surfaces are clean and ready for use. This approach would provide information necessary to help minimize the transfer of residue from surface to surface, or from surface to products destined for patient administration. A recent Danish study demonstrated the use of frequent wipe sampling to assess contaminated locations and improve the cleaning processes to greatly reduce positive samples.[17] Similar results were also demonstrated in a recently published U.S. study, with a 46% reduction in hazardous drug contamination after incorporating a closed system drug-transfer device (CSTD)

into clinical workflows along with surface testing. Across time points and sites, hazardous drug contamination reported by the BD HD Check device was 91% accurate against liquid chromatography–MS and 98% accurate within its limits of detection. The study concluded that "collectively, the evaluated CSTD and lateral flow immunoassay device may help to reduce HD contamination and provide real-time measures of contamination, respectively. As part of a multifaceted approach, these devices may help minimize barriers to routine monitoring, ultimately improving the safety of healthcare workers and patients."[18]

Conclusion

An environmental monitoring program for the compounding of sterile hazardous drugs must consider the requirements outlined in USP Chapters <797> and <800>. Without conducting a hazardous drug residue wipe analysis, facilities are blindly assuming their hazardous drug safety processes are adequate and immune to this widely established pattern of environmental contamination. Conducting regular hazardous drug residue wipe studies identifies the site's active risk, allowing the facility to either improve practices or praise staff for following well-defined standard operations procedures. Thereafter, a well-defined, systematic program for active environmental sampling will assist in monitoring the staff's diligence in following standard operating procedures.

BD HD Check Analyzer, assay cartridge and collection kit.

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