ISPE

Good Practice Guide

Assessing the Particulate Containment Performance of Pharmaceutical Equipment

Second Edition



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Good Practice Guide

Assessing the Particulate Containment Performance of Pharmaceutical Equipment

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This Guide describes methodologies for evaluating the containment capability of systems and equipment in the pharmaceutical and biotechnology industries under defined conditions. The ISPE cannot ensure and does not warrant that a containment system and equipment tested in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for involving professional industrial hygienists, engineers, or scientists.

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Preface

The purpose of the ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment is to provide technical guidance and consistent methodologies for evaluating the particulate containment performance (particulate emissions) of pharmaceutical equipment and systems.

This Guide aims to define current good practices in this area, providing information to allow organizations to benchmark their practices and improve on them. Specifically, the Guide provides a methodology to derive data associated with handling of pharmaceutical ingredients that can be useful in the assessment of potential risks such as:

1. the potential exposure of the operator

2. the potential for uncontrolled release of pharmaceutical ingredients within the facility

3. the potential exposure of the outdoor environment

The intended audience for this Guide is global, but is not intended to address any region-specific regulatory requirements. Users of this Guide should consult local authorities/experts to make sure that, in addition to addressing the above mentioned risks, worker safety, product quality, and environmental quality meet local regulations.

The information provided in this Guide reflects the cumulative knowledge and experiences of the authors, editors, and reviewers with input from members of the ISPE Containment Community of Practice (COP) and general membership.

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1 Introduction

1.1 Background and Purpose

This Guide is a second edition of the ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment. The revision was undertaken to allow the Guide to address a broader selection of containment technologies and processing equipment than those covered in the first edition of the Guide.

The containment capability of equipment is an important factor in evaluating the risks associated with the handling of pharmaceutical ingredients; of specific interest are:

1. the potential exposure of the operator

2. the potential for uncontrolled release of pharmaceutical ingredients within the facility

3. the potential exposure of the outdoor environment

For the purpose of this Guide, the term “equipment” applies to containment systems and technologies, and processing equipment.

The Guide intends to provide a set of principles and standardized methodologies for evaluating the containment capability of pharmaceutical equipment. The methodologies involve the sampling and analysis for airborne emissions and surface contamination of a surrogate material manipulated within the equipment.

The principles and methodologies are intended to provide a standardized and repeatable process for determining the containment capabilities of equipment used in the pharmaceutical and biotechnology industries under specific, defined conditions.

This Guide can be used to evaluate *in situ* equipment both prior to use and over time. The Guide also may be used to evaluate and compare similar or different types of equipment from different suppliers.

Test data generated by following this Guide can be used to help to identify limitations of equipment being tested.

The materials and conditions specified in this Guide have been selected to reflect the “typical operation” of the equipment. This allows analysis of typical containment performance, while minimizing the risk of exposure to hazardous materials and background interference. Industry accepted test materials (surrogates) are recommended to best mimic the handling of actual pharmaceutical ingredients while allowing:

- safe handling

- ease of procurement

- sufficient limits of detection

The limits of detection should be sufficiently sensitive to evaluate the containment capability required for Active Pharmaceutical Ingredients (APIs), including potent or highly hazardous materials.

The methodologies recommended for sampling and analysis reflect pragmatic good industrial/occupational hygiene practice and should be followed to help to ensure reliable results.

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The Guide outlines the following factors that affect the quality of the containment performance assessment:

- test protocol
- surrogate materials handled
- test environment
- operator factors
- qualification of personnel responsible for designing and conducting the test protocol (including sample collection)
- data analysis, interpretation, and documentation

1.1.1 Test Protocol

Testing the effectiveness of equipment involves measuring airborne emissions and surface contamination to provide relevant data about the containment capability of the system. The test protocol should define:

- operations to be sampled
- types, numbers, and locations of samples to be collected
- containment performance target (if defined)
- surrogate to be used
- duration and frequency of sampling
- equipment necessary for sampling
- sampling methods and analysis
- cleaning method for the test equipment and its local environment
- other parameters of the test protocol relevant to the particular equipment being tested (e.g., quantities and rate of processing, representative temperature and humidity ranges in the local environment).

Data generated may be used to support the decisions regarding whether equipment is suitable for the desired containment required for a particular material and operating scenario. The test data also may define a “baseline” performance for equipment, where relevant experience can be applied and appropriate care is taken. The “baseline” performance could be used for anticipating the potential performance of the equipment under different conditions or with different materials. Such baseline information also can enable performance trending over time which in turn can help to establish preventative maintenance activities to ensure consistent performance.

1.1.2 Surrogate Materials Handled

The Guide recommends various surrogates appropriate for evaluating the containment performance of the equipment being tested. In order to represent control of the actual process to be performed, the surrogates should, where possible, mimic the materials associated with the operating process. Factors to be considered are described in Chapter 4 of this Guide.

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1.1.3 Test Environment

The Guide identifies the critical factors and components that need to be controlled and monitored during testing. This includes guidance on the essential features of the test environment with specific recommendations for finishes, air quality, temperature, humidity, and ventilation rate.

1.1.4 Operator Factors

The Guide identifies the critical factors involving operators including their apparel and personal protective equipment (if any) during testing, duties reflecting the representative type and range of equipment usage, and number of operators appropriate for performing the operations. It is essential that all operators are familiar with and are effectively trained in the operation of the equipment prior to testing in order to achieve useful results.

1.1.5 Data Analysis, Interpretation, and Documentation

The Guide describes how data should be recorded to allow interpretation by suitably qualified persons. The Guide also describes how data should be analyzed and recorded to allow interpretation by suitably qualified persons in order to provide comparable information on equipment performance. Assessment of data may help to identify where modifications, additional engineering controls, facility enhancements, or procedures are required.

1.2 Scope

The Guide provides a methodology for assessing the performance of equipment against a specific challenge, where the challenge can encompass such elements as the surrogate's selection, the quantity of surrogate to be used, the length of time the challenge will occur, and similar parameters which could affect performance.

The Guide is intended to have global application and has been developed to meet the requirements of supplier organizations as well as users. The proposed methodology applies to:

- powders (not liquids or vapors)
- airborne and surface contamination
- supplier and field installations (in situ installations)

Test protocols are included to evaluate the performance of equipment in supplier factory installations, as well as for establishing performance of field installations. The methodology is primarily applicable to the equipment identified in the test protocols contained within this Guide, but may be adapted to other systems that have similar features. The use of surrogates is meant to represent typical field performance in order to provide a baseline set of results, and should not be considered as a guarantee of field performance.

The materials and conditions described in this Guide have been carefully selected to mimic "typical operation," while allowing accurate analysis of containment capability without the risk of excessive background interference. The surrogate test materials recommended in this document allow detection at low concentrations to mimic the tolerable concentrations of highly potent or active materials.

Methodologies for comparing test results against other acceptance criteria (e.g., operator safety or cGMP) are outside the scope of the Guide.

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Note:

- Test results are **not** intended to be directly compared to the Occupational Exposure Limit (OEL) (performed in a workplace exposure assessment), or other personnel safety-related criteria, as this would require the performance of a complete work place risk assessment.

- Test results are **not** intended to be directly compared in order to assess cross contamination or outdoor environmental impact.

The methodologies described may be applied as part of commissioning to existing field installations, e.g., to provide confidence of continued effectiveness of containment or during the investigation of an incident; however, these other uses can present additional challenges and requirements that are outside the scope of this Guide.

1.3 Benefits

This Guide provides pharmaceutical and biotechnology organizations with an approach for the evaluation of the effectiveness of equipment for solids handling and processing operations. The Guide is intended to be flexible and to permit pharmaceutical organizations and their suppliers to consistently test equipment in order to evaluate its effectiveness of equipment for solids handling and processing operations.

With proper planning, containment capability assessments can be completed in a cost effective manner. The data can be used to evaluate the performance of the equipment and to allow comparison with equivalent systems or to assess field performance.

1.4 Structure of the Guide

Subsequent sections of this Guide elaborate on each of the factors that affect the quality of the containment performance assessment of specific contained solids handling systems, including:

- basic concepts
- testing environment
- test material
- measurement of airborne particulate matter and surface contamination
- sample analysis
- interpretation of results
- report

The Appendices to this Guide provide information on:

- test protocols for containment equipment
- surrogate identification and characterization, including the pros, cons, and typical applications of various surrogate materials
- the relationship between room particle concentration levels and air change rates, including room recovery times
- calculating the required sensitivity for an analytical method

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2 Key Concepts

2.1 Containment Equipment Test Protocols

Containment equipment test protocols included in this Guide address standard containment equipment and transfer systems that are in use in the pharmaceutical and biotechnology industries. These containment equipment test protocols should be used as a guide for assessing containment performance and can be modified and combined as appropriate to accommodate different individual and continuous process train containment systems.

2.1.1 Critical Issues Associated with Conducting Containment Performance Assessments

This Guide describes standardized methodologies for evaluating the effectiveness of containment equipment used in the pharmaceutical and biotechnology industries. In doing so, it identifies critical issues that should be addressed prior to, during, and/or at the completion of containment performance assessment studies, e.g.:

- test environment
- test material selection
- airborne particulate matter and surface contamination sampling methodologies
- sample analysis
- interpretation of results
- report preparation

2.1.2 Data Incompatibility

The Guide describes the monitoring of emissions as a measure of equipment performance.

Air sampling in the operator's breathing zone has been included in the containment equipment test protocols because the operator is considered an integral component of containment systems. Having both emissions and personal data can be of use in the overall interpretation of containment effectiveness. Because personal exposure sampling protocols are already well established in the industrial hygiene community, additional reference and description is not repeated here. Finally, it is important to keep in mind that personal exposure sampling and emissions sampling are not directly, statistically, or mathematically comparable.

Additional industrial hygiene ("personal exposure") sampling can be performed in conjunction with emissions sampling, where desired. The Guide does not address personal exposure sampling as traditionally performed by industrial hygienists.

2.1.3 Enhanced Data Analysis and Documentation

The following types of air sampling data can be collected simultaneously, but are not directly comparable:

- task specific data
- time-weighted averaged data
- "real-time" aerosol sampling data

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These types of data can enhance the overall interpretation of containment performance, but this depends on the placement and timing of data collection.

2.1.4 Emissions versus Exposures

Emissions of active pharmaceutical ingredients from pharmaceutical process equipment can result in an increased risk of adverse effects on:

- personal health
- product quality
- facility cleanliness
- outdoor ecosystems
- operational productivity

This Guide focuses on characterizing the emissions from a source (e.g., a piece of equipment or transfer device) in order to evaluate its containment capability and set a baseline of performance with respect to emission control for that source. This information is then available to be utilized, as the individual subject matter experts deem appropriate, to assess risk with reference to how those emissions may become exposures that could affect personnel health and safety, product quality, outdoor ecosystems, and operational productivity.

2.1.5 Equipment

For the purpose of this Guide, the term “equipment” is used to refer either to a piece of process equipment (e.g., a mill or a centrifuge) or to a containment system (e.g., a glovebox, a downflow booth, containment by air entrainment device, or local exhaust device).

“Equipment” also can refer to sampling/monitoring equipment, but will be specified as such in order to avoid confusion.

2.1.6 Particle (“Real-Time”) Sampling

Continuous airborne sampling of aerosols (also referred to as “real-time” sampling) provides data which is not chemical-specific, but which does demonstrate how total airborne particle concentrations vary with time.

Measured concentrations of particles can include additional ambient solid and/or liquid particles, as well as particles generated from clothing or personnel; therefore, “real-time” sampling cannot be used by itself as a definitive quantification of airborne levels of a specific material of concern.
“Real-time” sampling devices typically register aerosol concentrations in time increments (as small as once every few seconds, if desired) and permit the airborne concentration peaks and troughs to be readily seen over a given time period, rather than just an average value throughout the time period.

When used strategically (e.g., positioned close to suspected emission locations) real-time data can be used in conjunction with chemical-specific data to yield a more complete characterization of process emissions. A further benefit of real-time sampling is the ability to align its results with video recording or timed observations. This can allow identification of specific activities or elements of operations which produce significant emissions (peaks in real-time output data) and enables a focus for design modifications or changes in operator behavior.

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2.1.7 Particulate Material

For the purposes of this Guide, the term “particulate material” will be used to refer to the airborne surrogate material generated during a representative process. This term will be used in place of dust, as the term “dust” represents all airborne particulate matter that may be present during a containment assessment verification study.

2.1.8 Pharmaceutical Ingredient

For the purposes of this Guide, the term “pharmaceutical ingredient” refers to the API, synthetic intermediate, or pharmaceutical formulation for which the surrogate material is being substituted.

2.1.9 Sample Collection and Sampling Methodologies

The type and method of sample collection plays a key role in proper interpretation of the results. Orientation to the equipment, ambient airflow direction, and elevation of sample points, and other critical attributes may need to be considered in an effective sampling strategy.

2.1.10 Standardized Approach for Conducting Containment Performance Assessments

Standardizing emissions data between containment systems is key to the ability to make meaningful comparisons. When testing equipment that is in the production setting, the number of variables increases significantly, when compared to the number of variables for the closely controlled conditions in a test enclosure.

Typically, for the purposes of comparison, field testing results cannot be normalized sufficiently to those taken from other installations; however, the results of field testing can be valuable as part of the commissioning of containment equipment. In addition, when field results are compared against factory testing, differences in results between the two can be a basis for determining the impact of the field variables. Where appropriate, the differences in results can support and justify additional containment equipment modifications and improvements.

2.1.11 Surface Sampling

Surface contamination can be evaluated by performing surface sampling using surface wipes or swabs over a representative area with an acceptable material, which is analyzed in the laboratory. For the purpose of this Guide, this process is referred to as “surface sampling,” but may be called “wipe,” “swab,” or “swipe” sampling.

2.1.12 Surrogate Sampling

It may be desirable to use a surrogate material first, to simulate potential emissions as the material is processed through equipment, as a substitute for sampling an API. There can be several reasons for selecting surrogates, including:

- history of surrogate use in the facility
- hazardous nature of the API of interest
- relative sensitivities of analytical techniques available
- cost of material

A variety of surrogates is usually available. The characteristics of a surrogate should be considered in the selection and should resemble as closely as possible the behavior of the actual compound in the process and aerodynamically.

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2.1.13 Validation

The term validation in this document is used only in relation to quantitative, analytical methods and is not meant to denote a cGMP-related context. Also, the methodologies described are not meant to provide “validation” of these devices in the cGMP context, but rather a “verification” of their containment performance.

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3 Test Environment

This Guide considers two applications of the testing methodology:

1. testing of the equipment in a supplier factory environment as part of a Factory Acceptance Test (FAT)

2. field testing in a user's facility, either as part of a Site Acceptance Test (SAT) or for routine performance testing

The details of the enclosure for these tests may vary between supplier factory and user installation locations, due to the limitations and constraints associated with the specific location.

In a supplier factory environment, it is suggested that the enclosure used has a carefully controlled internal environment and gowning procedure to minimize variations due to extraneous factors. Where possible enclosures used to assess similar systems from different suppliers should be identical. This may not be feasible due to space constraints and the configurations of different systems.

For field testing in a user's facility, it is normally not feasible to provide an enclosed, controlled environment around a system; therefore, there may be a risk that measurement activities at the user site are affected by other local equipment and activities. Measurement results are also dependent on the inherent cleanliness of the location.

This chapter details the key areas and technical details to consider for each application of the testing methodology.

3.1 Suppliers Site Test Enclosure

3.1.1 Suppliers Test Enclosure Layout

Care should be taken to ensure that testing activities do not affect the containment performance of the equipment's anticipated normal operation.

Supplier enclosures should be identical to each other in all respects (e.g., layout, material, physical conditions), if feasible.

Significant variation from proposed standard conditions (e.g., temperature, relative humidity, and air change rate) may create significant variations in results and invalidate comparisons between different supplier datasets.

The layout of the test enclosure should provide:

- Sufficient access for the normal operation of the equipment item being tested (see Chapter 9 of this Guide) and to allow placement, operation, and removal of the sampling equipment or other testing devices. (For further information on typical sampling systems, see Chapter 5 of this Guide.) Where possible, the equipment being tested should be set up to approximate the position and alignment of a typical user location. Traditionally, the use of mock-ups to simulate equipment and setup at a user location has been considered helpful.

- Storage space for the placement of any clean articles required during the test to prevent them from having to be introduced during the test and potentially disturbing the integrity of the enclosure.

- Seating or standing areas for observers. This should be positioned to allow observation of the test, but not interfere with the normal movements of the operator performing the test, or interrupt the airflow patterns, which will have been considered in the positioning of the test equipment. Excessive personnel movements will create or disturb airborne particles, which may affect the sampling results. It may be useful to incorporate an observation window in the enclosure wall, and/or a remotely operated video camera.

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- A layout table for organizing and calibrating sampling equipment and filters, recording procedures and other observations, static instrumentation, swab samples, etc., should be located in a clean area outside the enclosure.
- Unobstructed and appropriately positioned exhaust and ventilation points
- All appropriate services to allow the equipment contained in the enclosure to be operated as designed (e.g., power, compressed air, nitrogen, exhaust ventilation, drains, etc.)
- All necessary safety features (e.g., access ladders and working platforms) to safely operate the equipment being tested. This also may include lifting devices to reduce the risk of manual handling injuries or oxygen or solvent concentration alarms, where appropriate.

The use of an airlock to control entry/egress and act as a useful area to change into coveralls is recommended to maintain and control the quality of the environment within the test environment. However, for enclosures created to test a specific piece of equipment, with tightly controlled entry/egress procedures, an airlock may not be necessary.

Surrogate materials should be stored and prepared (container opened and sub-divided) in an area separated and removed from the test enclosure.

The overall dimensions of the test enclosure should, as a minimum, support the requirements described above and allow for cleaning.

3.1.2 Test Enclosure Construction

The test enclosure should be built from materials that are non-shedding, easy to clean (non-porous and smooth), and capable of maintaining the required environmental conditions (see Section 4.3 of this Guide). If shedding materials are used (e.g., wooden framing) these should be kept outside of the test environment.

Construction materials may vary depending on whether the enclosure is to be permanent or temporary. Materials should be easy to make into an enclosure. Where reuse is intended, the materials should be easily cleanable to allow removal of residual contamination. Examples of temporary enclosure wall construction materials include:

- anti-static polyethylene or polyurethane sheet over wooden or scaffolding frame
- non-shedding board material on a wooden frame
- reinforced Polyvinyl Chloride (PVC) films (available in static dissipative (conducting) grades, but can be difficult to use as it adheres to itself)
- epoxy paint finish on wood

Adhesive tape should be used to seal around gaps and seams between floors, walls, and ceilings.

Examples of permanent enclosure construction materials include:

- epoxy paint finished walls and floors
- vinyl finished walls, floors, ceilings
- polyester or similar type material panel (walls)
- stainless steel (walls)
- non-flaking ceiling tiles (ceilings)

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- terrazzo (floors)

3.1.3 Test Enclosure Environmental Conditions

The environmental conditions within the testing enclosure should minimize the influence of the environment external to the enclosure. The conditions provided should be similar to those anticipated at the end-user site.

The testing enclosure should provide consistent conditions that do not adversely influence the test results throughout the test.

Where test results are to be used for comparison with datasets from other sources, common standardized conditions should be used (as far as possible) for comparisons to be valid.

Where test results are not intended to be used for comparison with other datasets (e.g., for routine or "baseline" performance assessments on site), normal operating conditions for the site environment should be applied. This may be critical where "normal" user operating conditions may include extremes of temperature, relative humidity, or local air change rate.

Relative humidity should be controlled and monitored, as it may affect test results.

Prior to and between tests, the air change rate should be sufficient to allow the reduction of airborne particles to an acceptable level within a practical period of time. Calculation of the time related to air change rate depends on the turbulence within the enclosure, the presence of "dead zones," and other factors. It is suggested that a minimum of 99% reduction is specified applying the figure included in Chapter 11 (Appendix 3), using C_s equal to zero, and $C_{final}/C_{initial}$ equal to 0.1.

Recommended environmental conditions for the purposes of this Guide are:

- Temperature Range: 20°C ± 5°C
- Relative Humidity (RH): 50% ± 10%
- Positive Room Pressure: +10 Pa (minimum) relative to the adjacent space
- Air Change Rate: 3 to 5 Air Changes per Hour (ACH)

Note: higher air change rates may be required to maintain stipulated conditions.

Excessively high air currents that may affect sampling should be avoided. Smoke pattern analysis may be used to detect high velocity currents prior to a test.

The conditions should be maintained and the values for each environmental condition documented for the duration of a test.

The inlet and exhaust air should be filtered to prevent contaminated air from entering or leaving the test enclosure. The selection of the inlet air filter should be based on the desired quality of the supply air. This is usually based on the required enclosure background particle level and a HEPA filter is normally adequate for this purpose. The exhaust air filter classification should be specified to prevent gross contamination of the external environment. Filter loadings should be monitored to confirm that air change rates are not significantly reduced by filter blockage during the test period.

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The background concentration of test material in the enclosure should be no higher than 10% of the level expected to be liberated during the tests to prevent the background levels from adversely influencing the interpretation of the test results. This value is not mandatory, but should be considered "good practice." In general, where anticipated concentrations may be very low (e.g., below 1 µg/m^3), achieving levels below 10% could be difficult or below the Limit of Detection (LOD). In such cases, judgment on the acceptable level of baseline contamination should be sought from experienced industrial/occupational hygienists.

The Guide does not stipulate a formal standard classification for particulates (e.g., in line with ISO 14644 or similar standard) to be met as the analysis is specific to the surrogate material used in the test.

It is recommended that the air inlet and extract points are positioned on opposite sides of a test enclosure to ensure that the room is adequately ventilated. Inlet and extract positions should be located to prevent directly affecting test results.

Smoke pencils, smoke tubes, or similar smoke generation devices may be used to observe the direction of the airflow to ensure that the particle samplers are located in appropriate positions to sample potential high concentrations. Samplers should not be located in static air locations or "dead zones" (see Chapter 9 of this Guide).

3.1.4 Requirements for Personnel Performing Containment Verification Assessments

Personnel carrying out the test ("test personnel" or "operators") should be trained in the use of the equipment and understand the test procedure.

Test personnel should remain within the enclosure during the tests. Where this is not possible, proper gowning/de-gowning techniques should be employed.

The number of operators and their movements should be limited to those required to perform the test or operate the equipment.

A checklist should be developed to ensure that the sampling system and operation tasks are identified and that owners for the tasks are identified.

Other personnel in the enclosure during the test, e.g., industrial/occupational hygienists operating the sampling equipment, should adhere to the same requirements as the operators.

3.1.5 Clothing

Clean, non-shedding garments should be used to reduce the risk of contamination from clothing. Recommended clothing includes:

- coveralls
- shoe covers
- hair/head covers or hoods
- gloves (for open-handling of surrogates and air samples and surface samples)

A gowning procedure that prevents significant effects on the test results, e.g., the use of a controlled gowning/de-gowning area, should be established.

Contaminated clothing should not be re-introduced into the test enclosure.

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3.2 User Site Test Location

3.2.1 Enclosures at the Site Test Location

Site test locations may not be suitable for installation of a test enclosure; where possible, guidance provided in Sections 3.1.4 and 3.1.5 of this Guide should be followed. (Guidance provided in Sections 3.1.1, 3.1.2, and 3.1.3 of this Guide may not be applicable.)

Where a physical test enclosure cannot be built, a designated test area should be defined. Access to the area should be limited to minimize the risk of physical transport of contamination into the area.

Nearby processes may present a risk of exposure to personnel performing the containment verification assessment and are a potential for cross contamination

A risk assessment should be completed before proceeding with a test. The risk assessment should evaluate the hazards of other processes in the area and their potential impact on the testing process.

A clean area should be established for setting up air sampling equipment and supplies see Section 3.1.1 of this Guide. Pumps should be calibrated pre- and post-sampling; a table and clean area should be provided. In addition, air and surface sampling media should be organized before sampling and reconciled after sampling in a clean area.

3.2.2 Review of the Test Location

A review of the test location should be completed before developing the sampling strategy for the user location. The review should include an assessment of processes, equipment, and materials which are associated with or near to the test location. Current and historical activities, environmental conditions, and other co-located activities should be identified. Where the purpose of the measurement exercise is comparison against a previously derived baseline, conditions of previous tests also should be identified.

The assessment should answer the questions:

1. Has any activity currently or previously been performed within the location that could affect the accuracy of the results? For example:

    - the presence of contaminant residues that could affect sample analyses

2. Where a comparison is to be performed, has any element of the system, closely located systems, or support systems (e.g., HVAC) been modified or changed in a way that could cause a significant effect on anticipated results? For example:

    - changes to HVAC airflow regimes

    - changes to Standard Operating Systems (SOPs)

    - modifications to equipment

Where a risk of potentially significant effects on testing results is identified, remedial actions should be taken to minimize or remove the effect. For example, if significant residues of a surrogate or contaminating materials could be present in the test area and these could cause false readings, the following steps may be taken to minimize the effect:

- Thoroughly cleaning all areas prior to test to remove residues as much as possible. This could include changing ventilation filters to remove the risk of release of captured material.

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- Performing air and surface sampling of the test area environment prior to the test to prove residue levels are insignificant or to establish a baseline.

- Ensuring that gowning and degowning protocols are followed (see Section 3.1.5 of this Guide). Items brought into the test area should be inspected and wiped clean, as appropriate, to minimize the risk of material ingress on the surface of clothing and equipment.

Details of the test area should be carefully recorded, both to:

- document the equipment and area status at the time of testing for future comparison studies

- aid the analysis of data particularly where outlying data is obtained

Video or still photography is recommended as a way of providing a concurrent record, where safe and acceptable.

Critical elements of the test system which should be recorded and incorporated into the report include:

- general arrangement of equipment, people, and test locations

- number of people participating and their roles

- equipment details – type, operating mode, operating detail, and SOP version followed

- service conditions and flow rates, including inert gases, compressed air, and local exhausts/venting

- pre-test cleaning methodology and test results

- ventilation detail during test period – temperature/relative humidity/filtration quality/air change rate and general flow direction or pattern

- details of the test room if appropriate (dimensions/finishes)

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4 Test Material

4.1 Introduction

Where appropriate, operation of the containment equipment can be verified using a substitute or "surrogate" test material, rather than the actual pharmaceutical ingredient. Surrogate testing data can be used to anticipate performance with other materials under similar operating conditions. The surrogate test material may have different properties to those of the materials to be used in the actual application of the equipment.

Surrogate data is an indicator of potential equipment performance and surrogate data should not be used as a guarantee of performance under all conditions. Where possible, subsequent testing with the drug substance in the user facility should be performed to verify the results obtained using the surrogate.

If an actual pharmaceutical ingredient cannot be used, a suitable surrogate should be selected. Use of a surrogate may be warranted if a suitably sensitive analytical method does not exist for the actual pharmaceutical ingredient, the pharmaceutical ingredient is extremely expensive, or the pharmaceutical ingredient is extremely hazardous. The performance of engineered containment systems without the use of additional protection systems, e.g., PPE, should be verified prior to introducing potent materials. As there is a variety of surrogates available for use, the chemical and physical properties and characteristics of the powder should be considered. These should approximate the behavior of the actual drug substance as closely as possible.

Some of the physico-chemical properties to be considered in the selection of a surrogate include:

- powder flow characteristics
- analytical sensitivity/Limit of Detection (LOD) requirements
- potential prior contamination of facility
- pharmacological activity (no effect on testing personnel or risk of cross-contamination)
- cost and availability of surrogate
- complexity and cost of analytical methods
- available particle size range and "dustiness index" to provide a sufficient challenge
- other special features, such as easy visual detection
- properties that will enable the surrogate to mimic the pharmaceutical process
- consistency of particle shape, (from different suppliers)
- ease of disposal (environmental consideration)
- solubility in water and other solvents (ease of cleaning)
- stability of the test material and air or surface sample degradation
- combustible dust properties

A surrogate should be selected that appropriately mimics the behavior of the drug substance intended to be used. Most of the surrogates suggested in this Guide are relatively non-hazardous and can usually be handled safely using gloves, but

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without using other personal protective equipment. (**Note:** care should be taken to ensure that the operators and sampling personnel are not allergic to and/or have sensitivity to the selected surrogate material (e.g., lactose intolerance).)

A hygiene risk assessment should be performed to identify whether the use of additional personal protective equipment is required, especially when considering alternative surrogates for specific reasons (e.g., silicon dioxide for systems handling extremely fine dusty materials).

Surrogates should be free of contaminants that could present a separate health hazard. Specific local or organization regulations may apply and should be identified. If surrogate testing is to be performed, the capability to safely handle and clean the surrogate from the equipment to be tested should be assessed, prior to commencing of the test.

4.1.1 Potential Surrogates

The table in Chapter 10 (Appendix 2) of this Guide lists surrogates which have been used successfully. The table includes comments about the positive and negative attributes of the surrogates, as well as where they may typically be used.

4.2 Storage of Test Material

The test material should be kept in conditions (e.g., light, humidity, and temperature) in accordance with the manufacturer's instructions. The storage conditions should not result in significant changes to critical parameters, such as particle size or dustiness index.

The test material should not be stored within the test enclosure or in the test area, as this will increase risk of contamination of the enclosure, test environment, sampling equipment, and may result in false positives during testing.

4.3 Handling of Test Material

It is important that good handling technique is observed when handling the test material to prevent false positives during testing, due to mechanical transfer of the surrogate to the test area. Mechanical transfer can occur via:

- contamination of personnel garments (overalls/shoes/gloves)
- contamination of exterior of test material containers

To minimize the risk of mechanical transfer it is recommended that:

- Test materials are dispensed in a segregated and qualified controlled environment (e.g., down flow booth, dispensing module, isolator system) in a location sufficiently segregated from the test environment to avoid potential, inadvertent airborne contamination of the latter by material released during the dispensing process.
- If the test material container needs to be fitted with a contained material transfer technology, this component should be fitted to the container in a segregated and qualified controlled environment (e.g., down flow booth, dispensing module, isolator system).
- The personnel carrying out the dispensing or fitting of contained material transfer technology components should follow strict gowning and hygiene procedures. It is recommended that the personnel who dispense the surrogate are different to the personnel who perform the containment verification assessment.
- Ensure all test materials and associated components (e.g., contained material transfer technology) are sealed and wiped clean before transfer into the test enclosure or area. Where possible, it is recommended the surrogate containers be over-bagged.

Containers of raw test material should be opened as late as practicable in order to minimize changes in moisture content.

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5 Measurement of Airborne Particulate Matter and Surface Contamination

5.1 Introduction

This Chapter defines the factors that should be considered when developing a sampling strategy for performing containment verification assessments. A sampling strategy should include the:

- type of sampling (air and/or surface sampling)
- where to sample
- the number of samples to be taken
- the duration of each sample

The design of a sampling strategy can significantly influence the results of the assessment; therefore, the personnel responsible for designing the sampling strategy should have an appropriate level of training and adequate practical experience in industrial hygiene sampling.

5.2 Airborne Particulate Matter Sampling

Airborne particulate matter sampling involves the filtration of airborne particles present in defined volumes of air followed by laboratory analysis to measure the quantity of the analyte collected. For the purpose of this Guide, the particulate matter of concern is the surrogate or Active Pharmaceutical Ingredient (API) selected for evaluating the containment performance of the equipment.

Historically, operator exposures to aerosols, including dusts, were evaluated as total or respirable fractions. At the time of publication, there is an increased application of other size-selective criteria, including inhalable and thoracic fractions, in the establishment of Occupational Exposure Limits (OELs).

For size selective aerosol sampling, definitions of three health related aerosol fractions have been adopted by EN 481 (1993) [1] and ISO 7708 (1995) [2], these are:

1. Inhalable – the particle size-dependent fraction of particles that enter through the nose and/or mouth during breathing.
2. Thoracic – the fraction of particles that penetrate the respiratory tract below the larynx and enter the trachea, bronchi, and alveolar regions of the lung.
3. Respirable – the fraction of particles that penetrate the bronchioles and enter the alveolar region of the lung.

For pharmaceutical airborne particulate matter, the relevant aerosol fraction of concern is usually the inhalable fraction, as it represents material that has the potential to be absorbed within the body.

Airborne particulate matter sampling is normally performed using calibrated pumps. These pumps can be attached directly to an operator (personal) or set in a static position (fixed).

Sampling should be performed before, during, and after each cycle or run of the equipment under test. For descriptions of suggested sampling positions, see Chapter 9 of this Guide.

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5.2.1 *Airborne Particulate Matter Sampling Equipment*

Airborne particulate matter sampling requires calibrated pumps that are capable of maintaining a smooth and constant flow rate throughout the sampling period. The standard sampling trains consist of Institute of Occupational Medicine (IOM), 25 mm or 37 mm polypropylene cassettes connected via a flexible plastic tube to a calibrated pump typically operated at a flow rate of 2 to 3 liters/min. The IOM sampling head needs to be operated at precisely 2 liters/min in order to classify the collected material as “inhalable dust.” It is necessary to capture sufficient material on the filter to meet the Limit of Detection (LOD). Higher flow rates can be used:

- with 25 mm and 37 mm cassettes
- where airborne emissions are very low
- where activity/sample time is very short

The analytical method should be validated for the sampling device, the recovery of material at that flow rate, and the anticipated volume of air that may be drawn through the sampling media. Typically, flow rates no greater than 4 liters/min should be used, unless validated as described above.

The pumps used should have:

- automatic flow control which keeps the volumetric flow constant to within ± 0.1 liters/min in case of backpressure changes
- a malfunction indicator or automatic pump stop mechanism
- a flow-rate adjustment that cannot be inadvertently changed during use
- appropriate electrical rating or classification if being used in an electrically classified area

The flow rate for the pump is typically set at 2 liters/min using a calibrated flow meter capable of measuring the desired volumetric flow rates to within 0.1 liters/min and calibrated against a primary standard (i.e., a flow meter for which the accuracy is traceable to national standards).

In order to ensure the best possible method performance to ensure consistency with the requirements of international standards for workplace particulate matter measurement, other publications may be consult for detailed advice on sampling methods. (See Chapter 13 of this Guide.)

Methods for setting up and using both the IOM and polypropylene cassette heads are listed in see Attachment B of this Guide. An adequate number and type of field blanks should be submitted with the samples. Blanks are typically handled in the same manner as the samples, without air being drawn through the filters. In addition, as an added quality control check, a number of filters can be spiked with known quantities of the test material, e.g., one filter with an amount at the Limit of Detection (LOD) of the method, one or several filters with quantities in the range of the expected sampling results, and a filter with a quantity well above the expected results. Blanks should be stored and shipped in separate sealed bags to prevent cross contamination from sample filters. At minimum allocate one field blank per 10 samples.

5.2.2 *Pump Calibration*

Air sample pump calibration is performed before and after sampling to set the pump at the desired flow rate and to ensure that the flow rate is maintained throughout the duration of sampling. It is important to quantify the flow rate because the concentration of contaminant is a function of the amount of air passing through the filter. The pre- and post-calibration airflow rates, which should be recorded, can then be used to calculate the volume of air pulled through the sampling head by the pump. This sample air volume will then be sent to the laboratory along with the samples.

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5.2.3 Samplers (Filter Cassettes or Sampling Heads)

The performance of aerosol samplers relative to the conventions for health-related sampling varies. Several aerosol samplers may give satisfactory performance. The IOM, 25 mm and 37 mm cassettes are considered industry standard sampling heads for airborne particulate matter sampling. Less commonly used sampling cassettes include the British 7-hole cassette and the German conical cassette. Both devices also deliver results that are compatible with the ISO standard for inhalable dust (ISO 7708) [2].

Note: Although many of the techniques and conditions applied to the use of the various samplers are similar, the results obtained may not be directly comparable. Care should be taken when trying to compare sets of data from two different samplers. It is recommended that testing is performed on a single sampling head type for comparison of test results.

IOM Sampler

The Institute of Occupational Medicine (IOM) sampler has been shown to give agreement with the ISO 7708 [2] target specification for the inhalable fraction, under the widest range of workplace conditions.

IOM samplers require additional handling of the filter media for analysis; therefore, good practices should be applied to avoid contamination. The IOM sampler is not compatible with *in situ* extraction procedures in the laboratory. Recovery of all potential material from the sampling device should be achieved using other (swabbing) techniques to ensure that as much of the sample material as possible is analyzed. This becomes increasingly important as airborne target concentrations become increasingly lower and approach the LOD.

IOM samplers are validated for inhalable particulates at a flow-rate of 2 liters/min

25 mm and 37 mm Cassettes

25 mm and 37 mm filters, mounted in polystyrene or polypropylene cassettes, are considered the most commonly used alternatives to the IOM for respiratory dust sampling. These types of samplers are cited in most NIOSH and OSHA methods. They can accommodate direct extraction of the analyte in the sampling device (*in situ* extraction), avoiding the potential analyte loss associated with wall effects, and disassembling of the sampler for sample analysis.

The 25 mm and 37 mm samplers are not validated for inhalable particulates.

5.2.4 Personal Sampling

Personal air samples are normally collected by placing the sampling head in the operator's breathing zone (near the nose or mouth) so that the air drawn into the sampling equipment is similar to that inhaled by the operator.

Note: When sampling within the breathing zone, the sampling train should not interfere with the operator's ability to complete their tasks. Sampling in the breathing zone is considered the most accurate way to determine actual operator exposure, because the aggregate of the operator's movements and activities relative to emission sources are taken into account.

The sampling head should be attached to the shirt collar or lapel of the operator, within close proximity to the breathing zone (i.e., within 30 cm of the mouth). The sampling pump should be secured on a belt, harness, or inside a pocket and attached to the sampling head via a length of flexible tubing.

5.2.5 Fixed Sampling

Fixed sampling (also known as static, area, or stationary sampling) is usually performed to:

- determine the background levels of dust in the atmosphere

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- determine the particulate concentrations at specific locations relative to an emission source
- provide information of the spread of contamination to locations remote from the equipment being tested

The data can be used to identify areas with the potential for particulate matter to be emitted.

Note: It is not considered appropriate to compare fixed sampling results with the exposure limit because the distribution of dust in the workplace may not be uniform. In addition, due to aerodynamic effects, fixed samplers may not behave like personal samplers. (For further information on a fixed static sampling method, see Chapter 9 (Appendix 1) of this Guide.)

5.2.6 Baseline Sampling

Baseline sampling should be performed prior to the start of the containment verification assessment to ensure that background contamination of equipment or the test area has not occurred and does not affect the sample results. Baseline sampling should be considered especially for field testing where there may be a background level of the surrogate being used (e.g., lactose in formulation facilities).

Baseline sampling may provide data to evaluate against the actual test data collected during the containment verification assessment to help to evaluate the actual containment effectiveness of the containment equipment.

Baseline airborne sampling should be performed in the test area, in close proximity to the containment equipment transfer, and make/break points, as a minimum. The baseline sampling time period should be of an adequate duration to capture sufficient material on the filter to confirm that the background level is not significant compared to the anticipated emission levels during the containment verification assessment.

5.2.7 Real-Time Sampling

Real-time aerosol samplers are usually direct-reading, light-scattering photometers capable of measuring total airborne particles. They are not substance specific, but when properly utilized can provide very useful information on the pattern of exposure and help to identify the sources of particulate matter emissions.

In several applications, especially for *in situ* testing, the background level of airborne dust can be significantly higher than the levels typically of concern for specific material sampling. Variations in emissions of the material of concern can frequently be buried in the “noise” of the much larger background count.

Some real-time aerosol measurement equipment only measures the respirable fraction; therefore, they will not capture the total fraction of concern (inhalable) and may potentially under report the actual emissions. They also have limited sensitivity and do not account for emissions outside of their particular measurement range.

Real-time aerosol samplers can be bulky and are more suitable for use as fixed samplers although some can be worn and the sampling head can be positioned in the breathing zone of an operator using a harness or other apparatus.

Real-time aerosol samplers can be used side-by-side with a chemical-specific sampler to help identify causes of peak exposures. They can also provide useful information on dust levels during a short cycle of operations when other sampling methods may not have adequate sensitivity. Real-time samplers should **not** be used as a substitute for chemical-specific airborne sampling.

Real-time aerosol samplers are usually easy to use and do not require subsequent laboratory analysis. Some real-time aerosol samplers contain filters that can be analyzed post-test to determine the actual mass and identity of the particulate matter collected. This information can be used to calibrate the real time aerosol sampler. As noted by most equipment manufacturers and suppliers, real-time aerosol samplers should be calibrated on a yearly basis.

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Additional calibration data can be obtained using side-by-side sampling (i.e., airborne sampling pumps versus real-time aerosol samplers). In addition to estimating time-weighted averages over the actual period of measurement, data logging can provide detailed information on variability in particulate matter concentrations over time, which can be used immediately to identify sources of emissions. Detailed notes and/or video of the operation of equipment can provide information for effective interpretation of short term or transient peaks in the data. Where applicable, a time signature synchronized to the data should be obtained. Short term peaks may represent a significant portion of the total leakage or emissions from a piece of equipment; therefore, accurate identification and interpretation is critical for leakage diagnostics. A real-time aerosol sampler also can be used to determine when a stable baseline level of airborne particulate matter has been achieved in the test enclosure, prior to the start of testing.

There is no recognized international standard for real-time aerosol samplers. They may not measure the larger inhalable particles; therefore, the results measured by these devices may not be directly comparable to the results from the chemical-specific samplers.

5.3 Surface Sampling

Surface sampling (also known as “swab sampling” or “wipe sampling”) is a technique used to assess the level of product contamination on a surface. It is a tool used for verifying the containment performance of equipment. Surface sampling also can identify emissions that may not be directly attributed to airborne emissions, such as the mechanical transfer of particulate matter on equipment surfaces, operator’s clothing, or operator’s hands/gloves.

For the purpose of this Guide, the use of surface sampling is to obtain semi-quantitative data that indicates a level of contamination. The surface concentration is purely a function of the containment performance of the equipment under consideration and cannot be used directly to infer quantitatively an exposure risk to the operator or risk of cross contamination to the facility or product. Variability in the equipment or containment system and other causes for transfer of material from the surface to the operator’s body or alternative product may confound attempts for quantitative comparison.

As with airborne sampling, surface sampling should be performed with a validated method that has considered the recovery of the surrogate from specific surfaces and the solvent to be used in the process. The sample is typically taken over a 100 cm^2 (10 cm × 10 cm) area, unless the geometry or contamination profile of the surface dictates otherwise, in which case the area sampled should be measured. The results should be presented in units of mcg/cm^2 or mcg/100 cm^2 (see Attachment A of this Guide for a surface sampling method.)

Surface sampling should be performed before use of equipment to establish a baseline and after each cycle or run. For descriptions of positions where surface sampling should be performed, see Chapter 9 (Appendix 1) of this Guide.

5.4 Sampling Strategy

The development of a sampling strategy is part of the overall containment verification assessment. When performed correctly, it can provide the maximum amount of information to evaluate the effectiveness of a containment system with the minimum number of samples. It also can provide a suitable data set for the comparison of similar containment systems.

The scope of a containment verification assessment is defined by identifying all potential/plausible sources of emissions. The process documentation should be reviewed and the activities to be performed should be discussed. Collecting samples at points of emissions which are anticipated to be at a maximum can help to enhance the collection of relevant data points; however, a containment device should not be tested with quantities of material or operating conditions that will never be used. Where a system may potentially have multiple operating modes or conditions, the need for multiple tests based on these different conditions should be considered.

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The equipment test protocols should be used as a guide in developing the sampling strategy. They can be modified and combined when developing the sampling strategy in order to perform an efficient and effective containment verification assessment. The development of a sampling strategy should result in a written detailed sampling plan that includes information such as:

- each unit operation to be sampled
- sampling locations and types
- anticipated sampling times (based on prior review of the process)
- minimum detection calculation for each sampling cycle (as calculated from analytical method sensitivity and anticipated cycle time)
- frequency of sample media changes
- number of cycles and estimated total number of samples to be collected

For further information on sampling locations for standard containment systems, see Chapter 9 (Appendix 1) of this Guide.

5.5 Task Analysis of Most Probable Failure Modes

It is recommended that the most probable failure modes for the equipment are identified prior to testing to ensure the containment equipment is adequately challenged during the containment verification assessment. Probable failure modes should be based on the design and purpose of the containment equipment or system. Possible failure modes should include those actions related to transfer of materials in and out of the containment equipment, and connection and disconnection points for the system components.

Containment system components, which should be considered in association with probable failure modes, include (and are not limited to):

- glove ports
- transfer chambers
- RTPs
- transfer bags
- continuous liners
- valves
- ports

Performing a qualitative process hazard analysis that identifies design faults, potential hazards, and operating problems can be useful in identifying these probable failure modes. Standard methods, including Hazard and Operability (HAZOP) Analysis or Failure Mode and Effects Analysis (FMEA), can be used to identify and document the probable failure modes.

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5.6 Test Cycles/Runs

A sufficient numbers of samples should be taken to establish a degree of accuracy and consistency for the containment verification assessment to be valid. Performing less than three test runs can result in uncertainty of the accuracy of data and significant statistical variability. It is recommended that additional runs are completed to improve statistical precision, where practical.

For further information on the nature of the test cycles and test run for each equipment type, see Chapter 9 (Appendix 1) of this Guide. For further information on the methods for the analysis and interpretation of data, see Chapter 7 of this Guide.

5.7 Recording of Field Data

Sampling activities should be observed and should be recorded along with any observations of unexpected occurrences, manner of working, problems with processing or operation, etc. These observations may help in the interpretation of the data obtained during the sampling process.

Sampling Data Sheet

All sampling information should be collected at the time of the sampling and documented on the Emissions Sampling Data Sheet. As a minimum, the sampling information should include:

- date
- process
- name
- participants
- types of samples
- values
- time of sample

A sample field data sheet is given in Attachment E.

Sampling Data Management

Sampling results received from the laboratory should be input into the industrial hygiene sampling summary sheet.

A sample industrial hygiene sampling summary sheet is provided as Attachment E of this Guide.

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