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Handling highly potent active pharmaceutical ingredients

Equipment containment performance

ABSTRACT

Potent and highly potent active pharmaceutical ingredients have the potential to cause serious health effects in workers at very low airborne concentrations. The use of containment equipment as part of a systematic approach to potent compound safety is advised to control worker exposure. However the containment performance of equipment can not be assumed, evaluation of containment performance, using a standardised approach, should be adopted.

INTRODUCTION: SAFE HANDLING OF POTENT ACTIVE PHARMACEUTICALS

The manufacture and production of potent and highly potent active pharmaceutical ingredients (APIs) is becoming commonplace in pharmaceutical and biopharmaceutical industries. Safe handling systems to protect a healthy workforce against the adverse effects of these materials are routinely used by many of the large multi-national (bio)pharmaceutical manufacturing companies and are increasingly being taken up by smaller companies and contract manufacturing organisations. Based on toxicological evaluations, APIs can be placed into control bands depending on their potency. This is the first step in a systematic approach to ensure worker safety when handling potent and highly potent APIs. Each control band should be associated with a safe handling guideline (1) which describes in detail how a material of that potency should be handled in the different environments encountered in the workplace. In general, most parties define a potent API as one with an occupational exposure limit (OEL) at or below $10 \mu\text{g}/\text{m}^3$ and highly potent API as having an OEL below $1 \mu\text{g}/\text{m}^3$. Though there are a number of factors which must be considered to control worker exposure, one of the most important approaches to ensuring safe handling of potent and highly potent APIs is the containment equipment selected. Containment equipment such as isolators, contained transfer systems and other contained chemical and pharmaceutical process equipment represents considerable investment for an organisation. Understanding the range of devices available, their containment performance and how to verify this is a necessary prerequisite for any organisation embarking on a project to handle potent and highly potent APIs.

CONTAINMENT DEVICE SELECTION

Containment equipment is available for the full range of pharmaceutical operations, from chemical production of bulk API through to product formulation, and from pre-clinical through to full scale production. In each case the

principles of selecting containment equipment and verifying its effectiveness are the same:

- A step by step analysis of the process to produce a detailed list of all tasks involved.
- Setting a containment performance target (CPT).
- Specifying and selecting containment equipment based on the task list and the CPT.
- Verifying containment performance at the factory acceptance test (FAT) and the site acceptance test (SAT).
- Assessing occupational exposure to workers during actual operations involving the API.

The step by step analysis must be sufficiently detailed to identify all aspects of the process that may be encountered operationally. Examples of important issues that are often missed during this analysis are contained transfer of waste, decontamination of materials and equipment prior to transferring out of containment and ergonomic factors involved in carrying out the operations.

CONTAINMENT PERFORMANCE

This analysis will provide the information required to specify the design of the containment system and the containment performance target (CPT) for the containment device will usually be based on the OEL of the material being handled. The aim of containment performance verification should be to demonstrate that this airborne concentration will not normally be exceeded. The containment performance is broadly defined as the airborne particulate concentration measured around the containment device and in the operator's breathing zone during simulated or actual operations. The methodology for this evaluation is detailed in the ISPE Guide, *Assessing Particulate Containment Performance* (2). The Guide specifies a methodology using a surrogate material to verify containment performance. A commonly used surrogate is lactose, other materials such as naproxen sodium, mannitol and paracetamol (acetaminophen) may also be used. These materials are selected based on their relatively low toxicity and that analytical methods are available, capable of detecting very low levels of these materials on filters, thereby enabling quantification of airborne samples at concentrations below the CPT.

CONTAINMENT DEVICES

A wide range of devices are available which allow contained operations to be carried out during chemical production of potent and highly potent APIs and during the formulation of pharmaceutical products containing these APIs.

These range from small straightforward isolators (for example for reactor charging) through to specialised highly integrated pieces of equipment for specific tasks such as combined filter dryers used in chemical production and contained fluid bed granulators for formulation operations. A significant majority of approaches to contained operations rely on relatively few key technologies, these include the barrier isolator, with associated transfer devices, and the split butterfly valve. Recent innovations in flexible containment systems will also be considered below.

THE BARRIER ISOLATOR

The rigid or fixed walled isolator provides a contained environment within which a wide range of tasks can be performed. Typically, an isolator will operate at a slight negative pressure, though in some cases (usually to ensure product sterility) isolators can operate at a slightly positive pressure (3). The contained environment inside the isolator is ventilated with air entering and leaving the isolator being HEPA filtered. Operator access to the isolator chamber is usually via glove ports, which allow materials and equipment to be handled and to facilitate transfers into and out of the isolator. The isolator is a versatile piece of containment equipment and can be used independently or integrated with other pieces of equipment to allow contained manipulations. One of the limiting factors for the containment performance of an isolator are the transfer devices used to transfer materials and equipment into and out of the isolator. Though a well designed and fabricated isolator by itself is capable of containment performance well below $0.05\mu\text{g}/\text{m}^3$ *. Where leakage is found, transfer devices, such as transfer chambers, rapid transfer ports (RTPs) and bag-out ports are often found to be the source of that leakage so reducing overall containment performance of the integrated isolator.

TRANSFER CHAMBERS (PASSIVE)

The transfer chamber is an enclosed chamber attached to the isolator with one sealable opening with a door into the isolator and one sealable opening with another door to the outer environment (3). The chamber is not under negative pressure. This arrangement can be used to pass materials into a clean isolator opening only one door at a time. However, the containment performance can be compromised if materials are passed back out of a contaminated isolator using this route, due to potential airborne contamination and possible surface contamination of items passed out from the main isolator chamber. The use of a passive transfer chamber to pass out items from a contaminated isolator is therefore not good practice. To achieve high containment performance it is usually recommended that items are only passed into the isolator with this arrangement. It is recommended that materials are removed via a bag-out port or RTP.

AIRLOCK (ACTIVE)

The airlock is similar to the transfer chamber except in this case the airlock is ventilated and under negative pressure. This will reduce the potential for airborne transfer from the contaminated isolator. If in addition decontamination of



View from inside an isolator: open RTP looking into a Beta Canister (picture provided courtesy Hosokawa Containment).

materials leaving the isolator is possible, then this arrangement can be suitable for safe transfers out of the isolator whilst maintaining very high containment performance. Secondary decontamination of articles transferring out of the isolator (following primary decontamination in the isolator) requires that glove ports are fitted to the airlock chamber. Secondary decontamination of items leaving the isolator in the airlock is preferable where very high containment performance is required. Careful design and operation of this transfer system can allow highly potent APIs to be handled safely. Actual containment performance achieved will vary depending on, inter alia, the operation, the material, the quantities handled and the technique of the operators. Containment performance should therefore be verified by containment performance testing.

RAPID TRANSFER PORT (RTP)

The rapid transfer port is a robust solution to the challenge of highly contained transfers of materials and equipment, into and out of a contaminated isolator. The operation of the RTP involves docking a sealed container (beta canister) onto the isolator (alpha door), opening the RTP alpha door/beta canister door from within the isolator, transferring materials in or out and re-closing the door. Once removed from the isolator, the inside of the beta canister may be contaminated with API. Accessing the inside of the contaminated beta canister should preferably be achieved via a second isolator though another control device (such as a ventilated enclosure) may be suitable. Careful use of the RTP and beta canister can give containment performance of $0.05\mu\text{g}/\text{m}^3$ * and below.

BAGGING DEVICE

The bagging transfer device (or bag-in/bag-out port) uses a specially constructed tube of flexible film material such as polythene (or continuous liner), attached to a port and fitted with double-seal rings. This arrangement enables continuous closed bags to be produced which can be used to enclose items transferred in or out of the isolator in a sealed bag. This solution to transferring materials and equipment is capable of high levels of containment, however, this device is less robust than an RTP for two main reasons: the high degree of dependence on operator technique during the sealing and cutting of the bag film and the risk of puncturing the bag film so allowing a release of the potent or highly API. The containment performance achieved using the bagging device depends on a number of factors, however, with careful use and good operator technique high levels of containment of $0.05\mu\text{g}/\text{m}^3$ * and below can be routinely achieved.

MANUFACTURERS CONTAINMENT PERFORMANCE DATA

The containment performance of any one piece of equipment is dependent on the circumstances of use. Some factors which can affect containment performance are:

- The nature of the operation being conducted, for

example energetic operations such as milling offer a greater challenge to containment systems.

- The particle size and properties of the powdered API being handled.
- The quantity of API being handled.
- Operator practice and technique.
- The integrity of the containment device.

These variations mean that fixed containment performance cannot be assigned to containment equipment and are the main reason for the lack of definitive containment data available in the public domain. Manufacturers will therefore tend to offer either a range or a "better than" containment performance values for their equipment. The potential difference between the manufacturers claimed containment and the actual performance can be illustrated by using public domain data available for the split butterfly valve and a flexible charging bag.

SPLIT BUTTERFLY VALVE

The split butterfly valve (SBV) is widely used for transfers of potent and highly potent APIs. It is particularly useful where large quantities of material are being transferred. The details and principle of operation of the valve are well established and allow for good containment performance during contained transfers. Manufacturers' quoted containment performance for high containment SBVs are typically $1-10\mu\text{g}/\text{m}^3$ (4). However enhanced performance SBVs are available which can provide higher levels of containment performance. Vendor's are understandably unwilling to quote highest levels of achievable containment performance as operational factors outside of their control can be the biggest influence on performance. The difference between quoted and actual performance can though be significant. For example the manufacturers stated performance for the GEA Buck TC split butterfly valve is $< 1\mu\text{g}/\text{m}^3$ (ref 4). However in an article published in the Pharma Bulletin (5), Pfizer in the U.S. reported significantly better containment performance during surrogate testing, for this high performance SBV, of $0.03\mu\text{g}/\text{m}^3$. This



Barrier Isolator showing RTP with Beta Canister fitted (top right) and Bagging Port (bottom right) (picture provided courtesy Hosokawa Containment).

represents performance for this type of SBV under ideal test conditions and demonstrates the potential difference between the manufacturers specified performance and that which can be achieved. However containment performance must be considered on a case by case basis, especially where very high level of containment performance are needed.

FLEXIBLE CHARGING BAGS

A relatively recent innovation in containment equipment is the flexible charge bag. This device can deliver contained charges of small quantities of API with good containment performance. One advantage of this device is its cost, allowing potent and highly potent APIs to be pre-packaged in a disposable contained transfer device. The manufacturer's stated containment performance for the GEA Buck Hicoflex® bag is $1-10\mu\text{g}/\text{m}^3$ (4). In this case the claimed performance appears to be close to the actual performance. Containment performance test data published on GEA's website (6) shows airborne concentrations, as assessed using the ISPE methodology (2), during charging of lactose, to be in the range $0.7-4.9\mu\text{g}/\text{m}^3$. This demonstrates performance similar to the high containment SBV.

KEY ELEMENTS IN CONTAINMENT PERFORMANCE VERIFICATION

Containment Performance Target

- Set a containment performance target (CPT) as an airborne concentration ($\mu\text{g}/\text{m}^3$) based on the occupational exposure limit (OEL) of the API to be handled.
- The object of containment performance verification is to show that the CPT is met (see Reporting below).

Simulated Operations

- Select a surrogate material to use during containment performance verification.
- Devise a programme of operations that simulates the containment which includes the use of all associated equipment (e.g. RTPs, bag-out ports, etc.).
- The simulated operation must be carried out at least three times and, if possible, using a different operator for each evaluation.

Sampling Plan

- Develop a written sampling plan which includes the operations to be performed, their duration and the location of area samples and operator samples used to detect airborne releases.

- The sampling plan will include the limit of detectable concentration of the surrogate, this should be no more than 25 percent of the CPT over the sampling period.
- Include wipe samples in the sampling plan if required.

Sampling and Analysis

- On-site sampling during FAT or SAT should be conducted in accordance with the ISPE Guide and good occupational hygiene field practices with particular attention paid to careful handling of the surrogate prior to the use.
- The accredited laboratory selected for the analysis must have a validated method for the airborne surrogate samples with sufficient sensitivity to evaluate the containment performance.

Reporting and Interpretation of the Results

- The containment performance report should describe the testing methodology and provide an objective interpretation of the results.
- The use of EN 689 (7), Bayesian statistics or classical statistics (if sufficient samples are taken) should be employed to confirm that airborne release concentrations will not normally exceed the CPT.

CONTAINMENT PERFORMANCE VERIFICATION

The containment performance of a device may not be guaranteed by vendors, especially if the required performance specifications is better than that quoted by the vendor. Overall containment performance of an isolator system or a device will depend on the factors listed above and may not be predictable. It is therefore usually necessary to verify containment performance prior to handling the potent or highly potent APIs in the containment device. Containment performance verification assesses performance of the contained device or system either as built at the factory (FAT), when newly installed in a production facility (SAT) or when in routine use (ongoing occupational hygiene testing). Where several ancillary devices are present, such as with transfer devices fitted to an isolator, the use of all devices must be included in the containment performance evaluation. A standardised method is available for these evaluations (2). To verify that the containment performance target is being achieved, surrogate particulate containment performance verification should, as a minimum, be carried out during the SAT (site acceptance testing) of the containment device and, arguably, also during the FAT (factory acceptance testing). The main argument for containment verification at the vendor's site prior to delivery is to address correctable leakages and therefore reduce the chances of failure to achieve the containment performance target during FAT with the associated impact on timelines. Containment performance verification testing should only be undertaken by competent occupational (industrial) hygienists (see side bar (box) for key elements of containment performance verification testing). The use of contained systems in the manufacture of potent and highly potent API can provide a safe working environment. However the actual containment performance may not be known due to the various factors discussed above. The final step in a systematic approach to worker safety, must be to assess

worker exposure during routine production operations by measuring airborne worker exposure to the potent or highly potent API against a derived occupational exposure limit (OEL) for the material. Evaluation of operator exposure to the potent or highly potent API during contained operations against an OEL, using a sensitive occupational hygiene analytical method is the final stage of containment performance evaluation. Ongoing evaluations of operator exposure will then give confidence that potent or highly potent APIs are being handled safely.

REFERENCES AND NOTES

- * Containment performance levels are highly dependent on circumstances of use, any containment performance levels given in this article must therefore be treated as indicative only.
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