Importance of risk assessment for aseptic transfer in pharmaceutical compounding

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Abstract

Aseptic transfer is a critical contamination control issue, carried out over a series of stages. If any stage is performed in an uncontrolled manner then microbial contamination of a product can occur. Contamination risks can arise from a number of sources, including incoming materials, air and personnel. To address these risks appropriate controls include controlled environments, personnel gowning and behaviour, and the use of disinfectants. This article considers the key risks and risk mitigation strategies using a case study of aseptic transfer within a pharmacy unit for the purpose of preparation or compounding of a medicinal drug product.

Introduction

Aseptic transfer applies to various aspects of pharmaceuticals and healthcare, covering everything from the inoculation of agar plates in a microbiology laboratory to the transfer of items into a cleanroom as part of sterile products manufacturing or pharmaceutical compounding. Across this range of applications the overriding requirement is asepsis, to either render the material free of microbial contamination (through bioburden reduction) or to prevent adventitious contamination, from operators or the environment, affecting the quality of the product or materials.

This article focuses on the best practices for aseptic transfer within a pharmaceutical facility or pharmacy specialising in drug compounding. Compounding is a process whereby the facility combines, mixes, or alters ingredients of a drug to create a medication suitable for the needs of patients. This can range from the larger scale production of intravenous bags of nutrient fluid for babies to the preparation of individual cytotoxic drugs.

With these activities microbial contamination in the environment can result in product adulteration and, in turn, in a potential infection of the patient. In order to minimise the possibility of cross-contamination, a risk-centric approach is required. This is a topical subject in light of several high profile product contamination events which have occurred worldwide (some with serious consequences for patients)[i]. These cases demonstrate that microbial contamination risks remain an ever present concern. The article considers where these risks arise from and the types of risk mitigation step that can be implemented. Mitigation steps require the use of strict biocontamination control measures. The article also emphasises the importance of environmental monitoring.

Contamination risks

Microbial contamination risks can arise from the environment (with microorganisms on surfaces or carried on particles in the air-stream); from personnel; or from the product. Environmental contamination can arise from material containers and packaging or from the cleanrooms where processing takes place. These areas are discussed below.

Environmental risks

Airborne environmental risks are controlled through cleanrooms and clean zones. Cleanrooms will be of different grades, with in-coming materials typically held in an EU GMP Grade D area. Here outer packaging should be removed. Items are then transferred into Grade C cleanrooms and then into Grade B. In the Grade B area assembly will occur, prior to transfer of kits and products into a Grade A zone. The Grade A zone is typically an isolator. Within the Grade A zone dispensing, along with any required final formulation, will take place.

Cleanrooms should be designed with the protection of product quality in mind. Control is achieved through the use of HEPA (high efficiency particulate air) filters; pressure differentials between rooms of different grades; and an appropriate airflow system. Turbulent, or non-unidirectional airflow, dilutes airborne contaminants down to an acceptable level and keeps smaller particles in suspension as the air is removed[ii]. This type of airflow is used in the lower grade areas. Unidirectional airflow provides a supply of clean air to the critical work zone and any contamination generated is removed in the airstream. This type of airflow is used in the highest grade areas such as Grade A. The use of an isolator creates an additional barrier between personnel and the product being handled.

With the cascade of increasing cleanroom standards described, not only should the concentration of airborne particulates reduce but there should also be a reduction in microbial numbers and in the diversity of the microbial species. Spore forming organisms, for example, will more likely be present in Grade D areas, where packaging is removed, than in Grade C or B environments where outer packaging is not present. Therefore, the careful removal of packaging layers and effective disinfection are important[iii]. In the higher graded areas the most common types of contamination are from skin bacteria, such as Staphylococci and Micrococci[iv]. Nevertheless, the risk of microorganisms that are more challenging to kill with standard disinfectants remains, and thus the assessment of risks should extend to the possibility of endospore forming bacteria being present (see below).

With the cleanroom cascade and process flow (Figure 1), the objective is to reduce bioburden by disinfection as the different layers of wrapping are removed. Care should also be taken to avoid recontamination from personnel practices, inadequate cleaning and disinfection; or cleanroom operation environmental failures. The most important stage of aseptic transfer is into and out of the Grade A zone. For optimal contamination control, the Grade A zone will be an isolator.

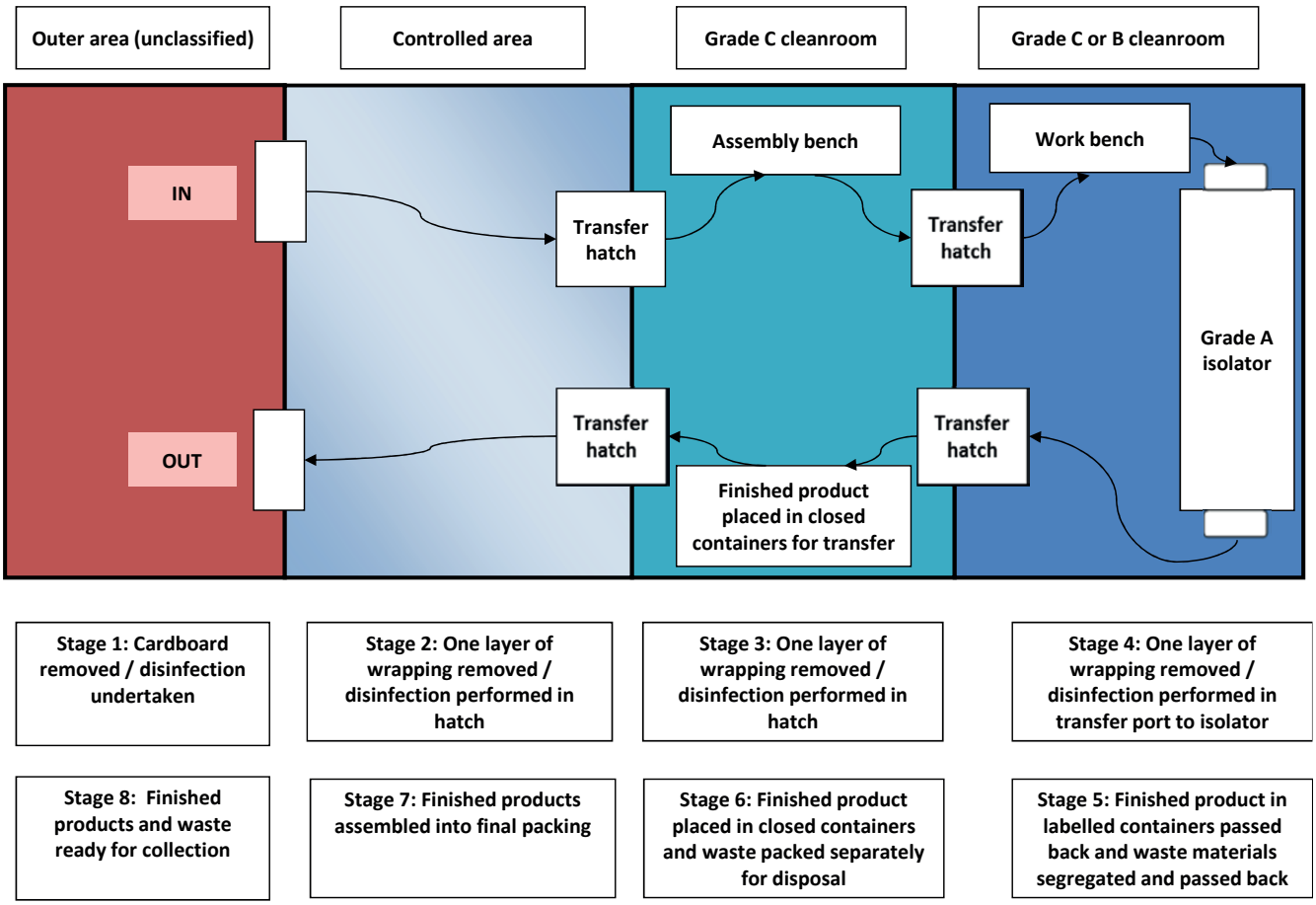

Figure 1: Simplified diagram of a typical aseptic transfer process for aseptic compounding

Personnel risks

Modern cleanrooms are generally well-designed; the main risk variable is people. People are the most significant source of contamination during the aseptic processing of medicines. This can be due to errors with gowning and use of gloves and masks; general behaviours; and a tendency to touch one object or surface and then another. Nonetheless, personnel risks can be reduced through[v]:

- Good quality gowns and standardised gowning techniques;
- The use of gloves, masks and head covers;
- Appropriate training;
- Controlled behaviours;
- Regular glove sanitisation (70% isopropyl alcohol is the most effective);
- Reducing direct personnel intrusions into the processing zone.

Attention should also be given to ergonomics, particularly when using an isolator. The better the design, the more comfortable the operator is, and the less likely the operator is to make errors[vi].

Product risks

Contamination risks can arise from the product itself and its associated components. This can happen if the product is not sterile due to issues with sterilising grade filtration or with an intended terminal sterilisation cycle, or materials are not sterile, or where packing used for components has been compromised. These factors can be addressed through identity checks on materials and careful handling; the latter leads into risk mitigation through practising biocontamination control.

Biocontamination control

Although the risks described above are faced by pharmaceutical processes during each work session, experience suggests that, in most cases, the risk of product contamination and, subsequently, patient infection is low. When incidents occur these are normally through a breakdown of a system (such as a HEPA filter becoming damaged) or a failure to follow an established system (such as a failure to disinfect at the appropriate stage). To further negate these risks, there are practices that can be undertaken with strengthen risk control. These are examined next.

Contamination transfer

Arguably transfer is the weakest link in the biocontamination process. To mitigate the risk, disinfection is necessary at each transfer stage (the stages are represented in Figure 1, above). Items transferred include medicinal products, active ingredients, needles, Luer connectors, and so on.

At the start of the process, such items should be held in the lowest grade of cleanroom, within protective packaging. The storage of paper and cardboard in the preparation room should also be avoided (any outer packaging that has been exposed to outside air should ideally not be taken into a cleanroom). Items should be removed from storage boxes and spayed and wiped with disinfectant on transfer into the cleanroom. Items can then be taken through the necessary stages, via transfer hatches, to reach the Grade A workzone. Some transfer hatches are fitted with localised airflow. Items at these stages should have an outer wrapper removed and then be disinfected. Items should be double or triple wrapped. An example of a triple wrapped item is shown in Figure 2.

Figure 2: A triple wrapped item (outer layer removed)

The wiping process, whether by 'wipe-and-spray' or using pre-saturated wipes, is preferable to simply 'spraying.' Studies suggest greater microbial kill is obtained through the act of wiping[vii]. One problem is that wiping is often inconsistent, especially where removing bacterial spores is a concern. Here the ability to remove spores is effected by the spore surface structure and the weave of the wipe, as well as the technique of the person carrying out the task (it is common for wiping techniques to be poorly defined). It is important that the number of wiping motions and the requirement to use a different side of the wipe for each wiping motion is practiced (this is commonly either the three-fold or four-fold technique).

An example of a wiping technique is:

- Wipe the surface to be sampled using a saturated wipe.
- Hold the fingertips together and apply a gentle but firm pressure.
- Use an overlapping 'S' pattern to cover the entire surface with horizontal strokes (see Figure 3).
- Fold the exposed side of the wipe in and wipe the same area again using vertical 'S'-strokes (see Figure 4).
- Fold the exposed side of the wipe in once more and wipe the same area using diagonal 'S'-strokes (see Figure 5).

In addition, the contact time for the disinfectant needs to be observed. With wiping of product vials, particular attention should be paid to the rubber septa of vials and the break lines of ampoules. Over-seals should therefore be removed at the first sanitisation stage.

In selecting between pre-impregnated sterile wipes and wipes onto which a disinfectant is sprayed, pre-saturated wipes add greater consistency since spraying biocide into dry wipes may leave some portions of the wipe with limited biocide. Pre-saturated wipes are prepared in a manner where the disinfectant is uniformly applied across the surface. Pre-saturated wipes should be assessed to show that they are low particle shedding.

Furthermore, some transfer hatches are "locked" for a set time period. This is both to allow for adequate "clean air" changes to occur within the hatch before the inner doors are opened; and to ensure that a suitable contact time, between the item and the disinfectant, is achieved[viii]. Materials should be dry before proceeding to the next stage.

The closer the process is to the EU GMP Grade A zone, the more important it is that the disinfectant used is a sporicide. Some would take a counter view and argue that a sporicide should be used at the early stage, where the bioburden is theoretically greater. This issue can be examined through profiling and characterisation of the microorganisms recovered. The use of a sporicide, at the appropriate stage, is important, given the risk of bacterial endospores which might be carried through from outer packaging or result from an environmental control failure. Alcohol based disinfectants, which have traditionally been used, are not sporicidal.

Periodic verification of sanitisation effectiveness should be carried out at intervals based on a risk assessment. This will require an assessment of the typical bioburden recovered from materials transferred through each stage. For product vials, rolling a representative vial across an agar plate or immersing a vial into microbiological broth culture medium are common bioburden assessment methods. Such methods are more effective than swabbing.

Barrier technology

The use of isolators during final processing and formulation provides an effective means for ensuring biocontamination control. This is because such devices provide a physical barrier between the operator and the product. As an additional measure, isolators can be decontaminated, either through a validated bio-decontamination process or through periodic spraying with a sporicidal disinfectant. The greatest advantages can be realised through hydrogen peroxide vapour rapid gassing systems. Gassing systems are expected to demonstrate a reproducible six log reduction in *Geobacillus stearothermophilis* spores. However, such technology is often unaffordable in the hospital pharmacy sector and manual disinfection is commonplace. It is important with manual disinfection that the disinfectant is suitable and has been qualified through efficacy studies according to a recognised standard.

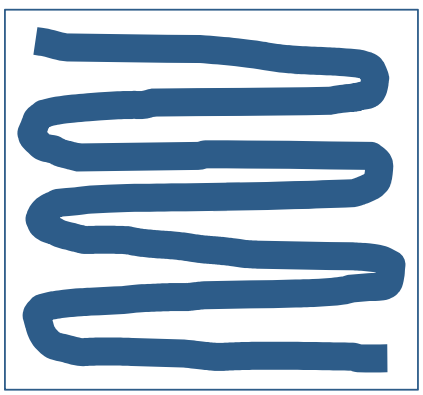

Figure 3: Horizontal 'S' shaped wiping technique

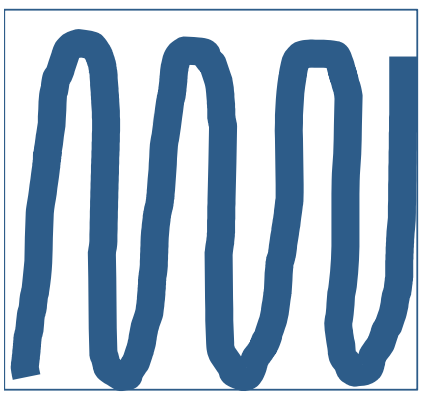

Figure 4: Vertical 'S' shaped wiping technique)

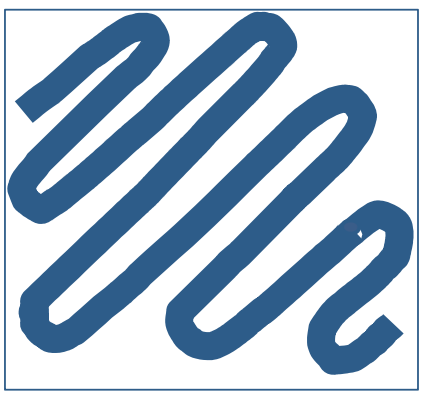

Figure 5: Diagonal 'S' shaped wiping technique)

Aseptic manipulations

When carrying out aseptic operations and manipulations of product, any product exposure must be carried out under localised Grade A airflow protection and the time of exposure kept to a minimum. Good design of the workspace is important. The airflow above and around the product containers must be unobstructed.

With manipulations, personnel must adopt a disciplined 'no-touch' technique to avoid contact with any surface which will be in contact with the product. This is especially important for the ends of transfer tubing, needle tips and vial closures.

The risk of contamination ingress can be assessed through risk based studies, such as the use of Whyte and Eaton's contamination transfer equation,[ix] for which the simplified version reads:

Number of microorganisms deposited into a product:

Deposition rate of microbe carrying particles (no/cm^2) x Area of product exposed (cm^2) x Time exposure (seconds)

The deposition rate of microbial carrying particles can be estimated through settle plate exposure, provided the plates are positioned in suitable locations and exposed for the duration of the activity.

Closed system

In traditional aseptic processes, drugs are compounded using syringes and needles (into or out or vials or other syringes). This process, while necessary, is cumbersome and carries the risk of cross-contamination. More advanced systems are available (as discussed below). Where syringe-and-ampoule transfer remains the most appropriate, only single entry to ampoules must be practiced.

The greater use of closed systems and single-use sterile disposable technology, introduced in the last decade, has helped to lower contamination risks. Examples include sterile bags and aseptic connectors. Many of these are made of plastics that are subject to gamma radiation for sterilisation[x]. In combination, bag technology and interlocking connectors allow the transfer of fluid from a reagent into a medical device or for the mixing of two materials together (as with pharmaceutical drug compounding.)

More advanced transfer systems use docking ports, which allow the transfer of fluid into a cleanroom or an isolator. Bags can be pre-filled with vials and closures and subject to a sterilisation process. Such bags can then be passed ino the Grade A environment.

An important consideration with plastic disposable systems is whether there is a risk of leachables or extractables[xi]. This can occur when a fluid or powder comes into contact with the plastic. The risk is dependent upon time, temperature and pH and any study run to assess this must take into account the maximum hold time.

Other control measures

Other measures that can be taken to minimise contamination risks include:

- Controlled entry of personnel into the processing area;
- Maintaining the integrity of the aseptic processing area, and monitoring the work area (such as an isolator) and its environment;
- Disciplined handling and preparation of starting materials, especially disinfection before transfer into the critical zone (in line with the section above);
- Correct loading and positioning of materials within the critical zone of the controlled workspace;
- Practicing good aseptic processing techniques during manipulation of the product, including 'no-touch' of critical surfaces;
- Segregation and flow of materials to ensure no inadvertent cross-contamination or substitution of products;
- Removal of product and waste materials from the processing area;
- Effective post-activity cleaning and disinfection.

In addition completing all required documentation helps to verify that each control measure is in place and that the necessary steps have been completed. Documentation is a requirement of Good Manufacturing Practice (GMP).

Environmental monitoring

Where risks cannot be wholly eliminated, then environmental monitoring should take place. Importantly, environmental monitoring is not a substitute for poor control. Environmental monitoring should be conducted once controls have been reviewed and risk assessed; thus the purpose of monitoring is to verify the suitability of controls and to assess how well control is being maintained over time.

Environmental monitoring is very much bound-up with risk assessment and risk methodologies should inform about monitoring locations. Sites for monitoring should be orientated towards points of greatest product contamination risk, such as fingers of operators in close proximity to the product (for finger dabs). Other monitoring sites should be chosen for the assessment of cleaning and disinfection efficacy.

In terms of aseptic operations, finger dabs taken by operators at the end of the activity provide important information as to the risk of contamination transfer. A key metric is the incident rate, more so than the level of counts obtained. In a well controlled facility the incident rate should be below 1 percent. A rate above 5 percent would suggest operator activities are potentially out of control.

Other important samples are air samples, especially settle plates which can provide information about contamination rate transfer (in relation to the formula presented earlier) and post-activity contact plates, which can give an indication of whether the typical bioburden on the in-coming materials has been affected by levels of environmental contamination outside of the norm[xii].

With environmental monitoring, examining data for trends provides useful information about the state of control. Data can be analysed for total counts, incident rate and the types of the microorganisms recovered.

Conclusion

This article has outlined the process of aseptic transfer within a typical pharmaceutical compounding or hospital pharmacy setting. The article has presented the main risks and risk stages and has gone on to show how these primary risks can be mitigated. The most important of these mitigation steps is with the use of disinfectants. Here, at the appropriate stages, a sporicidal disinfectant should be used and its application undertaken with a defined

wiping technique. The article ended with a brief consideration of environmental monitoring. The review of trends drawn from the monitoring programme is an important activity and it can inform about a potential out-of-control situation arising.

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