

# Microbiological Risk Assessment european pharmaceutical review

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Risk assessment of microbiological contamination to a pharmaceutical production cleanroom is essential. This article describes a method that utilises risk factors derived from the fundamental mechanism of microbial contamination.

This method can be utilised to identify the areas of greatest microbial risk that can then be selectively targeted to reduce the possibilities for product contamination.

Identification of microbiological contamination sources and assessment of the associated risk to a pharmaceutical product within the cleanroom manufacturing area, will provide a number of potential advantages to the manufacturing operation. Product contamination will have a significant disruptive effect upon manufacturing and the associated product supply chain. This will incur costs, particularly if multiple production batches or lots are implicated, and will almost certainly require intensive application of resources to investigate and rectify the problem. By proactively identifying the areas of greatest microbial risk, resources can be targeted at these areas to either eliminate or reduce the risk. Alternatively, methods used to control the risk and procedures to monitor the risks can be employed.

A comprehensive identification of all sources of microbial risk and an accurate assessment of the associated microbial risks are fundamental to the success of this approach. Although risk assessment methods have been utilised for pharmaceutical cleanroom production applications, the fundamentals of microbial contamination have not been definitively considered. These fundamentals are required to define the variables needed to correctly assess the risk.

## Routes and sources of contamination

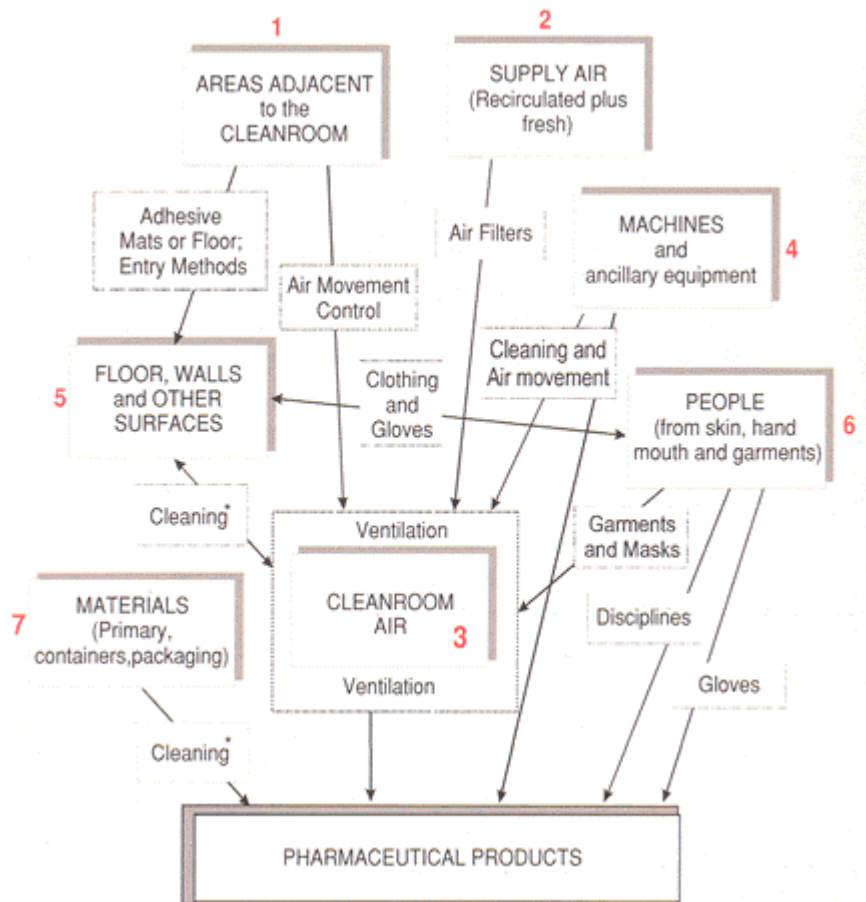
A model that can be utilised for comprehensive identification of all potential sources of cleanroom microbial contamination has previously been suggested by Whyte and is indicated in Figure 1. This model can be utilised and modified accordingly, to derive the potential sources for any specific cleanroom production process.

## Fundamentals of microbial contamination

The fundamental mechanism for the transfer of microorganisms from source to product has been derived mathematically and is indicated in Equation 1. This equation is universally applicable to all sources and routes.

## Figure 1. Routes and sources of contamination in a pharmaceutical cleanroom

\* includes disinfection and sterilisation



### Equation 1

No. of microbes deposited on a product = C X S X Pd X Pa X A X T

C = concentration of microbial contamination on, or in, a source (number/cm<sup>2</sup>, or number/cm<sup>3</sup>)

S = quantity of surface material, or air, that is dispersed from a source in a given time (cm<sup>2</sup>/s for surfaces and cm<sup>3</sup>/s for air dispersion);  
this can also be expressed as the quantity dispersed per frequency of occurrence.

Pd = proportion of micro-organisms dispersed that are transferred to the area adjacent to the product

Pa = proportion of micro-organisms that arrive at the adjacent area carrying micro-organisms in the concentration C that are deposited per unit of the product area (/cm<sup>2</sup>)

A = area of surface onto which microbes are deposited (cm<sup>2</sup>)

T = time, during which transfers occur(s); this can also be expressed as frequency of occurrence.

### Derivation of risk factors

With the exception of the first variable indicated in Equation 1, concentration of microbes in the air, or on surfaces, numerical values for the remaining variables indicated in Equation 1 are unlikely to be known. The time duration or frequency of microbial contamination in cleanrooms can be continuous, or unknown. For example, the rate of deposition of microbes from cleanroom air is continuous, the rate not varying significantly during production. Also, the frequency of incidents of surface contamination, such as when personnel touch the product, is normally unknown as personnel are often unaware of its occurrence. Thus, for purpose of an overall risk assessment, the variable of time (T) is not used. The numerical values of the variables in Equation 1 associated with the dispersion, transfer and deposition are also unlikely to be known. Consequently, risk factors that most closely represent these variables have to be utilised and an analogous risk equation, based upon such risk factors, is indicated in Equation 2.

## Equation 2

$$\text{Risk from microbial contamination (risk rating)} = A \times B \times C \times D$$

A = microbial contamination on, or in, a source

B = ease of dispersion and transfer

C = proximity of source from critical area

D = effectiveness of control method

The variables associated with dispersion, transfer and deposition of micro-organisms are collectively represented in Equation 2 as risk factors relating to ease of dispersion and transfer (B) and proximity of source from the critical area (C). The effectiveness of the method used to control the associated hazard is the fourth risk factor (D) to be employed. By assigning scores to each of the risk factors, risk ratings for all potential sources of contamination can be determined. An example of risk scores that can be used is given in Table 1.

**Table 1. Scores for risk factors used for assessing hazards**

Risk Factor A Amount of microbial contamination on, or in, a source	Risk Factor B Ease of dispersion, or transfer, of micro-organisms	Risk Factor C Proximity (location) of source from critical area	Risk Factor D Effectiveness of control method
0.0 = nil	0.0 = nil	0.0 = remote	0.0 = full barrier control
0.5 = very low	0.5 = very low	0.5 = in outside corridor, air lock	0.5 = very good control
1.0 = low	1.0 = low	1.0 = periphery of cleanroom	1.0 = good control
1.5 = medium	1.5 = medium	1.5 = general area of cleanroom	1.5 = some control
2.0 = high	2.0 = high	2.0 = critical area	2.0 = no control

**Table 2. Calculation of the risk rating for an identified sources**

Source	Risk Factor A Amount of microbial contamination on, or in, a source	Risk Factor B Ease of dispersion, or transfer, of micro-organisms	Risk Factor C Proximity (location) of source from critical area	Risk Factor D Effectiveness of control method	Risk Rating
4. Machines & ancillary equipment Surfaces in direct contact with product	0.5	2	2	0.5 (Sterilisation)	1
6. People Transfer to product via gloves with hole	2	2	2	0.5 (two pairs of gloves)	4

### Assessment of risk for identified sources of contamination

The sources of microbiological contamination identified utilising the model shown in Figure 1 can be assessed against the risk factors indicated in Table 1. Example, transfer of microbes from a person's hand to product via a glove with a hole is influenced by the work by Hoborn, who showed that a 1mm hole, artificially made in a latex glove, allowed several thousand bacteria to pass through in ten minutes of manipulation. This results in a risk factor score with the maximum value of 2.

When all of the identified sources have been assessed in a similar manner, the resultant risk ratings provide information regarding the greatest risks. Risk ratings with values of less than 2 may be categorised as 'low'; 2 and above but less than 4 categorised as 'medium' and 4 and above categorised as 'high'. Generally, only the high- and medium - scored risk ratings

require further review. In the case of the two sources assessed in Table 2, the potential to transfer contamination to product via holed gloves would require further consideration as part of an overall risk management program. One likely follow up action would be the testing of gloves for the presence of holes, following their use.

This will determine if the gloves are robust enough and will indicate if double gloving is a satisfactory control method or if alternatives, such as better quality glove, may need to be considered.

### **Assessment of risk within critical areas**

The method of risk assessment discussed previously can be used to carry out an overall assessment of all microbial risks in all areas of the pharmaceutical production cleanroom suite. However, it will normally be found that the highest risk occurs in the critical area where the product is exposed to contamination. A detailed risk assessment of potential microbial contamination arising from the contact contamination or airborne deposition is required. Any such assessment must relate to the fundamental mechanisms that govern contamination via each of these routes, in order to provide some level of accuracy and credibility to the resultant method. Again, Equation 1, which describes the fundamental mechanism for the transfer of microorganisms from a source to a product, can be utilised to define some accurate assessment criteria for contact contamination and airborne deposition. This more complex aspect of risk assessment is the subject for further consideration and development.