Risk assessment and microbiology

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18.1 Introduction

Risk assessment and risk management are important factors in the manufacture and quality control of pharmaceuticals and biopharmaceuticals. Although pharmaceutical manufacturers can rely upon process validation and on in-process and finished product testing to assure the quality of the drug products reaching the patient, it is arguably more effective for pharmaceutical manufacturers and regulators to focus on product and process defects that have significant impact on the patient. This philosophical point has formed the basis of the risk assessment and analysis initiatives that have been implemented globally within the pharmaceutical industry, to different degrees of application.

Risk is always prevalent with the production of pharmaceutical products, and in relation to microbiological risks in particular. The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug product remain consistent with those used in the clinical studies. While risks have been ever-present, the formal review of risk became part of the regulatory landscape at the turn of the twenty-first century.

The drive toward risk assessment began when the US Food and Drug Administration (FDA) announced what was then a new initiative: "Pharmaceutical cGMP (current good manufacturing practice) for the 21st century in 2002." This resulted in the FDA implementing a new science-based regulatory strategy emphasizing quality systems, risk assessment, and risk management. Several guidance documents have been issued to support the initiative. These included the adoption of a quality system approach to pharmaceutical the organization of good manufacturing practice (which also became a model for conducting inspections); recommendations for the use of process analytical technology (PAT) to allow for "real-time" process monitoring; and the use of a range of risk assessment tools and techniques [1].

Around the same time, the International Conference on Harmonization (ICH) published a document (ICH Q9) on Quality Risk Management. This was followed by companion documents outlining pharmaceutical development (Q8) and quality systems (Q10). Of these, the document of the greatest importance was ICH Q9. This document outlined a risk management strategy that involved the concepts of risk identification, assessment, control, communication, and review. In time, ICH Q9 became "adopted" by FDA and incorporated into EU GMP.

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What the recent regulatory approaches do is direct the manufacturer to the fact that an effective quality risk management approach can further ensure the high quality of the medicinal product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better, and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

This chapter considers the nature of risk, outlines some risk assessment approaches, and contextualizes these within the context of microbiological risks.

18.2 The nature of risk

Risk is a difficult concept to define, in that it can only be considered as a relationship to something else (that is comparing one risk to another provides some kind of measure as to whether the risk is greater or lesser than the other). In more systematic terms, risk can be defined as the combination of the probability of occurrence of harm and the severity of that harm [2]. Thus, risk can be derived from a consideration of:

1. what might go wrong?
2. what is the likelihood (probability) it will go wrong?
3. what are the consequences (severity)?

Failure modes and effects' analysis (FMEA), as a risk analysis tool, provides the best means of representing risk, based on the above, and this is expressed as:

$$\text{Risk} = \text{criticality of the occurrence} \times \text{frequency of occurrence}$$

To this, detection can be used for risk mitigation. Various schemes enhance the risk assessment process by using a numerical scoring system so that one risk can be examined relative to another (which allows a risk to be considered as high, medium or low) [3]. Importantly, such risk schemas are highly generalized and, being applied cross industry, do not deal with the particularities of microbial contamination. The conception of risk as "the combination of the probability of occurrence of harm and the severity of that harm." Harm, in the pharmaceutical processing context, is damage to health, including the damage that can occur from loss of product quality or availability. With this latter point, the concern is not only with an adulterated medicine reaching the marketplace but also with an incident that prevents a pharmaceutical organization from releasing a medicine that consequently leads to a patients going without a much needed medicinal product. An important term in risk assessment is hazards. A hazard can be best defined as the potential source of harm.

Once risk is defined, an attempt can be made to understand if the risk acceptable and what controls are available to mitigate the risk. This can be understood by posing the following questions:

1. is the risk above an acceptable level?
2. what can be done to reduce or eliminate risks?
3. what is the appropriate balance among benefits, risks, and resources?
4. are new risks introduced as a result of the identified risks being controlled?

The pharmaceutical industry and regulators assess and manage risk using recognized risk management tools. A nonexhaustive list of some of these tools includes [4]:

1. basic risk management facilitation methods (flowcharts, check sheets, etc.);
2. FMEA;
3. failure mode, effects, and criticality analysis (FMECA);
4. fault tree analysis (FTA);
5. hazard analysis and critical control points (HACCP);
6. hazard operability analysis (HAZOP);
7. preliminary hazard analysis (PHA);
8. risk ranking and filtering;
9. supporting statistical tools.

These tools differ in structure and whether they are qualitative or quantitative in output. Nevertheless, they share commonality in approach in that they involve:

- identifying hazards;
- analyzing the risk associated with each hazard;
- evaluating how significant the risks are.

The correct identification of all of the hazards, their routes of transfer and their control methods and an accurate assessment of the degree of risk that these hazards provide is a fundamental stage in ensuring the effectiveness of any risk management system. Risk management is fundamentally about understanding what is most important for the control of product quality and then focusing resources on managing and controlling the important aspects in order to ensure that risks are reduced and contained. Before risks can be managed, or controlled, they need to be assessed, hence the centrality of "risk assessment."

A detailed evaluation of a risk management strategy is beyond the scope of this book; however, it is important to be aware of the initiatives within the pharmaceutical industry with respect to risk management and some of the tools available. The knowledge and understanding of the areas of the greatest risk associated with any manufacturing process enables resource and funding to be focused upon these areas, optimizing the security, and productivity of the process.

With risk assessment, whichever tool is adopted, there are two important points to bear in mind:

- there is no such thing as "zero risk," and therefore, a decision is required as to what is "acceptable risk." This must be qualified before the risk assessment begins;
- risk assessment is not an exact science—different people will have a different perspective on the same hazard.

The outcome of the risk assessment should be used to determine appropriate control strategies needed to reduce the risk to a level that is deemed acceptable. These strategies are typically focused on reducing the probability of a risk occurring. Where

risk cannot be reduced down to a satisfactory level, then a mitigating strategy is to increasing the probability of the associated hazard being detected. An example is with environmental monitoring, where monitoring can be targeted to specific areas such as exposing settle plates near open product [5].

Risk assessments and the actions arising from them need to be documented and subject to periodic review to ensure that the assessment reflects the actions taken and the most recent data.

18.3 The need for microbiological risk assessment

Microbiological risk assessment should be carried out for both sterile and nonsterile manufacturing activities to establish what microbial risks are involved with the facility, equipment, and processes used. Whether such risk assessments should be activity specific (such as producing purified water, cleaning equipment, or freeze drying) or product specific, will depend upon the type of organization. In many cases, a generic risk assessment can cover a number of products; however, in doing so, product-specific considerations and the nature of operations should not be forgotten.

The outcome of a microbiological risk assessment can help determine the appropriate controls associated with the running of the facility or specific processes and an appropriate monitoring program.

When undertaking microbiological risk assessments, a description of the full manufacturing process is a useful starting point in assessing the risks involved. This may be simply done as a process map or flow diagram, with activities, equipment used and process parameters added on. Important factors to consider in the manufacturing process, and in relation to the nature of microorganisms, include:

- solvents used:
  - water-based processes provide a more favorable environment for microorganisms;
  - the use of other solvents might decrease the risk of microbial growth;
- pH:
  - values above 10 or below 2 generally being detrimental to microorganisms;
- osmolarity of solutions:
  - high osmolarity is typically detrimental to microbial growth;
- temperatures used:
  - a temperature range of 25–35 °C generally promotes microbial growth; significantly higher or lower temperatures are detrimental to most microorganisms. However, any risk assessment should consider common microbiota to see if psychrophiles or thermophiles (bacteria or fungi) are present;
- drying:
  - water is a vector and a growth source, areas should be kept as dry as possible and water supplies need to be controlled;
  - in relation to product contamination risk, if the water activity of the product is reduced below 0.6, then microbial growth will be suppressed [6]. A fundamental component of assessing the risk for microbiological control in nonsterile manufacturing is an understanding of whether the product or intermediates during the production process are able to support growth or sustain viability of microorganisms is water activity. Water activity

(aw) is a measure of the free water in a material and is, therefore, a useful measure to aid the determination of microbiological risk. Water activity is a more accurate index for microbial growth than water content as microorganisms have a limiting water activity below which they cannot grow (typically a level of 0.6, on a scale of 0–1.0). Water activity can vary according to different temperatures; thus, temperature control is important for assessing product risk in relation to storage;
    - understanding water activity, in the context of risk, allows the microbiologist to: develop product formulations; set microbiological release specifications; establish microbial testing programs; and determine the potential shelf life stability from microbial growth;
- hold times and overall campaign length:
    - longer processing times may increase the opportunity for microbial proliferation unless the conditions are detrimental to microbial growth;
- open processing:
    - open processing is at greater risk compared with closed processing. Protective measures can be put in place through the use of unidirectional airflow and staff gowning and glove spraying;
    - in general, the longer the exposure period with open processing then the greater the likelihood of contamination transfer (as discussed below);
- fixed or mobile equipment:
    - equipment that has an in-build clean-in-place or sterilize-in-place capability is generally under less risk, provide that it has been qualified, than equipment that needs to be taken out of the process area and to a wash bay;
- personnel interaction [7]:
    - the higher the level of personnel activity then the greater the risk of contamination, given that people are the primary source of contamination in cleanrooms;
    - a related factor is the level of room occupancy;
- environmental control:
    - the level of environmental control, such as the way that the heating, ventilation and air conditioning system (HVAC) operates will affect how contamination is distributed or the rate at which it is removed from the critical area. Here an understanding of factors like air distribution, air change rates, pressure differentials, recovery times, filter efficiency, and so on is important;
    - environmental monitoring, although distinct from environmental control, can inform about the capability of environmental control systems;
- types of microorganisms:
    - the microbiologist must know and understand the microflora within the facility and trend the findings. Shifts in what is normally recovered can provide valuable information about risks. For example, a rise in the population of *Pseudomonad*-related genera may suggest a breakdown in water control. To take a second example, a rise in the population of *Bacillus* species could be linked to in-coming materials or the presence of dust; whereas Gram-positive cocci, such as a species from the genera *Micrococcus* or *Kocuria*, will probably have an association with personnel;
    - in addition, for terminal sterilization, the likely bioburden is not simply about microbial numbers for the types of species and theoretical resistance to the sterilization process will affect the success or otherwise of the sterilization cycle;
    - with aseptic processing, identifying microorganisms in different locations informs about the likelihood of contamination transfer and helps to identify points of origin (for example, linking a Grade A settle plate with a finger plate taken from an operator who performed a filling machine intervention);

- nature of microorganisms:
  - microorganisms in different states can survive for long periods. As the book has considered, microorganisms that can enter dormancy through forming endospores (such as *Bacillus* and *Clostridium* species) can survive in conditions that vegetative microorganisms cannot. The risk is elevated should endospores be given the opportunity to germinate;
  - furthermore, while the water activity, as indicated above, provides a useful indicator of the ability of the formulation to support growth, it should be remembered that some organisms present may remain viable and be pathogenic at low levels (such as *Salmonella* species);
  - with these examples it remains that good control during manufacturing is still essential.

For the manufacture or processing of nonsterile and sterile pharmaceutical products, such risk assessments can only be undertaken accurately if the correct models of contamination are understood and utilized.

This chapter proceeds to describe the fundamental mechanism of contamination transfer and details how this can be utilized to provide an effective assessment of the risk of contamination, from both microorganisms and microbial carrying particles, to pharmaceutical products.

18.4 Microbial contamination transfer

Important to microbial risk is the concept of contamination transfer. If microorganisms are deposited onto a surface some distance from a site of risk (such as exposed product), then the likelihood of product contamination is dependent upon the possibility of the microorganisms being transferred to the product. For this to happen, a vector is required. The common vectors are air, water, or physical movement (such as via the hands of a production operative) [8].

The chance of microorganisms being transferred from a source of contamination to a product is dependent on the likelihood of them being dispersed from the source, transferred to and then deposited onto or into a product. Where contamination transfer occurs, the important variable is time, and the microbiologist needs to account for the number of microorganisms deposited onto a given area in a given time. An attempt to express this phenomenon as a universal equation has been made by Whyte and Eaton [9]:

$$\text{Contamination deposited on a product} = C \times S \times P_d \times P_a \times A \times T$$

where C is the concentration of contamination on, or in, a source (number/cm^2 for a surface, or number/cm^3 for air); S is the quantity of surface material, or air, that is dispersed or transferred from a source in a given time (cm^2/s for surfaces, and cm^3/s for air dispersion); P_d is the proportion of contamination dispersed from a source that are transferred to the area adjacent to the product; P_a is the proportion of contamination in the adjacent area that are deposited per unit area of the product (/cm^2); A is the area of surface onto which the contamination is deposited (cm^2); and T is the time, during which transfers occur (seconds).

The equation expresses the fact that the amount of microbial contamination is dependent on:

1. the concentration on a contaminating surface, or within air;
2. how much of this contamination is dispersed, transferred, and deposited onto, or into, the product;
3. a variable of time or event frequency.

A practical example of the mechanisms outlined would be the airborne transfer of skin microorganisms from personnel to a product. Here, the number of microorganisms that would deposit on a product is dependent upon:

1. the concentration of microorganisms per area of a skin surface;
2. the surface area of skin that is dispersed in a given time;
3. the proportion of microorganisms dispersed and transferred through cleanroom clothing and the cleanroom air to the area adjacent to the product;
4. the proportion of microorganisms adjacent to product that will be deposited onto a given area of exposed product;
5. the time over which this deposition occurs.

While this general model is useful for conceptualizing risk, for airborne and surface contamination, assessing microbial risk sometimes requires more detailed discussion. These areas are considered next.

18.4.1 Airborne deposition

Most of the microorganisms found in cleanroom air derive from the skin of personnel within these areas. A proportion of these skin cells carry microorganisms, and cleanroom personnel can disperse several hundred microbial carrying particles per minute through cleanroom clothing. For these reasons, microorganisms are normally found in cleanrooms attached to skin particles (or very occasionally, a clothing fiber). The average size of microbe carrying particles will vary between about 8 and 20 µm and can deposit, mainly by gravity into, or onto, the product [10].

The number of microbial carrying particles that will deposit onto a given area of product, and hence the proportion of product contaminated can be calculated using the deposition rate obtained from microbiological settle plates. This approach, also first postulated by Whyte, can be used for most pharmaceutical-manufacturing process where airborne contamination deposits passively from the air, mainly through the force of gravity, into, or onto, the product [11].

The general equation (above) can be modified by combining the first four variables of the equation into a single variable that provides the number of microorganisms that will deposit onto a given area of product in a given time (termed the deposition rate). This can be expressed as:

$$\begin{array}{c}\text{Number of airborne microorganisms}\\ \text{deposited onto a product in}\\ \text{a given time (deposition rate)}\end{array} = \begin{array}{c}\text{area of product}\\ \text{exposed}\left(\text{cm}^2\right)\end{array} \times \text{time of exposure}\left(\text{s}\right)$$

With the answer expressed as number of microorganisms per square centimeter at a given rate of time.

Therefore, in cleanrooms settle plates can provide information about the deposition rate and thus the likelihood of product contamination over a period of time. In addition, by capturing microorganisms, settle plates allows the contaminated to be characterized, which helps with assessing the point of origin.

18.4.2 Surface contact

The equation used to calculate the number of microorganisms deposited by surface contact is also derived from the general equation. This risk is calculated by considering surface contamination as something that occurs as discrete events, and by combining the dispersion, transfer, and deposition variables into one overall term, that is, the "transfer coefficient." This equation can be reformatted to the following equation that calculates the number of microbes deposited on a given area of product over a known time. The equation is:

$$\begin{array}{l}\text{Number of}\\ \text{microorganisms}\\ \text{deposited by}\\ \text{surface contact}\left(\text{no.}\right)\end{array} = \begin{array}{l}\text{microbes or}\\ \text{particles on}\\ \text{source surface}\\ \left(\text{no.}/\text{cm}^2\right)\end{array} \times \begin{array}{l}\text{transfer}\\ \text{coefficient}\end{array} \times \begin{array}{l}\text{area of}\\ \text{contact}\left(\text{cm}^2\right)\end{array} \times \begin{array}{l}\text{frequency of}\\ \text{contact}\left(\text{no.}\right)\end{array}$$

The "transfer coefficient" represents the proportion of microorganisms on the source surface that are transferred onto the product with each contact. A practical example would be contacts of a finger with the surface of a product. The number of microbes transferred could be calculated from (a) the concentration of microorganisms on the finger surface, (b) the proportion of microorganisms on the finger surface that are transferred to the product (i.e., the transfer coefficient), (c) the area of contact between the finger and product, and (d) frequency, that is the number of times the product is touched.

18.5 Identification of sources and routes of contamination

The key step in the risk assessment process is the identification of the sources of microorganisms, their routes of transfer and control methods. All sources of contamination must be identified and their risk to the product assessed. With this, grouping of the sources and the use of a risk diagram are useful.

18.5.1 Sources of contamination

Examples of sources of contamination in a typical cleanroom are as follows:

- adjacent areas;
- supply air;
- cleanroom air;
- surfaces;

- people;
- machines;
- ancillary equipment;
- materials;
- containers;
- packaging;
- liquids.

Areas adjacent to product processing areas, such as change rooms, transfer hatches, and external corridors, are likely to be more contaminated than the cleanroom or controlled area used for processing. The transfer hatches and change areas will be contaminated by the activities in these areas, and there may be less control of the dispersion of contamination in the outside corridors. The transfer of this contamination into the production cleanroom should be minimized. The air supplied to a cleanroom, if not correctly filtered, is a source of contamination and the air within the cleanroom is a major source of contamination and contains contaminants dispersed from people and machinery.

The floor, walls, ceilings, and other surfaces in the cleanroom, such as tables, tools, paper, and so on, are fair examples of sources of surface contamination which is normally derived in a secondary way from personnel touching them, or from contamination deposited from the air. These surfaces can also be primary sources of contamination if poor quality constructional components have been used, as they break up and disperse fibers of wood or particles of plaster.

As discussed, personnel within the cleanroom are a major source of contamination. People can disperse vast quantities of contamination from the skin, hair, and mouth. This contamination can be transferred to the product through the air, or by contact with their hands or clothing. Cleanroom clothing, gloves, and masks are used to control the contamination being dispersed from the people wearing them. These items of clothing can, however, become contaminated by the people wearing them and from other cleanroom sources [12].

Machines are a source of particles, as they can generate contamination by the movement of their constituent parts, or a secondary source from contamination deposited on them from the air or by contact with personnel. Ancillary equipment such as chairs, air samplers, and calculators will have contamination similar to the surfaces previously considered. Raw materials, containers, and packaging that are transferred into the cleanroom may be contaminated and liquids, such as those used for the product formulation, may also be a source of contamination.

18.6 Routes of transfer

The routes of transfer of contamination, by airborne and surface contact, should also be identified because by minimizing these routes, the risk of contamination can also be reduced.

Airborne contamination is normally sourced from people and machines and is dispersed into the air and then deposited onto the product. If the particles are small, like skin cells, they can move around in the air before depositing. However, if they are

large particles, like spittle, dandruff, or cuttings of plastic or glass, they will remain within a short distance from where they were generated, and fall directly into, or onto, the product; this is called intimate airborne spread.

Contact contamination occurs when contaminated items such as machinery, ancillary equipment, cleanroom surfaces, containers, packaging, gloves, and clothes come into contact with the product. Contact contamination can occur in many ways; one example is when personnel touch a contaminated surface with their gloves, which then become contaminated. If product is then touched with that glove, contamination is transferred onto the product.

Using information of the type discussed above, the sources and routes of transfer of contamination can be determined, especially when superimposed over a process risk diagram.

18.7 Risk assessments for general cleanroom areas

Risk to cleanroom products from surface contact and airborne deposition contamination can be assessed, either at the preliminary design stage of the cleanroom and associated manufacturing process or, retrospectively, for an established manufacturing operation.

All microbial sources, such as those outlined earlier, should be considered to be potential hazards and assessed to determine their degree of risk. The likelihood of deposition of contamination onto or into a product is very much dependent upon factors associated with the product itself, such as the exposed area and the time of exposure. In order to compare the hazards in the cleanroom areas on an equal footing, the variable of deposition of microorganisms is assumed to be constant and can, therefore, be ignored for this particular assessment.

Furthermore, the variable of frequency maybe continuous, as in the case of the hazard associated with air supplied to the cleanroom areas, or it may be associated with the transient transfer of contamination by personnel during the manufacturing operation. The variable of frequency is, therefore, also not utilized. Therefore, a version of the fundamental equation should be used for this assessment. This is:

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

where A is the microbial contamination on, or in, a source; B is the ease of dispersion of contamination from the source; C is the ease of movement of contamination to product; and D is the proximity of contaminating source from the product.

The risk rating of each source of contamination can be determined by assigning risk scores to the risk factors A–D. It should be noted that these risk factors, and the associated risk scores, take into account the measures that have been utilized to control the identified hazards and therefore the resultant risk rating relates to the risk in the controlled (operational) state. This method can also be used to assess the level of risk in the uncontrolled or partially controlled state simply by re-assessment of the risk score and re-calculation of the risk rating for the level of control employed. This approach of considering the risk in the controlled state has found to provide the best and most flexible method for this type of overall risk assessment.

18.8 Risk scoring systems

Risk scores are usually assigned to hazards and an associated scoring method must be established. It is easier to describe risk by simple words modified to denote greater or lesser importance and to then allocate a score to these words. The most accurate scoring system must also have the meaning of the word descriptions to be in direct proportion to the score magnitude, and it should span the whole range of the risks considered. Three possible systems are shown in Table 18.1.

An example of how risk scores can be allocated to different risk factors is shown in Table 18.2. This example uses the five-stage scoring system.

With Table 18.2, for each identified contamination source, the risk scores for each risk factor should be determined and then multiplied together (the fundamental equation shows that multiplication and not addition is required) to obtain a risk rating. This risk rating determines the degree of risk associated with each contamination source.

Keeping with this approach, general sources of contamination and calculated risk ratings are shown in Table 18.3.

Alternatively, in place of a numerical system, the risk rating can be assigned a "low," "medium," or "higher" category.

Table 18.1 Risk scoring system

7 Stage		5 Stage		4 Stage	
Not possible	0	Nil	0	Nil	0
Very unlikely	1	Very low	0.5	Low	1
Unlikely	2	Low	1	Medium	2
Possible	3	Medium	1.5	High	3
Likely	4	High	2		
Very likely	5				
Definite	6				

Table 18.2 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 of microorganisms from the source	Risk factor (C) Ease of movement of contamination to product	Risk factor (D) Proximity of source from product
0 = nil	0 = nil	0 = nil	0 = remote
0.5 = very low	0.5 = very low	0.5 = very low	0.5 = outside corridor, air lock
1 = low	1 = low	1 = low	1 = periphery of cleanroom
1.5 = medium	1.5 = medium	1.5 = medium	1.5 = general area of cleanroom
2 = high	2 = high	2 = high	2 = critical area

Table 18.3 **A general model for assessing risk within pharmaceutical processing areas**

Source	Microbial counts Surface- counts/24 cm^2; air-counts/m^3	Risk factor A Conc. of microbes	Risk factor B Ease of dispersion from source	Risk factor C Ease of movement to product	Risk factor D Proximity to product	Risk rating
1. Areas adjacent to production cleanrooms (change and transfer areas)						
1.1 Air outside production cleanrooms	>10 (terminal air filtration, air supply rates)	1.5	2	0.5 (differential air pressure, physical barriers)	0.5	0.75
1.2 Floor surfaces outside production cleanrooms	>5 (floor disinfection, overshoes, tacky mats)	1.5	1	0.5 (physical barrier, footwear change)	0.5	0.38
2. Supply air						
2.1 Air supplied to unidirectional air flow areas	<1 (terminal air filtration)	0.5	2	2 (unidirectional air flow)	2	4
2.2 Air supplied to turbulently ventilated cleanroom	<1 (terminal air filtration)	0.5	2	0.5 (physical barrier, air dilution with turbulent airflow)	1.5	0.75
3. Air within unidirectional air flow areas and cleanrooms						
3.1 Unidirectional air flow areas	1 (garments, unidirectional airflow velocity)	1	2	0.5 (unidirectional airflow)	2	2
3.2 Turbulently ventilated cleanroom	10 (garments, air supply rates)	1.5	2	0.5 (physical partition, unidirectional air flow)	1.5	2.25
4. Machines and ancillaries						
4.1 Machine surfaces not in contact with product	1 (surface disinfection, environmental control)	1	0.5	1 (aseptic behaviors)	2	1
4.2 Machine surfaces in direct contact with product	<1 (sterilization)	0.5	0.5	2	2	1

4.3 Ancillaries (product scissors, forceps, etc.) in direct contact with product	<1 (sterilization)	0.5	0.5	2	2	1
5. Non-machine surfaces						
5.1 Ceilings, walls, floors, doors in turbulently ventilated cleanroom	>1 (disinfection, aseptic behaviors, garments)	1 (aseptic behaviors)	0.5	1 (aseptic behaviors)	1.5	0.75
5.2 Trolleys, chairs, tables, eyewash, calculator, waste bins, paperwork, pens, bin bags, labels, press buttons, and switches etc. in cleanroom	1 (surface disinfection, glove disinfection)	1	0.5	1.5 (aseptic behaviors, glove disinfection)	1.5	1.1
5.3 Walls, floors, and ancillaries; and for microbial samplers, located in unidirectional air flow area	1 (surface disinfection, aseptic behaviors, garments)	1	0.5	2 (aseptic behaviors, glove disinfection)	2	2
6. People						
6.1 Transfer to product via gloved hands [1]	<100 (hand washing)	2	2	0.5 (2 pairs of gloves)	2	4
6.2 Transfer to product via gloves with secondary contamination [1]	<1 (glove disinfection, aseptic behaviors)	0.5	2	2 (aseptic behaviors)	2	4
6.3 Airborne transfer of microorganisms from personnel working in unidirectional air flow area	>2000	2	2	0.5 (garments, aseptic behaviors, unidirectional air flow)	2	4
6.4 Surface transfer to product from cleanroom clothing	>1 (garments and aseptic behaviors)	1	2	1 (aseptic behaviors)	2	4
7. Material - primary and packaging						
7.1 Liquid product from clean process area	<1 (sterile filtration)	0.5	2	2	2	4
7.2 Container	<1 (sterilization)	0.5	2	2	2	4

The magnitude of the risk ratings can be used to determine the degree of effort to be allocated into controlling and monitoring each source. However, it should be appreciated that the risk assessment method should only be used to *assist* in assessing the risks. The quality of the input information and the inexact nature of the model ensure that exact predictions cannot be made.

18.9 Conclusion

This chapter has presented an introduction to the important subject of risk in biopharmaceuticals and with microbiological risks in particular. Understanding where microorganisms may reside, together with the typical types of organisms helps with building in risk mitigation into pharmaceutical and healthcare processes. What is also of importance is mapping out the possibility of contamination transfer through air-streams or direct transfer through personnel. Knowing the likelihood and severity of such risks is important for an assessment of environmental monitoring. As well as these proactive measures, risk assessment is also helpful for dealing with contamination events. While risk assessment is a complex and wide-ranging subject, this objective of this chapter was provider a lead in to the subject and to assist those who need to understand the fundamentals of contamination control.

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