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A cleanroom contamination control system

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Analytical methods for hazard and risk analysis are being considered for controlling contamination in pharmaceutical cleanrooms. The most suitable method appears to be the HACCP system that has been developed for the food industry, but this requires some reinterpretation for use in pharmaceutical manufacturing. This paper suggests a possible system.

To control contamination effectively, it is necessary to have a good appreciation of the routes and sources of contamination, and the means of controlling them. An overview of these is given.

Introduction

Cleanrooms must be operated so that the contamination of the manufactured product is controlled. Standards of particle and microbial contamination, such as found in the European Union guide to good manufacturing practice[1] are set, and controlled, so that they are not exceeded. Unfortunately, such standards do not take account of different degrees of risk, the varying routes and sources of contamination in different processes, and whether the product supports the growth of micro-organisms. To ensure that the correct control measures are taken, a scientifically based contamination control system is needed to analyse the degree of risk posed by the varying hazards. This approach has been advocated by ISO 14698-1[2].

Hazard and risk analytical systems

A contamination control system should assess the degree of risk of potential hazards found in a cleanroom. A number of systems exist for assessing risk during manufacturing, and ISO 14698-1 suggests *Fault Tree Analysis (FTA)*[3], *Failure Mode and Effect Analysis (FMEA)*[4] and *Hazard Analysis and Critical Control Point (HACCP)*[5, 6, 7]. The first two systems appear to have been written mainly for electrical and mechanical systems, but can be applied to all types of risks. Those who are expert in dealing with such systems will be able to apply them to contamination risks. However, the majority of cleanroom users will more easily understand the *Hazard Analysis and Critical Control Point (HACCP)* system, which is the basis of the system used in ISO 14698-1. This system was devised for use in preventing contamination in the food production industry. It has the following seven principles [7]:

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1. Conduct a hazard analysis
2. Determine the critical control points (CCPs)
3. Establish critical limit(s)
4. Establish a system to monitor control of the CCPs
5. Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control
6. Establish procedures for verification to confirm that the HACCP system is working effectively
7. Establish documentation concerning all procedures and records appropriate to these principles and their application

It is also suggested in some HACCP documents that personnel associated with the HACCP system need to be trained.

The HACCP system is explained in various documents[5, 6, 7]. However, these documents and explanations apply to the food industry. The HACCP system clearly needs reinterpretation if it is to be used in pharmaceutical production. There has been a considerable amount of discussion as to how this can be done, and its application to the wider aspects of pharmaceutical manufacturing has been reported[8, 9]. However, HACCP can be applied just to the control of microbial and particle contamination. Used in this way, it should add a scientific rationale to existing quality assurance systems. In the pharmaceutical industry, where the regulation process is often based on what is achievable rather than a scientific assessment what is required, this is a welcome addition.

A cleanroom contamination control system

As indicated in the previous paragraph, the HACCP system requires some reinterpretation if it is to be used in the manufacture of non-food items in cleanrooms. A reinterpretation of the first three principles of HACCP is particularly needed. To achieve this, a cleanroom contamination control system (CCCS), based on HACCP, is suggested. This contains the following steps:

1. Identify the sources of contamination in the cleanroom. Construct a risk diagram, or diagrams, to show these sources and their routes of contamination.
2. Assess the importance of the sources to determine how great a hazard they are.
3. Identify methods that can be used to control these hazards.
4. Determine valid sampling methods to monitor the hazards, or their control methods, or both.
5. Establish a monitoring schedule with 'alert' and 'action' levels, and corrective measures to be taken, where appropriate, when these levels are exceeded.
6. Verify that the contamination control system is working effectively by reviewing the product contamination rate, sampling results and control methods and, where appropriate, modifying them.
7. Establish and maintain appropriate documentation.
8. Train the staff.

CCCS Step 1: Identification of sources and routes of contamination

The first step of the CCCS system is the identification of the sources and routes of contamination, and can be carried out as follows:

1. Sources of contamination

All sources of contamination should be identified for the process being analysed. Examples of sources of contamination in a typical cleanroom are as follows:

- areas adjacent to the cleanroom
- unfiltered air supply
- room air
- surfaces
- people
- machines
- ancillary equipment
- materials
- containers
- packaging

Areas adjacent to the cleanroom are likely to be more contaminated than the production cleanroom; the material airlock and clothing-change areas will be contaminated by the activities going on in these areas and the contamination in the outside corridors and service areas may not be controlled. The air supplied to a room, if not correctly filtered, is a source of contamination. Room air is also a source as it contains contamination dispersed into it from other sources, such as people and machines.

The floor, walls, ceiling and other surfaces in the cleanroom are examples of surface sources, their contamination being derived in a secondary way from personnel touching them, or contamination depositing from the air. These surfaces can also be primary sources of contamination if poor quality constructional components are used, which break up and disperse fibres, wood chips, plaster, etc. Cleanroom clothing, gloves and masks are other surfaces that are contaminated, either by the people wearing them or from other cleanroom surfaces.

Personnel within the cleanroom are a major source of contamination and normally the sole source of micro-organisms. They can disperse contamination from the skin, mouth and clothing. This contamination can be transferred to the product through the air, or by contact with their hands or clothing.

Machines are another source, as they can generate contamination by the movement of their constituent parts or may be a secondary source from contamination deposited on them from personnel; ancillary equipment used in the process should not be forgotten, although many can be considered in the 'surfaces' category. Raw materials, containers and packaging that are brought in, or piped into the cleanroom, may be contaminated and should be considered as sources.

2. Routes of transfer

As well as identifying the sources of contamination in a cleanroom, the routes of transfer must be considered. The two main routes are airborne and contact.

Contamination can be dispersed into the air from sources and transferred to the product. If the particles are small, like skin cells, they can float off to other parts of the cleanroom. However, if they are large, like spittle or cuttings, they will remain within a short distance from where they were generated, and fall directly into, or onto, the product; this is often called intimate airborne spread.

Contact routes of contamination occur when contaminated machines, ancillary equipment, containers, packaging, raw materials, gloves, clothes, etc. come directly into contact with the product. Contact contamination can occur in several ways; one example is when personnel handle a surface and the contamination on their gloves is transferred onto the product. Another is when the product is filled into contaminated containers.

Using information of the type discussed in this and the previous section, the sources and routes of transfer can be ascertained and a risk diagram constructed for any cleanroom.

3. Construction of a risk diagram

Construction of a 'risk diagram' is a good method of understanding how contamination arises from sources, as well as the routes by which it reaches the product. The risk diagram is equivalent to the HACCP flow diagram. The way in which a product is contaminated is often poorly understood, but by constructing a risk diagram a greater understanding will follow. The risk diagram should show possible sources of contamination, their main routes of transfer, and methods of controlling this transfer. It may be necessary to construct several diagrams where (a) the process is carried out in several rooms (b) one part of the process is very complex or (c) where it is necessary to control different contaminants, e.g. particles and micro-organisms.

Figure 1 is an example of a risk diagram that is produced for a single cleanroom and shows the main sources of microbial and particle contamination. It includes the main routes of transfer of contamination and the means of controlling them. The transfer of contamination around the room can be very complicated

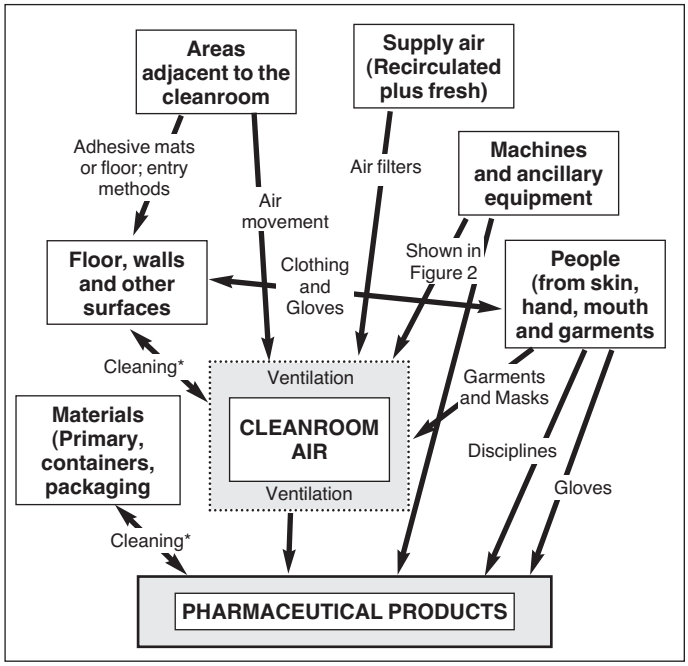

Figure 1. Sources and routes of particle and microbial contamination in a cleanroom along with preventative measures. The boxes give sources and the connecting lines give the means of control.
* Cleaning includes disinfection and sterilisation where appropriate.

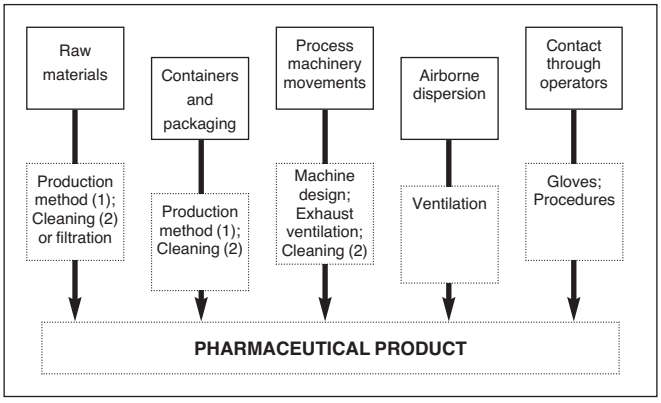

Figure 2. Sources and routes of control often associated with process machinery. (1) Contamination of the raw materials, containers and packaging can be controlled by production in suitably clean conditions. (2) Cleaning methods include disinfection or sterilisation.

as, in theory, everything in the cleanroom can be contaminated by everything else. However, in practice, it should only be necessary to consider the major ones. It is interesting to note the central role of air, which receives and transports many of the sources in a cleanroom. This agrees with the fact that airborne microbial contamination has been shown to have a central role in contamination in aseptic production[10, 11, 12, 13]. Because of its complexity, the means of controlling the manufacturing process has not been fully shown in **Figure 1**, and is shown separately in **Figure 2.** which has been drawn to include manufacturing materials.

CCCS Step 2: Assessment of the importance of hazards

When all possible sources of contamination in the cleanroom, and their routes of transmission, have been identified, the next task is to carry out a risk assessment. This is also called a hazard or risk analysis and ascertains what sources of contamination are important, i.e. their relative importance, or degree of risk.

It may be difficult to determine which contamination sources are the most hazardous. This is especially so if the cleanroom is new and not yet operational, as few useful results will have been collected of the concentration of contaminants in the environment. However, lack of results should not prevent a preliminary assessment being made, as it will be necessary at a later stage (Step 6) to return to these tentative conclusions for a reappraisal and, if necessary, make changes.

To determine the likely importance of a hazard, the following method may assist. Firstly, a set of variables known as risk factors should be determined. These are:

1. The amount of contamination on, or in, the source in its uncontrolled state and available for transfer (risk factor A);
2. The ease by which the contamination is dispersed or transferred (risk factor B);
3. The proximity of the source to the critical point where the product is exposed (risk factor C);
4. How well the contamination is controlled (risk factor D).

Table 1 shows the risk factors and score values that can be used to assess the overall risk rating, or hazard, of each individual source. Each of these factors (A to D) should be assessed and given a score of 0 to 2.

Using **Equation 1**, the four scores should be multiplied together to obtain a risk rating. This will have a value of between 0 and 16.

$$\text{Risk rating} = A \times B \times C \times D \qquad \textbf{Equation 1}$$

A risk rating can therefore be obtained for each contamination source and this rating can be used to determine the importance of each source and whether it is

Table 1. Risk factors for assessing hazards

Amount of contamination on, or in, a source (A)	Ease of dispersion, or transfer (B)	Proximity from critical area (C)	Effectiveness of control method (D)
0 = nil	0 = nil	0 = remote	0 = barrier control
0.5 = very low	0.5 = very low	0.5 = outside corridor, air lock	0.5 = very good control
1 = low	1 = low	1 = periphery of cleanroom	1 = good control
1.5 = medium	1.5 = medium	1.5 = general area of cleanroom	1.5 = some control
2 = high	2 = high	2 = critical area*	2 = no control

*A critical area is where the product is open to contamination, or where any materials that come into intimate contact with the product are placed.

a hazard to the product. If required, the risk rating can assigned a 'low', 'medium' or 'high' category. For example, a risk rating of less than 4 can be considered as 'low', between 4 and 12 as 'medium' and higher than 12 as 'high'. Experience with the system will help develop a useable system. This risk rating can then be used to help determine how much effort should be put into controlling and monitoring each source. However, it should be appreciated that this method should only be used to assist in assessing the risks. The quality of the information available as input and the inexact nature of the mathematical model means that it cannot give exact predictions.

Two examples of a risk assessment will demonstrate the general method.

Example 1

A risk assessment is required to answer the question 'how great a hazard are cleanroom walls?'. Firstly, the 'amount of contamination' factor (A) should be assessed. As the amount of contamination on the walls is 'low', a score of 1 could be given. The 'ease of dispersion or transfer' (B) is likely to be 'very low' and given a score of 0.5. As the wall is at the periphery of the room, a value of 1 is given to the 'proximity' score (C). A score of 1 might be an appropriate score for the 'effectiveness of control method' (D) if the wall was cleaned frequently, 1.5 if it was cleaned irregularly and 2 if it was never cleaned. Thus, the overall hazard assessment score of between 0.5 and 1 would be obtained. This demonstrates that walls are not an important hazard.

Example 2

The hands of a person handling a product are considered. Maximum scores of 2 could be given for both the 'amount of contamination' in the uncontrolled state' (A) as well as 'the ease of dispersion, or transfer' (B), as ungloved hands have very large amounts of particles, bacteria and salts, and these are easily transferred when personnel handle the product. A maximum score of 2 could also be assigned to the 'proximity from the critical area' if the operator handles the product, although this should be changed to 1 if the product is infrequently handled. The overall hazard assessment score is now dependent on how the hand contamination is controlled. If no gloves were worn, a hazard score close to the maximum of 16 can be calculated from **Equation 1**. If gloves were worn, then, depending on how likely they were to be punctured, an overall hazard score of about 8 would be obtained. The use of double gloves, or gauntlets in an isolator, would give either very good control, or barrier protection; this would reduce the overall hazard score to close to 0. It can be seen from this example that hands can be a high potential hazard and their control is important.

Ljungqvist and Reinmüller[14,15] describe a method that can be used to determine the risk caused by imperfect air protection of production machinery. They suggest that the airflow round the machinery should firstly be investigated by smoke visualisation techniques. The area outside the machinery should then be seeded with a known concentration of particles $\geq 0.5\mu$m, and the number of particles that penetrate into the critical areas where the product is open to contamination should be counted. The ratio of particles found at the critical area, to those seeded outside is then calculated and this ratio used as an indication of the risk of product contamination. The authors consider that if the ratio is 10^{-4} or better, then there is no chance of microbial contamination during production. This is a useful approach, but does not take into consideration the following variables: (a) the concentration of micro-organisms in the air outside the machinery, (b) the area of the product that is open to contamination, e.g. the neck of a container, and (c) the time that the product is exposed to contamination. Their method can be improved if account is taken of these variables.

If a settle plate is used to determine the deposition rate of the micro-organisms at the point of production, then the contamination of a product can be ascertained[11,12,13]. It is also possible to use sampling results from an active sampler, but deposition velocity of the microbe-containing particles has to be determined; the settle plate method is best. The following simple equation can then be used to determine the likely contamination rate of products:

$$\text{Contamination rate} = \text{Settle plate count} \times \frac{\text{area of product}}{\text{area of petri dish}} \times \frac{\text{time product exposed}}{\text{time settle plates exposed}}$$

This equation assumes that the settle plate count has been taken at the process filling point. However, if the settle plate count is taken in the area outside the machinery, and this count multiplied with the risk ratio then the count at the critical point can be estimated. The likely contamination rate of the product can then be ascertained. This is illustrated by the following example:

A cleanroom room where a machine and its air protection system is situated gives a microbial count of 30 from a 14-cm Petri dish (154 cm^2 area) exposed in the room air for four hours. The number of micro-organisms likely to deposit into the container of a neck area of 1 cm^2, when they are open during filling, for an average of 10 minutes, and when the risk factor ratio has found to be 10^{-3} is therefore:

$$10^{-3} \times 30 \times \frac{1}{154} \times \frac{10}{60 \times 4} = 0.000008 \text{ (i.e. 8 containers in } 10^6\text{)}$$

Comparisons can be made between different risk ratios, and hence the hazard assessed for a specific process.

CCCS Step 3: Identification of methods to control hazards

When all the contamination hazards in the cleanroom have been identified, and their degree of risk assessed, it is then necessary to review the methods available to control them. This is approximately equivalent to the HACCP requirement that critical control points should be identified. The importance of obtaining an effective control method should be related to the risk assessment described in Step 2; the greater the risk, the more effective the control method should be. It is also necessary to show

that the control method is effective. If it is not, then either a more effective control method should be adopted, or the control method applied to a different point or place. **Figures 1** and **2** show methods that can be used to control the routes of spread of contamination. These are:

1. HEPA air filters can be used to prevent any contaminants entering with the supply air. However, unfiltered air can pass through holes in damaged filters, or by-pass the filter owing to poor filter housing construction.
2. Airborne contamination from areas outside the cleanroom, e.g. outside corridors and service areas, can be prevented from entering the cleanroom by ensuring that the air moves from the cleanroom outwards, i.e. from clean to less clean. Air locks and/or a cascade flow of air through the doorways will ensure this. The use of adhesive cleanroom mats and flooring, as well as the removal, or covering, of dirty outdoor shoes prevents surface contamination being transferred into the cleanroom.
3. Although cleanroom air is a transfer route, it is also a source. Such airborne sources of contamination can be reduced by the use of a conventional turbulent ventilation system to dilute it, a unidirectional ventilation system to sweep it away, or an isolator to provide a barrier.
4. The possibility of transfer of contamination from surfaces such as floors, walls, ceiling, trolleys, etc. is minimised by cleaning and disinfecting, and any contamination that becomes airborne is controlled by ventilation.
5. People disperse contamination from their mouth, hair, clothing and skin. Cleanroom garments and gloves will minimise this dispersion, and contamination that cannot be controlled (as well as that produced by their clothing) can be minimised by the ventilation system.
6. Contamination from machines and ancillary equipment can be minimised by design, or by the use of local ventilation to control it, e.g. unidirectional flow or exhaust air systems. Cleaning and disinfection can control surface dirt and micro-organisms.
7. Raw materials, containers and packaging, should be uncontaminated. They should be made from suitable materials and manufactured in an environment that ensures that they have minimal concentrations of contamination on or within them. They should be correctly wrapped to ensure that they are not contaminated during delivery to the process, and that when the packaging is removed, contamination does not occur. Materials that are not sufficiently clean will require to be cleaned and either disinfected or sterilised; fluids can be filtered.

CCCS Step 4: Sampling methods to monitor hazards and control methods

It will now be necessary to set limits and monitoring methods to ensure that contamination of the manufacturing process is kept under control. This step is equivalent to the HACCP fourth principle. If air is taken as an example, then there are well-established methods of measuring particles and micro-organisms, and standards such as ISO 14644-1[16] and the EU guide to good manufacturing practice[1] should be used to set limits. However, if personnel handling the product cause the hazard, and the control measure is the wearing of gloves, monitoring could be by inspecting for punctures and tears in the gloves, or measurement of micro-organisms on the surfaces. Some well-known cleanroom hazards, their routes of transfer and control, and typical methods used to monitor them are given in **Table 2**.

Step 4 of the HACCP system requires that '*valid* sampling methods' be used. The term 'validate' is defined here as 'ensuring that something is fit for the purpose, or works well in the situation in which it is being used'. In terms of monitoring, the following may be need to be demonstrated to ensure that valid sample methods are being used:

1. Collection efficiency of sampling instruments;
2. Calibration of sampling instruments;
3. Determination that the hazard is of sufficient importance to need to be monitored, and if it is, the frequency of monitoring;
4. Determination that the sampling method used is the best available for *directly* measuring the hazard, or its control method.

The last two requirements are not easy to determine, but, if done scientifically in relation to the risk, they will ensure that monitoring effort is not wasted.

CCCS Step 5: Establishing a monitoring schedule with alert and action levels

In the third principle of HACCP there is a requirement to establish critical limits. In most pharmaceutical cleanrooms, the setting up of critical limits would be equivalent to establishing 'alert' and 'action' limits for environmental samples obtained during monitoring procedures. These limits can only be established after sampling methods have been decided upon, and some initial results obtained. Hence it is best that the principles of HACCP be re-arranged so that the limits are set now.

It is also necessary to consider the vulnerability of the product to microbial growth. This requires an assessment of both the likelihood of a micro-organism being deposited onto the product, and its chance of multiplying. The likelihood of a micro-organism being deposited into or onto a product is dependent on the area of the product that is open to contamination, and the time that it is open. Hence, a 500-ml bottle with a wide neck that is open to contamination for many minutes will have several magnitudes more microbial contamination than a closed ampoule that is opened and sealed in a few seconds. The likely rate of airborne contamination can be determined by the use of settle plate sampling and the use of the equations discussed at the end of Step 2[11,12,13]. The likelihood of the pharmaceutical products supporting the growth of micro-organisms should now be considered[17]. It is possible to assess the vulnerability of the product to this danger by submitting the product to growth tests with a selected range of micro-organisms[17]. If the product is

Table 2. Examples of sources, routes of transfer and control and monitoring methods used in cleanrooms.

Hazard	Route	Control method	Monitoring methods
Supply air	airborne	air filters	filter and filter housing integrity test
Areas adjacent to the cleanroom	airborne	overpressure; air movement	room pressure differential control
	contact	cleanroom mats	mat inspection
Various airborne dispersions	airborne	ventilation	air supply rate or velocity; counts of airborne particles; counts of airborne micro-organisms; control of airflow
Floors, walls and other surfaces	contact	cleaning (and, where required, disinfection)	surface contamination counts
Personnel	airborne	cleanroom garments	surface counts; inspection for tears; clothing testing
	contact	gloves	inspection for punctures; surface contamination counts
Machines	airborne	ventilation	air supply and extract rates; air-flow patterns and risk ratios
	contact	design of machine;	-
		cleaning or disinfection	surface contamination counts
Raw materials	mainly contact	control of manufacturing of raw materials	contamination counts within, or on, the materials.
		cleaning if solid, or filtration if fluid; sterilisation	filtration and sterilisation systems
Containers and packaging	mainly contact	control of their composition and manufacturing environment;	contamination counts on surface
		sterilisation	sterilisation system

likely to support growth then, logically, the environmental standards must be higher than products that have no nutritional base, or contain antimicrobial agents. The chances of the product being contaminated, as well as the probability that the micro-organism will grow, are important consideration that should influence the amount of effort needed to control contamination; these properties will help determine the alert and action limits to be set.

Some control methods may be continuously monitored, as is the case with a cleanroom's air supply and over-pressure. On the other hand, some inconsequential hazards, such as the ceiling surface, may not be monitored. The frequency of monitoring should be determined for each hazard or control method. This should be set up with due regard to the importance of the hazard: the higher the risk, the more frequent the sampling should be.

It is also necessary to decide what corrective actions should be taken when the monitoring result gives a higher result than expected. A normal approach in pharmaceutical manufacturing is to set 'alert' and 'action' conditions. The 'alert' level could be set to indicate that the contamination concentrations are higher than might be expected, but are still under control. Nothing will normally be done if the 'alert' level is exceeded, as this is a warning to be on the alert for future problems. However, several 'alerts' in a relatively short time, or an unusual result, might suggest that action is required. When the 'action' level is exceeded there must be an investigation. An assessment should be made as to whether it is a spurious result caused by natural variation, a mistake in the collection of the results, or a real result. For those results that are considered 'real', there should be an investigation by an agreed method; this should assess whether or not the result is acceptable and, if not, what action is required to bring the situation under control.

Analysing the monitoring results and setting 'alert' and 'action' levels is quite a complicated subject if a statistical approach is used. Knowledge of statistical techniques is required and a discussion of this topic is outside the scope of this paper.

CCCS Step 6: Verification and reappraisal of the system

A method must now be set in place to check that the system has been correctly implemented. This is equivalent to the sixth principle of HACCP.

Verification that the contamination control system is working well can be carried out by measurement of the particle or microbial levels in samples of the final product. Simulation of the process, e.g. filling containers with microbiological medium and ascertaining the microbial contamination, is a method also used in pharmaceutical manufacturing. As long as these give satisfactory results, then the system could be considered to be working well. However, depending on the vulnerability of the product to microbial growth, it is also possible at this time to attempt to reduce the contamination rate by introducing further controls. Another additional approach is to verify the effectiveness of the control measures by inspection and assessment of the monitoring results. However, this is not as rigorous a scientific method, as the contamination limits may have been incorrectly set at the level that is above the concentration that has any effect on the quality of the product.

We can now reassess the following:

1. The relative importance of the hazards
2. The necessity and the methods for controlling the hazards

3. The effectiveness of the control methods
4. The correctness of the monitoring schedule
5. Whether the 'action' and 'alert' levels should be lowered or raised.

It should be noted that this verification step requires an appraisal of both the requirements for controlling the hazard and to whether the 'alert' and 'action' levels need to lowered or raised. Many of the present-day quality assurance methods are based on the principle that if the standards can be improved, they should be. Little thought is given to whether they *need* to be improved and, inevitably, standards and financial costs are raised. A scientific approach requires a justification of the raising of standards. This may indicate that control measures should be reduced.

CCCS Step 7: Documentation

An effective contamination control system will document (1) the methods described in the preceding steps of this chapter, (2) the monitoring procedures and (3) results from the monitoring. These groups should be regularly updated to incorporate changes.

Regular reports should be issued of an analysis of the monitoring results and any deviations from the expected results. When 'action' levels are exceeded these should be reported. The actions taken to correct the deviations, or the explanations as to why no action was necessary, should also be documented. 'Alert' levels can also be reported, particularly those with a multiple or unusual occurrence.

CCCS Step 8: Staff training

HACCP does not specify in its principles that staff have to be trained. However, a reading of the various official publications concerned with HACCP require training in the principles of HACCP. This is clearly needed, but all efforts to control contamination through a scientific system will fail if the personnel working in the cleanroom are not trained. They should be trained to understand how the room works, and how to conduct themselves within the cleanroom to minimise contamination. They should be trained in these aspects of contamination, both when they first arrive at the cleanroom, and at regular intervals throughout their careers.

Conclusions and discussion

The purpose of writing this paper was two-fold. The first was to give an overview of the sources and routes of contamination in cleanrooms, and the means of controlling these. A good knowledge of these is necessary to control contamination in cleanrooms effectively. The second reason, which is the more difficult, was to discuss the application of the HACCP system to pharmaceutical manufacturing. The HACCP system has been written for the food industry and needs reinterpreting and modification for use in non-food cleanroom situations. It is hoped that this paper will assist in this.

The advantage of a HACCP-based system over what exists today in the pharmaceutical manufacturing is that it is scientifically based. Although existing methods of pharmaceutical manufacturing are scientifically based, there are aspects of a quality assurance based system that can be improved. At present, there is often little in the way of assessing the degree of risk of a hazard. This means that the methods of controlling a hazard, the alert and action limits set, and the frequency of monitoring may not bear a close relationship to the degree of risk of contamination. Clearly, this is a problem if a hazard has been underestimated, but the contrary is also true. It is the author's opinion that, in some parts of pharmaceutical manufacturing, both the control measures and the frequency of monitoring are too great for the actual degree of risk. Hospital patients must not get contaminated medicines. However, there is a point at which contamination control will fail to give improvements in the quality of the product and add to the cost of providing medicines. A contamination control system, such as described above, will give a scientific dimension to ensuring that there is a correct balance between too little and too much control.

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