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Assessing microbial risk to patients from aseptically manufactured pharmaceuticals

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The microbial risk to patients from aseptically manufactured pharmaceuticals is dependent on the chance that a product contains sufficient microbes to initiate an infection. This possibility is dependent on risk factors associated with the method of production and product formulation, and can be calculated. An analysis of these risk factors can be used to minimise patient risk and assist in determining the appropriate level of contamination control required for manufacturing.

Introduction

To determine the cleanliness standards required during pharmaceutical production, and the effort required to control and monitor the associated hazards, the degree of microbial risk to the patient should be considered. Products with a greater microbial risk require a cleaner environment, more effective controls, and more critical monitoring methods.

Regulatory authorities accept that pharmaceutical products with a low microbial risk to patients can be produced in an environment with lower cleanliness standards than products with a higher risk. For example, aseptically produced pharmaceutical products applied topically or administered via body orifices need not be sterile and can be manufactured in cleanrooms with lower environmental standards than those required for sterile products. It is also accepted that terminally sterilised products do not require as high cleanliness standards as those produced aseptically¹.

For aseptically produced parenterals, it is tacitly accepted that different pharmaceutical products have different risks of infecting a patient, and therefore require different cleanliness standards. Little or no advice is available on this topic, from regulatory or other sources.

Patients can be infected with microorganisms during the administration and use of pharmaceutical products. There is also a probability of a risk from the use of multidose containers. This paper does not consider these risks but only the risk from microbes in a product before administration to the patient.

Several factors influence the likelihood that a pharmaceutical product can infect a patient. These are:

1. The probability that a pharmaceutical product contains microorganisms immediately after manufacture. This depends on:
 - the likelihood of the product being contaminated during production, and,

- the treatments given to the product during, or at the end of production, that will kill or eliminate microorganisms.

2. The ability of the product formulation to support the growth or survival of microorganisms, from the completion of manufacture until administered to the patient, i.e. during its shelf life;

These risks are best assessed for a specific manufacturing area, process, product type and formulation.

Probability that a pharmaceutical product contains microorganisms immediately after manufacture

The probability that a product contains microorganisms immediately after manufacture is dependent on a microorganism being deposited onto it during manufacture, and whether any such microorganism is killed or eliminated during the process.

Microbial contamination during manufacture

An estimate of microbial contamination during manufacture can be obtained by the following methods.

Estimate from product simulation tests

The amount of microbial contamination during production is best estimated by process simulation tests (PSTs), such as carried out by filling containers with bacteriological growth promoting broth. PSTs do not simulate exactly the microbial contamination expected during routine production, as they are often devised to have a greater microbial challenge than normal e.g. there can be more process interventions. However, it is reasonable to consider that they usually estimate microbial contamination rates close to the 'worst case scenario'.

If sufficient product simulation tests have been completed this provides an estimate of the proportion of products contaminated at the end of production. However, during initial development of the manufacturing process, or if manufacturing has been established for a short time only,

there are unlikely to be sufficient results to provide a good estimate. In these cases it is best to enhance these results by further information obtained by risk assessment and calculation.

Estimate by risk assessment and calculation

The risk of microbial contamination during aseptic manufacture will vary according to the type of manufacturing process. Shown in **Table 1** is an indication of likely microbial contamination rates to be found during different types of aseptic manufacture. This table is based on known theoretical calculations, research and practical results.

It is known that that amount of airborne microbial contamination can be calculated from a fundamental equation that relates airborne contamination to:

- the surface area of the product exposed to the deposition of microorganisms from the air,
- the time the product is exposed and,
- the deposition rate of airborne microorganisms present in the critical area^{2,3}. It has also been established that the more frequently products are contacted by contaminated surfaces, such as gloves, the more likely they will be contaminated⁴. Thus, microbial contamination of the product has been shown to decrease as both the airborne and surface contact factors decrease, from about 1 in 10³ to less than 1 in 10⁶ products^{3,5}. It should be noted that the first row of **Table 1** suggests that for the associated type of manufacturing process there would be an unacceptable contamination rate of 1 in 10³. It would be abnormal with current manufacturing conditions to have such types of processes but, if they did exist, it is the likely contamination rate.

Table 1 only provides an approximation of the likely contamination rate. A more accurate alternative is to calculate the likely airborne contamination rate and then modify it by using an estimate of the risk of contamination caused by surface contact.

Most microbes exist in the cleanroom air rafted on particles of skin, their average size being between about 8µm and 20µm^{2,6}, and these microbe-carrying particles can deposit into, or onto, the product. The amount of deposition, and hence the airborne contamination of the product, can be calculated using the method described by Whyte and Eaton^{7,8}. In addition to this it is necessary to estimate the contamination from other sources such as surface contact. This is more difficult and is best done by using a risk assessment technique to compare the amount of contamination from non-airborne sources with the calculated amount of airborne contamination. Two such examples are given below, and based on the risk assessment method more fully explained in the paper of Whyte and Eaton⁸.

Example 1:

Containers with an internal neck area of 1cm² are open to

Table 1. Likely product contamination rates by microorganisms for various types of aseptic manufacturing

Type of process	Likely contamination rate
Product that has: (a) large area for deposition, (b) long exposure time, and (c) manual interventions occur often during production	1 in 10 ³
Product has two of the factors (a), (b) or (c) given above	1 in 10 ⁴
Product has one of the factors (a), (b) or (c) given above	1 in 10 ⁵
Product has small deposition area, a short exposure time, and there is little or no intervention during production	1 in 10 ⁶
Manufactured within a barrier system*	less than 1 in 10 ⁶

* isolator, or a unidirectional workstation with a physical barrier through which manipulations are carried out with gauntlets or half-suits.

airborne deposition for 1 minute; this is the time, after sterilisation, when the product is open to airborne contamination until closed.

The average number of airborne microbe carrying particles found to deposit onto settle plates of 14cm diameter (154cm²), exposed during filling in the filling area for over 100 exposures of 4 hours, was 0.1 per plate. The deposition rate i.e. the number of microbe carrying particles that will deposit onto a given area of surface in a given time (no.cm².h⁻¹) of the microorganisms in the filling area can be calculated from this settle plate data as follows.

Deposition rate (no.cm².h⁻¹) = average count on settle plate ÷ [area of plate (cm²) × time plate exposed (h)]

$$= 0.1 \div [154 \times 4] = 1.6 \times 10^{-4}$$

The number of microbe carrying particles that will be deposited from air onto, or into, a known area of the product (1cm²) open to contamination for a known time (1/60th hr) can now be calculated i.e.

Number of microbe carrying particles deposited from air onto the product = deposition rate (no.cm².h⁻¹) × surface area exposed (cm²) × time product exposed (h)

$$= 1.6 \times 10^{-4} \times 1 \times [1 \div 60] = 2.7 \times 10^{-6}$$

Because the activity of personnel is distributed through the process, airborne microbial deposition into the product will occur throughout manufacture and will be distributed randomly⁵. The number of microbe carrying particles deposited from the air i.e. 2.7 × 10⁻⁶ therefore relates to a contamination rate of 3 contaminated containers in 1,000,000 containers.

Filling was known to utilise a reliable automatic machine, which required very little attention or intervention, and a risk assessment concluded that the possibility of contamination from surface contact or other sources contributed very little additional contamination. It was therefore considered that the proportion of

containers contaminated during production was the same as that calculated for airborne contamination i.e. 3 containers in 1,000,000.

Example 2:

A solid product with a surface area of 2cm^2 was aseptically produced by a process that left the product exposed for 10 min. The average settle plate count was the same as for the previous example 1, and hence the deposition rate was $1.6 \times 10^{-4} \text{ .cm}^{-2}.\text{h}^{-1}$. The number of microbe carrying particles that will deposit from air onto the product can be calculated as:

Number of microbe carrying particles deposited from air onto the product = deposition rate ($\text{no.cm}^{-2}.\text{h}^{-1}$) \times surface area (cm^2) \times time product exposed (h)

= $1.6 \times 10^{-4} \times 2 \times [10 \div 60] = 5.3 \times 10^{-5}$ i.e. 5 contaminated containers in 100,000 containers.

The process machinery was complicated to set up and needed attention during normal production, and there were many unplanned interventions. A risk assessment concluded that the contribution of microbial contamination from surface contact and other sources was likely to be 10 times more than from the air and this factor was applied to give a contamination rate during production of 5.3×10^{-4} i.e. 5 contaminated containers in 10,000 containers

Chance of microbial contamination being killed during manufacture

The pharmaceutical industry uses steam sterilisation cycles with high temperatures and long holding times to ensure that there is a very high chance that all microbes, including temperature-resistant spore-bearing bacilli, are killed. However, much lower temperatures and times will kill many of the type of microorganisms found in cleanrooms. Similarly, some radiation, chemical and filtration treatments will also kill many of the cleanroom microorganisms.

Some aseptic production processes include stages where microorganisms are killed or eliminated. If, for example, products are held in an antimicrobial solution, or raised to a sufficient temperature, then vegetative, or even some of the mesophilic spore-bearing microorganisms of the type found in cleanrooms, may be killed. Consequently, a smaller number of products will be contaminated by microorganisms at the conclusion of manufacture, and the likelihood of a patient receiving a contaminated pharmaceutical product is reduced.

Microorganisms found in pharmaceutical cleanrooms come almost entirely from people. They are mostly vegetative bacteria, with occasional yeasts^{9,10}. Mesophilic spore-bearing bacteria are also occasionally found in cleanrooms, these being much more difficult to kill. It is the principal author's experience that the proportion of spore-bearing bacteria is likely to be between 1 in 100 and 1 in 500 of all the microbes found in cleanrooms. It is also the principal author's experience that spore-bearing bacteria can be reported more frequently, but this is likely

Table 2. Approximate survival factor scores and associated treatments.

Type of heat, chemical or radiation treatment	Microbial survival factor
No anti-microbial treatment	1
Heat, chemical, or radiation treatment effective against vegetative microbes	between 10^{-2} and 10^{-3}
Heat, chemical, or radiation treatment effective against spores	likely to be less than 10^{-3}

to be caused by identification methods that fail to confirm spore production and mistakenly identify some Gram-positive rods as *Bacillus* species.

Inspection of records at AstraZeneca, Macclesfield shows that 10 out of 1865 microorganisms isolated from production areas, and identified, were spore-bearing bacilli i.e. 1 in 187, or a proportion of 5.4×10^{-3} . Shown in **Table 2** is the proportion of microorganisms likely to survive different treatment processes; these proportions are termed in this paper as survival factor scores. If there is no stage in the process that uses heat, chemical, or radiation treatment then the microbial survival factor is taken as 1, i.e. all will survive. If the treatment is effective against vegetative microbes, the proportion of microbes likely to survive is the same as the proportion of spore-bearing bacilli present i.e. its survival factor score is between 10^{-2} and 10^{-3} (our value is 5×10^{-3} , as discussed above). If the treatment is effective against spores then the proportion of microorganisms that survive i.e. its survival factor score, will be less than 10^{-3} .

The values in **Table 2** give an indication of the proportion of microorganisms likely to survive a process, and can be used if no better information is available, or sought. A better estimate can be obtained by simulating, in the laboratory, the steps of the process where microorganisms might be killed. Suitable test microorganisms, typical of the type found in a cleanroom, should be used:

- a vegetative bacteria such as *Staphylococcus epidermidis* (NCTC 11047, equivalent to ATCC 14990),
- spores from a mesophilic spore-bearing bacteria such as *Bacillus atrophaeus* (ATCC 9372, equivalent to NCIB 8058), previously known as *Bacillus subtilis* var. *niger* and prior to that as *Bacillus globigii*. Its spores have been demonstrated to have mid-range thermal death characteristics similar to the type of bacterial spores found in manufacturing cleanrooms¹¹.
- any other microorganisms considered to be a problem within the manufacturing area.

The test microbes should be incorporated into the product and counts taken before and after a simulation of the treatment, and the proportion of surviving microorganisms determined so as to obtain a survival factor score.

Two examples of how the survival factor score might be determined are as follows:

Example 1 (first continuation): In the previously

considered Example 1, it was known that there was no heat, chemical, or radiation treatment applied to the product that would reduce the microbiological population. Therefore, the survival factor score was taken as 1 and the proportion of product contaminated remains as before.

Example 2 (first continuation): In the previously considered Example 2, it was known that at the end of the process the product was heated to 100°C to remove solvent contained within it, and this was considered to kill all vegetative bacteria. The spore-bearing bacteria in the cleanroom occurred as 1 in 200 of the total microbial flora, i.e. a proportion of 5×10^{-3} . It can be firstly assumed that no vegetative bacteria, but all of the spores would survive, and therefore a survival factor of 5×10^{-3} can be used. However, experiments were carried out that confirmed the solvent and heat treatment killed all vegetative bacteria but also 50% of the spore-bearing bacteria. This gave a likely survival of 1 in 400 i.e. a survival factor score of 2.5×10^{-3} .

In some processes a heat, chemical or radiation treatment may not be the last stage, and other stages of production may provide additional contamination risks. These risks should be calculated separately and the resultant probabilities added together.

Calculation of the overall chance that a product contains microorganisms at the end of manufacture

The overall chance that a pharmaceutical product contains viable microorganisms at the end of manufacture can be calculated by the use of **Equation 1**:

Equation 1

Overall proportion of product contaminated at the end of manufacture = proportion of products contaminated during production \times microbial survival factor score

Two examples have been given in the previous sections where the proportion of products contaminated during production and the microbial survival factor scores have been calculated. The chance that microorganisms might be present in the manufactured product at the end of production can now be calculated. It should be noted that both of the examples given assume that the manufacturing process is carried out in one phase. If the production is a multi-phased operation then the probability of contamination should be calculated for each phase and then added together to give the total product contamination.

Example 1 (second continuation): It was previously calculated that the proportion of containers contaminated during production was 2.7×10^{-6} and the survival factor score was 1. The final proportion of the product likely to be contaminated at the end of production therefore remains at 2.7×10^{-6} .

Example 2 (second continuation): It was previously calculated that the proportion of containers contaminated

during production was 5.3×10^{-4} and the survival factor score was 2.5×10^{-3} . The overall proportion of contaminated product at the end of production can therefore be calculated as follows:

Overall proportion of product contaminated at the end of manufacture = $(5.3 \times 10^{-4}) \times (2.5 \times 10^{-3}) = 1.3 \times 10^{-6}$

Therefore, the best estimate that the solid product considered in Example 2 has microbial contamination at the end of production is about 1 product in 1 million.

Risk from growth after manufacture

Little consideration has been given in the scientific literature as to what happens to microorganisms during the shelf life of the pharmaceutical product. If a product is contaminated, and remains contaminated during production then, during its shelf life, the microorganisms have been shown¹² to either:

- (a) die,
- (b) remain viable but not multiply, or
- (c) multiply to as many as 10^7 microorganisms per ml.

Products administered to a patient that contain a few dead microorganisms can be considered harmless, as there is insufficient toxin to cause harm. Products containing a few live microorganisms of the type found in cleanrooms i.e. from the skin of personnel can also be considered relatively harmless. This is supported by the fact that between 2.4% and 3.8% of needles used for injection will, as they pass through the epidermis, inoculate skin bacteria into the bloodstream¹³; this is not considered a source of infection. In addition, it is well established that people are resistant to microbial invasion, being constantly subjected to microbial invasion. Everett¹⁴ has reviewed this and reported that, for example, rocking of teeth during eating, bowel movements, etc, cause bacteria to enter the blood stream.

If microorganisms multiply in the product during their shelf life then this radically changes the risk of infection to patients, as a patient's immunological system has difficulty in dealing with a high dose of microbes, especially if these are of a more pathogenic variety. However, people are surprisingly resistant to invasion by microorganisms. For example, it is known that manipulation of skin boils will allow *Staphylococcus aureus* to enter the blood stream¹⁴ and Elek and Conen¹⁵ have shown that it needed between 10^6 and 10^7 of *Staphylococcus aureus* injected intradermally to initiate an infection. Sampling of surgical sites before closure has shown that hundreds of thousands of bacteria can be introduced into the wound during surgery without sepsis occurring^{16, 17}. However, the model we propose assumes that if a pharmaceutical product contains a large dose of microorganisms it presents a risk of infection to all patients.

Whyte *et al*¹² studied the growth of microorganisms in aseptically manufactured pharmaceuticals. Such pharmaceuticals were inoculated with a range of test microorganisms associated with the contamination of pharmaceutical products. It was found that:

- the majority of microbes died in the container within 4 weeks,
- Gram-negative bacteria were much more likely to grow than Gram-positive bacteria,
- an inoculum of a few bacterial cells could multiply to levels of up to 10^7 /ml,
- the presence of preservatives influenced the likelihood of growth; 12 out of 19 (63%) of the pharmaceuticals without preservatives supported growth of one or more microorganisms; only 3 out of 24 (13%) of those with preservatives supported growth.

For microorganisms to multiply, they require water, nutrition, and the absence of antimicrobial substances. Aseptically prepared products can be tested to determine if a product contaminated during manufacture will support microbial growth. The test suggested¹² is similar to the pharmacopoeial tests used to ascertain the efficacy of antimicrobial preservatives^{18, 19} but differs in that a small inoculum of test microorganisms of the type that might be found in the cleanroom environment is used. A 0.1ml inoculum of a 10^4 organisms/ml of thoroughly-washed bacterial cells is added to the product and the ability of the bacteria to grow, survive, or die over a period of up to 4 weeks at a temperature between 20°C and 25°C is determined. The determination of the growth of test microbes in a given product, along with a knowledge of the proportion of microbes in the cleanroom that are similar to the test microorganisms, can be used to determine the chance of microbes multiplying in the product.

The microbial flora of a cleanroom is predominantly made up of Gram-positive bacteria with a small proportion of Gram-negative bacteria. Gram-positive bacteria are generally much more fastidious in their growth requirements than Gram-negative bacteria and therefore much less likely to grow in pharmaceutical products. Consequently an aqueous solution, or emulsion, that supports the growth of Gram-positive bacteria typical of many of the microbes found in a cleanroom e.g. *Staphylococcus epidermidis* (NCTC 11047, equivalent to ATCC 14990) is likely to support the growth of many other microbes in a cleanroom and the product is at high risk. Because of this, a growth risk score of 1 i.e. all will grow, may be allocated.

Gram-negative bacteria will grow in products that do not support Gram-positive bacteria, as they can grow in low concentrations of nutrition, and even in solutions of preservatives¹². However, Gram-negative bacteria are less common in the cleanroom environment. Out of 1865 isolates identified in AstraZeneca in Macclesfield, 11 were Gram-negative i.e. a proportion of 5.9×10^{-3} . *Acinetobacter* species are the most frequent of the Gram-negative skin microorganisms found in cleanrooms⁹ and *Acinetobacter lwoffii* (NCTC 5866, equivalent to ATCC 15309) can be used as a suitable test organism. If an aqueous solution or emulsion supports the growth of this Gram-negative test organism, it is reasonable to assume that most Gram-negative bacteria are likely to grow in the product. The proportion of microbes that are likely to grow can therefore be taken as the proportion of Gram-negative bacteria in the cleanroom i.e. about 5.9×10^{-3} ,

and this should be allocated as the growth risk score.

In Whyte's experiments, *Burkholderia cepacia* (NCTC 10743, equivalent to ATCC 25461) was the most aggressive grower and would grow when no others would. This fact, and the low frequency of occurrence of this type of microbe suggests that if this organism grows in a product a growth risk score of about 1×10^{-4} should be allocated.

Products that will not support the growth of any of the test organisms will have a very low chance of supporting the growth of any microbes typically found in the cleanroom. The allocation of a growth risk score of less than 1×10^{-4} for this type of product is a reasonable starting point. The score can then be refined by using a risk assessment of the likelihood of microbial growth with respect to the nutritional and antimicrobial properties of the product.

For microorganisms to multiply, they require water. Oils, water-free ointments, powders, freeze-dried, and any other water-free pharmaceutical products, will not support the growth of microorganisms, which will be suspended in animation, or die. The allocation of a growth risk score of 1×10^{-4} , or less, for these types of products is a reasonable starting point. If the product is freeze-dried there is a small possibility of growth of microorganisms before freeze-drying. However, this is unlikely because of the restricted time, the bacterial lag phase, the low growth temperature, and possible poor nutrition of the product; this is the experience of the principal author. However, this likelihood can be determined by carrying out the growth tests suggested above on the product prior to freeze-drying, using as an incubation time the time between filling and freeze-drying, and an incubation temperature close to room temperature. Proper statistical methods should be used to demonstrate a significant increase in growth.

Table 3 gives estimates of the proportion of microbes found in a cleanroom that are likely to grow in different products i.e. microbial growth risk scores. This can be used during the design of the manufacturing process, as the actual type and proportion of microorganisms to be found during manufacture will not be known. However, the growth risk scores given in **Table 3** are approximations to be used if firm data is not available, or sought. A more accurate estimate of risk can be obtained if the actual microorganisms isolated during manufacture are tested to see if they will grow in the product. The microorganisms used should reflect their exact proportion of occurrence in the cleanroom environment. The proportion that grows in the product can then be used as an accurate estimate of the microbial growth risk score. Thus, if 2 out of 100 microorganisms isolated in the cleanroom environment were found to grow in a product, the microbial growth risk score is 2×10^{-2} .

Overall assessment of product risk prior to patient administration

The overall microbial risk to patients through infection can now be assessed. By combining:

- (a) the proportion of products containing microorganisms at the end of manufacture, and

- (b) the ability of microbial contaminants to grow in a pharmaceutical product during its shelf-life, an overall risk to patients from infection can be obtained. This is shown in **Equation 2**, with the risk to patients being considered as the probability that a product contains a large dose of microorganisms prior to administration to the patient:

Equation 2

Risk to patient = proportion of products containing microorganisms after manufacture \times proportion of product that will support microbial growth i.e. growth risk score

The two risk factors are best entered into the equation as proportions i.e. 1 in a million should be entered as 1×10^{-6} , and total risk to patients given in the same style. By taking a negative value of the logarithm of the total risk to patients, a simpler value can be obtained and known as a 'Patient Risk Index' e.g. 1×10^{-6} gives a Patient Risk Index of 6. It should be noted that the higher the Index number, the lower the risk to the patient.

Two examples of how this can be calculated are now given:

Example 1 (third continuation): The product considered in the previous Example 1 was estimated to have a proportion of contaminated containers at the end of production of 2.7×10^{-6} . It was known that the product was an aqueous product and it was found that one microorganism out of 997 isolated from the cleanroom environment would grow in the product i.e. a proportion of approximately 1×10^{-3} ; this is the microbial growth risk score.

The total risk to the patient, which is the probability that the product at administration will contain a large dose of microorganisms is calculated as follows:

$$\text{Risk to patient} = 2.7 \times 10^{-6} \times 1 \times 10^{-3} = 2.7 \times 10^{-9}$$

Therefore, the Patient Risk Index = $-\log [2.7 \times 10^{-9}] = 8.6$

Example 2 (third continuation): The product considered in the previous Example 2 was found to have an estimated contamination rate at the end of production of 1.3×10^{-6}

The product was freeze-dried and hence there should be no growth during the shelf life. It was also demonstrated that there would be no growth of microbes in the product prior to freeze-drying. However, the few microorganisms held in suspended animation might have a small amount of patient risk and hence a microbial growth risk score of 1×10^{-5} was allocated and the risk to patients calculated as follows:

$$\text{Risk to patients} = 1.3 \times 10^{-6} \times 1 \times 10^{-5} = 1.3 \times 10^{-11}$$

Therefore, the Patient Risk Index = $-\log [1.3 \times 10^{-11}] = 10.9$

Table 3. Approximate growth risk scores given in relation to the type of product and its ability to support growth of different types of microbes.

Pharmaceutical formulation	Risk of growth associated with formulation and test organisms	Microbial growth risk score
aqueous solution, or emulsion	<i>Staphylococcus epidermidis</i> grows – high risk of product supporting growth of many microbes found in cleanroom	1
aqueous solution, or emulsion	<i>Acinetobacter lwoffii</i> grows – some microorganisms in cleanroom will grow – some risk	about 5×10^{-3}
aqueous solution, or emulsion	<i>Burkholderia cepacia</i> grows – only very few species of microbes will grow – low risk	about 1×10^{-4}
aqueous solution, or emulsion	No microorganisms grow – very low risk	$\leq 1 \times 10^{-4}$
freeze-dried / powder/ oil / water-free ointment	no growth likely – very low risk	$\leq 1 \times 10^{-4}$

Discussion

The object of this paper is to provide a method to assess the microbial risk to patients receiving aseptically produced pharmaceuticals. No predictive model exists at present. The probability of a patient being at risk is considered to be dependent on whether or not the product is contaminated during production, and whether its formulation allows the growth of microorganisms during the shelf life.

The first component of the risk assessment model is the proportion of products likely to contain a microorganism at the end of production i.e. before storage. This probability is dependent on the chance of a microbe being deposited or entering a product during manufacture, and the chance that any microbe introduced will be killed or eliminated by some step in the process that has sufficient heat, chemical or radiation. The second component of the risk assessment model is the chance that the microbes introduced during production will survive and grow in the product during the shelf life. Methods are given by which these proportions can be calculated. These two proportions are multiplied together to calculate the risk to patients from infection. If several production phases are involved in the manufacturing operation then all the contamination probabilities must be calculated and added to obtain an overall risk. A Patient Risk Index may then be calculated.

Evidence is presented in this paper to show that patients are unlikely to be at risk from a few microbes administered with a product, as the human body continually deals with the entry of microorganisms. Patients with an unimpaired immunological system can also deal with relatively large doses of microorganisms of low and even high pathogenicity. However, the basis of the Patient Risk Model is that patients are at risk if they receive a product with a large dose of any type of microorganism.

The proposed model does not consider individual or unusual risks but predicts the risk to the whole patient

population. Thus, it is possible that a proportion of immuno-compromised patients may be infected with a small dose of microbes. However, the basis of the model i.e. a large dose of microbes is a danger to a patient, still applies to immunological deficient or similar patients, although the model may underestimate the risk.

The Patient Risk Model assumes that aseptically manufactured products may be occasionally contaminated during manufacturing. As long as personnel are involved in the manufacturing process, they will disperse microbes into the environment and there will always be a risk, however small, of products being contaminated. Sterility of all products is impossible. However, it was calculated in two examples given in the paper that the risk of a patient receiving a large dose of microorganisms, was in the region of 1 in 10^9 to 1 in 10^{11} . This is very reassuring, especially when compare to the high chance of contamination occurring during administration of the product to the patient²⁰.

The risk model discussed in this paper can be used to calculate the patient risk in the product design stages. The risk of a formulation supporting growth can then be optimised to reduce the risk. The manufacturing process and facility can also be designed to reflect the type of product and to minimise the microbial risk within the facility. The risk model can also be used in an established cleanroom manufacturing operation to assess and optimise the process to minimise microbial contamination and ensure that the risk is adequately controlled and monitored; methods for managing risk in a manufacturing cleanroom are described elsewhere⁸. Finally, it is also clear that the regulatory authority resources are not infinite. If, as implied in a recent FDA publication²², more scrutiny should be reserved for the facilities where the product is most at risk, an assessment using the above method should be of assistance.

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