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Specification of limits for particulate contamination in pharmaceutical dosage forms

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Limits for the control of particulate contamination in large volume parenteral solutions and metered-dose aerosols are discussed. It is suggested that it would be desirable to use limits based on measurement of both the mean and the standard deviation of the particle counts obtained for each of the containers tested. Use of the statistic s_T, assuming a target value of zero, is considered to be an appropriate means of measuring the container to container variation in particulate contamination.

Considerable effort has been devoted to the development of adequate analytical methods and appropriate limits for particulate contamination in large volume parenteral products (LVP's). Use of apparatus relying on the light blockage principle has been widespread in the pharmaceutical industry and has formed the basis of Australian official testing of this type of product for many years (Proposed General Standard for Injections 1974). The British Pharmacopoeia (B.P. 1980) specifies the use of apparatus based either on electrical resistance zone sensing (Coulter counter) or light blockage. The United States Pharmacopeia (U.S.P. XX) has adopted microscopy as its primary method, while permitting the use of other methods if these can be shown to have equivalent reliability.

All three of these standards make use of a two point specification, stated in terms of the number of particles above a certain size (equivalent diameter) which are present in a container. These requirements are summarized in Table 1. The pharmacopoeial requirements for particulate matter in LVP's are not specific with regard to the number of containers to be tested. The requirements of the B.P. 1973 were framed with respect to a sample of five containers but reference to sample size is not made in the 1980 edition. The U.S.P. XX requirements include a caution that 'statistically sound sampling plans based upon a known set of operational factors must be elaborated if valid inferences are to be drawn from the observed data to characterize the level of particulate matter in a large group of units'. Both the B.P. and U.S.P. monographs specify definite limits which apply to all containers tested. Any container fails if its contents have a count for particulate matter which exceeds the limit. It is unclear whether a failure of the pharmacopoeial tests by one container in a sample implies that the whole sample should also fail.

The approach adopted at National Biological Standards Laboratory (NBSL) has been to consider the mean and standard deviation of the results from ten individual containers, and has been discussed by Kendall (1969). The limit at present in use for particles which have effective diameters greater than 5 μm is that the mean particle count is not more than 100 particles ml^{-1} and that the sum of the mean and twice the standard deviation is not more than 200 ($\bar{x} \leqslant 100$; $\bar{x} + 2s \leqslant 200$).

The NBSL specification attempts to take into account the appreciable variation in particulate contamination which frequently occurs in samples of LVP's. The results of testing this type of product at NBSL indicate that the standard deviation for a sample of ten containers is commonly of the order of half the mean particle count (Kendall 1969). The pharmacopoeial requirements for content of particulate matter in LVP's give no indication of actual distribution of levels of contamination between containers and imply that all containers with particle counts above the specified limits are equally bad while all those passing the test are equally good. In fact, the situation is more likely to bear some resemblance to the considerations of uniformity of content of active substance discussed by Flann (1974).

All particles in an LVP container have a potential to cause an adverse reaction, and Groves (1973) has pointed out that the number of foreign particles is relevant to the hazard presented to a patient. Thomas & Lee (1974) have reviewed the earlier literature on particles in intravenous solutions. Adverse effects due to particulate contamination included formation of foreign body granulomas,

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Table 1. Official requirements for particulate matter in large volume parenterals.

Standard	Method	Particle size	Number of particles/ml permitted	No. of containers
B.P. 1980	Conductivity	>2 μm	1000 (conductivity)	Not specified
	or		500 (light blockage)	
	Light blockage	>5 μm	100 (conductivity)	
			or 80 (light blockage)	
U.S.P. XX	Microscopy (or other method of demonstrated equivalent reliability)	>10 μm	50	Number not specified, caution on need for suitable sampling plan
		>25 μm	5	
Draft Australian Standard	Light blockage	> 5 μm	100 and $\bar{x}$ and $2s \leq 200$	10, with 5 × 50 ml samples taken from container
		>20 μm	2 and $\bar{x} + 2s \leq 4$	

platelet agglutination and thrombi formation. Turco & Davis (1971) suggested that pulmonary oedema may sometimes be due to particulate damage in the lungs rather than to volume overload. Wildsmith (1978) refers to autopsy studies which have shown granulomatous reactions around fibre like and crystalloid material in the pulmonary vessels of patients who received intravenous infusions. Dorris et al (1977) have demonstrated that removal of particles by an in-line filter reduces the incidence and severity of infusion phlebitis. De Luca (1979) has commented that it is naive to assume that particles in parenterals are not detrimental, especially if administered in large quantities and for extended periods of time.

It is reasonable to assume that the probability of adverse reaction will be proportional to the number of particles. In addition to serving as a safeguard against the risk of adverse reactions, a test for foreign particles in LVP's is also a measure of the cleanliness of manufacturing conditions. As numbers of particles vary appreciably from container to container, it seems appropriate to control levels of this type of contamination with a limit that takes into account the container to container variation by use of a statistic such as standard deviation. Use of a limit which links the mean count with standard deviation makes better use of available data than a test by attributes and reduces the risk of a container with a high particle count being available for use.

The statistic s_T (root mean square deviation about target) has been applied to the control of uniformity of content of solid dosage forms (Kendall et al 1981). The statistic has characteristics which are helpful in forming suitable official requirements, and conveniently controls both the mean and the variation about the mean. Consideration has been given to the use of the statistic s_T in setting limits for content of a contaminant (particulate matter). The statistic is defined by the expressions:

$$s_T = \sqrt{[\Sigma(x - T)^2/n]}$$
$$= \sqrt{[s^2(n - 1)/n + (\bar{x} - T)^2]}$$

where $\bar{x}$ is the mean value of n results, s the standard deviation and T the target value (the value of the attribute being measured in an ideal sample). In the case of an LVP, an ideal sample would have no particles. The target value for particulate matter contamination in this case is zero, and:

$$s_T = \sqrt{(\Sigma x^2/n)}$$
$$= \sqrt{[s^2(n - 1)/n + \bar{x}^2]}$$

A limit for content of particles with diameters greater than 5 μm which specifies a value for s_T of not more than 100 is comparable to the linked limit

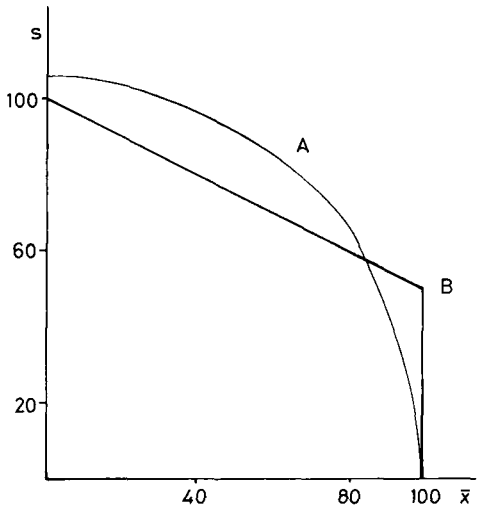

FIG. 1. Variation of permitted standard deviation with particle count. Curve A $s_T \leq 100$. Curve B $\bar{x} \leq 100$; $\bar{x} + 2s \leq 200$.

for mean and standard deviation used at present by NBSL. Fig. 1 shows plots of permitted standard deviation against mean count of particles ml^{-1} given by the limits $s_T \leqslant 100$ (curve A) and $\bar{x} \leqslant 100$; $\bar{x} + 2s \leqslant 200$ (curve B). The areas below the curves correspond to the conditions which meet the requirements for content of particulate matter. It is apparent that the limit given by the statistic s_T is more

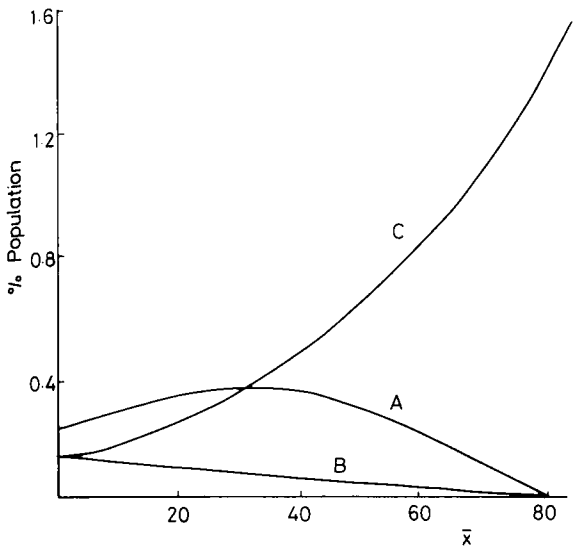

FIG. 2. Variation of percentage of population with counts of more than 300 particles ml^{-1} with particle count. Curve A $s_T \leqslant 100$. Curve B $\bar{x} \leqslant 100$; $\bar{x} + 2s \leqslant 200$. Curve C $\bar{x} \leqslant 100$; $s \leqslant 100$.

lenient over most of the permitted range for $\bar{x}$ and does not have a discontinuity at $\bar{x} = 100$. At the lower end of the range of $\bar{x}$, the permitted value for s tends to a limiting value (105·41 in this case) as the value for $\bar{x}$ tends to zero.

Fig. 2 shows the variation with particle count of the proportion of containers expected to have counts of more than 300 particles ml^{-1}. Curve A corresponds to a limit defined by $s_T \leqslant 100$, curve B to $\bar{x} \leqslant 100$; $\bar{x} + 2s \leqslant 200$, and curve C to the case where mean and standard deviation are permitted to vary independently, that is $\bar{x} \leqslant 100$; $s \leqslant 100$. The advantages of using a limit in which $\bar{x}$ and s are linked are obvious. If these statistics are allowed to vary independently, as represented by curve C, the chance of a patient receiving the contents of a container which is badly contaminated is greatly increased.

Data from tests carried out on eight commercially available LVP's are presented in Table. 2. The data refer to the number of particles ml^{-1} with effective diameters greater than 5 μm and in each case a sample size of ten containers was used. For each sample, the values for mean particle count ($\bar{x}$), $\bar{x} + 2s$, s_T and highest particle count are given and also the number of containers with counts of more than 100 particles ml^{-1}. Sample A would pass the B.P., Australian and s_T requirements. Samples B–D would pass the Australian and s_T requirements but, if all containers are considered, would presumably fail B.P. requirements as some containers have counts of more than 100 particles ml^{-1}. In these cases, it might be necessary for an analyst working to the pharmacopoeial limits to exercise judgement as to whether the 'high count' containers should be treated as rare events and the sample passed or if the compendial limits should be strictly applied and the sample failed. Sample E passes the Australian requirements, but fails the s_T test which is more stringent on samples near the limit for mean particle count which also have significant standard deviation. Samples F–H fail both the Australian and s_T requirements. In these three cases it is of interest that some containers complied with B.P. limits. In Sample H, for example, if only one container were tested, there would be a 20% chance of passing a sample with a

Table 2. Data on contents of foreign particles in large volume parenteral products.

Sample	Mean particle count ($\bar{x}$)	$\bar{x} + 2s$	s_T	No. of containers >100 particles	Highest particle count	Compliance with limits		
						B.P.	Australian draft standard	s_T
A	36·7	60·4	38·8	Nil	78	Pass	Pass	Pass
B	45·8	124·0	58·9	2	124	Fail?	Pass	Pass
C	61·3	123·1	68·0	1	130	Fail?	Pass	Pass
D	69·4	111·4	72·2	2	103	Fail?	Pass	Pass
E	100·0	134·4	101·3	3	134	Fail	Pass	Fail
F	103·2	122·5	126·1	7	114	Fail	Fail	Fail
G	121·5	192·5	126·1	8	189	Fail	Fail	Fail
H	137·1	230·6	144·1	8	219	Fail	Fail	Fail

All counts refer to the number of particles per ml with diameters greater than 5 μm. Each sample consisted of ten containers.

mean count of 137 particles ml^{-1}. The converse situation is illustrated by Sample D, where if only one container were tested there would be a 20% chance of failing a sample with a mean of 69·4 particles ml^{-1}. Use of limit which is based on a realistic sample size, and makes efficient use of available data, overcomes difficulties of this sort and enables the analyst to make a more valid judgement on the quality of a product.

The approach adopted in the use of s_T assumes that sufficient containers are available to the official analyst to carry through the proposed sampling scheme. The experience of this laboratory has been that ten or more LVP containers are usually available for testing. In the situation where only a single container is available, the limiting value for $\bar{x}$ implicit in the equation for s_T provides a guide to the acceptability of the one-unit sample.

Metered dose aerosols

Metered dose aerosols for oral inhalation are another type of dosage form where foreign particles (typically plastic, rubber and aluminium from the aerosol valves and containers) can readily be introduced into the body. Control of the level of foreign particles in order to minimize adverse reactions is desirable. A test which has been developed by NBSL for measuring foreign particles in metered-dose aerosols (Proposed Standard for Metered Dose Aerosols 1980) makes use of microscopy to count all particles with longest dimensions of greater than 100 μm (Lea et al 1981). A sample size of ten aerosol containers is used and the total contents of each can are sampled. The limit for content of foreign particles is expressed as the total number of particles per container. In a survey conducted by these workers, it was found that the mean numbers of particles per container for a number of commercial products were less than 150 with standard deviations of between 7 and 25% of the means. The container to container distribution of particulate contamination is therefore narrower than is the case with LVP containers. From the data obtained (Fig. 3) it appeared that the products tested would in general comply with the limit $\bar{x} \leqslant 150$; $\bar{x} + 2s \leqslant 200$ (Curve B). Each data point in this Figure corresponds to the results obtained from a sample of ten aerosol containers. As noted above, this type of limit produces a discontinuity. In this case, use of the statistic s_T as an alternative limit presents problems because of the apparent narrowness of the inter-container distribution of foreign particles. If the limit is set at $s_T \leqslant 150$, the requirements (Curve A) are

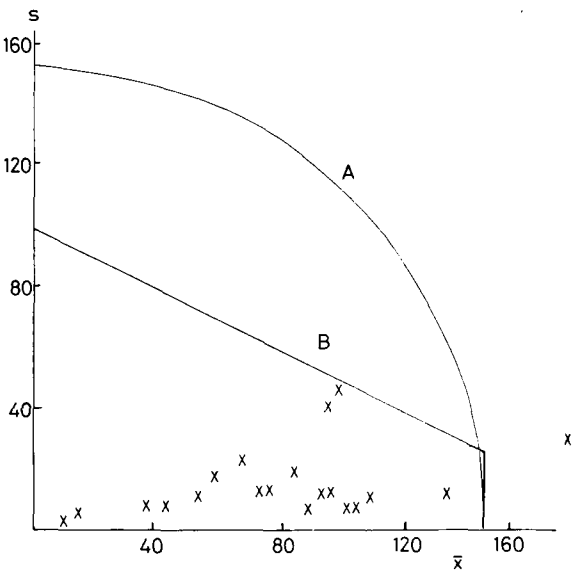

FIG. 3. Foreign particulate matter data for metered-dose aerosol products. Each data point refers to results obtained from ten individual containers. The limit curve corresponds to $\bar{x} \leqslant 150$; $\bar{x} + 2s \leqslant 200$.

very lenient in terms of what is currently achieved by manufacturing industry. If a lower value for s_T is specified, a number of products with low standard deviations would fail. A possible solution is to introduce constants into the equation for s_T, so that the shape of the characteristic produced is such that the limit curve corresponds more closely to the linear plot given by $\bar{x} + 2s = 200$. If the modified statistic is termed s'_T, then:

$$s'_T = \sqrt{[as^2(n - 1)/n + \bar{x}^2/b]}$$

where a and b are constants. Increasing the value of a in the equation will produce flatter curves with lower permitted values for the standard deviation, while increasing the value of b has the effect of extending the standard deviation versus $\bar{x}$ characteristic to higher values of $\bar{x}$.

Fig. 4 shows plots of s against $\bar{x}$ for $s'_T = 150$ in the cases where a = 3, b = 1 (Curve A) and a = 3, b = 1·2 (Curve B). A plot corresponding to $\bar{x} \leqslant 150$; $\bar{x} + 2s \leqslant 200$ (Curve C) is included for comparison. Curves A and B appear to provide suitable alternatives to the linear condition. Fig. 5 shows the variation with $\bar{x}$ of the expected proportion of units having particle counts of greater than 300 for each of these limits. Curves A and B, corresponding to $s'_T \leqslant 150$, permit a higher proportion of aerosol cans with high particle counts than does curve C but provide reasonable consumer protection and some latitude for manufacturer.

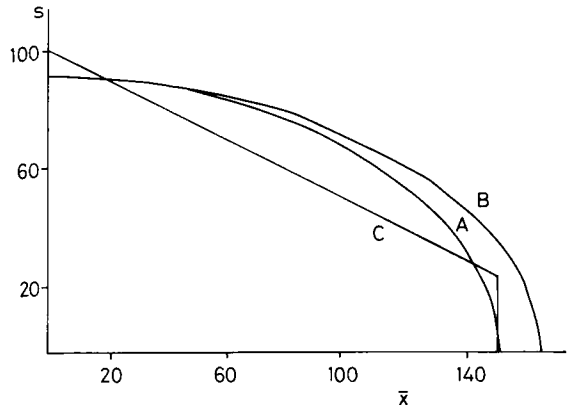

FIG. 4. Variation of permitted standard deviation with particle count. Curve A $s'_T \leqslant 150$; a = 3; b = 1. Curve B $s'_T \leqslant 150$; a = 3; b = 1·2. Curve C $\bar{x} \leqslant 150$; $\bar{x} + 2s \leqslant 200$.

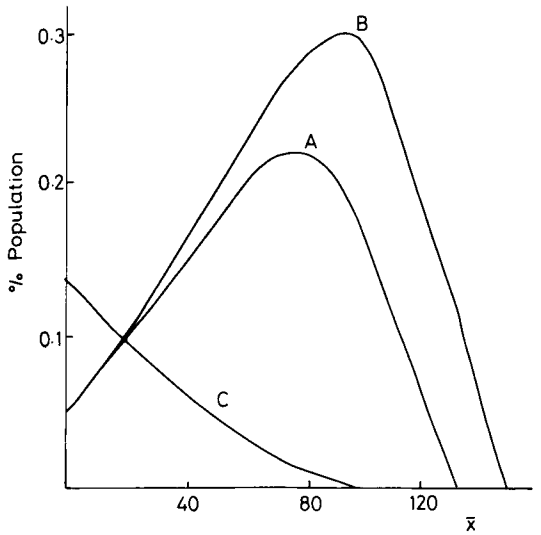

FIG. 5. Variation of percentage of population with particle counts of more than 300 particles per container with particle count. Curve A $s'_T \leqslant 150$; a = 3; b = 1. Curve B $s'_T \leqslant 150$; a = 3; b = 1·2. Curve C $\bar{x} \leqslant 150$; $\bar{x} + 2s \leqslant 200$.

Problems with the use of the statistic s_T in the control of particulate contamination

A possible objection to the use of the statistic s_T based on zero target is that this represents an impossible goal, a level of cleanliness that can never be achieved. Zero particle count is not achievable with LVP's, although very low counts have been obtained on some batches of metered-dose aerosols, so that the ideal of no foreign particles greater than 100 μm may be approached in certain cases. However, use of the concept of zero contamination seems reasonable provided that unrealistic constraints on manufacturers are not introduced. There is no compulsion on manufacturers, in the use of an s_T-based limit, to achieve near-zero levels of particulate contamination. The target of zero is an ideality which defines a suitable scale for the expression of uniformity of particulate contamination.

An alternative approach would be to use a non-zero target, but this would introduce additional problems. In the first place, a non-zero target would introduce an arbitrary definition of cleanliness into the requirements. It would also be unrealistic to consider instances where the counts were less than target, so that any standard would have to be phrased in a somewhat cumbersome fashion. More seriously, if the same limits for s_T were used, the stringency of the requirements would be reduced because of the decreased deviation from target. Fig. 6 shows plots of s versus $\bar{x}$ for the cases where $s_T \leqslant 100$, T = 0 and $s_T \leqslant 100$, T = 30. The higher permitted standard deviation in the second instance could result in a higher proportion of badly contaminated containers being available in a batch.

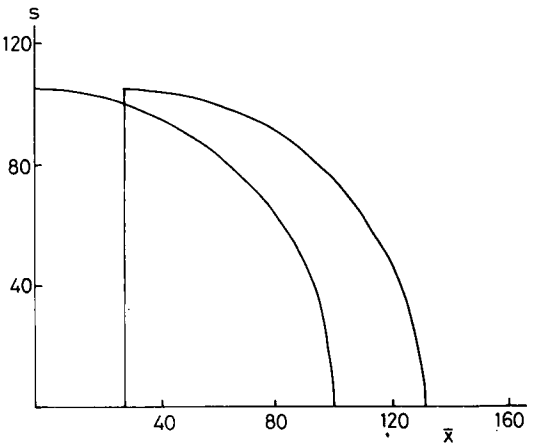

FIG. 6. Variation of permitted standard deviation with particle count for $s_T \leqslant 100$, T = 0 and $s_T \leqslant 100$, T = 30.

An operational problem, which will affect other methods of expressing limits for particulate contamination, is that the precision of some counting methods will be relatively poor close to the target value because of instrumental noise, counting errors and apparatus-generated particles. These factors will reduce the confidence that can be placed in the value obtained for s_T. The problem would seem, in practice, to be non-critical as the increased permitted standard deviation close to target would compensate for methodological problems. A low particle count

will indicate an acceptable product, and there is no need to place a premium on high accuracy as the target is approached.

A further operational difficulty in the framing of requirements for uniformity of content of a contaminant in LVP's or metered dose aerosols is that the sample size will be relatively small because of the tedium of the test methods and the cost of the dosage units. The Australian requirements for both LVP's and metered dose aerosols specify a sample size of 10, which is seen as appropriate in terms of cost, laboratory workload and speed of testing. The arguments and data on the effect of sample size put forward by Flann (1974) with respect to tests for uniformity of content of active substance are also applicable to tests for uniformity of content of a contaminant. An appreciable increase in reliability can be expected in going from a sample size of ten dosage units to one of twenty units for any type of limit. With present methods, an increase in sample size of this magnitude is not considered feasible, and the benefits of the greater reliability inherent in testing larger numbers of dosage units must await the arrival of improved testing technologies.

The types of limit for concentration of a contaminant proposed in this communication are considered to be desirable from the point of view of protecting the consumer from the chance of receiving a badly contaminated product. The suggested limits for LVP's and metered-dose aerosols have been framed with regard to the levels of cleanliness currently achievable by manufacturers of these products and would not present difficulties for industry. The suggested s_T-based limits are in general rather more lenient than the type of limit based on the mean plus twice the standard deviation which is already widely accepted by industry in this country. It is suggested that limits for content of particulate matter based on the statistic s_T would be appropriate in future specifications for therapeutic goods.

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