Sampling Plan for Cleanroom Classification with Respect to Airborne Particles

Niels Væver Hartvig, Novo Nordisk A/S
Gordon J. Farquharson, Critical Systems Ltd.
Robert Mielke and Mark Varney, Abbott Laboratories
Mike Foster, Consultant

Abstract

The concentration of airborne particles is a critical parameter for cleanrooms, clean zones, and controlled areas. Particle concentration must be measured at representative locations for classification and monitored routinely or continuously at critical locations during operation. Both ISO 14644-1:1999[1] and the new Draft International Standard (DIS) edition provide nine classes of cleanliness and specify both the number of sample locations for classification and the acceptance criterion for the data.

In the 1999 version of the Standard, the minimal number of sample locations is not based on statistical principles. The acceptance criterion is based on a statistical test, but only if the number of sample locations is less than 10. Thus, classification is based on statistical methods only for a small number of locations.

The revised ISO/DIS 14644-1[2] replaces this method with a statistical principle for selection of the sample locations. The acceptance criterion in the revised version eliminates the need for applying a statistical test to the data, and thereby simplifies the classification process.

The purpose of this paper is to present and discuss the new sampling plan for cleanroom classification and compare it with the previous approach in ISO 14644-1:1999. Section 2 of this paper presents and discusses the previous method, section 3 describes the new method in the ISO/DIS 14644-1 revision, and section 4 provides a discussion and conclusion. All of the authors are members of ISO Technical Committee (TC) 209, Working Group 1, the group of experts who developed the new ISO/DIS 14644-1. This paper was written on behalf of the entire Working Group.

KEYWORDS

Cleanroom, particle concentration, airborne particle, sample location, classification, statistical sampling

INTRODUCTION

The concentration of airborne particles is a critical parameter for cleanrooms, clean zones, and controlled areas. The particle concentration must be measured at representative locations in the room when classifying the room and during periodic re-classification. Additionally, the particle concentration must be monitored routinely or continuously at critical locations during operation. The number and placement of sample locations for classification is an important choice in this measurement process, as is the acceptance criterion for the data.

Both the 1999 Standard and the new Draft International Standard (DIS) edition of ISO 14644-1 provide nine classes of cleanliness, where the maximum allowed particle concentration is specified as a function of the particle size for each class. Both ISO 14644-1:1999[1] and the new ISO/DIS 14644-1[2] also specify the number of sample locations for classification and the acceptance criterion for the data.

In the 1999 Standard, the minimal number of sample locations is not based on statistical principles, but is given as the square root of the area of the cleanroom or clean zone, measured in

square meters. The acceptance criterion is based on a statistical test, but only if the number of sample locations is less than 10. In the process of revising the Standard, it was realized that the objective of the statistical test is not entirely appropriate, and that it is unfortunate that the classification is based on statistical methods only for a small number of locations.

A new principle for selection and acceptance of the sample locations has therefore been incorporated into the revised ISO/DIS 14644-1. A central element is that the measurement locations must be selected randomly in the room, and that new locations must be selected at every re-classification. ISO 14644-1:1999 did not prescribe how to select locations, but it is common practice to select these on a regular grid across the room. The advantage of a randomized sampling plan is that it ensures a *representative* sample of the room in the sense that all parts of the room have the same chance of being measured. This allows us to quantify and control in a statistical sense the risk induced by only measuring at a limited number of locations, and it ensures that we can reliably generalize the results to the entire room.

The acceptance criterion for the measured concentrations is simpler in the revised version; the criterion eliminates the need for applying a statistical test to the data, and thereby simplifies the classification process. Instead the sample locations are selected by a statistical sampling plan that ensures that at least 90% of the cleanroom area complies with the maximum particle concentration with a 95% statistical confidence. The number of sample locations has increased with the revision, thus requiring more measurement efforts; this is the consequence of moving from a non-statistical sampling plan to a statistically based plan. The benefit of the increased sampling effort is a more scientific and risk-based approach to cleanroom classification, which is in the interest of operators and consumers alike.

The purpose of this paper is to present and discuss the new sampling plan for cleanroom classification and compare it with the previous approach in ISO 14644-1:1999. Section 2 of this paper presents and discusses the previous method, section 3 describes the new method in the ISO/DIS 14644-1 revision, and section 4 provides a discussion and conclusion.

ISO CLASSIFICATION, 1999 STANDARD METHOD

The maximum allowable particle concentration per the new ISO/DIS 14644-1 for each cleanroom class is given in Table 1.

The table has changed only slightly in the new DIS edition compared to the version in the 1999 Standard. The purpose of this paper is not to discuss the limits, but rather how to demonstrate compliance with the class limits during classification and re-classification.

Let C_n denote the maximum allowed concentration for the particle sizes under consideration, i.e., the class limit. The procedure to demonstrate compliance with this class limit in the 1999 Standard is as follows:

1. Select N_L sampling locations in the room, where N_L is the square root of the cleanroom area, measured in square meters (rounded up to a whole number). The Standard does not prescribe how to select the sampling points, but it is widespread industry practice to select the points evenly distributed throughout the room.
2. At each sample location, sample a volume of air with a particle counter and calculate the concentration of particles per m^3. The volume must be at least 2 L of air sampled during a period of at least 1 minute, and the volume must be sufficiently large that at least 20 particles would be detected if the particle concentration was at the class limit. Let x_i denote the measured concentration from sample location i, i=1,…, N_L.
3. If the number of sample locations, N_L, is between 2 and 9, calculate the upper confidence limit for the mean particle concentration by:

$$UCL = \bar{x} + t_{0.95} s / \sqrt{N_L} \tag{1}$$

Table 1. Air cleanliness classification table by particle concentration. (Reproduced from the new ISO/DIS 14644-1 with permission of ISO.)

ISO classification number (*N*)	Maximum allowable concentrations (particles/m^3) for particles equal to and greater than the considered sizes shown below [a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	*10* [b]	d	d	d	d	e
ISO Class 2	100	*24* [b]	*10* [b]	d	d	e
ISO Class 3	1 000	237	102	*35* [b]	d	e
ISO Class 4	10 000	2 370	1 020	352	*83* [b]	e
ISO Class 5	100 000	23 700	10 200	3 520	832	e
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7	c	c	c	352 000	83 200	2 930
ISO Class 8	c	c	c	3 520 000	832 000	29 300
ISO Class 9	c	c	c	35 200 000	8 320 000	293 000

[a] All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10 200 particles shown at 0,3 µm include all particles equal to and greater than this size.

[b] These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

[c] Concentration limits are not applicable in this region of the table due to very high particle concentration.

[d] Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

[e] Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification inappropriate, due to potential particle losses in the sampling system.

Here $\overline{x}$ is the sample mean of the measured concentrations (x_i) and *s* is the sample standard deviation,

$$\overline{x} = \frac{1}{N_L}\sum_{i=1}^{N_L} x_i \qquad s = \sqrt{\frac{1}{N_L - 1}\sum_{i=1}^{N_L}(x_i - \overline{x})^2} \tag{2}$$

and $t_{0.95}$ is the 95% quantile of a *t*-distribution with N_L-1 degrees of freedom, which is tabulated in the Standard. The acceptance criterion is that the upper confidence limit is below the maximum allowed concentration, $UCL \le C_n$, and that all individual values are below the limit, $x_i \le C_n$, for all *i*.

4. If the number of sample locations, N_L, is greater than or equal to 10, the classification is passed if all individual values are below the limit, $x_i \le C_n$ for all *i*.

Additionally, the 1999 Standard provides rules for excluding a single outlying sample location or averaging several sequential measurements of the concentration at the same location. These details are not relevant to this discussion.

The approach described raises a number of issues, which are discussed in the following:

A. While the number of sample locations is simple and convenient, it is not statistically based. The "square root of *n* plus one" rule is a convenient rule-of-thumb, which is widely used for sampling and inspection[3] and cited by regulatory documents such as the US Food and Drug

Administration's (FDA) Investigations Operations Manual.[4] However, the rule is not based on specific statistical confidence requirements, nor is it justified by physical considerations of the particles. Particularly for small rooms, the rule provides fewer sampling locations than would a typical sampling plan based on statistical confidence requirements. Another problem is that the sampling theory is applied under the implicit assumption that the room consists of a number of independent sub-regions, each of which is 1 m^2 in size. Again this is convenient, but arbitrary.

B. The requirement on the upper confidence limit is based on the assumption that all measured particle concentrations statistically follow a normal distribution, with the same mean and standard deviation. The requirement then ensures with high confidence that the mean particle intensity in the room is below the class limit.

The assumption of a common distribution may not hold in general, particularly for non-unidirectional airflow cleanrooms, wherein the particle density may depend on the position in the room. This means that the cleanroom may fail the test, not because the particle intensity is unacceptably high, but simply because the distribution is uneven throughout the room. To demonstrate this point, particle counts of 3150, 3150, 3150, and 3150 would be satisfactory, whereas counts of 3150, 3150, 700, and 700 would not be (vs. the class limit of 3520 for ISO Class 5 at ≥ 0.5 μm).

Even if the particle density is homogeneous throughout the room, the confidence interval requirement is inadequate, because the confidence interval only ensures with high confidence that the mean particle intensity is below the class limit, but the confidence interval does not provide any assurance regarding individual particle measurements.

C. Finally, it is problematic that the UCL requirement is applied only when the number of sample locations is 2 to 9. That approach introduces a discontinuity in the requirement for 10 locations or more. For instance, today one may choose to classify an 81-m^2 room either by measuring at 9 locations and applying the UCL acceptance criteria, or by measuring a total of 10 locations and only comparing individual measurements with the class limit.

For these reasons, it was necessary to reconsider the sampling plan and acceptance criteria in the DIS revision of the Standard, and propose a method with more appropriate statistical assumptions and assurances. It was also considered important to obtain a single acceptance criterion that can be applied to all rooms independent of size, establishing for the first time a uniform approach to all particle count testing and room classification.

ISO CLASSIFICATION, NEW ISO/DIS 14644-1 METHOD

The new ISO/DIS 14644-1 does not assume homogeneous particle distribution throughout the cleanroom; the approach allows for different concentration levels in different parts of the room.

The test is designed to ensure with 95% confidence that at least 90% of the cleanroom complies with the class limit.

For rooms with an area less than 500 m^2, the test proceeds as follows:

1. Determine the number of sample locations, N_L, from Table 2.
2. Divide the room into N_L sub-regions of the same area and measure the particle concentration at a randomly selected location within each sub-region.*
3. If all N_L measured particle concentrations comply with the class limit, the classification is passed.

Rooms larger than 500 m^2 should be subdivided into zones of 500 m^2 or less for classification purposes, and each zone should be classified according to the test above.

* Note: As with the 1999 Standard, the revised DIS only *requires* that one particle count be taken at each sample location. However, multiple measurements *may* be taken at one or more of the locations. If more than one particle count is taken at each sample location, the average of those readings must comply with the class limit.

Table 2. The minimum number of sample locations as a function of cleanroom size in the revised classification procedure.

Area (m^2) less than or equal to	Minimum number of sample locations (N_L)
2	1
4	2
6	3
8	4
10	5
24	6
28	7
32	8
36	9
52	10
56	11
64	12
68	13
72	14
76	15
104	16
108	17
116	18
148	19
156	20
192	21
232	22
276	23
352	24
436	25
500	26

Following is an explanation of how the test is derived and a discussion of some of the assumptions made in the derivation.

Statistical Sampling Model

For the purpose of determining the number of sample locations, it is assumed that the cleanroom can be divided into independent regions ("unit areas"), and that within each region the particle density is homogeneous. For classification purposes, the concern is not the particle concentration itself but only whether the concentration is above or below the class limit. Furthermore, it is assumed that the particle concentrations in different unit areas are statistically independent, i.e., if the particle density increases or decreases in one area, this will not affect the density in the adjacent areas.

We now randomly select N_L areas and measure the particle concentration in these areas. If the concentration in all measured areas is below the class limit, we pass the test. Here N_L is chosen to be sufficiently large that it may be inferred with 95% confidence that at least 90% of all the unit areas are below the class limit. We will denote the 90% as the verification level.

More specifically, N_L is calculated using the hypergeometric distribution, which is the statistical model for sampling without replacement.[5] In this case, sampling is the process of selecting a number of unit areas to measure, which are sampled randomly from the population of all unit areas in the cleanroom.

For example, in classifying a 100 m^2 cleanroom, using unit areas of 4 m^2 provides 25 possible sample locations to choose from. This situation is illustrated in Figure 1. Suppose we measure the particle density in 4 randomly selected locations, and all 4 samples comply — how well do those data reflect the air cleanliness of the entire room?

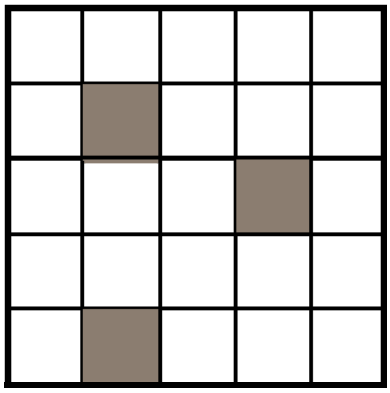

Figure 1. The assumption for sampling purposes is that the cleanroom can be divided into homogeneous "unit areas," each of which represents a possible sample location. In each unit area, the particle density is either above or below the class limit, and the areas are independent of each other. In the illustration, a 100-m^2 cleanroom is divided into 25 unit areas, each of which is 4 m^2. In three of the unit areas, the particle concentration is above the class limit.

The probabilities of interest depend on the total number of possible sample locations, M=25, the number of locations sampled, n=4, and the (unknown) number of non-compliant locations, K. The probability that none of the non-compliant locations are included in the sample is given by the hypergeometric probability density function,[5]

$$p(0) = \frac{\binom{M-K}{n}\binom{K}{0}}{\binom{M}{n}} = \frac{\binom{M-K}{n}}{\binom{M}{n}} \tag{3}$$

In the above probability, the quantity

$$\binom{M}{n} = \frac{M!}{n!(M-n)!} \tag{4}$$

is the binomial coefficient, i.e., the number of combinations by which n items can be selected from M items. Suppose, for example, that 22 locations were compliant, but 3 possible sample

locations were above the class limit, i.e., K=3. The probability of not including any of these in a random sample of 4 locations would be

$$p(0) = \frac{22 \times 21 \times 20 \times 19}{25 \times 24 \times 23 \times 22} = 0.578 \quad (5)$$

which means that there would be a 57.8% chance of not discovering the 3 non-compliant locations in the measuring process. Or formulated differently: Based on measurements of only 4 random locations, we cannot with any certainty rule out the possibility there could be 3 non-compliant locations in the room.

To understand exactly how much information a sample size of 4 locations provides, we can repeat the calculation above for other hypothetical values of K, the number of non-compliant locations or equivalently, M-K, the number of compliant locations; results are given in Table 3. If only 13 locations were compliant, there still would be a non-negligible risk of 5.7% that our 4 randomly selected samples would not include any of the 12 non-compliant locations. However, if only 12 locations were compliant, it would be unlikely (3.9%) that the sample did not contain any of the non-compliant locations. Thus, from a sample of 4 locations, we can conclude with high confidence (>95%), that the number of locations in compliance is at least 13, corresponding to 52% of the room area.

Table 3. Probability of selecting 4 compliant locations out of 25 possible sample locations.

If the actual number of compliant locations is...	*...then the probability of the sample result is:*
25	100.0%
22	57.8%
19	30.6%
16	14.4%
13	5.7%
12	3.9%
10	1.7%
7	0.3%
4	0.0%

The whole analysis may now be repeated for other possible sample sizes (see Table 4). To ensure that more than 90% of the cleanroom — or 23 sample locations — is in compliance, it would be necessary to measure 16 locations or more. In comparison, the 1999 Standard's recommended sample size of $\sqrt{100} = 10$ locations would only ensure that 80% of the cleanroom is in compliance, if sample locations were selected randomly.

Table 4. Confidence in compliance with class limit when sampling from 25 possible sample locations in a 100 m^2 cleanroom.

Number of sample locations measured	*Lower 95% confidence interval for number of locations that comply with class limit*	
	Number	*Percent*
1	2	8%
2	7	28%
3	10	40%
4	13	52%
5	15	60%
6	17	68%
7	18	72%
8	19	76%
9	20	80%
10	20	80%
11	21	84%
12	21	84%
13	22	88%
14	22	88%
15	22	88%
16	23	92%
17	23	92%
18	23	92%
19	24	96%
20	24	96%
21	24	96%
22	24	96%
23	24	96%
24	25	100%
25	25	100%

Application of the Sampling Model to Cleanroom Classification

The statistical model is a general model for sampling with replacement. The general assumptions of the model and the translation to the specific application in cleanroom classification are summarized in Table 5.

Table 5. The assumptions of the statistical sampling model and their interpretation in terms of cleanroom classification.

General assumption of sampling model	*Specific assumption for cleanroom classification*
1. The population consists of a number of units that are sampled randomly without replacement.	Measurement locations must be selected randomly, and each unit area should be measured only once.
2. A unit belongs to exactly one of two categories.	A unit area is either compliant or non-compliant. The actual particle density is not relevant, only if it is above or below the class limit. Furthermore, the unit area must be homogeneous; the particle density must not be so variable across a unit area so that some parts of the area are compliant and others are non-compliant.
3. All units are independent.	There is no (positive or negative) correlation between the particle densities in adjacent unit areas.

Assumption 1 reflects an important difference between the classification paradigm in ISO 14644-1:1999 and the new model in the ISO/DIS 14644-1 revision — Sample locations must be selected randomly throughout the room, and not at fixed, regularly spaced locations. Furthermore, new locations need to be sampled at every re-classification of the cleanroom. In the section "Choice of Sampling Locations," a practical procedure to conduct this is proposed.

Assumptions 2 and 3 are the most difficult in terms of applying the model: In practice, it may be difficult to divide a cleanroom into *homogeneous* yet *mutually independent* subregions for classification purposes. The selection of the unit areas, which is discussed in the next section, aims at striking the right balance between these two objectives. Generally, if assumption 2 is violated, the number of measured locations will be too small and if assumption 3 is violated, the number of measured locations will be unnecessarily large.

Determining the Unit Areas

Since the unit areas determine the population from which a sample is drawn in the model, the definition of the unit areas is an important parameter in the calculation of the sample size. For the same cleanroom, the larger the unit areas are, the smaller is the population to sample from and hence the smaller the required sample size. How then does one determine the unit areas?

From a statistical point of view, it is important that the unit areas are sufficiently large that the particle counts in different areas can be considered statistically independent. Intuitively, this means that even if an increased particle concentration is observed in one unit area, the particle concentration in the adjacent areas is not expected to change because the areas are sufficiently separated. If the areas are not independent, the mathematical model used for calculating the sample size would not be valid, and the sample size typically would be too large.

Working Group 1 considers the physical area as the primary factor that determines whether the independence assumption is fulfilled; if the unit areas chosen are sufficiently large, it seems plausible that an increase in the particle concentration in one area of the cleanroom will not necessarily mean there is an elevated concentration in adjacent areas.

On the other hand, the unit area chosen should be sufficiently small that the particle density can be considered homogeneous within the area.

Thus, the selection of the unit areas depends on how the particle concentration may vary throughout the room. It should be noted that the area of the unit areas is only one of the relevant parameters in this context. Perhaps more critical are the dynamics of the airflow in the cleanroom, as determined by the placement of machines, equipment, doors and ventilation vents. In theory, the unit areas would be most accurately determined by a careful examination (by smoke studies, for example) of the flow patterns in the cleanroom. This could lead to the conclusion that in parts of the room with open spaces and little turbulence the unit areas should be large, but near equipment or ventilation vents, the unit areas would be smaller and more precisely outlined.

While examining airflow dynamics would likely be the most scientific approach to determining the unit areas, it would also be unnecessarily costly and complicated in many situations. Therefore, the authors of this paper believe it is not justifiable to require such a study in a Standard that must be applicable across all types of industries.

Therefore, Working Group 1 has taken a more pragmatic approach, and has proposed to define unit areas based on size alone, defining a unit area generally as a 4-m^2 area. For smaller rooms (with an area of less than 12 m^2), the unit area is set to 2 m^2. These areas were selected as a compromise between what is physically reasonable and the resulting sample requirements, which are discussed in the next section.

Choice of Verification Level and Confidence Level

The new Draft International Standard uses a default verification level of 90%, meaning that we ensure with high confidence that at least 90% of the room complies with the class limit.

The choice of this parameter represents a trade-off between the sampling effort and the risk that a certain part of the room may be non-compliant with the particle requirements. As such, it is difficult to set a general value for the verification level. The level of 90% has been proposed by evaluating the verification level implied by the 1999 Standard's square-root-of-*n* sample size, but using the same definition of unit areas and random sampling as for the new procedure. In general, the verification level assured by the 1999 Standard's sample size varies from 80% for cleanrooms smaller than 100 m^2, up to just below 90% for 500-m^2 rooms (Figure 2). The authors believe that a fixed verification level of 90% is reasonable in this comparison.

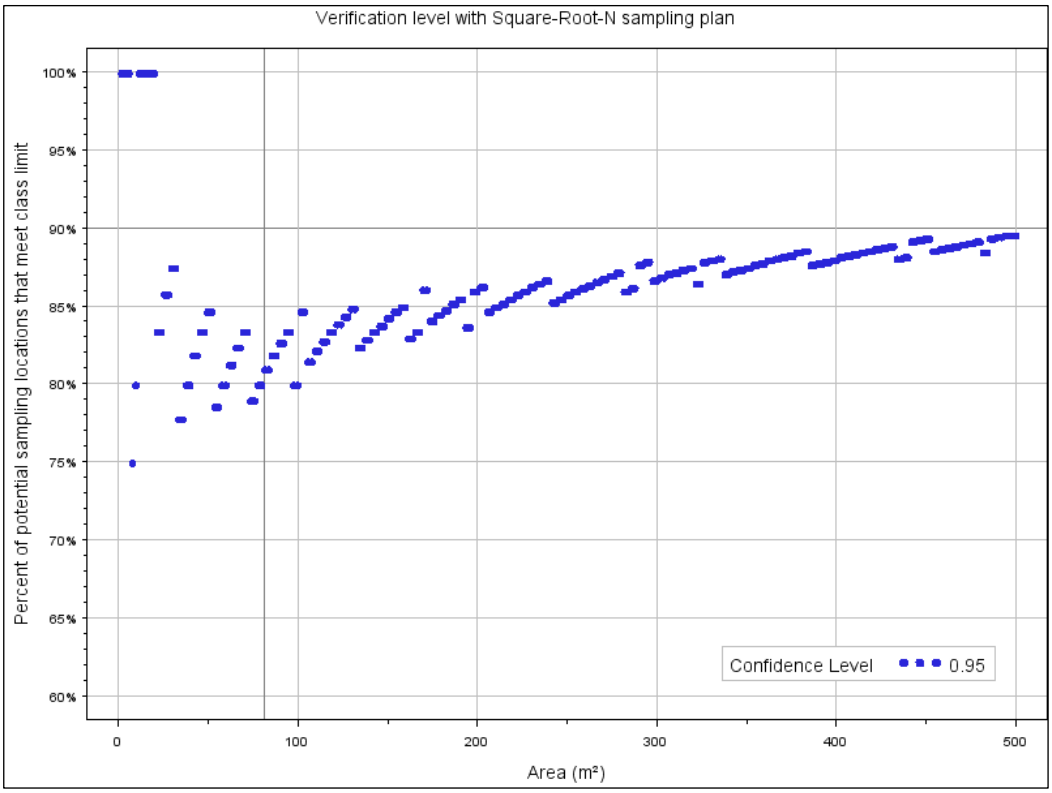

Figure 2. Verification level ensured by the square-root-of-n sample size (95% confidence level), assuming random sampling and the same definition of unit areas as in the new ISO/DIS 14644-1 method. The new sampling plan ensures a 90% verification level for all room sizes. Notice that the extra assurance that the upper 95% confidence limit requirement for cleanrooms smaller than 81 m^2 has not been taken into account here.

The revised ISO/DIS 14644-1 uses a confidence level of 95%, as is common practice. The resulting sample sizes are displayed graphically in Figure 3.

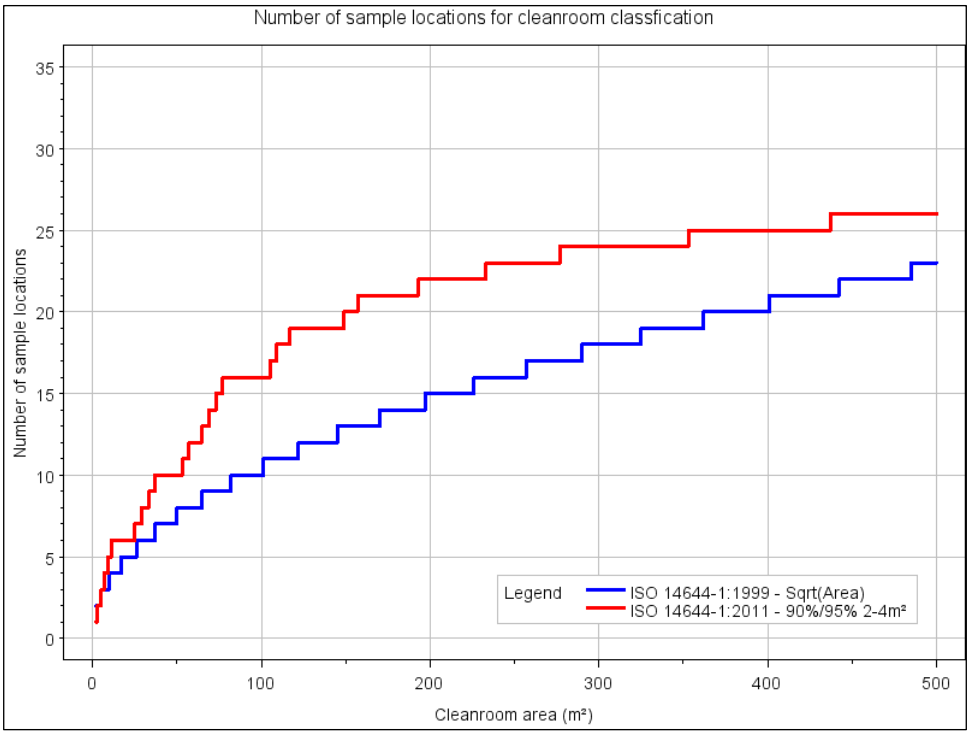

Figure 3. Comparison of the number of sample locations for cleanroom classification by ISO 14644-1:1999 and the new ISO/DIS 14644-1.

Both the verification level and the size of the unit areas have been determined as a balance between what is practically and physically reasonable as well as a balance between the verification requirements of the 1999 Standard and the revised DIS. Figure 3 shows that in general, the sampling plan in the revised Standard requires a larger number of sample locations than did the square-root-of-*n* approach in the 1999 version of the Standard. This reflects a compromise that Working Group 1 felt was necessary to obtain a specific statistical control over the verification and confidence level. As shown in Figure 2, with the sample size outlined in the 1999 Standard, there is a risk that up to 20% of the room may be non-compliant, even if the verification passes; this risk is controlled to no more than 10% (with 95% confidence) by using the approach provided in the revised DIS.

On the other hand, with the choice of 4-m^2 unit areas, the new sampling plan would actually result in fewer sample locations for rooms with an area of less than 12 m^2, thus resulting in both reduced sampling requirements and a less strict acceptance criterion, which would not be justifiable. To avoid this problem, the ISO/DIS 14644-1 revision uses a unit area of 2 m^2 for rooms smaller than 12 m^2, as this keeps the number of sample locations the same or within 1 or 2 more sample locations than the 1999 method.

Choice of Actual Sampling Locations

For the statistical sampling principles in the revised DIS to work correctly, sample locations should be selected randomly throughout the cleanroom. More precisely, each point in the room must have the same probability of being selected.

This is different from the practice commonly used to comply with the 1999 Standard, where sample locations typically have been selected in a regular grid across the cleanroom. The advantage of a randomized sampling plan is that it ensures a *representative* sample of the room, which allows us to quantify and control — in a statistical sense — the risk induced by only

measuring at a limited number of locations, and it ensures that we can reliably generalize the results to the entire room.

While the selection of random sampling locations sounds simple on paper, it is actually not easy to do in practice. When asked to select randomly, people typically select points dispersed throughout the room, and do not select points close to walls or corners.

Furthermore, when sampling is completely random, a valid result could by coincidence be one in which all samples are taken from one part of the room and a large section of the room is not measured. This situation is not likely but will occur occasionally if the sample is truly random, and when it does occur, it may seem unacceptable to classify the room based on these data.

The authors therefore propose the use of the following stratified random sampling procedure, which is easier to undertake in practice and ensures that all parts of the room are represented:

Suppose 16 sample locations are to be selected randomly from a 100-m^2 room. Divide the room evenly into 16 regions of the same size (6.25 m^2), using a drawing of the cleanroom. Select a sample location randomly within in each region, remembering that all locations within the region should have the same likelihood of being selected.

At this time, the new ISO/DIS 14644-1 does not provide any further guidance on how to select the random location within each region, nor is such guidance within the scope of this paper. A new set of random locations should be selected every time the cleanroom is classified.

Large Cleanrooms

One noticeable difference between the square-root-of-*n* principle and the statistically based sampling plan is that the sample size for the latter converges to a fixed number as the size of the cleanroom becomes very large. For a 90% verification level and 95% confidence, the sample size converges to 29. From a statistical perspective, this is natural: If we measure randomly across a room where 10% of the room is non-compliant, there is a 10% chance of failing each measurement. Thus, chances are high (95.3%) that at least one of the 29 samples would fail if more than 10% of a room was non-compliant, irrespective of room size. When no samples fail, one can conclude that it is unlikely that 10% of the room is non-compliant, and the room is therefore acceptable according to the specified verification level.

In practice, however, this means that 29 samples are sufficient to characterize any cleanroom, irrespective of how large it is, and that is not generally considered to be an acceptable conclusion. What is the source of this dilemma? One explanation is the specified quality requirements: If 90% of the room should be acceptable, we also implicitly accept the risk that 10% of the room may unacceptable. For a 100-m^2 room this corresponds to 10 m^2, which may be acceptable, but for a 1000-m^2 room, the implied risk is that 100 m^2 may not be compliant, which is not generally acceptable.

The solution to this dilemma is either to tighten the quality requirements (the verification level) for larger cleanrooms, or to accept the fact that the statistical sampling analogy breaks down at a certain point.

Working Group 1 has chosen the latter option, and has therefore restricted the use of the sampling plans to rooms smaller than 500 m^2. Rooms larger than 500 m^2 should be divided into smaller zones, each zone being 500 m^2 or less, for the purpose of cleanroom classification and each zone should be separately classified according to the principles outlined in this paper.

DISCUSSION AND CONCLUSION

This paper has presented the approach for determining sample locations for cleanroom classification with respect to airborne particles in the new DIS revision of ISO 14644-1. The aim of the new approach is to provide a scientific, risk-based approach to cleanroom classification, wherein the assumptions and conclusions are transparent and interpretable.

To summarize, the revised classification method entails:

- Determining the number of sample locations, N_L, from Table 2.
- Dividing the room into N_L sub-regions of the same area.
- Measuring the particle concentration at a random location within each sub-region.
- If all N_L measurements comply with the class limit, the test is deemed a "pass."

The classification plan is not perfect in a scientific sense: The number of sample locations, N_L, is determined from a theoretical sampling model. The model is a convenient mathematical formulation of the test, but not fully accurate, and the assumptions of the model in Table 5 may be questioned. For instance, to obtain homogeneous yet independent unit areas we define a unit area as a region of 2 m^2 or 4 m^2, depending on the room size. This choice may be discussed in specific applications, either where 4 m^2 may seem too large to justify the homogeneity assumption within a unit area, or where 2 m^2 may seem to small to justify the assumption of statistical independence between concentrations in adjacent areas. The specific choices for the parameters have been made with the intention of obtaining a balance between what is reasonable from the theoretical formulation of the sampling process, and what is reasonable from practical experience, including the general practice applied with the 1999 Standard.

However, the revised DIS only states a minimum requirement for classification. Supplier and customer requirements may increase the number of sample locations, thus increasing the verification and confidence level.

The revised DIS is generally more consistent and scientifically based than the 1999 version of the Standard, and the revised DIS is intended to be easy to use and interpret for all professionals involved in cleanroom classification.

REFERENCES

1. International Organization for Standardization (ISO). 1999. *ISO 14644-1:1999, Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness*. Geneva, Switzerland: ISO.
2. International Organization for Standardization (ISO). 2010. *ISO/DIS 14644-1, Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration*. Geneva, Switzerland: ISO.
3. Saranadasa, H. 2003. The square root of *n* plus one sampling rule: How much confidence do we have? *Pharmaceutical Technology*, 27 (5): 50–62.
4. US Food and Drug Administration. 2009. *Investigation Operations Manual*, Chapter 4. Washington, DC: US FDA. http://www.fda.gov/ICECI/Inspections/IOM
5. Montgomery, D. C. 2001. *Introduction to Statistical Quality Control*, 4th edition. New York: John Wiley & Sons.

ABOUT THE AUTHORS

Niels Væver Hartvig is principal specialist in statistics at Novo Nordisk A/S, Gentofte, Denmark. He holds a PhD in mathematical statistics from University of Aarhus and has 10 years of experience in the pharmaceutical industry.

Gordon J. Farquharson, BSc (Hons), CEng, is a principal of Critical Systems Ltd., Guildford, UK, and a Chartered Consulting Engineer. He is a founding member of the UK Pharmaceutical & Healthcare Sciences Society (formerly Parenteral Society), and is editor in chief of the *European Journal of Parenteral & Pharmaceutical Sciences*. He serves as Convenor of ISO Technical Committee 209 (ISO/TC 209), Working Group 1.

Mark Varney is program manager, Statistics, at Abbott Laboratories, North Chicago, Illinois. He received his MS in statistics from Pennsylvania State University.

Robert Mielke is a principal metrology engineer with Abbott Laboratories, North Chicago, Illinois. He is Secretary for ISO/TC 209, a Fellow of IEST and chair of IEST Working Group CC006 (Testing Cleanrooms).

Mike Foster is an independent consultant based in Winchester, UK. He has 30 years experience in the design and construction of cleanrooms and other controlled environments, such as high-integrity glovebox and containment facilities.

Contact author: Niels Væver Hartvig, Novo Nordisk A/S, Nybrovej 80, 2820 Gentofte, Denmark.
