

以连续或接近连续的方式对悬浮颗粒进行监测，对保障某一生产流程的稳定和产品的质量都是很有效的手段
Continuous or nearly continuous airborne particle monitoring is an effective aid to maintaining process stability and product quality

采样点的选择

在干净区域对空气中的悬浮颗粒进行监测不仅仅是法规的问题，同时还是关系到质量的问题

Selecting sample points

Monitoring airborne particles in clean zones is not just a regulatory issue; it's a question of quality

用连续或接近连续的监测系统对空气中颗粒进行监测的时候，采样点的选取需要在两个相互排斥的需要中进行权衡：对数据完整性的追求和降低成本的需要。通过在精心选择的采样点每天进行监测，上述两个要求都可以满足。

精心选择的位置可恰当地勾画出干净区域内的生产流程，并可拿出优良的数据以供监管部门检查。精心制定的抽样策略也可以在对根本原因分析的时候提供足够的信息，从而改善内部质量。

抽样位置当或数量不足这可能会使监管部门对得到的数据提出质疑。

设计连续或接近连续监测方法来计算空气中有害颗粒的数量的用户，最常问的两个问题就是“如何选择抽样点”和“需要多少抽样点”。可惜的是，尽管法规文件中有关于房间认证的具体说明，但是关于连续监测系统的标准和指导性文件中很少提及采样数量和位置。

监管部门只是明确指出，综合监测系统应在经过灭菌处理的加工区域进行。

欧洲和美国的监管部门都鼓励运用更详细和自动化程度更高的方法。对于无菌化的生产过程，其污染情况更令人担心，因为生产商往往对最终产品不做最后的杀菌处理。这些区域被称作关键区或A级区，在与有害微粒监测有关的标准中受到格外的关注。

然而，这些文件在每日监测的取样点和位置方面往往是空白。这方面最直接的说明来自美国FDA的文件，FDA建议关键区域内的采样点应设在离暴露在空气中的成分或产品一英尺（约30cm）内的地点，该点要有气流通过，且采样必须在进行加注和封装过程中进行。但是对采样点的数量和位置却根本没有提及，并且欧洲《良好药品生产规范》（GMP）中的附录一中也没有提供任何有帮助的信息。

在已经投入使用的生产区域，最终用户常会在开始的时候采用其质量小组所选择的每日、每周和每月采样数和采样点。毫无例外的是，这样的采样数都太大，经常比连续监测系统能实现的大10倍左右。

系统的设计者还必须同时考虑到最终用户和系统需要采集的数据量。如果每分钟进行一次抽样，每个点针对每一颗粒等级在8小时生产时间内将产生将近500个数据点。经常会有对两个等级的颗粒进

遥控技术器的主要优点是它可提供每分钟的空气质量信息

The key benefit of remote counters is that they provide minute-by-minute information about the air quality

Choosing sampling points for a continuous or near-continuous monitoring system for airborne particles in a clean zone requires a compromise caused by two opposing needs: the drive for comprehensive data and the desire to lower costs. With day-to-day monitoring basis from carefully selected sample points, both of these requirements can be met.

Well chosen positions can offer a solid profile of the process occurring in the clean zone and provide good data to satisfy regulatory scrutiny. Carefully planned sampling strategies also improve internal quality by providing enough information for root cause analysis.

Poor or insufficient sample positions will leave the quality group without good knowledge of the quality of the air envelope surrounding the process if the results are less than adequate. This can lead to regulatory authorities challenging the data obtained.

"How do I select the best sampling positions?" and "How many sample positions are needed?" are the most frequent questions from users designing a continuous or near-continuous monitoring system for counting airborne unwanted particles. Unfortunately, regulators offer little guidance here. Although regulatory documents provide specific directions for room certification, there is little offered in standards or guidance documents regarding the number and placement of positions for continuous monitoring systems.

What regulatory authorities have made clear is that comprehensive monitoring systems are expected for aseptic processing areas. Both the European and American authorities are encouraging the shift towards more detailed and automated systems. For aseptic processes, the effects of contamination are of greater concern because there is no terminal sterilisation of the final product. These areas, known as critical or grade A zones receive specific attention in the guidance on monitoring unwanted airborne particles.

However, these documents are mute regarding the number and placement of sample points for day-to-day monitoring. The most direct guidance is from the US FDA document, which suggests that the sample positions for the critical area should be set within 1 foot (30cm) of the exposed components or product and within the airflow, and that sampling must be done during the filling and closing operations. But no mention is made about the number of positions and the EU's Good Manufacturing Practice Annex I provides no assistance in these decisions either.

For a process area already in use, it is common for the end user to start with the number and position of points selected by the quality group for their daily, weekly and monthly sampling. Invariably, this number of points is too large, often by a factor of 10, for an affordable continuous monitoring system.

精心选择的采样位置可以恰当地勾勒出发生在洁净区域的生产流程

行监测，0.5微米和5微米级，这样数据点会再多一倍，达到每个抽样点每班1000个数据点。

用户经常参照的另一个依据是国际标准组织（ISO）的ISO14644-1文档，那里面根据悬浮颗粒的计数对洁净房间和区域进行了分类。这些标准用于每隔6到12个月进行一次的正式测试而非每天监测。ISO 14644-2倒是提到了每天监测，但没有提供具体的说明。在即将发布的14644-1和14644-2的修订版中，也许会更多地涉及此问题，但在目前，这些文档建立采样策略帮助不大。另外，所有这些文档都不是针对制药行业的。

假设有这样一个无菌装药车间，其左侧是药瓶清洗系统，右侧是冷冻干燥机，无菌面积为80平方米。按照ISO14644-1，这个车间必须每六个月进行一次认证。ISO标准上规定车间里的空气必须在以大于洁净区域面积的平方根（四舍五入取整后）的点数进行监测。那么80平方米的无菌面积将需要至少9个测量位置，因为80的平方根是8.94。

但是当我们考虑到该车间实际使用的瓶装设备、门口的存在以及保证冷冻干燥机的送料区附近的空气质量的需要，看起来需要在14个位置上进行采样，才能对这片区域进行符合ISO标准的认证。然而，这比通常的，目的在于或取足够的信息以对日常工作进行控制的连续监测系统所需要的点数多。

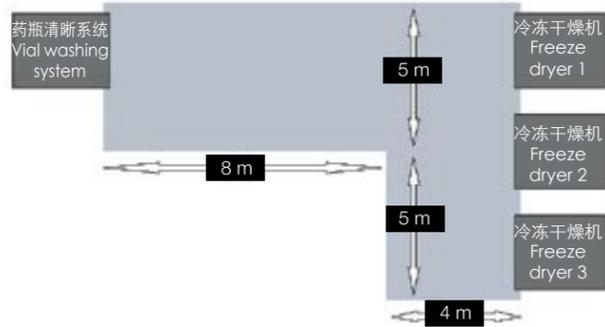
因此每日监测最好的方法就是只选用最能帮助我们分析问题根源的关键位置。这些点取决于这些位置上的操作人员是不是最有可能人为地干涉加工过程。因为操作人员及由于其运动对空气流动造成的干涉是最有可能导致污染的，对这些干涉点应该加以监测。

另外，在靠近门口处选取一个针对整个车间的监测点将会以为B级及其附近区域作为参照点，以及在污染物即将进入房间的时候可以进行预警。如果监测区域进行的是严格的液体装药过程，并不需要冷冻干燥机，那么房间右端两干燥机之间的监测点就不需要了。所有的采样点都必须设在工作高度，以便有效地确定暴露在空气中的无菌物质经过的某一区域的空气质量。

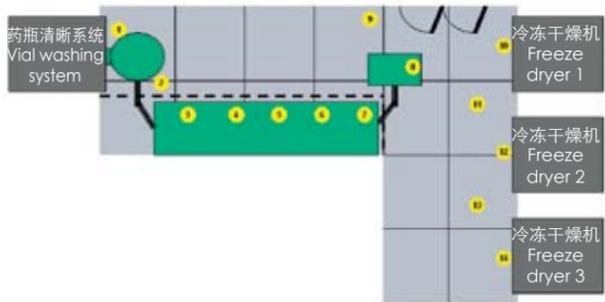
设立监测点的关键在于：1)工作地点在何处，2)在工作地点附近，产品或组分暴露在空气中的可能性3)在生产过程中操作员产生干涉的可能性。这些采样点应能显示出，在每点上产品受到污染的风险值得在此点进行连续监测。

Well chosen positions can offer a solid profile of the process occurring in the clean zone

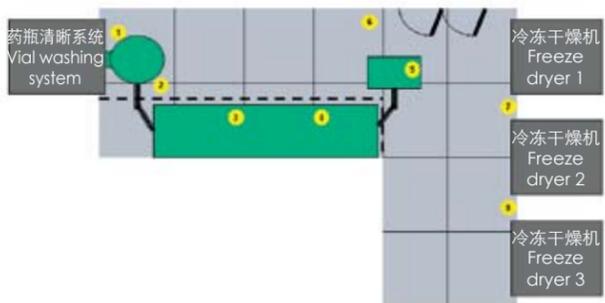
按照ISO14644-1, 采样点的数量可用以下方法得出:
假设洁净区域的面积为80平米, 取平方根为8.94。四舍五入取整后得到9个采样点
The number of sample points can be calculated according to ISO 14644-1:
This clean zone area is 80 sq m, the square root of which is 8.94.
Rounded up to nearest integer this amounts to nine sample points



建议在一些可能发生问题的点上, 如入口、出口和操作位置等。根据ISO14644-1, 选取10个以上的采样点就不必计算置信区间的上限
It is advisable to sample near potential problem spots such as entrances, exits and operator positions. According to ISO-14644-1, sampling at 10 or more positions avoids having to calculate the upper confidence limit



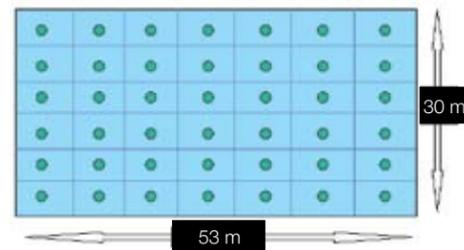
对于每天进行的监测, 如果精心选择的话, 8个采样点都可能是够用的。因为药瓶的口有可能没塞紧, 在第5点处的支撑位置有一定的风险。门口和干燥机前方的送料区也必须进行监测
For day-to-day monitoring, as few as eight sample points can be enough if they are carefully chosen. As vials may not be fully stoppered, the holding position at point 5 presents some risk. The doorway and loading areas in front of the dryers should also be monitored



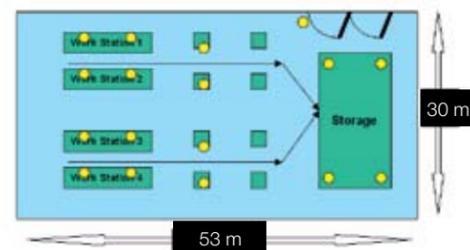
to have enough information to ensure that the area is under control for day-to-day work.

So the best approach for day-to-day monitoring is to use only the key positions that will give us the most help in root cause analyses. These points are determined by the places where the operators are most likely to make an intervention during the process. Because operators and the interference with the air flow caused by their movements represent the greatest opportunity for contamination occurring, these points of intervention should be monitored.

Additionally, a general room sample point located near the doors will provide a view of the grade B or surrounding area as well as offer the possibility of an alarm if contamination were to enter the room through the doorways. If the area were strictly a liquid filling process and the freeze dryers were not used then the points between the dryers at the far right of the room would not be needed. All of the sample points would be mounted near working height in order to effectively determine the particulate air quality that the



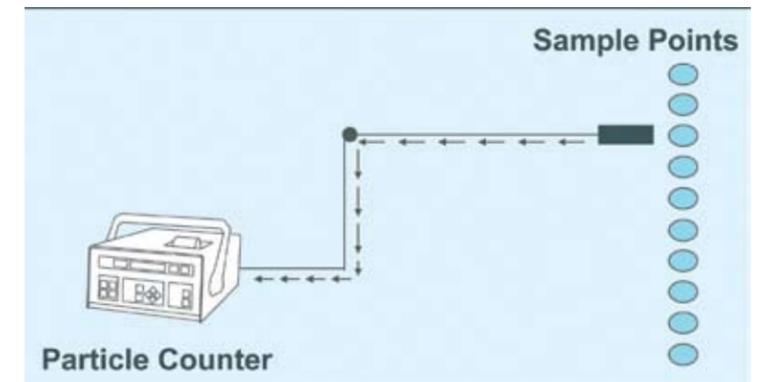
对于更大的35x53m(1590平米)的房间, 用于认证的最小采样点数量为40, 即最接近1590平方根的证书。网格法建议的采样点为42个
For a larger room of 30m x 53m (1590sq m), the minimum number of sample points for certification is 40, the nearest integer above the square root of 1590. A grid approach would suggest using 42 sample points



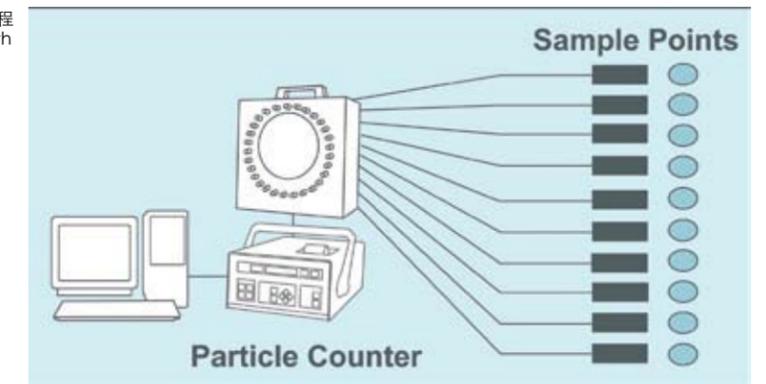
在同样大的房间内, 进行每天连续监测只需17个采样点就够了
As few as 17 sample points may be enough for day-to-day monitoring in the same large room

The US FDA document suggests that the sample positions for the critical area should be set within 30cm of the exposed components and within the airflow

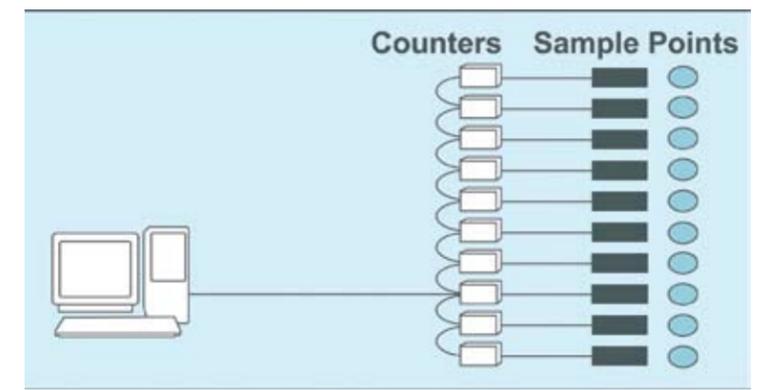
据美国FDA所说, 便携式计数器的干涉性大
Portable counting units can be more invasive, according to the US FDA



用一个计数器, 借助气体歧管, 依序在每个采样点进行监测被认为是接近连续的过程
Monitoring with one counter that is sequenced through sampling points with the aid of a manifold is considered a nearly continuous process



使用遥控的计数器, 每个测量点都专门配一个传感器, 这样才是真正的连续采样方式
The remote style of counter, where a dedicated sensor is placed at each sample point, is a true continuous sampling style



大的房间也可用少于网格法所要求的采样点进行监测。假设在一个ISO7级或C级的更大的房间内进行非消毒过程，按照ISO14644-1对设立采样点的要求，须按照网格法选取至少40个位置进行一年两次的采样才能给予认证。

但这种方法没有考虑到已安装设备的性质，操作人员的行为以及产品的流向等因素。再次强调一下，通过对产品在不同位置发生污染的风险加以考虑，可以确定对连续监测系统最有价值的采样点。

最后的结果是，应该在这么大的面积内选择17个采样位置，这对于理解生产过程中的空气质量以及如何在报告中体现都是最关键的。这一位置数比ISO14644-1要求的少的多。更重要的是，采样点的选取有助于理解在产品最容易发生污染的地方，人员或加工设备对产品造成污染的潜在风险的理解。

对悬浮颗粒的计数方法分为3大类：人工，顺序和连续。每种方法使用不同类型的设备。尽管欧洲的GMP法规的附录1中在提到A级区域的采样时使用了“连续”字样，在许多关键区域采用人工的顺序法也是可行的。

这一类用一个计数器，借助气体歧管，依次在各个采样点处进行计数。的方法被业内多数人看作是“接近连续的”，然而采用遥控的计数器，在每一个采样点上都放置专门的传感器的方法才是真正的连续采样法。

exposed sterile materials are moving through.

The key issues in setting up monitoring points are a) where the work is being done, b) the potential exposure of product or components at that point and c) the possibility of operator intervention in the process. The sample points should reflect that the risk to the product at each point is high enough to justify the expense of monitoring it continuously.

Larger rooms can also be monitored using fewer points than the grid pattern approach would suggest. Consider a non-sterile process being conducted in a larger room rated as ISO Class 7 or grade C. Setting up sample points following ISO 14644-1 would dictate that a minimum of 40 positions should be sampled using a grid pattern to provide certification for that area on a biannual basis.

But this method does not reflect the nature of the installed equipment, the operators' activities and the flow of the product. Again, thinking about the activities and risk of contamination of the product at the various positions can help to determine the most valuable points for a continuous system.

The end result is the selection of 17 sampling positions in this large area as being the most crucial for understanding and reporting air quality during a process. This number of positions is far fewer than the number dictated by ISO 14644-1. More importantly, the sample points are selected to help understand that potential contamination to the product by operators and process equipment can occur at positions where the product is most vulnerable.

There are three general styles of monitoring for airborne counting: manual, sequential and continuous. Different types of instrumentation are used in each style. Although the EU GMP Annex I uses the term "continuous" for sampling in grade A areas, sequential systems based on manifolds have been deemed acceptable in many critical areas.

This style of monitoring, using one counter that is sequenced through the sampling points with the aid of a manifold, would be considered "nearly continuous" by most in the industry, whereas the remote style of counter, where a dedicated sensor is placed at each sample point, is a true continuous sampling style.

The key benefit of remote counters, and the reason that the regulatory agencies encourage their use in critical areas, is that they provide minute-by-minute information about air quality and can catch very short-lived events. Due to the unidirectional flow in most critical areas coupled with the high rate of air changes, most contamination events are short-lived but often they exist long enough to contaminate the exposed product.

It is very helpful to know exactly when and where an event occurred so that the cause can be understood and corrective action taken to prevent a recurrence. Many events are triggered by the actions of operators and their interventions, so the typical positions of the operators during a process should be a

采用遥控计数器的最大优点以及监管部门鼓励在关键区域使用此类计数器的原因在于，它可提供每分钟的空气质量信息，从而可以将极短促的事件记录下来。由于多数关键区域的产品是单向流动的，加上气流变化的频率很快，大多数的污染都是很短促的，不过通常都足以对暴露的产品产生污染。

如果能确切的知道何时以及在那一点发生污染事件就能了解原因并采取防止再次发生。很多污染事件是由操作人员以及其干涉行为引起的，因此操作人员的典型位置可作为微粒采样点位置的主要参考。

不仅仅是极大地改善了数据，对关键区域进行连续监测还有经济上的好处。ISO 14644-2允许将正式、昂贵的认证过程的间隔期延长，ISO5级可以超过6个月，ISO6、7、8、9级可以超过12个月。尽管能让监管机构接受的关键区域的待认证时间为两年，这仍然意味着每两年要做一次认证。对于A级，或ISO5级区域，规定是每24个月进行4次认证。

以连续或接近连续的方式对悬浮颗粒进行监测，对保障某一生产流程的稳定和产品的质量都是很有效的手段。在产品暴露在空气中且易受污染的地方选取关键点可提供有用的信息，以保障产品质量。

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main guide to the location of airborne sampling point.

In addition to significantly improved data, there is a secondary financial benefit to continuous monitoring key areas. ISO 14644-2 permits the interval between formal, and expensive, certification of areas to be extended beyond the stated six months for ISO Class 5 areas and 12 months for ISO Class 6, 7, 8, or 9 areas. Although the longest period that regulators might be comfortable with a user not having certified a key area would be about 24 months, this still would mean only one certification over two years. For a grade A, ISO Class 5 area, four certifications in 24 months is the specified requirement.

Continuous or nearly continuous airborne particle monitoring can be an effective aid to maintaining the stability of a process and the quality of a product. Choosing the key points where the product is exposed and vulnerable as sampling points will provide solid information to help ensure the quality of a product. ■

This article was written by Joe Gecsey, life sciences application manager at Hach Ultra

“用遥控计数系统监测非生物颗粒通常对比使用便携式计数装置对系统的干涉更小”

— FDA 行业指南

“A remote counting system is generally less invasive than portable counting units”

— FDA Guidance for Industry



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