Clean air in non-sterile production areas

Results of an online survey

8 min reading time

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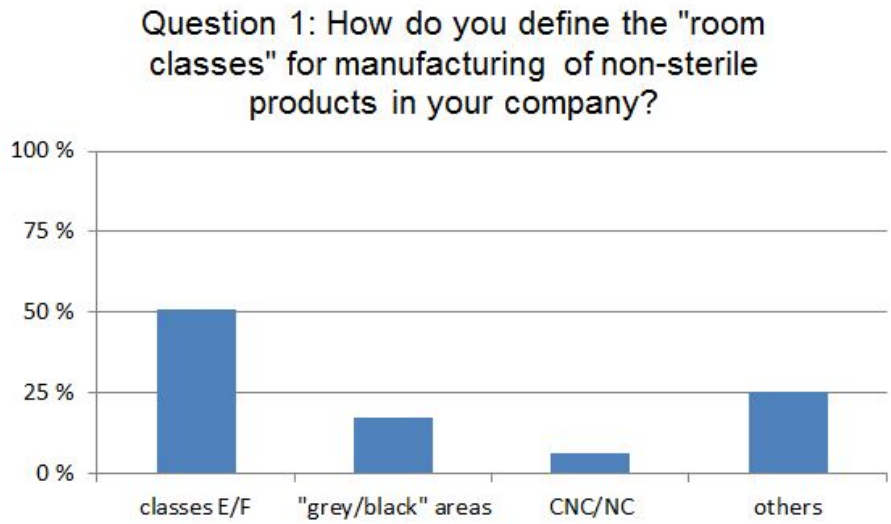
There are no regulatory requirements for the definition of air quality and its monitoring in non-sterile production areas. The topic was discussed by our team of experts and in some cases very different answers were received. The different points of view made us curious - how is this question solved in pharmaceutical practice?

To find this out, we started an online survey in our newsletter in German language. The lively participation showed that this topic moves many people.

Read here how your colleagues deal with the topic "Clean air in non-sterile production areas".

Question 1: How do you define the "room classes" for manufacturing of non-sterile products in your company?

The obvious favourite for the designation of the non-sterile "room clas-ses" is the continuation of the "alphabet" as stated in Annex 1 – namely the letters E and F. 51% of the participants choose this classification scheme for designation of their non-sterile production areas. Designating such areas by "grey/black" is less common, at around 17%.



About 25% of those taking part in the survey chose options other than those we provided. A more detailed evaluation revealed that about 11% of the respondents chose a class D environment for non-sterile produc-tion – partly with reference to corresponding requirements from abroad. Also, ISO 8 and even ISO 7 are used as reference for classification. In practice, this of course also means that the requirements for classifica-tion, qualification and monitoring listed

in Annex 1 and ISO 14644 must be complied with. For the respective companies this means considerable (additional) expenditure, which must not be underestimated!

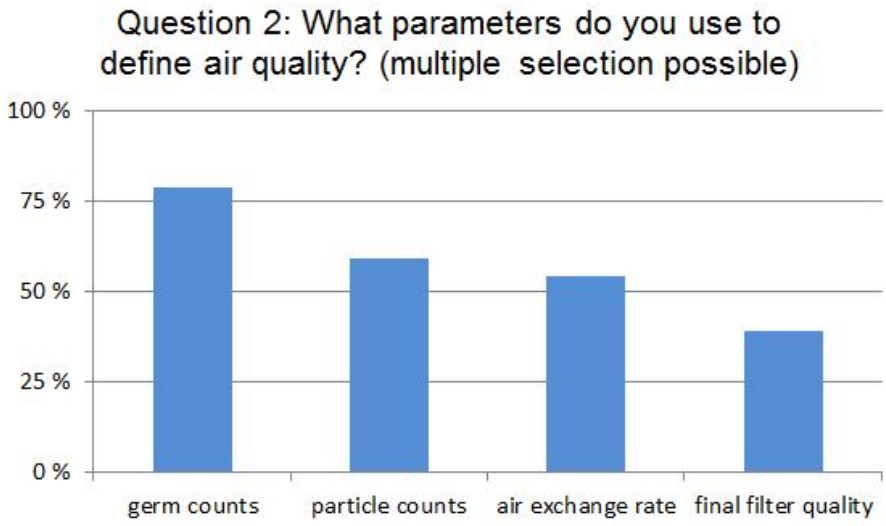
Question 2: What parameters do you use to define air quality? (multiple selection possible)

One result is clearly evident: almost 80% of those surveyed define air quality on the basis of a permissible **bacterial count**. But also the **particle count** is used by almost 60% of the participants, followed by the **air exchange rate**, which 54% of respondents use to define air quality. The **final filter quality** also frequently serves as a criterion for defining the air quality in non-sterile production, at almost 40%.

Since multiple selection was possible for this question, we took a closer look. How do the answers relate to the results of Question 1?

Those who classify their non-sterile production areas as **ISO 7** or **ISO 8** according to ISO 14644 inevitably have to define air quality on the basis of the particle count – this is also confirmed in the survey. In this context, the air exchange rate was stated as an additional criterion.

The answers of those companies that define their non-sterile production areas as **Class D** are also hardly surprising: Annex 1 contains clear specifications for particle counts (only for at-rest conditions) and germs. Accordingly, particle and germ counts were mentioned by all participants. Another parameter used to define air quality is the air exchange rate.



However, the vast majority of respondents – around 86% – have chosen their own concepts for non-sterile manufacturing and therefore cannot rely on requirements from GMP regulations or standards. The interesting question is: What kind of picture does this produce?

Definitely a very heterogeneous one!

In the large group of those who designate their non-sterile production areas as "**E/F**", germ counts are the most frequently used parameter (85%). Particle counts (55%), air exchange rate (42%) and final filter quality (36%) follow at some distance.

From our point of view, it is surprising that within this group 15% do not specify any demands on the microbial air purity, at all. It is also noteworthy that the type and number of parameters used to define air quality vary widely. Some companies go all out and specify all four parameters. Almost one third is satisfied with defining only one parameter – predominantly germ count. A majority of 40% follows the strategy "two is better than one" and uses 2 parameters – mainly germ count and particles, but also all other combinations are represented.

Anyone who now believes that a similar picture emerges in the group of those who designate their non-sterile production areas as "**grey/black**" will be disappointed: although the number of selected parameters ranges from one to four, all parameters are represented at equal rates here. A similar picture is obtained for those who designate their production areas as **CNC/NC** (controlled not classified / not classified) or have chosen other, individual designations such as "hygiene zone" or "surrounding area".

Question 3: Do you monitor air quality in the non-sterile manufacturing area?

The answer to this question is quick and easy: a large majority of 78% answered "yes". The structure and scope of such monitoring processes was dealt with in questions 4-6 (see below). At this point, we were also interested in the people who answered "no": we wanted to know which alternative to monitoring they would choose (question 7). All were asked whether their decision was based on a risk analysis (question 8).

Question 4: What impurities do you monitor? (multiple selection possible)

A look at the graph shows that almost all participants monitor the bacterial counts (96%). Around 63% monitor particulate air purity.

Here, it is important to take a closer look, too: Most people/companies who do monitoring monitor particles and germs (58%). Around 38% rely on monitoring of germ counts alone. Those who define their production areas according to ISO 7 or 8, only monitor the particle count.

It is interesting to see that not all the parameters used to define air purity are applied in monitoring. In some cases, however, particle or germ counts are also monitored, although these were not used to define air quality.

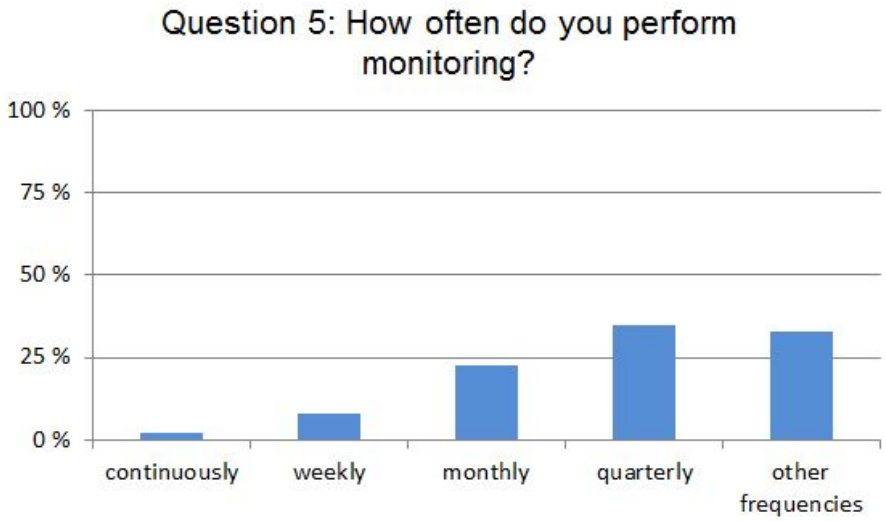
Question 5: How often do you perform monitoring?

Quarterly performance was the most frequent (35%). About every fifth company carries out monitoring on a monthly basis. A differentiated look at the category "other intervals" is very informative:

Many differentiate by area types, whereby production areas are examined more frequently than airlocks. Others differentiate by type of examination, whereby germ counts are monitored more frequently than particles:

- Frequencies for microbiological examinations:
  weekly to 6 months
- Frequencies for particle measurements:
  3 months to 2 years

Such a differentiation by areas and/or type of examination seems to be reasonable and reveals a risk-based approach.

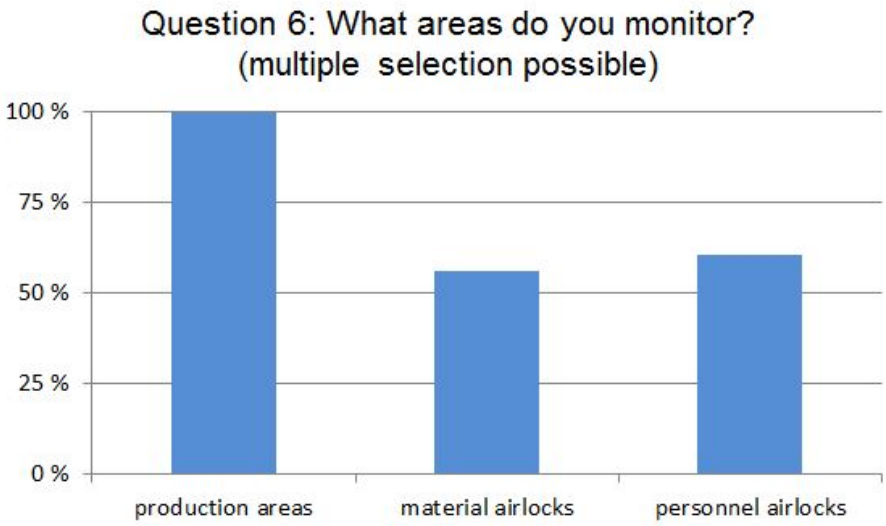


Question 6: What areas do you monitor? (multiple selection possible)

It is evident that all those who carry out monitoring will monitor the ac-tual production areas. However, it is interesting to see that around 60% also monitor the personnel and material airlocks.

Again, multiple selection was possible in this context, which requires a closer look at the answers:

- 38% limited monitoring to the production areas.
- 8% also monitor the personnel airlocks in addition to production areas.
- 54% go all out: they carry out monitoring in production areas, personnel and material airlocks.



Question 7: How do you define the air quality/purity class in non-sterile areas and how do you ensure it?

This question was addressed to all those who DO NOT carry out monitoring and had to be answered individually. Unfortunately, not everyone took the time to do so. It can be seen from the responses given that regular checks are carried out, even if they are not referred to as "monitoring". These include air filter checks, measurements of germ and particle counts and regular re-qualifications.

Question 8: Did you make the decision to monitor as a result of a risk assessment?

In times of risk-based thinking and acting, the answer is surprising: around 42% of participants gave an honest "no" as their answer. One possible reason for this is that the underlying rules have been in place for a long time and have therefore not been reassessed in terms of risks. 58% state that they have carried out a risk assessment. But let's take a closer look here as well:

Within the monitoring group, 55% carried out a risk analysis to justify the nature and scope of the examinations. The remaining 45% should ask themselves whether they are doing the right thing in terms of the nature, scope and frequency of examinations. If you do too much of a good thing, it costs time and money unnecessarily. If you do too little or perhaps the wrong thing, risks may arise that will have to be addressed at the next inspection.

Among those who do not monitor, this decision is based on a risk as-sessment in 50% of cases and is justified by different arguments. The remaining 50% may well be confronted with unpleasant questions during an audit or inspection.

It would certainly be better for one group as well as the other to justify your decision in a comprehensible way in the sense of a risk assessment.

Summary:

What can we deduce from the results?

Well, a lot is being done to define and control air quality even in "non-sterile" production. This advocates the efforts of manufacturers to ensure a high quality level of the production environment even without regulatory requirements.

However, the picture is not very consistent. The options for structuring and designing monitoring, which we queried in questions 4-6, provide a large range of implementation variants in practice. In simplified terms, these range from the annual germ count determination in the production areas to the monthly monitoring of germs, particles and air exchange rates in production areas, staff and material airlocks. Some have set the requirements very high, others content themselves with a minimal approach.

In practice, such different approaches are certainly justified. Unfortunately, the results of our survey do not provide any information about the underlying products, processes or premises. However, these ultimately form the basis for decisions in favour of or against the necessity of monitoring and interpretation of monitoring results. But only about one in two can attribute their decisions to a risk assessment. This result is thought-provoking. Neither minimalism nor actionism are justifiable from a GMP point of view if there is no comprehensible justification.

The question of the requirements for non-sterile manufacturing areas is dealt with in many companies in the pharmaceutical industry. As can be seen from the answers of our experts, that we presented in LOGFILE 09/2019, there is a lack of guidelines, recommendations or data for comparison that make it easier for companies to take their decisions and implement a

benchmarking process. We will continue to pursue this topic and are planning a new contribution to the GMP Compliance Adviser in the future.

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