New USP <1116> Approach: Contamination Recovery Rates

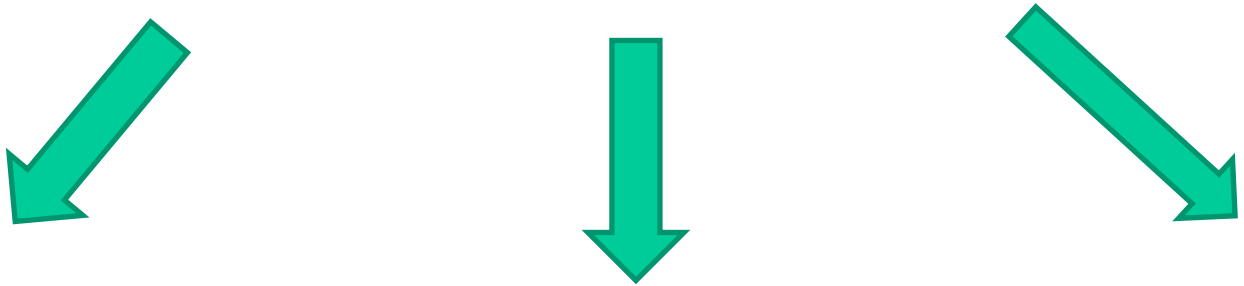
Raphael Bar, **Ph.D.**

BR Consulting
rbar@netvision.net.il

November 28, 2016

BR Consulting

Sampling of Microbes in an Environment



Air:

* Passive sampling (static)
* Active sampling (dynamic)

Surfaces:

* Product contact surfaces
* Floors, Walls,
* Equipment
* Garments
* Gloves

Water

What Microbial Limits?

Limits by the EU GMP Annex 1

19. Recommended limits for microbiological monitoring of clean areas during operation:

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes

(a) **These are average values.**

(b) Individual settle plates may be exposed for less than 4 hours.

Limits by the FDA Guidance

FDA Guidance on
Sterile Drug Products Produced by Aseptic Processing, 2004

TABLE 1- Air Classifications[a] during periods of activity

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
d- The additional use of settling plates is optional.
e- **Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants**.

EU GMP requires trending!

Chapter 6: Quality Control (March 2014)

6.7……the following details should be readily available to the Quality Control Department:

6.7 VI. **Data from environmental** (air, water and other utilities) monitoring, where required;

6.9 Some kinds of data (e.g. tests results, yields, **environmental controls**) should be recorded in a **manner permitting trend evaluation.**

Any **out of trend** or **out of specification** data should be **addressed and subject to investigation**.

Recommendation

In the absence of **any adverse trend**, a **single result above an action level** should **trigger an evaluation** and a determination about whether remedial measures may be appropriate.

Guidance for Industry for Sterile Drug Products Produced by Aseptic Processing - FDA, 2004

FDA requires trend examination!

Warning Letter

Environmental Monitoring

*For example, you **did not utilize environmental monitoring data** to identify environmental control issues and identify appropriate follow-up actions.*

*There were repeated **out-of-action-level (OAL) results from microbial testing**, but **you did not examine the data for trends or take appropriate follow-up action.***

*Your SOP "No. MIP/047/R7 Microbiological Evaluation of Clean Rooms and Other Controlled Environments of Suite **(b)(4)** Area" describes **OALs** as **(b)(4)** CFU for setting plates inside the RABS (ISO 5) and **(b)(4)** CFUs for your ISO 6 area.*

Warning Letter WL: 320-15-14
Mylan, India; August 6, 2015

Contamination Recovery Rates

USP <1116> is changing the approach to microbial monitoring!

Current regulatory Action Limits
have been eliminated from the USP <1116>!

Contamination Recovery Rates

Definition: CRR

$$\%\ \textit{Contamination Recovery Rate}:$$

$$= \frac{\textit{Number of all contaminations obtained till a given month}}{\textit{Total number of samples tested till a given month}} \times 100\%$$

Contamination Recovery Rates

CRR

Cumulative % ***Contamination Recovery Rate***:

$$= \frac{Number\ of\ all\ contaminations\ obtained\ till\ a\ given\ month}{Total\ number\ of\ samples\ tested\ till\ a\ given\ month} \times 100\%$$

A long-term measure of performance!

Monthly % **Contamination Recovery Rate**:

$$= \frac{Number\ of\ contaminations\ within\ a\ given\ month}{Number\ of\ samples\ tested\ within\ a\ given\ month} \text{x} 100\%$$

A short-term measure of performance!

Limits by the USP <1116>

Table 3. Suggested Initial Contamination Recovery Rates in Aseptic Environments[a]

Room Classification	Active Air Sample (%)	Settle Plate (9 cm) 4 h Exposure (%)	Contact Plate or Swab (%)	Glove or Garment (%)
Isolator/Closed RABS (ISO 5 or better)	<0.1	<0.1	<0.1	<0.1
ISO 5	<1	<1	<1	<1
ISO 6	<3	<3	<3	<3
ISO 7	<5	<5	<5	<5
ISO 8	<10	<10	<10	<10

These recommendations do not apply to production areas for nonsterile products or other classified environments in which fully aseptic gowns are not done.

Why Contamination Recovery Rates?

Because of the **inherent variability** of microbial sampling methods, contamination recovery rates are a **more useful measure of trending** results than is focusing on the number of colonies recovered from a given sample.

USP <1116>

Contamination recovery rates: Main features

1. The CRR concept seems to be a useful general metric of the quality of the monitoring process.

It is:

* *easy to compute*
* *simple to understand*
* *easy to communicate*
* *easy to trend*

When to act?

Action should be required when the contamination recovery rate trends above these recommendations for a significant time.

USP <1116>

Counting every colony!

Warning Letter

*For example, on August 22, 2012, an FDA investigator observed your microbiologist reading an **environmental monitoring** (personnel) plate. The **microbiologist reported** the result for that plate as **zero**; however, **our FDA investigator** **observed one (1) colony forming unit** (CFU) on the plate. Your microbiologist corrected this observation on the form WI-MI-150-108-J Microbiology Laboratory after the FDA investigator pointed it out to him.*

Warning Letter WL: 320-13-09
Apotex, Inc., Canada, February 21 , 2013

SIGNIFICANT EXCURSIONS

USP <1116>

Excursions beyond **approximately 15 cfu recovered** from **a single ISO 5 sample**, whether from airborne, surface, or personnel sources, should happen very infrequently.

When such ISO 5 excursions do occur, they **may be indicative of a significant loss of control** when they occur within the ISO 5 critical zone in close proximity to product and components.

Thus, any ISO 5 excursion >15 cfu should prompt a careful and thorough investigation.

A value of 15 cfu should not be considered significant in terms of process control, because realistically there is no difference between a recovery of 14 cfu and one of 15 cfu. Microbiologists should use practical scientific judgment in their approach to excursions.

SIGNIFICANT EXCURSIONS

USP <1116>

Microbiologists should review recovery rates **for at least two weeks before the incident** of abnormally high recovery so that they can be aware of other recoveries that might indicate an unusual pattern.

Microbiologists should carefully consider all recoveries, including those that are in the more typical range of 1–5 cfu.

The identity of the organisms recovered is an important factor in the conduct of this investigation!

Some References

1. General Chapter <1116> Microbiological control and monitoring of aseptic processing environments. USP 39.
2. R. Bar, Charting and trending of microbial environmental monitoring data, Journal of Pharmaceutical Science and Technology 2015, 69, 743-761.
3. R. Bar, Approaches to charting and setting control limits for environmental monitoring microbial data. Chapter 10 in PDA/DHI Contamination Control in Healthcare Product Manufacturing, Volume 4,Eds. R. E. Madsen and J. Moldenhauer, pp. 277 – 310, 2016
4. R. Bar, PDA Letter, September-October, 2016.