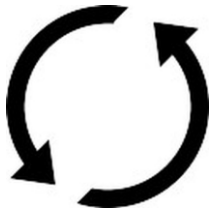
CBE
Centre for Biopharmaceutical Excellence

# Facility Operation and Monitoring

# Evolution, not Revolution

# Progression of Cleanrooms

**REVOLUTION (1)**
**(Past / Now)**

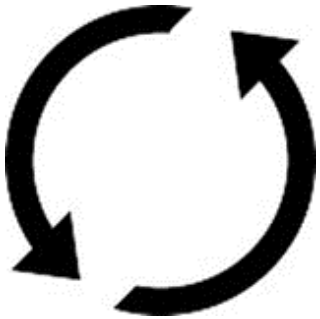


**EVOLUTION**
**(Now / Future)**

**REVOLUTION (2)**
**(Future)**

# Current Issues

**R E V O L U T I O N (1)**



# Current Issues

- Limited Understanding of Cleanrooms
- Poor design
- Over-design
- Poorly tested and characterised cleanrooms
- Out-dated regulations

# Current Cleanroom Testing Practices

- Little to no interaction between customer (manufacturer) and supplier (testing company)
- Testing company nominates sample locations
- Little to no consideration of occupancy states
- Some test methods questionable. e.g Room Recovery
- Pressure on tester to give a compliant result
- Cleanroom owner has no engagement with the facility
- No analysis or scrutiny of room design or effectiveness of operation
- Cleanrooms do not improve

# New ISO 14644 Standards

**E V O L U T I O N**

# New ISO 14644 Standards

Part 1 – Classification of air cleanliness by particle concentration (Published 2015)

Part 2 – Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration (Published 2015)

Part 3 – Test Methods (Under review)

Part 4 – Design, Construction and Start-Up (Under review)

Part 16 – Code of practice for improving energy efficiency in cleanrooms and clean air devices (Committee Draft prepared)

Part 17 – Particle Deposition Rate (Under development)

# ISO 14644 Part 1 & 2 History

| | |
|---|---|
| 1999 | First edition of Part 1: Classification of Air Cleanliness published |
| 2000 | First edition of Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1 published |
| 2001 | Notice of cancellation of FED-STD-209E. US adoption of Parts 1 & 2 |
| 2002 | AS/NZS ISO 14644 Part 1 and AS/NZS 14644 Part 2 published (mirror document with extra appendices) |
| 2005 | First meeting to discuss update to Parts 1 & 2 |
| 2015 | New Parts 1 & 2 published |
| 2017 | AS (/NZS) ISO 14644 Part 1 & 2 to be published (mirror document) |

# What is affected by the updated Parts 1&2?

**Legislated Guidelines**

- PE 009 (Annex 1) References **EN** ISO 14644 Part 1 & 2
  - EN ISO 14644 Parts 1 & 2 2015 already released (mirror copy)
- Blood products references PE 009 Annex 1
- Veterinary Code references **AS/NZS** ISO 14644 Part 1

**Other Guidelines & Standards**

- PE010 References **EN** ISO 14644 Part 1 & 2
- USP797 references ISO 14644 Parts 1 (1999) & 4 (2001)
- AS2252.5 (CDSCs) AS/NZS ISO 14644 Parts 1 & 3
- AS2252.6 (Clean workstations) AS/NZS ISO 14644 Parts 1, 4 & 5

**NATA**

- NATA references **AS/NZS** ISO 14644 Parts 1 & 3

# Part 1 classification changes

Table 1 — Selected airborne particulate cleanliness classes for cleanrooms and clean zones

| ISO classification number (*N*) | Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below [concentration limits are calculated in accordance with equation (1) in 3.2] | | | | | |
|---|---|---|---|---|---|---|
| | 0,1 µm | 0,2 µm | 0,3 µm | 0,5 µm | 1 µm | 5 µm |
| ISO Class 1 | 10 | | | | | |
| ISO Class 2 | 100 | 24 | 10 | | | |
| ISO Class 3 | 1 000 | 237 | 102 | 35 | | |
| ISO Class 4 | 10 000 | 2 370 | 1 020 | 352 | 83 | |
| ISO Class 5 | 100 000 | 23 700 | 10 200 | 3 520 | 832 | |
| ISO Class 6 | 1 000 000 | 237 000 | 102 000 | 35 200 | 8 320 | 293 |
| ISO Class 7 | | | | 352 000 | 83 200 | 2 930 |
| ISO Class 8 | | | | 3 520 000 | 832 000 | 29 300 |
| ISO Class 9 | | | | 35 200 000 | 8 320 000 | 293 000 |

NOTE Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level

# Other Classification Changes

ISO 9 now only an “in operation” classification

Intermediate decimal classes – now only 0.5 increment

- “Uncertainties associated with particle measurement make increments of less than 0.5 inappropriate”

Definition of a macroparticle descriptor M

- For particles larger than 5µm

# Impact to Annex 1

| Grade | Maximum permitted number of particles/m³ * | | | | | |
|---|---|---|---|---|---|---|
| | At rest | | | In operation | | |
| | ≥0.5µm | ≥5.0µm | ISO** Equivalent | ≥0.5µm | ≥5.0µm | ISO** Equivalent |
| A | 3,520 | 20 | ISO 4.8 | 3,520 | 20 | ISO 4.8 |
| B | 3,520 | 29 | ISO 5 | 352,000 | 2,900 | ISO 7 |
| C | 352,000 | 2,900 | ISO 7 | 3,520,000 | 29,000 | ISO 8 |
| D | 3,520,000 | 29,000 | ISO 8 | Not Defined | Not Defined | Not Defined |

* Table derived from PE009-8 Annex 1 Clause 4

**Approximate (e.g. for ISO 7 ≥5.0µm limit is 2,930 as per AS/NZS ISO 14644 Part 1)

5µm concentration for Grade A and Grade B at rest no longer recognised

ISO 4.8 no longer recognised

# Points to Consider

Updated Annex 1?

Federal Standard 209E only considered one particle size - 0.5µm.

- Grades A and B will be out of step with other Annex 1 grades
- However there is no requirement to qualify to more than one particle descriptor in ISO 14644 Part 1

# Points to consider cont…

Why keep the 5µm descriptor?

- From Annex 1 – Regular counts of particles ≥5µm… *"may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation."* Clause 13 (part)
- Microbe Carrying Particles (MCPs). Micro contamination in this space typically occurs when a microbe attached to a large particle (>5µm) enters the work space.
- ISO 14644-1 gives permission to use ≥5.0µm through the macroparticle descriptor M.
- **Classify** according to ISO 14644-1 using ≥0.5µm only. **Monitor** according to Annex 1 using both ≥0.5µm and ≥5.0µm .

# The new sampling method

Old method based on the “square root of n+1” sampling technique

New number of samples based on a unit area, where the particle distribution is considered homogenous

- $2m^2$ for cleanrooms $<12m^2$
- $4m^2$ for cleanrooms $>12m^2$

To make sampling cost effective, statistical model is applied that…

*“…provides at least 95 % confidence that at least 90 % of the cleanroom or clean zone area does not exceed the class limits.”*

*ISO 14644-1 :2015 A.4.1*

# Table A.1 from ISO 14644-1:2015

| Area of cleanroom (m2) less than or equal to | Minimum number of sampling locations to be tested ($N_L$) |
|---|---|
| 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 |
| 636 | 26 |
| 1000 | 27 |
| >1000 | See Formula (A.1) |

If a room area falls in between two areas, the greater of the two should be selected.

Note that these are minimum samples. Additional locations or samples within a location can be selected.

Statistical model asymptotes at around 29, for cleanrooms above 1000m².

Above 1000m² a new formula is applied:

$$N_L = 27\ x\ \left(\frac{A}{1000}\right)$$

Formula A.1

# Location of samples

From section A.4.2:

a) use the minimum number of sampling locations $N_L$ derived from Table A.1

b) divide the whole cleanroom or clean zone into $N_L$ sections of equal area

c) select within each section a sampling location considered to be representative* of the characteristics of the section, and

d) at each location, position the particle counter probe in the plane of the work activity or another specified point.

In addition to the above:

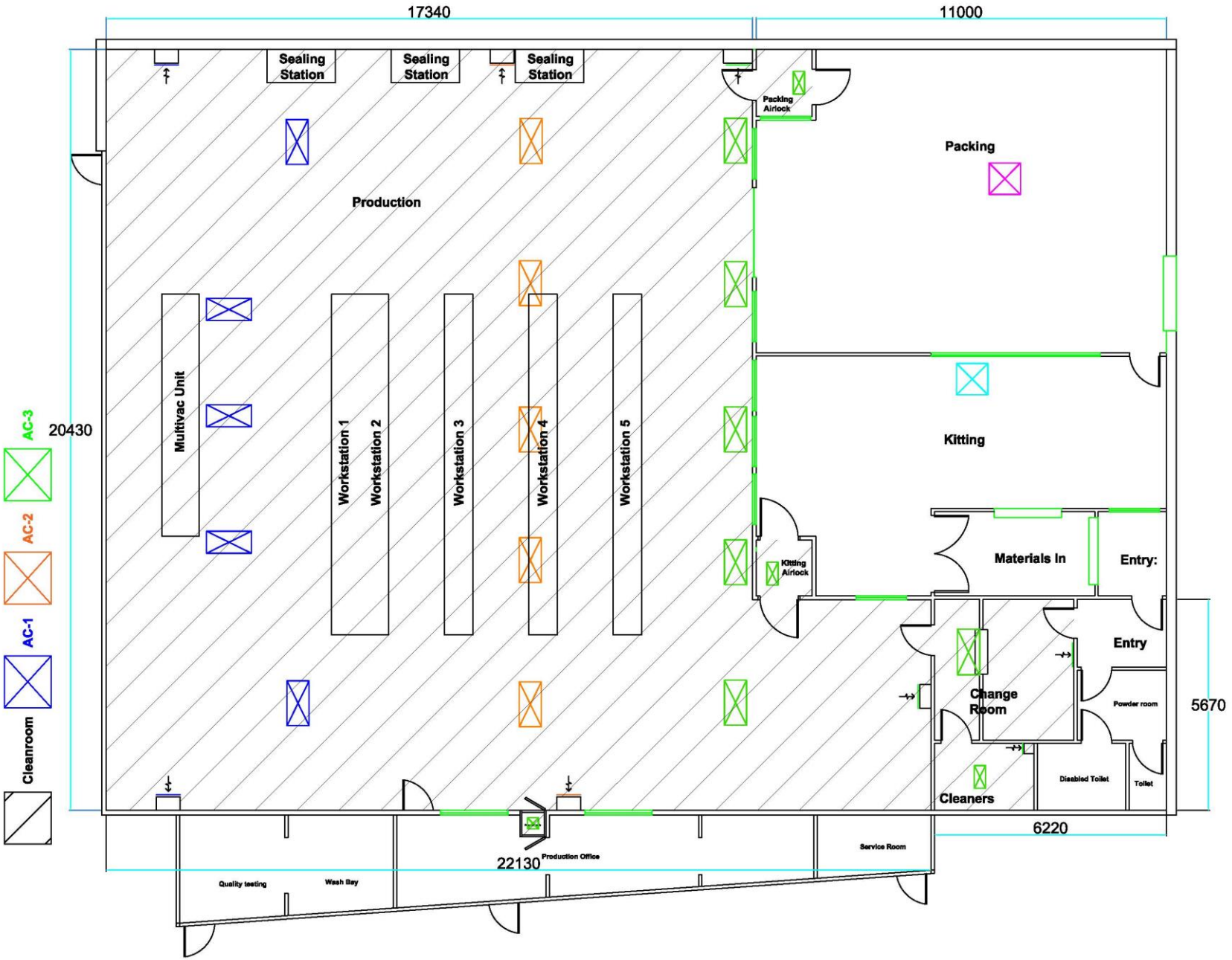
- You can choose other locations considered critical
- You can use additional sampling locations to facilitate subdivision into equal sections

* Locations may not be representative if they are located directly beneath non-diffused supply air sources (A4.2.1)

# CASE STUDY – Lovell Surgical Supplies

- Medical device company
- Cleanroom renovation project
- Designed for the preparation of surgical packs before terminal sterilisation
- Facility to operate to Grade C
- Rooms certified to the new ISO 14644-1:2015

# Facility layout

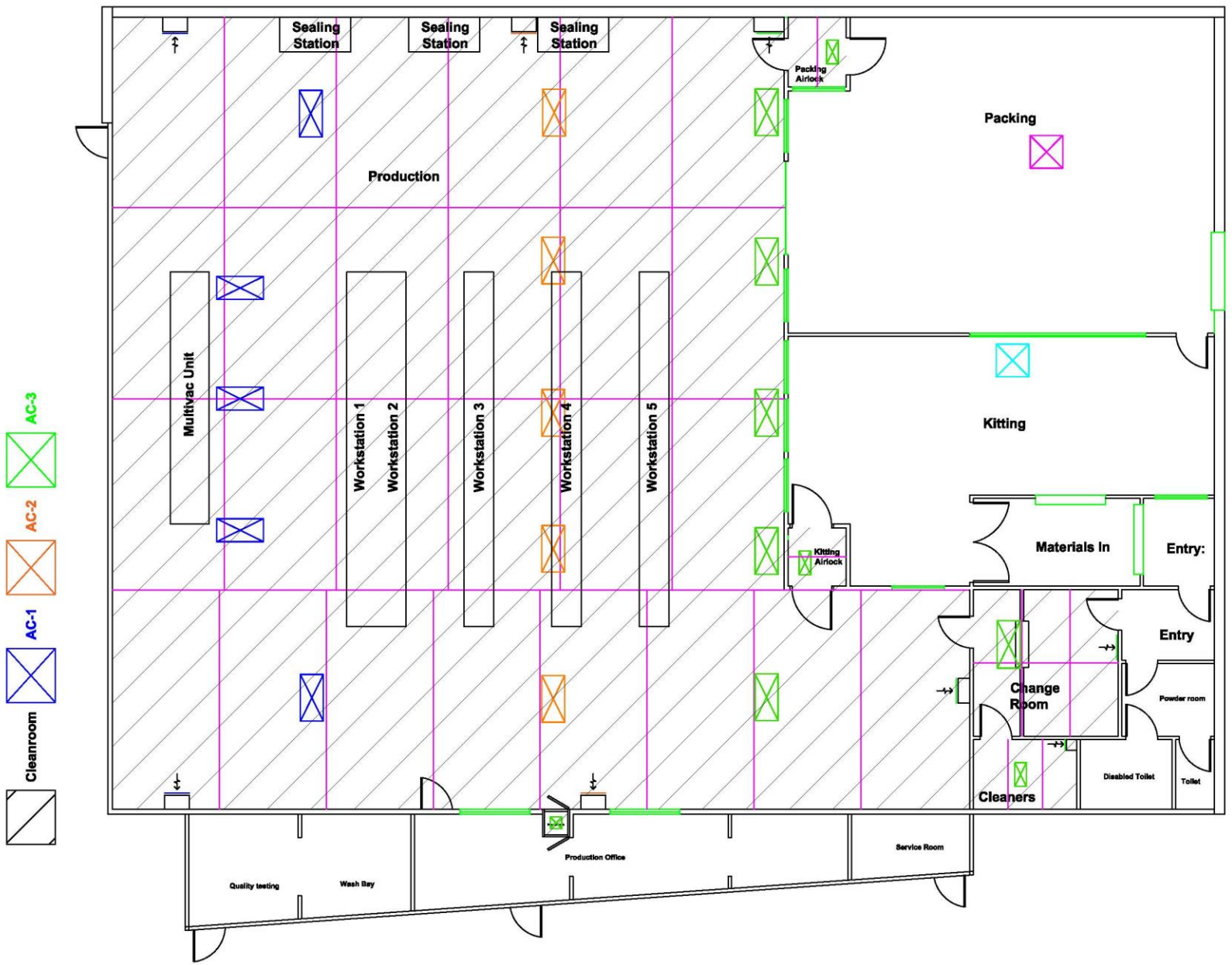


# Applying Table A.1

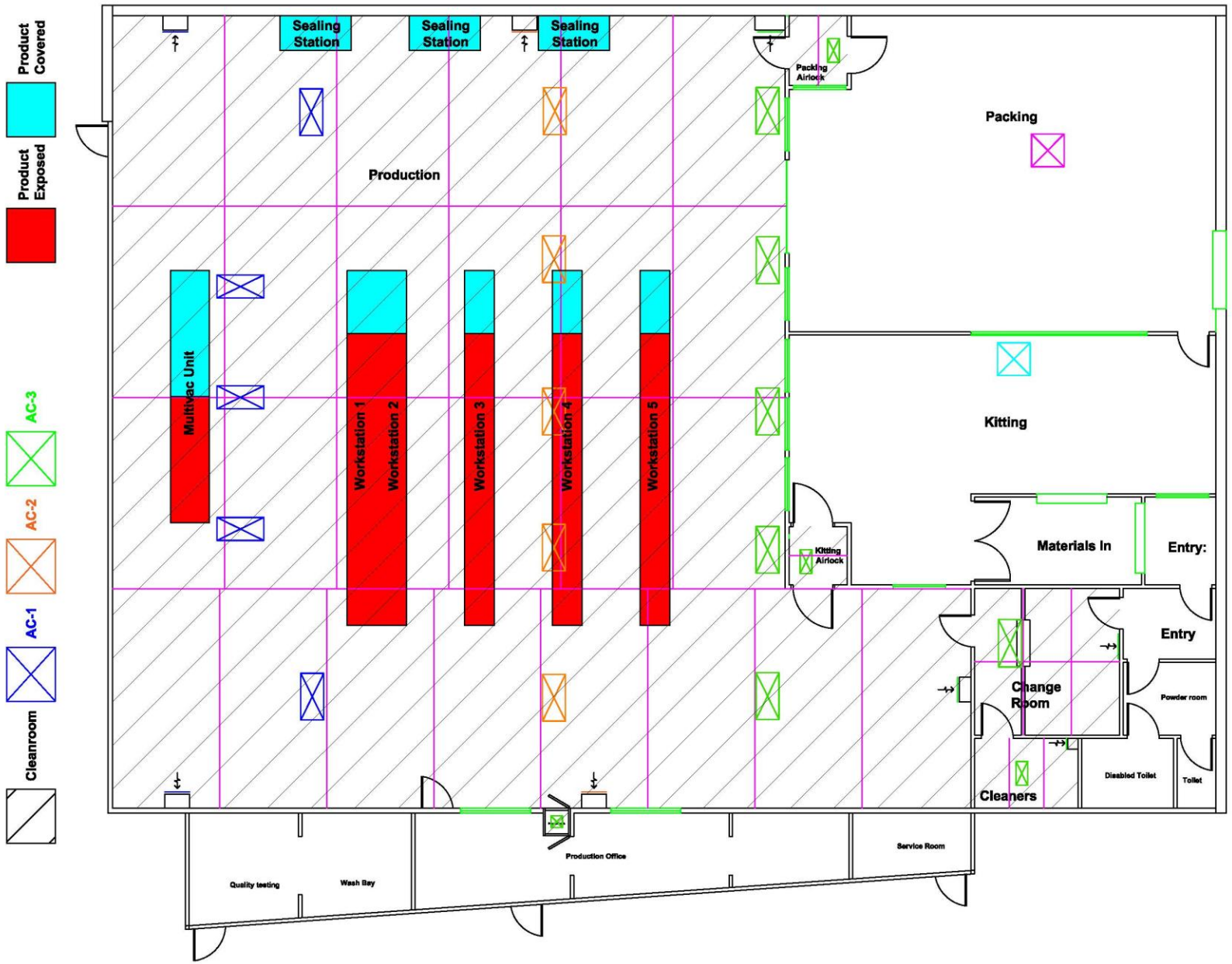
| Room | Area | Supply | Class At-Rest | No. of Samples |
|---|---|---|---|---|
| Change Room | 14.1 | 220 | 7 | 6 |
| Cleaner | 4.8 | 50 | 7 | 3 |
| Kitting Airlock | 2.3 | 60 | 7 | 2 |
| Production | 381.4 | 4200 | 7 | 25 |
| Packing Airlock | 2.7 | 60 | 7 | 2 |

- Extra sample provided for Production to maintain sample area size (26).
- Total samples 39. Under old standard, would require 31.

# Sampling areas



# Analysis of sampling areas



# Choosing a “representative” sample location

- Document what is happening in each location
- Consider areas you are interested in
- Consider directional flow of air (smoke studies)
- State a reason for your choice
- Remember guidance provided in A4.2.1
- Use coordinates (X,Y) from one corner when documenting locations
- Determine height of working plane
- In this case we used the same locations for at-rest and in operation. Other facilities may consider different or extra locations for in operation

# Sample Area Matrix

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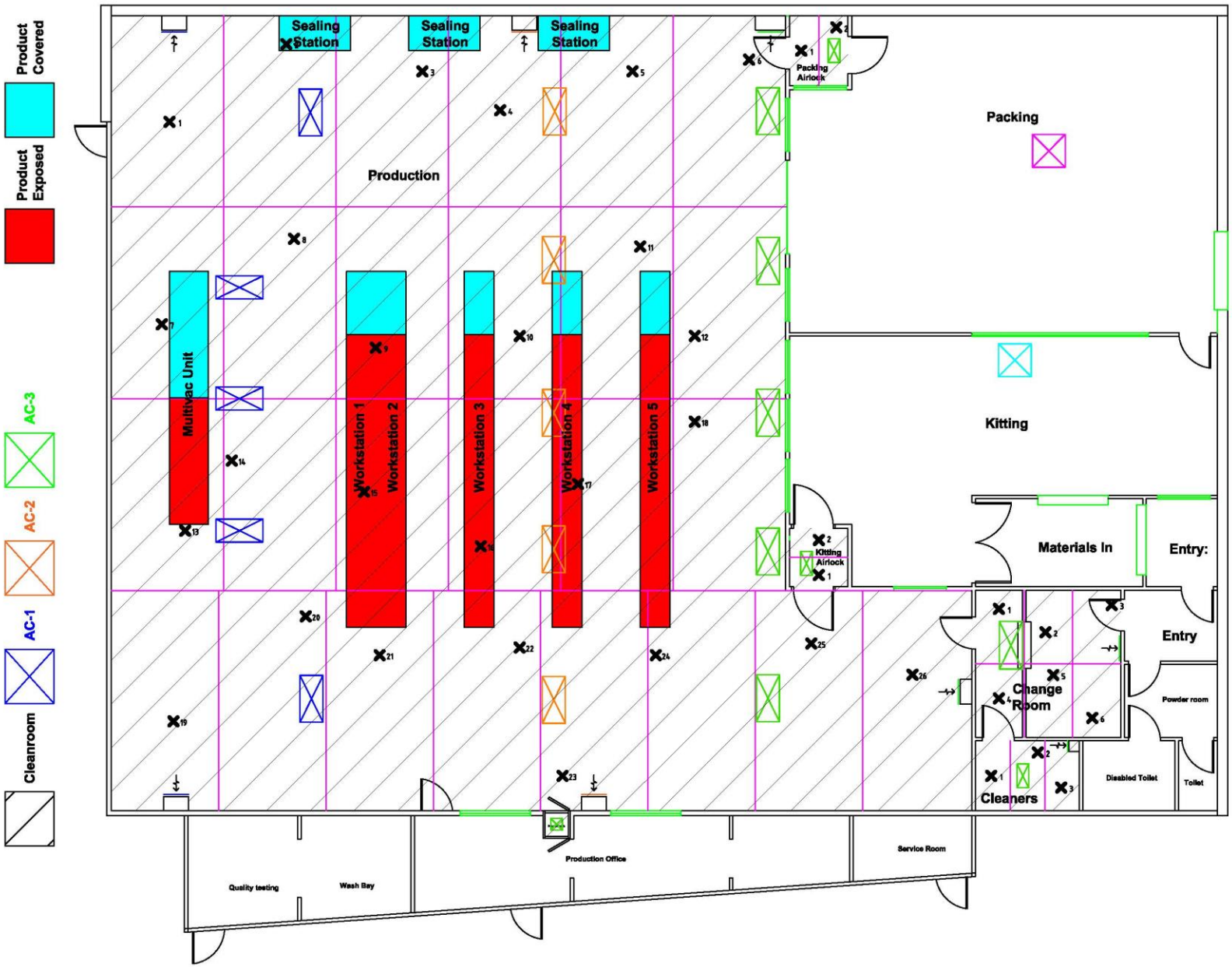
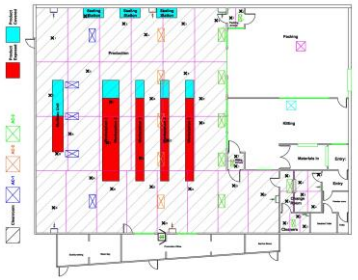
| Room | Section | Coordinates | | Activites in Section | Product | | HEPA | Return | Entry / Exit / | Rationale for Location | At-Rest | In Operation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | X Coord | Y Coord | | Exposed | Covered | Supply | | Em. Ex | | Requirement | Requirement |
| Change Room | 1 | 600 | 3300 | Gowning | | | X | | X | Monitoring gowning location | ISO 7 | ISO 8 |
| | 2 | 1800 | 2700 | Preparation for Gowning | | | | | | Monitoring airflow off gowning location | ISO 8 | N/A |
| | 3 | 3500 | 3400 | Entry to Change Room | | | | X | X | Monitoring entry to Change Room | ISO 8 | N/A |
| | 4 | 600 | 1000 | Gowning, Entry to Cleaner | | | X | | | Monitoring exit from Cleaner | ISO 7 | ISO 8 |
| | 5 | 2000 | 1600 | Preparation for Gowning | | | | | | Monitoring entry to gowning location | ISO 8 | N/A |
| | 6 | 3000 | 500 | Preparation for Gowning | | | | | | Monitoring entry to gowning location | ISO 8 | N/A |
| Cleaner | 1 | 400 | 900 | Entry to Cleaner Room, Storage | | | | | X | Monitoring entry to Cleaner | ISO 7 | ISO 8 |
| | 2 | 1600 | 1500 | Storage | | | X | | | Monitoring cleaning preparation location | ISO 7 | ISO 8 |
| | 3 | 2200 | 600 | Preparation of Cleaning Equipment | | | | X | | Monitoring cleaning preparation location | ISO 7 | ISO 8 |
| Kitting Airlock | 1 | 750 | 300 | Transition of Material into Production | | X | X | | X | Monitoring conditions at Airlock Exit | ISO 7 | ISO 8 |
| | 2 | 750 | 1200 | Transition of Material into Production | | X | X | | X | Monitoring condition at Airlock Entry | ISO 8 | N/A |
| Production | 1 | 1500 | 17700 | Setdown Space | | X | | X | X | Monitoring setdown location | ISO 7 | ISO 8 |
| | 2 | 4500 | 19700 | Sealing of Packages, Setdown Space | | X | X | | | Monitoring conditions at Sealing location | ISO 7 | ISO 8 |
| | 3 | 8000 | 19000 | Sealing of Packages, Setdown Space | | X | | | | Monitoring conditions at Sealing location | ISO 7 | ISO 8 |
| | 4 | 10000 | 18000 | Sealing of Packages, Setdown Space | | X | X | X | | Monitoring conditions at Sealing location | ISO 7 | ISO 8 |
| | 5 | 13400 | 19000 | Sealing of Packages, Setdown Space | | X | X | | | Monitoring conditions at Sealing location | ISO 7 | ISO 8 |
| | 6 | 16400 | 19300 | Pathway to Packing Airlock | | X | X | X | X | Monitoring conditions at Cleanroom Exit | ISO 7 | ISO 8 |
| | 7 | 1300 | 12500 | Multivac Unit - Packed Material | | X | X | | | Monitoring conditions at Multivac | ISO 7 | ISO 8 |
| | 8 | 4700 | 14700 | Standing Space Between Workstations | | | X | | | Balancing sampling distribution | ISO 7 | ISO 8 |
| | 9 | 6800 | 11900 | Workstations, Packed and Unpacked Materials | X | X | | | | Monitoring exposed product location | ISO 7 | ISO 8 |
| | 10 | 10500 | 12200 | Workstations, Packed and Unpacked Materials | X | X | X | | | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 11 | 13600 | 14500 | Workstations, Packed and Unpacked Materials | X | X | X | | | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 12 | 15000 | 12200 | Standing Space Between Workstations | | | X | | | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 13 | 1900 | 7200 | Multivac Unit - Unpacked Material | X | | X | | | Monitoring airflow to Multivac | ISO 7 | ISO 8 |
| | 14 | 3100 | 9000 | Standing Space Between Workstations | | | X | | | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 15 | 6500 | 8200 | Workstations - Unpacked Materials | X | | | | | Monitoring exposed product location | ISO 7 | ISO 8 |
| | 16 | 9500 | 6800 | Workstations - Unpacked Materials | X | | X | | | Monitoring exposed product location | ISO 7 | ISO 8 |
| | 17 | 12000 | 8400 | Workstations - Unpacked Materials | X | | X | | | Monitoring exposed product location | ISO 7 | ISO 8 |
| | 18 | 15000 | 10000 | Standing Space Between Workstations | X | | | | | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 19 | 1600 | 2300 | Setdown Space | | X | | X | | Monitoring setdown area | ISO 7 | ISO 8 |
| | 20 | 5000 | 5000 | Setdown Space | | X | X | | | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 21 | 6900 | 400 | Workstations - Unpacked Materials, Setdown Space | X | X | | | X | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 22 | 10500 | 4200 | Workstations - Unpacked Materials, Setdown Space | X | X | | | X | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 23 | 11600 | 900 | Workstations - Unpacked Materials, Setdown Space, Pass Thru | X | X | X | X | X | Monitoring conditions at Cleanroom Exit | ISO 7 | ISO 8 |
| | 24 | 14000 | 4000 | Workstations - Unpacked Materials, Setdown Space | X | X | | | | Monitoring airflow to workzone | ISO 7 | ISO 8 |
| | 25 | 18000 | 4300 | Exit of Kitting Airlock, Path to Workstations | | | X | | | Monitoring conditions at Cleanroom Entry | ISO 7 | ISO 8 |
| | 26 | 20600 | 3500 | Exit from Changeroom, Path to Workstations | | | | X | X | Monitoring conditions at Cleanroom Entry | ISO 7 | ISO 8 |
| Packing Airlock | 1 | 300 | 900 | Transition of Material into Packing | | X | | | | Monitoring conditions at Airlock Entry | ISO 7 | ISO 8 |
| | 2 | 1200 | 1500 | Transition of Material into Packing | | X | X | | | Monitoring conditions at Airlock Exit | ISO 8 | N/A |

# Sampling locations

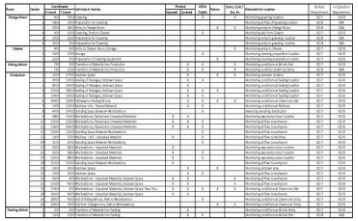


# A useful tool…


- Much more suitable for a cleanroom than a measuring tape
- Needs a clear line of site to the “X” wall and the “Y” wall
- Also useful when preparing layouts
- Give this device to your room certifier along with:
  - The Sampling Locations Map



  - The Sample Area Matrix



# ISO 14644 Part 2 Changes

- Instead of “Specifications for testing and monitoring”, now just about monitoring
- Very little that will be new to the Life Sciences industry

Note:

From PE009-8 Annex 1, Clause 7 (part)

*EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.*

This is no longer the case. The test frequencies will be moved to the updated Part 3. Currently they are in limbo (TGA has provided guidance on this)

From the introduction of ISO 14644-2:2015:

*In some circumstances, relevant regulatory agencies may impose supplementary policies, requirements or restrictions. In such situations, appropriate adaptations of the monitoring procedures may be required.*

# ISO 14644 Part 3 Changes

A much delayed update to this standard is pending

Important meeting held in June

Many editorial and technical challenges to current draft

Unlikely to be published this year. Perhaps an updated DIS prepared by end of October

Structure will be largely the same. Extra test described - segregation

A key message is the importance of communication between the tester and the owner

Standards Australia committee to consolidate AS 1807 standard for cabinets only. All cleanrooms to be tested to Part 3

# ISO 14644 Parts 4 and 16

ISO 14644 Part 4: Design, Construction & Start-up is being updated.

ISO 14644 Part 16: Energy Savings is a new Code of Practice.

Both are being revised / developed con-currently.

Both re-think the way cleanrooms are designed and operated.

# The science of cleanroom air supply

Designing a cleanroom by air change rate, based on room volume, is bad science

For non-unidirectional flow cleanrooms, clean air dilutes contamination as it is generated. The ceiling height is irrelevant

This can be represented by the following equation:

$$Q = \frac{D}{\varepsilon . C}$$

Where:

Q = Supply air (flow rate) ($m^3/s$)

D = total particle dispersion rate from personnel and machinery/s

ε = Contamination Removal Efficiency

C= required airborne particle concentration (no./$m^3$) in the considered location (i.e. from ISO 14644 Part 1, Table 1)

# Using the science

Uncertainties on particle generation and the contamination removal efficiency make calculations difficult without real data

Useful as a guide, but this formula cannot be used as the sole basis for designing a cleanroom

For an existing cleanroom, data can be gathered and the equation applied

Thus, for a new cleanroom, the ability to reassess the air supply rate at a later date and reset to a lower energy position can be justified

Most of your contamination is coming from your people

Simply improving your gowning or increasing your cleaning frequency can allow you to reduce your air supply

# Turndown / Setback

If there is nothing happening in a cleanroom, then there is minimal contamination being generated

Room air pressures MUST be maintained

Variable air flow rate during manufacturing is possible:

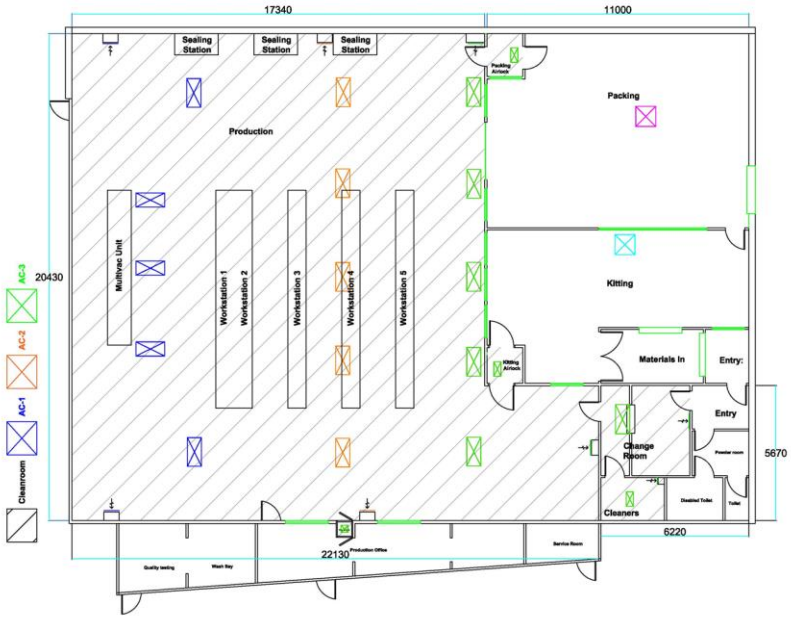
- Specific manufacturing activities
- Number of personnel in the room
- Control programs that can anticipate contamination

# Lovell example

Cleanroom operates successfully at a traditionally low air change rate (<15 air changes an hour)

Main cleanroom had three air conditioners:

- AC-3 provides conditioned air and maintains the room pressures
- AC-1 & AC-2 just moves conditioned air around
- AC-1 & AC-2 are turned off overnight
- AC-3 ensures that central cleanroom pressure is maintained



# The future

R E V O L U T I O N (2)

# The future

Even with current technology, non-viable particle counting is an inexact science

Viable particle count results take time with old technology. The new technology still needs more work, but will revolutionise eventually

Do we need to continue to care about the particle concentration of particles between 0.5 and 5.0 micron in the corner of the room near the low level return?

Are we underestimating, or ignoring, something very important?

# What do we know?

- Viable particles getting into our products is bad for business
- Viable particles are typically carried on non-viable particles that are >12 micron in size (Microbe Carrying Particles – MCPs)
- Particles <5 micron are easily entrained in moving air and removed from the cleanroom
- Particles >5 micron tend to settle out in low air flow and are re-entrained into the air through movement of personnel. They are only removed through cleaning
- In general, the critical area in a cleanroom is a very small proportion of the overall area.

Therefore the greatest threat in a cleanroom is a large particle that settles in a critical area. This can be evaluated through the Particle Deposition Rate.

# ISO 14644 Part 17

ISO 14644 Part 17 – Particle Deposition Rate (PDR)

Committee draft (CD) currently being prepared by WG14

Proposed to provide guidance on:

- How the PDR for particles (or macro-particles) should be measured in a cleanroom at critical locations in order to establish control of airborne contamination, and how it should be monitored to demonstrate control;
- describe major mechanisms of particle deposition;
- methods used to measure the PDR;
- how to establish the required maximum level of a range of particles sizes;
- how to use the relation between PDR and product contamination by macro-particles;
- aspects of operational methods in a cleanroom that impact on the PDR during manufacturing.

# Application

The particle deposition rate is an important characteristic for most cleanrooms. Considers particles between 5 and 500 micron.

It highlights the importance of gowning, cleanroom behaviour and cleaning practices.

New technologies are allowing us to monitor these particles in critical areas in real-time.

Traditional technologies allow us to characterise other variables – e.g. proportion of viable particles attached to macro-particles.

Cleanrooms will become smaller, cheaper, more efficient and more effective.

Standard will be adopted readily by electronics, optics, aerospace industries. Life sciences will probably take a little longer.

# Questions ?