CBE
Centre for Biopharmaceutical Excellence

Cleanroom Myths

20th November 2019 – PDA

Introduction

Cleanrooms are an essential element of life science manufacture

Yet we barely understand how they work

This presentation will look at the myths that persist with cleanrooms

It will also look at the opportunities that reality provides

Finally, some simple activities that can be performed, armed with the science

Rules of Thumb

Principals to use when thinking about cleanrooms

- Air moves from high to low pressure
- There are two types of cleanrooms or clean zones:
  - Unidirectional (Grade A) – uses displacement
    - Displacement – clean air pushes contamination out (“leaf blower”)
  - Non-unidirectional (Grade B, C & D) – uses dilution
    - Dilution – clean air dilutes contamination (“mixed drink”)
- Air that comes out of a properly tested HEPA filter should be considered “clean”.

Rules of Thumb cont…

- Particles are sticky. Displaced by impact, or cleaning action
- Particles <5.0 micron are easily entrained in air streams and removed from the room.
- Particles >5.0 micron will quickly settle to the floor and will only be removed by:
  - Low level returns (small portion)
  - Cleaning, or;
  - Cleanroom activity.
- Microbes are transported around cleanrooms attached to particles
- These particles are generally >10 micron in size.

Air Change Rates

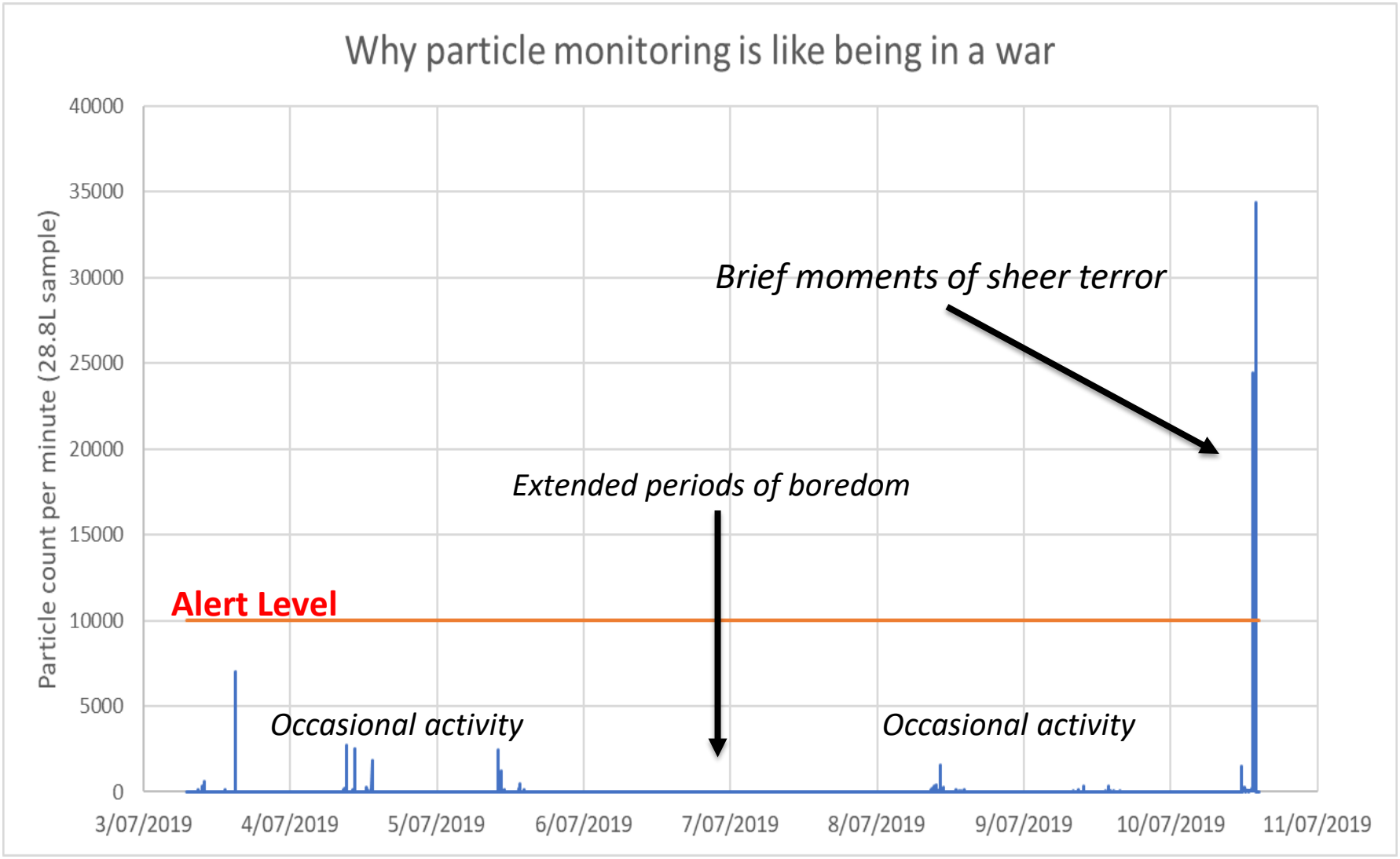
Myth

There is a defined number of air change rates required to maintain a Grade B, C or D cleanroom

Reality

The actual particle concentration depends on what contamination is being generated at any point in time and the air supply rate at that point.

- Even basic cleanrooms spend extended periods at very low particle concentrations
- The reality is that most cleanrooms operate at a far higher air supply rate than is necessary
- Occupancy states very important
  - At-rest – should be easy to achieve within the guidelines
  - In operation – should be hard to achieve within the guidelines
- Our testing and monitoring is focused on results rather than a tool to make our cleanrooms better


Why particle monitoring is like being in a war
Particle count per minute (28.8L sample)
40000
35000
30000
25000
20000
15000
10000
5000
0
3/07/2019
4/07/2019
5/07/2019
6/07/2019
7/07/2019
8/07/2019
9/07/2019
10/07/2019
11/07/2019
Brief moments of sheer terror
Extended periods of boredom
Alert Level
Occasional activity
Occasional activity

Opportunity

We talk about Pharma 4.0 when our cleanrooms are still stuck in 1.0.

- They cost us a fortune to run
- Most of us don't have a clue how they work
- We react to the tiniest deviations, without properly understanding the risk to the patient
- We structure our certification testing protocols in our favour, sometimes to the point that the data we gather is meaningless

A key point of a cleanroom is to remove "the background noise". A white background that brings other errors, either physical or procedural, into sharper focus.

Activity

To move into the next phase of cleanroom design and operation we need data:

- Proper “in operation” evaluation
- An honest assessment of current monitoring locations
- Stress testing of the system
- An understanding of the degrees of freedom you have with your assigned air supply rate

There are challenges:

- This is a new concept. Results may be unexpected and may not give you good news
- We have to get out of the mindset of “don’t poke the bear”
- We need support and of course the permission of cleanroom owners
- We need support, but not necessarily the permission of regulators

Humidity

Myth

Room humidity must be kept low in order to inhibit microbial growth

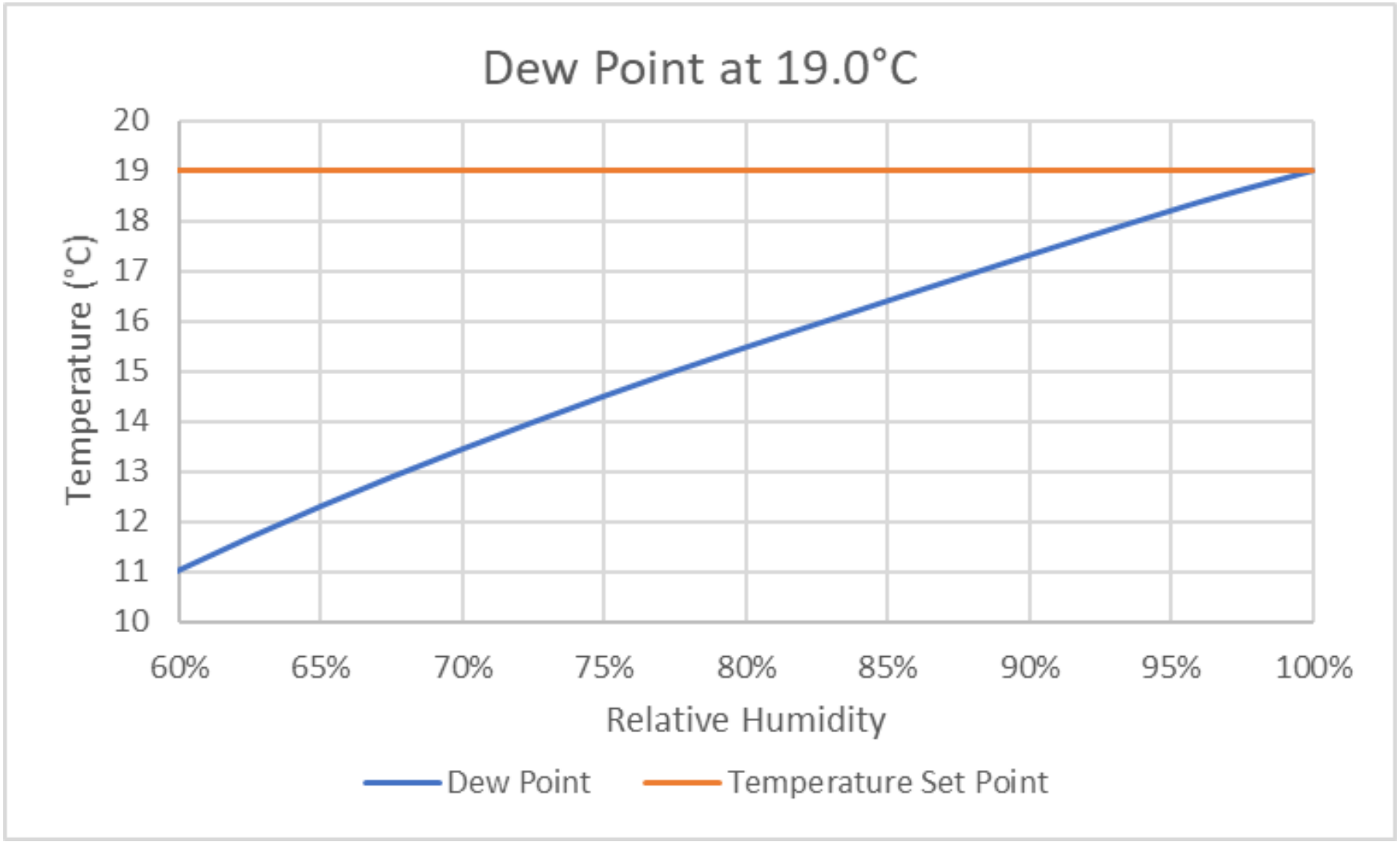
Reality

Air must be kept above its “dew point”

Dew Point – temperature at which water vapour in air will condense

- The higher the relative humidity the closer the air temperature is to the dew point
- Surface water will provide a medium for microbes to grow
- Making low humidity air is expensive – cool it down, then heat it up

Long term high humidity is still a problem


Dew Point at 19.0°C
Temperature (°C)
20
19
18
17
16
15
14
13
12
11
10
60%
65%
70%
75%
80%
85%
90%
95%
100%
Relative Humidity
Dew Point
Temperature Set Point

Opportunity

Most cleanrooms are a “box in a box” – minimal external temperature effects

Temperature control is generally very tight (± 1.0°C)

Look for problem areas for condensation:

- Windows
- External walls
- Services pipes e.g cooling water
- Starting up after shut down

Warning: Humidifiers

- Fail catastrophically
- Many installed, most turned off
- Provide little benefit for Australian conditions

Benefits:

- Real humidity risk
- Data for targeted microbial monitoring locations
- Is only an alert limit required for humidity excursions?

Activity

- Trend your temperature and humidity data
- Evaluate surface temperatures in your cleanroom
- Beware of surfaces colder than room temperature
- Pay particular attention to:
  - Mornings
  - Service connections
  - Windows
  - External walls
- Re-evaluate your alert and action limits
- Re-assess your microbial monitoring locations
- Re-assess your HVAC humidification / de-humidification

Contractor Competency

Myth

“These guys should know what they’re doing…”

Anonymous (with good reason)

Reality

Installation of a sensing device in a Grade D cleanroom

Testing Fraud

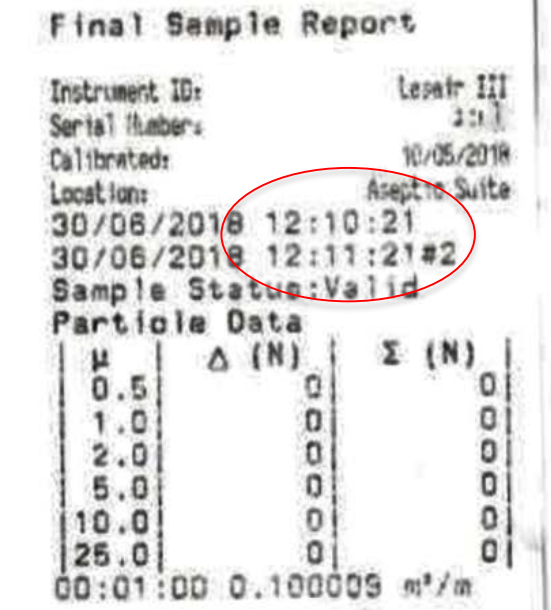
- ISO 5 Cytotoxic cleanroom
- “Protocol required four samples to be taken across the cleanroom

Final Sample Report

Instrument ID: Lasair III
Serial Number: [illegible]
Calibrated: 10/05/2018
Location: Aseptic Suite
30/06/2018 12:09:21
30/06/2018 12:10:21#1
Sample Status:Valid
Particle Data

µ	Δ (N)	Σ (N)
0.5	1	3
1.0	0	2
2.0	2	2
5.0	0	0
10.0	0	0
25.0	0	0

00:01:00 0.089970 m³/m

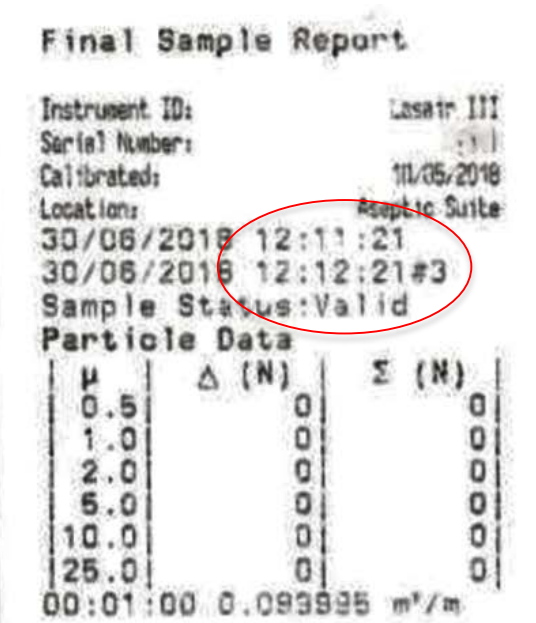


Final Sample Report

Instrument ID: Lasair III
Serial Number: [illegible]
Calibrated: 10/05/2018
Location: Aseptic Suite
30/06/2018 12:10:21
30/06/2018 12:11:21#2
Sample Status:Valid
Particle Data

µ	Δ (N)	Σ (N)
0.5	0	0
1.0	0	0
2.0	0	0
5.0	0	0
10.0	0	0
25.0	0	0

00:01:00 0.100009 m³/m

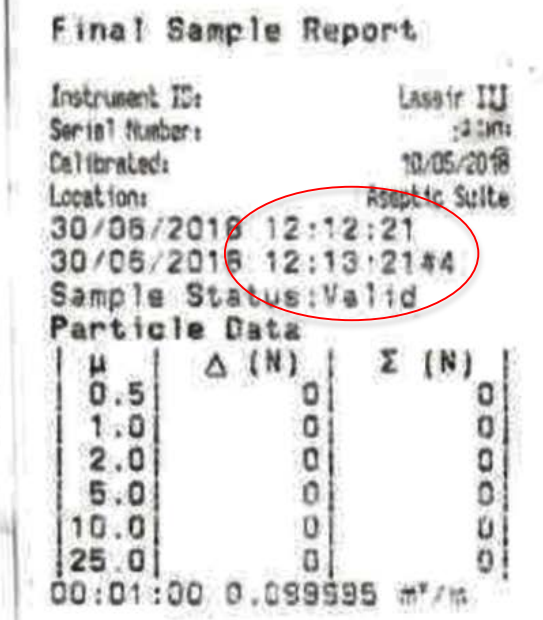


Final Sample Report

Instrument ID: Lasair III
Serial Number: [illegible]
Calibrated: 10/05/2018
Location: Aseptic Suite
30/06/2018 12:11:21
30/06/2018 12:12:21#3
Sample Status:Valid
Particle Data

µ	Δ (N)	Σ (N)
0.5	0	0
1.0	0	0
2.0	0	0
5.0	0	0
10.0	0	0
25.0	0	0

00:01:00 0.093995 m³/m



Final Sample Report

Instrument ID: Lasair III
Serial Number: [illegible]
Calibrated: 10/05/2018
Location: Aseptic Suite
30/06/2018 12:12:21
30/06/2018 12:13:21#4
Sample Status:Valid
Particle Data

µ	Δ (N)	Σ (N)
0.5	0	0
1.0	0	0
2.0	0	0
5.0	0	0
10.0	0	0
25.0	0	0

00:01:00 0.099995 m³/m

Warning Sign

- Very low values for ISO 5 at-rest in a cleanroom

Evidence

- No time gap between samples

Other issue

- Sample size too low (should be ~700L for ISO 5)

WHO Global Guidelines for the Prevention of Surgical Site Infection

4.23 Laminar airflow ventilation systems in the context of operating room ventilation

Recommendation

The panel suggests that laminar airflow ventilation systems should not be used to reduce the risk of SSI for patients undergoing total arthroplasty surgery.
(Conditional recommendation, low to very low quality of evidence)

Opportunity

Educate ourselves on the tasks that contractors are engaged to do

Don’t leave cleanroom testers to their own devices

- Dictate what they do, where they go and what they use
- Supervise, watch, question, nag, demand and review, review, review
- There are many who are knowledgeable and are very good at their job. Knowledge and competence do not necessarily come cheap

When hiring contractors:

- Qualify previous experience
- Beware of the use of “clean room” in place of “cleanroom” or worse still calling them a “lab”
- If you don’t have all the answers, have access to an independent person that does

Activity

Review your vendor assurance programs…

…before the TGA next read your cleanroom certification reports

Other Myths and Realities

Myth : *Grade A air is an effective cleaning agent*

Reality : *Settled particles can only be effectively removed by wiping actions.*

Myth : *For environments where toxic and infectious agents are handled, negative pressure rooms are essential*

Reality : *Occasional internal contamination versus constant infiltration of external contamination*

Myth : *HEPA filters do not capture bacteria and viruses*

Reality : *They actually do a pretty good job of it.*

Other Myths and Realities cont…

Myth : *All pass thrus on the market are appropriately designed*

Reality : *Many ventilated units are no more effective than static pass thrus.*

Myth : *The more airlocks you have, the cleaner your critical environments will be.*

Reality : *Once gowned, you shed particles at the same rate, regardless of your environment.*

Myth : *Faster air in Grade A is better*

Reality : *In some cases <0.36m/s would be better*

Myth : *You can't perform a room recovery for Grade D*

Reality : *You can, but its very easy to get bad data.*

Nothing can be done?

Myth

We are beholden to the standards and guidelines and how they are applied by regulators

Reality

In terms of creation and revision of standards and local guidelines:

- Technically limited by your own imagination
- Realistically limited by resources

In terms of how regulators apply them:

- …that's a little more difficult

However, there are a number of other areas where we can have an impact

Opportunity

From a Standards Australia perspective, we need more “doers”.

People from the coal-face with experience of the English written language.

Other things we could do:

- Set up an accreditation course for cleanroom testing
- Special interest groups – local and national to discuss standards and guideline interpretation and implementation
- Mentoring with a technical focus
- TGA liaison, not with lobbyists but engineers, scientists, microbiologists and others who deal with guidelines every day

There is something even more important needed, however:

“I’m really not qualified to say.”

Never spoken by a man in late middle age

Activity

Experience is one thing. But…

…enthusiasm, energy, curiosity and a passion for the topic is what gets things done.

More women on technical committees is essential.

Pathways for young professionals to contribute is also needed.

While the participation at the drafting and approval levels are quite rigid, there are many informal pathways to have your say.

Where these pathways don’t exist, we need to create them

Summary

So…

Once we understand the science we find a range of opportunities, including:

- Improving our operations
- Reducing our costs and footprint
- Better dealing with deviations
- Being more aware with our dealings with contractors
- Opening pathways for further improvement

Thanks

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