As required by Annex 15 and further detailed in Annex 1. CPP's need to be defined, their limits determined and qualification performed at worst case conditions. This is for all direct impact systems. Current audit approaches by many EMA inspectors is to ask these questions directly:-

- What are the CPP's for this system?
- How are the CPP limits qualified?
- How are these limits monitored?

The CPP's of relevance to the Tunnel air flows as referenced in the new Annex 1 have an impact on the temperature distribution and consequently the primary objective of the Tunnel (Depyrogenation and Sterilisation). These are:-

- Differential pressures
- Air flow
- Temperature
- Baffle heights

The last of these, Baffle heights throughout the tunnel, should be verified at OQ stage to be correc t for the various recipes (vial sizes) and control of these (stepper motor control, position feedback and gears) assessed for any potential variability. A well designed tunnel that is well maintained can usually conclude that the baffle height will be fixed for each recipe / vial size and therefore based upon these OQ tests and risk assessment do not need to be adjusted to any 'worst case' limit for qualification. Note however, this is generally not done correctly.

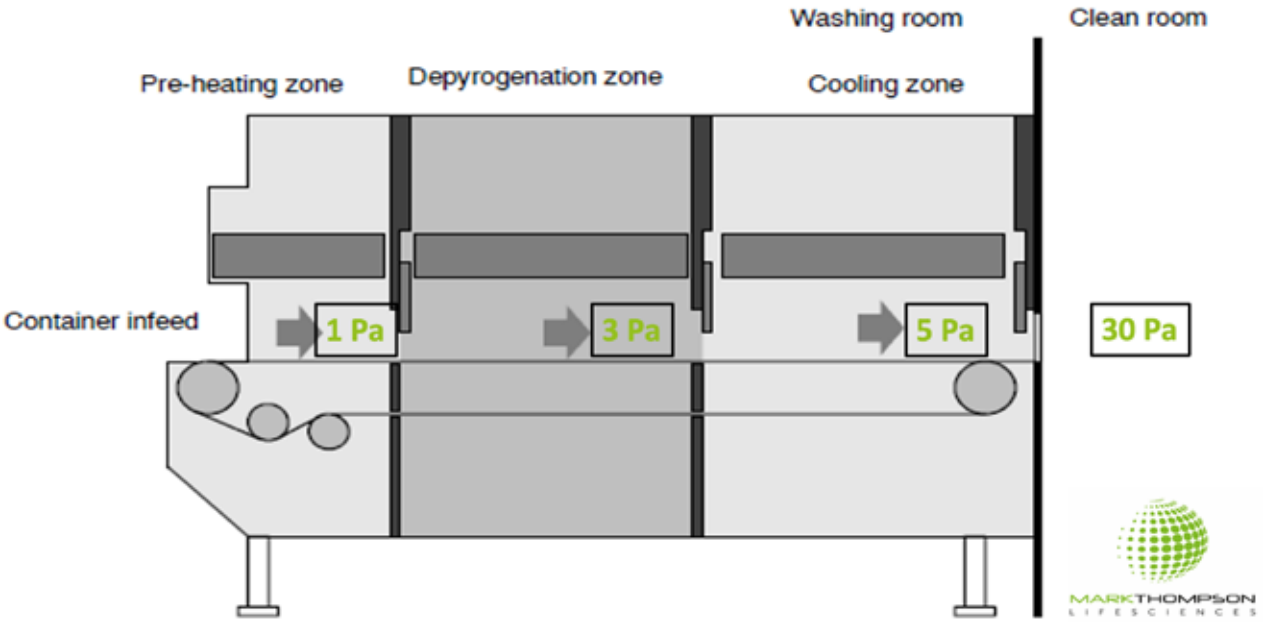
Therefore we are left with three variables (CPP's):-

- Differential Pressures
- Air Flow Velocity
- Temperature

To further assess these the control needs to be understood. This varies from Tunnel to Tunnel, on older tunnels (1980's, 90's) the fan speeds and dampers tend to be fixed and set every 6 monthly qualification. On more modern tunnels the fans and dampers are controlled to achieve the required conditions, on the latest tunnels this is quite complex control to maintain the whole pressure cascade and air flow velocities.
NOTE; In audit I often ask the question how does the Tunnel control. A good site SME will know, a bad site will have no idea what is going on.

This understanding should be included at the DQ stage and the associated risk assessment will identify the CPP's from this.

A well designed and controlled Tunnel will monitor the differential pressures and air velocities in each zone to achieve the required setting, of course these will each have high and low alarms on them. A simple Tunnel with a pressure cascade along the Tunnel will look something like this:-



NOTE; Some Tunnels, particularly feeding isolators at higher pressure will have a sink pressure stage in cooling, possible 2 stage air lock.

So, this will be different for all Tunnels based on physical and control system design, but a simple example of the worst case challenges we would build into CD would be a minimum of the following:-

Differential Pressure Worst Case

If the differential pressure between Cooling Zone and Depyrogenation zone is higher, more likely that cold air will ingress into Depyro zone ; WORST CASE. Therefore understand what it's normal set point is, what the high alarm is and design a challenge run with this differential pressure at its highest.
Differential pressure to the infeed section, generally not tested in terms of thermal performance but is tested in terms of air flow.
Any Impact that the Isolator or Grade A RABS pressure has needs to be assessed, and qualification needs to be performed with isolator closed and operational pressure, however, the DP between Cooling Zone and Depyro Zone is greatest impact.

Depyrogenation Zone Velocity Worst Case

Both high and low velocity can have an adverse impact on temperature distribution, therefore the high and low alarms need to be challenged. Pushing hot (320C air down is hard) and a badly designed Tunnel will not get this right.

Temperature Control

Typically the depyrogenation zone temperature is reduced to the low alarm level, this has always been the case. Temperature distribution can change at higher temperatures but it never goes lower anywhere therefore worst case is the low temperature.
Also the cooling zone air temperature will impact therefore needs to be operating at its lowest limit also.

Cycle Develpoment Approach

To understand the above and verify the limits a minimum approach that we would take would be:-

Cooling Zone Temperature at its low alarm level, as low as it can be in normal operation without alarming.

Depyro Zone Temperature at its low level, low alarm point.

Differential Pressure between Cooling Zone and Depyro Zone at its high alarm level, as high as it can be.

Depyro Zone air velocity control; Under the above worst case conditions run the Tunnel with the Depyro zone velocity at its high level (high alarm) and another run at the low velocity alarm point.

This would initially be done in static conditions for different (bracketed extreme) vial / bottle sizes as the air flow gaps are different and will be considered in the bracket.

Once this is understood, a worst case set of parameters can be established for a running Tunnel Qualification with thermal data. Generally the 'as found' parameters and alarms from the supplier do not work and alarm limits etc are not properly linked to performance as described above, therefore an iterative process.

This package of work establishes evidence that all the associated alarms are set at the correct limits and the Tunnel will still deliver effective performance at all of the worst case limits. It is typically 1 week of work at Cycle development stage pre PQ.

These trials can also provide evidence that the variability is detected by installed Zone Temperature monitoring. But often this is not the case, we are entirely dependent on the other alarms for DP and Velocity.

A modern tunnel will generally have such tight control on DP and velocity that the alarms can be set quite close to normal operational settings. However, all variables need to be considered that can impact the tunnel, such as:-
Supply air pressure to the Tunnel.
Isolator pressure
Room background pressures and changes (doors opening etc)

Full PQ can then be performed at normal operational settings other than reducing the Depyro Zone Temperature. But that needs to be assessed on the data.