Annex 1 update;
The deadline for coming into operation of Annex 1 is 25 August 2023.

A Review the site Contamination Control Strategy.

Keep the CCS open throughout the audit to verify its accuracy. Common deviation here is that the CCS has been developed without proper consultation or knowledge of what really happens, therefore does not reflect actual operational controls and practices. Also questioning how it is actively reviewed, continuous improvement strategy.

B Ask for the Process Flow Risk Assessment and defined Critical Control Points.

How is Risk Assessment maintained live and used in Deviation investigation, change control, annual reviews etc.

C For the defined CCP's ask what the Critical Process Parameters are.

(CPP's Annex 15 and ISPE for CQV). Then verify that the CPP's are in control/monitored/alarmed and link properly to the qualified limits.

D Use the CCP's defined to audit the CPP's and link to new Annex 1 requirements for CCP's.

This way the application of new Annex 1 is linked to criticality, a good way of focusing effort onto the things that are most critical and will therefore have the greatest patient safety impact. Rather than just going through Annex 1 line by line.

Well prepared sites with knowledgeable SME's are ready to clearly present the above. Less well prepared sites are struggling and have a lot of work to do in the next 4 months!

In no particular order, over the next 4 pages, we have listed the top observations / deviations being identified.

1. Re assessment of aseptically filled products that could take some heat treatment.

2. Aseptic process Simulation (Media Fill strategy) not defined considering all variables of process, people, environment.

3. Personnel Training inadequate.
    a. Personnel monitoring inadequate
    b. No procedure for disqualifying personnel (Grade A/B) based on evidence or observed behaviour.
    c. No assessment or monitoring of personal hygiene.
    d. No responsible person identified for personnel monitoring.
    e. Clean Room sock procedure.

4. Sterilisation of Indirect Product Contact Parts (Aseptic processing) and proper definition of which parts are indirect contact.

5. Qualification and Requalification of worst case. No definition or evidence of what worst case loads are.

6. No justification for requalification of all sterilisation load patterns in the CCS.

7. No qualification of the integrity of wrapping materials and sealing systems together with hold time.

8. Sterilisation Processes not monitored independent of control or the monitoring / control locations not independently verified by validation sensor at the same location.

9. Sterilisation Process continuous verification; Defined CPP's and effective monitoring of the CPP's.

10. Unloading autoclaves loads not adequately protected outside the autoclave while cooling to ambient (e.g. Grade A air flow)

11. Load dryness not part of autoclave unloading checks and/ or not reliably achieved. Wet loads!

12. BDT not performed daily on autoclaves without an air detector.

13. Depyrogenation Tunnel differential pressures / pressure cascades not effectively monitored / controlled.

14. Not integrity testing the Tunnel HEPA filters 6 monthly.

15. Endotoxin challenge vials for depyrogenation Tunnel not representative of routine production.

16. No adequate control over the sterilisation of clean room clothing and goggles etc.

17. How are Maintenance Plans established, linked to discussions around maintaining the qualified state.

18. Monitoring CQA's and CPP's, trend analysis etc.

19. Assessment of Maintenance (including breakdown maintenance) impact on sterility. A documented procedure for handover / handback.

20. Strategy for EM:-

    a. EM Risk assessment as part of CCS or linked.

    b. Alert limits set to identify adverse trends for viable and non viable data. Set based upon data analysis of historical EM.

21. EM alarms not based on ft3 measurements. No action defined for particle alarms, ft3 excursions not reported on batch release data.

22. Air flow visualisation studies not performed correctly and not demonstrating compliance under all operational conditions. Lots of bad practice here! Lots of focus on loading isolators and interventions into RABS.

23. Particle counter tubing length, bend radius and tubing spec (Bev for non VHP Tygon for VHP etc).

24. Clean room finishes. Lots of detail on smooth, crevice free etc, but also coved corners, door recesses (feeling top and bottom of doors/frames etc.)

25. Use of keyboards in clean rooms.

26. Clean Room access to Tech spaces and 'black areas' not controlled.

27. Material Transfer; Following material from goods receipt, particularly single use disposable and bought in sterile (stoppers etc). Focusing on transfer into clean room and limitations of IPA spray and wipe.

    a. Approved list of material transfer for Grade A/B, specific risk assessment on these materials and their wrapping.

    b. Active air filtration.

28. Depyrogenation Tunnel belt reversal (during campaign batches) contaminating Garde A Isolator.

29. Pressure Testing high risk heat exchangers (e.g. Tunnel cooling zone)

30. Clean Compressed Air not defined quality specification (ISO8573) and/or specification not correct for Oil, moisture, particulates.

31. Steam Condensate Quality not tested to WFI standards for SIP systems.

32. Steam Physical Properties (NCG/Dryness/Superheat) not tested or tested incorrectly.

33. WFI storage tank vent filter not integrity tested. Trace heating not monitored.

34. WFI not monitored daily by sampling.

35. WFI does not include on line (continuous) TOC.

36. Not monitoring all differential pressures between clean areas, not effective alarms, alarm delays not justified, not linked to CCS.

37. Alarm Criticality Assessments and testing lacking.

38. No deterministic Container integrity test methods. Not giving SVP fusion sealing process 100% Integrity testing. Not qualifying appropriate limit of detection for integrity test process.

39. CCI not linked to time limitations.

40. Visual inspection; No defect criticality assessment, no justification for AQL levels, re inspection process, inadequate training (no training on bias) and requalification of VI operators.

41. Automated VI not qualified against manual VI. Automated VI not challenged as part of every batch.

42. No Rationale for Lyophiliser CIP/SIP, no consideration of product damage impact and requirements for CIP/SIP following vial breakage / ALUS problems. No assessment of Lyo Sterile integrity maintained.

43. Lyo Nitrogen filter not SIP'd or integrity tested in relation to batch release.

44. Grade A detail:-

    a. No visual assessment of APS, in addition to the results, the visual assessment of APS should be part of acceptance criteria. CCTV?

    b. No assessment of the principal of 'First Air'.

    c. No accurate list of inherent and corrective interventions, and/or no risk assessment and qualification of these interventions.

    d. No process for review and engineering out interventions (particularly corrective).

e. No document justifying the scope and approach to APS. Where documents do exist, often weak and not assessing the clear risks defined in new Annex 1). New Annex 1 very comprehensive in this regard and this should be the minimum assessment in APS justification.

f. APS does not include Lyo venting (air filtration rather than Nitrogen)

g. Aseptic processing times and holding times not properly defined and controlled. Not using calibrated time stamps / records.

h. Air flow visualisations not performed under all circumstances. Particular focus on loading Isolators!

i. Gauntlet testing not linked to a qualified limit of detection and inspection not including visual inspection before use.

j. Leak testing isolators not linked to Iso leak test limits for Class 2 or Class 3 leak rate.

k. No EM active (viable and non viable) during isolator loading.

l. Viable monitoring in Grade A and B areas not identifying species level (only if OOS).

m. VHP cycle monitoring! Lots of focus and observations here. Sites generally have no idea what the CPP's are and they are not monitored. This is a finding on many sites – regulatory observations.

n. Gauntlet exposure during VHP – Not separating fingers.

o. 6 monthly requalification of Grade A/B not including full scope of required testing.

p. Stopper hight detection for Stoppering in Grade A air flow missing.

q. Disinfectant Efficacy not being reviewed.

r. Aseptic connections not performed in Grade A and not assessed for asepsis operation.

s. Aseptic product filtration parameters not monitored / controlled within validated range (CPP's) and/or not linked to original validation of the filter. Not recorded or assessed (alarm absence) in the batch record.

t. Unnecessary number of aseptic connections/ manipulations post final filtration.

u. No documented assessment of the challenge organism for BCT, e.g mycoplasma risks or small water born organisms identified in EM programmes. No link to assess this.

v. No maximum time for filter holding post SIP and post FIT.

w. No PUPSIT and no assessment.

x. Inadequate control and validation of SUS. Supplier auditing, VDmax studies not reported, VDmax studies not representative of the SUS used, Supplier agreements lacking.

Issue 5
Data representative of findings over the last 6 months prior to 6th April 2023