David Buckley & Associates Pty Ltd (DBA) ABN 69 103 221 129 7 Catani Place Monash ACT 2904 Australia www.navigategmp.com Phone/fax (61) 2 62914626 info@navigategmp.com.au	**Document #** **BIO001**:	**IND REV**	**Rev.: 2**

Title:

Review of ---------- (company name)
Validation of Dry Heat Steriliser …… (equipment number)

Name of company	
Address	
Company contact name	
Name of product	
Filling line	
Name or reviewer	
Date of review	
Files reviewed	

Full Title

Review of xxx report #. ….

Executive summary

The validation report …: (does or does not) support the validation of xxx when packed in (containers) filled on (equipment name and location)

Recommendations

The company should:

1. Provide evidence

I declare that I have provided this part of the independent review of (company name) validation with no conflicts of interest

Signed

(name and date of reviewer)

Validation requirement	*Observation*	*Acceptability or Recommendation(s)*
1. The sterilisation cycle used should use forced circulation of air inside the chamber in overpressure which prevents non-sterile air from entering. The air entering the chamber should pass through a HEPA filter. Load tests using endotoxins should be a part of validation tests if the sterilisation procedure is also designed to remove pyrogens. The steriliser should preferably be double door and the loading and unloading should take place in areas defined as for loading: not less than Class D, and for unloading open ampoules, or containers which are not hermetically sealed: Class A, or for unloading hermetically sealed containers: Class B for aseptic filling processes, or for other terminally sterilised processes Class C.		1.
Calibration		
2. The requirements for calibrations are: 3. calibration of measuring probes before and (highly advisable) after the calibration measurement, calibration of times, chart recorders, chart speed, 4. check of the calibration of internal probes which measure the temperature and, if necessary, pressure 5. air flow measuring devices, photometers, etc for HEPA air filter integrity test. 6. calibration instruments required are: thermocouples, pressure calibrator, timers, temperature bath, incubator etc.		2.
7. Calibration requirements for EXTERNAL temperature probes – Suggested acceptance criteria for dry heat depyrogenation before validation: accuracy ± 2.0 °C (maximum deviation from the temperature standard after the implementation of correction factors) in two points out which one is near to the depyrogenation temperature		4.

Validation requirement	*Observation*	*Acceptability or Recommendation(s)*
8. stability ± 0.3 °C for a period of 3 minutes (maximum change of temperature under the stable temperature source) for extremely non-linear types of probes (for example: thermistors, some thermocouple probes) 9. linearity ± 2.0 °C under the third medium temperature (the maximum deviation from the temperature standard in the third medium calibration temperature) 10. EXTERNAL temperature probes *after* validation, in the same two points as in course of the calibration before the measurement, also in the third medium temperature in case of non-linear types of probes: 11. accuracy ± 2.0 °C (maximum deviation from the temperature standard) 12. stability ± 0.3 °C for a period of 3 minutes (maximum change of temperature under the stable source of temperature) 13. Twenty per cent of probes out of specifications are tolerated for the post-calibration measurement, ***provided*** they are not the probes placed in critical spots. The validation team has to decide the acceptability of the result of calibration. 14. INTERNAL probes *before* measurement *15.* accuracy ± 0.6 °C (maximum deviation from the temperature standard after the implementation of correction factors) in two points out which one is near to the sterilisation temperature (less than 15 °C) 16. stability ± 0.2 °C for a period of 3 minutes (maximum change of temperature under the stable temperature source) 17. linearity ± 0.6 °C under the third medium temperature (the maximum deviation from the temperature standard in the third medium calibration temperature) 18. INTERNAL temperature probes *after* validation 19. in the same two points as in course of the calibration before the measurement, also in the third medium temperature in case of non-linear types of probes 20. accuracy ± 0.6 °C (maximum deviation from the temperature standard) 21. stability ± 0.2 °C for a period of 3 minutes (maximum change of temperature		

Validation requirement	*Observation*	*Acceptability or Recommendation(s)*
under the stable source) 22. Twenty per cent of probes out of specifications are tolerated for the post-calibration measurement, ***provided*** they are not the probes placed in critical spots, or temperature controlling probes. The validation team has to decide the acceptability of the result of calibration.		

IQ

Validation requirement	*Observation*	*Acceptability or Recommendation(s)*
23. The installation qualification (IQ) demonstrates and documents that equipment and supporting systems have been suitably chosen, correctly installed and that they are in harmony with the required specifications. The following should be checked at least within the installation qualification of the sterilizer:		
24. description of the sterilizer		
25. list of functional specifications, engineering drawings (diagrams, ground plans, piping, etc.)		
26. check of the documentation for completeness		
27. diagrams describing the link-up between individual sub-systems (eg air, power, etc) and the sterilizer		
28. description of supporting systems; connection to the supporting systems (wiring, air, etc.)		
29. indication of critical instruments (chart recorders, temperature probes, etc.)		
30. check of installation of the sterilizer on the spot (all the necessary verifications that the installation reaches the designed intention)		
31. list of spare parts or reference to the list		

32. draft for the SOP for preventive maintenance		
33. draft for the SOP for cleaning or sanitation of the equipment, system, environment		
34. the Installation qualification has to be documented by the validation protocol and by the approved validation report in which the installation is evaluated and further procedure of validation steps proposed.		

OQ		
35. The operational qualification (OQ) documents that the equipment may repeatedly and reliably perform the proposed functions within the operational parameters. The following has to be done within the operational qualification: 36. SOP for sterilisation procedures 37. training records for the operators 38. reliable function of the sterilizer demonstrated during sterilisation procedures with the following tests performed 39. integrity test of filters and tightness test of the installation in the rest state 40. temperature distribution in empty chamber 41. speed and homogeneity of air flow 42. number of particles in buoyancy 43. tests of critical alarms of the control system		
PQ		
44. The Performance qualification should demonstrate appropriate efficiency of the sterilisation cycles used for particular loads. The particular load is defined by the type of material, quantity and geometry of placement. The following tests have to be carried out within the framework of the performance qualification: a. temperature distribution in chamber with load b. heat penetration into the load 45. It is suitable to complete the above mentioned physical tests by the test with biological indicators or with endotoxins		10.

46. The value F_H (T=170°C, Z=20°C) equal to or more than 60 minutes OR F_D (T=250°C, Z=46.4°C) equal to or more than 30 minutes must be demonstrated in every part of the chamber for the depyrogenation process.		11.

Validation requirement	*Observation*	*Recommendations*
47. The difference of temperatures (ΔT^oC) in the chamber may not exceed 25°C during 75 % of the sterilisation period. The USP 26 has +/-15°C when the unit is operating at not less than 250° with no time period specified		12.
48. Filter integrity proof and integrity of the air filter installation • maximum penetration of ≤0.1 % of the concentration before the filter, provided the number of particles in the chamber is met (applies for the filter through which the air enters the chamber, the other filters as per the specification) • proof of the number of particles in buoyancy in hot chamber • maximum permitted number of particles sized 0.5 µm and more - 3500 particles /m^3 • maximum permitted number of particles sized 5 µm and more - 0 particles /m^3 • speed and homogeneity of air flow deviation of speed should not exceed 30 % of the mean value in the output band of filters • steadiness of the speed has to be better than ±20 % from the mean value for every filter in the output band of filter		13.

Validation requirement	*Observation*	*Recommendations*
49. There should be a biological test with biological indicators showing a minimum reduction of spores of Bacillus subtilis by 6 orders of magnitude. Alternatively a load test with endotoxins with a minimum reduction of the quantity of endotoxin by 3 orders of magnitude. The manufacture of the Endotoxin-contaminated containers should be subject to a batch numbering system, for traceability, and a stability study should determine an expiry date.		14.
50. Acceptance criteria: There should be acceptance criteria for all parameters		15.
51. Monitoring and revalidation: If the results of monitoring show standard level of the process (eg if it is demonstrated by statistical evaluation, for example: Process capability $C_{PK}(F_H)$ must be ≥1.33), a revalidation period of not less than one year may apply. If process control is not demonstrated, all the performance qualification (PQ) must to be carried out again.		16.

Other observations	*Recommendations*
	17.
	18.
	19.

Annex 1: F Value

Sterilisation efficacy can be assessed on the basis of temperature and time or on the basis of the calculation of "F" values:

$$\mathbf{F \sum_i 10^{(Ti-Tstd)/Z} . \Delta t_i}$$

Ti instantaneous temperature value

Tstd standard temperature for a given type of sterilisation

Δt_i time interval

Z rate of change of D; temperature change which will cause change of the value D by 1 log

D decimal death rate; time necessary to reduce micro-organisms by 90 % under the given temperature

a) saturated steam sterilisation: $F_o = \sum_i 10^{(Ti-121)/10} .\Delta t$

b) dry heat sterilisation: $F_H = \sum_i 10^{(Ti-170)/20} .\Delta t$

c) dry heat depyrogenation: $F_D = \sum_i 10^{(Ti-250)/46.4} .\Delta t$