SUMMARY

Porous Loads requiring Sterilisation are often a Critical Control Point for the manufacture of Sterile products. Particularly Aseptically filled products. Regulatory guidance in this area is not well documented, other than the fact that all loads should be validated and based upon the validated loading patterns. This leads to load presentations that are inflexible and also a significant amount of qualification and requalification work for all of the presentations that are required on a multi product, multi presentation facility.

The Cycle Development, Qualification and Requalification approach must be rigorous, particularly for Equipment loads destined for Aseptic manufacture, much of this equipment is direct product contact post final filtration and there are no second chances here.

The generally accepted approach is to define the maximum load presentations required and to qualify these maximum loads and a minimum load of each presentation. This qualifies a 'Bracket' and everything in this bracket is qualified by the extremes (Maximum and Minimum load Qualifications with Thermal and BI Challenges).

NOTE; It is also generally accepted, and has been documented by the HPRA that to allow this Bracket the autoclave must have a properly set up and qualified air detector, set up on the small load test pack (Ref; EN285) and on the defined loads.

This document discusses the considerations to be taken in cycle development and load definition stage in defining these brackets and also goes further to discuss if load items within the defined load can also be bracketed. For example a site that has many different filling parts loads all basically the same but with a range of vessels, tubing lengths or equipment sizes. Can these variables within a load also be bracketed this discussion document suggests an approach to bracketing and qualifying such loads. There are 10 challenges set up for load control and assessment, discussed in this document and further detailed in Appendix 1.

1. PHYSICAL LOCATION
2. SPACE OCCUPIED
3. ORIENTATION
4. WRAPPING
5. MASS
6. AIR VOLUME
7. AIR REMOVAL PATH
8. AIR VOLUME TO AIR REMOVAL PATH RATIO
9. DRAINABILITY
10. MATERIALS OF CONSTRUCTION

Annex 1 of the EU GMP Guide requires validated loading patterns to be established. Annex 15 of the EU GMP Guide requires the window of operation and limits to be established and qualified for processes.

1.0 SCOPE

This document is intended to provide guidance for the definition of porous loads requiring moist heat sterilisation. This should be read in conjunction with key reference documents:-

ISO 17665-1	Sterilisation of healthcare products – Moist heat Requirements for the development, validation and routine control of a sterilisation process for medical devices.
EN 285:2016	Sterilisation – Steam – Large Sterilisers.
PDA TR1	Validation of Moist Heat Sterilisation Processes; Cycle Design, Development, Qualification and Ongoing Control.
EU GMP guide	Annex 1 of the EU GMP Guide requires validated loading patterns to be established. Annex 15 of the EU GMP Guide requires the window of operation and limits to be established and qualified for processes.

Porous loads are often also referred to as equipment loads or hard goods loads. These loads will generally be wrapped with single, double or triple layers of wrapping to protect the sterility of the load during transportation when unloaded from the autoclave.

ISO 17665-1 references 'Product Families' for sterilisation; Groups or Subgroups of product characterised by similar attributes such as mass, material, construction, shapes, lumens, packaging system – which present a similar challenge to the sterilisation process. This approach is incorporated here also.

This guidance should be followed when new loads or load items are being introduced to ensure that the load is presented in the most appropriate manner for sterilisation and also that the required qualification work can be defined. Any variability in load items (size, mass, shape, wrapping) can be assessed using this guidance document.

If new or modified load items are to be introduced or changed on an existing load then the assessment described here can be performed to determine whether or not the new or modified load item can be introduced within the Bracket. If the assessment concludes that the new or modified load item fits within the Bracket and meets all of the criteria set out in this guidance document then the review shall be documented, reviewed and approved by all the same responsible people who would review and approve change controls and qualifications on the

sterilisation processes. Physical Qualification (Thermal and Biological Challenges) may not be required.

This guidance document does not discuss or address the autoclave cycle design, autoclave variables or parameters to achieve sterilisation. This document is limited to the impact of the load definition and layout.

2.0 REQUIREMENTS FOR POROUS LOAD STERILISATION

This section discusses the requirements for porous load sterilisation in terms of the load impact so that the analysis of loads can be performed based upon an understanding and not just a set of rules.

The key requirements for the effective Sterilisation of Porous loads are as follows:-

2.1 Air Removal.

Air removal must be achieved from all parts of the load to enable steam to penetrate to all parts of the load. This is measured directly during qualification by measuring the Equilibration Time (EN285 definition) within all parts of the load, particularly the parts of the load which have been assessed as challenging for air removal. In addition this is challenged further through the air detector performance testing.

Any obstruction or restriction to air removal must be considered when analysing load layout and assembly. Particularly:-

2.1.1 The amount of air that needs to be removed from a load item proportional to the air removal path. For example :-
A 60 litre vessel with no top on will be an easier air removal challenge than the same 60 litre vessel with top in place and only a filter for air removal.
A 10 litre vessel with a DN15 valve for air removal may be a more difficult air removal challenge than a 20 litre vessel with a DN50 valve for air removal.

2.1.2 Tubing length and internal diameter have a big impact on air removal performance therefore long lengths of tubing will generally be difficult for air removal.

2.1.3 The difficulty in removing air through material (porosity). If air removal is achieved through a filter the specification of the filter must be considered as the restriction to air flow will be different on different filters.

Also the filter condition prior to and during the sterilisation cycle should be considered. For example; A filter that is put in wet (either due to filter integrity testing or manufacturers recommendations) will behave differently to a dry

filter. Some filter manufacturers recommend filters be put into sterilisation cycles wet to aid with moist heat conditions within the filter. Whilst this may assist with moist heat conditions in the filter it will generally have a detrimental impact on air flow through the filter. Therefore if this filter is being used as an air removal path from a vessel or pipework then air removal will be effected. A filter that is put in dry but may become wet due to the pipework or filter housing draining condensate will also impact air removal.

2.1.4 Physical Barriers to air removal must be considered. Any variability in physical barriers should be clearly identified and controlled. Such as:-

2.1.4.1 Valves that need to be open to allow air removal, fully open.

2.1.4.2 Tubing that needs to be a certain bend radius and unkinked.

2.1.4.3 Blanks that should be removed.

2.1.4.4 Parts that are to be assembled loosely.

2.1.4.5 Wrapping variability

2.1.5 Condensate Collection can also impair air removal. During the air removal phase of the cycle (negative and positive pulses) condensate build up can block or partially block tubing to make air removal harder.

2.2 Steam Penetration.

The considerations for steam penetration are very similar to air removal as the same path is used. Also air removal must be achieved before steam penetration can be achieved. However there are some additional considerations in addition to those listed in 2.1.

2.2.1 As the load gets hotter (during negative and positive pulsing) the load may not have the same physical strength and therefore may move or change shape affecting air removal and steam penetration. For example, silicon tubing will become very soft at high temperatures and may not support the same bend radius as it does at room temperature. Also silicone tubing can collapse and stick together so sealing the line and stopping steam penetration.

2.2.2 Surfaces that become less able to be penetrated when wet need to be considered for changing steam penetration performance.

For example again, a filter that becomes wet during the air removal phase (negative and positive pulsing) will have a greater resistance to steam

penetration due to the filter membrane being wet. If this filter is the path to other items of equipment, attached to a manifold, tubing or vessel, then steam penetration to those other items of equipment can be compromised.

2.3 Load Dryness.

The load and wrapping removed from the autoclave must be dry. A wet load is much more easily re-contaminated than a dry load, also wet wrapping does not have the same mechanical strength as dry wrapping and so can be compromised.

The load being sterilised has to be heated from room temperature to 121°C and will therefore make condensate. This condensate will try to drain away with gravity and will also move with air and steam flows through equipment. The load must therefore by visually assessed to ensure that as far as possible the condensate can drain away from the load or into areas where it will be less of a problem. This drainability assessment should be considered very early on in the load definition as it may be possible to re engineer the load item, orientation or support structure to aid draining as much as possible.

2.4 Equipment / Load Undamaged.

The equipment items, load and wrapping materials must be undamaged by the autoclave cycle. This is primarily an equipment specification check to ensure that the equipment and materials used are suitable for moist heat sterilisation at the temperature and time used. However, from a load layout consideration the impact of other load items should be considered.

Plastic items can deform during the sterilisation cycle if subjected to too much load. Examples of this are; Plastic triclover gaskets clamped tight at room temperature may change shape at sterilising temperature under this load and then may leak post sterilisation, also plastic items supporting heavier items may change shape under sterilising conditions.

Therefore, even if the equipment / material is suitable for steam sterilisation, consider the load on potentially flexible materials to ensure the load is not changed during the cycle.

2.5 Wrapping Integral.

Wrapping is there to protect the load item post sterilisation therefore must not be damaged during the sterilisation cycle.

During air removal and vacuum drying stages the wrapping is subjected to significant air flows and steam flows in both directions, the wrapping has to effectively breath. Therefore the size of the wrapping, the volume of air inside the wrapping needs to be controlled.
For example the same load item in the same wrapping material but with different bag (wrapping) size will potentially perform differently during the cycle.

For this reason the bag size and orientation is equally important to the load definition itself.

3.0 BRACKETING OF LOADS AND LOAD ITEMS

3.1 Minimum and Maximum Loads

A generally accepted approach for the qualification of porous loads is that a maximum load will be defined and qualified for each autoclave cycle.

A minimum load (single load item from this defined maximum load) may also be defined and qualified. Following this qualification any load up to the maximum load may be run in production provided no load items are moved, changed, wrapped differently, oriented differently etc. A simple way of defining this is that you can remove items from the maximum load but not move or substitute anything.

This qualification approach is often referred to as 'bracketing' where the range has been qualified (Max and Min loads) and this has qualified everything within that bracket.

NOTE : The Maximum load defined may be a load that is never run in production but contains items that will be run in production. For example if two filling parts set up loads fit inside the same maximum defined load then this may be qualified as the maximum load knowing that in production only half of this load will be run at any one time. This is an efficient approach to qualification and requalification and still compliant with the Minimum and Maximum Bracket.

For further clarity :-

3.1.1 Load items cannot be moved anywhere other than the qualified and defined location.

3.1.2 Load items cannot be substituted for other load items no matter how similar (unless defined and included in this load bracketing assessment).

3.1.3 The maximum number of any particular load item cannot be exceeded regardless of what else is removed from the load.

3.2 Minimum and Maximum Load Items and Bracketing Assessment.

Bracketing within a load may be considered where a load item has a number of size or specification options. Examples of this would be as follows:-

a) A vessel which is located within the load that could be a number of different sizes dependent upon the product being manufactured.

b) Tubing that has a range of lengths.

c) Filling needles in different internal diameter specifications.

d) Same specification filter in a range of filter sizes.

e) Change Parts of a filling machine for different size vials where the change parts are similar but have a range of sizes.

If this approach is to be taken it must be considered and assessed prior to implementation.

A detailed assessment of the load item being considered for bracketing shall be based upon the following approach.

3.2.1 The load item position within the autoclave chamber must be unchanged.

3.2.2 The load item must not extend beyond the physical space occupied by the maximum load item qualified.

3.2.3 The load item orientation within the wrapping must be unchanged.

3.2.4 The wrapping material used, sealing system and number of layers of wrapping must be unchanged.

3.2.5 The load item total mass must be within the range of maximum and minimum load items at that location.

3.2.6 The load item total volume of air removed must be within the range of maximum and minimum load items at that location.

3.2.7 The length of any air removal paths (tubing, pipework etc) must be within the range of maximum and minimum load items at that location.

3.2.8 The air removal volume proportional to the air removal areas must be within the range of maximum and minimum load items at that location.

3.2.9 The drain ability of condensate from the load must be no worse than the drain ability of condensate from the maximum and minimum loads qualified at that location.

3.2.10 The materials of construction must be the same as the materials of construction of the load item qualified.

APPENDIX 1: ASSESMENT FOR LOAD ITEM BRACKETING.

The detail below relates to the bracketing of a set of load items within a qualified load. For example; if one load item had a range of size options such as a vessel that could be 5L, 20L, 60L or 100L in size.

If the assessments described below can demonstrate that the range of load items all fall within a minimum and maximum bracket then the load items will be qualified by challenging the load extremes only.

If the assessments defined below are completed, documented and conclude that load item bracketing is required then the maximum load shall be qualified with three PQ (Thermal and Biological Challenge) runs. The defined Minimum shall be qualified with one PQ (Thermal and Biological Challenge) runs.

There may also be a requirement to qualify any other extremes of unique load challenges of the individual bracketed items. If any extremes are identified for individual assessment within the 'bracket' then these defined extremes shall also be subject to one PQ (Thermal and Biological Challenge) run. The data is consistent with the data obtained from the load minimum and maximum loads.

Therefore a filling parts load with individual load bracketing on vessel, tubing, filling needles etc. may result in the following qualification approach:-

- Defined Maximum load; based upon maximum load size / mass etc as usual
  - (3 x PQ runs Thermal and BI Challenges).
- Defined Minimum load; based upon single difficult to sterilise load item
  - (1 x PQ runs Thermal and BI Challenges).
- Defined extremes from the Bracketed load; based upon full load but with each bracketed load item at the extreme point defined, based upon the assessment in the following 10 criteria.
  - (1 x PQ run Thermal and BI Challenges).

The following 10 Criteria should be assessed and documented prior to Cycle development and Performance Qualification of the load.

A1.1 The load item position within the autoclave chamber must be unchanged.

The range of load items being considered for bracketing must be located on the same shelf, at the same height and in exactly the same location on that shelf.

The orientation of the wrapped load item must be identical in every aspect.

Photograph all load item variants and describe on these photographs how this criteria is met.

Ensure load preparation and loading SOP's are clear regarding load positioning.

A1.2 The load item must not extend beyond the physical space qualified in the autoclave chamber.

No parts of the load or the load wrapping must extend beyond the volume of the chamber which has been qualified.

This includes any tubing, attachments and the wrapping material itself. Everything must be within the boundaries (Envelope) of the maximum load to be qualified.

Photograph all load item variants and describe on these photographs how this criteria is met.

Ensure load preparation and loading SOP's are clear regarding load positioning.

Example; It may be possible to determine that a 20 Litre vessel configuration is within the 'bracket' to be qualified (Brackets of 5L and 100L vessels) when addressing all of the criteria listed here and therefore the 20L vessel may not require qualification directly. However, in making this assessment is important to determine that no part of the 20 litre vessel, tubing, filters or other components extend beyond the area of the chamber qualified by the maximum load.

If the 20 litre vessel extended higher into the autoclave chamber or closer to the side wall than any part of the maximum load area qualified, then this would need to be qualified as it is moving into a different space where superheat may occur.

If the 20 litre vessel is entirely within the space qualified by the maximum load then the 20 litre vessel would not require qualification and would sit within the bracketed load, provided all other criteria are met.

A1.3 The load item orientation within the wrapping must be unchanged.

Although load item sizes may vary, the orientation of the load within the wrapping or autoclave bags must be unchanged.

This applies to the load item itself and also any attached equipment, tubing, filters, valves etc.

Ensure that smaller load items cannot move into a different orientation which could affect drainage or air removal.

Ensure that lighter load items are positioned in the same orientation. For example, lighter load items on the end of silicone tubing may not weigh on the tubing to put the tubing in the same position as when heavier load items are attached.

Photograph all load item variants and describe on these photographs how this criteria is met.

A1.4 The wrapping material used, sealing system and number of layers of wrapping must be unchanged.

An assessment should be made of the bag / wrapping size in proportion to the load item. For example, load items that are fully bagged; if the smaller load item is placed in the same size bag as the larger load item the bag can move more, and relatively more air has to be removed from the bag.

If the same size bag is used for every load item in the range to be bracketed then the physical challenge / qualification of the minimum and maximum load items in this range will be sufficient.

If a number of different bag sizes are used for the range of load items in the bracketed load then consideration should be given to performing some qualification on the different bag sizes. This may be one PQ run in the range.

Ensure bag sizes are accurately defined in the load preparation SOP and if any different bag or wrapping sizes are used then assess and document the requirements for qualification of the different bag / wrapping dimensions.

A1.5 The load item total mass must be within the range of maximum and minimum load items at that location.

The load item total mass will impact on the amount of condensate made within and on the load. This in turn can impact air removal, sterilisation conditions and load dryness. Therefore the total mass of the load and individual mass of component parts must be within the bracketed range.

For example; with our range of vessel that could be 5L, 20L, 30L or 100L in size. If the 30L vessel was made of a much thicker walled Stainless Steel and was a greater mass than the 100L vessel then it cannot be justified to be within the bracket and must be qualified separately.

The same argument will also stand for component parts. If each of these example vessels has a valve attached and the 20L vessel valve is heavier than the 100L vessel valve then that could produce relatively more condensate which could have an adverse effect on air removal, sterilisation conditions and load dryness.

This assessment must be made and documented for the range of load items.

Example for A 1.5 : Range of vessels

A range of vessels may be considered for bracketing and if all other criteria are met then the maximum and minimum vessels will be the only vessels directly qualified.

However, this load total mass assessment should be performed to ensure that one of the 'bracketed' load items does not exceed the load total mass qualified. In this example, because the 30 litre vessel is supported on a frame, it is possible that the mass of the vessel and the frame will exceed the total mass of the 60 litre vessel, if this is the case then the load item can no longer be bracketed and will be challenge that requires qualification.

(The total mass of the 30 litre vessel assembly AND its supporting wheeled frame may exceed the total mass of the 60 litre vessel.)

A1.6 The load item total volume of air removed must be within the range of maximum and minimum load items at that location.

The total volume of air removed from the load item must be within the bracketed range. This is very likely to be the case if the physical size is within the range, however this should be checked and documented.

For example a range of filling set ups with Manifold, Tubing and Filling needles; if one of the medium sized filling needles (within the bracketed range) had a larger manifold volume then this would fall outside of the qualified (bracketed) range and must be qualified individually.

This requirement is unlikely to be a problem but should be assessed and documented for all bracketed load items.

A1.7 The length of any air removal paths (tubing, pipework etc) must be within the range of maximum and minimum load items at that location.

Particularly relevant to lengths of tubing which are notoriously difficult for air removal and steam penetration, the longer the tubing the greater the challenge.

Tubing lengths and air removal paths must be assessed and documented for all load items in the bracketed range.

A1.8 The air removal volume proportional to the air removal areas must be within the range of maximum and minimum load items at that location.

An assessment of the air removal volume that is required to be taken through the air removal paths should be made if air removal path sizes vary.

Example for A1.8

Our range of vessel that could be 10L, 20L, 30L or 50L in size. If the 50 L vessel had a 15mm diameter line for air removal but the 30 L vessel had a 10mm line for air removal, the 30 L vessel can no longer be assumed to be bracketed.

50 L vessel with 15mm air removal path.
To remove the 50L of air through the 15mm line during a vacuum pulse over 2 minutes would be a volume flow rate of 25 L / min which would be 2.35m/s velocity of air.

(Calculated based upon the area for a 15mm OD line as 1.77×10^{-4} m^2 and the 50 litre volume of air requiring removal 5×10^{-2} m^3)

30 L vessel with 10mm air removal path.
To remove 30 L of air through its 10mm line during the same 2min vacuum pulse would require a volume flow rate of 15 L / min which would be 3.2m/s velocity of air, consequently a greater challenge.

(Calculated based upon the area for a 10mm OD line as 7.85×10^{-5} m^2 and the 30 litre volume of air requiring removal 3×10^{-2} m^3)

Therefore in this example the 30 litre vessel would require a specific qualification challenge as air removal is possibly more difficult.

A1.9 The drain ability of condensate from the load must be no worse than the drain ability of condensate from the maximum and minimum loads qualified at that location.

Very few loads are free draining completely, however, some condensate can be removed by draining. An assessment of the drain ability of the loads in the bracketed range must be made.

Example for A1.9

A filling manifold, tubing and filling needles assembly. If this assembly has a range of filling needle sizes (needle gauge) then the smaller size needles may be less easily drained, in such an example the maximum and minimum needle sizes should be qualified.

Similarly the smaller needles may have smaller tubing and smaller tubing ferrules for connection onto the manifold. Therefore the drain ability of the manifold is affected.

A1.10 The materials of construction must be the same as the materials of construction of the load item qualified.

Different materials of construction and surface coatings react differently to heat transfer, heating and drying. If the load item were identical in every aspect other than material of construction an assessment should be made of what difference this could make to heating and drying phases. The most likely impact of material changes is an effect on load drying and end of cycle load dryness, with plastic materials generally being harder to dry (like for like) than metals.

This assessment may conclude that a change in material may only require a visual review of performance to ensure the load item is undamaged by the cycle and is removed dry from the cycle.