SUMMARY

The Annexe 1 requirement for the annual requalification of sterilization processes is a huge resource requirement as well as a significant amount of downtime for many sites running complex sterilisation processes. Is there a better way?

The following article summarises some examples of applying risk based approaches to the management and control of sterilisation processes. It is a move from a 'tick box' list of compliance activities to a more thoughtful and science based approach. This is delivering improved confidence in better-managed sterilisation processes as well as significantly reduced annual requalification periods.

However, any such development has to be based upon strong foundations, including but not limited to :-

-**THE AUTOCLAVE** : Thorough understanding of the autoclave engineering, cycle development, commissioning and operation.

-**THE LOAD DYNAMICS** : Thorough understanding of the chamber and load dynamics through cycle development, qualification and requalification data analysis.

-**THE DESIGN / OPERATIONAL WINDOW** : Established limits for performance understood and challenged. Foe example on Porous Load autoclaves; properly set up Air Detector, set to induced leak rate of 10mB/min and qualified across the range of loads.

The Majority of Sterilisation Processes **do not** have these strong foundations, therefore these ideas and approaches should not be applied without first understanding the process, the operation and design window.

NOTE : The MHRA have discussed this approach with the author and confirm that although acceptable in principal, each case will be reviewed in detail and must be based upon sound science, thorough risk analysis and well engineered processes.

BACKGROUND

The Annexe 1 requirements for the annual revalidation of sterilisation processes has been interpreted for many years as a requirement to thermally map and biologically challenge autoclaves every year. This is a very significant amount of work and downtime. For some larger sites this is 'like painting the Forth Bridge'.

Historically, an unthinking 'blanket' application of guidelines such as HTM2010 has led to a significant amount of work and cost to demonstrate process effectiveness and regulatory compliance.

- Daily Bowie and Dick type test
- Warm up cycles
- Weekly Leak Rate Test
- Weekly Air detector testing (ADFT)
- Quarterly small load pack thermal testing
- Annual Requalification (Thermal and Biological Challenges)
- Annual Benchmark testing (Empty Chamber, Small load pack test, Air detector performance testing etc)
- Annual Steam Quality Testing (NCG, Dryness, Superheat)

Many of these guideline requirements are unique to Europe and in some cases only rigorously applied to UK and Ireland.

Every one of the tests, challenges and requalifications has a justification. But is this the best way to run a sterilization process??.....

- **Daily Bowie and Dick type test.**

  A simple test to demonstrate effective air removal and steam penetration. However, many sites have run these tests daily on all autoclaves for many years and never seen a failure. If this was any other PM or Calibration we would review this data and reduce the frequency. Also, it can be argued that a properly set up air detector is better monitor of air removal performance and is active on every cycle.

  Based upon other control and indication measures (such as a properly set up air detector and an air detector performance test run with a 10mB/min bleed) some sites have moved this to a weekly test, some sites have stopped running this test altogether saving a cycle on the autoclave every morning and in some cases £10,000 a year on daily test packs, operational and QA review.

- **Warm up cycles.**

  Can be important for porous load / equipment cycles to ensure the autoclave starts from a 'known' state, generally a warm and dry state. However, for a machine that is dedicated to porous loads / equipment loads, has a jacket pre heat and cycle development / PQ work that demonstrates effective operation without a warm up cycle it may not be required. Some sites have re engineered the cycles on autoclaves and produced qualification data to show that a warm up cycle is not required to achieve adequate performance. This potentially saves another test cycle each day.

- **Weekly Leak Rate Test**

  With a correctly set up air detector, the risk of a leak affecting air removal or sterilization efficacy is protected by the air detector alarm. The primary justification for the leak rate test is that throughout the vacuum drying phase 'dirty' air is potentially leaking into the autoclave.
  This needs to be critically accessed. If the autoclave is sterilizing stoppers for use in aseptic fill and the stoppers are unwrapped (stopper washer processor) then the leak rate test will probably be required on every cycle. However if the autoclave is sterilizing equipment held in rapid transfer ports protected by sterilizing grade filters, then the leak rate test may be performed less frequently.

- **Weekly Air detector testing (ADFT)**

  If an air detector is fitted and set up on a porous load autoclave, the air detector will generally be assessed as a critical alarm that requires testing. Whether or not weekly is the correct interval will depend upon the air detector design and the alarm set points. Pressure type air detectors are generally regarded to be more 'fail safe' and may be tested less frequently.

- **Quarterly and Annual Tests**

  - Quarterly small load pack thermal testing.
  - Annual Requalification (Thermal and Biological Challenges)
  - Annual Benchmark testing (Empty Chamber, Small load pack test, Air detector performance testing etc)

All of the above quarterly and annual testing with thermal and biological challenges should be regarded as being too late! If a process is designed and operated so that failure modes can only be identified by this quarterly or annual intervention or test it is badly designed and operated.
If the only test that will identify a failure is an annual requalification, what action would be taken with regard to the previous years production and product?

- **Annual Steam Quality Testing (NCG, Dryness, Superheat)**

  Again, based upon the load being sterilised, and the steam generation system the steam physical testing should be considered as appropriate. For example:-
  Superheat is in some cases impossible to generate on a low pressure clean steam distribution systems. If no failure modes can be identified that would cause superheat there is no benefit in performing this annual test.
  Non condensable gases can be generated at source by feeding cold water to the steam generator, or by failure of the degasser u it in the steam generator. Or by a poorly designed steam distribution system. Again, it makes more sense to monitor the operation of feedwater temperature, degasser operation and design a good steam distribution system. If all failure modes can be monitored then annual testing of NCG may not be required.

  The arguments here are similar to the arguments for the effectiveness of the annual requalification challenges. If we have to rely on an annual test it is too late. It is poor system design. An annual test of steam quality for Porous load autoclaves is still going to be highly recommended as a monitoring tool in the FMEA, however, the point here is that relying on an annual test is too late if there is a problem. Other control measures need to be added to these parameters.

As process risk assessments and process analytical technology develop our understanding of how to improve confidence and control of our manufacturing processes, the value behind these annual tests has become unclear. Indeed a process which relies on an annual check of performance is not going to deliver continued confidence in operation. The main justification that often remains is that it is a regulatory expectation. Annexe 1 makes it clear that sterilization processes should be requalified annually, but goes into no further detail. Annexe 15 explains that a documented review with evidence satisfies the needs for revalidation. Taken together, it is clear that there is no documented requirement for physical thermal and biological challenges.

There is a better way…….

Designing a Sterilisation process that delivers confidence in every production cycle . Delivered through sensible design, a thorough understanding of the criticality and potential failure modes, and operational/QA vigilance on every production cycle. Everything else is too late; the equipment has been used the product has been shipped!

There are now many sites that have taken a more thoughtful scientific approach to the operation of their sterilization processes and moved away from the unthinking 'blanked bomb' approach of testing and requalification to deliver confidence.

These sites have benefited significantly from:-

- Reduced operating costs and increased autoclave availability day by day.
- Improved up time over the year through reduced annual requalification work.
- Reduced Requalification costs.
- IMPROVED CONFIDENCE AND UNDERSTANDING IN EVERY PRODUCTION CYCLE.

The sections below are summaries and extracts from a number of projects that we have undertaken to deliver these benefits:-

RE ENGINEERING THE APPROACH.

The key phases in re engineering the approach to sterilization operation and requalification are as follows:-

1. CRITICALITY ASSESSMENT OF AUTOCLAVE LOADS.
2. FMEA OF AUTOCLAVE OPERATION
3. ACTION TAKEN ON ALL FMEA FINDINGS AND HIDDEN FAILURE MODES
4. OPERATION AND MAINTENANCE DEFINED
5. ANNUAL REQUALIFICATION DEFINED.

1. CRITICALITY ASSESSMENT OF AUTOCLAVE LOADS

Based upon a review of all load items and intended use of the load items, load criticality can be assessed. A load criticality assessment would usually concentrate on areas of manufacture that were critical control points from a sterility perspective, i.e. stages in the process beyond which there is no ability to add to sterility assurance.

CRITICAL CONTROL POINTS

These autoclave loads must be qualified (PQ) to demonstrate a Sterility Assurance Level of greater than 10^{-6}.

These autoclaves must be revalidated annually and this revalidation must include physical requalification using thermal and biological challenges to demonstrate a Sterility Assurance Level of greater than 10^{-6} and comparable performance with the PQ and previous re qualifications.

The worst case Critical Control Point Load on each autoclave that has such a load must be physically re qualified annually (1 run with thermal and biological challenges).

AUTOCLAVE LOADS NOT CRITICAL CONTROL POINTS

Autoclave loads which are not Critical Control Points may be classified as Sanitisation loads, Bio burden reduction loads or Sterilisation loads.

The qualification and requalification requirements will be defined appropriately. The cycles will generally be developed to deliver the same lethality, but the qualification can be based upon the criticality of the operation.

The purpose of defining Sterilisation loads which are not Critical Control Points, is to assist in assessing worst case load challenges (e.g. if two loads had the same equilibration time and could be described as equally difficult challenges, it would make sense to ensure that the Critical Control point load was the one chosen for annual requalification as the worst case / most critical challenge load.)

Any autoclave that has a load which is classified as a Sterilisation cycle (whether Critical Control point or not) will require annual requalification. This annual requalification **may** include physical work (thermal and BI) the assessment of which 'worst case' load to use for this requalification should include an assessment of load criticality.

OTHER LOADS

The qualification and requalification will be defined in line with EU GMP requirements and an understanding of process risk. In all cases annual review of performance will be undertaken as a minimum.

2. FMEA OF AUTOCLAVE OPERATION

The Intent behind the proposed approach is to increase confidence in every production cycle by designing and engineering improved processes, this may include increased monitoring and routine testing. Whilst annual requalification of sterilisation processes is important and a GMP requirement, it is only an annual check on performance. The approach recommended here will increase confidence in every production cycle.

Therefore more emphasis will be placed upon cycle review and acceptance by trained and competency assessed operations and QA personnel. This ensures that any problems or adverse trends are identified at the time; a decision can be taken with regard to the load that has been processed.

To assist with this rationale and the scope of monitoring, testing and requalification, potential failure modes, causes and methods of identification are listed below. The starting point assumption for this analysis is that a successfully validated (PQ) load is defined, the failure modes that could occur to this successfully validated load are listed. The below example table is a simplified (summarized) FMEA on part of the system.

The below table is an extract from more than one project site and significantly summarized (not a complete FMEA) The conclusions reached here are site and load specific, all projects / sites are unique. However as an example of the approach and discussions that can take place it is valid.

Porous Loads : Potential Failure modes (***Example extract of FMEA***)

Failure Mode	Cause	Method of detection
Poor air removal from centre of load.	Load presented incorrectly. Such as tubing kinked, valves closed, blanks in place, incorrect load assembly.	Operator training and vigilance.
	Load wrapped incorrectly. Such as too much wrapping, incorrect size, wrong material.	Operator training and vigilance.

Failure Mode	Cause	Method of detection
	Change in air removal pulsing (number of pulses, depth, ramp rate etc)	Operator training and vigilance. Cycle review of the critical aspects of the cycle in terms of air removal. Any change in air removal performance from autoclave will be detected by the air detector before it has a detrimental impact on the air removal from the load itself. This has been proven during air detector performance testing and will be repeated every year as part of the EN285 benchmark testing (Air detector performance testing on small load test pack). Also the air detector functionality as a critical alarm is tested weekly by engineering.
	Change in vacuum performance.	Vacuum pump changes will be identified in ramp rate of vacuum at air removal and drying phase. Operator training and vigilance of the cycle performance will detect this. See also above comments and testing with the air detector.
	Chamber leak	Weekly leak rate check. The weekly leak rate check ensures autoclave leakage is well below the levels that have proven to work during the air detector set up, there is a safety factor of at least 2 times the air leakage rate. See also above comments and testing with the air detector.

Failure Mode	Cause	Method of detection
Sterilisation conditions not maintained.	Incorrect control of cycle	All autoclaves have independent chart recorders fitted and these have independent temperature and pressure inputs. Operational checks ensure that both sets of data correspond and that temperature and pressure correlate. Therefore there is a high degree of confidence that the control is correct and that any deviation would be detected. Instrumentation is calibrated, including 'as found' checks every six months.
Non condensable gases building up in the load.	Poor quality steam supply with high levels of non condensable gases.	Annual steam quality testing. Air detector would alarm
Poor control of sterilisation conditions throughout the sterilisation hold time	Instrumentation failure.	Ensure the independent critical instrumentation is checked against the control system printout to ensure correlation. Check temperature and pressure correlation. Operator training and awareness of the role of independent chart recorder and the temperature pressure correlation check. 6 monthly calibrations with 'as found' instrumentation checks.
	Instrumentation and Control failures (Control loop performance, steam valve / drain valve control)	Chamber is monitored at the worst case location (Drain temperature) Cycle acceptance criteria and in built alarms ensure sterilisation conditions of temperature and pressure are maintained throughout the hold phase.

Failure Mode	Cause	Method of detection
Superheat / Overheat in the load, causing dry heat conditions.	Superheated steam supply to autoclave.	This is very unlikely failure mode with a clean steam supply, however the steam is tested annually at all user points for superheat. Small load Pack testing checks for free space temperature overshoot / superheat annually.
	Jacket temperature controlling too high.	Operator vigilance and training. Check jacket temperature during cycle.
	Low thermal mass or dry goods in the chamber.	Initial PQ of the minimum load and particularly dry goods (e.g. clean room paper) has validated this performance and demonstrated moist heat conditions are achieved by showing BI kill. Operator vigilance and training must ensure that min loads are defined and controlled.
Condensate build up in the load.	Wet steam supply (low dryness level)	Steam quality tested annually to ensure dryness value greater than 0.9. Steam trap inspection and maintenance. Operator vigilance on load inspection post autoclaving.
	Low Jacket temperature causing condensate build up (condensate raining on the load)	Operator vigilance checking jacket temperature throughout the cycle.

CONCLUSION

People intimately involved in the management, operation, engineering and requalification of sterilization processes will generally agree that the current approach adopted by the industry is adding very little value.

Annual requalification of sterilization processes would fail to identify many of the problems that have been defined above because they are operational or transient problems that would not remain through to requalification but have never the less had the potential to affect the load being run on the autoclave.

Annual requalification is too late, even if it is successful in identifying a problem, a years worth of production has been shipped!

There is a better way to engineer, operate and qualify sterilization processes that deliver improved confidence in every sterilization cycle.

- **Improved Confidence in every production cycle.**
- **Improved daily availability of autoclaves (Improved capacity)**
- **Reduced downtime for annual requalification**
- **Reduced costs for annual requalification**

Win! Win! Win! Win!

The Regulatory position? Is this approach accepted by your regulatory body?
The author has had the opportunity to present this article to the MHRA who have confirmed that this approach is acceptable in principal, although each case will be viewed in detail and must be based upon sound science, thorough risk analysis and well engineered processes.

This approach is based upon every current trend in the industry in terms of Risk assessments, Criticality assessments, designing quality in rather than testing it in, moving from QC to QA etc…….

Many sites have now implemented this thinking, we have worked with a number of sites around the world to deliver these improvements, including Ireland and the UK where the regulatory interest is high in this area.

Implemented properly, there is nothing left to question. If all potential failure modes have been thoroughly assessed and action taken to ensure these failure modes are monitored and controlled. There is nothing left to question!!