NOTE: This document was originally prepared by the Author in 2012 as an inspection guideline for the Chinese FDA regulatory authority.

It is however relevant as an inspection guideline for many moist heat sterilisation processes and not just Water Spray LVP TS machines.

ORIGINAL GUIDELINE DOCUMENT:-

1.0 SCOPE

The scope of this inspection guideline is the Terminal Sterilisation Stage of Large Volume Parenteral Manufacture utilising Water Spray or Water Cascade Autoclaves. Although the autoclave is the key piece of equipment this inspection guideline also covers the pre sterilisation bio burden data and post sterilisation product testing.

Reference documents to be read in conjunction with this guide are as follows:-

1.1 Example FMEA : The Terminal Sterilisation Process is a Critical Control point in the manufacture of sterile product and therefore the risks and hazards associated with this process step should be understood and managed. FMEA is a typical tool to use in this assessment. An example FMEA is attached to this inspection guide.
Each autoclave, product, process is different and therefore FMEA's or other risk assessments will always be site specific.
The risk assessment should show evidence of process improvement to reduce unacceptable hazards.
The risk assessment should also show signs of on going management activity to ensure remaining hazards are understood and controlled.

© MARK THOMPSON LIFESCIENCES LTD.

1.2 Example Performance Qualification Protocol : Of all the qualification activities it is the PQ which demonstrates two critical parameters; firstly that the product license requirements are being met and secondly that the Sterility Assurance Level is being achieved. This is done through thermal and biological challenges and investigation.
The example PQ protocol attached to this guide demonstrates the minimum content of such a study.

2.0 PROCESS OVERVIEW

Start by gaining an understanding of the whole process scope on site. The range of products, fill volumes and packaging presentations manufactured on the site. This information will be referred to throughout the inspection but will also provide an indication as to how well the site understand their own process / manufacturing systems.

2.1 Product range.

Obtain list of products licensed for manufacture on this site.

2.2 Packaging Range

Obtain list of packaging Presentations, and provide samples to look at.

Examine the samples for any unusual packaging, differences in stopper / seals, areas where heat penetration will be different etc.
For double bagged LVP, establish what claim is made regarding the sterility or bio burden between the bags? Is this area expected to be sterile?

© MARK THOMPSON LIFESCIENCES LTD.

2.3 Filling lines / machines

- Which filling lines make which products?
- Which filling lines supply which autoclaves?
- What products are qualified on what autoclaves?

Get a clear map of product routes through filling machines and autoclaves and keep referring to this throughout the inspection.

2.4 Autoclaves

Ask for an introduction to the autoclaves. A good technical team will be able to demonstrate a thorough understanding of the equipment, product, process and why it is set up the way it is. If the technical team do not know how the equipment or process works they cannot possibly hope to have proper control and supervision of it.
For each autoclave get the following information:-

2.4.1 Autoclave size and type

Ask the technical team for details on the autoclaves. These details should be verified on site.

2.4.1.1 Autoclave size

2.4.1.2 Water spray or water cascade

- Ask for an explanation as to the spray patterns:-
- Is the spray from the top and sides or only the top?
- Is the spray through open holes or spray nozzles?
- Is the cascade through pipes or drilled trays?

© MARK THOMPSON LIFESCIENCES LTD.

- Is the recirculation through one or two pumps?
- Is the recirculation through one or two heat exchangers?
- Is the recirculation through one or two drains?
- How many water feeds to the top of the chamber?
- Are fans fitted to the autoclave?
- Are fans used in the cycle?

2.4.2 When installed and qualified

- Obtain the history for each autoclave:-
- When installed?
- When qualified?
- Who performed IQ, OQ and PQ?
- What modifications have been implemented since PQ?
- What annual requalification is performed?
- Who performs annual requalification?
- What problems have they had on each autoclave?

2.4.3 What products are qualified on which autoclaves

Check which products have actually been qualified on which autoclave. Claims that autoclaves are 'equivalent' are cause for concern.
If autoclaves are claimed to be equivalent then the site will claim that qualifying a product on one autoclave means it is qualified on another equivalent autoclave. Equivalence must first be proven before this statement can be made. Autoclaves are rarely 'equivalent'.

© MARK THOMPSON LIFESCIENCES LTD.

3.0 STERILITY ASSURANCE LEVEL AND PRODUCT LICENSE REQUIREMENTS

3.1 Product License

For the range of products, presentations etc described above. Understand what the product license requirements are? E.g. 115°C for 30 mins, 121°C for 15 mins, Fo of 15, Fo of 10….

Compliance with the product license requirements is generally regarded and as absolute requirement, i.e. a license requirement of 121°C for 15 minutes, does not mean an Fo of 15, or any other equivalent, it means that all parts of the load have achieved a minimum of 121°C for 15 mins. The compliance with the product license requirements should be a primary objective of the qualification of the autoclaves and will be checked later in the audit.

3.2 Sterility Assurance Level

The Sterility Assurance Level for Terminally Sterilised products must be greater than 10^{-6} . Demonstrating this will also be a requirement of the qualification of the autoclaves. This is generally based upon knowledge and confidence in pre sterilisation bioburden.

If an 'overkill' cycle is employed then pre sterilisation bio burden does not necessarily have to be monitored on every batch, however, good practice would still be to routinely check pre sterilisation bioburden. An overkill cycle would be a cycle at 121°C for 15 mins (All parts of the load achieving greater than 121°C for more than 15 minutes. A 15Fo cycle is not an overkill cycle.

All other cycles (115°C for 30 mins, low Fo cycles) require knowledge and confidence in pre sterilisation bio burden data so this should be investigated.

© MARK THOMPSON LIFESCIENCES LTD.

3.2.1 Pre Sterilisation Bioburden Data

Pre sterilisation bio burden data should be obtained for every filled batch. Samples taken from the beginning, middle and end of fill. Also samples taken after filling machine interventions.

3.2.1.1 Population (cfu)

The pre sterilisation bioburden population will be quoted as cfu/ ml, cfu/100ml or cfu/bag. Check the volumes, a common mistake is for the micro lab to be recording cfu/ml and then for this data to be used directly in calculations without scaling up for the filled volume. E.g. if the pre sterilisation bio burden is 3cfu / ml and the maximum fill volume is 500ml bags, then the pre sterilisation bio burden is 1500cfu/unit (3cfu x 500ml fill volume).

The monitoring of pre sterilisation bioburden should be trended over time for each product / filling machine. This should include alert and action levels on the graphs. An alert level being exceeded should initiate an investigation, an action level being exceeded should quarantine the batch until investigations are concluded and a decision taken on batch release.

Basic identification of the micro biology should be performed including gram staining, and identification of objectionable organisms (similar to what is expected for wfi monitoring). If gram positive rods are identified then further analysis will be required as described below.

© MARK THOMPSON LIFESCIENCES LTD.

3.2.1.2 D value assumptions and calculations.

As well as understanding the pre sterilisation population an assumption needs to be made regarding maximum D value of any micro organisms (heat resistance). Gram positive rods could be spore formers and these spores could be heat resistant. A low lethality cycle (Fo of 8 to 12) is dependent upon low pre sterilisation bioburden both population and heat resistance.

Therefore the site should have a procedure for heat shocking gram positive rods and determining a rough D_{121} value for the organisms. (Example heat shock procedure supplied).

3.2.1.3 Worst case bio burden assumptions

Based upon the above population and D_{121} value data a worst case bioburden assumption should be documented. This is the value that will be used in calculation of the Sterility Assurance Level.

A typical example would be:-

- Filled products : 100ml to 500ml

- Population
  - -Alert Level 5 cfu / 100ml
  - -Action Level 20 cfu / 100ml

The worst case assumption for population would be based

© MARK THOMPSON LIFESCIENCES LTD.

upon the 500ml bag therefore the action level would be multiplied by 5 giving 100cfu / 500ml bag. It is good practice to add a 1 log safety margin therefore the 100cfu becomes 1000cfu.

Worst case population assumption < 1000cfu / unit

This would be a good example of a thoughtful approach with a good safety margin built in to the process.

Heat Resistance

See the heat shock procedure for more detail on the determination of D_{121} value. Typical data would show D_{121} values of less than 0.1 minutes. Based upon this a worst case D_{121} value of < 0.5min may be set.

These would be typical worst case assumptions therefore:-

Population $< 10^3$ cfu / unit

D_{121} value < 0.5 min

The data and trends must be there to support these worst case assumptions.

Typical Problems include

3.2.1.3.1 Bioburden data not monitored on all products or all filling lines.

© MARK THOMPSON LIFESCIENCES LTD.

3.2.1.3.2 Unbelievable data; Unless the product is being aseptically filled in a validated aseptic process, pre sterilisation bio burden is going to exist and from time to time alert levels will be exceeded. If not then I would go straight to the micro lab and audit current pre sterilisation bioburden work.

3.2.1.3.3 No heat shock data; the population alone is not sufficient, if heat resistant spores are present this could be a significant challenge to a 115°C or low Fo process.

3.2.2 Filling operation

Although terminally sterilised product can be filled in a grade C environment, normal practice is to fill in a grade A environment in a grade C background.

After review of the pre sterilisation bio burden data I would review the environmental monitoring data for the filling room (A and C data).

Also ask about the sterilisation of filling equipment, particularly post filtration. Is this equipment sterilisation in place (SIP) or in a component (porous load) autoclave. Are these sterilisation processes validated.

This review of the filling operation is to gain confidence in the pre sterilisation bioburden data and control.

© MARK THOMPSON LIFESCIENCES LTD.

3.2.3 Cycle lethality and Sterility Assurance Level

The cycle lethality and Sterility Assurance Level calculations will be reviewed in detail during the qualification review. However, based upon the data presented so far the process capability can be assessed.

Example 1

Bio burden data presented:

Action at 100cfu / ml
1000ml product
Therefore population <100,000 cfu / unit
Add 1 log safety margin <1000,000 cfu / unit

No heat shock procedure and therefore no D_{121} value.
Worst case assumption would therefore be that the bio burden would have a D_{121} value of < 1min.

With this bio burden data (pop < 10^6/unit and D_{121} < 1min) a minimum cycle lethality of 12 Fo would be required to deliver the minimum SAL of 10^{-6}.

If the data already presented shows a low Fo cycle (<12 Fo) or a low heat cycle (115°C for 30mins) then immediate concerns regarding the sterility assurance of this product.

Example 2

Bio burden data presented:

Action at 10cfu / 100ml
1000ml product
Therefore population <100 cfu / unit
Add 1 log safety margin <1000 cfu / unit

© MARK THOMPSON LIFESCIENCES LTD.

Heat shock procedure in place and worst ever recorded / calculated D_{121} value is 0.05min. Action level set at 0.5min
Worst case assumption would therefore be that the bio burden would have a D_{121} value of < 0.5min.

With this bio burden data (pop < 10^3/unit and D_{121} < 0.5min) a minimum cycle lethality of 4.5 Fo would be required to deliver the minimum SAL of 10^{-6}. An Fo of 8 is the usually accepted minimum, even for very low bioburden product, so this process is immediately looking very robust.

However, the bio burden data should always be checked by auditing sampling and micro laboratory procedures.

3.3 Sterility Testing Data

The Sterility testing will be audited separately to this inspection guide. However it is worthwhile asking at this stage how many Sterility Test failures have been observed and what was the outcome of these failure investigations.

© MARK THOMPSON LIFESCIENCES LTD.

4.0 PRIMARY PACKAGING INTEGRITY

4.1 Container Closure Integrity Study (CCI study)

During the sterilisation cycle the temperature inside the product will cause the internal pressure to increase and potentially damage the primary packaging where the LVP is flexible bottles or bags. Therefore this internal pressure is balanced by adding compressed air to the chamber. However, the terminal sterilisation cycle can still be damaging to the packaging and seal integrity. Two areas need checking:-

4.1.1 Cycle pressure control consistency.

The 'as validated' cycle. (as validated by the CCI study) should be repeatable in production. RTeview cycles for pressure consistency. Check what the acceptance criteria area for pressure control / consistency.

4.1.2 CCI Study

The CCI study will challenge the seal integrity by running growth media through the sterilisation cycle and following sterilisation these bags of growth media are soaked in a broth of micro organisms to challenge the seal / container integrity. If the sterilisation cycle has caused any problems with the seal integrity, then the micro organisms will be able to enter the broth and growth will be observed in the container.

4.2 Leak testing Prior to Sterilisation

It is normal practice to take samples from the filing line and leak test then on a routine basis (time or quantity based).

© MARK THOMPSON LIFESCIENCES LTD.

Check that if leaks are found the correct corrective action is taken. A potential problem is that when leaks are observed the filling machine / sealing process is adjusted, but no impact assessment is performed on the rest of the filled batch.

4.3 Leak testing Post Sterilisation

Samples should be taken from every autoclaved load and leak tested. Failures should instigate an impact assessment on the rest of the autoclave load.

© MARK THOMPSON LIFESCIENCES LTD.

5.0 CYCLE CONTROL, MONITORING AND REVIEW

5.1 Cycle Control

5.1.1 Pressure Control

Pressure control is critical to minimise stress on the product during the sterilisation process.

Ask the technical team to explain how pressure control works during the sterilisation process. Then check this on some production cycles by looking at pressure variations / fluctuations.

It should be noted here that pressure and temperature are linked. When the temperature control adds more heat to the autoclave the pressure will rise because of the heat addition. Also a large amount of pressure rise by compressed air addition can cause the temperature to drop.

Investigate the chart traces from this perspective to understand the process dynamics.

There should be a minimum and maximum pressure defined for an acceptable cycle, during the sterilisation hold period.

5.1.2 Temperature Control

Temperature control is critical to maintain product temperature in the sterilisation temperature band during the sterilisation process. Temperature control would normally be set mid way on the temperature band for sterilisation. E.g. for a 121°C cycle (controlling

© MARK THOMPSON LIFESCIENCES LTD.

121°C to 124°C) the set point would be 122.5°C

Ask the technical team to explain how temperature control works during the sterilisation process. Then check this on some production cycles by looking at temperature variations / fluctuations.

The temperature control can be based upon the supply water temperature (Top of the autoclave water supply to the spray bars / nozzles) often referred to as T_h (T high). Alternatively the temperature control can be based upon the supply and return temperature together (T_h and T_L). Ensure the technical team know how control is programmed.

5.1.3 Sterilisation hold time start

The sterilisation hold time would normally start based upon the load probes reaching the sterilisation temperature band. Check if this is all of the load probes or 3 from 4, or 5 from 6 etc.

5.1.4 Water Quality and Monitoring

The water used for heating and cooling within the autoclave is the main source of heat transfer throughout the cycle. It is recirculated through a heat exchanger which has plant steam for heating and sterilising and cooling water for the cooling stage.

Ensure the heat exchanger is a double plate type so that leakage will not result in 'dirty' services (plant steam or cooling water) being taken through into the clean recirculating water.

© MARK THOMPSON LIFESCIENCES LTD.

The quality of the recirculating water is dependent upon CCI confidence and also cycle pressure control (stress risks). It could be argued that if we are confident about seal integrity then the quality of the recirculating cooling water is not important. However, this is bad GMP. We do not surround a grade A filling zone with any quality of air, no matter how good the grade A filling zone is, we still have controlled environment around it. The same argument applies to water quality.

A study on water quality and water quality deterioration should have been carried out. The minimum quality charge water should be Purified Water specification.

The quality of water should be monitored in-between cycles for a period of time to determine the rate and nature of deterioration. The following should be monitored and understood as a minimum:-

5.1.4.1 Conductivity

5.1.4.2 TOC, TIC, TC

5.1.4.3 Microbiology TVC

5.1.4.4 Endotoxin

5.1.5 Spray pattern / Cascade consistency

Any risk assessment performed on a water spray or water cascade machine is going to identify the water flow rate and spray consistency as

© MARK THOMPSON LIFESCIENCES LTD.

a critical control measure. Therefore this must be monitored by some means. The monitoring will depend on the design of the water recirculating route.

This monitoring could utilise pressure, differential pressure or direct flow monitoring.. the monitoring should be in real time and must be part of cycle review and acceptance.

5.2 Data recording

5.2.1 Critical data

The critical data will be determined by the risk assessment but will be the following as a minimum:-

- Chamber pressure
- Recirculating Temperatures (T_h and T_L)
- Load probe temperatures
- Flow rate data (Pressure, differential pressure or flow)
- Water quality data (conductivity)
- Time

5.2.2 Independent record

The temperature and pressure control should be independently recorded, this allows operations to compare one set of data (control system printout) with another set of data (independent chart recorder). This provides more confidence in data accuracy as it is very unlikely that both sets of data will be inaccurate to the same degree at the same time.

© MARK THOMPSON LIFESCIENCES LTD.

Therefore these temperatures should all be duplex probes. The pressure requires two separate pressure transmitters, one connected to the control system and the other to the independent chart recorder.

Operations should have to review both sets of data, the SOP should make this clear and practice should be observed.

5.2.3 Critical Alarms

The risk assessment process will have identified critical alarms. These should be defined and the requirements for testing these critical alarms documented.

Critical alarms are likely to include as a minimum :-

Temperature limits during sterilisation hold period
Pressure limits during sterilisation hold period
Services supply pressures (steam, compressed air, water)

5.3 Cycle Review and Acceptance

The SOP should have a specific section on cycle review and acceptance.

5.3.1 Operations review

The operators are the first line of defence and the best people to identify a problem with a cycle. Therefore there training should be detailed enough to ensure they understand how the equipment works,

© MARK THOMPSON LIFESCIENCES LTD.

the consequences of failure and how to observe failures.

The operational review should include practical aspects of loading operation and unloading as well as data review.

The data review should include the control system printout and the independent chart recorder printout.

5.3.2 Load Probe Inspections and procedures

Load probe placement is critical and should be cheked at loading and unloading by trained and diligent operators.

5.4 Routine testing

5.4.1 Leak testing / Pressure Hold test.

Leaks from the autoclave can be a problem to pressure control and also to recirculating water conditions. Therefore it is good practice to perform a weekly pressure hold test to ensure leaks are not getting too large. Typically this would involve pressurising the chamber to 200KPa and then holding the pressure for 30 minites and seeing no more than a 5KPa drop in pressure. This should be performed weekly.

5.4.2 Spray pattern / water cascade consistency

In addition to the monitoring discussed above in terms of flow rate

© MARK THOMPSON LIFESCIENCES LTD.

monitoring, a visual check should be performed weekly. There are two requirements here :-

5.4.2.1 Visual inspection of spray nozzles or holes. This involves walking through the autoclave check ing that all pipework is in good contrition, properly aligned, no blocked holes no blocked spray nozzles.

5.4.2.2 Visual inspection of the water spray in operation. Running the water recirculation with the autoclave door open.

© MARK THOMPSON LIFESCIENCES LTD.

6.0 WALK THE PROCESS : Physical observations.

6.1 Loading operation

Water spray and water cascade autoclaves are very susceptible to variation sin loading patterns. Therefore the load, shelves and trolleys should be repeatable and 'as validated'. This is best controlled by having detailed layout instructions in the SOP and trained knowledgeable operators who understand the importance of this. Check:-

6.1.1 Trolleys are consistent and undamaged. No bent trolleys, bent loading rails etc. Check for every shelf being horizontal and straight.

6.1.2 Shelves are consistent and undamaged with drain holes all consistent and clear.

6.1.3 Product is laid out consistently on each shelf. Ideally with gaps between each product to enable water flow

6.1.4 Check loading rules. Are partly filled trolleys filled from the top (usual) or from the bottom. Are empty shelves always put on the top of the trolley. Are partly filled chambers filled from the unloading end backwards or from the loading end. Check all of these details in the SOP for clarity, observe the practice and also ask the operators. These notes will be checked against the qualification work to ensure the operation is what was qualified.

© MARK THOMPSON LIFESCIENCES LTD.

6.2 Autoclave preparation

Establish the autoclave preparation procedures, including cleaning, checks, door seal checks, water filling, any pre heating etc.

6.3 Autoclave condition

6.3.1 Door seals

Badly maintained door seals will lead to leaks during the cycle. Leaks cause two problems to cycle efficiency.

6.3.1.1 Pressure control

High leak rates will make pressure control difficult and will also result in more compressed air (which is cold) being added to the chamber. The pressure fluctuations can effect bag integrity. The cold compressed air can cause temperature fluctuations in the chamber.

6.3.1.2 Water recirculation

If water leaks out during the cycle it can cause the recirculating water pump to be starved of water and this will impact the water spray / cascade pattern significantly.

Therefore visually check the door seal condition at either end of the autoclave. Check for large amounts of dirt build up, a sign of poor maintenance and sticking door seals. Check for twisted door seals.

© MARK THOMPSON LIFESCIENCES LTD.

6.3.2 Chamber leaks in plant room

Another sign of leaking door seals but also leaks from other areas of the autoclave pipework. Water leakage which can be seen will cause the same problem as identified above. Air leakage which may be heard will also cause the same problem with pressure fluctuations as described above.

6.3.3 Internal condition.

NOTE : You may wish to ask for the autoclave to be drained and to walk into the chamber to inspect internal condition. Ensure that the autoclave has been properly isolate and a safe entry permit issued before entering the chamber with a good torch to inspect elements. This is particularly important for larger chambers where not everything can be observed from either end of the autoclave.

6.3.3.1 Internal spray bars, plates, nozzles.

Do all internal spray bars and plates look straight, undamaged and 'as built'. Check that bars are not twisted, check spray nozzles are not visibly scaled or blocked, check holes in spray bars are no scaled or blocked.

6.3.3.2 Witness spray pattern test

The spray pattern can be witnessed with the door open. The pumps run with water in the chamber with one door open to

© MARK THOMPSON LIFESCIENCES LTD.

witness the spray pattern consistency.

The whole chamber cannot be observed because after 2 to 3m into the autoclave the spray cannot be seen, however it is still worth witnessing what can be seen. The test can be run from either end of the autoclave so that the pattern can be observed at the loading end and the unloading end.

Check that the flow rate is consistent and not varying or pulsing.

This is a test that the site should do regularly (weekly), so they should be set up to run this test.

6.3.3.3 Internal panelwork

Check that internal panelwork and fitting are undamaged and 'as built' particularly where they could affect water flow / spray patterns.

6.3.3.4 Drain Strainers

Check that the drain strainers are clear and unblocked. This may require the water to be drained out of the chamber to observe properly. There may be more than one drain strainer.

As well as the main drain strainers (for recirculating water, there will be smaller drain strainers or pipework for the level transmitter or level switch. Check that these are clear also.

© MARK THOMPSON LIFESCIENCES LTD.

6.3.4 Cleanliness

Observe the debris in the chamber. If the water is held in the chamber in between cycles, check for any floating debris in the chamber.

Ask for the chamber to be drained down and when empty check the bottom of the chamber for other debris (metal parts, metal debris etc).

Poor maintenance and cleaning regimes will result in a large amount of dirt being present in the base of the chamber when drained down.

6.3.5 Load probe operation

6.3.5.1 Load probe placement

Duplex load probes should be used so that these critical measurements have an independent record as well as the control system record. The use of two separate probes is not good practice as they cannot be located at the same location and they require two entry points into the bag.

The duplex probe must be designed so that it can be reliably located at the geometric centre of the fluid in the bag. Check all load probes locations, check to see that the load probes are central and are not touching the outside of the bag as they will heat up too quickly.

© MARK THOMPSON LIFESCIENCES LTD.

6.3.5.2 Load probe bag size and starting temperature.

Check that the correct size bags are used on all load probes, check all of the load probes, check from both ends of the autoclave.

Good practice is to use fresh product as load probe bags on every cycle and not to keep the same bags in position. This ensures that the most representative bags are in place on all the load probes. Also that the starting temperature is representative of the load starting temperature.

Check that the load probe bags are still full of product at the end of the cycle and no noticeable amount has leaked out during the cycle.

6.3.6 Trolley positioning in chamber

Check for consistent trolley positioning in the chamber.

The trolleys should be positioned in a repeatable location. A common failure mode here is that the trolleys are pushed to far in and push up to the unloading end door. This will place the front 200mm or 300mm of the trolley into the door recess and out of the water flow in the chamber. Nothing will detect this other than operator vigilance.

© MARK THOMPSON LIFESCIENCES LTD.

6.3.7 Unloading inspection checks

Load probes should be checked to ensure that they are still held securely in the geometric centre of the product and that the product is still in the load probe bags.

Product movement: Check that product has not been moved by the process. Can be an issue on water spray autoclaves where spray from the sides is also utilised.

Water spray autoclaves with top and side sprays work very well but the side sprays can move product, particularly taller product or product on shallower trays. Check that this is not the case by checking at the end of the cycle.

6.3.8 Leak testing product

Samples should be taken from every autoclave batch and leak tested. Generally the pressure test. As well as checking for pressure hold over a period of time, visible leakage is to be observed. Therefore check that the leak test machine and the product being tested is dry before testing. The use of blue paper or similar to show fluid leakage is good practice.

Check what action is to be taken if a leak is observed. The autoclaved batch should be quarantined pending investigation and further testing.

© MARK THOMPSON LIFESCIENCES LTD.

6.3.9 Operator understanding

At all stages, ask the operators questions to check their understanding of the critical aspects of the process. There are many failure modes that can only be observed by vigilant operators. Ask operators to explain how the cycle works and controls, what are the load probes used for. Why do you check load consistency and layout, what would you do if a load robe bag had split during the cycle.

6.3.10 Training

Check training and competency assessment for Operators, Engineers and Qualification staff.

© MARK THOMPSON LIFESCIENCES LTD.

7.0 PERFORMANCE QUALIFICATION

7.1 Cycle development and investigation work.

Before PQ can commence, the cycle must be developed and the SOP finalised.

Cycle development will involve detailed temperature mapping to ensure that the developed cycle and method of control achieves the required lethality throughout the load. The load layout will be develop to provide the best possible consistency in cycle heat up and heat penetration. The slow to heat or low lethality locations will be defined.

Cycle development can either be documented against a protocol or in a cycle development log book, but it must be documented with justifications for:-

7.1.1 Cycle design and control methodology.

The different control options will have been investigated for temperature control, pressure control, load probe control, Fo values etc. The reason behind each of these should be documented and justified.

7.1.2 Load presentation and layout / loading patterns.

Cycle development thermal mapping will have tried different load layouts, a compromise between load packing density and even temperature distribution throughout the load must be reached. Photographs of the final load layout should be taken and used in the PQ protocol.

© MARK THOMPSON LIFESCIENCES LTD.

7.1.3 Load probe placement locations and conditions

Load probe locations, and methods of locating the probes in the product will have been determined. It may be that 'equivalent' product has to be used as load probes cannot easily be put into the actual product (e.g. double bagged product) in such cases equivalence should be demonstrated with a thermal study.

7.1.4 Load dynamics, slow to heat points.

The slow to heat points cannot be provided by the autoclave manufacturer as they are product and lad specific.

It is essential that these studies be performed on site with the actual load and actual product to determine the slow to heat or low Fo locations.

Cycle development work should investigate each trolley of product within the autoclave as follows:-

Slow to heat locations or low Fo locations

Fo or temperature spread (max and min)

This will be used as justification for thermal challenges and BI challenges in the PQ exercise.

© MARK THOMPSON LIFESCIENCES LTD.