

# THERMAL VALIDATION

Information

Manual & Guide

The purpose of this manual is to provide an overview to those involved Systems's products and systems in the Healthcare industries.

It provides a summary of the rationale and history of thermal validation, the processes primarily served, the need for specialist temperature monitoring equipment, an explanation of the more specialist terminology involved and an analysis of the main competitive equipment.

## VALIDATION

- What is it?

There are several documented definitions of validation, including some suggesting it being a tool to provide consultants with many and varied reasons for a comfortable existence!

Perhaps a more accepted definition reads :-

**“The action of proving that any procedure, process, equipment, material, activity or system actually leads to the expected result.”**

- Why and how did it evolve?

Before 1978, drug product quality and sterility was based solely on spot testing of finished product, e.g. using the USP (U.S. Pharmacopeia) Sterility test.

During the 1960's and 70's it became increasingly evident these measures were patently inadequate as a result of many deaths and serious injuries resulting from inadequate sterilisation. The US FDA acted and many manufacturing facilities were temporarily closed as a result of FDA inspections and more than 600 products were recalled from sale.

In 1976, the FDA proposed changes to manufacturing practice that were focused on sterilisation. The procedures targeted were sterilisation by :-

**Steam (moist heat)**

**Dry heat**

**Gas/Steam (Ethylene Oxide and Formaldehyde)**

**Depyrogenation**

**Sterilisation in Place (SIP) and Filtration.**

## **THE PROCESSES LISTED ABOVE ARE PRECISELY THOSE SERVED BY OUR EQUIPMENT.**

Later, in 1978, the FDA recognised the concept of validation would also be invaluable in correcting deficiencies for processes not intended to be sterile and so the range of operations to be validated was extended to include :-

Aseptic Filling Operations  
Solution Preparation Systems  
WFI (Water for Injection) systems  
Filtration Processes  
Packaging Systems

Sanitation Processes  
Utilities  
Environmental Systems  
Labelling Systems

In addition, **products** included under the GMP (Good Manufacturing Practice) remit was extending from parenteral (broadly injectable) drugs to:-

Medical Devices  
Veterinary Products  
Ophthalmics (Contact lenses etc)  
Bulk Chemicals.

In summary then, organisations with a need for Thermal Validation equipment will be manufacturers of parenteral drugs, medical devices, veterinary products, ophthalmic products, together with users of sterile equipment (Hospitals, Dental Facilities) and Third Party organisations undertaking the work on a contract basis (Contract Validation Service Providers).

- What does it involve?

The FDA defines validation as a “documented program which provides a high degree of assurance that a specific process will consistently and repeatedly produce a product meeting its predetermined specification and quality attributes.”

The systematic series of actions and procedures undertaken in a validation exercise is referred to as a **Validation Protocol**.

This is an approved document which outlines:-

- I. The defining objective of the validation study
- II. Identifying the departments involved and their project responsibilities
- III. The SOP (standard operating procedure) for operation and calibration of all test instrumentation
- IV. The tests that will be made
- V. The acceptance criteria for those tests.

The validation of a process plant, from new, will involve a number of discrete stages:-

- I. Design Qualification - DQ – to ensure the needs of the users will be met by the equipment finally specified.
- II. Installation Qualification – IQ – to provide assurance that the installation has been implemented in accordance with the information detailed in the design.
- III. Operation Qualification – OQ –to prove the equipment functions safely and in compliance with the equipment specification (commissioning).  
Repeated when significant maintenance has been undertaken.
- IV. Performance Qualification – PQ – to prove that the equipment operates, repeatedly, in a manner required to meet stated objectives for product quality. A process repeated at regular intervals as defined in the SOP.

Our equipment will be used in the OQ and PQ stages, i.e.

**OQ** – Listing of critical components of the steriliser, operating ranges as defined in the specification, and actual performance of these components.

- Control System
- Temperature Monitoring System
- Door Interlocks
- *Validation Equipment and calibration thereof*

**PQ**

- Heat Distribution Studies – used to validate the uniformity and stability of the sterilising vessel.
- Container Mapping Studies – used to determine the coolest location in a product container ( bottle, flask etc) during the sterilising period.
- Penetration Studies – used to assure that the coolest container within the load will consistently be exposed to sufficient energy for proper sterilisation of the product.

What is sterile?

A product is considered sterile when the probability of survival of any micro-organism is reduced to  $10^{-6}$  regardless of the number and resistance of the micro-organisms. One of the objectives of a Penetration test is to calculate the lethality for containers studied using the normal production cycle. Lethality is often referred to as  $F_0$ .

What is meant by the term  $F_0$  or Equivalent value of energy?

The conditions for sterilisation are achieved when a sufficient quantity of energy has been received by the material to destroy the most resistant bacterial spores (for steam *Bacillus Sterothermophilus*). **No one autoclave runs an exactly similar cycle to another**, even though users with different autoclaves talk in similar terms. e.g. a cycle of 121C with a holding period of 20 minutes. The energy transposed can vary from one similar cycle to another according to precise temperature fluctuations in the chamber and also the amount of energy accumulated at the beginning of the cycle as the autoclave is heating up to the holding time temperature..

Microbiologists, unlike most sterilisation managers at hospitals do not talk in holding times but in the value of energy accumulated during the whole cycle. They calculate the energy value

and describe it in terms of  $F_0$ . Quite simply an energy value of 1  $F_0$  is the equivalent of energy accumulated if exposed to a cycle of 1 minute at 121°C with saturated steam. Therefore 20 minutes at 121°C =  $F_0$  20.

As previously mentioned this  $F_0$  value is used mainly by microbiologists not (Hospital) sterilisation managers, though it has begun to be appreciated more and more in sterilisation. It is not important to know how to calculate it but just to understand what it is and how it is relevant. TQSoft provides a comprehensive Lethality display and monitoring facility.

## TYPES OF STERILIZATION

What types of sterilisation?

STEAM  
ETO  
DRY HEAT  
FORMALDEHYDE

An overview of industry trends shows that high temperature steam sterilisation is still used for a broad spectrum of sterilisation activities ranging from sterilisation of equipment and garments to the sterilisation of products in their final containers (**terminal sterilisation**). In all these processes, our fundamental objective is to deliver a process of known lethality for the purpose of ensuring the product or item is devoid of viable microbiological contamination. In all cases the sterilisation process depends fundamentally on the delivery of a lethal energy dose to the load by way of heat transfer from the steam to the load. An effective cycle will combine an optimisation of temperature and time of exposure. The most efficient heat transfer is achieved by utilising the latent heat of condensation of the steam. Furthermore, steam close to *saturation* is known to be the most effective for the inactivation of bacterial spore forms. Failure to achieve the optimum conditions can occur due to the presence of inappropriate unwanted quantities of air, or other non-condensable gases. Failure can also occur if the steam is not of the appropriate quality. The most common problems are when the steam is delivered to the autoclave in a superheated state or too wet. Both these conditions can cause failure of a critical sterilisation cycle. The avoidance of these problems can be achieved through application of good engineering practices to utility systems, combined with sound cycle development and supported by effective process monitoring.

### **STEAM STERILISERS** (Autoclaves)

A steam steriliser is a specially constructed metal vessel with a sealable door or lid in which high temperatures may be obtained by means of steam under pressure. Steam sterilisers were developed during the Nineteenth century. Initially, they were used for the sterilisation of aqueous fluids, but developments have taken place which today allow autoclaves to be used for many process applications including fluids, instruments, hollowware and porous loads, such as textiles. Machines similar in basic construction to the steam autoclave are used for other sterilisation processes such as ethylene oxide and low temperature steam and formaldehyde (LTSF). With the publication of European standards for steam autoclaves, such as EN 285 for large steam sterilisers, and EN 13060 for the smaller bench top sized machines, machine specification and performance is becoming standardised and similar. The European standard EN 554 specifies the requirements for validation and routine monitoring of steam sterilisation processes. Sterilizer chambers are designed to accommodate a **sterilisation module** (300mm x 309 mm x 600mm), or multiples thereof. Steam sterilisers vary enormously in their size and complexity. The largest are used in industry and have chamber volumes of many cubic metres. Small automatic bench top autoclaves have chamber volumes generally below one **sterilisation module** (54 litres). These are used in community health care (general practice, dentistry etc) and in operating theatres, for example, to sterilise instruments that need to be re-sterilised during the course of an operation. These smaller machines were originally designed to process only unwrapped instruments, as they relied on downward or gravity displacement of air by steam. Steam entering the autoclave pushes the heavier, more dense air downward out of the autoclave. This passive method of air removal will not reliably remove air that may be trapped in sterilisation bags, pouches and textiles. Historically, for these applications the larger autoclaves as found in hospitals were used, as they are generally equipped with a vacuum pump to actively remove the undesirable air. More recently small machines equipped with vacuum pumps (vacuum benchtops) have

become available, which are capable of processing either single wrapped goods, or have full porous load capability as per full sized hospital machines. The larger automatic porous load steam sterilisers are to be found in hospital sterile supply departments, where they are used primarily for the sterilisation of medical devices such as surgical instruments.

#### Steam Sterilisation Cycles

The temperature of steam increases progressively in proportion to the pressure of the steam. There are specific charts that describe the relationships maintained between pressure, temperature and time in order to obtain the final result of sterilisation.

Therefore during the phases of the sterilisation cycle the temperature and pressure must be maintained at stable and standardised levels.

In the latest computerised autoclaves there are set levels chosen by pre-programmed cycles. The cycles must be selected according to the materials to be sterilised.

Material	Temperature in °C	Time in Min.	Pressure in bar
Textiles, instruments and glass wrapped and packaged	134°C	7 min.	2.1
Instruments and glass NOT wrapped and packaged	134°C	4 min.	2.1
Rubber or autoclavable plastic	121°C	15 min.	1.1
Aqueous solutions and parenterables	115 - 121°C	variable	

In addition to accurate temperature and steam pressure measurement, especially in the case of Porous Load (vacuum) sterilisers, rigorous testing of the quality of the steam for non condensable gases, superheat and dryness is imperative as part of the validation process.

### **STERILISATION USING DRY HEAT**

Dry heat sterilisation is carried out in hot air ovens using times at temperatures that appear at first to be much more demanding than in moist heat processes.

Dry heat sterilisation is generally carried out at temperatures of at least 160°C that must be maintained for a holding period, in this instance, of at least 120 minutes.

Thus, when one allows for the necessary time taken to heat loads up from cold and for cooling down to a safe handling temperature, it is clear that dry heat sterilisation processes can take a very long time indeed to complete.

The *reason* for the high holding temperature and prolonged holding period in dry heat sterilisation processes is basically because micro-organisms are much more heat resistant in the dry state, (as in the oven) than when heated in the presence of moisture (as in the autoclave

Given this situation, one may well ask why use dry heat sterilisation at all. The answer is that some sealed containers of medicinal products do not contain moisture or water and could not therefore be sterilised as fluids at Steam sterilisation temperatures. Medicinal products such as petroleum jelly would not permit steam to contact all parts of the load, due to its oily nature. Other loads may be damaged by moisture. In addition, many instruments and items of glassware may be sterilised by dry heat. Dry heat sterilisation must, however, be used with care since the high temperatures used may cause serious damage to items containing plastics or rubber.

## Dry Heat Sterilisation

### Dry Heat Oven

Heated air enters into contact with the objects to be sterilised increasing the temperature and causing the destruction of micro-organisms. Temperatures range from 160 –180°C between 1 and 2 hours.

### IT IS POSSIBLE TO STERILISE WITH DRY HEAT

- Glass objects
- Metal objects
- Powdered and oily substances

### IT IS NOT POSSIBLE TO STERILISE WITH DRY HEAT:

- Thermolabile materials
- Textiles and aqueous solutions
- Glazed or enamelled materials

## Sterilisation with Ethylene Oxide

### Gas Autoclave.

Ethylene oxide works by alkalisng (substituting a hydrogen atom with an alcohol group) the sulphide, ammonium, carboxyl, phenol and hydroxyl groups of micro-organisms, which causes an alteration in the ionisation process of proteins and enzymatic activities resulting in the death of the micro-organisms

The process of sterilisation requires the interaction of 5 factors

#### 1) GAS (Ethylene Oxide) CONCENTRATION

the mean suggested concentration is 700-800mg/l

#### 2) HUMIDITY

the value of relative humidity inside the sterilisation chamber should be between 30%-60%. Before the sterilisation phase it is necessary to humidify the materials for 6-12 hours in an environment of at least 50% relative humidity.

#### 3) TEMPERATURE

the temperature increases the efficacy of the gas, the greater the temperature the less time needed for sterilisation. As this is a sterilisation method chiefly for thermolabile materials generally the temperatures never exceed 50-60°C in order to avoid damaging materials.

#### 4) CONTACT TIME

can vary with respect to the preceding factors, generally the sterilisation cycle is maintained for 4-5 hours.

#### 5) PRESSURE

varies related to the gas used. In order to avoid the problems of flammability and the explosiveness of Ethylene Oxide it is mixed with Freon or Carbon dioxide

### IT IS POSSIBLE TO STERILISE WITH E.T.O.

- All thermolabile materials in plastic, rubber, latex, electric cables, fibre optics, vascular prostheses, delicate instruments

### IT IS NOT POSSIBLE TO STERILISE WITH E.T.O.

- Materials which can be steam sterilised, chiefly low cost medical-surgical instruments.
- Objects previously treated with gamma radiation because they can form peroxides which are toxic to humans.

### ADVANTAGES

Possible to sterilise thermolabile materials

### DISADVANTAGES

Toxicity  
Excessive sterilisation time  
Lengthy forced aeration time

### Sterilisation with Formaldehyde

Formaldehyde Autoclave.

Formaldehyde acts on contact as an alkylating agent, irreversibly altering the reagent groups of the micro-organisms' proteins causing their destruction.

Sterilisation is obtained through the combined interaction of the following factors:

1) Gas concentration:

With the addition of steam under vacuum the minimum effective concentration of gas needed is 50 mg per litre.

2) Temperature:

the duration of the cycle varies according to the preselected temperature, considering that this method of sterilisation is used primarily for thermolabile materials, the selected temperature is approximately 55°C

3) Pressure:

during the cycle the introduction of formaldehyde brings the pressure to a value, such that it will maintain a state of saturated steam.

Compared with ethylene oxide formaldehyde has the advantage of not being flammable or explosive, and of being more economical at a ratio of 1:10.

### Depyrogenators

Depyrogenation involves dry heat exposure at temperatures in excess of 250°C for periods in excess of 1 hour. The process is often in the form of a continuous "tunnel" with items travelling through on a slow moving conveyor.

Depyrogenation is the destruction of endotoxins, essentially by combustion, whereas sterilisation is the destruction of living cells (microbes) to prevent activity through reproduction.

### Lyophilisers

Lyophilisation is a process which extracts the water from products so that the products remain stable and are easier to store at room temperature (ambient air temperature).

Lyophilisation is carried out using a simple principle of physics called sublimation. Sublimation is the transition of a substance from the solid to the vapour state, without first passing through an intermediate liquid phase. To extract water from products, the process of lyophilisation consists of:

1. Freezing the product so that the water in the product becomes ice;
2. Under a vacuum, sublimating the ice directly into water vapour;
3. Drawing off the water vapour;
4. Once the ice is sublimated, the products are freeze-dried and can be removed from the machine.

Steam sterilisable machines will be sterilised between batches.

### **The need for accuracy and specialist equipment.**

Most temperature measurements are not so much concerned with absolute accuracy as repeatability, since they are concerned whether the temperature is stable, moving up or moving down and by what rate of change. This is **not** the case however with temperature measurement within sterilisers.

The purpose of a thermal steriliser is to supply a predetermined quantity and type of heat energy, under the right conditions, to ensure a suitable eradication of micro-organisms together with, in many cases, minimal degradation of the desirable properties of the material to be made sterile.

The concept of lethality (F) is universally accepted as the main criterion by which sterility assurance is measured and is an equivalent time spent at a base or target temperature.  $F_0$  is a calculated variable where the measured temperature inaccuracies have an exponential effect.

$$F = 10^{(T-T_b)/z}$$

Where T = Measured temperature,  $T_b$  = "Base" temperature, (for  $F_0 = 121.1^\circ\text{C}$ )  
 Z = resistance value. Normally a Z value of 10 is used for steam, as this is the value for the most heat resistant bacteria encountered,  
 ( Bacillus stearothermophilus).

### **At a sterilising temperature of 121<sup>0</sup>C a 1<sup>0</sup>C error will result in a 25+% error in F<sub>0</sub>.**

There needs to be confidence that in the event the validation data being at variance with that from the steriliser's own recorded or indicated data, the validation data can be assumed to be correct.

Regulatory authorities have always emphasised the use of high quality instrumentation and procedures. A CEN standard on Moist Heat Sterilisation (BS EN 554:1994) refers to validation instrumentation being not less than 3 times more accurate (less uncertainty) than that required to judge the performance of a steriliser. The factor of 3 is chosen as it provides approximately a 10:1 guarantee that any difference noted in readings is not caused by any inaccuracy of the validation instruments.

### Why use thermocouples?

For use in the harsh environments where validation studies are necessarily performed, thermocouples have proved to be far more rugged, durable and economical than RTDs. The temperature sensors are inevitably subject to mechanical shock and rough handling, making the sensitive RTD devices unable to provide accurate and repeatable data.

### Why aren't thermocouples as "accurate" as RTDs?

They can be! The common inaccuracies associated with thermocouple measurement come from the measuring equipment rather than the sensors.

A thermocouple produces a much smaller signal for a change in temperature (approx. 39 microvolts / °C for type T) than a RTD and requires much greater consideration with regard to signal conditioning and calibration.

**Software is compliant with 21 CFR part 11.** (see Regulations)

In addition, software provides all the essential elements for meaningful and successful validation for both continuous and discontinuous (batch) operations.

- All parameters including calibration data associated with a validation study are stored in a specific secured, configuration file, printable for hardcopy filing.
- During the test, data is time stamped and stored at a default scan value of 1 second/scan in an **unmodifiable, replayable binary data file**.
- Operators can view in real time any or all parameters being measured with both graphical and digital displays.
- Data presentation facilities are configurable prior, during or after test. **Remember all data is available for processing from the 1 second time stamped, secure binary data file.**
- The configured validation test data can be printed for hardcopy in both graphical and tabular format.
- Any form of the configured data report can be copied into ASCII format for subsequent spreadsheet analysis.

**What is SVR and what does it do?**

SVR (Steriliser Validation Reports) software is a powerful final reporting tool that effortlessly accesses the acquired secure binary data from the study and, using the database of user sterilisers and report formats provided, constructs the final report documentation for appropriate signature.

The report format database includes all HTM2010/2030 recommended reports (daily, weekly, quarterly, annually etc.) for all types and loads as described in the memoranda.

For those users not following the HTM2010/2030 format, custom templates are provided. As an optional additional feature, SVR provides a “designer” module permitting users to construct their own unique validation reporting documents. Alternatively, Isopharm Systems can construct and supply such custom templates as required.

**Report Manager** is a component of SVR and provides for collation and archiving of Word documents, TQSoft Test Data and Validation Reports under a single Validation Reference.

The facility is provided to instantly reproduce the collated documents as a PDF file for supplementary archiving or E-Mail distribution.

This package alone will save substantial man hours per validation.

## REGULATIONS

This industry is among the most highly regulated in existence.

Published regulations abound regarding GMP (Good Manufacturing Practice), with European, US, and Japanese variations.

Whilst it is not necessary to be conversant with all and every standard, references to certain aspects frequently arise in conversations and discussion. A simple basic understanding of the meaning or significance of the terms used is very useful for obvious reasons.

Familiarisation of the following publications (all European) would provide a basic, working understanding of the issues involved.

**BS EN 554** – Sterilisation of Medical Devices. Validation and routine control of moist heat sterilisation.

**ISO 1134** - Sterilisation of Healthcare Products. Validation and routine control of industrial moist heat sterilisation facilities.

It is important to note that recently the United States adopted ISO 1134: 1994 as an American ANSI standard related to medical device sterilisation.

**HTM2010. Part 3.** HTM2010 is a comprehensive 6 part set of documentation developed by the UK NHS Estates as a reference for UK NHS sterile supplies. It has been adopted by a number of non UK hospital organisations for validation/operation of sterilisation facilities. Part 3 concerns itself with the validation of sterilisation processes.

All the standards referred to above focus most strongly on the issues associated with sterilising what are frequently called **porous loads**. These are the most demanding loads to sterilise within autoclaves since the success of the process cycle is dependent upon removal of air, not only from the autoclave chamber but also from the body of the load. Much of the original work carried out in relation to porous loads was associated with the need in the hospital world to sterilise bed linen and garments by moist heat sterilisation.

Within the pharmaceutical industry this has direct parallels with the sterilisation of cleanroom garments. Whilst sterilisation of complex process equipment is very different from treating woven fabrics, we find many similar problems concerning removal of air and achieving effective steam penetration.

Examples of complex process equipment include items such as product filters, flexible hoses, filling machine pumps, vessels and the example of the isolator canister.

### **21 CFR part 11 Electronic Records and Signatures.**

A topic of much discussion, interpretation and confusion.

The long and complex regulations that set forth the criteria under which the US FDA considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

Compliance must be appropriate and applicable to the following (section):-

- Validation Plan (Acceptance Tests) (11.10a)
- PDF file creation (11.10b)
- File security (11.10c)
- Security window operator access control (11.10d)
- Security window password controls (11.300b)
- Audit Trail Window (11.10e)
- Login Window (11.10g) (11.300d)
- Electronic signature window (11.50) (11.200) (11.300)
- Electronic signature management (11.70)