

With Changing Sterilization Challenges is it time to think again?

By Dr Brian Kirk and Mr Colin Hunt

Monitoring Every Sterilization Load.

An essential component of an effective sterility assurance program.

Popular “keep awake at night” worries.

I worry about my Steam Quality?

- Steam for saturated steam / surface steam sterilization processes must be pure. Many of the problems associated with steam sterilization arise from steam quality problems. Steam may carry fine liquid water droplets within it. If too much liquid water is present the sterilization process will be incapable of drying the load items after the sterilization stage is complete and this can compromise the sterility of the packs. During steam generation fine water droplets can be carried over with the steam into the sterilizer chamber. Contamination of the steam generator feedwater with inorganic (eg lead) or organic (eg endotoxins) contaminants may lead to contamination of biopharmaceutical or pharmaceutical products which can then cause adverse reactions in patients in which they are used. Steam can carry non condensable gases within it which unlike steam do not condense when they encounter a cold surface. This can lead to an accumulation of air pockets on or in load items during processing resulting in incomplete sterilization. Such gases should be measured¹ and control measures put in place to prevent their formation.²

My sterilizer is validated but do I need to do any further testing?

- Every sterilization cycle is a unique event.^{1,3} A sterilizer is a complex electromechanical device which is inevitably subject to variability. Components age over time resulting in a change in process. If a component becomes unreliable then the process may no longer be effective in delivering sterile goods and patient safety will be compromised.^{5,6} As such load variation will inevitably impact process variation.⁸ **For these reasons monitoring every load with suitable indicators devices is mandatory.**

I monitor pressure and temperature to prove the presence of saturated steam (moisture); is this acceptable?

- This is a dangerous practice. Steam tables⁹ show the relationship between temperature and pressure in a saturated steam environment. It is assumed that if there is a correlation between the measured temperature and that calculated from the measured pressure according to saturated steam tables⁹, saturated steam must be present. Such techniques may be used to demonstrate the presence of superheated steam but certainly cannot be used to indicate the presence of an air steam mixture which may give rise to formation of air pockets within load items thus preventing sterilization. This has been discussed and established in literature and standards.^{10,3} **Standards prescribe the measurement of temperature and time but also require the use of a PCD to ensure adequacy of air removal and steam penetration and therefore acceptability of the moisture content within the process.**

My sterilizer is modern and has been validated. Surely the process is stable?

- All processes exhibit variability. The degree of variability is a measure of how well it is under control. Studies by Hoskins^{5,6} examined the failure rate in sterilizers used in hospital sterile service departments. Similar studies in industrial sterilizers would be of immense interest. Recent studies by van Doornmalen¹⁰, Kirk⁸ and Lapanaitis¹¹ have discussed failure rates and sources of process variability. All these studies show that even modern sterilization equipment exhibits process variability and therefore every process run is a unique event. This is why standards^{1,3} require that every load be monitored to ensure sterility assurance is guaranteed (see later).

For more detailed information about these and other considerations read on.

Sterility and how it is achieved.

The purpose of a sterilization process is to render a product free of viable micro-organisms. For a sterilization process to be effective certain “process variables”¹², which are those variables which contribute to microbial lethality (death), need to be applied at a level (the process parameters) which are known or demonstrated to be effective at killing micro-organisms. Table 1 shows the process variables for a range of commonly used sterilization processes.

Sterilization Process	Process Variable	Standard
Gamma Irradiation	Dose (a combination of radiation intensity and time)	EN ISO 11137
Dry Heat	Temperature, Time	EN ISO 20857
Moist Heat (Steam)	Temperature, Time, Presence of Moisture	EN ISO 17665
Ethylene Oxide	Temperature, Time, Gas Concentration, Humidity	EN ISO 11135
LTSF	Temperature, Time, Gas Concentration, Moisture	EN ISO 25424
Vaporized H ₂ O ₂	Temperature, Time, Vapour Concentration, Water (?)	<i>In Preparation</i>

Table 1: The process variables (those contributing to microbial kill) for commonly used sterilization processes.

Specification, Validation and Routine monitoring.

The International Standards Organisation (ISO) publishes a number of standards which describe the development, validation and routine control of a number of sterilization processes for medical devices, biopharmaceutical and pharmaceutical products (see table 1), all of which take their format from ISO 14937, a generic standard for any sterilization process. All of these standards describe a fundamental approach which can be summarized in three steps.

- 1. Specification;** define the objectives of the process and how they shall be achieved (including process, equipment and expected load).
- 2. Validation;** define and then carry out a series of tests which demonstrate that the specified process can be reliably delivered in order to achieve a sterile load.
- 3. Routine monitoring;** carry out a defined series of tests on **every** production run carried out in order to demonstrate that the process variables have been satisfactorily attained and sterility achieved.

Monitoring Process Variables.

Sterilization process variables (see table 1) involve the application of conditions which have microbicidal properties. These may be physical or chemical in nature. In order to prove that satisfactory conditions have been achieved during a process a number of monitoring systems can be used (usually mentioned in standards and in some cases covered by their own series of standards). These are normally divided into one of three categories;

- 1. Physical Indicators;** those indicators or instruments which physically monitor a process variable eg temperature measuring systems.
- 2. Biological Indicators;** indicators which contain viable micro-organisms, usually bacterial spores, which exhibit a high resistance to the process but are themselves killed by the process if satisfactory microbicidal conditions have been achieved.
- 3. Chemical Indicators;** indicators which contain chemical reagents which react with the sterilizing agent(s) in order to yield a visible change. The visible change is often a colour change which is clearly observable by the naked eye (eg the sterilization indicators tapes). Alternatively, it may be a physico-chemical change which gives rise to a visible change observable by the naked eye (eg the moving front chemical indicators in which a dye migrates along a wick eg 3M™ SteriGage™).

All sterilization processes will have a process variable which can be measured by a physical measuring system but not all process variables can be measured by a physical measurement alone. Thus;

Moist Heat Sterilization and Steam Quality

In steam sterilization the measurement of temperature and time is possible by use of physical measurement. The measurement of the presence of moisture is however more difficult. Temperature measurements alone cannot differentiate hot air from moist vapour (steam) and the correlation of measured temperature with that calculated from measured pressure according to steam tables, whilst being a crude indicator of the presence of superheated steam (which acts as a dry gas) is wholly insensitive for the detection of saturated steam or air steam mixtures. It is common practice to use an indirect measurement of the presence of moisture by virtue of the fact that air is absent. Thus, if air is absent then by inference moisture must be present. The absence of air can be measured using process challenge devices which challenge the air removal and steam penetration capabilities of the process (see later).

High Risk Processes and Loads

In some low temperature sterilization processes, for example ethylene oxide or vaporized hydrogen peroxide sterilization it is a more difficult to demonstrate that process variables have been attained at a satisfactory level throughout the load and it is these processes where biological indicators are at their most useful. Thus table 1 shows the process variables which must be monitored in these low temperature processes. Close examination of this table shows that complex instrumentation must be used to physically monitor the process variables and that in many cases it is difficult to establish a direct relationship between what is measured at the reference measurement location, and what conditions are present in individual load items. In this respect this is where biological and chemical indicators come into their own.

The placement of a biological indicator in a suitable PCD will ensure all of the process variables are integrated together in terms of microbial kill. If the BI survives, inadequate conditions have been achieved and sterility may be compromised. If the BI is killed then there is a high probability that sterility has been attained.

Process Variability

All processes exhibit variability.

The degree of variability is a measure of how well it is under control. Measurement of process variability is best carried out using a statistical approach and such techniques are well described in the literature. Deming was an early proponent of statistical process control in manufacturing processes.⁴ Hoskins^{5,6,7} has examined sterilizer reliability using similar techniques. Thus far the field of sterilization process control has not adopted these extremely valuable process analysis and control techniques in routine practice. Studies have been carried out and are underway showing that steam sterilization processes exhibit variability and some examples are described below.^{8,11}

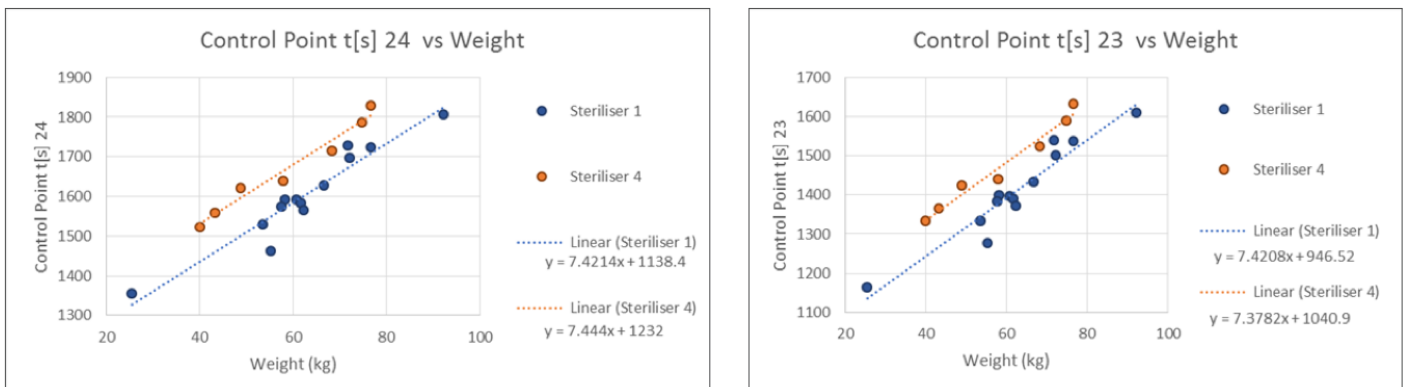
Figure 1 shows the variability of a saturated steam production process as a result of different load configurations and weight. The total cycle time is dependent on the loading weight. The Bowie and Dick test which is carried out in an empty chamber first thing in a morning, appears to be the fastest. In a study carried out in hospital sterilizer loads, a heavy load consisting of several sterilization containers holding heavy metal surgical instrument sets appears to be the slowest. A similar study in industrial production loads would generate data of immense value. Studies (ISO TC 198 working group 6, round robin studies to establish the performance of the hollow load test process challenge device cited in EN 867-5¹³) suggest the quality of the air removal is affected by the cycle velocity (ie rate of pressure change during the evacuation and pressurization pulses).

Every sterilization process is a unique event and no two processes are identical. Even a validated process will have variability associated with it.



Figure 1: Process Variability

Figure 2 shows the results of an extended study by Kirk and provides similar evidence showing a correlation between load weight and cycle speed.



Bearing in mind standards require routine monitoring and scientific literature describes process variability, the practice of monitoring every load for process efficacy is not an option but a requirement in any sterility assurance quality system.

Routine monitoring techniques.

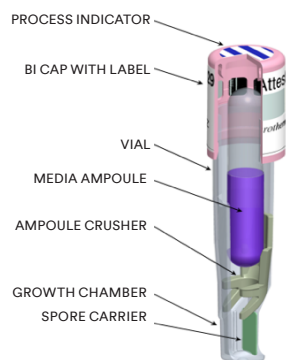
Measurement of Physical Parameters.



Standards clearly state that parameters, where at all possible, should be monitored and this would almost certainly involve measurement of temperature, pressure (a cycle NOT a process variable), time and in some cases (see below) the degree of air removal achieved during the first stage of a saturated steam sterilization process (air removal). In more complex processes such as those using vaporized hydrogen peroxide it is difficult to identify parametric monitoring systems which truly reflect the process conditions attained throughout the sterilizer chamber and load items. In such circumstances biological indicators offer the best alternative by virtue of the fact that they integrate the microbicidal effects of all the process variables yielding a simple pass or fail result.¹⁴

Biological Indicators.

There is a popular misconception that biological indicators are old fashioned and take too long to provide a result. Nothing could be further from the truth. Modern biological indicators employing extremely sensitive techniques to detect indicator organism growth at the earliest possible time are now available giving results in minutes rather than hours or days (see below for more detail). The use of a biological indicator (in combination with an appropriate PCD – see below) ensures microbicidal conditions have been achieved, regarded by some experts as the Gold Standard for sterilization process monitoring.¹⁵



Chemical Indicators.

Chemical Indicators provide a simple and easy to read indication of the attainment of process variables at the point of placement. Type 5 chemical indicators¹⁶ provide a result which can be correlated with the microbicidal properties of the process and therefore provide results similar to those which may be obtained from biological indicators.



The most valuable type 5 chemical indicators are the so-called moving front devices (see below). These provide a semi-quantitative result by virtue of the fact that a blue ink migrates along a white wick at a rate dependent on the temperature of the process. Such devices are marked with an exact accept/ reject line and therefore require minimal interpretation and the user can identify if a good safety margin has been achieved or if the process is marginal and close to failure.

Process Challenge Devices.

Process Challenge Devices (PCDs) are regarded as a defined challenge (often considered a “worst case”) to certain attributes of the sterilization process. PCDs are used in combination with one of the indicator devices described above. The simplest form is that encompassing a chemical indicator which is responsive to the presence of moisture and will provide a colour change. More useful are those which include a biological indicator which are then capable of showing that microbicidal conditions have been achieved at the most difficult to reach point in the PCD and therefore provide the user with confidence that the less challenging load has been exposed to a satisfactory sterilization process. PCDs may come in the form of long thin tubular devices with a capsule which contains the indicator device. Alternatively, they come in the form of a porous stack of material which has the indicator located in the centre. In both cases the PCD, often of commercial provenance, should be designed to mimic a standardized test device as described in standards.^{1,13,15}



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