Keywords
- STERRAD® 100**S** sterilizer
- Validation protocol
- Performance Qualification
- Independent data management system
- Low-temperature, Low-pressure sterilization
- RF energy
- Hydrogen peroxide, vaporized aqueous
- Plasma

Validation of a low-temperature, low-pressure, vaporized aqueous hydrogen peroxide-based, plasma sterilization system – STERRAD®100S sterilizer

A proposal qualified by experience with reference to ISO 14937

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Abstract

As in the past decade more medical devices have been introduced that are not only fragile but also (very) temperature sensitive, new avenues were searched to circumvent the traditional (tedious) methods of sterilization with equal sterilization efficacy. With the introduction of the new ISO 14937 guideline ("Sterilization of Health Care Products – General criteria for characterization of a sterilizing agent and development, validation and routine control of a sterilization process") Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) became mandatory. In this report a practical approach is presented for installation of materials for independent monitoring and in this way to deal with the aspects of OQ, PQ and Requalification. This will ultimately lead to parametric release of the STERRAD® 100S sterilization process offering single-day turnaround practice.

Introduction

In 1998 GMP compliant STERRAD® 100**S** sterilizers (medical device marked class CE IIa according to European Directive 93/42/EEC; ASP, Johnson&Johnson, Irvine, Ca,USA) were introduced in several Dutch Hospitals. The new concept was highlighted in an article published in the same year (1) by one of the holders to the patent (2). In follow up of IQ and OQ, the question was put forward: "How does one validate a STERRAD® 100**S** sterilizer; more specifically how does one set up a PQ and Requalification procedure of a process fairly new in the hospital area of a Central Sterilization Department (CSD).
Several sterilization procedures are in use, such as by heat (wet or dry), chemicals (Ethylene oxide, Formaldehyde or Glutaraldehyde based), radiation (Beta, gamma or UV radiation based) or laser based apparatus.
All have certain drawbacks it being in operating use and/or the creation of possible toxic residuals or of environmental conditions in the release of toxic substances.
As is the case in the hospital environment of a CSD the medical devices introduced nowadays are becoming more fragile in use i.e. cannot withstand sterilization heat of high temperature nor of long duration nor is the material durable or compatible with such a process.
Means have been sought to circumvent these impracticalities. At the basis of the STERRAD® 100**S** sterilizer is the germicidal property of hydrogen peroxide already known at the beginning of the 20th century (3). In the STERRAD® 100**S** sterilizer, aqueous hydrogen peroxide is vaporized in a cylindrical chamber at low temperature and low pressure. The sterilizing action of aqueous hydrogen peroxide is most likely by it's lethal oxidizing capacity of viable elements on or in the microorganism, after condensation into the liquid phase (4,5).
Development, validation and routine control of a sterilization process has attained high priority in maintaining of quality standards. Not only in the pharmaceutical industry but also in the hospital setting one is obliged to develop quality measuring instruments, validate, check, and adhere to them or follow national, European or International standards. Numerous reports have been published either as an example of recommendation (6,7,8) or as general requirement (9,10).
As it was deemed necessary to be able to perform a proper validation of the STERRAD® 100**S** sterilization process, critical parameters were defined. Additional instrumentation was required as the sterilizer was delivered without independent monitoring equipment necessary for hospital validation procedures.

Critical parameters

Operating time-sequences of a STERRAD® 100 plasma-based sterilizer have been published in 1993 and are depicted in Fig. 1 (11). The STERRAD® 100 is no longer available.

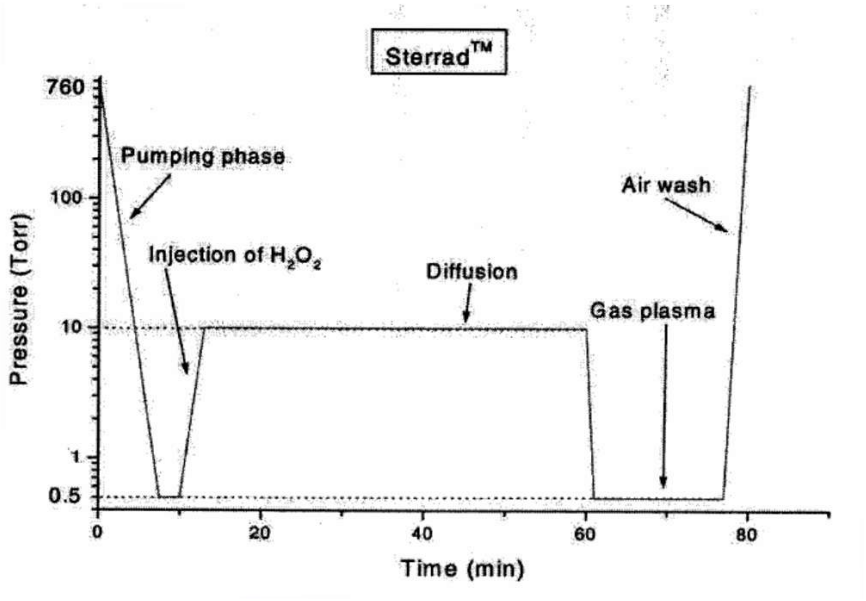


Fig 1: operating time-sequences of the Sterrad® 100.
(Temperature, delivered RF energy, and H_2O_2 concentration are not shown)

To comply with GMP mode and to be able to attain a sterility assurance level (SAL) of 10^{-6} a two-phase "double-kill" cycle of equal duration was introduced into the sterilization process. This device is marketed as the STERRAD® 100S sterilizer.
The operating time-sequences are depicted in Fig. 2 (Technical manual ASP; STERRAD® 100**S** sterilizer**).**

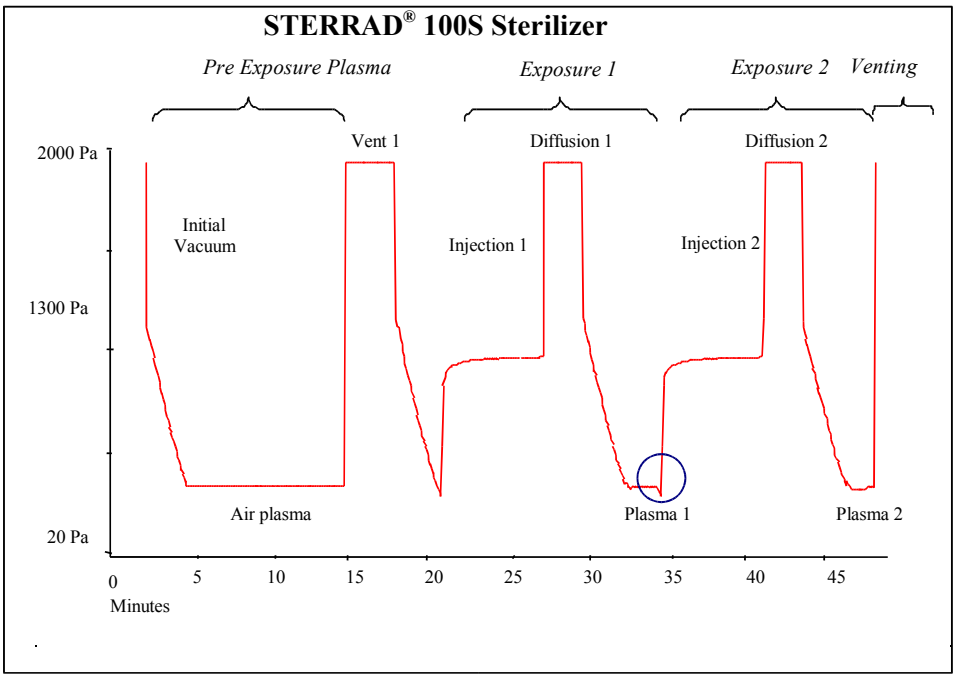


Fig 2: operating time-sequences of the two-phase "double-kill" cycle (STERRAD® 100S).
Note that duration of exposures 1 and 2 are identical. The "extra pump down", shown "in circle" before injection 2 is to insure identical operating conditions during both exposures. See also Table 2 for more details.
(Temperature, delivered RF energy, and H_2O_2 concentration are not shown)

Analysis of the separate phases involved of the STERRAD® 100**S** revealed that (low) pressure, delivered RF energy, and hydrogen peroxide concentration in the sterilization chamber are critical parameters. In order to be able to monitor these critical parameters on-line in real time mode, instrumentation was installed secondary to the present equipment without violating the CE status of the STERRAD® 100**S**.
The kill kinetics were not taken into consideration as this component has been covered in detail elsewhere (12,13,14).
In the following the materials and methods are described to perform an OQ and PQ procedure. The materials necessary for independent monitoring of the mentioned parameters during normal use are listed in detail in the Materials and Methods section. Finally a protocol (one scheme) is put forward in the conclusion section with a description of the implementation of these procedures, including the Requalification of the STERRAD® 100**S.**

Materials and Methods required for Validation procedures

- OQ

Following installation and completion of the IQ requirements, an OQ procedure is set up according to the specifications issued by Johnson&Johnson ASP, and the ISO 14937 standard. The following instrumentation was installed:

- Baratron (measuring range 0 - 1000 Torr (0 – 133,41 kPa);
- Second Baratron (measuring range 0 - 15 Torr (0 - 2 kPa);
- Thermovac TM 20;
- Chessell recorder (Eurotherm®, Netherlands);
- MKS power supply;
- Control unit (PC);

All installed units were calibrated before performing the qualification procedures. In Fig. 3 an overview is given of the parallel instrumentation of ASP and the hospital STERRAD® 100**S.**

Fig. 3: instruments in parallel for monitoring low pressures and delivered RF energy during Qualification procedures

After verification of all instrumentation, three full sterilization procedures (no load) are performed. All graphical data and the numerical data printout of the STERRAD® 100**S** are compared to the required standard. This will lead up to an OQ report.

- PQ

After successful completion of the OQ procedure a PQ will be performed in conjunction. Three sterilization cycles will be performed with either a Challenge Pack/Validation kit as defined by ASP (CycleSure® challenge Pack Kit, code 20232) or a customer's defined load (worst case). The sterilization procedure will be performed half cycle only. In total 12 packs will be used during first time (new installed units) performed PQ procedures. When one has passed all requirements, requalification will be performed on a yearly basis with a one full cycle (no load) sterilization OQ mode in conjunction followed by a one PQ procedure at half cycle mode. The latter is in accordance with ISO 14937 article 9. At least 10 biological indicators are sterilized along with the defined load and spaced at critical places in the load inside the sterilization chamber.

- VERIFICATION OF THE BI (Biological Indicator) INCUBATOR

The incubator has also been validated for the correct temperature read out. All BI's should show negative growth after a full cycle mode (OQ) and half cycle mode (PQ; with customers load or ASP reference pack). The BI contains spores of B. stearothermophilus ATCC 7953 (American Type Culture Collection). As per May 13th 2003 a name change has been implemented now renaming the spores Geobacillus stearothermophilus ATCC 7953 without any other effect on the spores [Technical bulletin ASP posted May 27th 2003].

- INDEPENDENT, IN LINE, REAL TIME, MONITORING SYSTEM (hardware and software)

After performing IQ, OQ, and PQ procedures the instrumentation necessary for a fully independent, calibrated (second), monitoring system (complete listing) in order to evaluate the STERRAD® 100**S** sterilization process as stipulated by ISO 14937 is as follows:

- Pressure transducer 0-15 Torr
- Thermocouple, J-type adhesive
- Reducer KF40/KF16; 21-03939-001
- Centering ring KF 16 alu; 21-00477-016
- Clamp ISO KF 16 alu; 21-00476-016
- RF signal cable device
- Eurotherm Chessel 5000B-06-BRIDGE
- Montage DIN rail 40 cm
- Start – stop signal/device ASP, USA.
- Control unit (PC) with printer and soft/hardware:
    - Windows 98 ,95,ME,2000, or NT4.0, XP with Internet Explorer 4.01 or higher
    - Review Software
    - Bridge software
- Internetmodule and cable 10/100Mbit for TCP/IP address

As was shown in Fig. 3, the graphical display unit is mounted on top of the STERRAD® 100**S.** In the near future the data-extraction unit will be built into the STERRAD® 100**S** and the graph displayed on the computer screen. Completion of a full sterilization cycle is followed by a hard copy printout (color) of the sterilization process permitting an instantaneous inspection of the critical parameters. This document will be attached to the documents pertaining to the sterilization load.

In Fig. 4 the installed second baratron for monitoring the low pressures is shown.

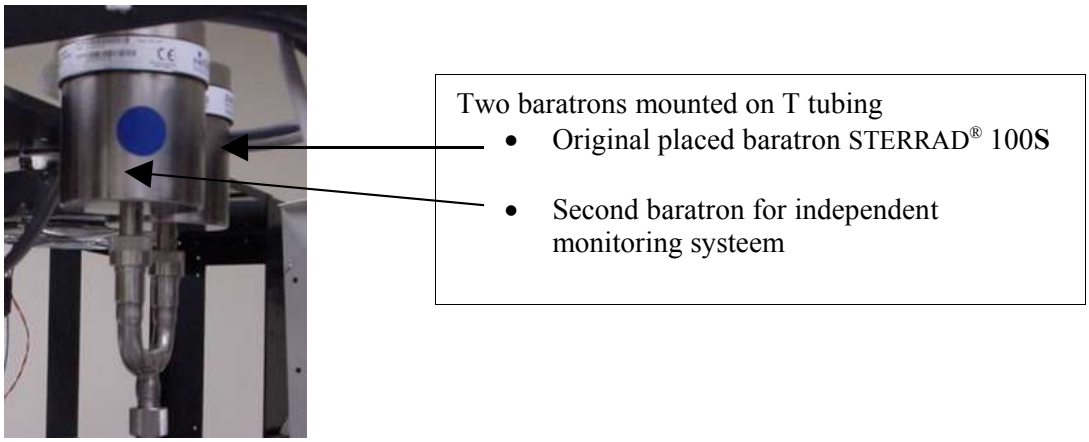


Fig. 4

Results

After installation and calibration of the required instruments, all graphical and numerical data recorded on a hard copy of the computer printout and the standard delivered hard copy (numerical data) supplied by the STERRAD® 100**S** are compared. The obtained values were compared to the values set by ASP for a correct completion of a sterilization cycle. All BI's are also checked for negative growth, with exception of the two non-sterilized BI's. In Fig. 5 a graphical display of two critical parameters (pressure and delivered RF energy) during a full sterilization cycle of a STERRAD® 100**S** validation process is presented; the temperature, a non-critical parameter, is also depicted.

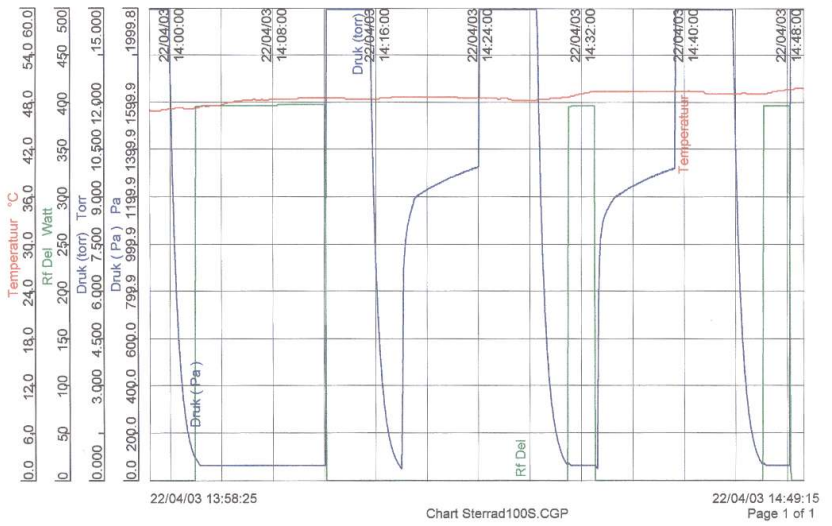


Fig. 5: graphical display of two critical parameters (pressure and RF energy) during a full sterilization cycle of a STERRAD® 100**S**.
(Temperature is also depicted)

In Fig. 6 a graphical display is shown for the half cycle process.

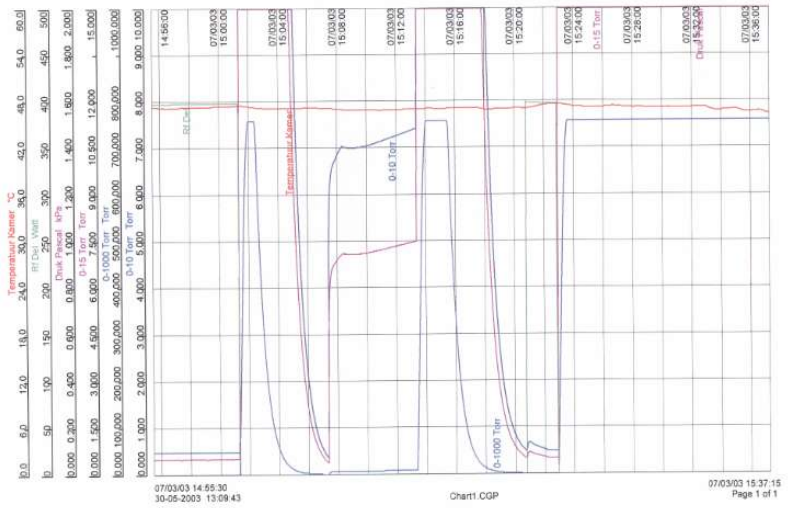
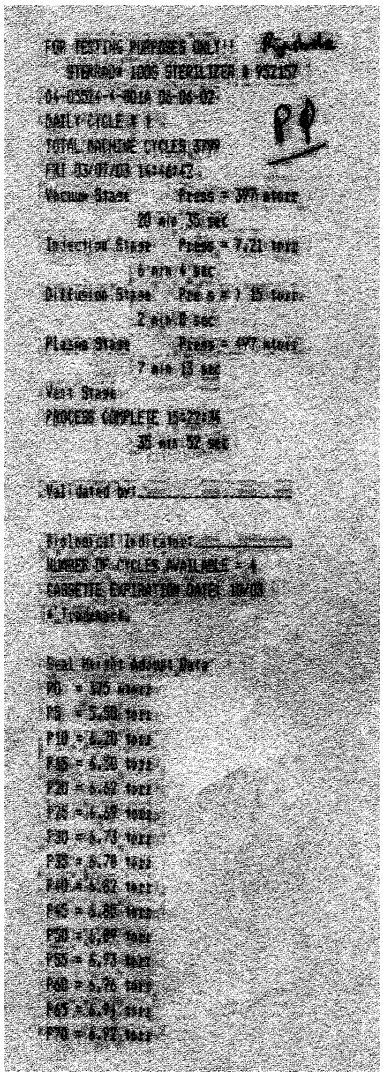


Fig. 6: a graphical display of a half cycle process during PQ of a STERRAD® 100**S**.
(Red: Temperature; Green: RF energy delivered; Blue 1: pressure (measured by baratron 1: 0 – 1000 Torr or 0 – 133,41 kPa); Blue 2: pressure (measured by baratron 2: 0 – 15 Torr or 0 - 2 kPa) Time: every vertical bar represents 4 minutes).

In Fig. 7 an example display is given of the numerical printout of the PQ procedure with the CycleSure® challenge Pack Kit code 20232. When a PQ is based on the hospital defined load (worst case), ASP recommends also a validation with the CycleSure® challenge Pack Kit (code 20232) to compare results.



For testing purposes only!!

STERRAD* 100 S STERILIZER # 952157
04-05524-4-00IA 06-06-02
DAILY CYCLE # 1
TOTAL MACHINE CYCLES 3799
FRI 03/07/03 14:46:42

Vacuum stage Press = 397 mtorr
20 min 35 sec
Injection stage Press = 7.21 torr
6 min 4 sec
Diffusion stage Press > 15 torr
2 min 0 sec
Plasma stage Press = 497 mtorr
7 min 13 sec
Vent Stage
PROCESS COMPLETE 15:22:34
35 min. 52 sec

Validated by:……

Biological Indicator:……
NUMBER OF CYCLES AVAILABLE = 4
CASSETTE EXPIRATION DATE: 10/03
*** Trademark.**

Seal Height Adjust Data
P0 = 375 mtorr
P5 = 5.50 torr
P10 = 6.20 torr
P15 = 6.50 torr
P20 = 6.62 torr
P25 = 6.69 torr
P30 = 6.73 torr
P35 = 6.78 torr
P40 = 6.82 torr
P45 = 6.85 torr
P50 = 6.89 torr
P55 = 6.93 torr
P60 = 6.96 torr
P65 = 6.94 torr
P70 = 6.92 torr

Fig. 7: printout of numerical data of the PQ procedure with the ASP defined CycleSure® challenge Pack Kit

In Fig. 8 a view is presented of the BI incubator.

Fig. 8: display of temperature verification of the used incubator

In Fig. 9 a document specimen of growth results of incubated BI's is presented

Performance Qualification ISO-EN 14937 Advanced Sterilization Products Sterrad Sterilization Systems	ASP.DOC 003 Datum: 22-12--2002 blad 11 van 21

3.1 Beladingsrapport en resultaten BI.

Instelling Ziekenhuis Rijnstate — Afdeling: Centrale Sterilisatie Afdeling
Type Sterrad: 100 S — Serienummer: J 30 57113 952157
Datum PQ/RQ 07-mrt-03
Lading samengesteld door: R.E. van der Werf iom: R. Bulten, hoofd CSA, Ziekenhuis Rijnstate — Functie: Sterilization Technologist

Lading/ nr. BI	verpakking	gewicht in gram	plaats in Sterrad	resultaat dagen incubatie: n= negatief p= positief cycle 1, half cycle nr. 3799							cycle 2, half cycle nr 3800							cycle 3, half cycle nr							cycle 4, full cycle nr						
				1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Neuro bipolair instrument; 2 BI's	dub. Lam	280	A-Y-2	n	n	n	n	n	n	n																				
accu; 2 BI's	dub. Lam	470	B-Z-2	n	n	n	n	n	n	n																				
optiek 0o/10mm 3537163; 2 BI's	dub.lam	910	B-X-1	n	n	n	n	n	n	n																				
optiek 0o/10mm 3545266; 2 BI's	dub. KC	824	B-Z-1	n	n	n	n	n	n	n																				
test naaldendoos2x (Faradaytest) 2 BI's	dub KC	2010	C-Y-2	n	n	n	n	n	n	n																				
siliconeslang; 2 BI's (geen foto)	dub. lam	130	A-Y-1	n	n	n	n	n	n	n																				
losse BI's onderste tray achter: 2 BI's	dub. Lam		C-Y-2	n	n	n	n	n	n	n																				
totaal PQ lading: 14 BI's, gewicht:		4524																												
validatie/challenge pack; 4 BI's totaal	dub. KC		B-Y-1 en 2								n	n	n	n	n	n	n													
validatie/challenge proces 2 BI's los	dub. Lam		C-Y-2								n	n	n	n	n	n	n													
Controle: 2 BI's niet steriel				p							p																			

Discussion

With relatively simple measures it is possible to perform validation procedures on the sterilization cycle of a STERRAD® 100**S** without any infringement on the actual concept and breaching of the CE status.
Essential to the validation procedure is the defining of which parameters are critical for this "low-temperature, low-pressure, vaporized aqueous hydrogen peroxide-based, plasma sterilization system" prior to installation of a second independent monitoring system for these parameters (Table 1, and 2). The critical parameters were defined in intensive discussions with members of the Dutch Inspectorate (Mr J.J.A.M. Kraus and Mr A. Hoekstra) and a member of the RIVM (Mr A. van Drongelen; The Center of Biological medicines and Medical Technology, Bilthoven, Netherlands). For the sake of completeness the view on aspects of these parameters on packaging, load, and sterilization chamber is also displayed.

Parameter	*Packaging*	*Load*	*Chamber*	*Sterilisation process*
Pressure (kPa or Torr)	+	+	++	++
Temperature (°C)	< 60	< 60	> 6*	-
H_2O_2 conc. (mg/L)	+	+	++	++
RF energy (Watt)		+		++
Residual H_2O_2				++

Symbols: "-" : n.a.; "+": applicable; "++": important and critical; "<" lower than; ">" higher than.
"*": this is appreciated ONLY in laboratory circumstances; normal practice is roomtemperature

Table 1: display of critical parameters of the
"low-temperature, low-pressure, vaporized aqueous hydrogen peroxide-based, plasma sterilization system;
STERRAD® 100**S** "

In Table 2 an overview is presented of the critical parameters at different stages of the observed sterilization cycle and their margins. These margins are governed by the computer steering system. When any one of the defined parameters fails to meet its predetermined (critical) value the sterilization process will be automatically cancelled. Total operating time per sterilization cycle will be approx. 57 minutes depending on sterilization load.

Parameter	*Observed Ranges*
Pre-Vacuum Plasma ☐ Pressure ☐ Time	~ 70 Pa ~ 10 minutes
Injection Stage 1 ☐ Pressure ☐ Time ☐ Concentration H_2O_2	800 - 1600 Pa ~ 6 minutes 2 – 6 mg/L
Diffusion Stage 1 ☐ Pressure ☐ Time	100 kPa ~ 2 minutes
Plasma Stage 1 ☐ Pressure ☐ Time ☐ RF power	~ 70 Pa ~ 4 minutes 365 – 420 Watt
Injection Stage 2 ☐ Pressure ☐ Time ☐ Concentration H_2O_2	800 - 1600 Pa ~ 6 minutes 2 – 6 mg/L
Diffusion Stage 2 ☐ Pressure ☐ Time	100 kPa ~ 2 minutes
Plasma Stage 2 ☐ Pressure ☐ Time ☐ RF power	~ 70 Pa ~ 4 minutes 365 – 420 Watt
Vent stage ☐ Time	~> 2 minutes

Table 2: overview of the critical parameters and their computer controlled/checked margins during different sterilization stages ;

(Hydrogen peroxide concentrations are put in for completeness; see under heading "critical parameters" for further explanation).

Critical parameters

- Pressure
  The pressure phases can be divided into several stages as displayed in Fig. 2. Besides the fact that the sterilization process will be cancelled when this critical parameter will not meet up to its requirements, the graphical display will help visualize and appreciate the pressure rise after injection of the 1.8 ml's of 58% hydrogen peroxide. Although the STERRAD® 100**S** is not equipped to measure the concentration of H_2O_2 in the sterilization chamber a nomogram is available to deduct the available concentration in respect to the observed pressure rise (Fig. 10).

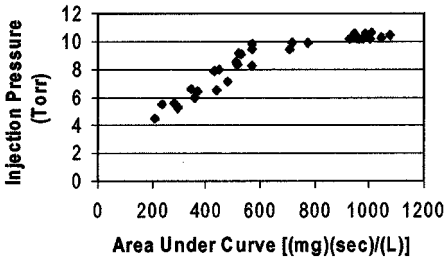


Fig. 10: nomogram for AUC of injected hydrogen peroxide versus pressure rise

As can be viewed from Fig. 10 a positive conclusion can be reached on the effective rise and thus availability of hydrogen peroxide in the sterilization chamber. This conclusion can be matched with the conversion of two different types of indicators present in the sterilization chamber. After sterilization the chemical indicator (present on the packaging material) based on a change of pH and the second type of chemical indicator (present on the lid of the BI) based on a redox reaction after interaction with the hydrogen peroxide in the sterilization chamber have changed in color. Own research (not published) has shown no color change of the redox-based indicator after treatment with "water for injections" nor in contact with methanol (not injected as the methanol vapor can be explosive).

- H_2O_2 concentration (mg/L)
  As mentioned in the previous paragraph no direct measurement of the hydrogen peroxide concentration is possible with the present STERRAD® 100**S** medical device. Inference can however be made on basis of the nomogram in Fig. 10. It should be emphasized that this nomogram has been constructed for the STERRAD 100S sterilizer only.

- RF energy (Watt)
  If one views the obtained, full cycle, validation graph (Fig. 5) one can discern three stages in which the RF energy (approx. 400 Watt; 13,56 MHz) is delivered. During the first stage, the so-called preconditioning stage in which the chamber with sterilization load is evacuated and ridded of as much moisture as possible, energy is transferred to the sterilization chamber. If the correct vacuum level cannot be reached cancellation of the sterilization process will follow. After this "drying mode" a second pulse of RF energy will be transferred prior to the second injection phase i.e. during the plasma stage of the first hydrogen peroxide injection. The result of this second energy burst is that highly reactive, hydrogen peroxide derived species (one of these species is the highly reactive hydroxyl radical) will be formed. This will result in further killing of possibly still viable microorganisms. In both stages vaporized aqueous hydrogen peroxide has penetrated the packaging material (TYVEK®) and condensed on the microorganism as preferred nucleation sites and killed them off. The generation of plasma is limited to the duration of the delivered RF energy pulse and continues at most several milliseconds after shutdown. This previous cycle is repeated in an identical manner; hence the term two-phase "double-kill" cycle. After shutdown of the supplied energy any reactive species will recombine to form water and oxygen. Repressurization to atmospheric level will follow prior to opening the sterilization chamber and obtaining the sterilized packaged materials.

- Residuals (nanogram)
  By use of these procedures there will only be a minimal residue of hydrogen peroxide on the sterilized materials. This has been confirmed in practice. The delivered RF energy in the final step of the sterilization cycle will ensure that any hydrogen peroxide present will be destructed into oxygen and water.

- [Temperature; °C]
  Although it was established that the temperature variable was not considered a critical parameter (maximum chamber *wall* temperature is set at 55 °C) we have performed measurements with a remote sensing device recording the temperature inside the packaging material during a complete sterilization cycle (Fig. 11). Indeed the recording showed that the temperature did not rise above 60 °C, as was put forward by the Inspectorate as the upper advisable limit (Tmax: 52.06 °C) . However the validity of data obtained by means of these types of measurements is still under investigation. As was the case during our measurements the transponders can still be easily damaged (deranged) during the plasma phase.

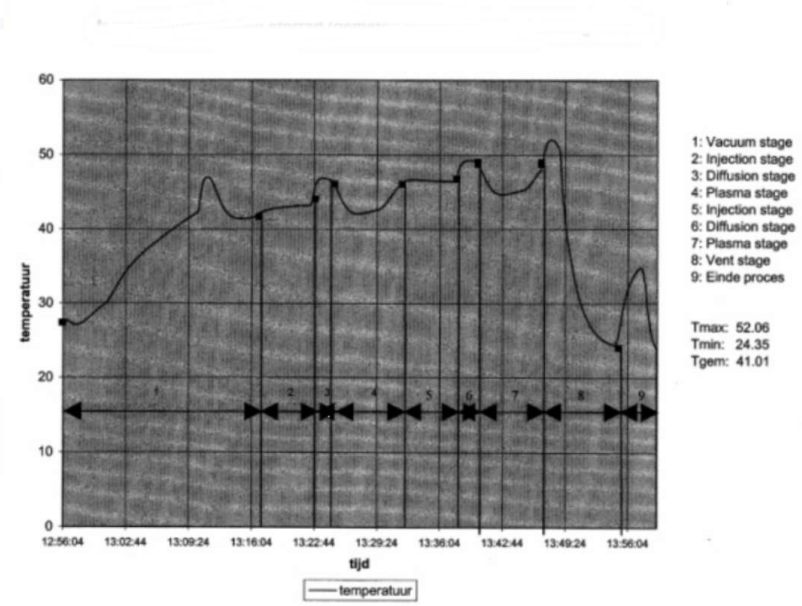


Fig. 11: temperature (°C) vs time (minutes) recording by remote sensing in packaging material (Tyvek®) during a sterilization cycle of a
"low-temperature, low-pressure, vaporized aqueous hydrogen peroxide-based, sterilization system; STERRAD® 100**S** " (Courtesy KW2; Ing. JJJ Patijn)

Conclusion

In the foregoing we have described a simple and efficient method of an independent measuring system capable of monitoring the critical parameters of a "low-temperature, low-pressure, vaporized aqueous hydrogen peroxide based, sterilization system; STERRAD® 100**S**".
Based on the requirements put forward by the ISO 14937 guideline we propose the following scheme for the different aspects of validation (Fig. 12).

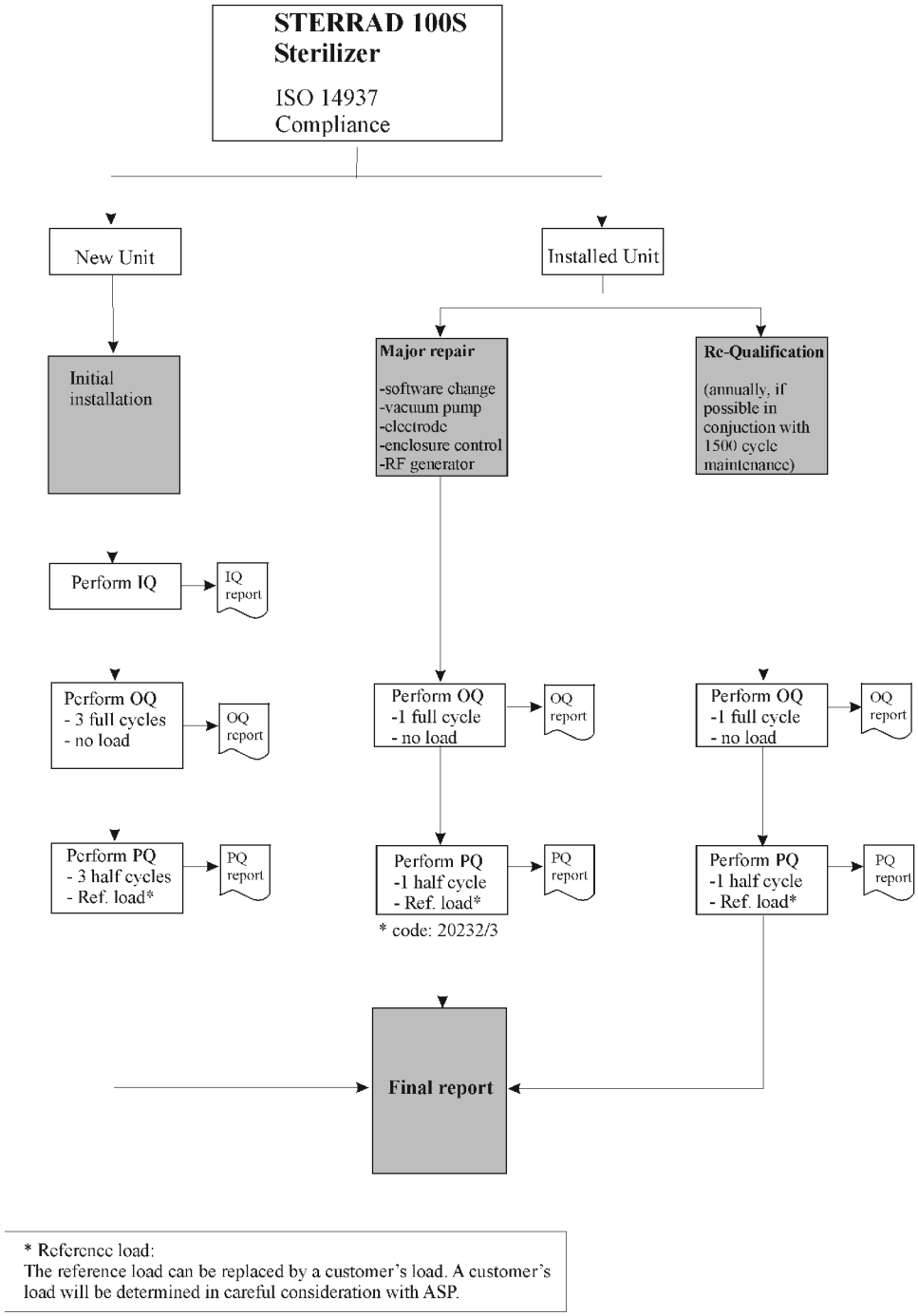


Fig. 12: validation scheme for "low-temperature, low-pressure, vaporized aqueous hydrogen peroxide-based, sterilization system; STERRAD® 100**S** "

Although we have put forward a practical proposal based on considerable experience in establishing this scheme we realize that new standards are underway (GMP's for the new Millenium). With this new approach of the FDA "a science- and risk-based approach to product quality regulation incorporating an integrated quality systems approach" we believe more work lies ahead to be able to be compliant with newly devised systems (15,16,17). Ultimately our research will lead to parametric release for the "low-temperature, low-pressure, vaporized aqueous hydrogen peroxide based, sterilization system; STERRAD® 100**S**" as has also been published and proposed for Ethylene oxide sterilization (18). This possibly could be more inviting and necessary all the more as the manufacturing of a biological indicator would prove to be more cumbersome or compelling than anticipated. We believe that the proposal put forward to Annex 17 to the European guide to Good Manufacturing Practice titled "Parametric release" will be applicable to the STERRAD® 100**S** sterilizing system with the intention of operating "A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release" (19,20).

References

1 Jacobs PT, Smith D: The new STERRAD® 100S Sterilization system: features and advantages. Zentral Sterilisation Central Service 1998;6:86-94.
2 United States Patent 4,643,876 and 4,756,882.
3 Turner FJ: Hydrogen peroxide and other oxidant disinfectants: in Block SS (Editor): Disinfection, Sterilization, and Preservation, 3d edn, Lea & Febiger 1983, Philadelphia, USA, ISBN:0-8121-0863-9.
4 Marcos-Martin M-A, Bardat A, Schmitthaeusler R, Beysens D: Sterilzation by vapour condensation: Pharm Tech Eur 1996;8:24-32.
5 Schaffer S, Pflug IJ: vaporized hydrogen peroxide at low pressures as an agent to kill bacterial spores: Zentral Sterilisation Central Service 2000;8:198-204.
6 Dennhöfer E: Special guideline No. 1 – processing sterile medical devices: Zentral Sterilisation Central Service 2002;11:101.
7 Vidière B: Integriertes konzept für engneering und qualifizierung von apparaten und ausrüstungsgegenstanden: Pharm Ind special issue 8a:2002;64:880-886.
8 Powell-Evans K: Quasi-Validation or Good Validation Practice: Pharm Tech Eur 2002;14:60-65.
9 NEN-EN-ISO 14937; EN ISO 14937; ISO 14937: Sterilization of health care products – general requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices: December 15th 2000.
10 Berg Th et al: Convention for the mutual recognition of inspections in respect of the manufacture of pharmaceutical products: Principles of qualification and validation in pharmaceutical manufacture: recommendations on Validation master plan, Installation and Operational qualification, non-sterile process validation, cleaning validation: Document PH 1/96: January 1996.
11 Jacobs PT, Kowatsch R: Sterrad sterilization system: a new technology for instrument sterilization. Endosc Surg 1993;1:57-58.
12 Choi SJ, Thralls VV, Smith DF: Bacillus stearothermophilus spores (ATCC 7953) in a hydrogen peroxide gas plasma sterilization system; Evaluation of inactivation rates using both the survivor curve method and MPN method: Zentral Sterilisation Central Service 2002;10:152-157.
13 Gaspar MC, Peláez B, Fernández C, Fereres J: Microbiological efficacy of Sterrad 100S and LTSF sterilization systems compared to ethylene oxide: Zentral Sterilisation Central Service 2002;10:96-99.
14 Favero MS: Low temperature sterilization: Zentral Sterilisation Central Service 2002;10:190-191.
15 Clinton P: getting ready for risk-based GMPs: Biopharm International April 2003;26-32.
16 FDA: A risk-based approach to pharmaceutical current good manufacturing practices (cGMP) for the 21st century: a progress report: April 22-24,2003
17 Dennhöfer E: Development, validation and routine control of a sterilization process: Zentral Sterilisation Central Service 2003;11:101.
18 Matthews IP, Dickinson W, Zhu Z, Samuel AH: Parametric release for EtO sterilization: Medical Device Technology 1998;july/august:22-26.
19 Proposal for a Annex 17 to the EU guide to Good Manufacturing Practice: Parametric release: Brussels, 7th April 2000, ENTR/6270/00
20 PIC/S: Pharmaceutical Inspection Convention: PR 2/99-1 Draft 7, 13 October 1999: Guidance on parametric release.

Acknowledgements

Dr. M. Favero, Advanced Sterilization Products, Johnson&Johnson Medical, Irvine, California, USA
Mr D.F. Smith, Director Microbiology & Industrial Science, and Staff, Advanced Sterilization Products, Johnson&Johnson Medical, Irvine, California, USA.
Dept of Clinical Physics (Rijnstate Hospital; Alysis zorggroep, Arnhem) for instrumental computer support.
Mr J.E.H. van Oirschot (Eurotherm BV, Alphen a/d Rijn, Europe) for instrumental graphical support.