VALIDATION

OF A LOW TEMPERATURE, LOW PRESSURE,

HYDROGEN PEROXIDE GAS PLASMA (HPGP) STERILIZATION SYSTEM

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Department of Pharmacy and
Central Sterile Supply Department,
Rijnstate Hospital Arnhem, The Netherlands

London, England, UK. Issm and EFHSS. DSc 2005; Decontamination Sciences Congress
Session 7B at 14.00; Conference room E

ZIEKENHUIS Rijnstate

1998

Sterrad 100S

in

Dutch hospitals

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Rijnstate hospital Arnhem

- Teaching Hospital (affiliated with University Hospital, Nijmegen)
- 770 Beds,
- All specialties
- Central Sterile Supply Department
  - *26.26 FTE*
  - *GMP procedures*
- 26000 u/month for surgical procedures

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ZIEKENHUIS
Rijnstate

2005

University Hospitals
Amsterdam and Maastricht
STERRAD 200

Other hospitals
14 STERRAD 100 S
1 STERRAD 200

DUTCH STERRAD
Density Factor:
1 in approx. 10^6 inhabitants

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Some Reasons for purchase STERRAD

- Longer life cycle optical instruments
- Longer life cycle batteries (Orthopedic instruments)
- Short turnaround time

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Problem

STERRAD® 100S STERILIZER # 38117
04-05524-4-001A 06-06-02
DAILY CYCLE # 1
TOTAL MACHINE CYCLES 7
SHORT CYCLE
FRI 08/15/03 11:33:43
Vacuum Stage Press = 397 mtorr
19 min 47 sec
Injection Stage Press = 8.57 torr
6 min 1 sec
Diffusion Stage Press) 15 torr
2 min 0 sec
Plasma Stage Press = 500 mtorr
6 min 54 sec
Injection Stage Press = 9.36 torr
6 min 1 sec
Diffusion Stage Press) 15 torr
2 min 1 sec
Plasma Stage Press = 500 mtorr
6 min 47 sec
Vent Stage
PROCESS COMPLETE 12:23:15
49 min 32 sec

Validated by:_____

Biological Indicator:_____
NUMBER OF CYCLES AVAILABLE = 4
CASSETTE EXPIRATION DATE: 01/04
® Trademark.

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PRINCIPLES OF INFORMATION

- Incomplete information will get you precisely nowhere
- Check the validity of your information at regular intervals

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14937

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“Umbrella” standard

EN ISO 14937: 2000

Sterilization of Health Care Products

Most interesting is **paragraph 9**

VALIDATION

and

ANNEX E

Guidance on application of this international standard

and

allocation of responsibility

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General Requirements

for

- Characterization of a

  STERILIZING AGENT

- Development, Validation and Routine Control of a

  STERILIZATION PROCESS

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Characterization of a STERILIZING AGENT

Hydrogen peroxide is

- known since end of 19th century as a disinfectant
- relatively inexpensive
- leaves no residue, and is
- effective in disinfecting open wounds.

The reactivity of hydrogen peroxide is easily seen in the foaming that occurs when it is applied to an open wound. The foaming occurs because the hydrogen peroxide **dissociates into water and oxygen** in the presence of enzymes found in open wounds. However, hydrogen peroxide is known to be relatively slow in disinfecting. At ambient temperatures and pressure, 20 minutes of contact is recommended to disinfect a wound.

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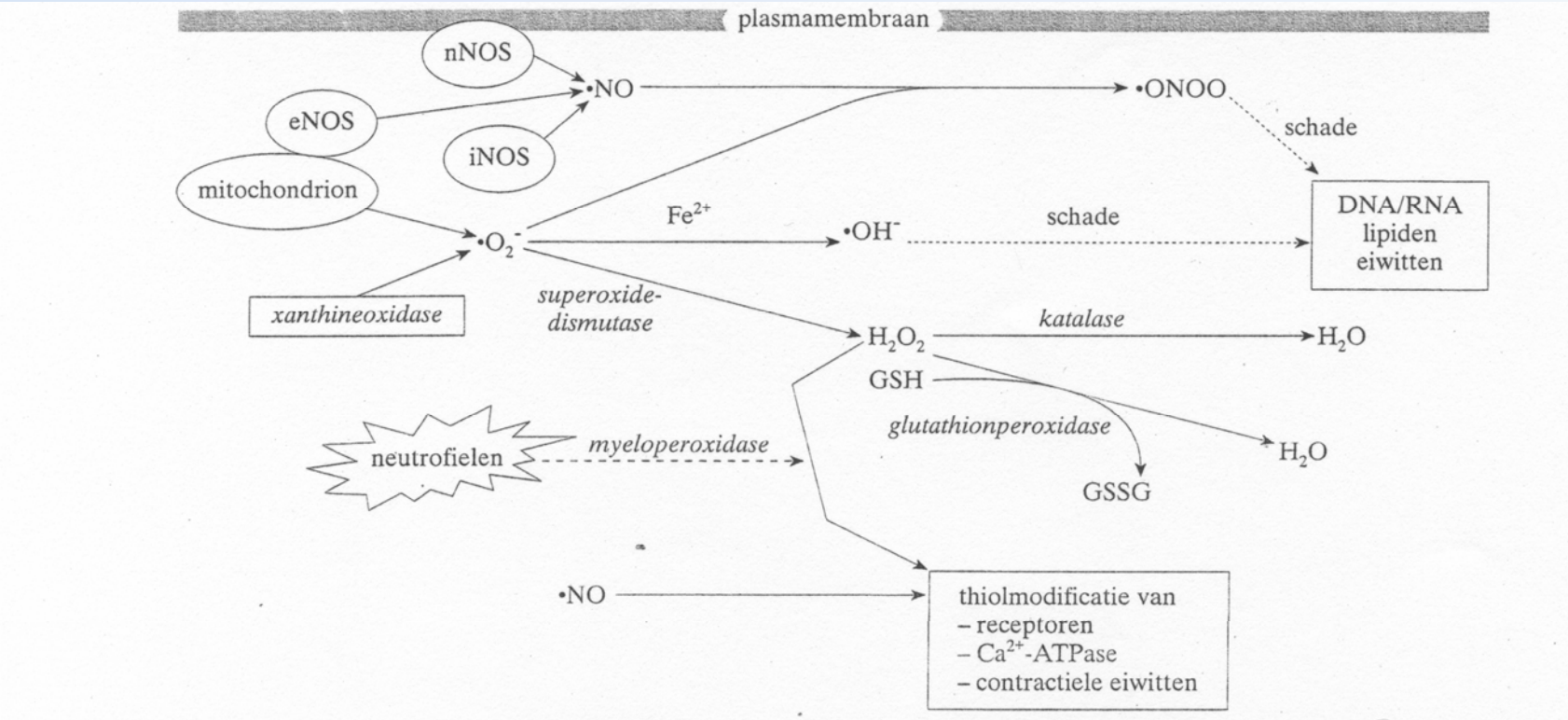
Hydrogen peroxide is

- naturally present in the human body and used as a defence mechanism against e.g. bacterial invaders
- eliminated by enzymes like:

katalase, glutathionperoxidase and myeloperoxidase



Rijnstate

STERRAD 100S

parameter	Packaging	Load	Sterilisation process	Chamber	Venting stage
Pressure	X	(X)	XX	**XX**	
Temperature	< 60°C	< 60°C	< 60 °C	> 6°C	non critical
H_2O_2 Conc.	Compatible	Compatible	XX	**XX**	**XX**
RF energy			X	X	**XX**
Residual H_2O_2			XX		**critical**

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VALIDATION

- IQ ⟶ 9.2 Technical Manual Company
- OQ ⟶ 9.3 Procedures Company
- **PQ ⟶ 9.4 Procedures Hospital**

Validation = Qualification
= Veiligheid=Sûreté

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PARAGRAPH 9.4

9.4.3

Data shall be generated to demonstrate the attainment of the defined physical and/or chemical conditions, within specified tolerances, throughout the sterilization load.

9.4.8

Performance qualification shall include a series of at least **three consecutive exposures** of product to the sterilization process, **within defined tolerances**, in order to demonstrate the reproducibility of the process.

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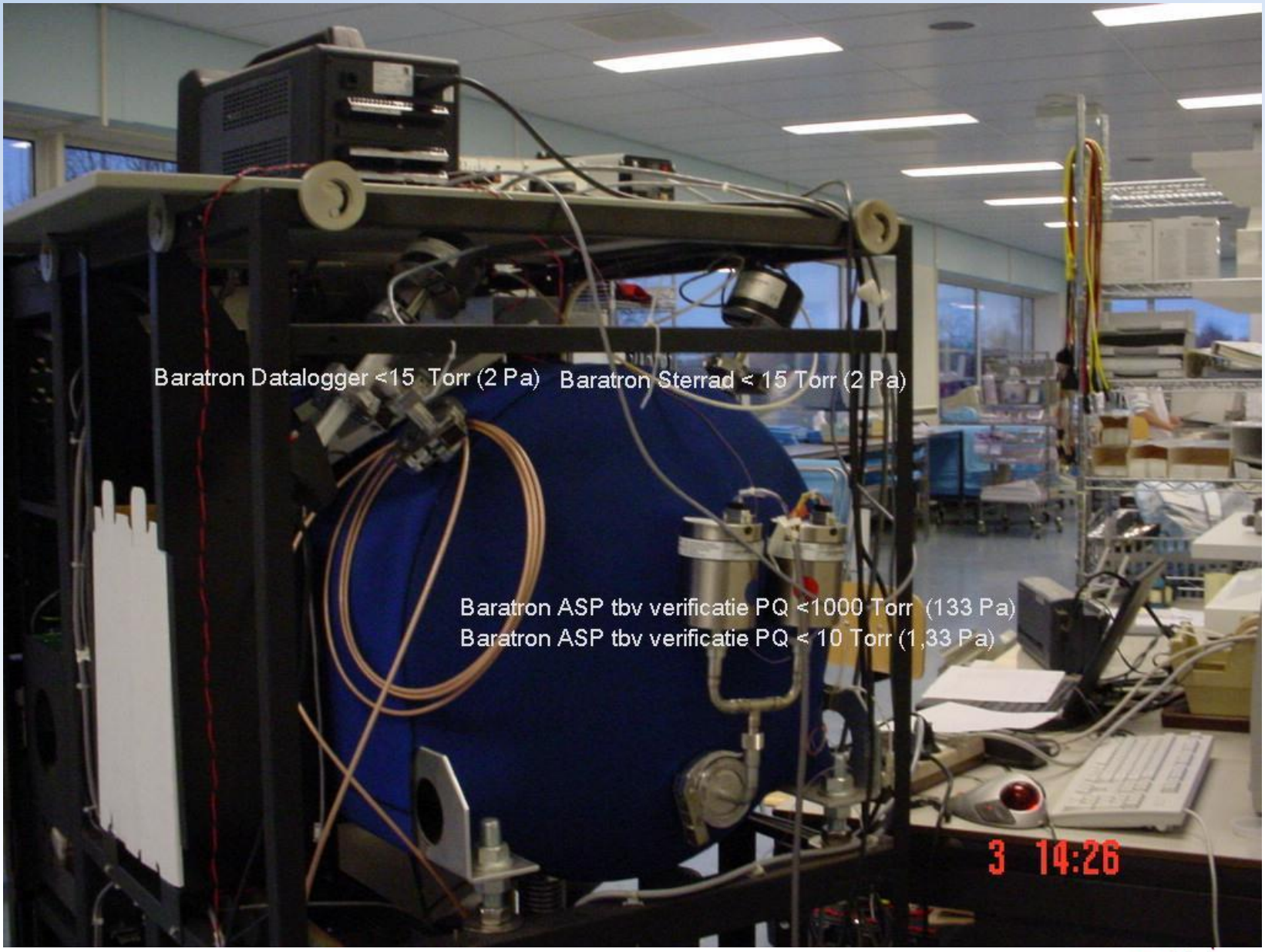
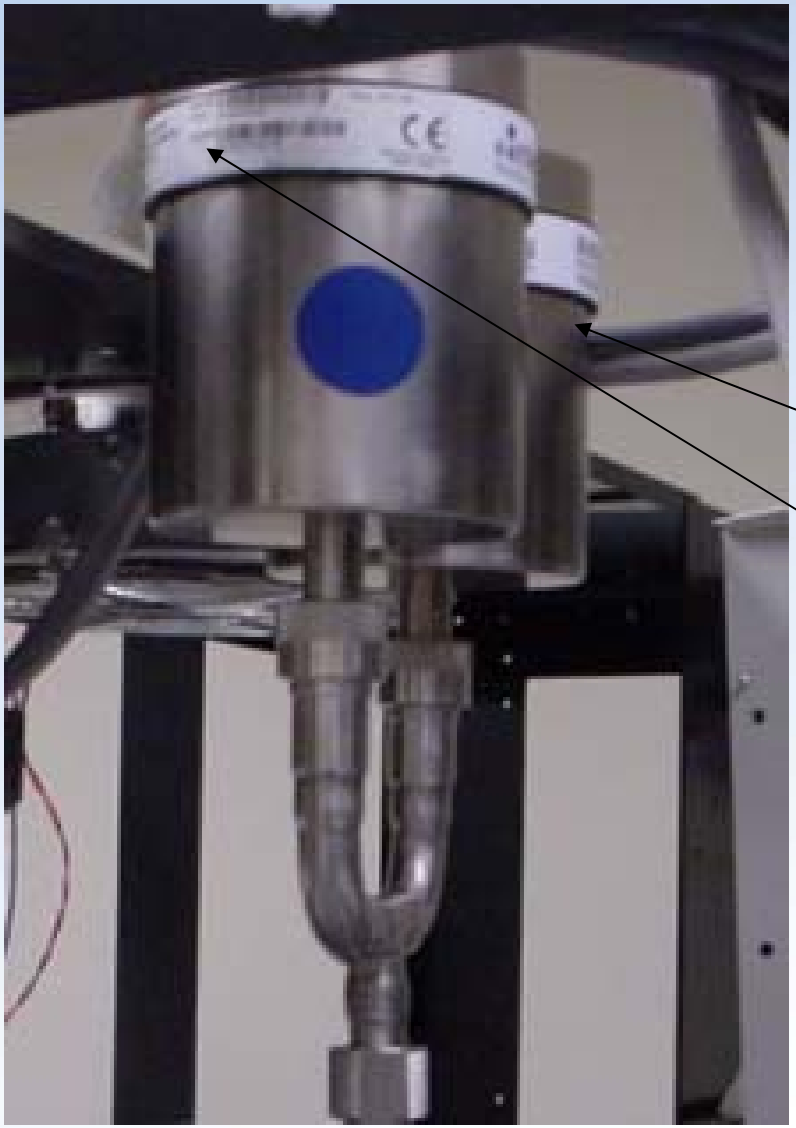

Baratron Datalogger <15 Torr (2 Pa)
Baratron Sterrad < 15 Torr (2 Pa)
Baratron ASP tbv verificatie PQ <1000 Torr (133 Pa)
Baratron ASP tbv verificatie PQ < 10 Torr (1,33 Pa)
3 14:26

Rijnstate



Two baratrons mounted on T tubing

- Original placed baratron STERRAD®100**S**
- Second baratron for independent monitoring systeem

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Instruments in parallel for independent monitoring of low pressures and delivered RF energy, (and temperature) during Validation procedures

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Display of

temperature verification

of the used incubator

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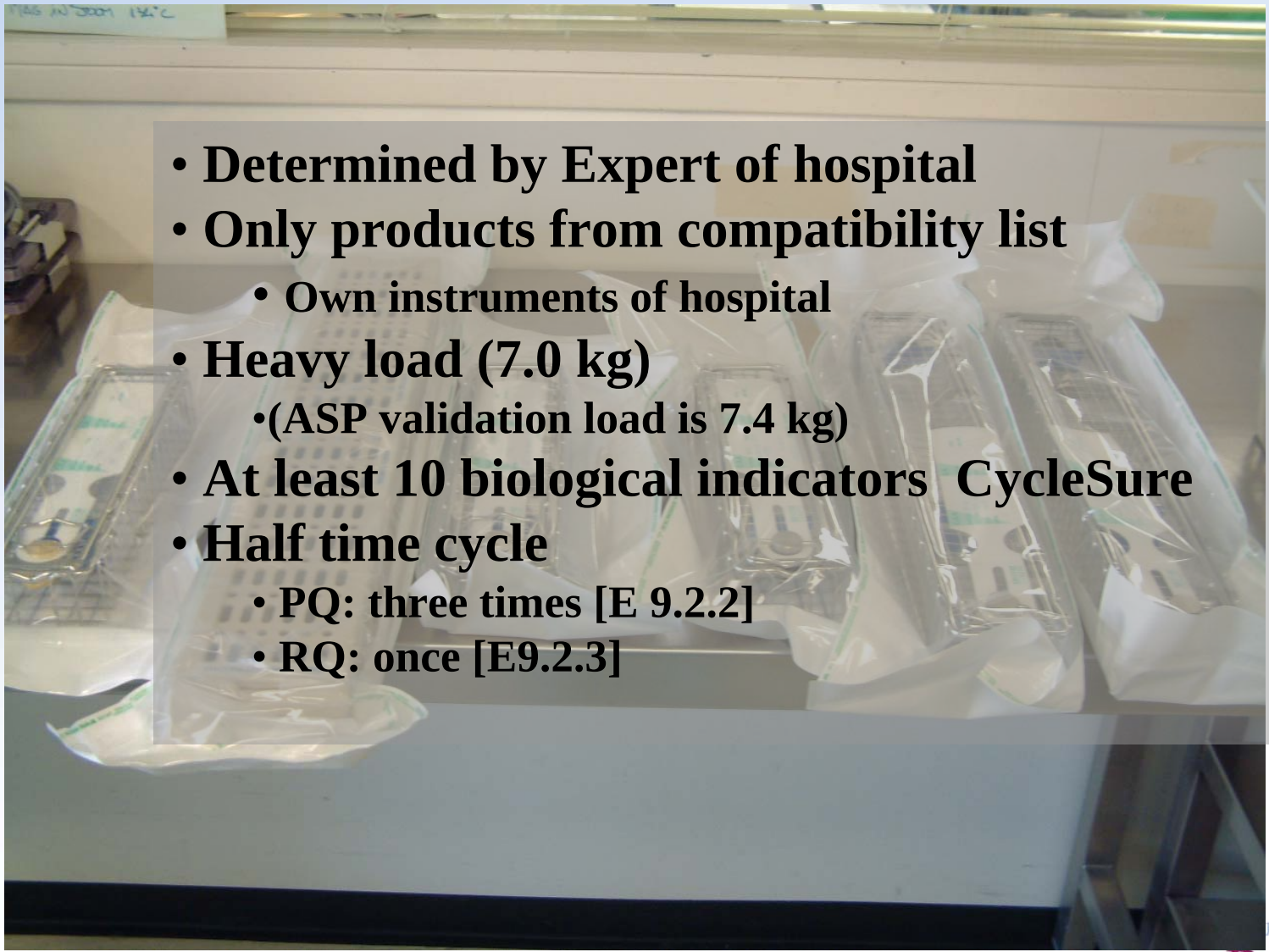
Validation load Hospital



- Determined by Expert of hospital
- Only products from compatibility list
  - Own instruments of hospital
- Heavy load (7.0 kg)
  - (ASP validation load is 7.4 kg)
- At least 10 biological indicators CycleSure
- Half time cycle
  - PQ: three times [E 9.2.2]
  - RQ: once [E9.2.3]

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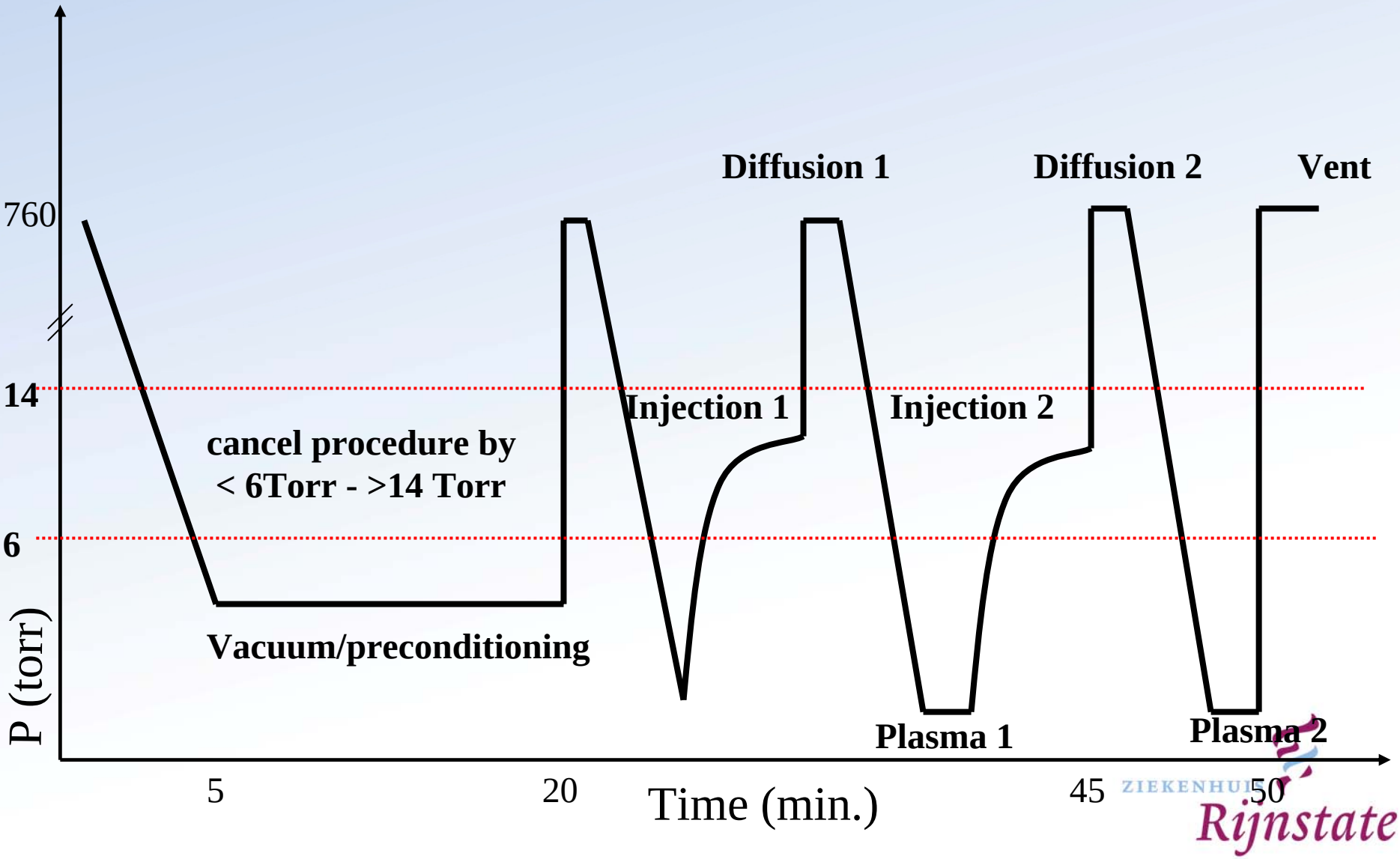
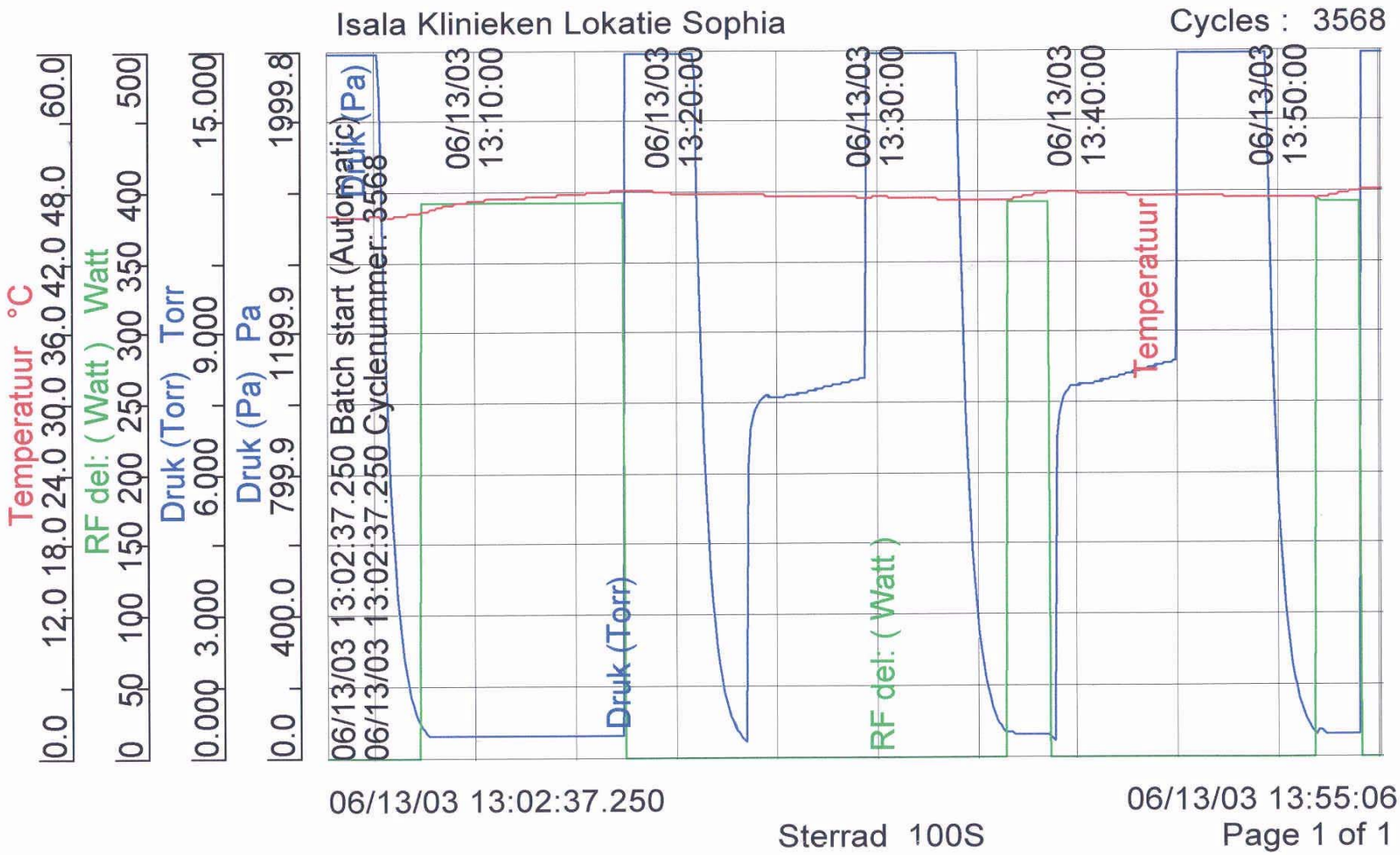
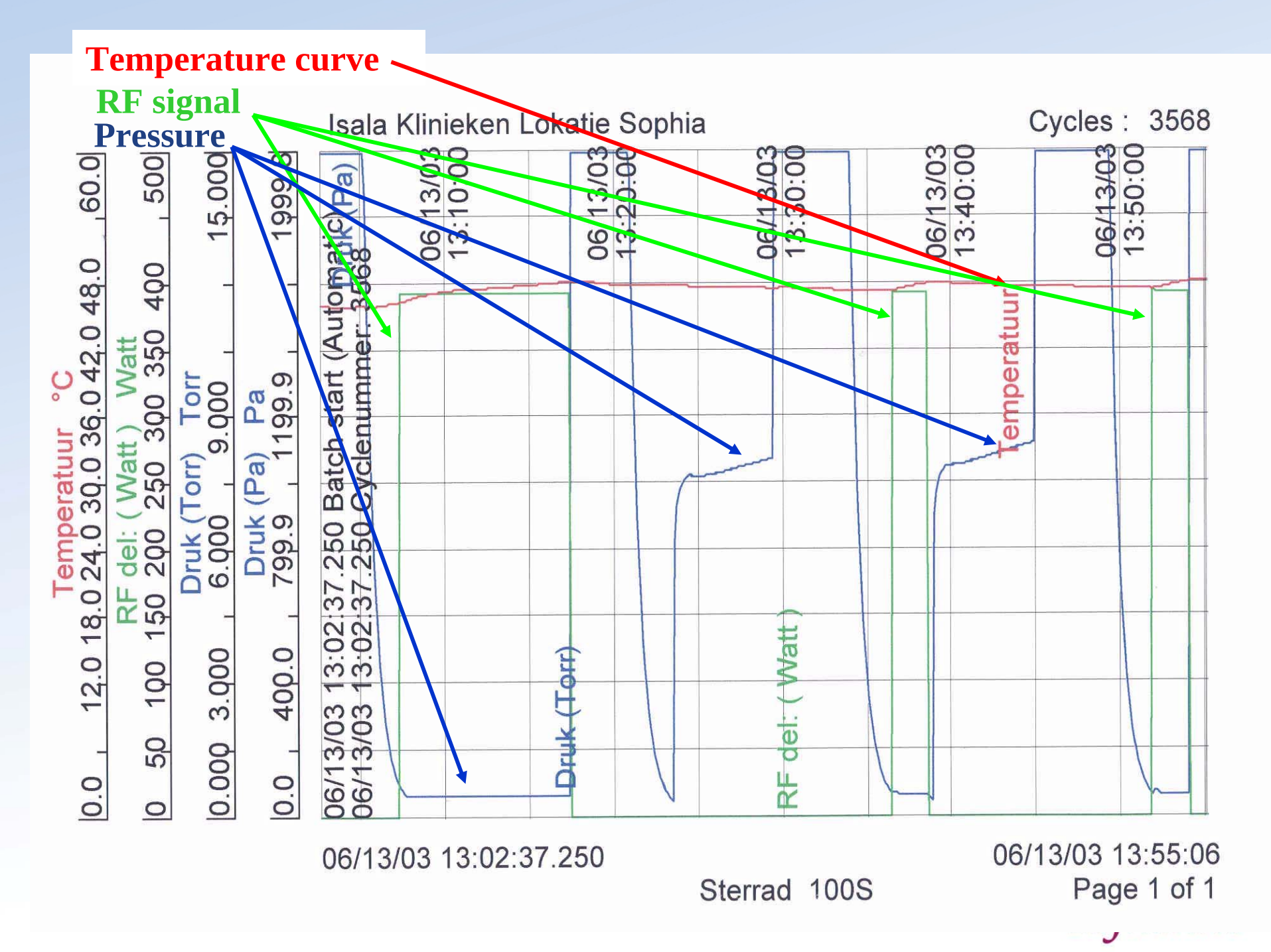
Proces: The Phases



Full cycle process



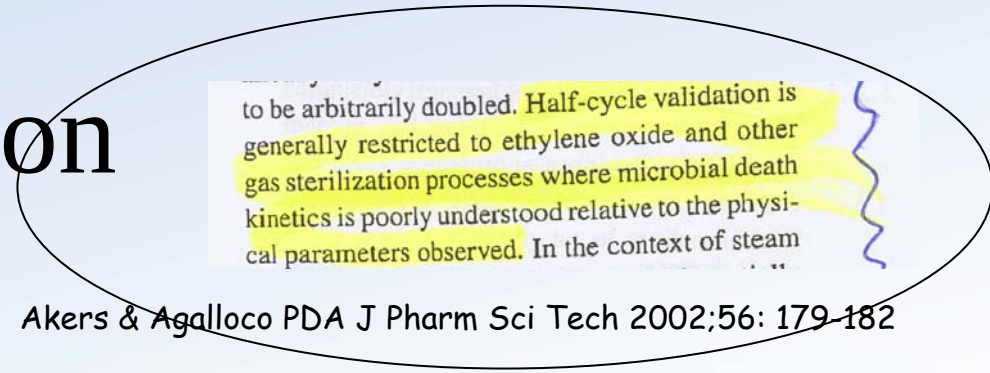

Temperature curve
RF signal
Pressure
Isala Klinieken Lokatie Sophia
Cycles : 3568
Temperatuur °C
RF del: (Watt) Watt
Druk (Torr) Torr
Druk (Pa) Pa
06/13/03 13:02:37.250 Batch start (Automatic)
06/13/03 13:02:37.250 Cyclenummer: 3568
Druk (Torr)
RF del: (Watt)
Temperatuur
06/13/03 13:02:37.250
06/13/03 13:55:06
Sterrad 100S
Page 1 of 1

PARAGRAPH 9

9.4.4:

Microbiological performance qualification studies shall comprise delivery of the sterilizing agent under conditions designed so that the extent of treatment is reduced relative to that in the sterilization process.

- Half cycle validation


to be arbitrarily doubled. Half-cycle validation is generally restricted to ethylene oxide and other gas sterilization processes where microbial death kinetics is poorly understood relative to the physical parameters observed. In the context of steam

Akers & Agalloco PDA J Pharm Sci Tech 2002;56: 179-182

- Proof of SAL 10^{-6}

Sterility Assurance Level: the expected maximum probability of an item being non-sterile after exposure to a valid sterilization process

PARAGRAPH 8

8.3:

Biological indicators

- Minimal 10 per 100 Liter chamber
- At designated places (pictures!)

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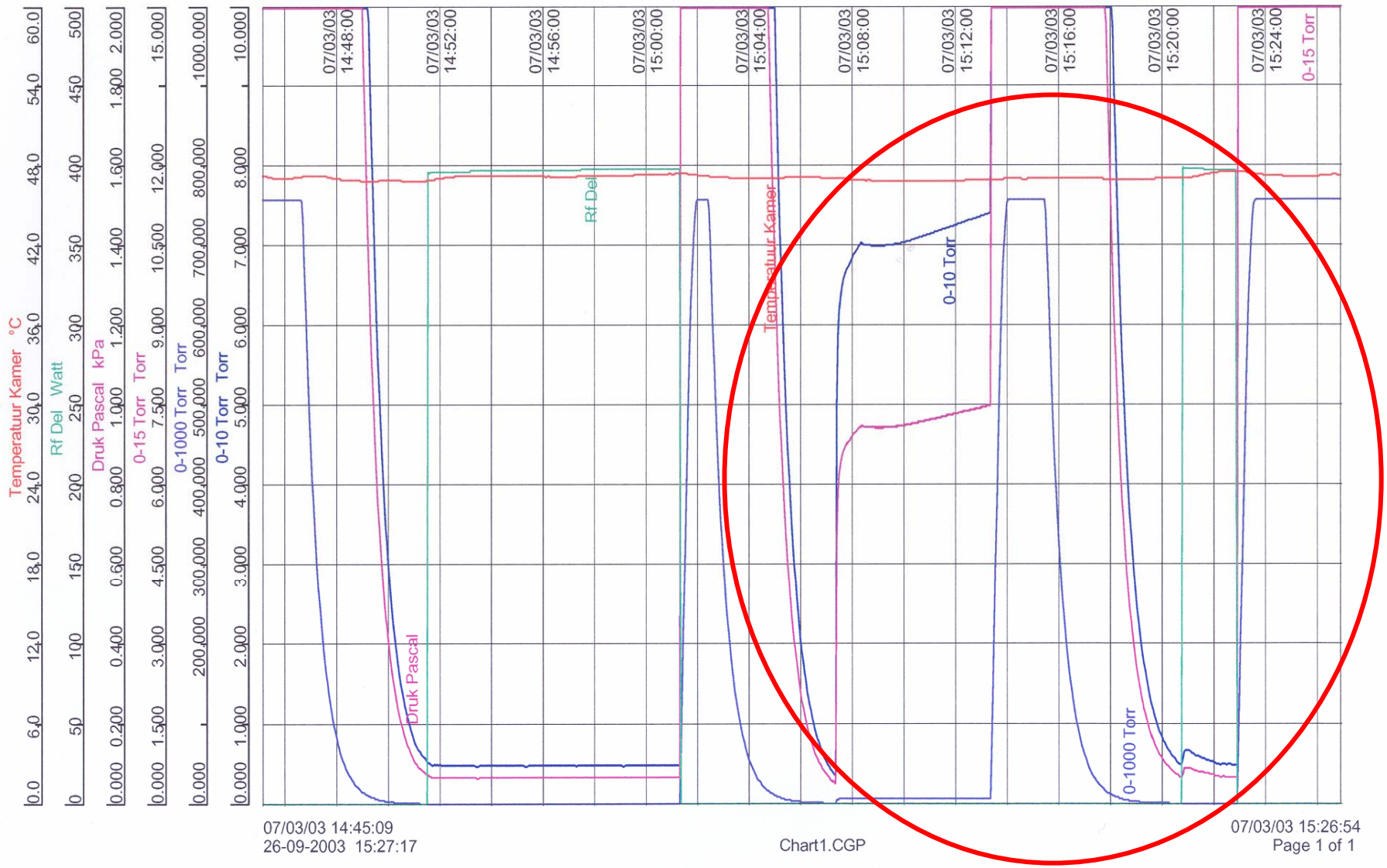
PQ half cycle process

One injection, diffusion and plasma stage

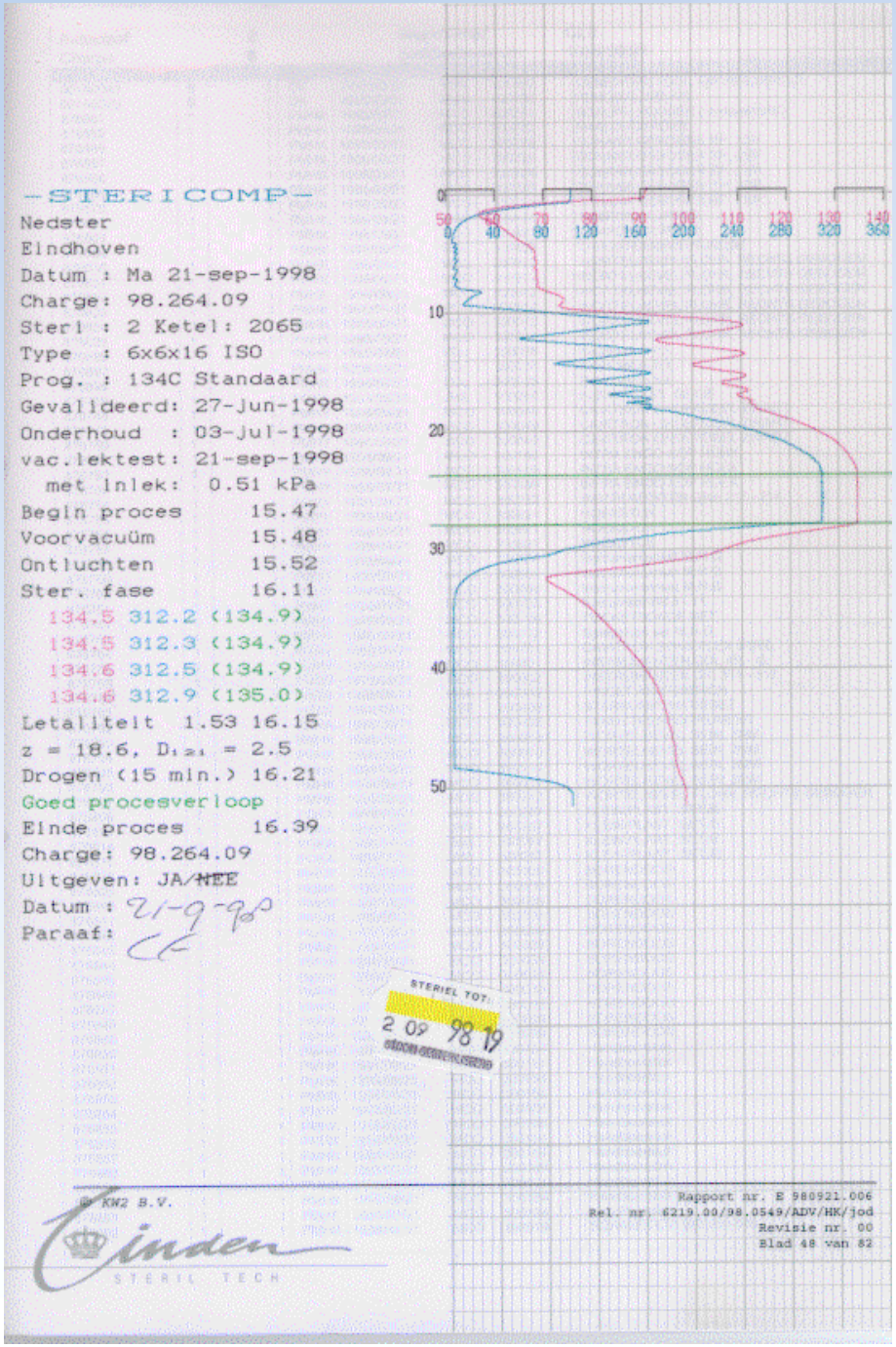


Performance Qualification ISO-EN 14937 Advanced Sterilization Products Sterrad Sterilization Systems	ASP.DOC 003 Datum: 22-12--2002 blad 11 van 21

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: — Functie: Sterilization Technologist
R. Bulten, hoofd CSA, Ziekenhuis Rijnstate

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																								



Print and diagram of a steam sterilization process used for parametric release

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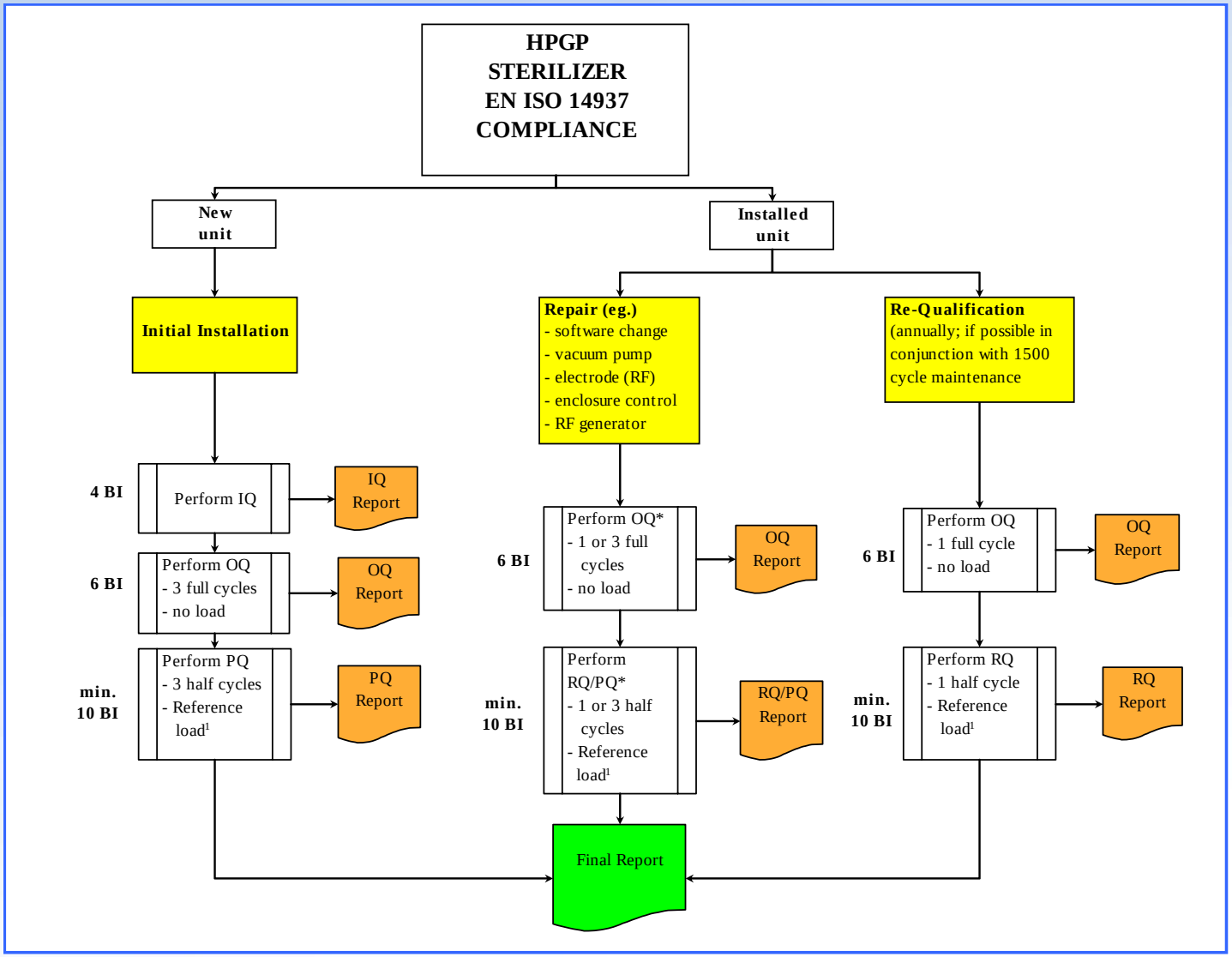

*1 or 3 cycles; at discretion of Director of CSSD

[1] The reference load can be replaced by a customer's load ("worst case"). A customer's load will be determined in careful consideration with the supplier of the HPGP-sterilizer.

van Sorge/ Ackerman
Februari 2005

ZIEKENHUIS Rijnstate

ADVANCED STERILIZATION PRODUCTS®
a Johnson&Johnson company

Samenvattend verslag:

Sterrad type:	100 S
Sterrad serienummer:	J 30 57113 / 952157
Datum van installatie:	3 maart 1999
Naam instelling:	Ziekenhuis Rijnstate
Adres, postcode en plaats	Wagnerlaan 55 6815 AD Arnhem

Validatiedatum: 14 oktober 2004
Validatie werd uitgevoerd door: R.E. van der Werf, Sterilization Technologist

Reden van validatie:
Jaarlijkse OQ en RQ

Verslag van validatie:
De validatie werd uitgevoerd conform de validatieprocedure beschreven in ISO-EN 14937, inclusief de ASP procedure:

- Technische manual, behorend bij het type van het apparaat
- Biologische validatie, beschreven in document werkinstructie ASP.QA.W1002

De validatie bestond uit:
Proces 5243: OQ procedure, inclusief technische metingen, volgens procedure en beschreven in bovengenoemde documenten
B's los verpakt: 4

RQ procedure half time validatie, uitgevoerd met eigen lading ziekenhuis en een validatielading ASP bestaande uit validation kit/challange pack nr. 20232/20233

Proces: 5244:	BI's validation kit/challange pack: 4,	los verpakt: 6.	Totaal BI's: 10
Proces: 5245:	BI's eigen lading ziekenhuis:12,	los verpakt: 4.	Totaal BI's: 16

Bevindingen:
Alle biologische indicatoren van de processen 5243, 5244 en 5245 bleken steriel.
Het Sterrad Sterilisatiesyteem voldoet aan de validatie-normen voor sterilisatie. (Sterility Assurance Level SAL 10^{-6})

Aanbevolen datum voor hervalidatie:
Na 1500 cycli of ten laatste ; oktober 2005

Getekend:
Advanced Sterilization Products
Johnson & Johnson Medical NV/SA

Datum:
18 oktober 2004

R.E. van der Werf

ASP.DOC014

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Recent Inspectional Trends: Are Regulatory Requirements for Sterile Products Becoming Scientifically Undoable or Unpractical?

James E. Akers[1] and James P. Agalloco[2]

[1]Akers Kennedy and Associates, Kansas City, MO, and [2]Agalloco and Associates, Belle Meade, NJ, USA

We have commented in the past about escalating process control and validation expectations being imposed in ways that are contrary to reasonable scientific principles or are simply operationally impractical. We, like all right minded industry professionals, believe that every appropriate effort must be made to ensure the quality and safety of sterile products. However, we see no virtue in the ratcheting up of standards without evidence that a real consumer safety concern exists and, even worse, with no objective evidence that a new standard will make things any better. In fact, in our opinion, more testing in combination with greater expectation for data review is not required unless clearly warranted by objective weaknesses in process integrity.

The following is a list of some recent issues in regulatory inspection or process review that we believe would benefit from open discussion between regulatory authorities and industry. We fear that, in the current environment, the majority of firms are reticent to oppose escalating validation and in-process control requirements that will result from these regulatory initiatives for fear of delayed product approval or increased compliance scrutiny being placed on them. We are also concerned that the implementation of these requirements by a few firms will make it appear that these new standards are "CGMP" and therefore would hasten their broad-scale, and unfortunately largely inappropriate, application across the industry. We hope that this brief communication will lead to frank discussions among industry scientists and relevant international regulatory authorities regarding the current performance levels achieved in aseptic processing and what validation and control testing is required to ensure product safety.

1. *Employees must not participate in aseptic filling of commercial lots unless they have successfully participated in a media fill test.* This requirement is both burdensome and unnecessary. Firms are rightly expected to fully qualify their employees prior to allowing them to work in aseptic processing. Certainly, this qualification should include verification of gowning effectiveness, training regarding aseptic technique, specific process related training on equipment, and evaluation of cleanroom aptitude. We believe the employee qualification described above is enough to enable an operator to be given a work assignment in an aseptic processing area. We also believe that an employee should be given only a provisional or restricted clearance to work in aseptic processing until they do participate in a media fill. However, given the 5-10% staff turnover in the industry, requiring a firm to schedule a special media fill to introduce a new employee could result in an unreasonable amount of production downtime. Even more importantly, we are not convinced that immediate participation in a media fill, as an aseptic processing work prerequisite, would provide product safety benefits. The effectiveness and concentration required to work in a cleanroom can only be evaluated over a long period of time through supervision. The achievement of one satisfactory result in a media fill test does not validate an operator. We do agree that the individuals charged with the initial assembly of an aseptic fill system be evaluated via a media fill before being allowed to perform that task for a production fill.

2. *Media fill tests must cover the full duration and output of a filling operation.* Media fill tests that cover the full duration or lot size of an operation are impractical and unreasonable. Tests of this kind require the manufacture of huge quantities of bacterial media in equipment and locales that were not designed for this purpose. Regulators have even opposed the terminal sterilization of these large lots of media, arguing that media should be filter-sterilized in the same manner as the product. This means that large quantities of growth-promoting media must be held in formulation vessels that are often not capable of being sterilized. This can result in gross microbial contamination

Akers & Agalloco

PDA J Pharm Sci Tech 2002;56: 179-182

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2511 VX Den Haag
Postadres Postbus 16119
2500 BC Den Haag
Telefoon (070) 340 79 11
Telefax (070) 340 71 59
Internet www.igz.nl

STAATSTOEZICHT OP DE VOLKSGEZONDHEID
INSPECTIE VOOR DE GEZONDHEIDSZORG

Z.A. RIJNSTATE 4042
Secr. Dir. 24.2
20 OKT. 2004

Cc: G. de Bey
W. Gruijthoe (afwikkelaar)
A. v.d. Sluge
MTCIE

Alysis Zorggroep
T.a.v. de Directie
Postbus 9555
6800 TA Arnhem

Ons kenmerk	Inlichtingen bij	Doorkiesnummer	Den Haag
FMT/MT-U 04-39249	J. Kraus	(070) 340	19 oktober 2004
Onderwerp	**Bijlage(n)**	**Uw brief**	**Uw kenmerk**
Enquête sterilisatie	1	-	-

In 2000 heeft de Inspectie voor de Gezondheidszorg (IGZ) een onderzoek uitgevoerd naar de validatiestatus van sterilisatoren in de Nederlandse ziekenhuizen. In december 2000 zijn de bevindingen en aanbevelingen gepubliceerd in het rapport 'Validatiestatus sterilisatoren voor medische hulpmiddelen in de Nederlandse ziekenhuizen'. Dit rapport is destijds naar u verstuurd.

De IGZ wil weten in hoeverre haar aanbevelingen op dit moment zijn geïmplementeerd en de geconstateerde tekortkomingen zijn opgelost. Ik heb het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) opdracht gegeven om een enquête op te stellen en de ontvangen gegevens te verwerken tot een rapport. Voor dit onderzoek krijgen alle algemene en academische ziekenhuizen in Nederland deze enquête toegestuurd.

U wordt verzocht de enquête te laten invullen door de deskundige steriele medische hulpmiddelen (ex. artikel 4 van het Besluit gesteriliseerde medische hulpmiddelen in ziekenhuizen) en deze met de gevraagde kopieën van de kwaliteitsdocumenten voor 10 november 2004 te sturen naar onderstaand adres.
Indien in uw instelling geen medische hulpmiddelen worden gesteriliseerd, verzoek ik u de enquête onder vermelding 'geen sterilisatie-activiteiten', te sturen naar onderstaand adres.

Bij voorbaat hartelijk dank voor uw medewerking.

Hoogachtend,

de inspecteur voor de medische technologie

J. Kraus

Enquête en documenten gaarne sturen naar:

RIVM
Afd. BMT-50
T.a.v. de heer drs. A.C.P. de Bruijn
Antwoordnummer 3206
3720 VB BILTHOVEN

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CONCLUSION

Parametric release

Declaring a product as sterile is feasable

based on the records **demonstrating that**

the process parameters **were delivered within**

specified tolerances

rather than on the basis of sample testing or biological indicator results.

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Acknowledgements

- ER van der Werf, ASP, J&J, Netherlands
- J van Oirschot, Eurotherm, Netherlands
  (Chessell recorder)
- E Kreugel, ASP, J&J, Netherlands
- D Smith and Staff, ASP, Irvine, California, USA
- All Dutch colleagues with a STERRAD
- Dutch Inspectorate; J Kraus et al.

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