VALIDATION
OF A LOW TEMPERATURE, LOW PRESSURE,
HYDROGEN PEROXIDE
GAS PLASMA (HPGP)
STERILIZATION SYSTEM

A.A. van Sorge,
Department of Pharmacy and
Central Sterile Supply Department,
Rijnstate Hospital Arnhem, The Netherlands

Session 7B at 14.00; Conference room E
1998

Sterrad 100S

in

Dutch hospitals
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
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
Some Reasons for purchase
STERRAD

- Longer life cycle optical instruments
- Longer life cycle batteries (Orthopedic instruments)
- Short turnaround time
Problem
PRINCIPLES OF INFORMATION

• Incomplete information will get you precisely nowhere

• Check the validity of your information at regular intervals
“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
General Requirements for

• Characterization of a STERILIZING AGENT

• Development, Validation and Routine Control of a STERILIZATION PROCESS
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.
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
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Packaging</th>
<th>Load</th>
<th>Sterilisation process</th>
<th>Chamber</th>
<th>Venting stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
<td>X</td>
<td>( X )</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt; 60°C</td>
<td>&lt; 60°C</td>
<td>&lt; 60 ºC</td>
<td>&gt; 6°C</td>
<td>non critical</td>
</tr>
<tr>
<td>$\text{H}_2\text{O}_2$ Conc.</td>
<td>Compatible</td>
<td>Compatible</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>RF energy</td>
<td>X</td>
<td>X</td>
<td>XX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual $\text{H}_2\text{O}_2$</td>
<td>XX</td>
<td></td>
<td></td>
<td></td>
<td>critical</td>
</tr>
</tbody>
</table>
PARAGRAPH 9

VALIDATION

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

Validation = Qualification
= Veiligheid=Sûreté
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.
Two baratrons mounted on T tubing

- Original placed baratron
  STERRAD®100S
- Second baratron for independent monitoring system
Instruments in parallel for independent monitoring of low pressures and delivered RF energy, (and temperature) during Validation procedures.
Display of temperature verification of the used incubator
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]
Proces: The Phases

- Vacuum/preconditioning
- Injection 1
- Plasma 1
- Diffusion 1
- Injection 2
- Plasma 2
- Diffusion 2
- Vent

cancel procedure by $< 6 \text{Torr} \rightarrow 14 \text{Torr}$
Full cycle process

Isala Klinieken Lokatie Sophia

Cycles: 3568

06/13/03 13:02:37.250 Batch start (Automatic) (Pa)
06/13/03 13:10:00
06/13/03 13:20:00
06/13/03 13:30:00
06/13/03 13:40:00
06/13/03 13:50:00

Temperatuur

06/13/03 13:02:37.250 Cycle number: 3568

Druk (Torr)

RF del. (Watt)

06/13/03 13:02:37.250 Sterrad 100S

06/13/03 13:55:06

Page 1 of 1

ZIEKENHUIS

Rijnstate
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
- 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.

8.3: Biological indicators
  - Minimal 10 per 100 Liter chamber
  - At designated places (pictures!)
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
Type Sterrad: 100 S
Datum PQ/RQ 07-mrt-03
Lading samengesteld door: R. E. van der Werf
Functie: Sterilization Technologist
R. Buiten, hoofd CSA, Ziekenhuis Rijnstate

<table>
<thead>
<tr>
<th>Lading/ nr. BI</th>
<th>verpakking gewicht plaats in</th>
<th>resultaat dagen incubatie: n= negatief p= positief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro bipolair instrument; 2 BI's</td>
<td>dub. Lam 280</td>
<td>cycle 1, half cycle nr. 3799</td>
</tr>
<tr>
<td>accu; 2 BI's</td>
<td>dub. Lam 470</td>
<td>cycle 2, half cycle nr. 3800</td>
</tr>
<tr>
<td>optiek 00/10mm 3537163; 2 BI's</td>
<td>dub. Lam 910</td>
<td>cycle 3, half cycle nr. 3800</td>
</tr>
<tr>
<td>optiek 00/10mm 3545266; 2 BI's</td>
<td>dub. KC 824</td>
<td>cycle 4, full cycle</td>
</tr>
<tr>
<td>test naaldendoos2x (Faradaytest) 2 BI's</td>
<td>dub. KC 2010</td>
<td>cycle 1, half cycle</td>
</tr>
<tr>
<td>siliconesiang; 2 BI's (geen foto)</td>
<td>dub. Lam 130</td>
<td>cycle 2, half cycle</td>
</tr>
<tr>
<td>losse BI's onderste tray achter; 2 BI's</td>
<td>dub. Lam 4524</td>
<td>cycle 3, half cycle</td>
</tr>
<tr>
<td>totaal PQ lading: 14 BI's, gewicht:</td>
<td></td>
<td>cycle 4, full cycle</td>
</tr>
</tbody>
</table>

validatie/challenge pack; 4 BI's totaal | dub. KC B-Y-1 en 2 | 
validatie/challenge proces 2 BI's los | dub. Lam C-Y-2 | 
Controle: 2 BI's niet steriel | 0 | 0 |
Print and diagram of a steam sterilization process used for parametric release
Perform OQ - 1 or 3 full cycles
- no load

Perform RQ/PQ* - 1 or 3 half cycles
- Reference load

*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
Samenvattend verslag:

Sterrad type: 100 S
Sterrad serienummer: J 30 57113 / 952157
Datum van installatie: 5 maart 1999
Naam instalter: Ziekenhuis Rijnstate
Adres, postcode en plaats: Wagnerlaan 55
6815 AD Arnhem

Validatie datum: 15 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 manuel, behorend bij het type van het apparaat
• Biologische validatie, beschreven in document werkmodule ASP.QA.W 1002

De validatie bestond uit:
Proces: 5243: OQ procedure, inclusief technische metingen, volgens procedure en beschreven in bovengenoemde documenten
Pak: Ios verpakt: 4

RQ procedure half time validatie, uitgevoerd met eigen lading ziekenhuis en een validatielading ASP
Proces: 5244: IIs validation kit/challenge pack: 4, Ios verpakt: 6, Totaal III's: 10
Proces: 5245: IIs eigen lading ziekenhuis: 12, Ios verpakt: 4, Totaal III's: 16

Bevindingen:
Alle biologische indicatoren van de processen 5243, 5244 en 5245 bleken steril.
Het Sterrad Sterilisatiesysteem voldoet aan de validatie-normen voor sterilisatie (Sterility Assurance Level SAL 10^5)

Aanbevolen datum voor hervatting:
Na 1500 cycles of ten laatste: oktober 2005

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

Datum:
18 oktober 2004
COMMENTS

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

James E. Akers1 and James P. Agalloco2

1Akers Kennedy and Associates, Kansas City, MO, and 2Agalloco 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

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Akers & Agalloco
PDA J Pharm Sci Tech 2002;56: 179-182
In 2002 heeft de inspectie voor de Gezondheidszorg (IGZ) een onderzoek uitgevoerd naar de veiligheid van medische hulpverleners in de Nederlandse ziekenhuizen. In december 2002 zijn de bevindingen en aanbevelingen gepubliceerd in het rapport "Veiligheidshulpverlening voor medische hulpverleners in de Nederlandse ziekenhuizen". Dit rapport is destijds reeds u versoond.

De IGZ wil weten in huidige en door de bevindingen op dit moment zijn uitgevoerd wordt de veiligheidscontrole in betrokken ziekenhuizen. In het Rijnstate ziekenhuis werden zowel de medische hulpverleners als de medische hulpverleners ter厨师, om een ruimte te schaffen om de bevindingen te overleggen en de richtlijnen te volgen. Voor dit onderzoek zijn als regel een academische ziektenhuis is in Nederland deze enquête toegestaan.

U wordt verzocht de enquête te beantwoorden door de door u ontvangen medische hulpverleners ter heerst (met name van de medische hulpverleners in aantallen) en deze met de gevorderde kapitein van de hersteldocumenten voor 10 november 2004 ter厨师 naar ondersteund adres.

Indien in uw inslag aan medische hulpverleners verder gevorderde, verzocht u de enquête onder vermelding "geen standaard-activiteit", te steunen naar ondersteund adres.

Bij voorbaat hartelijk dank voor uw medewerking.

Hoogachtend,

de Inspecteur voor de medische technologie

J. Kraus

Enquête en documenten gaan sturen naar:

Rijn

Afd. BMN

T.s.v. dr. drs. A.C.P. de Ruiter

Antwoordnummer 9200

3720 VS BILTHOVEN

ZIEKENHUIS

Rijnstate
CONCLUSION

Parametric release

Declaring a product as sterile is feasible 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.
Acknowledgements

- ER van der Werf, ASP, J&J, Netherlands
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- All Dutch colleagues with a STERRAD
- Dutch Inspectorate; J Kraus et al.