74 OR

Subj: **REMINDER: Upcoming STERIS Isomedix Seminar For Your Interest**
Date: 7/14/2005 6:04:50 P.M. Eastern Standard Time
From:
To:

STERIS Isomedix Services would like to invite you to an exciting one day seminar:

Author: Dan Prince 8/4/05

STERIS Isomedix Services

Current Issues in Medical Device & Pharmaceutical Ster

Seminar 4 Aug 05

Presented by:

Team

We're Here to Help

[illegible]

[illegible]

Learn From Experts at STERIS Isomedix Services.
Topics include:

- [illegible] of Gamma, EO, and E-beam processing
- Introductions to our Gamma, EO, and E-beam [illegible] teams
- Current standards and guidelines
- Parametric release, biological indicators, and the EO process
- Dose mapping for radiation
- Materials compatibility and selection

Learn From Industry Experts
Topics include

- Effects of sterilization on pack[illegible]
- [illegible]
- Gamma, EO validation [illegible]
- AAMI [illegible]
- Laboratory services

STERIS

Isomedix Services

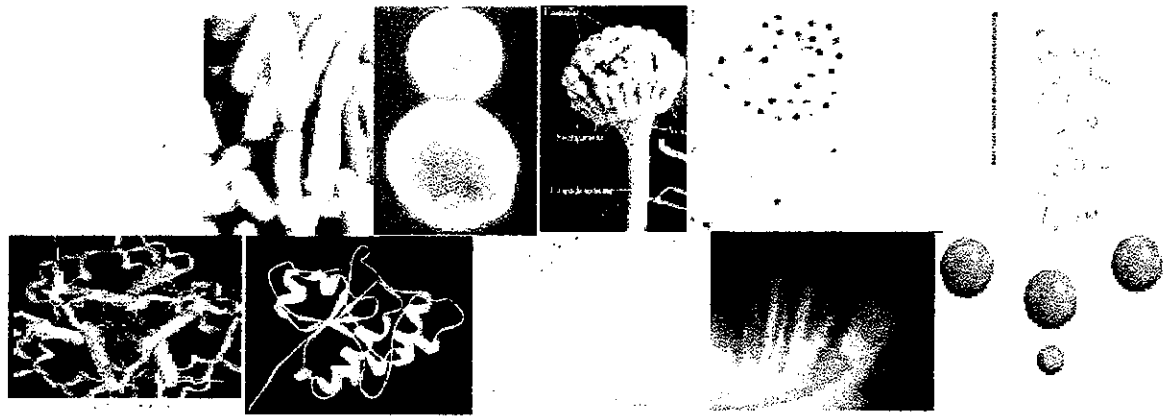
About us: [illegible]

Please click on the image for more details.

Team

We're Here to Help

GIBRALTAR LABORATORIES, INC.



Bacteria
Yeast
Mold
Virus
DNA, RNA, Protein, Amino Acids, Sugars
Endotoxin
Irradiation
Ethylene Oxide

Team

We're Here to Help

AAMI- Association for Advancement of Medical Instrumentation
ISO- International Standards Organization
USP <71> Sterility United States Pharmacopeia Convention
Bacteriostasis & Fungistasis- a USP Microbiological Validation that a negative sterility result is not compromised due temporary masking of the presence of an underlying organism

GIBRALTAR LABORATORIES, INC.

Team™

We're Here to Help

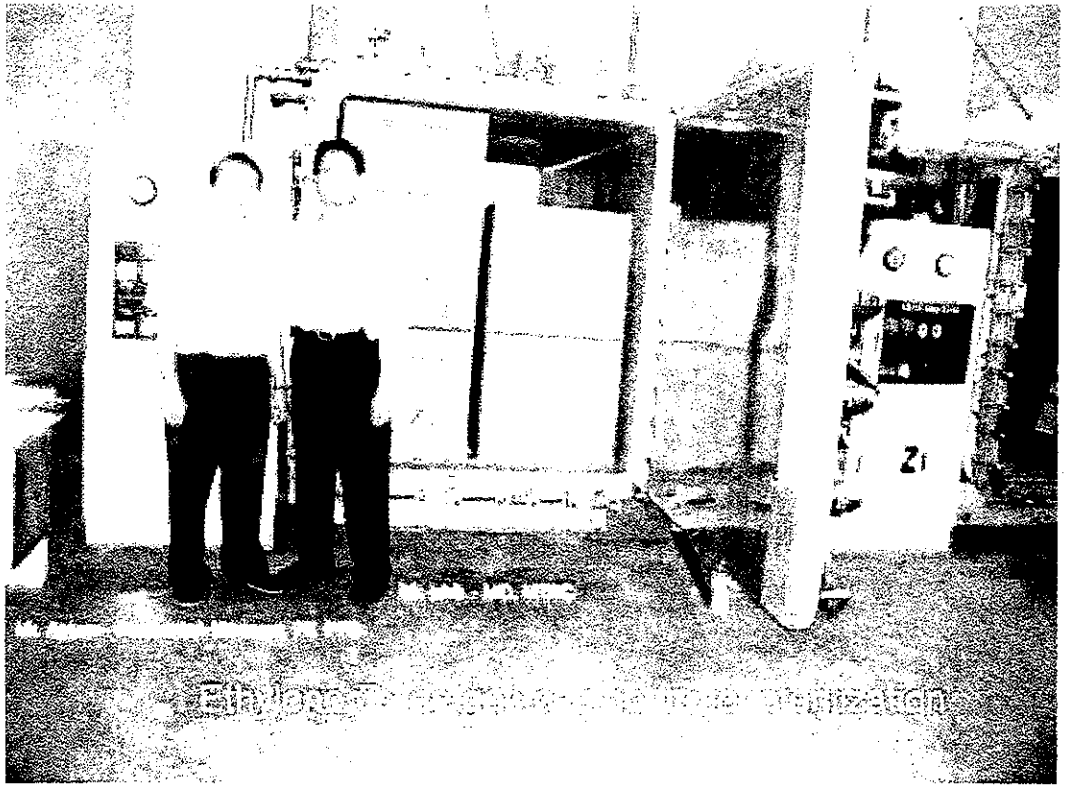
Qualification of Vendors -3 sources? If possible no single source
Possible Acceptance Criteria-No Pathogens, < 100CFU/gram?,
No viruses ?, No DNA?
Qualification of Manufacturing- Is a sterile product always likely to be made?—trained personnel, calibrated equipment, supervision
Cleaning Validation-Removal of objectionable organisms-use of disinfectant, sanitizers and chemical sterilants
Qualification of Personnel—Gowning Procedure
Environmental Monitoring—Alert and Action Levels
Trending

GIBRALTAR LABORATORIES, INC.

Team

We're Here to Help

GIBRALTAR LABORATORIES, INC.



Team

We're Here to Help

Ethylene Oxide is a poisonous gas that naturally decomposes into relatively non-toxic residuals, Ethylene Chlorohydrin and Ethylene Oxide

GIBRALTAR LABORATORIES, INC.

It must penetrate the product packaging and the product itself yet it must not be tenaciously bound to the substrate less there may be health issues.

Team

We're Here to Help

Heat and Humidity are used to facilitate penetration of the Gas

GIBRALTAR LABORATORIES, INC.

Aeration over time is used to remove the gas.

Successful aeration is demonstrated by testing a few devices for the presence of ETO gas and its residuals. ISO 10993-7 1995 Limits are 20 and 12 mg per device for ETO and Ethylene Chlorohydrin, respectively.

Team

We're Here to Help

GIBRALTAR LABORATORIES, INC.

Vacutainer BI sterility failure of spore disks
Engineer decides to Switch from Natural to Synthetic Rubber diaphram
Lack of ETO permeability
Spore strip did not receive same ETO exposure due to Synthetic Rubber being less permeable

Team

We're Here to Help

Blend of Art and Science
Based on Sterilization Facility Experience
Density of Product in Chamber
Product and Package Material Composition

GIBRALTAR LABORATORIES, INC.

Team

We're Here to Help

GIBRALTAR LABORATORIES, INC.

Half cycle Test product and Spore Strips in three loads Specification is no positive BIs nor products. Do Direct Immersion Sterility Test

Sublethal cycle on Biological Indicators (*Atrophaesus subtilis).* Expect some kill but not 100%

If successful Half cycle do three Full Cycles where the sterilization exposure to the ETO is twice what was used for the Half cycle. Test the BIs only. Expect all BIs to be sterile.

Perform ETO testing to demonstrate low levels of ETO residuals in the product

When X = 1

$P(X) = \lambda^x e^{-\lambda} / X!$

λ = NP where P = Probability of a failure event being detected in a single observation e.g. 0.001

N= number of observations e.g. 20 in USP <71>

NP=20 x 0.001= 0.02

e= 2.718

$e^{-\lambda} = 2.718^{-0.02} = 0.98$

P(1) = 0.02/0.98 = 0.02

Or, there is only a 2% likely hood of detecting a failure in a 20 unit sterility test when the contamination rate of the product is one in a thousand [10^{-3}]

Team

We're Here to Help

- Objective is Environmental Control
- Proper Sampling is required for Statistical Power
- Primary Source of contamination are people

STERIS

GIBRALTAR LABORATORIES, INC.

Isomedix Services

Direct Calculation requires at least 100 data points
Alert is the 95th percentile. Action is the 99th percentile

Alternatively, transform data to log 10
Alert is the 95th percentile = 1.96 SD
Action is the 99th percentile = 2.326 SD

Team

We're Here to Help

1. AAMI TIR27: 2001 - Sterilization of health care products—Radiation sterilization—Substantiation of 25 kGy as a sterilization dose— Method Vdmax

2. AAMI TIR12: 1994 - Designing, testing and labeling reusable medical devices for reprocessing in health care facilities: A guide for device manufacturers

3. ANSI/AAMI/ISO 11737-1:1995 - Sterilization of medical devices – Microbiological methods - Part 1: Estimation of the population of microorganisms on product

GIBRALTAR LABORATORIES, INC.

4. ANSI/AAMI/ISO 11737–2:1998- AAMI Association for the Advancement of Medical Instrumentation Sterilization of medical devices—Microbiological methods—Part 2: Tests of sterility performed in the validation of a sterilization process

5. ANSI/AAMI/ISO 11737-3:2004 – Sterilization of medical devices – Microbiological methods – Part 3: Guidance on evaluation and interpretation of bioburden data

6. ANSI/AAMI/ISO 11137:1994 - AAMI Association for the Advancement of Medical Instrumentation Sterilization of health care Products -Requirements for validation and routine control – Radiation sterilization, 3ed.

7. AAMI/ISO TIR15844:1998 - AAMI Association for the Advancement of Medical Instrumentation Radiation sterilization— Selection of a sterilization dose for small or infrequent production batches

8. ANSI/AAMI ST72:2002 - Bacterial endotoxins—Test methodologies, routine monitoring, and alternatives to batch testing

Team

We're Here to Help

GIBRALTAR LABORATORIES, INC.

1 year subscription

USP28-NF 23 **CD** [2005 Single-user subscription]

$949 $15 $44 $61

1. The *USP-NF* CD is published on a calendar year basis. Subscriptions include all *USP-NF* information that becomes official in that calendar year.
2. *USP-NF* CD subscriptions are offered for one or two year subscription terms.
3. New and renewal prices are the same.
4. The *USP-NF* Online is a rolling subscription that includes cumulative updates published during a 12-month period.
5. *USP-NF* Online is compatible with Microsoft Internet Explorer, versions 5.5 and 6.0. Also compatible with Netscape 7.0

Team

We're Here to Help

GIBRALTAR LABORATORIES, INC.

Pre-determined sterilization doses

VD^{15}max and VD^{25}max

Product-specific sterilization doses

Bioburden dependent – Method 1

D-value by incremental dosing – Method 2

Team

We're Here to Help

Frequent production but don't want VDmax.....Method 1

Single batch but don't want VDmax.....TIR15844

Frequent production or single batch and want 25 kGy..TIR27

Frequent production or single batch and want 15 kGy..draft 11137-2

Frequent production with low dosing or failure.....Method 2

GIBRALTAR LABORATORIES, INC.

Initial Validation

1 Bioburden Testing on 10 samples from each of 3 different lots for aerobic bacterial (aerobic) and fungal counts. Testing of the primary packaging is strongly recommended.

2 Efficiency Recovery by Exhaustive Recovery

Testing is performed to validate the above bioburden test and consists of washing one of the submitted samples an additional 5 times or by spore incoulation.

3 Microbial Characterization of Bioburden Isolates

This is recommended to help trend organism occurrence and in the event of a sterility failure. Representative organisms will be selected.

4 Determination of Sublethal Audit Dose

5 Performance of Bioburden Resistance Test (Sublethal 10^{-2} Audit Dose) (Sterility Test)
Sterilize 100 units from any of the above lots at the 10^{-2} audit dose assuming that none of the lots has a bioburden average greater than twice the average of all three lots. Sponsor should submit 103 units.

6 Bacteriostasis and Fungistasis
Performed to validate the above bioburden resistance test.

Quarterly Testing

7 Quarterly Bioburden Test
Ten products will need to be performed once each quarter or as directed by the sponsor so as to confirm that the bioburden estimate established in the above validation is correct

8 Quarterly Bioburden Resistance Test, Sublethal Audit 10^{-2} Dose (Sterility Test)
Sterilize 100 units from the same lot as the quarterly bioburden at the 10^{-2} dose (established during validation). Sponsor should submit 103 units.

Team

We're Here to Help

GIBRALTAR LABORATORIES, INC.

Same as Method 1 except only 10 units for bioburden

Note: Verification Dosing is conducted at an SAL of 10^{-1} with only 10 products.

Validation

1. Obtain 10 products from each of 3 lots before sterilization. Perform bioburden testing and determine if one lot is two or more times greater than the overall average.
2. Go to Table 2 and calculate verification dose based on average bioburden.
3. Select at random 10 products from a single batch and irradiate at the verification dose derived from Table 2.
4. Interpretation

a. If not more than one positive test of sterility is obtained in the 10 tests, a sterilization dose of 25 kGy is substantiated and the confirmatory verification dose experiment is complete.
b. If two positive tests of sterility are obtained in the 10 tests, the confirmatory verification dose experiment shall be conducted.
c. If three or more positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is not substantiated. An alternative method shall be used.

Confirmatory Verification Dose Experiment

1. Select at random 10 products from a single batch and irradiate at the verification dose derived from Table 2.
2. Interpretation

a. If no positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is substantiated.

b. If one or more positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy has not been substantiated. An alternative method shall be used.

Sterilization Dose Audit

Once the sterilization dose has been established, periodic quarterly audits are required to reaffirm the sterilization dose.

1. Obtain 20 products from one lot before sterilization. Perform bioburden testing on 10 of the products.
2. Using the same verification dose, irradiate the remaining 10 products and perform the sterility test.

3. Interpretation

a. If not more than one positive test of sterility is obtained in the 10 tests, a sterilization dose of 25 kGy is reaffirmed.

b. If two positive tests of sterility are obtained in the 10 tests, the confirmatory verification dose experiment shall be conducted.

c. If three, four, five or six positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is not reaffirmed. The 25 kGy sterilization dose shall immediately be augmented and an alternative method shall be used.

d. If seven or more positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is not reaffirmed. The 25 kGy sterilization dose cannot be augmented and an alternative method shall be used.

Note: Single batch validation is available – See Annex A

B.3.4.2 Method 2: Dose setting using fraction positive information from incremental dosing to determine extrapolation factor

NOTES

29 In the following procedures and examples, notation is lower case when it refers to results derived from product samples of a single batch, and upper case when it refers to a summary of all three batches.

30 Calculations for A kGy, DS kGy, and sterilization dose are not the same for Methods 2A and 2B: therefore close attention should be paid to the use of the correct calculations.

31 Method 2B requires that the entire product unit (SIP = 1.0) be used, while Method 2A may be used for either an entire product unit or a portion of product unit (SIP £ 1.0).

© 2000 Association for the Advancement of Medical Instrumentation

B.3.4.2.1 Rationale

With Method 2, information is obtained about the resistance to radiation of microorganisms as they occur on product. The method uses the results of sterility tests conducted on samples of product that have been exposed to a series of incremental doses to estimate the dose at which one in 100 product units is expected to be non-sterile (that is, a SAL of 10-2). The microorganisms surviving exposure to such a dose should have a more homogeneous D10 value than the initial bioburden. From the incremental dose experiment, an estimate is made of this D10 value, and this estimate is used for extrapolation to SALs below 10-2 in order to determine the sterilization dose.

The validity of the calculated sterilization dose generally depends upon the validity of the extrapolation beyond the verification dose. In extensive tests of the experimental protocol employing computer simulation of inactivation of microorganisms on items, the validity of this extrapolation has been established for microbial populations for which distributions of resistance have been measured.

An elaboration on the rationale outlined above, and the results from the computer simulation, are contained in Davis, Strawderman and Whitby (1984).

The following text describes two procedures:
a) Method 2A for products with bioburdens as would be expected from normal manufacturing processes.
b) Method 2B for products with a consistent and very low bioburden.

B.3.4.2.2 Procedure for Method 2A ("normal" product)

For dose setting Method 2A, the four stages below shall be followed.
NOTE 32 Worked examples appear in clause B.4.

B.3.4.2.2.1 Stage 1: Select SAL and obtain samples of product units

Record the sterility assurance level (SAL) to be used. Take random samples of at least 280 product units

Team

We're Here to Help

New and old approaches being used to assure tissue and bone are sterile.

AAMI Method 1, AAMI Method 2

GIBRALTAR LABORATORIES, INC.

Different natural flora than used in database for medical devices

Tissue must remain osteogenic—clinically effective

Anaerobes and virus more of a real threat

Bioburden requires more method development and Validation

Team

We're Here to Help

Dr Herbert Prince, Gibraltar Laboratories, Inc

Kristah Kohan, Gibraltar Laboratories, Inc

GIBRALTAR LABORATORIES, INC.

Team

We're Here to Help

GIBRALTAR LABORATORIES, INC.

Steris for the Invitation

You the attendees for your attention and efforts on behalf of our Industry and Patients