TECHNICAL SUPPORT SECTION EFFICACY REVIEW - I

Disinfectants Branch

IN 07-22-85 OUT 08-12-85

Reviewed By Dorothy M. Portner Date 08-12-85

EPA Reg. No. 8383-5

EPA Petition or EUP No. None

Date Division Received 07-19-85

Type Product Disinfecting/Sterilizing Solution

Data Accession No(s). 257700 & Unaccessioned Data

Product Manager PM-31 (Lee)

Product Name Sporicidin

Company Name The Sporicidin Company

Submission Purpose Resubmission with efficacy data and proposed label to support disinfectant reuse claims for manual use systems.

Type Formulation Liquid concentrate to used diluted and undiluted

Active Ingredient(s):	%
Phenol	7.05
Sodium tetraborate	2.35
Glutaraldehyde	2.00
Sodium phenate	1.20

200.0 Introduction

200.1 Use

The submitted back label amended to reflect reuse is attached.

200.2 Background Information

The submissions, received 12-17-84, 2-5-85, 5-10-85, and 7-19-85, relate to the simulated reuse study conducted for the subject product.

The 12-17-84 submission included: (1) basic bactericidal data developed on the reuse solution but not the detailed decriptive protocol actually employed in performing the simulated reuse test, (2) barely legible chemical chromatographs to show the active ingredient concentration of the test solution during the study but not the description of the analytical method employed, and (3) proposed labeling for a 30-day reuse claim inclusive for all recommended patterns of use that can not be related to the reuse study accepted.

The 2-5-85 submission included only supplemental fungicidal and virucidal data developed on the reuse solution.

The 5-10-85 submission included: (1) barely legible copies of the previously submitted chemical chromatographs plus an unrelated chromatograph and (2) the 27-day test schedule employed in conducting the simulated reuse study.

The 7-19-85 submission included: (1) supplemental tuberculocidal data developed on the reuse solution, (2) additional basic bactericidal data developed on another reuse study performed as indicated on the submitted 30-day test schedule, (3) additional procedural information relative the first reuse study, (4) additional chromatographs and analytical procedural information and (5) a proposed back panel of product label amended to reflect reuse which supercedes the labeling submitted on 12-17-84.

The previously accepted data, developed to support efficacy for a 21-day old activated solution diluted 1:35 in hemodialysis systems (TSS Efficacy Reviews of 8-31-82, 8-30-83 and 12-2-83), may be utilized to support a new proposed efficacy claim indicated on the revised submitted basic product label for disinfecion (bactericidal, fungicidal and virucidal) in 10 minutes with a 1:32 dilution of unused stock solution activiated up to 21 days.

200.3 Administrative Policy For Review Of Tuberculocidal Data

The current administrative policy concerning review of tuberculocidal claims for glutaraldehyde products is addressed in TSS Efficacy Review of 8-3-85 for EPA Reg. Nos. 46851-2 and 46851-4. The current interpretation of this policy is that, pending completion of an EPA-initiated peer review process concerning tuberculocidal testing methodology, the Agency will permit registrants who have successfully relied on the existing AOAC method to also rely on the new protocol on a voluntary basis in those cases where the use directions would be revised to be more stringent, and thus more protective. This policy applies to all tuberculocidal claims, including reuse claims. This policy was promulgated in letters to Honorable Tony Coelho (U.S. House of Representatives) and to Mr. W.J. McQuade (Surgikos, Inc.) by Steven Schatzow (Director, OPP) on 5-10-85.

In addition, strict interpretation of the concept of "existing AOAC method" appears to preclude modifications intended to be reflected in the directions for use, and permitted by the product performance guidelines, such as a different exposure time or temperature. Adherence to the "existing AOAC method" limits exposure conditions to 10 minutes at 20°C. The new quantitative test, however, expressly allows variable exposure time and temperature.

201.0 Data Summary

The simulated reuse testing and the basic bactericidal data were performed by R.E. Pepper at Elizabeth Town College, Elizabeth Town, PA. The fungicidal, tuberculocidal, and virucidal data were developed by H.N. Prince at Gibraltar Biological Laboratories, Inc., Fairfield, NJ. The chromatographs were derived by J.E. Girard at American University, Washington, D.C. None of the above data have been accessioned except for the fungicidal and virucidal data under Accession No. 257700.

201.1 Simulated Reuse Testing

The attached simulated reuse protocol, approved be EPA, was modified as follows for the 2 studies conducted:

First Reuse Study

A 27-day simulated reuse study was conducted at a 1:16 dilution with Solution A (Buffer # L-2330 and Glutaraldehyde # E-1743) from 10-13-84 to 11-8-84 and with Solution B (Buffer #H-1543 and Glutaraldehyde # E-1743) from 10-17-84 to 11-14-84 as verified by the attached test schedules.

One quart of activated solution was added to a 6-gallon plastic bucket with lid and filled with 15 quarts of tap water. Then 240 ml from a second activated quart plus 3600 ml of tap water was added to the bucket to make a total of 5 gallons of activated solution at a 1:16 dilution. Then 2 sections (about 4 feet long) of corrugated plastic tubing, 1 rebreathing bag, 1 face mask, and 1 endotracheal tube, and 1 "Y" connector were added to the bucket for the simulated-use treatment. It is noted that equipment employed in this study constitutes only 1 set of anesthesia equipment. The accepted protocol states that 2 sets of anesthesia equipment are to be treated per 5 gallons of solution.

At 3 different times during the day, the above equipment was washed with Sparkleen detergent, rinsed, dried, and returned to the bucket. Each day, 60 cylinders contaminated with P. aeruginosa (bioburden) were added to 1 liter of solution for a 1-hour soak before returning to the pail. The additional 180, 270, and 360 bioburden cylinders were added to Solution A on days 11, 20, and 28 and to Solution B on days 14, 20, and 27, respectively, as indicated on the attached test schedules.

The following microbiological assays were conducted on Solutions A and B:

1. Basic bactericidal data on 27-day old reuse Solutions A and B, report dated 12-7-84 from R.E. Pepper.

2. Supplemental fungicidal data on 14, 21, and 27-day old reuse Solutions A and B, report dated 1-3-85 from H.N. Prince.

3. Supplemental virucidal data on 14, 21, and 27-day old reuse Solutions A and B, reports from H.N. Prince for Herpes simplex, Type 1 and 2, and Influenza A_2 (J-305) viruses, dated 12-14-84 and for Poliovirus Type 1, dated 1-29-85.

4. Supplemental tuberculocidal data on 21-day old reuse Solution A, report dated 4-22-85 from H.N. Prince.

Second Reuse Study

A 30-day simulated reuse study was conducted at a 1:16 dilution with Solution C (Buffer # B-0650 and Glutaraldehyde # A-1850) and Solution D (Buffer # K-2643 and Glutaraldehyde # H-3143) from 4-10-85 to 5-9-85 as verified by the attached test schedules.

For the second reuse study, 5 gallons of test solution at a 1:16 dilution were prepared in a 6-gallon plastic bucket with lid as indicated above. However, this repeat test different from the first one in the following respects: (1) 2 sets of anesthesia equipment were used instead of 1 set, (2) the equipment was washed with soap instead of detergent, (3) contaiminated cylinders of S. aureus was used as bioburden instead of P. aeruginosa, (4) the additional 180, 270, and 360 bioburden cylinders were added to the two test solutions (C and D) on days 13, 20, and 29, respectively, instead of the schedule indicated above, and (5) the reuse testing was conducted for 30 days (as indicated by the attached test schedules) instead of 27 days.

Basic bactericidal data on 30-day old reuse Solutions C and D, report dated 6-3-85 from R.E. Pepper.

201.2 Brief Description Of Test

A. Bactericidal Testing

Method: AOAC Use Dilution Test
Exposure Period: 10 minutes at 20°C
Subculture Medium: Letheen Broth for both primary and secondary subcultures
Incubation Period: As specified in the method

B. Fungicidal Testing

Method: AOAC Fungicidal Test
Organic Load: 5% Blood Serum
Subculture Medium: Glucose broth containing neutralizer (10% serum)
Incubation Period: 10 days at 25°C

C. Tuberculocidal Testing

Method: AOAC Tuberculocidal Activity Test
Exposure Period: 45 minutes at 20°C
Incubation Period: 90 days at 35°C

D. Virucidal Testing

Method: 0.2 ml of virus pool spread onto the surfaces (petri dishes) and allowed to dry to a film at 35°C for 30-45 minutes. 2.0 ml of the germicide test solution was spread over the film and allowed to remain in contact for 10 minutes at 20-25°C. Then the mixture was removed and diluted in trypticase soy broth (TSB) up to 10^{-4} to 10^{-7}. Decimal dilutions were then inoculated into appropriate hosts. The virus-germicide mixture represents 10^{-1} virus in the presence of the test germicide.

5

Organic Soil: 5% Serum (for Herpes simplex, Type 1 and Polio, Type 1 viruses, and 100% chorioallantoic fluid (for Influenza A_2 Japan)

Controls: Virus control, 0.2 ml viral film treated with 2.0 ml TSB and titrated ED_{50}.

E. Determination Of Active Ingredient Concentration

The concentration of the glutaraldehyde and phenol (buffer) in the reuse solutions was determined by gas chromatographic studies conducted under the attached conditions.

201.3 Test Results

A. Bactericidal Testing

First Reuse Study

Test Organism	No. Positive/Total Tested Solution A*	Solution B*
S. aureus	0/60	0/60
P. aeruginosa	2/60	0/60
S. choleraesuis	0/60	0/60

Phenol Resistance - Not indicated.
* Test solution was reused for 27 days before assayed.

Second Reuse Study

Test Organism	Test Solution	No. Positive/Total Tested 7-10*	14-17*	14-22*	29-31*
S. aureus	C	0/60	0/60	0/60	0/60
	D	1/60	0/60	0/60	1/60
P. aeruginosa	C	1/60	0/60	0/60	0/60
	D	0/60	2/60	1/60	0/60
S. choleraesuis	C	0/60	1/60	0/60	0/60
	D	1/60	1/60	1/60	0/60

Phenol Resistance - Not indicated.
* Number of days of reuse when the test solution was assayed.

B. Fungicidal Testing

Sample	Exposure Time (Minutes)* 5	10	15
Solution A	-	-	-
Solution B	-	-	-

Phenol Resistance of T. mentagrophytes = 1:70
* Test solution was reused 27 days before assayed. Identical test results were obtained when the test solution was reused 14 and 21 days, respectively, before assayed.

C. Tuberculocidal Testing

	No. Positive/Total Tubes Tested		
	Proskauer-Beck	Middlebrook	Dubos
Solution A*	0/10	0/10	0/10
Phenol Control 1-50	0/10	0/10	0/10
1-75	3/10	0/10	1/10

* Test solution was reused for 21 days before assayed.

D. Virucidal Testing

Influenza A_2 (Japan) Virus

	Solution A	Solution B
Virus titer EID_{50}	6.5	6.5
Virus + disinfectant ELD_{50}	<1.0	<1.0
Cytotoxicity ETD_{50}	<1.0*	<1.0*
Log reduction in titer	$\geq$5.5	$\geq$5.5

* Chick embryo

Herpes simplex, Type 1 Virus

	Solution A	Solution B
Virus titer $TCID_{50}$	6.5	6.5
Virus + disinfectant $TCLD_{50}$	$\leq$2.5	$\leq$2.5
Cytotoxicity $TCTD_{50}$	2.5*	2.5*
Log reduction in titer	$\geq$4.0	$\geq$4.0

* Hep-2 cells

Herpes simplex, Type 2 Virus

	Solution A	Solution B
Virus titer $TCID_{50}$	6.5	6.5
Virus + disinfectant $TCLD_{50}$	$\leq$2.5	$\leq$2.5
Cytotoxicity $TCTD_{50}$	2.5*	2.5*
Log reduction in titer	$\geq$4.0	$\geq$4.0

* Hep-2 cells

Polio Virus Type 1

	Solution A	Solution B
Virus titer $TCID_{50}$	6.5	6.5
Virus + disinfectant $TCLD_{50}$	$\leq$2.5	$\leq$2.5
Cytotoxicity $TCTD_{50}$	2.5*	2.5*
Log reduction in titer	$\geq$4.0	$\geq$4.0

* MRC-5 cells

The above data were developed on test solutions that were reused for 27 days before assayed. Similar test results against the above viruses were obtained when the test solutions were reused for 14 and 21 days, respectively, before assayed.

E. Determination Of Active Ingredient Concentration

The pH and computed percent of glutaraldehyde and phenol in the reused test solution is indicated below for Solutions C and D.

Days Of	Solution C			Solution D		
Reuse	pH	% GA	% PL	pH	% GA	% PL
0	8.0	-	-	8.1	-	-
6	7.9	0.129	0.679	7.9	0.120	0.543
13	7.8	-	-	7.7	-	-
20	7.7	-	-	7.7	-	-
28	7.6	-	-	7.5	0.113	0.507

The submitted chromatographs derived for Solutions A and B did not include the computed percent GA (Glutaraldehyde) and PL (Phenol) in the reuse test solution. No pH determinations were provided for these test solutions.

201.4 Conclusions

Presumptive evidence of effectiveness for a 1:16 dilution of the product for disinfection in a manual system is provided by the data developed in the submitted simulated reuse studies. However, these data are inadequate to fully support the claims for reuse indicated on the label because data were developed by a protocol that deviated appreciably from the one accepted by EPA, as indicated below:

1. Inadequate bioburden. The required additional contaminated cylinders were not added to the liter of test solution used for the microbiological assays.

2. Inadequate equipment. In the first reuse study, only 1 set of anesthesia equipment was used instead of 2 as specified in the accepted protocol.

3. Bioburden challenge with only one test organism. This minor deviation from the approved protocol and the significant deficiencies indicated above probably resulted because the investigator, who conducted the reuse studies, did not attend the meeting where EPA thoroughly discussed the test protocol design, and did not subsequently receive an adequate briefing regarding the purpose of the test.

In addition, the following procedural data/information was not included in the submitted reports:

1. The computed percent glutaraldehyde and phenol concentration in the reuse Solutions A and B. The submission of this information to complete the report will not be requested since the reuse solution concentration does not seem to decrease appreciably in a manual reuse system.

2. The phenol resistance data against S. choleraesuis, S. aureus, and P. aeruginosa. These data are required for validation of the basic bactericidal data developed developed in both reuse studies.

It should also be noted that 2 positive subcultures out of 60 against P. aeruginosa, which were obtained in two instances, are considered to be just a manifestation of random variation rather than product ineffectiveness since all the subcultures were negative when the final 29-31 day reuse solution was tested in the second reuse study.

Since reuse data, developed by protocols that do not meet the EPA Re-Use Test Protocol Specifications, do provide presumptive evidence of reuse efficacy, the data have been utilized to support reduced claims for reuse efficacy as indicated in TSS Efficacy Review of 12-20-84 for EPA Reg. No. 43573-1. Therefore, the submitted reuse data for the subject product may be utilize to support the reduced claims of reuse efficacy indicated in TSS Efficacy Review II.

Sporicidin efficacy review

Page _____ is not included in this copy.

Pages 10 through 17 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Technical Support Section Efficacy Review-II

Disinfectants Branch

EPA.Reg. No.or File Symbol 8383-5

Data Division Received 07-19-85

Data Accession No(s). 257700

Product Manager No. PM 31 (Lee)

Product Name Sporicidin

Company Name The Sporicidin Company

202.0 Recommendations

202.1 Option II Manual Reuse Protocol

Your EPA approved Option II protocol entitled "General Protocol - Multiple Use Glutaraldehyde Testing, Using Sporicidin Sterilizing Disinfecting Bucket System", dated September 11, 1984, was designed to determine the effectiveness of a 1:16 dilution of Sporicidin under stringent simulated reuse conditions for a period lasting 14, 21, or 30 days, respectively. The pertinent features of the test design were:

1. Treatment of defined equipment (2 sets of anesthesia equipment) in a specified volume (5 gallons of disinfecting solution) conducted 3 times per day under conditions that simulate actual use.

2. A defined bioburden challenge for the specific liter of disinfecting solution subjected to microbiological testing after a specified period of reuse, i.e., 180 contaminated carriers/liter of solution tested after 14 days of reuse, 210 contaminated carriers/liter of solution tested after 21 days of reuse, or 390 contaminated carriers/liter of solution tested after 30 days of reuse.

The cumulative bioburden load for reuse solutions by Option I and Option II is discussed in the attached Re-Use Test Protocol Specifications that was previously provided to you in our letter of September 10, 1984. In Option I, the required number of contaminated cylinders (300/day) is added directly to the 5 gallons of solution in the pail. In Option II the total number number of contaminated cylinders to achieve the same cumulative bioburden is reduced by adding only a token amount of contamination (60 cylinders/day) to the 5-gallon solution in the pail and then challenging the liter of solution intended for microbiological assay after various periods of reuse with an additional number of contaminated cylinders as indicated above.

202.2 Submitted Reuse Studies

A review of the submitted reuse studies indicate that the basic design of the EPA approved reuse protocol indicated above was not followed.

1. In both reuse studies, the additional cylinders of bioburden (180, 210 and 390, respectively) were added to a liter of solution taken from the bucket; then after soaking one hour, the liter of solution was returned to the original container. The liter of solution that was used for the microbiological assays after various periods of reuse (14, 21, 27, 30 days) were not subject to this additional bioburden load and thus did not have an adequate bioburden challenge as specified in the EPA requirements.

2. The use of only 1 set of anethesia equipment in the simulated reuse testing with Solutions A and B is a a significant deviation from the accepted protocol.

202.3 Lesser Efficacy Claims

The effectiveness of a 1:16 dilution of Sporicidin for disinfection when reused as indicated on the proposed label is not supported by the data developed in the submitted reuse studies because the studies were not conducted under the required stringent conditions specified in the EPA approved protocol. The challenge of approximately 2,400 carriers to the 5-gallon disinfectant solution by the end of the study is, in essence, a modification of the Option I procedure for bioburden addition and equivalent to the cumulative bioburden that would be in the solution after 8 days of reuse. Therefore, the data will support a lesser efficacy claim for a 1:16 dilution of Sporicidin as a disinfectant (bactericide) in 10 minutes at 20°C for an an 8-day reuse period, provided that adequate phenol resistance data against Pseudomonas aeruginosa, Salmonella choleraesuis, and Staphylococcus aureus (as indicated in the DIS/TSS-3 enclosure) are submitted for validation of the basic bactericidal data derived in the 2 reuse studies.

However, the data will only support reuse claims for the 1:16 dilution of Sporicidin in 10 minutes at 20°C as a fungicide and virucide for a 4-day reuse period because the reuse solution used in developing these data was stressed with only one set of anesthesia equipment rather than the 2 sets required under EPA reuse specifications.

A lesser efficacy claim for tuberculocidal activity, which would be equivalent to 3 days of reuse under the EPA reuse specifications, can not be considered for acceptance because the data were not developed according to the "exisiting AOAC method" as explained in 202.4 below.

20

202.4 Tuberculocidal Efficacy

You should be aware of the recently formulated Agency policy with regard to acceptable tuberculocidal test methodology, as follows:

Pending completion of an EPA-initiated peer review process concerning the methodology, the Agency will permit registrants who have successfully relied on the existing AOAC method to also rely on the new quantitative tuberculocidal activity test on a voluntary basis in those cases where use directions would be revised to be more stringent, and thus more protective. This policy applies to all tuberculocidal claims, including reuse claims.

Therefore, in light of the current policy, tuberculocidal claims for the subject product, in conjunction with reuse claims, must be supported by data developed according to the existing AOAC Tuberculocidal Activity Method. The strict interpretation of the concept of "the existing AOAC method" appears to preclude modifications such as different exposure times or temperatures. Adherence to the "existing AOAC method" limits exposure to 10 minutes at 20°C.

The new quantitative tuberculocidal method, which expressly allows variable exposure time and temperature, could then be considered for developing data to support the proposed tuberculocidal activity claim for the reuse solution in 45 minutes at 20°C since the revised use directions would be more stringent, and thus more protective.

The Agency should be consulted about any questions concerning this policy before initiating any further testing to support tuberculocidal claims for reuse.

202.5 Labeling

The following revisions for the submitted label are required to reflect the supporting data and to comply with the EPA Label Improvement Notice of May 2, 1984:

1. Revise the reuse claim to indicate that a 1:16 dilution of stock solution is recommended for complete disinfection (bactericidal, fungicidal, and virucidal) in manual (bucket and tray) systems for a 4-day reuse period. An 8-day reuse claim for a 1:16 dilution of Sporicidin as a bactericidal disinfectant may also be indicated on the label.

2. Indicate that a 1:16 dilution of unused stock solution is to be used for tuberculocidal activity in 10 minutes. A reuse claim for tuberculocidal activity is not acceptable.

3. Indicate that the "unused, undiluted stock solution" is to be used for sporicidal action and complete sterilization.

4. Clarify the efficacy claim under "Note: B." to read " Unused, undiluted stock solution will disinfect in 2 minutes." The claim "completely disinfect" is inappropriate since fungicidal and virucidal data have not been submitted and accepted for this pattern of use.

5. Provide a complete identification for the viruses claimed on the label, i.e., Influenza A_2 (Japan), Poliovirus Type 1, Herpes simplex Type 1 and 2.