[redacted]

ANTIMICROBIAL TREATMENT

HEALTH TECHNOLOGY ASSESSMENT SECTION

MEDICAL DEVELOPMENT DIVISION

MINISTRY OF HEALTH MALAYSIA

009/2013

DISCLAIMER

Technology review is a brief report, prepared on an urgent basis, which draw on restricted reviews from analysis of pertinent literature, on expert opinion and / or regulatory status where appropriate. It has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

Please contact: htamalaysia@moh.gov.my, if you would like further information.

Health Technology Assessment Section,
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre
62590 Putrajaya

Tel: 603 88831246

Fax: 603 8883 1230

Available at the following website: http://www.moh.gov.my

Prepared by:

Dr. Roza binti Sarimin
Senior Principal Assistant Director
Health Technology Assessment Section
Ministry of Health Malaysia

Reviewed by:

Datin Dr. Rugayah binti Bakri
Deputy Director
Health Technology Assessment Section
Ministry of Health Malaysia

Pn. Noormah binti Mohd. Darus
Senior Principal Assistant Director
Health Technology Assessment Section
Ministry of Health Malaysia

External reviewer:

Dr Ker Hong Bee
Consultant Infectious Disease Physician
Hospital Raja Permaisuri Bainun, Ipoh, Perak

DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Introduction

Sanitizer is a type of antimicrobial that reduces the number of bacterial contaminants to safe level as judged by public health requirements. It is commonly applied to inanimate objects (food contact and non-food contact area). Disinfectants destroy many or all pathogenic microorganisms on inanimate objects, except bacterial spores. [redacted] antimicrobial treatment was an organosilane biostatic molecule with Quartenary Ammonium compounds as its active ingredient. [redacted] antimicrobial treatment was claimed effective to be applied as surface disinfectant and environmental mould prevention, however its claim remains uncertain. This review was requested by the Senior Principal Assistant Director, Disease Control Division, Ministry of Health Malaysia to review the evidence on [redacted] antimicrobial treatment to be used as surface disinfectant in the MOH hospitals and healthcare facilities following proposal from a company to introduce them in the MOH facility.

Aims/Objectives

To assess the efficacy, safety and cost effectiveness of [redacted] antimicrobial treatment to be used as surface disinfectant in the MOH hospitals and healthcare facilities.

Results and conclusion

There was no retrievable published evidence on the efficacy, safety and cost effectiveness of [redacted] antimicrobial treatment or self sanitizing technology. Only limited unpublished evidence provided by the manufacturer was available. Nevertheless the microbiological testing provided demonstrated that [redacted] antimicrobial treatment seemed to be effective against bacteria, fungi and virus. [redacted] antimicrobial treatment was also registered with the USEPA (Registration number: 70871-16-23). Quartenary Ammonium compounds, which is the active ingredient of [redacted] antimicrobial treatment is low-level disinfectant which can be used in ordinary environmental sanitation of non-critical surfaces, as classified by USCDC.

Methods

Literature were searched through electronic databases which included PubMed, Medline, Cochrane Database of Systematic Reviews, Cochrane Database of Controlled Trial, Health Technology Assessment, National Horizon Scanning, other websites; INAHTA, ASERNIP-S, CADTH, FDA, MHRA and general databases such as Google. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. A critical appraisal of all relevant literature was performed using Critical Appraisal Skills Programme (CASP) checklists and the evidence graded according to the US/Canadian Preventive Services Task Force Level of Evidence (2001).

[redacted] ANTIMICROBIAL TREATMENT

1. INTRODUCTION

Sanitizer is a type of antimicrobial or an agent that reduces the number of bacterial contaminants to safe level as judged by public health requirements.[1] Sanitizing is a process which destroys microorganism that may be present on equipment and utensils after cleaning.[2] Cleaning is removal of visible soil (organic and inorganic material) from objects and surfaces, accomplished by a manual or mechanical process using water with detergent or enzymatic products.[3]

Most sanitizers are based on toxic chemicals such as chlorine, iodine, phenol, or quaternary ammonium compounds which may never be taken internally.[1] It is used to reduce but not necessarily eliminate microorganism from the inanimate environment to level considered safe as determined by public health code or regulation and registered by United States Environment Protection Agency (USEPA) for public health uses. Sanitizer is commonly applied to inanimate objects. [1]It can be applied to food contact (such as food processing plants, eating and drinking establishments, cooking utensils and equipments) and non-food contact area (carpet sanitizers, air sanitizers, laundry additives and in-tank toilet bowl sanitizers).[3]

Chemical sanitizer use shall meet the requirements of 21 USFDA Code of Federal Regulation (CFR) 178.1010 for food-processing equipment and utensils, and on other food-contact articles.[4] In order to be registered as sanitizer for inanimate, non-food contact surface, the test results for a product must show a reduction of at least 99.9% in the number of each test microorganism over the parallel control count within 5 minutes.[5]

Disinfection is a process that eliminates many or all pathogenic microorganisms on inanimate (nonliving) objects, except bacterial spores (not sporicidal) as compared to sterilization.[1] Disinfectants are classified by product label claims (USEPA) and by germicidal activity (USCDC/USFDA) as described in Appendix 3. Basic difference between disinfectant and sanitizer in the use and characteristics is as below;[3]

Disinfectants	Sanitizers
Used on hard inanimate surfaces that are not food-contact surface • Hospital use : Medical equipments, floor, wall, bed linens and other surfaces • General use : Household, water purifier	Used on food-contact surfaces and non food-contact (soft contact) surfaces such as textiles, fabrics, carpeting
Tend to be used at much higher concentrations and usually have a longer contact time	Tend to be used at lower concentrations for a shorter period of time

Factors affecting sanitizer effectiveness include physical factors (surface characteristics, contact time, temperature, concentration; chemical factors (pH,

water properties) and biological factors (microorganism load, type of microorganism).[6]

This review was requested by the Senior Principal Assistant Director, Disease Control Division, Ministry of Health Malaysia to review the evidence on [redacted] antimicrobial treatment to be used as surface disinfectant in the MOH hospitals and healthcare facilities following proposal from a company to introduce them in the MOH facility.

2. OBJECTIVES

To assess the safety, effectiveness and cost effectiveness of [redacted] antimicrobial treatment to be used as surface disinfectant in the MOH hospitals and healthcare facilities.

3. TECHNICAL FEATURES

[redacted], is a silicon quartenary ammonium salt consisted of 3-(Trimethoxysilyl) propyldimethyloctadecyl Ammonium Chloride in aqueous solution (71.2%), and inert ingredient (28.8%). There are four versions of EndoStat™ product line which include: ready-to-use (RTU) formulation, a 5% concentrate, a 36% biostatic/disinfection concentrate and a 72% concentrate. The RTU and 5% dilutions are stabilized in aqueous solution, while the 36% and 72% are low solvent based formation designed for infection control and manufacturing application respectively. It is manufactured in the USA at EPA approved and ISO 9001:2008 certified facility.[7] It is also known as [redacted] Antimicrobial Treatment or a revolutionary Self Sanitising Technology.

It is claimed this substance is highly effective bonded, broad spectrum durable, anti microbial treatment to be applied as surface disinfectant and environmental mould prevention which can be used on all porous and non-porous surfaces, textiles, upholstery, fabrics, building materials for domestic and industrial setting which is active against bacteria, fungus, virus and spores when used as directed.[5,7] It provides a Bio-Static protective barrier on the surface to which it is applied. It is also claimed that [redacted] is the only product of its kind registered by the USEPA and it is approved for use on nappies, dressings, theatre gowns, concrete, wood, floors and tiles etc.[7]

3.1 MECHANISM OF ACTION

The organosilane Biostatic molecule is comprised of three parts; a silane coupling polymer for surface attachment, a positively charged Nitrogen group and a long-chain C-18 methal grouping of molecules.[7]

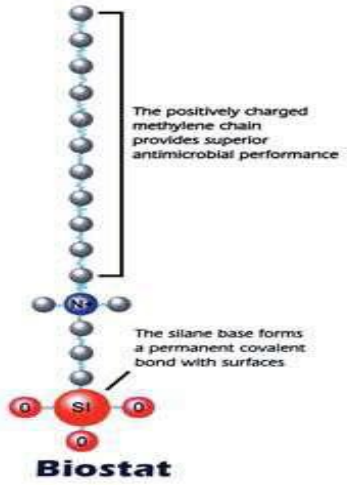

Figure 1: Chemical structure of [redacted]

It will destroy microbes through a mechanical process, by which micro-organisms are drawn through ionic attraction onto the [redacted] coating which resembles a series of needles bonded to a surface. Upon contact the cellular membrane is destroyed, thus neutralising the microbe.[5]

When applied to a surface, the silane coupling polymer covalently bonds to the surface while the positively charged methal chain points away from the surface. In effect, the Biostatic coating resembles a series of needles bonded to a surface. Through ionic attraction, negatively charged microbes are drawn onto the positively charged [redacted] coating. Upon contact, the methal group molecules penetrate and compromise the lipid bilayer (cellular membrane) associated with microorganisms. As a result of intercellular hydrostatic pressure, the lipid bilayer disassociates upon contact with [redacted] and the microorganism is destroyed. [7]

Cellular death is achieved through a physical process without the use of toxic or volatile chemicals. All known enveloped microorganisms and many non-enveloped microorganisms are susceptible to this process. Because [redacted] forms a permanent bond with surfaces, its antimicrobial performance does not dissipate with time or exposure.[7]

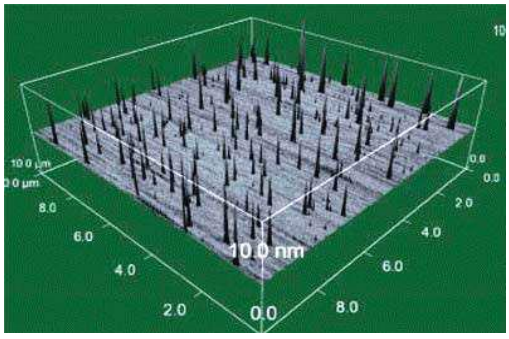

Diagram 1: Electron microscope image of a surface treated with [redacted]

4. METHODOLOGY

4.1 SEARCHING METHODS

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present
- EBM Reviews - Cochrane Central Register of Controlled Trials – January 2013
- EBM Reviews - Database of Abstracts of Review of Effects (1st Quarter 2013)
- EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to January 2013
- EBM Reviews - Health Technology Assessment - 1st Quarter 2013
- NHS economic evaluation database - 1st Quarter 2013

Other databases:

- PubMed
- Horizon Scanning database (National Horizon Scanning Centre, Australia and New Zealand Horizon Scanning Network, National Horizon Scanning Birmingham)
- Other websites; INAHTA, ASERNIP-S, CADTH,
- USFDA
- US Environmental Protection Agency (USEPA) website
- National Institutes for Health and Clinical Excellence (NICE) website
- Medicines and Healthcare products Regulatory Agency (MHRA) website

General databases such as Google scholar and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. No limit was applied during search. **Appendix 1** showed the detailed search strategies.

The last search was conducted on 15 February 2013. The search was re-run in June 2013. The search strategy used these terms either singly or in various combinations: [redacted] OR 3-(Trimethoxysilyl) propyldimethyloctadecyl Ammonium Chloride OR Quaternary Ammonium salt OR organosilane OR [redacted] OR sanitizer OR disinfectant.

4.2 SELECTION OF STUDIES INCLUDED /EXCLUDED

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.
The inclusion and exclusion criteria were:

Inclusion criteria

Population	Hospital, health clinics
Interventions	[redacted] 3-(Trimethoxysilyl) propyldimethyloctadecyl Ammonium Chloride, Quaternary Ammonium salt, organosilane, [redacted] sanitizer, disinfectant
Comparators	Control or other sanitizer/disinfectant
Outcomes	• Germicidal activity • Bactericidal, virucidal, yeasticidal, fungicidal
Study design	Any primary study of acceptable quality
Type of publication	English, full text articles, human studies

Exclusion criteria

Intervention	-
Study design	Anecdotal, animal studies

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition) for diagnostic accuracy studies (Appendix 2). Data were extracted and summarized in evidence table as in Appendix 3. The data were not pooled and only qualitative analysis was carried out.

5. RESULTS AND DISCUSSION

The search strategy showed no retrievable evidence from the electronic databases on the efficacy, safety or cost-effectiveness of [redacted] antimicrobial treatment.

An unpublished efficacy compliance document consisted of microbiological testing of this product and Material Safety Data Sheet (MSDS) were submitted by the manufacturer.

5.1 EFFICACY/EFFECTIVENESS

There was no scientific evidence retrieved from the electronic databases on the efficacy of [redacted] antimicrobial treatment to be used as surface disinfectant in clinical settings.

The manufacturer provided an efficacy compliance document consisted of microbiological testing of this product, a Material Safety Data Sheet (MSDS) and another microbiological testing done in a local private hospital.

The efficacy compliance document consisted of microbiological testing of this product conducted against a wide range of gram positive and negative bacteria, viruses, fungi, algae, mould, yeast and spores in various surfaces in non-clinical setting.[7]

Bactericidal and fungicidal

The results showed that there was 100% reduction in *Klebsiella oxytoca*, *Streptococcus faecalis* and *Staphylococcus aureus* count per inoculation, and 99% reduction of *Escherichia coli* per inoculation on nylon rug material treated with EndoStat. Similar reduction was also demonstrated on treated nylon carpet with 99.9% reduction of *Klebsiella pneumonia* and *Staphylococcus aureus* after the fifth inoculation.

On treated textiles, effectiveness of [redacted] was also demonstrated with reduction of odour causing bacteria, mildew and mould. There was 99% reduction in *micrococcus sp*., *Acinobacter calcoaceticus* and *Staphylococcus aureus*, 96% reduction in *Staphylococcus epidermis* with 90% reduction demonstrated in *Enterobacter aglomerans*. Similar reduction (99%) of *Klebsiella pneumoniae* was also demonstrated on treated non-woven textiles delivered using buffered phosphate with a 15 minutes contact time.

More testing done on drape material showed that [redacted] was effective in reducing wound isolate loaded by bacteria namely *Staphylococcus aureus, Proteus mirabilis* and *Citerobacter diversus* by 99.7%, 99.5% and 93.6%. Similar reduction was observed in urine isolate loaded by *Psedomonas aeruginosa* and *Eschericia coli* by 99.9% and 98.6% respectively.

Test conducted on HiLoft fabric did show effectiveness of [redacted] in reducing 100% *Klebsiella pneumonia* after 5 minutes contact time. Similarly, effectiveness of EndoStat was demonstrated with 99.99% reduction in *Staphylococcus aureus* on treated air filter fabric.

Virucidal

For antiviral activity, additional testing conducted on treated alginate beads demonstrated [redacted] was effective in reducing 99.9% *Feline calicivirus,* which was used as an analogue for *Norovirus* after 15 minutes contact time (achieving a 3 log reduction).

5.1.1 LIMITATION

There were other microbiological testing conducted in an uncontrolled environment within a local private hospital and a testimony provided by the manufacturer, but they were of low quality where there was no comparison, microorganism quantified was not specified and results could not be interpreted.

5.2 SAFETY

There was no scientific evidence retrieved from the electronic databases on the safety of [redacted] antimicrobial treatment to be used as surface disinfectant in hospitals and healthcare facilities.

Material Safety Data Sheet on [redacted] provided information on its properties, safety data as well as ways in handling the substance in a safe manner. It is produced in accordance with European Directive; EC Directive 91/155/EC, with the aim to provide manufacturing operation with information on hazard profiles, risks associated with this substances and preparations in the work place to facilitate the workers' health and safety protection.[9]

It was registered with USEPA (Registration number: 70871-16-23) and its EPA Master Label Language is EndoStat-7200™/ BSTI-1860™/ProShield-7200™ Antimicrobial Agent: A Silicon Quaternary Ammonium Salt.[7] However its registration with FDA could not be retrieved and CE mark was also not available.

5.3 COST EFFECTIVENESS

There was no retrievable scientific evidence from the electronic databases on the cost-effectiveness of [redacted] antimicrobial treatment or self sanitizing technology to be used as surface disinfectant in hospitals and healthcare facilities. Its direct cost was also not available.

5.4 LIMITATION

This review has few limitations. Although there was no restriction in language during the search, only English full text articles were included in this report. The selection of studies was done by one reviewer.

6. CONCLUSION

There was no retrievable published evidence on the efficacy, safety and cost effectiveness of [redacted] antimicrobial treatment or self sanitizing technology. Only limited unpublished evidence provided by the manufacturer was available. Nevertheless the microbiological testing provided demonstrated that [redacted] antimicrobial treatment seemed to be effective against bacteria, fungi and virus. [redacted] antimicrobial treatment was also registered with the USEPA (Registration number: 70871-16-23). Quartenary Ammonium compounds, which is the active ingredient of [redacted] antimicrobial treatment is low-level disinfectant which can be used in ordinary environmental sanitation of non-critical surfaces, as classified by USCDC.

8.0 REFERENCES

1. US Centers for Disease Control and Prevention. Department of Health and Human Services. Guideline for Disinfection and Sterilization in Healthcare Facilities. 2008.
2. Alabama Department of Health. Cleaning and Sanitizing. Accessed at http://www.adph.org/environmental/assets/CleanAndSanitize on 20 January 2013.

3. US Environmental Protection Agency. Antimicrobial Pesticide product. Available at http://www.epa.gov/opp00001/factssheets/antimic.htm Assessed on 20 January 2013.
4. US Food and Drugs Administration, Department of Health and Human Services. Code of Federal Regulation 21. Part 178 Indirect Food Additives: Adjuvants, Production Aids, And Sanitizers. Assessed online at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=178.1010 on 15 February 2013.
5. US Environmental Protection Agency. Sanitizer test for Inanimate Surfaces. Efficacy data requirements. http://www.epa.gov/oppad001/dis_tss_docs/dis-10.htm Assessed on 15 January 2013.
6. Schmidt RH. Basic elements of equipment cleaning and sanitizing in food processing and handling operations. Food Science and Human Nutrition Department. Institute of Food and Agricultural Sciences, University of Florida. 1997.http://www.ag.auburn.edu/poul/virtuallibrary/pdf/curtiscleaningsanitizing.pdf Assessed on 20 January 2013.
7. EndoStat™. Efficacy Compliance Document. Document submitted by manufacturer.
8. EndoStat™. Product Information. Available at URL: http://www.biohealthsolutions.co.uk/endostat.php Accessed on 15 February 2012
9. EndoStat™. Material Safety Data Sheet.
10. Rehal M. Endo Entreprises Case Study. Deep Clean and Medical Equipment Decontamination Evaluation. Available at http://endoenterprises.com/wp-content/uploads/PDF/CaseStudyBarts.pdf accessed online on 15 February 2012
11. Regency Hospital Trial. 29 Nov 2012. Document submitted by manufacturer.

9.0 APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1	inorganic chemicals/ or organic chemicals/ or heterocyclic compounds/ or polycyclic compounds/ or pharmaceutical preparations/ or disinfectants/or endostat
2	limit 1 to (english language and humans)
3	Disinfection/cl, st [Classification, Standards]
4	Disinfectants/ and Disinfection/
5	2 or 3
6	4 or 5
7	3 and 4
8	Disinfectants/ and Disinfection/
9	surface disinfectant.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10	environmental disinfectant.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11	9 or 10
12	7 and 11

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	
INAHTA	Disinfectant, ammonium salt, [redacted]
FDA	Disinfectant, ammonium salt, [redacted]

9.2 Appendix 2

HIERARCHY OF EVIDENCE FOR DIAGNOSTIC TEST ACCURACY STUDIES

Level	Description	
1.	A blind comparison with reference standard among an appropriate sample of consecutive patients	
2.	Any one of the following	Narrow population spectrum
3.	Any two of the following	Differential use of reference standard
4.	Any three or more of the following	Reference standard not blind Case control study
5.	Expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles.	

SOURCE: NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition)

9.3 Appendix 3

SUMMARY OF DISINFECTANT CLASSIFICATION USED BY VARIOUS AGENCY

Agency	Disinfectant classification
USEPA	Classify disinfectants by product label claims of “limited”, “general” or ”hospital” disinfection. • Limited : disinfectant registered for use against a specific major group of organisms (gram-negative or gram-positive bacteria). Efficacy has been demonstrated in laboratory tests against either Salmonella choleraesuis or Staphylococcus aureus bacteria. • General : EPA-registered disinfectant labeled for use against both gram-negative and gram-positive bacteria. Efficacy is demonstrated against both Salmonella choleraesuis and Staphylococcus aureus. Also called broad-spectrum disinfectant. • Hospital : disinfectant registered for use in hospitals, clinics, dental offices, and any other medical-related facility. Efficacy is demonstrated against Salmonella choleraesuis, Staphylococcus aureus, and Pseudomonas aeruginosa. EPA has registered approximately 1,200 hospital disinfectants.

USCDC	Disinfection process can be classified as:
	• high level disinfectants
	  • agent capable of killing bacterial spores when used in sufficient concentration under suitable conditions. It is expected to kill all other microorganisms. At similar concentrations with chemical sterilant but with shorter exposure periods is expected to destroy all microorganisms except large numbers of bacterial spores
	• intermediate-level disinfectants
	  • agent that destroys all vegetative bacteria (including tubercle bacilli), lipid and some nonlipid viruses, and fungi, but not bacterial spores
	• low-level disinfectants
	  • agent that destroys all vegetative bacteria (except tubercle bacilli), lipid viruses, some nonlipid viruses, and some fungi, but not bacterial spores (<10 minutes)).

USFDA	The FDA definition of high level disinfection is a sterilant used for a shorter contact time to achieve a 6-$\log_{10}$ kill of an appropriate Mycobacterium species.