Defining Processes to Manufacture Sterile Antiseptics

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Abstract

Purpose: To assess the impact of various sterile manufacturing technologies on topical antiseptic products. These products are often used on skin to eliminate microorganisms prior to surgery and reduce the risk of infections. The common assumption is that these solutions kill microorganisms and manufacturing of the solutions does not require additional processing to render them sterile. However, recent product recalls resulting from microbial contamination have demonstrated that these products do support microbial growth. When this happens, the attempt to disinfect skin results in applying microbial contamination to the surgical site.

Methods: Analytical methods were validated for chlorhexidine gluconate (HPLC), benzalkonium chloride (HPLC), ethanol (GC), isopropanol (GC), and povidone-iodine (titration). Seventeen commercial products were purchased, tested, exposed to sterilization processes, and then re-tested. Sterilization processes included: standard autoclave (steam) cycle (121ºC / 15 min), low temperature autoclave cycle (118ºC / 25 min), standard ethylene oxide cycle (EtO), electron beam (12 kGy, E-beam), and filter compatibility testing.

Results: Steam sterilization destroyed package integrity for many products, even at low temperature cycle; however, most applicators were not affected by the processing conditions. E-beam and EtO maintained most package integrity; however, a noted potency reduction occurred in some E-beam samples and several alcohol samples had package integrity issues with EtO (dried out). Filter materials compatible with each liquid product were identified.

Conclusion: Sterilization techniques are available for processing topical antiseptic products. Implementation of sterilizing technologies may require multiple processing steps, additional specific equipment and/or aseptic processing for assembly and packaging of some products; however, this would mitigate the potential risk associated with microbial contamination of non-sterile topical antiseptic products.

Introduction

The purpose of this study was to conduct stability assessment of topical antiseptic products following various sterilization processes. Analytical methods were set up and verified for quantifying the active ingredients in each product. Product samples were assayed before and after sterilization to determine if the sterilization technique altered the amount of active ingredient in each product. Sterilization techniques were identified for processing each type topical antiseptic product studied.

Methods

The objective of the evaluation program was to assess compatibility of the materials being tested with the sterilization technique(s) employed. The intent was to use a process which could achieve sterilization for the products included in the testing. The project did not include intent to develop, verify or assess the sterility of the products as a result of the technique(s) employed.

Sterilization

The sterilization techniques employed fell into two categories: microbial destructive and microbial retentive. Microbial destructive techniques included autoclaving (steam sterilization), ethylene oxide sterilization and electron beam (e-beam) sterilization. The microbial retentive technique was filtration.

Sterilization Techniques

Autoclave (steam sterilization)
- Standard cycle (121ºC / 15 min)
- Low temp cycle (118ºC / 25 min)

Ethylene Oxide
- Standard cycle (55°C / ~3.75 hr)

E-beam
- 12 kGy

Filtration
- Compatibility

Analytical Methods

GC
- Ethanol Assay
- Isopropanol Assay

HPLC
- Benzalkonium Chloride Assay
- Chlorhexidine Gluconate Assay

Titration
- Povidone-Iodine Assay

Materials

Chlorhexidine Gluconate Products
Sage 2% Chlorhexidine Gluconate Cloths, Lot 33327/3/L6
ChloraPrep One Step Clear, Lots 55542, 56261, 54979
ChloraPrep One Step Hi-Lite Orange, Lot 39369
Dynarex Povidone Iodine Prep Pads, Lot 213023
Smith and Nephew IV Prep Antiseptic Wipes, Lot 1503
Hibiclens, Lots EBCE-1, EBCE-2
PDI Chlorascrub Swab, Lot 11200860

Benzalkonium Chloride Product
PDI BZK Antiseptic Towelette, Lot 11200895

Products containing Iodine
Purdue Betadine Solution, Lot 80738-11
Medline Povidone-Iodine Prep Pads, Medium, Lots LC029243 and LC029243
DuraPrep Surgical Solution Iodine Povacrylex and IPA, Lots 2015-05AM and 2015-05AS
Povidone-Iodine Swabstick (3s) PDI, Lots 11201340, and 11201572
Dynarex PVP-I2 Prep Pads, Lot 005084
Aplicare Betadine Solution 10%, Lot 49435A
Care Fusion Iodine Tincture 2%, Lot 50491

Products containing Ethanol or Isopropanol
Hydrox Isopropyl Rubbing Alcohol, USP, Lots 33183 and 33318
Dukal Sterile Alcohol Prep Pad, Lot JT34911
Actiprep, Lot DMHL-1

Filters
- Cellulose Acetate
- Cellulose Nitrate
- Polyacrylonitrile / Polyvinyl chloride (PAN/PVC)
- Polyamide (Nylon®)
- Polycarbonate
- Polypropylene
- Polyethersulfone
- Polyvinylindenediflouride (PVDF)
- Polytetrafluoroethylene (PTFE, Teflon®)

Results

Table 1 – Chlorhexidine Gluconate Products

Product	Label Claim	pre-Sterilization: Chlorhexidine Gluconate Average (w/v) Concentration	pre-Sterilization: %RSD	pre-Sterilization: % Label Claim	post-Sterilization: Standard Autoclave Cycle	post-Sterilization: Low T Autoclave Cycle	post-Sterilization: EtO	post-Sterilization: E-Beam
Chloraprep One-Step Clear	2%	1.82%	0.61%	91.0%	82.2%	90.8%	93.1%	93.1%
Chloraprep One-Step Hi-Lite Orange	2%	1.75%	1.30%	87.7%	86.1%	95.4%	87.5%	87.5%
Chlorascrub Swab	3.15%	2.92%	1.00%	92.7%	pkg fail	pkg fail	95.8%	95.8%
Hibiclens	4%	3.68%	0.96%	92.1%	pkg fail	pkg fail	91.3%	91.3%
Sage Cloths	2%	1.99%	1.58%	99.7%	pkg fail	pkg fail	101.9%	101.9%

Table 2 – Benzalkonium Chloride Product

Product	Label Claim	pre-Sterilization: Benzalkonium Chloride Average (w/w) Concentration	pre-Sterilization: %RSD	pre-Sterilization: % Label Claim	post-Sterilization: Standard Autoclave Cycle	post-Sterilization: Low T Autoclave Cycle	post-Sterilization: EtO	post-Sterilization: E-Beam
PDI Benzalkonium Chloride Antiseptic Towelette	0.1%	0.112%	4.79%	86.1%	pkg fail	pkg fail	83.80%	63.30%

Table 3 – Products Containing Iodine

Product	Label Claim	pre-Sterilization: Average Iodine Concentration	pre-Sterilization: %RSD	pre-Sterilization: % Label Claim	post-Sterilization: Standard Autoclave Cycle	post-Sterilization: Low T Autoclave Cycle	post-Sterilization: EtO	post-Sterilization: E-Beam
PDI Swabstick 3's	10%	9.55	1.00%	96%	pkg fail	pkg fail	92%	87%
DuraPrep Applicators	0.7%	0.683	0.36%	98%	95%	92%	95%	88%
Medline PrepPad Applicators	10%	9.46	1.08%	95%	pkg fail	pkg fail	91%	85%
Dynarex PrepPad Applicators	10%	10.4	1.03%	103%	pkg fail	pkg fail	102%	97%
SEPPS Applicators	2%	1.89	0.69%	94%	pkg fail	pkg fail	95%	91%

Table 4 – Products Containing Isopropanol (IPA) or Ethanol (EtOH)

Product	Label Claim	pre-Sterilization: IPA or EtOH Average (v/v) Concentration	pre-Sterilization: %RSD	pre-Sterilization: % Label Claim	post-Sterilization: Standard Autoclave Cycle	post-Sterilization: Low T Autoclave Cycle	post-Sterilization: EtO	post-Sterilization: E-Beam
ChloraPrep One Step Clear (IPA)	70%	69.79%	0.99%	100%	97.90%	99.80%	100.80%	94.40%
Smith and Nephew IV Prep (IPA)	70%	71.50%	0.74%	102.14%	pkg fail	pkg fail	111.50%	103.70%
PDI ChloraScrub Swab (IPA)	70%	67.12%	1.71%	95.89%	pkg fail	pkg fail	105.10%	98.20%
Dukal Alcohol Prep Pad (IPA)	70%	76.73%	1.01%	109.62%	pkg fail	pkg fail	118.10%	111.10%
SEPPS (EtOH)	47%	49.99%	1.19%	106.37%	pkg fail	pkg fail	108.70%	111.70%
DuraPrep (IPA)	74%	83.77%	1.02%	113.20%	115.70%	112.90%	101.00%	115.10%
ChloraPrep One Step Hi-Lite Orange (IPA)	70%	70.46%	1.23%	100.65%	102.70%	97.80%	98.80%	96.60%

Table 5 – Filter Compatibility

Filter | Compatibility with:	IPA	Iodine	Chlorhexidine	Actiprep/EtOH
Cellulose Acetate				
Cellulose Nitrate				
Polyacrylonitrile / Polyvinyl chloride (PAN/PVC)		viscosity	viscosity	viscosity
Polyamide (Nylon®)		2-3% Loss		viscosity
Polycarbonate	carbon effects		carbon effects	carbon effects
Polypropylene				2% loss + app.
Polyethersulfone				appearance
Polyvinylindenediflouride (PVDF)			~1.8% loss	appearance
Polytetrafluoroethylene (PTFE, Teflon®)				

Conclusions

Sterilization techniques are available for processing topical antiseptic products. Implementation of sterilizing technologies may require multiple processing steps, optimization of sterilization conditions, additional specific equipment and/or aseptic processing for assembly and packaging of some products; however, this would mitigate the potential risk associated with microbial contamination of non-sterile topical antiseptic products.

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Acknowledgement

This work was supported by FDA grant NIPTE-UO1-UW-002-2012 through the DHSS, PHS grant 5UO1FD004275-02 to the National Institute for Pharmaceutical Technology and Education (NIPTE).

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