Technical bulletin

Initial Safety and Pre-Clinical Study Summary for BD® Surgiphor™ Surgical Wound Irrigation System

BD

Abstract

Surgiphor™ Surgical Wound Irrigation System primary mode of action is to mechanically loosen and remove debris and foreign materials, including microorganisms from the surgical wound during surgery. The PVP-I serves as a preservative in the solution and provides an ancillary mode of action to further reduce bacterial load within the surgical wound.[1,2,^] Activity of the preservative was tested and demonstrated efficacy against a variety of microorganisms both *in vitro* and *in vivo*. The safety and sterility of the solution were evaluated with additional tests.

Preservative effectiveness

The Surgiphor™ solution was tested via a set of *in vitro* studies to determine the effectiveness of the preservative in preventing unwanted microbial growth. The PVP-I in Surgiphor™ has broad-spectrum antimicrobial effects against bacteria and yeast, reducing microorganisms in the solution and bacterial burden in surgical wound.[1–6]

Terminal sterility

In accordance with ISO 11137, Surgiphor™ Surgical Wound Irrigation System contains a terminally sterilized solution with a sterility assurance level (SAL) of 10^{-6}, providing customers with confidence that the product has only a one in a million chance of containing a single viable microorganism.[7]

Safety profile

Surgiphor™ solution exhibited no cytotoxicity at 1:8 and 1:16 dilution following 48 hours of incubation[8], and was found to be an irritant when intracutaneously injected in a standard biocompatibility rabbit model of a dermal irritation.[9]

Surgiphor™ solution demonstrated no potential for dermal irritation or sensitization in a human repeat- insult patch testing (HRIPT).[10]

Surgiphor™ solution did not inhibit wound healing in a porcine surgically created wound model.[11]

Product summary

Surgiphor™ includes a 450 mL compressible bottle with terminally sterile 0.5% PVP-I formulation with 0.9% saline, Potassium Iodide, Phosphate Buffer, and Vitamin E TPGS). Surgiphor™ is intended to mechanically loosen and rinse debris and foreign materials, including microorganisms from the surgical wound. The device consists of a screw cap and a sealed bottle containing 0.5% w/w PVP-I in a solution of phosphate-buffered saline, potassium iodide and Vitamin E TPGS. As an ancillary action, PVP-I serves as a preservative to protect the solution from microbial growth during use, whilst also reducing the bacterial load within the wound by killing the microorganisms that could lead to infection. The Surgiphor™ Surgical Wound Irrigation System is terminally sterilized by gamma irradiation. The irrigation system can be used multiple times during one procedure but should only be used in a single patient within 24 hours of opening the bottle.

Clinical Benefit Statement

Irrigation of the surgical wound with Surgiphor™ Surgical Wound Irrigation System aids loosening and removing debris from the surgical wound, while the PVP-I in the Surgiphor™ Solution acts as a preservative whilst also reducing the bacterial load within the wound that could lead to infection.

Mechanism of action

Surgiphor™ Surgical Wound Irrigation System is designed to mechanically loosen and rinse debris and foreign materials, including microorganisms from the surgical wound. Fluid moving across the wound provides the mechanical action, which aids in removal of debris and microorganisms from wounds. Surgiphor™ Surgical Wound Irrigation System delivers pressure within the range outlined by the Agency for Health Care Policy and Research (AHCPR).[12] PVP-I also reduces microorganisms in the wound.

*Product should be used within 24 hours of opening.
^Surgical wound was in an simulated animal model
a. Irritation and cytotoxicity testing was conducted in accordance with ISO 10993 series standards.
b. Surgiphor™ is not indicated for injection or infusion.

Preservative Effectiveness

Acute *Escherichia coli* Bacterial Challenge Study[2]

Introduction

The purpose of this study is to evaluate the mechanical and antimicrobial efficacy of Surgiphor™ solution against *E.coli* in a swine model that closely mimic human wound.

Methods

Eight dorsal incisions were made on each of two female Yorkshire swine. Each wound was inoculated with 1 mL of ~10^9 colony-forming units (CFU)/mL *E. coli* (ATCC 11775) and left for 5 minutes before irrigation.

Mechanical irrigation with the Surgiphor™ 0.5% povidone-iodine solution in buffered saline involved applying the full 450-mL bottle with continuous pressure from a distance of 3 – 6 in for approximately 1 min. Passive irrigation with Surgiphor solution involved holding the bottle above the wound and allowing the solution to drip with minimal pressure for up to 30 seconds. Two incisions per animal received no irrigation, and saline was used as a negative control with both irrigation methods.

Each site was swabbed with two sterile swabs before and after irrigation and placed in 5 mL of Dey-Engley neutralizing broth. Cultures were incubated at 35 ± 2 °C for 18 – 24 hours. Manual colony counts were used to determine CFU/swab before and after irrigation.

Results

The untreated controls recovered a mean 7.67 ± 0.35 $\log_{10}$ CFU/swabs. Passive-irrigation delivery of Surgiphor™ solution produced an average $\log_{10}$ reduction of 0.82 ± 0.15 CFU/swabs vs 0.16 ± 0.20 CFU/swabs with saline, whereas Surgiphor solution mechanical-irrigation delivery had a mean $\log_{10}$ reduction of 2.09 ± 0.19 CFU/swabs vs 0.92 ± 0.15 CFU/swabs with saline.

Conclusions

These swine model study results illustrate the antimicrobial effects of the Surgiphor™ solution, demonstrated by increased bacterial reduction vs saline when used under passive and mechanical irrigation. Mechanical delivery of Surgiphor™ solution had greater log reduction vs passive delivery, demonstrating that both antimicrobial activity and mechanical pressure facilitate microorganism removal from the wound.

USP <51> Antimicrobial Effectiveness Test[3]

Introduction

PVP-I is a well-known antiseptic agent with broad-spectrum antimicrobial activity. The PVP-I in Surgiphor™ serves as a preservative within the solution and helps reduce microbial load in the surgical wound.^,1,2,12 An *in vitro* study was performed to determine the antimicrobial efficacy of the preservative PVP-I in Surgiphor™ against five standard test organisms. The study involved incubating the test organisms with Surgiphor™ for a defined period of time, then comparing the number of surviving microorganisms to USP <51> testing requirements. Antimicrobial efficacy of the preservative is expressed as $\log_{10}$ reduction in test organisms for each time interval.

Methods

Three independent lots of Surgiphor™ solution and a positive control were inoculated with each of the five test organisms (Figure 1A). Immediately after inoculation, samples were taken to determine the challenge titer of test organisms from positive controls and preservative immediate-kill antimicrobial activity from inoculated Surgiphor™ samples (0 hours). All lots were sampled again 7, 14, and 28 days later. In order for the preservative to be considered antimicrobial, a minimum 4 $\log_{10}$ reduction in microbial count had to be observed against the bacteria and fungi test organisms.

Results

Initial concentrations of the test organisms inoculated within Surgiphor™ and positive controls were approximately 10^5 to 10^6 colony forming units per milliliter (CFU/mL). Final challenge titer concentration was determined from 0-hour positive controls (Figure 1A). The results of the average $\log_{10}$ reduction per microorganism after 0 hours, and 7, 14, and 28 days are found in Figures 1B-D. According to the greater than 4 $\log_{10}$ reduction USP criteria, the PVP-I preservative in Surgiphor™ was found to be effective after 7, 14, and 28 days for all tested fungi, gram-positive bacteria, and gram-negative bacteria. The preservative had immediate-kill activity against all tested microorganisms except *Staphylococcus aureus* and *Aspergillus brasiliensis*. At the 7-day post-inoculation time-point, the preservative had a complete kill for microorganisms *S. aureus* and *A. brasiliensis*.

Conclusions

The Surgiphor™ solution containing the preservative PVP-I to prevent unwanted microbial growth once the bottle is opened was found to meet the USP <51> criteria for *in vitro* antimicrobial efficacy, achieving at least 99.99% (4 $\log_{10}$) reduction on all bacteria and fungi test organisms at the initial time point of 7 days.†

Figure 1: Preservative antimicrobial effects on five standard test microorganisms. (A) Test organism challenge titers as determined from positive controls, (B) fungi mean $\log_{10}$ reductions, (C) gram-positive mean $\log_{10}$ reductions, and (D) gram-negative mean $\log_{10}$ reductions. An asterisk (*) above the data column represents the detectable limits of the test where zero CFU were recovered from the test article. We can be certain the $\log_{10}$ reduction is at least as high as indicated.

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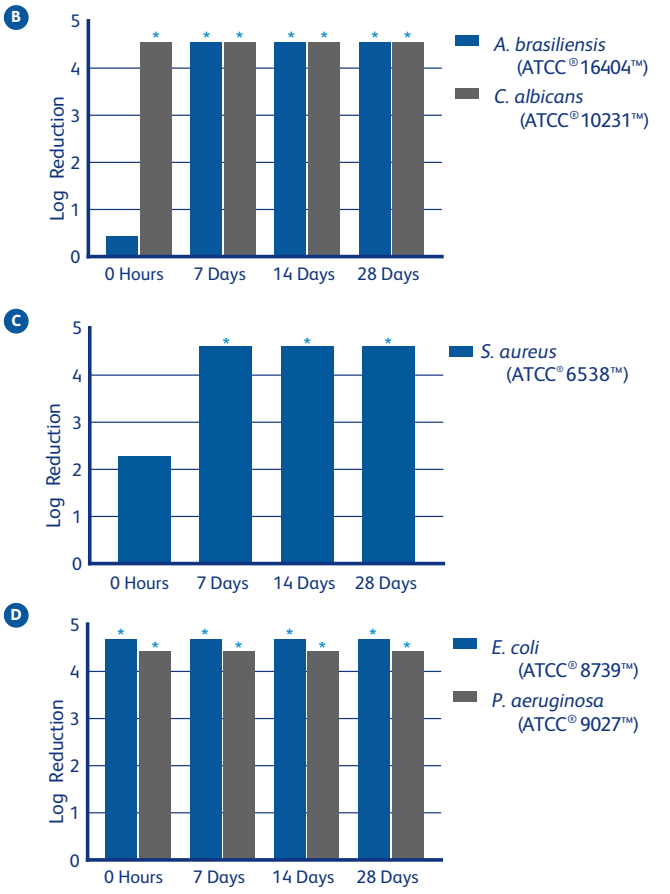
Organism	ATCC® Isolate	Challenge Titer at 0 Hour (CFU/mL)
Aspergillus brasiliensis (Mold)	16404™	7.5×10^5
Candida albicans (Yeast)	10231™	7.6×10^5
Escherichia coli (Gram negative bacteria)	8739™	9.9×10^5
Staphylococcus aueus (Gram positive bacteria)	6538™	8.8×10^5
Pseudomonas aeruginosa (Gram negative bacteria)	9027™	5.7×10^5



†Product should be used within 24 hours of opening.

Bactericidal Study[4]

Introduction

The primary objective of this study was to evaluate the bactericidal activity of the PVP-I in Surgiphor™ Surgical Wound Irrigation System alongside wound irrigants Bactisure™ and Irrisept® (0.05% CHG) on common nosocomial gram-positive and gram-negative bacteria.

Methods

The study was based on a method derived from the European Standard EN 1040:2005. Samples of Surgiphor™, Bactisure™ (0.13% benzalkonium chloride, 10% ethyl alcohol, 5.9% acetic acid, and 3% sodium acetate in purified water), and Irrisept® (0.05% chlorhexidine gluconate in sterile water, USP [99.95%]) were each inoculated against 12 clinically relevant gram-positive (6) and gram-negative (6) microorganisms. After 1-minute and 5-minute contact times, microorganisms were recovered from each test article in a neutralizing solution to inactivate test-article bactericidal properties. Testing was performed in triplicate, and all agar plating was performed in duplicate.
The mean $\log_{10}$ CFU/mL reductions from each challenge microorganism were determined after exposure at the specified contact times.

Results

After both contact times, Surgiphor™, Bactisure™ and Irrisept® produced a complete kill of 9, 11, and 3 of the 12 challenge microorganisms, respectively (Table 1). Surgiphor™ and Irrisept® demonstrated limited activity against the two *Enterococcus* species. Surgiphor™ produced a complete kill of 9 of the 12 microorganisms at both 1-minute and 5-minute contact times, with the exception of *Enterococcus hirae*, *Enterococcus faecalis*, and *Clostridioides difficile*. Bactisure™ produced a complete kill of all microorganisms at both contact times, except for *C. difficile*. Irrisept® produced a complete kill of three gram-negative microorganisms (*Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) at the 1-minute contact time and a complete kill of five gram-negative microorganisms (*E. coli, K. pneumoniae, P. aeruginosa, Enterobacter cloacae,* and *Acinetobacter baumannii*) at the 5-minute contact time. However, activity against the remaining gram-negative microorganism, *Ralstonia pickettii* was minimal (≤1 $\log_{10}$ reduction). The activity of Irrisept® against gram-positive microorganisms, *E. hirae* and *E. faecalis* was minimal (<1 $\log_{10}$ reduction) at both time points. The activity of Irrisept® for *S. aureus* and *Staphylococcus epidermidis* was significant (>4 $\log_{10}$ reduction) at the 5-minute contact time. None of the products tested had significant activity against *C. difficile*, a strict anaerobic organism, at either contact time.

Conclusions

Surgiphor™ provided 99.99% reduction in recovered living bacteria (4 $\log_{10}$) when tested against 9 of the 12 common nosocomial bacteria after 1 minute and 5 minute contact times in an *in vitro* time kill assay.*

*Product should only be used within 24 hours of opening per instructions for use.

Bactericidal Study (cont.)[4]

Table 1: PVP-I bactericidal activity on common nosocomial bacteria.

Bacteria	Challenge Titer (Log 10 CFU/mL)	Contact Time	Mean Log_{10} Reduction (Percent Reduction) BD® Surgiphor™	Bactisure™	Irrisept®
Acinetobacter baumannii ATCC® 19606™	6.86	1 minute	≥ 4.72 (≥ 99.9981%)	≥ 4.72 (≥ 99.9981%)	3.03 (99.8917%)
		5 minutes	≥ 4.72 (≥ 99.9981%)	≥ 4.72 (≥ 99.9981%)	≥ 4.72 (≥ 99.9981%)
Clostridioides difficile ATCC® 9689™	6.15	1 minute	≤ 2.32 (≤ 99.4619%)	≤ 2.63 (≤ 99.7643%)	≤ 2.63 (≤ 99.7643%)
		5 minutes	≤ 2.63 (≤ 99.7643%)	≤ 2.63 (≤ 99.7643%)	≤ 2.63 (≤ 99.7643%)
Cutibacterium acnes ATCC® 6919™ (f.k.a. *Propionibacterium acnes*)	7.91	1 minute	≥ 5.76 (≥ 99.9998%)	≥ 5.76 (≥ 99.9998%)	2.33 (99.4720%)
		5 minutes	≥ 5.76 (≥ 99.9998%)	≥ 5.76 (≥ 99.9998%)	≤ 4.39 (≤ 99.9959%)
Enterobacter cloacae ATCC® 13047™	7.84	1 minute	≥ 5.70 (≥ 99.9998%)	≥ 5.70 (≥ 99.9998%)	5.51 (99.9997%)
		5 minutes	≥ 5.70 (≥ 99.9998%)	≥ 5.70 (≥ 99.9998%)	≥ 5.70 (≥ 99.9998%)
Enterococcus faecalis ATCC® 29212™	7.97	1 minute	0.27 (46.1676%)	≥ 5.82 (≥ 99.9999%)	0.08 (17.2906%)
		5 minutes	1.21 (93.8146%)	≥ 5.82 (≥ 99.9999%)	0.28 (46.3458%)
Enterococcus hirae ATCC® 10541™	7.82	1 minute	0.26 (44.4444%)	≥ 5.67 (≥ 99.9998%)	0.01 (1.0101%)
		5 minutes	0.69 (78.9899%)	≥ 5.67 (≥ 99.9998%)	0.23 (40.4040%)
Escherichia coli K12 ATCC® 10798™	7.79	1 minute	≥ 5.64 (≥ 99.9998%)	≥ 5.64 (≥ 99.9998%)	≥ 5.64 (≥ 99.9998%)
		5 minutes	≥ 5.64 (≥ 99.9998%)	≥ 5.64 (≥ 99.9998%)	≥ 5.64 (≥ 99.9998%)
Klebsiella pneumoniae ATCC® 13883™	7.76	1 minute	≥ 5.61 (≥ 99.9998%)	≥ 5.61 (≥ 99.9998%)	≥ 5.61 (≥ 99.9998%)
		5 minutes	≥ 5.61 (≥ 99.9998%)	≥ 5.61 (≥ 99.9998%)	≥ 5.61 (≥ 99.9998%)
Pseudomonas aeruginosa ATCC® 15442™	7.68	1 minute	≥ 5.53 (≥ 99.9997%)	≥ 5.53 (≥ 99.9997%)	≥ 5.53 (≥ 99.9997%)
		5 minutes	≥ 5.53 (≥ 99.9997%)	≥ 5.53 (≥ 99.9997%)	≥ 5.53 (≥ 99.9997%)
Ralstonia pickettii ATCC® 700591™	7.91	1 minute	≥ 5.76 (≥ 99.9998%)	≥ 5.76 (≥ 99.9998%)	0.07 (14.6091%)
		5 minutes	≥ 5.76 (≥ 99.9998%)	≥ 5.76 (≥ 99.9998%)	1.05 (80.9877%)
Staphylococcus aureus ATCC® 6538™	7.87	1 minute	≥ 5.73 (≥ 99.9998%)	≥ 5.73 (≥ 99.9998%)	≤ 3.09 (≤ 99.7614%)
		5 minutes	≥ 5.73 (≥ 99.9998%)	≥ 5.73 (≥ 99.9998%)	4.41 (99.9960%)
Staphylococcus epidermidis ATCC® 12228™	7.63	1 minute	≥ 5.48 (≥ 99.9997%)	≥ 5.48 (≥ 99.9997%)	1.83 (98.5059%)
		5 minutes	≥ 5.48 (≥ 99.9997%)	≥ 5.48 (≥ 99.9997%)	4.47 (99.9966%)

Fungicidal Study[5]

Introduction

The primary objective of this study was to evaluate fungicidal activity of the PVP-I in the Surgiphor™ solution compared to wound irrigants Bactisure™ and Irrisept® (0.05% CHG) on common nosocomial fungi microorganisms.

Methods

The *in vitro* evaluation of the test products was based on a method derived from European Standard EN 1275:2005. Samples of Surgiphor™ solution, Bactisure™, and Irrisept® were inoculated against *A. brasiliensis* ATCC® 16404™ with contact times of 15, 30, or 60 minutes and *Candida albicans* ATCC® 10231™ and *Candida auris* AR# 0383 with contact times of 1-minute or 5-minutes. The mean $\log_{10}$ reductions from the initial population of each challenge microorganism were determined following exposure to each test product for the specified contact times.

Results

Surgiphor™ demonstrated a time-dependent reduction in $\log_{10}$ CFU for *A. brasiliensis* with a near-complete kill by 60 minutes and complete kill for the two *Candida* strains at all contact times (Table 2). Bactisure™ produced a complete kill of *A. brasiliensis* and the two *Candida* species at all contact times. Irrisept® produced less than a 2.67 $\log_{10}$ reduction of *A. brasiliensis* at the 60-minute contact time, compared to the complete kill for Bactisure™ (≥4.71 $\log_{10}$ reduction) and near-complete kill for Surgiphor™ (4.61 $\log_{10}$ reduction). The activity of Irrisept® against the two *Candida* species showed a $\log_{10}$ reduction of 4.17 and 3.46 for *C. albicans* and *C. auris*, respectively, after a 5-minute contact time.

Conclusions

Surgiphor™ solution provided 99.99% reduction in recovered living fungi (4 $\log_{10}$) when tested against *C. albicans* and *C. auris* at 1 minute and *A. brasiliensis* at 30 minutes.*

Table 2: PVP-I fungicidal activity on common nosocomial fungal microorganisms.

Fungi	Challenge Titer ($\log_{10}$ CFU/mL)	Contact Time	Mean $\log_{10}$ Reduction (Percent Reduction)		
			BD® Surgiphor™	Bactisure™	Irrisept®
Aspergillus brasiliensis ATCC® 16404™	6.86	15 minutes	2.13 (98.9653%)	≥ 4.71 (≥ 99.9981%)	2.08 (99.0671%)
		30 minutes	4.14 (99.9921%)	≥ 4.71 (≥ 99.9981%)	2.61 (99.7433%)
		60 minutes	4.61 (99.9975%)	≥ 4.71 (≥ 99.9981%)	2.67 (99.7824%)
Candida albicans ATCC® 10231™	7.00	1 minute	≥ 4.86 (≥ 99.9986%)	4.79 (99.9983%)	2.00 (98.9900%)
		5 minutes	≥ 4.86 (≥ 99.9986%)	≥ 4.86 (≥ 99.9986%)	4.17 (99.9932%)
Candida auris AR# 0383	7.39	1 minute	≥ 5.24 (≥ 99.9994%)	≥ 5.24 (≥ 99.9994%)	0.64 (77.1894%)
		5 minutes	≥ 5.24 (≥ 99.9994%)	≥ 5.24 (≥ 99.9994%)	3.46 (99.9655%)

*Product should only be used within 24 hours of opening per instructions for use.

In vitro Time-Kill Study[6]

Introduction

An *in vitro* assay was performed to determine time to kill for the PVP-I in Surgiphor™ solution as compared to the CHG preservative in Irrisept® (0.05% CHG).

Methods

Surgiphor™ and Irrisept® were each inoculated against methicillin-resistant *Staphylococcus aureus* ATCC® 33591™ (MRSA) with and without the addition of 5% fetal bovine serum (FBS). FBS serves as a standard interfering substance used to simulate a "dirty" testing condition. Samples from each test article were taken, neutralized, and plated on tryptic soy agar plates after 15-, 30-, 60-, and 300-second contact times. Test article inoculations were performed in triplicate, and all agar plating was performed in duplicate. Mean $\log_{10}$ CFU/mL reduction was calculated following plate incubation and subsequent colony enumeration. Additional testing was performed with Surgiphor™ solution against *Escherichia coli* ATCC® 25922™.

Results

Surgiphor™ produced a complete kill against MRSA after 15-, 60-, and 300-second contact times in the absence of FBS and a complete kill at all contact times in the presence of 5% FBS (Figure 2). In the absence of FBS, Surgiphor™ produced a mean log reduction of 5.68 after 30 seconds of contact time resulting in a greater than 99.999% reduction in MRSA. Irrisept® had increasing amounts of MRSA killing at each tested time point, but only produced a complete kill against MRSA in the presence of 5% FBS after a 300-second contact time. Surgiphor™ solution produced a complete kill for *E. coli* at all test timepoints and conditions.

Conclusions

Surgiphor™ solution provided greater than 99.9999% reduction in methicillin-resistant *Staphylococcus aureus* and *E. coli* (>6 $\log_{10}$) after a 15-second contact time.*

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Organism	Challenge Titer ($\log_{10}$ CFU/mL)	Contact Time	Mean $\log_{10}$ Reduction			
			BD® Surgiphor™		Irrisept®	
			0% FBS	5% FBS	0% FBS	5% FBS
Methicillin-resistant *Staphylococcus aureus* ATCC® 33591™	8-9	15 seconds	6.58*	6.58*	0.92	0.87
		30 seconds	5.68	6.58*	0.83	1.46
		60 seconds	6.58*	6.58*	1.21	3.81
		300 seconds	6.58*	6.58*	4.16	6.58*
Escherichia Coli ATCC® 25922™	8-9	15 seconds	7.11*	7.11*	-	-
		30 seconds	7.11*	7.11*	-	-
		60 seconds	7.11*	7.11*	-	-
		300 seconds	7.11*	7.11*	-	-

B Log Reduction over time

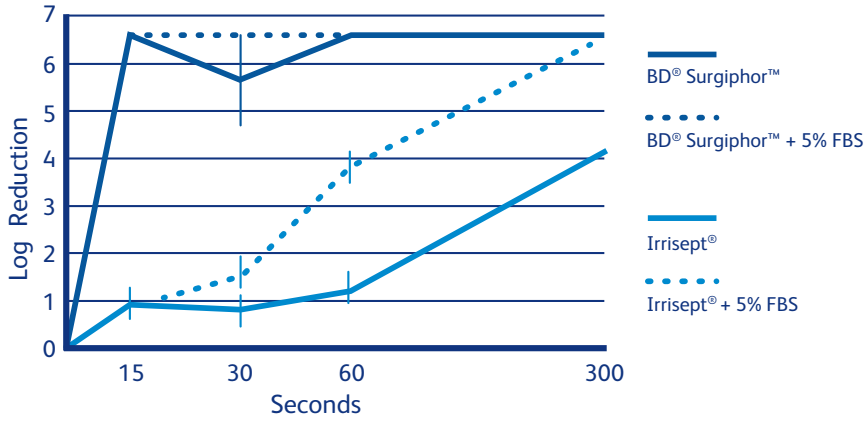


Figure 2: *In vitro* time kill assay. (A) MRSA and *E. coli* challenge titer, mean $\log_{10}$ reductions, and (B) rates of *in vitro* killing for Surgiphor™ and Irrisept® solutions with and without 5% FBS. An asterisk (*) denotes a complete kill and (-) denotes not tested in this study.

*Product should only be used within 24 hours of opening per instructions for use.

Terminal Sterilization[7]

Introduction

The establishment of a Sterility Assurance Level (SAL) provides confidence in a sterilization process' capability. The ability to provide a defined SAL differs between aseptic processing and terminal sterilization processes in that aseptic processing does not typically use SAL to describe the capability of the aseptic process, whereas terminal sterilization does allow for the establishment of an SAL. This is based on a validated sterilization process which has followed internationally recognized sterilization standards. The terminal sterilization process was validated to establish the minimum dose level needed to ensure a sterility assurance level of 10^{-6} for the gamma sterilization process used for Surgiphor™ Surgical Wound Irrigation System.

Methods

Gamma sterilization dose was determined, tested, and validated following the requirements defined in internationally recognized standards ANSI/AAMI/ISO TIR13004, ANSI/AAMI/ISO 11137-1, and ANSI/AAMI/ISO 11137-2. The contents of the irrigation system were subjected to a verification dose established based on product bioburden and following the defined target dose established in ANSI/AAMI/ISO TIR13004. Following exposure of samples to the verification dose, the product was sterility tested according to USP <71>.

Results

Sterility testing of the samples revealed none of the test samples exposed to the verification dose had viable microbes present which substantiated an SAL of 10^{-1}. Based on those results, a minimum sterilization dose for routine processing was established and deemed acceptable to reach the predetermined acceptance criterion of sterility assurance level 10^{-6}.

Conclusions

Surgiphor™ Surgical Wound Irrigation System includes a terminally sterilized solution with a sterility assurance level (SAL) of $10^{\text{^-6}}$, the same level required for injectable products and implantable devices.

Safety Profile

ISO Standardized Cytotoxicity Testing[8]

Introduction

The primary objective of this study was to evaluate the cytotoxicity of Surgiphor™ and Irrisept® (0.05% CHG).

Methods

Surgiphor™ solution and Irrisept® were tested for cytotoxicity by Minimal Essential Media Elution testing. The study was performed following ANSI/AAMI/ISO 10993-5 standard for biological evaluation of medical devices, Part 5: tests for *in vitro* cytotoxicity. Briefly, mouse fibroblasts cell-line L-929 (ATCC® CCL-1™) were incubated in triplicate with undiluted and increasing dilutions (1:2, 1:4, 1:8, and 1:16) of Surgiphor™ solution and Irrisept® in culture medium. After 48 hours, fibroblasts were examined microscopically and scored based on the degree of cellular destruction.†

Results

In accordance with USP <87> requirements, the test articles receive a passing score if the cytotoxicity score is not greater than 2, which equates with mild reactivity. Surgiphor™ was found to be cytotoxic undiluted and at 1:2 and 1:4 dilutions and non-cytotoxic at 1:8 and 1:16 dilutions (grade 2 and grade 1, respectively). Irrisept® was found to be cytotoxic at all tested dilutions (grade 4).

Cytotoxicity Scores

Dilution	Surgiphor™	Irrisept®
Neat	4	4
1:2	4	4
1:4	3	4
1:8	2	4
1:16	1	4

Pass

Fail

Conclusions

Surgiphor™ solution exhibited no cytotoxicity at 1:8 and 1:16 dilution following 48 hours of incubation.

Dermal Irritation Study [9]

Introduction

The primary objective of this study was to test for dermal irritation reactions to the Surgiphor™ solution and Irrisept® (0.05% CHG).

Methods

The study was performed following ISO 10993-10 Standards for Biological Evaluation of Medical Devices, part 10: Tests for Irritation and Skin Sensitization. A total of five sequential 0.2 mL samples of Surgiphor™ solution and normal saline control were injected intracutaneously on either side of the spine of three young, albino, female rabbits. Six additional rabbits were challenged using the same methodology for Irrisept®. Injection sites were rated for gross evidence of erythema and edema after 24, 48, and 72 hours using the Draize dermal irritation scoring system.

Results

Surgiphor™ solution elicited an average dermal irritation score of 3.6. All animals receiving Surgiphor™ injections had a dark red discoloration at the center of injection sites observed throughout the duration of the study. In comparison, Irrisept also elicited irritation with a score of 3.1 using identical test methodology.

Conclusion

Surgiphor™ and Irrisept exhibited irritation when intracutaneously injected in a rabbit model of dermal irritation®.*

† Referenced products are not intended to remain in wound beyond indication.
*Surgiphor™ solution is not indicated for injection or infusion.

Repeat-Insult Patch Test on Healthy Human Skin[10]

Introduction

The primary objective of this study was to determine the potential of Surgiphor™ to elicit dermal irritation and/or induce product sensitization following repeated patch applications in humans.

Methods

A semi-occlusive patch dosed with Surgiphor™ solution was applied to the same spot on healthy human volunteers' upper backs 3 times per week for 3 weeks to determine irritation. Application sites were evaluated and scored using a 0 to 4 dermal-irritation scoring system: 0 (no irritation), 1 (mild erythema and edema), 2 (well-defined erythema and edema), 3 (severe erythema and edema), or 4 (erythema and edema with vesiculations). Following a rest period, a challenge patch dosed with Surgiphor™ solution was applied to a virgin site on the lower back. Subjects returned for additional dermal evaluations 24, 48, 72, and 96 hours after challenge-patch application to determine sensitization to the test product.

Results

Fifty volunteers completed the repeat-insult irritation patch testing portion of the study. Surgiphor™ solution did not demonstrate a potential for eliciting dermal irritation in any of the tested 50 subjects, scoring zeros on all evaluated sites and time points. Forty-one subjects went on to receive a challenge patch dosed with Surgiphor™ solution following the rest period. Surgiphor™ solution did not demonstrate a potential for inducing dermal sensitization in any of the 41 tested subjects, scoring zeros on all evaluated sites and time points.

Conclusions

Surgiphor™ did not elicit an irritation or sensitization response when applied to the skin in a population of healthy human volunteers.

Wound-Healing Study[11]

Introduction

The purpose of this study was to evaluate wound-healing potential following the application of Surgiphor™ solution, Irrisept® (0.05% CHG), and sterile normal saline control on full-thickness dermal wounds in swine.

Pig skin is structurally similar to human epidermal thickness and dermal/epidermal thickness ratios. Pig skin wounds heal primarily by reepithelialization rather than contraction, so they are especially useful in studying wound healing and burn lesions.

Methods

Twelve 2 cm full-thickness wounds were surgically created on the backs of six animals. Each animal had four wounds treated with each of the test articles immediately following wound creation. Wounds treated with Surgiphor™ were irrigated with Surgiphor™ solution followed immediately by a saline rinse in accordance with the product instructions for use. Wounds irrigated with Irrisept® were followed by a 1-minute wait time and then rinsed with sterile saline solution in accordance with the product instructions for use. Wound-healing controls received only sterile saline irrigation. Dressings were applied to each wound site, and wounds were evaluated, measured, and photographed twice weekly. Wound healing was compared between the three test articles at 13 and 21 days after application by wound measurement and histological processing and microscopic evaluation by a pathologist.

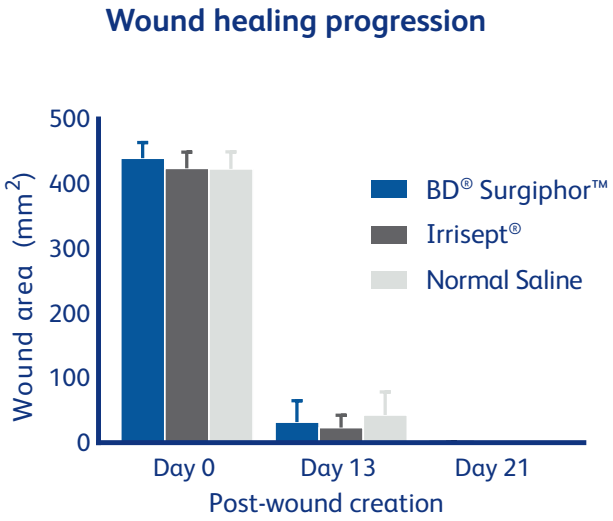
Results

No significant microscopic differences were found in the wound site or in the adjacent tissue between the three test articles at 13 and 21 days after wound creation. Wounds irrigated with Surgiphor™ solution followed a normal macroscopic healing progression, and Surgiphor™ was considered equivalent to Irrisept® and normal saline control at all intervals (Figure 3).

Conclusion

Surgically created wounds irrigated with Surgiphor™ solution healed similarly to wounds irrigated with sterile normal saline control in a population of swine.

Figure 3: Wound-healing progression after surgical creation for wounds irrigated with Surgiphor™, Irrisept®, and sterile normal saline control. Wound area was determined from an average of four replicate wounds from three animals per time point.



Mechanical Action Testing[12]

Introduction

The primary objective of this study is to evaluate the output pressure of the Surgiphor solution and assess variability in pressure results from compression of containers like in Surgiphor™ Surgical Wound Irrigation System.

Methods

The Surgiphor™ bottle designs were tested.

A predetermined acceptance criterion for output pressure was set at 4.0 – 15.0 psi per the original Agency for Health Care Policy and Research (AHCPR) guidelines for safe and effective wound irrigation.

Three test subjects each compressed appropriately filled (475 mL ± 25]) containers (n=30; 10 from each of the three production lots) and digitally recorded the maximum output pressure observed by using the electronic display of a pressure gauge.

An average value of maximum output pressure was used to compare overall results among subjects.

Results

Output pressure (in psi) of irrigation fluid calculated from each of the three test subjects:

Lowest	7.8	9.2	9.9
Average	9.4	9.6	11.1
Highest	10.7	10.0	11.8

The overall average output pressure of irrigation fluid of all test runs for the three-test-subject group was 10.0 psi ± 1.5.

Conclusions

In a preclinical study, the average output pressure of irrigation fluid from compression of Surgiphor™ containers was 10.0 psi, which is within the AHCPR recommended guidelines (4.0 – 15.0 psi) for safe and effective wound irrigation.

Abraded Human Skin Pyrogenicity Test[13]

Introduction

The purpose of this study is to evaluate the pyrogenic response of Povidone-Iodine 0.5% Surgiphor solution when applied to abraded human skin for 24 hours.

Methods

A baseline temperature was calculated from three oral measurements over the course of 1 hour before skin abrasion.

Skin abrasion was performed on the upper nondominant arm of volunteer test subjects (n=33) 19 – 54 years of age by using a standardized stratum corneum stripping method with D-Squame adhesive discs. After abrasion, 200 µL of BD Surgiphor Solution was applied by using Finn Chamber on Scanpor tape.

Oral temperature change was measured and compared with baseline temperatures at 15, 30 and 45 minutes and at 1 and 24 hours after application. A temperature increase ≤2.5 °F above each subject's baseline temperature over 24 hours was considered a negative pyrogenic response.

A board-certified dermatologist visually assessed skin responses for erythema, edema or dryness, and subjects were queried for adverse events (AEs) as part of the safety evaluation.

Results

No subjects (0/33) experienced a pyrogenic response to the Surgiphor™ Solution. Mean oral temperatures remained stable (≤2.5 °F difference) 24 hours after application.

No serious AEs were reported during the study. One subject (1/33) reported an AE of mild intermittent itching.

No subjects experienced edema or dryness during the study. Two subjects experienced erythema at 24 hours: One case was categorized as barely perceptible; the other, as slight.

Conclusions

No subjects (0/33) in a clinical study had a pyrogenic response to PVP-I 0.5% Surgiphor solution.

Acute System Toxicity Testing[14]

Introduction

Investigate the Surgiphor™ solution for signs of acute systemic toxicity, as outlined in the ISO 10993-11 guidance on systemic toxicity.

Methods

Albino Swiss mice *(Mus musculus)* receiving a single intraperitoneal dose of the Surgiphor solution at

20 mL per kilogram of body weight (n=5) or of saline at 50 mL per kilogram of body weight (n=5) were examined for abnormal clinical signs of toxicity (i.e., convulsion, prostration or body weight loss >10%) during the 72-hour test period vs control mice treated with normal saline (n=5).

If none of the mice injected with the test articles showed significantly greater biologic reaction vs the control mice, then the results were considered negative.

Death in ≥2 mice or other toxic signs in ≥3 mice were interpreted as significant biologic reactions.

Results

None of the mice injected with the test articles displayed signs of acute systemic toxicity during the 72-hour test period.

All mice were alive at the end of the test period, and body weight changes were within acceptable parameters.

Conclusions

Preclinical research in mice demonstrated that injection of the Surgiphor™ solution produced no clinical signs (i.e., convulsion, prostration or body weight loss >10%) that would indicate acute system toxicity. Surgiphor™ demonstrated similar wound healing properties when compared to sterile normal saline.[b]

Product Description: BD® Surgiphor™ Surgical Wound Irrigation System is a surgical wound irrigation medical device containing a ready-to-use sterile povidone-iodine (PVP-I) solution (Surgiphor™ Solution). Surgiphor™ Surgical Wound Irrigation System is primarily intended to mechanically loosen and rinse debris and foreign materials, including microorganisms from the surgical wound. The device consists of a screw cap and a sealed bottle containing 0.5% w/w PVP-I in a solution of phosphate-buffered saline, potassium iodide and Vitamin E TPGS. As an ancillary action, PVP-I serves as a preservative to protect the solution from microbial growth during use, whilst also reducing the bacterial load within the wound by killing the microorganisms that could lead to infection. Surgiphor™ Surgical Wound Irrigation System is intended to be used by healthcare practitioners, in a healthcare environment, in a general population of patients, excluding neonates, where surgical wound irrigation is appropriate. No specific training is required prior to using Surgiphor™ Surgical Wound Irrigation System. **Intended Purpose:** Surgiphor™ Surgical Wound Irrigation System is intended to mechanically loosen and remove debris and foreign materials, including microorganisms from the surgical wound. **Contraindications:** Do not use Surgiphor™ Surgical Wound Irrigation System in patients with history of allergic reactions to Surgiphor™ Solution components. Do not combine Surgiphor™ Surgical Wound Irrigation System with antiseptic solutions, such as octenidine due to potential reactions. Do not use Surgiphor™ Surgical Wound Irrigation System in neonates (less than 28 days after birth). **Warnings:** Do not use or mix Surgiphor™ Solution with antimicrobial cleansers, soaps, lotions, or ointments. Do not use Surgiphor™ Surgical Wound Irrigation System if the packaging is damaged or if the seal integrity is compromised. Surgiphor™ Surgical Wound Irrigation System is for single use only. Reprocessing or re-sterilization may compromise the integrity of the device. Reuse on more than a single patient may create a risk of contamination of the device and/or cause patient infection or cross-infection, including but not limited to, the transmission of infectious disease(s) from one patient to another. Surgiphor™ Solution may cause allergic reactions such as anaphylactic shock, rash, or skin irritation in patients with iodine allergy. Discontinue use immediately if irritation or an allergic reaction occurs. Do not use Surgiphor™ Solution for injection or infusion. Do not swallow Surgiphor™ Solution. Do not use and avoid contact with eyes and ear canals due to potential visual and ear (ototoxicity) impairment. Do not use more than 24 hours after puncturing the bottle. **Precautions:** May cause a temporary irritation and/or burning sensation on exposed skin in very rare cases. Single use only. Do not use past the expiration date. Not for at-home use. There is no evidence of mutagenic or embryo toxicity associated with the ingredients of the product. Due to lack of relevant clinical trials and clinical experience with pregnant or with breast-feeding women, Surgiphor™ Surgical Wound Irrigation System should only be used after a Health Care Practitioner's medical benefit-risk assessment in these patients. **Residual Risks and Undesirable Side Effects:** Allergic reaction is a potential residual risk that may occur with the use of Surgiphor™ Surgical Wound Irrigation System. **Please consult product insert for complete indications, contraindications, warnings, precautions, safety information and instructions for use.**

^Surgical wound was in an simulated animal model
*Product should be used within 24 hours of opening.
a. Irritation and cytotoxicity testing was conducted in accordance with ISO 10993 series standards.
b. BD Surgiphor™ is not indicated for injection or infusion.

1. BD data on file. REF-81425 **2.** BD data on file. REF-79641 **3.** BD data on file. REF-20098 **4.** BD data on file. REF-27478 **5.** BD data on file. REF-27477 **6.** BD data on file. REF-20103 **7.** BD data on file. REF-20100 **8.** BD data on file. REF-20101 **9.** BD data on file. REF-20102 **10.** BD data on file. REF-27853 **11.** BD data on file. REF-27496 **12.** BD data on file. REF-20099 **13.** BD data on file. REF-87000 **14.** BD data on file. REF-87001

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