



## *Performance Summary*



**Kimberly-Clark**

*Trusted Clinical Solutions\**

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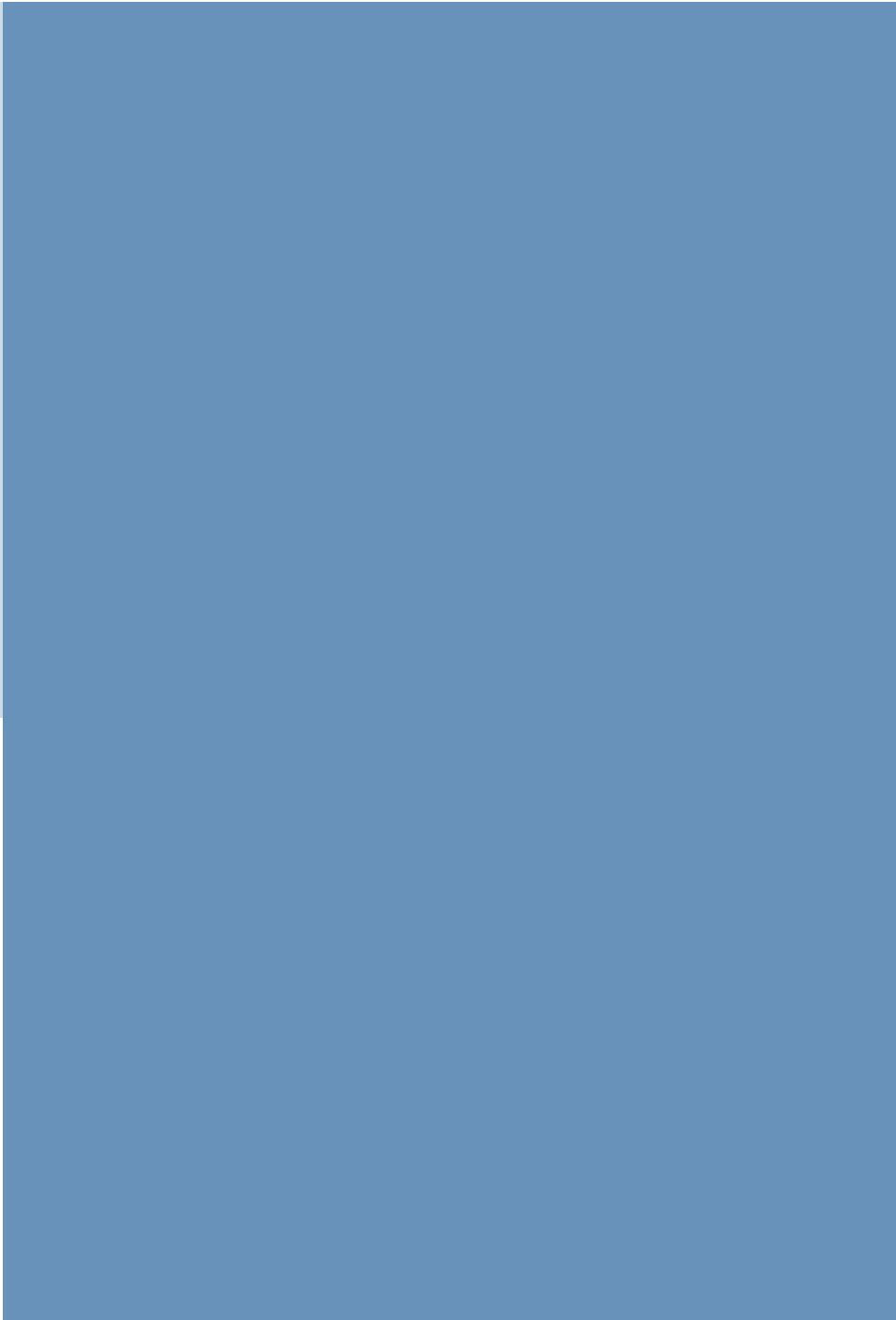
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**KIMBERLY-CLARK\* INTEGUSEAL\***  
**Microbial Sealant**

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## **1.0 Introduction**

### **1.1 HAI/SSI Summary**

Incisionally-based surgical site infections (SSIs) are estimated to account for 25 - 38% of all nosocomial infections among surgical patients.<sup>1,2</sup> It is estimated that 2 – 5% of surgical patients will develop a SSI.<sup>2</sup> As a result of these infections, length of patient care is extended and overall cost of care increases. The length of hospitalization is prolonged by an average of 7 days and the charges associated with each individual SSI range from \$3,000 - \$26,000.<sup>2,3</sup> These infections also significantly increase the risk of more serious complications and potential death of the patient.

Microbial contamination of the surgical site is a necessary precursor of a SSI. Studies have shown the rate of SSIs can be associated with the amount of bacteria present intra-operatively; 1-5% of clean surgeries performed will result in an infection and 10-20% of clean-contaminated surgeries will develop a SSI.<sup>4</sup> While a minority of the contamination sources are exogenous (surgical personnel, operating room environment, and tools, instruments and materials brought into the operating room), the source of pathogens for most SSIs, in the absence of damage to hollow viscera, is the endogenous flora of the patient's skin.<sup>5</sup> When skin is incised, the exposed tissues are at risk for contamination by endogenous skin flora.<sup>6</sup>

A number of preventive measures have been proposed to reduce the risk of SSIs<sup>1</sup>, including patient and skin preparation, surgical team hand/ forearm antisepsis, antimicrobial prophylaxis, operative room management, asepsis and surgical technique, and postoperative incision care. Of the skin preparation products, iodophors, alcohol-containing products, and chlorhexidine gluconate are the most common. In some cases, an antiseptic-impregnated adhesive incise drape is applied over the skin preparation product. While all of these applications act as broad spectrum topical antiseptics, each has its disadvantages and, despite rigorous disinfection, ultimately some skin bacteria continue to survive.<sup>7</sup> These surviving endogenous pathogens can be transferred into the surgical incision by irrigation fluids, gloves, instruments, sponges, or implants, and could cause a surgical site infection.

INTEGUSEAL\* has been developed to bond to the skin surface, immobilizing the bacteria which survive the application of conventional surgical skin preparation products.

## 1.2 Skin Flora

Despite refined surgical techniques, environmental changes in the operating room, and the use of preventive antibiotics, infection at the surgical site remains the second most frequent adverse event occurring to hospitalized patients and is a major source of morbidity and mortality following operating procedures.<sup>8</sup>

Wound contamination by skin flora is a key factor in the development of surgical site infections.<sup>9</sup> Because skin can never be completely sterilized,<sup>10</sup> incised skin exposes tissues to surviving endogenous skin flora thereby increasing the risk for contamination.

### **Skin Flora is the number one Cause of SSI**

The Centers for Disease Control (CDC) states that “for most SSIs, the source of pathogens is the endogenous flora of the patient’s skin, mucous membranes, or hollow viscera.”<sup>1</sup> In surgical procedures that do not involve entry into the hollow viscera or the mucous membranes, the patient’s own endogenous skin flora is the primary source of infection. When skin is incised, there is a risk for tissue exposure to endogenous skin flora; usually the organisms are aerobic gram-positive cocci.<sup>1</sup>

The CDC estimates the risk for surgical site infection according to three distinct variables: 1) the dose of bacterial contamination, 2) the virulence of contaminating bacteria, and 3) the resistance of the host. This relationship is conceptualized with the following equation from Mangram et al:<sup>1</sup>

$$\frac{\text{Dose of bacterial contamination} \times \text{Virulence}}{\text{Resistance of host patient}} = \text{Risk of surgical site infection}$$

Local contamination of a clean surgical wound was noted by Altemeier et al. who reported that “significant contamination may be carried into the wound from the skin of the patient, particularly when the skin is diseased or inadequately prepared preoperatively.”<sup>5</sup> Typical preoperative skin preparations involve applying a solution of chlorhexidine gluconate, povidone iodine, isopropyl alcohol, or a combination thereof. Thus, by inadequately performing the basic step of skin preparation, the risk of SSI increases. Moreover, as it is impossible to completely decontaminate the skin, the risk of wound contamination and subsequent SSI is always present, even under optimal conditions.

The source of surgical site infections is a complex issue and may originate from exogenous sources, endogenous sources, or both. To add to this complexity, the development of a surgical site infection is related to an individual's overall level of health, the immediate environment, the surgical situation (e.g. length of surgery and surgery type), and the presence of pre-existing conditions. Even in clean surgical procedures performed on healthy individuals, skin flora continues to be a major contributor to surgical site infections.

### **1.3 Formulation/Product Description**

Kimberly-Clark INTEGUSEAL\* Microbial Sealant (INTEGUSEAL\*) is a sterile film-forming cyanoacrylate-based product provided in a ready-to-use applicator. INTEGUSEAL\* is intended to be applied on the skin over commonly used surgical skin preparation products prior to a surgical incision. Upon polymerization, INTEGUSEAL\* bonds to the skin and immobilizes the bacteria which survive the application of antimicrobial surgical skin preparation products.<sup>2</sup> INTEGUSEAL\* can be used in combination with surgical skin preparations including iodophors and 2% chlorhexidine gluconate with alcohol. INTEGUSEAL\* is intended to remain on the skin following the completion of the surgical procedure without requiring removal. The incision is closed and dressed according to existing standards of care and, following surgery, INTEGUSEAL\* naturally sloughs off the skin over the course of a few days.

#### **Device Description**

INTEGUSEAL\* is a blue/violet-colored, free flowing liquid cyanoacrylate contained in a glass ampule. The INTEGUSEAL\* formulation consists of the monomer n-butyl cyanoacrylate, plasticizer, stabilizers, and color. INTEGUSEAL is contained within a glass ampule or ampules housed within a nylon applicator. The glass ampule(s) is broken by pushing the rear of the plastic applicator forward. Once broken, the INTEGUSEAL\* flows to the foam tip of the applicator and is ready to be applied to the patient. INTEGUSEAL\* is provided in two dispensing volumes: Model IS100 and Model IS200 for coverage of surgical sites up to approximately 100 in<sup>2</sup> (25cm x 25cm) and 200 in<sup>2</sup> (50cm x 25cm) respectively. The same applicator design is used to dispense both volumes; each model is distinguishable by color and model number.

INTEGUSEAL\* is applied to the surgical incision site by pressing the foam tip gently on the skin. Application is similar to painting with a foam pad to deposit a layer of INTEGUSEAL\* on the skin.

## 1.4 References

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## 2.0 Mechanism of Action

### 2.1 Microbial Immobilization

Upon contact with the pre-operative prepped skin, the moisture and proteins present in the stratum corneum trigger product polymerization. Subsequently, the liquid monomer polymerizes into a solid thin film sealed to the surface of the skin. This molecular bonding process provides a flexible film over the skin surface, including hair follicles and sweat glands, immobilizing the bacteria which survive the application of conventional surgical skin preparation products. In summary, the mode of action, mechanical immobilization, achieves the intended use of reducing the risk of skin flora contamination during a surgical procedure.

### 2.2 Works With All Bacteria

INTEGUSEAL\* reduces skin flora contamination by physically immobilizing microorganisms and not by antimicrobial activity. Because the mechanism of action is different from that of antimicrobials, INTEGUSEAL\* is equally effective at immobilizing all types of bacteria without regard to antimicrobial susceptibility. In fact, INTEGUSEAL\* has been shown to significantly immobilize three different pathogenic and one non-pathogenic bacteria (Methicillin Resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Staphylococcus epidermidis*, and *Bacillus stearothermophilus*, respectively). These claims have been tested using *in vitro* and *in vivo* test methods/models at four separate test facilities.

### 2.3 Microbial Barrier

An *in vitro* study was conducted to evaluate the performance of INTEGUSEAL\* as an effective barrier against the penetration of microorganisms.

#### **Methods:**

A polymerized INTEGUSEAL\* film, approximately 1 mm thick, was placed on an agar surface and a bacterial inoculum (100 µ) was applied to each film. The Agar Petri plates containing microbiological growth medium with a pH indicator changed color when in contact with the acid byproducts indicative of microbial growth. The chosen media types were those that afforded maximal color change for each microbe studied to ensure the sensitivity of the assay. The resulting plates were incubated and the color of the media was recorded after 24, 48, and 72 hours of incubation.

#### **Results:**

After 72 hours of incubation, there was no evidence of microbial growth on any of the plates with INTEGUSEAL\*. Therefore, there was no microbial penetration through the INTEGUSEAL\* film.

## KIMBERLY-CLARK\* INTEGU SEAL\* Microbial Sealant

Code	Test Organism	Challenge population (CFU/mL)	Number tested	Number Showing Penetration After 72 Hours	% Penetration
INTEGU SEAL*	<i>S. epidermidis</i>	$1 \times 10^6$	3	0	0
INTEGU SEAL*	<i>E. coli</i>	$1 \times 10^6$	3	0	0
INTEGU SEAL*	<i>S. aureus</i>	$1 \times 10^6$	3	0	0
INTEGU SEAL*	<i>P. aeruginosa</i>	$1 \times 10^6$	3	0	0
INTEGU SEAL*	<i>C. albicans</i>	$1 \times 10^6$	3	0	0

### Conclusions:

These *in vitro* findings demonstrate that INTEGU SEAL\* is an effective barrier against microbial penetration.

### 2.4 Incision Model

An *in vitro* skin incision protocol was developed to evaluate the effectiveness of skin treatments meant to reduce the number of bacteria recovered from surgical incisions. In this model, sterile (gamma irradiated) porcine skin was inoculated with a known amount of bacteria. The skin was treated with test articles of interest and incised. In an effort to mimic the duration of a typical surgical procedure, the skin model was set aside for two hours.

Two hours after incision, the skin models were sampled to evaluate the bacteria present in the simulated surgical wound. Incision sampling was accomplished by five sequential irrigation procedures. To model physical pressures and activity during a typical surgical procedure, the incision was manipulated prior to each step of the irrigation. The fluid collected from the irrigation steps was pooled and the bacteria recovered were enumerated using standard plate count procedures.

### 2.5 Incision Model Results: MRSA, *S. epidermidis* and *E. coli*

*In vitro* studies demonstrate the ability of INTEGU SEAL\* to immobilize methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* and *Escherichia coli* on skin incision models.

#### Methods:

*In vitro* experiments were performed using three bacteria species: a) methicillin-resistant *S. aureus* (MRSA), b) *S. epidermidis*, c) *E. coli*. In each experiment, porcine skin samples were randomly assigned to one of the following three test conditions (n = 7 replicates per condition):

1. Non-inoculated skin (negative control)
2. Inoculated skin (positive control)
3. Inoculated skin with INTEGU SEAL\*

*Table 1. Results of the microbial barrier challenge of INTEGU SEAL\* by five microorganisms after 72 hours of incubation.*

**Results:**

Topical application of InteguSeal\* to skin inoculated with MRSA recovered 99.9% fewer MRSA CFUs compared to recovery from the inoculated control ( $p \leq 0.05$ ). When InteguSeal\* was applied to skin inoculated with *S. epidermidis*, the mean number of bacteria recovered from the incisions was reduced by 99.5% compared to the inoculated control ( $p \leq 0.05$ ). Similarly, when InteguSeal\* was applied to skin inoculated with *E. coli*, the mean number of bacteria recovered from the incisions was reduced by 96.6% compared to the inoculated control ( $p \leq 0.05$ ).

The differences between mean microbial recovery from inoculated skin with and without InteguSeal\* were found to be statistically significant ( $p \leq 0.05$ ) for all three bacteria.

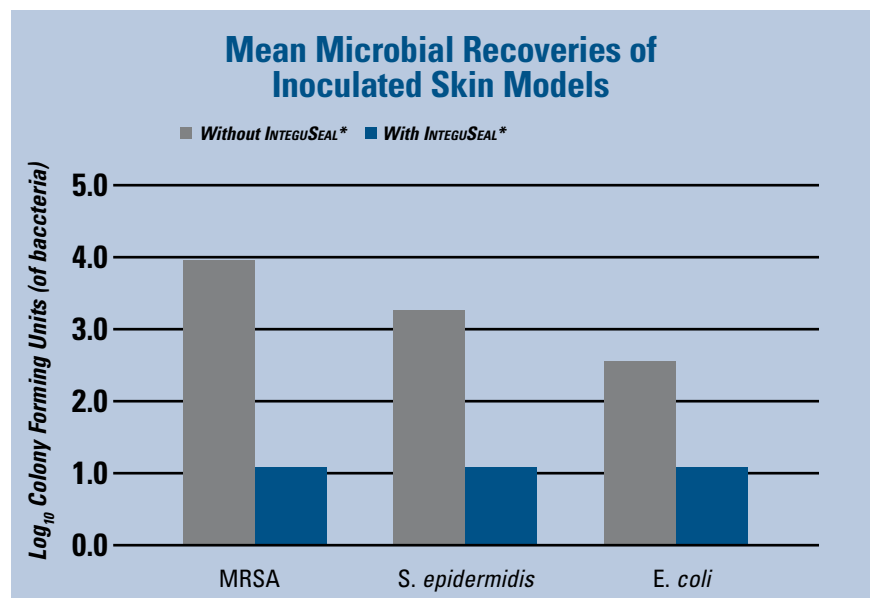


Figure 1. INTEGUSeal\* Microbial Sealant significantly reduces the amount of MRSA recovered in an in vitro surgical incision model by 99.9%, *S. epidermidis* by 99.5% and *E. coli* by 96.6% ( $p \leq 0.05$ ).

**Conclusions:**

INTEGUSeal\* significantly reduces the number of bacteria recovered from model surgical incisions relative to the baseline inoculation by at least 96.6% for all organisms evaluated.

## 3.0 Efficacy Testing

### 3.1 INCISION MODEL WITH INCISE DRAPES

An *in vitro* study was performed by a facility external to Kimberly-Clark under Good Laboratory Practice (GLP) conditions. This study compared the bacterial immobilization attributes of INTEGU SEAL\* in relation to an antimicrobial incise drape using an *in vitro* skin incision model inoculated with methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*, and *Escherichia coli*.

#### Methods:

This study consisted of three experiments, one for each bacterial organism. In each experiment porcine skin samples were randomly assigned to one of the following four test conditions (n = 7 replicates per condition):

- INTEGU SEAL\* applied over inoculated skin
- Antimicrobial incise drape applied over inoculated skin
- Inoculated skin without skin preparation product (positive control)
- Non-inoculated skin without skin preparation product (negative control).

#### Results:

##### Methicillin-resistant *Staphylococcus aureus* (MRSA):

INTEGU SEAL\* reduced the number of *S. aureus* colony forming units (CFUs) recovered from model incisions relative to the control by a mean greater than 3 Log<sub>10</sub> (p ≤ 0.05). By comparison, the antimicrobial incise drape reduced the mean bacterial recovery by only 0.5 Log<sub>10</sub> (p ≤ 0.05).

##### *Staphylococcus epidermidis*:

INTEGU SEAL\* reduced the number of *S. epidermidis* CFUs recovered from model incisions relative to the control by a mean of 2.4 Log<sub>10</sub> (p ≤ 0.05). By comparison, the antimicrobial incise drape reduced the mean bacterial recovery by only 0.6 Log<sub>10</sub> (p ≤ 0.05).

##### *Escherichia coli*:

INTEGU SEAL\* reduced the number of *E. coli* CFUs recovered from model incisions relative to the control by a mean of 1.49 Log<sub>10</sub> (p ≤ 0.05). In contrast, the antimicrobial incise drape reduced the mean bacterial recovery by only 0.33 Log<sub>10</sub>, a statistical difference between the positive control and the incise drape was not detected.

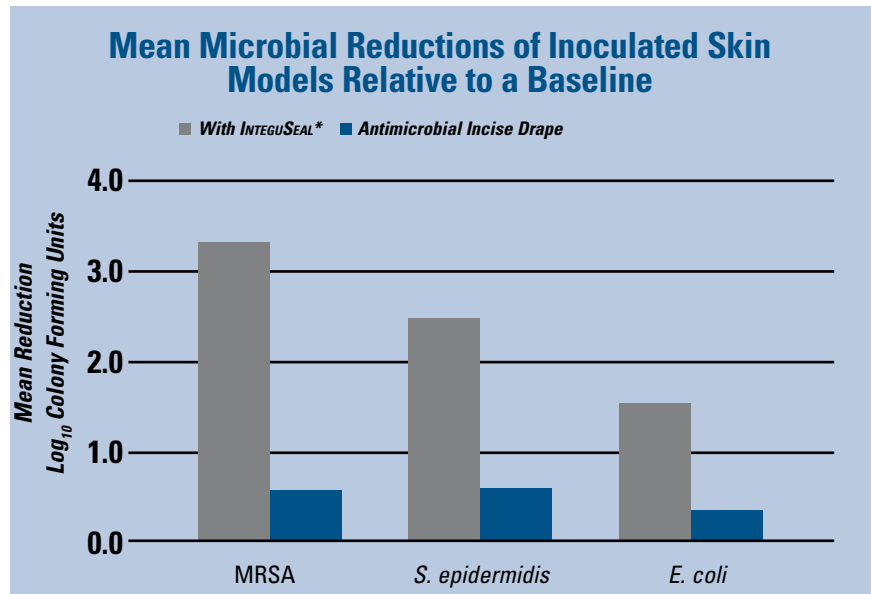


Figure 2. Mean reductions in microbial recovery from incisions made in porcine skin that was inoculated with MRSA, *S. epidermidis*, or *E. coli* and treated with INTEGU SEAL\*, antimicrobial incise drapes or nothing (baseline) ( $p \leq 0.05$ ).

#### Conclusions:

INTEGU SEAL\* significantly reduces the number of bacteria recovered from model surgical incisions relative to the baseline and relative to antimicrobial incise drapes. This result was consistently observed across three important microorganisms: methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*, and *Escherichia coli*. These results demonstrate that INTEGU SEAL\* has microbial immobilization attributes which are desirable for surgical products designed to reduce the risk of skin flora contamination throughout a surgical procedure. Moreover, for each microorganism evaluated, the microbial immobilization attributes of INTEGU SEAL\* were significantly superior to antimicrobial incise drapes ( $p \leq 0.05$ ).

### 3.2 Bacterial Immobilization: INTEGU SEAL\* and 10% Povidone Iodine

A clinical study was performed to determine the bacterial immobilization attributes of INTEGU SEAL\* and evaluate the ability of INTEGU SEAL\* to reduce the risk of skin flora contamination. The study was performed by a facility external to Kimberly-Clark and was conducted in compliance with Good Clinical Practice (GCP) regulations. A standard cup scrub procedure quantified the recoverable bacteria present on the skin when used with 10% povidone iodine (aq) preoperative skin preparation.

Test subjects participating in the study underwent a two-week wash-out period during which they were instructed to use only pre-defined, non-antimicrobial, personal care products for personal hygiene. The subjects were also provided with specific instructions to avoid activities that might alter natural skin flora. Following the wash-out period, subjects returned to the clinic and hair was removed from the test sites.

Quantification of skin micro-flora on the test sites was performed using a cup scrub procedure based on an internationally recognized method, ASTM E-1173-01, 1874-97.

#### Methods:

A total of 43 subjects with indigenous counts  $\geq 1 \times 10^4$  CFU/cm<sup>2</sup> on their inguinal skin were included. Baseline samples were collected from each inguinal site. Each site was then treated with one of the following randomly assigned treatments:

- INTEGU SEAL\* applied over inguinal skin
- INTEGU SEAL\* applied over inguinal skin pretreated with 10% povidone iodine (aq)
- 10% povidone iodine (aq) applied over inguinal skin
- Nothing applied to inguinal skin (untreated)

Each subject was treated with two of the four treatment conditions, one on one thigh and the other on the contra lateral thigh. Samples were collected from randomly assigned sub-sites at 15 minutes, 4 hours, and 24 hours after treatment.

#### Results:

All three treatments were found to significantly reduce the recovery of indigenous microorganisms from inguinal skin at each of the three time points relative to baseline values (Figure 3 and Table 2). In all cases, the application of INTEGU SEAL\* significantly reduced the recovery of indigenous microorganisms relative to povidone iodine treated sites. This was true whether the INTEGU SEAL\* was applied over untreated skin or skin pretreated with povidone iodine.

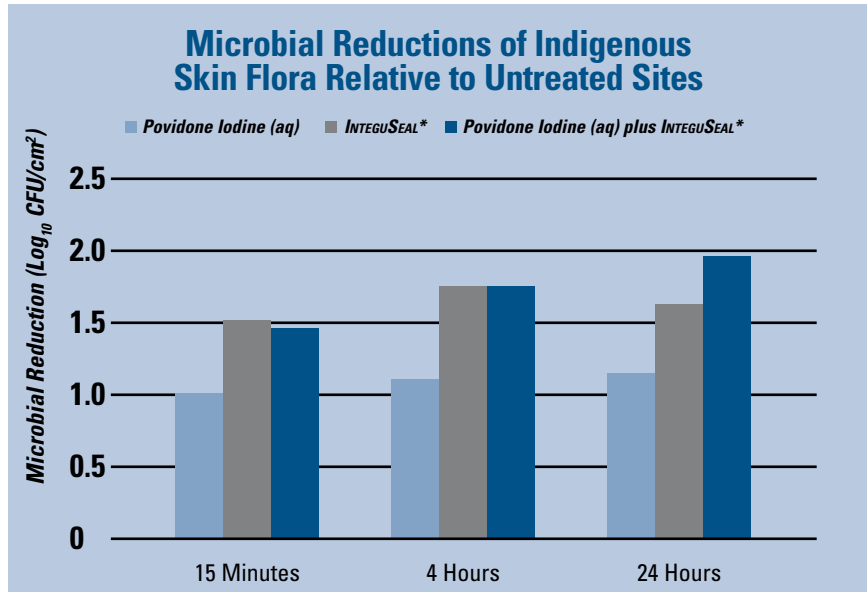


Figure 3. Mean reductions in the recovery of indigenous microorganisms (Log<sub>10</sub> CFU/cm<sup>2</sup>) from inguinal skin at all time points evaluated relative to baseline values. All treatments significantly reduced microbial recovery ( $p \leq 0.0001$ ). Greater reductions in microbial recovery from sites treated with INTEGUSeAL\* were observed relative to sites treated with povidone iodine (aq) alone at all time points evaluated ( $p \leq 0.05$ ).

<b>Log<sub>10</sub> Reductions of Indigenous Skin Flora Relative to Baseline Values</b>			
<b>Treatment</b>	<b>15 Minutes</b>	<b>4 Hours</b>	<b>24 Hours</b>
<b>Povidone Iodine (aq)</b>	<b>.99</b>	<b>1.10</b>	<b>1.14</b>
<b>INTEGUSeAL*</b>	<b>1.55</b>	<b>1.82</b>	<b>1.64</b>
<b>Povidone Iodine (aq) plus INTEGUSeAL*</b>	<b>1.45</b>	<b>1.81</b>	<b>1.97</b>

Table 2. Mean reductions for microbial recovery from inguinal sites relative to baseline values at each time point following the application of test treatments (n = 22 subjects for each data point). All reductions from baseline were significant ( $p \leq 0.0001$ )

**Conclusions:**

INTEGUSeAL\* has microbial immobilization attributes as evidenced by significant reductions in the numbers of indigenous microorganisms collected from human skin. INTEGUSeAL\* delivers these benefits when applied over a surgical preparation solution (10% povidone iodine, USP) and when applied directly to untreated skin. Therefore, the product can be readily incorporated into the most common surgical standard of care. Moreover, the benefit of reducing recoverable microorganisms from the skin is long lasting.

### 3.3 Bacterial Immobilization: INTEGU SEAL\* and Antimicrobial Incise Drapes

An *in vitro* study was performed by a facility external to Kimberly-Clark using a skin incision model to evaluate the bacterial immobilization attributes of INTEGU SEAL\* Microbial Sealant when used with and without an antimicrobial surgical incise drape.

#### Methods:

This study evaluated the immobilization attributes of INTEGU SEAL\* when used alone and in combination with a commonly used antimicrobial incise drape. The study was performed using an *in vitro* skin incision model seeded with *Bacillus stearothermophilus* spores. All skin models were inoculated with bacteria prior to the application of the test articles. Four test conditions were evaluated:

- Bacteria only, a microbial recovery control
- Bacteria followed by an antimicrobial incise drape
- Bacteria followed by INTEGU SEAL\* Microbial Sealant
- Bacteria followed by INTEGU SEAL\* Microbial Sealant plus an antimicrobial incise drape

After treatment application, skin incisions were evaluated to determine the number of bacteria present in each incision. Seven replicates of each condition were evaluated.

#### Results:

Application of INTEGU SEAL\* Microbial Sealant to the skin incision model significantly reduced the number of bacteria recovered from model incisions relative to the control by a mean of 2.70 Log<sub>10</sub> ( $p \leq 0.05$ ).

The application of INTEGU SEAL\* alone and INTEGU SEAL\* followed by the antimicrobial incise drape significantly reduced the number of bacteria recovered from model incisions relative to the incise drape alone by 1.2 and 1.4 Log<sub>10</sub> CFU respectively ( $p \leq 0.05$ ).

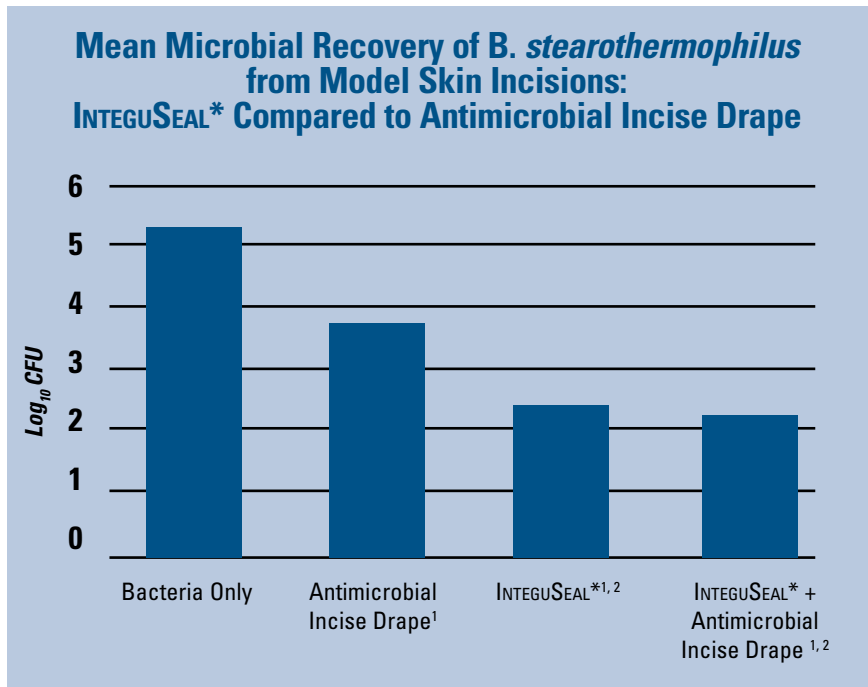


Figure 4. Mean microbial recovery from incisions in inoculated skin models treated with INTEGU SEAL\* microbial sealant, antimicrobial incise drapes, and the combination of products. Both INTEGU SEAL\* alone and INTEGU SEAL\* followed by the antimicrobial incise drape resulted in reduced microbial recovery relative to the control and the incise drape alone ( $p \leq 0.05$ ).

<sup>1</sup> significantly different from bacteria only ( $p \leq 0.05$ ).

<sup>2</sup> significantly different from antimicrobial incise drapes ( $p \leq 0.05$ ).

Treatment	Mean microbial recovery $\pm$ Std. Error ( $\log_{10}$ CFU)	Reduction from Baseline ( $\log_{10}$ CFU)
Bacteria Only	5.2 $\pm$ 0.03	N/A
Antimicrobial Incise Drape	3.7 $\pm$ 0.19 <sup>1</sup>	1.55
INTEGU SEAL*	2.5 $\pm$ 0.19 <sup>1,2</sup>	2.70
INTEGU SEAL* + Antimicrobial Incise Drape	2.3 $\pm$ 0.20 <sup>1,2</sup>	2.92

Table 3. Mean microbial recovery ( $\log_{10}$ ) from model skin incisions treated with bacteria only (Control), antimicrobial incise drape, INTEGU SEAL\* or both, and the attendant standard errors. N/A = not applicable.

**Conclusion:**

INTEGU SEAL\* has bacterial immobilization attributes as evidenced by a reduction in the recovery of bacteria from skin incisions. The treatment of skin models with INTEGU SEAL\* recovered significantly fewer bacteria than skin models treated with antimicrobial incise drapes ( $p \leq 0.05$ ). Skin models treated with INTEGU SEAL\* followed by the application of an antimicrobial incise drape demonstrated a significant improvement to the performance of antimicrobial incise drapes alone ( $p \leq 0.05$ ).

### 3.4 *In vivo* Porcine Study: INTEGU SEAL\* and Antimicrobial Incise Drape

A controlled *in vivo* porcine study was performed by a facility external to Kimberly-Clark under Good Lab Practice (GLP) standards to evaluate the effectiveness of INTEGU SEAL\* at reducing the risk of skin flora contamination throughout a surgical procedure.

#### **Methods:**

A total of 66 incisions were evaluated under simulated surgical conditions. Every surgical site was treated with 10% povidone iodine (aq) surgical preparation and one of the following treatments:

- INTEGU SEAL\* Microbial Sealant
- Antimicrobial incise drape (Acti-Gard®)

After treatment application, a full thickness incision was created in a simulated clinical setting which included a 60 minute surgical procedure involving wound retraction, simulated surgical manipulations, and wound lavage. Surgical incisions were sampled for bacterial contamination after incision and before wound closure. For each incision, contamination was evaluated according to the total colony forming units (CFUs) incubated from sample taken immediately after incision and again just prior to surgical wound closure. Of the sixty-six incisions, 4 were rejected due to a positive control sample which suggests possible contamination. Each wound sample was incubated for the duration of 24 hours and evaluated for the growth of CFUs. The total colony counts represent the sum of all CFUs from each incision transformed into a  $\text{Log}_{10}$  value.

#### **Results:**

The INTEGU SEAL\* treated incisions returned similar mean  $\text{Log}_{10}$  total counts as the Acti-Gard® treated incisions (-0.09 versus 0.12;  $p = 0.53$ ) for the samples taken just after incision. After the surgeries were completed, the samples from the INTEGU SEAL\* treated sites taken just prior to wound closure returned significantly lower mean  $\text{Log}_{10}$  total counts than the Acti-Gard® treated incisions (0.12 versus 0.80;  $p = 0.0017$ ). These results demonstrate that, after incision, INTEGU SEAL\* is non-inferior to Acti-Gard® and provide statistical evidence that, before closure, INTEGU SEAL\* is superior to Acti-Gard® in reducing the risk of skin flora contamination throughout a surgical procedure.

**Conclusion:**

INTEGU SEAL\* is effective in reducing the risk of skin flora contamination throughout a surgical procedure.

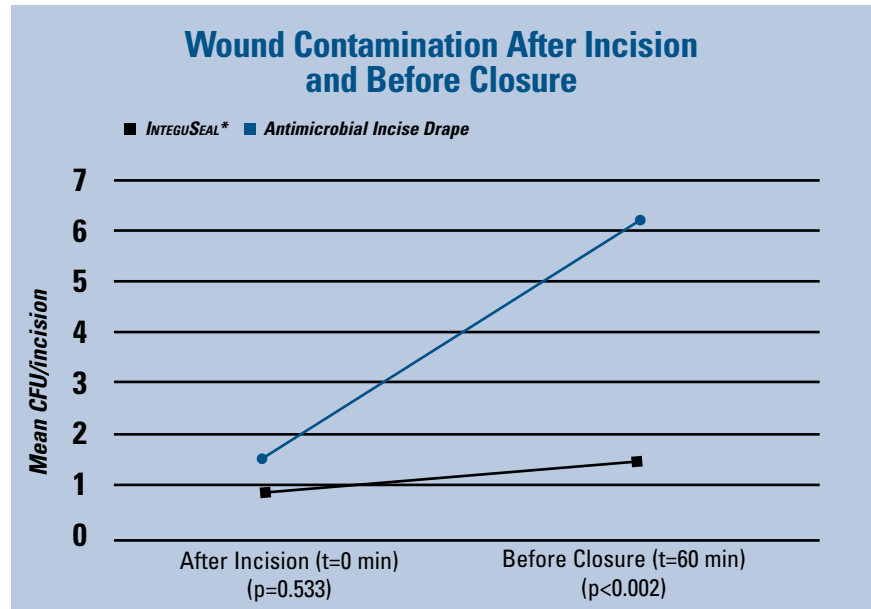


Figure 5. Mean colony forming units (CFUs) per incision of wound samples collected from in vivo porcine surgical incisions after surgical incision and before wound closure. Before wound closure, INTEGU SEAL\* demonstrates superior performance compared to anti-microbial incise drapes in reducing the risk of skin flora contamination throughout a surgical procedure ( $p < 0.002$ )

Treatment	Time Point	Log <sub>10</sub> (CFU)	Mean CFUs per incision
INTEGU SEAL*	After Incision	-0.093	0.808
	Before Closure	0.117	1.308
ACTI-GARD®	After Incision	0.117	1.309
	Before Closure	0.801	6.327

Table 4. CFUs per incision of wound samples collected from in vivo porcine surgical incisions after incision and before wound closure. Results reported in mean CFUs per Results reported in CFUs per incision and Log<sub>10</sub> (CFU)

### 3.5 WVTR (Water Vapor Transmission Rate)

An *in vitro* study was performed to determine the water vapor transmission rate (WVTR) of INTEGU SEAL\* relative to other surgical incise drapes.

#### Methods:

Test articles of interest were applied to collagen film supports. The films, with and without test articles, were mounted into WVTR measurement devices. Along with the untreated collagen film control, four test articles (Ioban®, Steri-Drape®, Acti-Gard®, INTEGU SEAL\*) were evaluated.

Water loss through the films was measured at time zero and every hour for up to 6 hours.

#### Results:

INTEGU SEAL\* has a mean WVTR that is almost 10 times higher than that of the commercially available surgical incise drapes, Acti-Gard®, Ioban® or Steri-Drape®, (Figure 6), indicating more breathability. Statistical differences in mean WVTR were not detected between any of the three surgical incise drapes evaluated.

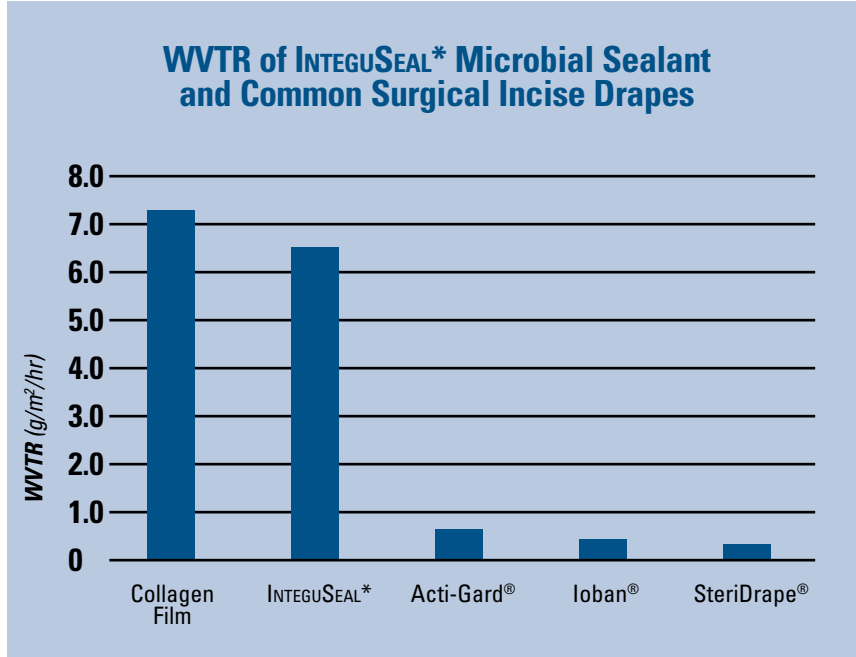


Figure 6. The mean WVTR of INTEGU SEAL\* compared to other commercial surgical drapes.

#### Conclusions:

*In vitro* results show that the cyanoacrylate-based INTEGU SEAL\* Microbial Sealant has a greater WVTR and therefore is more breathable than conventional surgical incise drapes.

### 3.6 Compatibility With Current Products

#### WORKS WITH A VARIETY OF PREP SOLUTIONS

*In vitro* results show that INTEGUSEAL\* Microbial Sealant has microbial immobilization attributes when used in conjunction with a variety of surgical skin preparation solutions. Solutions containing iodophors, less than 4% chlorhexidine gluconate, hydrogen peroxide and/or alcohol are compatible.

#### EFFECT OF INTEGUSEAL\* ON SURGICAL INCISE DRAPE ADHESION

An *in vitro* study was performed to evaluate the effect of INTEGUSEAL\* on the adhesion strength of commonly used surgical drapes.

##### Methods:

A skin model was used to evaluate commonly used surgical preps, INTEGUSEAL\*, and surgical drapes. Three (3) samples of skin model were randomly assigned to each of the following treatments:

- No preparation product (control)
- INTEGUSEAL\* alone
- Chloraprep® alone (2% CHG + alcohol)
- DuraPrep™ alone (Iodophor + alcohol)
- 10% Povidone Iodine (aq) alone
- INTEGUSEAL\* applied over Chloraprep®
- INTEGUSEAL\* applied over DuraPrep™
- INTEGUSEAL\* applied over 10% Povidone Iodine (aq)

After the skin model was prepared, a surgical drape was applied to the surface of each model and set aside for 30 minutes. The surgical drape was then peeled away from the skin model using a tensile testing instrument to determine the strength of adhesion in a standard 180° peel test at a cross-head speed of 2.0 in/min.

##### Results:

The presence of INTEGUSEAL\* does not interfere with drape adhesion.

<i>The Average Energy Required to Peel Surgical Drapes from Skin Model</i>	
<b>Treatment</b>	<i>Average Energy (lb-min/sq. in)</i>
<b>Untreated</b>	<b>.228</b>
<b>INTEGUSEAL*</b>	<b>.502</b>
<b>Povidone Iodine (aq)</b>	<b>.133</b>
<b>Povidone Iodine (aq) plus INTEGUSEAL*</b>	<b>.257</b>
<b>Chloraprep®</b>	<b>.214</b>
<b>Chloraprep® plus INTEGUSEAL*</b>	<b>.343</b>
<b>DuraPrep®</b>	<b>.521</b>
<b>DuraPrep® plus INTEGUSEAL*</b>	<b>.653</b>

*Table 5. Average energy required to peel common surgical drapes from skin models utilizing a standard 180° peel test.*

**Conclusions:**

The use of INTEGUSEAL\* did not negatively affect the adhesion strength of surgical drapes.

**EFFECT OF INTEGUSEAL\* ON WOUND CLOSURE STRENGTH**

An *in vitro* study was performed to determine the effect of INTEGUSEAL\* on the strength of wound closure when employing various wound closure devices.

**Methods:**

Three (3) samples were tested for each of 40 combinations of commonly used closure methods with skin preparation products. The five closure methods evaluated in this study included: Sutures, Staples, Wound Closure Strips (Steri-Strip™ brand), DermaBond® (cyanoacrylate suture product that is available in the US), and LiquiBand® (cyanoacrylate suture product that is available outside the US). Each of the wound closure methods was evaluated with each of the following combinations of skin preparation and INTEGUSEAL\*:

- No preparation product (untreated)
- INTEGUSEAL\* only
- Betadine® only
- Betadine® and INTEGUSEAL\*
- DuraPrep™ only
- DuraPrep™ and INTEGUSEAL\*
- Chloraprep® only
- Chloraprep® and INTEGUSEAL\*

Following preparation of the incision site, an incision was made at the midsection of the sample. The incisions were then closed according to standard surgical practice. After wound closure, the skin incisions were pulled apart on a tensile tester at a cross head speed of 1.0 in/min to determine wound strength.

**Results:**

INTEGU SEAL\* is compatible for use with common sutures and staples.

<i>Wound Closure Strength</i>	
<b>Treatment</b>	<b>Overall Average Tensile Strength (lb/sq. in)</b>
<b>Staples</b>	<b>7.0</b>
<b>Staples plus INTEGU SEAL*</b>	<b>7.5</b>
<b>Sutures</b>	<b>13.6</b>
<b>Sutures plus INTEGU SEAL*</b>	<b>15.8</b>
<b>Steri-Strips™</b>	<b>1.3</b>
<b>Steri-Strips™ plus INTEGU SEAL*</b>	<b>1.7</b>
<b>LiquiBand®</b>	<b>5.1</b>
<b>LiquiBand® plus INTEGU SEAL*</b>	<b>5.4</b>
<b>Dermabond®</b>	<b>4.7</b>
<b>Dermabond® plus INTEGU SEAL*</b>	<b>10.9</b>

*Table 6. Wound closure tensile strength of various combinations of wound closure devices measured with a tensile tester at a cross-head speed of 1.0 in/min.*

**Conclusions:**

Wound tensile strength in the presence of INTEGU SEAL\* was equivalent to or better than the wound strength with no INTEGU SEAL\* present.

**USE OF INTEGUSEAL\* WITH STERI-STRIPS™ OVER TIME**

An *in vivo* study was performed to evaluate the effect of surgical skin preparation solutions and INTEGU SEAL\* on the adhesion of 52 mm 3M Steri-Strips™ to the skin as a function of time.

**Methods:**

Twenty-four (24) subjects were enrolled. Four (4) test sites were marked on each subject’s back and each site was randomly assigned to one of the following four treatments:

- Steri-Strips™ applied over Chloraprep® only
- Steri-Strips™ applied over INTEGU SEAL\* and Chloraprep®
- Steri-Strips™ applied over Povidone Iodine (aq) only

■ Steri-Strips™ applied over INTEGU<sup>SEAL</sup>\* and Povidone Iodine (aq)

Subjects returned for follow-up 72 hours after the first visit and every 24 hours for four additional visits (a total of six visits). At each return visit, strips were observed for total failure and for the length of the retained strip.

**Results:**

As expected, the length of Steri-Strips™ attached to the skin lessened over time for all four treatment groups. No significant differences were found through Day 5. By Day 5, 30% of the strips on Chloraprep® treated sites completely detached while 10% of the strips failed on PVP-I treated sites. By Day 6, there were significant differences in the rate of failure between sites treated with INTEGU<sup>SEAL</sup>\* and their non-INTEGU<sup>SEAL</sup>\* counterpart sites.

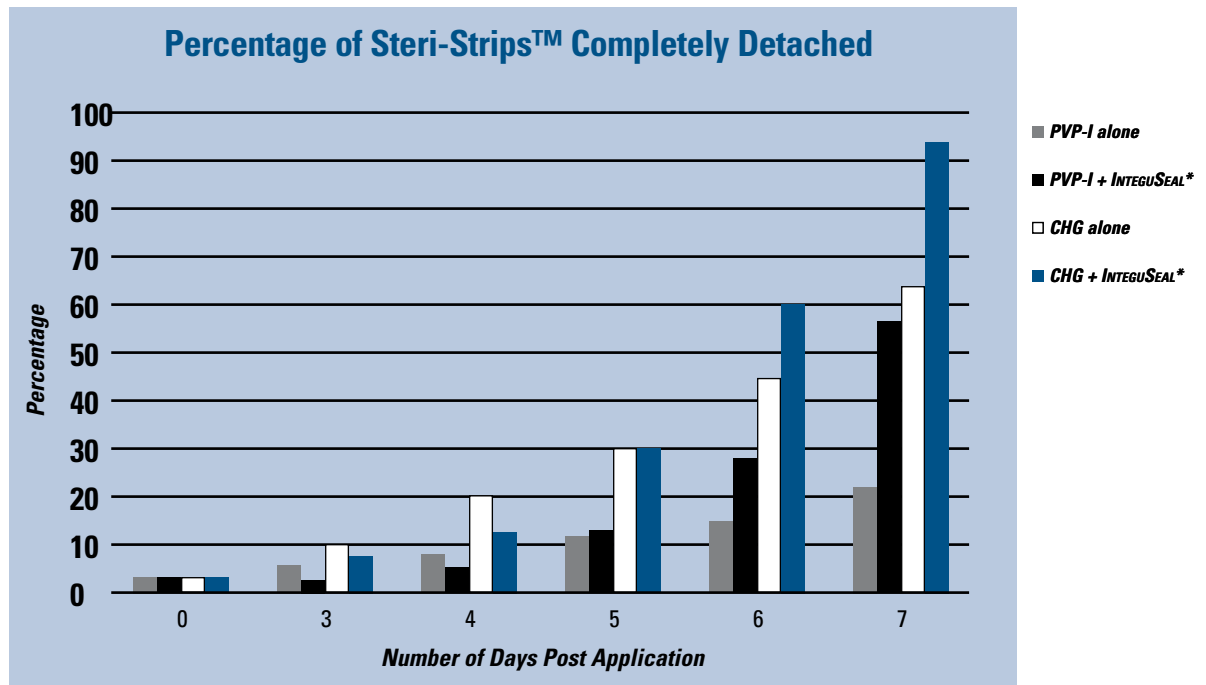


Figure 7. Percentage of Strips Completely Detached Over Time

**Conclusions:**

Steri-Strip™ adhesion was observed to lessen over time for all four treatment groups, including those devoid of INTEGU<sup>SEAL</sup>\*. The presence of INTEGU<sup>SEAL</sup>\* can impact the adhesion of wound closure strips after Day 5. This is likely due to the sloughing of the skin and INTEGU<sup>SEAL</sup>\* which typically takes place between Day 3 and Day 7. This difference should have minimal impact in the clinical setting.

## EFFECT OF INTEGUSEAL\* ON TISSUE ADHESIVES

An *in vivo* porcine study was performed by a facility external to Kimberly-Clark under Good Lab Practices (GLP) to determine if the presence of INTEGUSEAL\* affects the functionality of tissue adhesives used for wound closure.

### Methods:

A total of 24 incisions were evaluated using common wound closure methods. The three closure methods evaluated were: monofilament polypropylene sutures, Dermabond® (cyanoacrylate tissue adhesive), and Indermil® (cyanoacrylate tissue adhesive). All sites were prepped with Betadine® surgical skin preparation solution. Following the skin prep, INTEGUSEAL\* Microbial Sealant was applied to assigned sites and evaluated in the following combinations of INTEGUSEAL\* and wound closure:

- Suture only
- Suture and INTEGUSEAL\*
- Dermabond® only
- Dermabond® and INTEGUSEAL\*
- Indermil® only
- Indermil® and INTEGUSEAL\*

After preparation of the incision site, an incision was made at the midsection of the sample. Full-thickness skin incisions were manipulated and lavaged to simulate minor surgical procedures. Incisions were then approximated with subcuticular sutures and closed with sutures, Dermabond® or Indermil® as designated. The incisions were evaluated daily over a 14 day period for wound healing then underwent routine histology.

### Results:

Daily wound healing observations included documentation of redness, swelling, dehiscence, normal conditions, and other conditions such as scab formation, stitch abscess and granulation. For this study, dehiscence was an indicator for wound closure method failure.

Wound dehiscence was not observed in three wound closure methods: 1) sutures only, 2) sutures plus INTEGUSEAL\* and 3) Dermabond® plus INTEGUSEAL\*. Of the incisions with observed wound dehiscence, 17% of Dermabond® only and 20% of both Indermil® only and Indermil® plus INTEGUSEAL\* incisions showed wound closure failure.

All wounds appeared to be healed by day 14, the study end date.

Routine histology revealed that INTEGUSeAL\* has no negative impact on the healing of cutaneous surgical wounds and in some cases has a positive impact, producing lower inflammation scores.

<i>Failure by Wound Closure Method</i>		
<b>Code</b>	<b>Number Tested</b>	<b>% Wound Closure Failure</b>
<b>Suture only</b>	<b>1</b>	<b>0</b>
<b>Suture and INTEGUSeAL*</b>	<b>3</b>	<b>0</b>
<b>Dermabond® only</b>	<b>6</b>	<b>17</b>
<b>Dermabond® and INTEGUSeAL*</b>	<b>4</b>	<b>0</b>
<b>Indermil® only</b>	<b>5</b>	<b>20</b>
<b>Indermil® and INTEGUSeAL*</b>	<b>5</b>	<b>20</b>

*Table 7. Wound closure failure based on visual observation of wound dehiscence.*

**Conclusions:**

Wound closure failure rates were similar regardless of the presence or absence of INTEGUSeAL\* for each of the tissue adhesives tested. Based upon visual observations of the healing skin incisions and the microscopic findings from histology, INTEGUSeAL\* does not compromise the ability of Dermabond® or Indermil® to affect wound closure for the time needed for the wound to heal.

## 4.0 Safety Testing

### 4.1 Biocompatibility: ISO 10993

Biocompatibility testing of INTEGUSeal\* Microbial Sealant was conducted in accordance with ISO 10993 Part 1, "Biological Evaluation of Medical Devices." INTEGUSeal\* has satisfied the requirements for devices in contact with breached or compromised surfaces for a prolonged period of time (up to 29 days).

<i>Biocompatibility Tests and Related ISO Standards</i>		
<b>Biocompatibility Study</b>	<b>ISO 10993: Biological Evaluation of Medical Devices</b>	<b>Testing Results</b>
<i>Agar Diffusion Test</i>	<i>Part 5: Tests for Cytotoxicity: in vitro methods</i>	<i>Non-cytotoxic</i>
<i>Buehler Sensitization Test – Direct Contact</i>	<i>Part 10: Tests for Irritation &amp; Sensitization</i>	<i>Not a skin sensitizer</i>
<i>Chromosomal Aberration Assay n Human Peripheral Blood Lymphocytes</i>	<i>Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity</i>	<i>Non-Clastogenic</i>
<i>Intramuscular Implantation Test</i>	<i>Part 6: Tests for local effects after implantation</i>	<i>Does not induce local toxic effects following 4 weeks of implantation</i>
<i>Primary Skin Irritation Test</i>	<i>Part 10: Tests for Irritation &amp; Sensitization</i>	<i>Non-irritant</i>
<i>Rodent Bone Marrow Micronucleus Assay</i>	<i>Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity</i>	<i>Non-Clastogenic</i>
<i>Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay</i>	<i>Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity</i>	<i>Non-mutagenic</i>
<i>Systemic Injection Test</i>	<i>Part 11: Tests for Systemic Toxicity</i>	<i>No acute systemic toxicity</i>

Table 8. Biocompatibility studies and results to satisfy the requirements of ISO 10993.

## 4.2 Flammability

The flash point of INTEGUSEAL\* is 108.5°C as determined by the setaflash closed cup apparatus using the test method described in BS EN ISO 3679:2004, "Determination of flash point by rapid equilibrium closed cup method". Because typical operating room temperatures range between 23-27°C, far below the flash point of INTEGUSEAL\*, and the Upper and Lower Explosivity Levels are non-detectible, this product is deemed non-flammable.

## 4.3 Durability with TEWL (Transepidermal Water Loss)

An *in vivo* study was conducted to determine the transepidermal water loss (TEWL), durability, appearance, and biophysical attributes of skin treated with INTEGUSEAL\*.

### Methods:

Twenty (20) subjects participated in the single-blind, randomized study, to evaluate the durability of INTEGUSEAL\*. Four (4) test sites were randomly assigned to one of the following three treatments plus an untreated control:

- Untreated control
- INTEGUSEAL\* only
- INTEGUSEAL\* over 10% Povidone Iodine (aq)
- INTEGUSEAL\* over DuraPrep™

### Results:

TEWL values returned to baseline within 24 hours of treatment.

<b>Mean TEWL (g/m<sup>2</sup>/hr) of Skin Treated with INTEGUSEAL*, INTEGUSEAL with Surgical Skin Prep, and Untreated</b>					
<b>Test Article</b>	<b>Time (hours)</b>				
	<b>0</b>	<b>4</b>	<b>24</b>	<b>48</b>	<b>72</b>
<b>Untreated</b>	<b>4.34</b>	<b>4.29</b>	<b>4.31</b>	<b>4.15</b>	<b>4.06</b>
<b>INTEGUSEAL*</b>	<b>4.19</b>	<b>4.67</b>	<b>4.23</b>	<b>4.16</b>	<b>3.81</b>
<b>INTEGUSEAL*plus Povidone Iodine</b>	<b>4.34</b>	<b>4.76</b>	<b>4.37</b>	<b>4.15</b>	<b>4.05</b>
<b>INTEGUSEAL*plus DuraPrep™</b>	<b>4.21</b>	<b>4.56</b>	<b>4.26</b>	<b>3.95</b>	<b>4.17</b>

Table 9. Mean TEWL (g/m<sup>2</sup>/hr) as a function of time. The baseline, pre-treatment value, was measured at time zero.

### Conclusions:

INTEGUSEAL\* does not impact normal skin transpiration when applied directly to the skin or to skin pretreated with surgical skin preparation solutions.

#### 4.4 Bacterial Dissemination

An *in vitro* study was performed to determine that INTEGUSEAL\* does not contribute to the dispersion of microorganisms into the environment.

**Methods:**

Bacterial spores (*Bacillus stearothermophilus*) were applied to samples of a porcine skin model. Three samples of skin model were randomly assigned to each of the following treatment groups::

- Untreated
- Bacteria only
- INTEGUSEAL\* only
- 10% Povidone Iodine (aq) only
- ChloroPrep® only
- 70% isopropyl alcohol only
- 10% Povidone Iodine (aq) + INTEGUSEAL\*
- ChloroPrep® + INTEGUSEAL\*
- 70% isopropyl alcohol + INTEGUSEAL\*

Surgical skin preparation solutions 10% povidone Iodine (aq), ChloroPrep®, or 70% (v/v) isopropyl alcohol were applied to the skin model. Following the application of the surgical skin preparation products and the polymerization of INTEGUSEAL\*, the surface of each skin sample was scraped with a sterile scalpel to dislodge particles onto the surface of microbiological growth medium residing within a Petri plate. The plates were incubated under appropriate growth conditions and the resulting bacterial colonies enumerated.

**Results:**

Whether used alone or in combination with other commonly used surgical skin preparation products, INTEGUSEAL\* does not increase the dispersion of particles containing microorganisms into the environment.

**Conclusions:**

INTEGUSEAL\* will not result in elevated levels of microbial dispersion into the environment.

**KIMBERLY-CLARK\* INTEGUSEAL\***  
**Microbial Sealant**

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