

Attachment to Aplicare, Inc.'s August 27, 2003 comment to Docket No. 75N-183H Safety and Efficacy of Povidone-Iodine and Alcohols

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1.0 Introduction

An antiseptic product used in skin disinfection protocols should be broad-spectrum, fast-acting, and result in a significant reduction in the number of bacteria on intact skin. Products containing povidone-iodine (PVP-I) and/or alcohol (both isopropyl alcohol (or isopropanol or IPA) and ethyl alcohol (or ethanol or EtOH)) have been widely used by healthcare professionals as patient preoperative skin preparations, catheter site/venipuncture preparations, antiseptic handwashes, and surgical handscrubs. This document presents an evaluation of the available literature pertaining to the safety and efficacy of isopropyl alcohol and ethyl alcohol, povidone-iodine, and povidone-iodine in combination with isopropanol or ethanol for these indications.

Although the primary interest here is the combination of povidone-iodine and isopropyl alcohol, the body of literature reviewed includes available literature on all alcoholic iodine combinations that appear to have similar modes of action and safety and efficacy profiles. Because the mechanisms of action and the indications for use, as well as the safety and effectiveness, of PVP-I and EtOH combination products appear very similar to PVP-I and IPA combinations, we believe studies of PVP-I/EtOH combinations have relevance to evaluating PVP-I/IPA combinations. We further included literature on handwashes and surgical handscrubs, which although not preoperative patient preparation products, provide additional important evidence of the safety and efficacy of the combination for healthcare indications.

2.0 Alcohols

Alcohols, including IPA and EtOH, are among the most widely used topical antiseptics in surgical preparation, skin cleansing, and hand sanitizing. Of topical

antiseptics, use of alcohols dates back to the 14th century (Beck, 1985). Alcohols are used as microbicidal, virucidal and germicidal agents because of their ability to denature proteins at concentrations of 60-90% (for review see Boyce and Pittet, 2002; Spann et al., 2003). Isopropyl alcohol and ethyl alcohol have been shown to be as effective as (Ayliffe, 1984; Bryce et al., 2001) or more effective than (Ayliffe, 1984; Boyce and Pittet, 2002; Guilhermetti et al., 2001; Lowbury et al., 1960; Suzuki et al., 1997) other agents (hand soap, chlorhexidine, povidone-iodine) at reducing bacterial counts on the skin and hands following pre-surgical scrub or single application on the surgical site. Both isopropyl alcohol and ethyl alcohol are effective in reducing bacterial and viral bioburdens on the hands when applied as a wash or a scrub (Boyce and Pittet, 2002; Parienti et al., 2002; Furuhashi and Miyamae, 1979; Larson et al., 1990). Because satisfactory antisepsis results almost immediately after administration of alcohols (Cortopassi and Kikugawa, 1977; Boyce & Pitter, 2002), their use as single agents for antisepsis at the site of catheterization has also been recommended by the CDC (Garland et al., 2002). Use of an alcoholic solution was also well tolerated by health care workers, with few reports of irritation and drying compared to other agents (Boyce et al., 2000; Bryce et al., 2001; Tupker et al., 1997).

3.0 Povidone-Iodine

Aqueous or alcoholic tincture of iodine solutions have been used for over 150 years to reduce bacterial, fungal and viral contamination of the skin as a surgical preparation or hand wash (for review see McDonnell & Russell, 1999). Aqueous iodine is considered to be unstable; iodophors, which form a complex of iodine and a carrier agent, are more widely used and possess the same germicidal activity (McDonnell & Russell, 1999). Several commercially available iodophors such as Prepodyne[®], DuraPrep[™] and Betadine[®] have been used as a skin paint to sterilize the skin prior to surgery, for specimen collection, catheterization, wound debridement and blood collection, and as hand scrubs (Chavigny & Nunnally, 1974; Connell & Rousselot, 1964; Cortopassi & Kikugawa, 1977; Lowbury et al., 1964; Kilpatrick & Knight, 1975; McDonald et al., 2001; Russell et al., 1992; Strand et al., 1993).

4.0 Povidone-Iodine and Alcohol in Combination

Alcohols are rapidly germicidal when applied to the skin; however, they have no persistent activity (Boyce & Pittet, 2002). Povidone-iodine, on the other hand, may take up to 2 minutes to reach maximal antimicrobial effect (Mylotte & Tayara, 2000), but this effect may persist for 30 minutes to 6 hours (Boyce & Pittet, 2002). Hence the combination of PVP-I and IPA provides both immediate and persistent antimicrobial activity. Clinical experience with povidone-iodine and isopropyl alcohol in combination is as follows:

4.1 Operative Site Antisepsis

PVP-I and alcohol combinations have long been used in the preparation of patient skin prior to surgery. PVP-I plus IPA (Prevail-Fx[®]) was found equivalent in efficacy to PVP-I alone (Jeng, 2001). During a 15-year study period, no wound infections occurred in 1654 men undergoing

varicocelelectomy when the skin was prepared with PVP-I (Betadine[®]) followed by 70% ethyl alcohol (O'Connor & Goldstein, 2002). This translated to an infection rate of <0.2%, compared with a rate of 0.7% previously reported by Dubin and Amelar (1977) for the same surgery. (The Dubin & Amelar paper does not indicate the surgical preparation used.) While the alcohol used in the O'Connor and Goldstein study was ethyl alcohol, another study found no significant difference in antiseptic efficacy of PVP-I plus ethyl alcohol compared to PVP-I plus IPA (Arata, Murakami & Hirai, 1993). Furthermore, no adverse experiences were reported in that study and no subjects complained about color, odor, sticky feeling or irritation with any PVP-I plus alcohol solution (Arata, Murakami & Hirai, 1993).

4.2 Injection Site / Catheter Site Preparation

Arata et al. (1997) compared the agents most commonly used for antisepsis for injection sites, i.e., PVP-I/EtOH, chlorhexidine/EtOH. A slightly better reduction rate was seen with PVP-I/EtOH (Isodine[®]) compared to chlorhexidine/EtOH. PVP-I/EtOH was determined to be a safe and effective agent for injection site antisepsis as no adverse experiences were reported.

Recently, Benhamou, Mercier and Dounas (2002) published a recommended procedure for the prevention of infection after neuraxial blocks in obstetrics. They specified that the patient's back should be disinfected twice with sterile gauze or sponge soaked with alcoholic iodine or alcoholic solution of chlorhexidine or of PVP-I prior to puncture. The antiseptic should be allowed to dry 1-2 minutes after each disinfection. At least one controlled trial since then has supported this recommendation. Birnbach, Meadows, Stein, Murray, Thys and Sordillo (2003) found that compared to PVP-I alone, PVP-I and IPA in combination (DuraPrep[™]) provided a greater decrease in the number of positive skin cultures in women in labor who received epidurals at three points, 1) immediately after disinfection, 2) at catheter removal, and 3) on the catheter tip. An earlier report indicated a good success rate with a PVP-I and IPA protocol for total parenteral nutrition (TPN) line maintenance. At St. Michael's Hospital in Toronto, the TPN-line infection rate was at a seven-year low after the practice was instituted of wiping the skin surrounding the catheter with 70% IPA followed by cleansing of the site and hub with 10% PVP-I for two minutes (MacMillan, 1993).

Finally, results in healthy volunteers suggest that while PVP-I plus alcohol (ethyl alcohol in these studies) is similar in efficacy to 70% IPA alone and PVP-I alone in reducing bacteria on the skin, the shorter application time required for PVP-I plus ethyl alcohol (Persist[™]) may result in better compliance with catheter-site preparation protocols (Felton, 1996; Felton & Wolosyn, 1996; 1997). Furthermore, no adverse experiences were reported for PVP-I plus ethyl alcohol (Isodine[®]) (Arata et al., 1993; 1997).

4.3 Venipuncture Site Antisepsis

Mylotte and Tayara (2000) point out that poor skin preparation is the most common cause of blood culture contamination, which results in a large

unnecessary expense to hospitals. They recommend first applying 70% IPA to the skin followed by an iodophor or iodine which is left to dry for 1½ - 2 minutes in order to exert maximal antimicrobial effect. Three controlled studies support this recommendation to prevent contamination of blood cultures or donor blood products with skin flora. PVP-I and IPA in combination was found to be associated with a lower contamination rate than a cetrimide, chlorhexidine and IPA product (Hibicet) (Lee, Ho, Chan, Mak, Hong & Lin, 2002). Schiffman and Pindur (1993) found that a 70% IPA scrub followed by a PVP-I ampule was more effective in reducing the number of contaminants (including *Staphylococcus* spp) than applying the antiseptics in the opposite order (i.e., wiping with an IPA pad followed by a PVP-I swab).

4.4 Handwashing by Hospital Staff

Most of the available data on hand washing protocols that include a combination of PVP-I and alcohol utilize EtOH rather than IPA. This may be due to EtOH's popularity as a skin disinfectant (Hardman, Limbird, Molinoff, Ruddon & Gilman, 1996). However, EtOH and IPA are similar in antimicrobial efficacy (Boyce and Pittet, 2002; Parienti et al., 2002; Furuhashi & Miyamae, 1979; Larson et al., 1990).

A PVP-I (0.5%) and EtOH (83%) hand wash was found to have excellent bacterial reducing activity compared to baseline immediately after washing (75.4% reduction), and was still somewhat effective out to four hours post wash (27.6% reduction). One case of roughening of the skin of the hand was reported immediately after use which improved by 2 hours post wash. No other side effects were reported with PVP-I plus EtOH (Kawana, Matsumoto, Saito, Higuchi, Fujiwara, Takahashi, Yanagihara & Takahashi, 1993). Another study characterized this combination hand wash as effective for routine hygienic handwashing (77% bacterial reduction), and recommended triple disinfection (95% bacterial reduction) when stricter antisepsis was required, such as for surgical preparation (Nagai, Ogase, Takechi, Kodata, & Kumamoto, 1993). In this latter study, no adverse side effects were reported.

5.0 Conclusions

- PVP-I – alcohol combinations have been used in clinical practice for many years (e.g., O'Connor & Goldstein, 2002; MacMillan, 1993) and are recommended by experts in various fields (Benhamou et al., 2002; Mylotte & Tayara, 2000).
- PVP-I – alcohol combinations, including PVP-I/IPA products, are associated with a very low incidence of adverse experiences (Arata, et al., 1993; Kawana, et al., 1993; Nagai et al., 1993).
- Controlled trials have demonstrated similar antimicrobial efficacy of the PVP-I/IPA combination compared to PVP-I alone (Birnbach et al., 2003; Deshmukh & Kramer, 1998; Gilliam & Nelson, 1990) and compared to PVP-I alone and IPA alone (Felton & Wolosyn, 1997).

- The effect of IPA is rapid, as evidenced by a shorter application time required with the combination than with PVP-I alone (Felton, 1996; Felton & Wolosyn, 1996; 1997) and the superiority of the PVP-I/IPA combination compared with PVP-I alone at short sampling intervals (Jarvis et al., 1979; HillTop Study, 1997).
- However, the effect of IPA alone is of limited duration (Boyce & Pittet, 2002). Hence any persistent antimicrobial effect of the combination can be attributed to the PVP-I component (Felton & Wolosyn, 1996; 1997; Jeng, 2001).
- In sum, PVP-I – alcohol combinations, including PVP-I/IPA, have been used successfully for operative site disinfection, catheter/injection site antisepsis, venipuncture site preparation, and handwashing by hospital staff.

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7.0 Tabulation of Abstracted Articles

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
Gilliam & Nelson	1990	operative site disinfection	74% isopropyl alcohol	7%	<p>Sixty patients with total joint surgery were randomized to 1 of 2 groups:</p> <ul style="list-style-type: none"> - skin prep with the traditional 5 min aqueous iodophor scrub followed by aqueous iodophor paint - one-step application of iodophor-in-alcohol solution (DuraPrep™) applied as a paint <p>The skin was allowed to dry and was then covered with a sterile drape. Skin was cultured before preparation and after operation.</p>	Results/Conclusions: Bacterial counts were the same between groups, however, the DuraPrep™ led to improved drape adhesion and less incidence of "drape lift."
Jeng, DK	2001	operative site disinfection	72.5% isopropyl alcohol	8.3%	<p>30 subjects received a 30 s scrubbing application of PVP-I + IPA (Prevail-Fx®) and a 5 min application of PVP-I alone (Betadine®) scrub-and-paint on designated test sites. Sites were allowed to air dry, then were covered by a sterile gauze wrap until sampling.</p>	Results/Conclusion: Both Prevail-Fx® and Betadine® resulted in an average 4.5 log ₁₀ reduction of normal flora per cm ² for inguinal sites and a 3 log ₁₀ reduction per cm ² for abdominal sites both 10 min and 24 hr after application.

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
Arata, Murakami & Hirai	1993	operative site disinfection	50% ethyl alcohol or isopropanol	7.5- 10%	<p>15 healthy male volunteers; the abdomen was divided into 4 quadrants, and each quadrant was treated with one of the following:</p> <ul style="list-style-type: none"> - 100 mg PVP-I + 0.5 ml EtOH in 1 ml - 100 mg PVP-I + 0.5 ml isopropanol in 1 ml - 10 mg available iodine, 50 mg poloxamer & 0.64 ml isopropanol in 1 ml - 75 mg PVP-I in 1 ml (Isodine®) <p>and allowed to dry well. Specimens were collected before & after disinfection using the cylinder scrub method.</p>	<p><u>Results:</u> All preparations showed high antiseptic efficacy. PVP-I + EtOH yielded numerically the greatest bacterial reduction rate. This rate was significantly greater than the rate for Isodine, but no other significant differences among the preparations were found. No adverse experiences were reported, and no subjects complained about color, odor, sticky feeling or irritation with any PVP-I + alcohol solution.</p> <p><u>Conclusion:</u> PVP-I & EtOH is a safe and effective agent for operative site disinfection.</p>

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
O'Connor & Goldstein	2002	operative site disinfection	70% ethyl alcohol	10%	<p>1654 men undergoing varicocelectomy (unilateral or bilateral) only (no other surgical procedures) participated in the study.</p> <p>The skin was shaved and prepared with Betadine[®] gel which was washed away with 70% EtOH. The surgical wound was irrigated with 1% neomycin at the moment the incision was made and then every few minutes until the completion of the procedure.</p> <p>Infection was defined as any evidence of wound swelling, erythema or drainage. Wounds were inspected at 1 and 6 months postoperative and patients were questioned at 1 month regarding signs of infection.</p>	<p><u>Results:</u> No wound infections occurred during the 15-year study period and no adverse reactions were reported with PVP-I + IPA prep and topical neomycin. This translates to an infection rate of $\leq 0.2\%$, compared with a rate of 0.7% reported by Dubin & Amelar (1977).</p> <p><u>Conclusion:</u> PVP-I and IPA has been used successfully in the preparation of the inguinal area for varicocele surgery for 15 years.</p>

Authors	Year	Indication	% alcohol	% PVP-I	Method	Results/Conclusions
Arata, Kamitani, Miyai & Ito	1997	injection site antiseptis	Ethyl alcohol - % not specified	10%	<p>23 healthy volunteers were studied using a crossover design; indigenous bacteria were collected by the cylinder scrub method.</p> <p>A sterilized swab was dipped in either PVP-I + EtOH (Isodine® Field) or 0.5% chlorhexidine + EtOH (Maskin® Ethanol Solution), applied to the skin of the left cubital fossa and allowed to remain there for ~30 sec prior to taking post-disinfection sample.</p>	<p><u>Results:</u> A numerically but not statistically) better bacterial reduction rate (predominantly <i>S. epidermidis</i>) was seen with PVP-I + EtOH (95.1 +/- 11.2%) than with CH + EtOH (93.5 +/- 9.3%). No adverse reactions or hypersensitivity were experienced by any subjects in this study.</p> <p><u>Conclusion:</u> PVP-I & EtOH is a safe and effective agent for injection site antiseptis.</p>
Birnbach, Meadows, Stein, Murray, Thys & Sordillo	2003	catheter site antiseptis	74% isopropyl alcohol	7%	<p>Subjects were 60 women in active labor who requested epidurals. They were randomly assigned to skin preparation with either PVP-I or DuraPrep™ (PVP-I + isopropyl alcohol).</p> <p>Cultures were taken before and after antiseptis, and just before removal of the catheter. The distal tip of the catheter was also cultured.</p>	<p><u>Results:</u> Compared to PVP-I alone, DuraPrep™ provided a greater decrease in the number of positive skin cultures immediately after disinfection, at catheter removal, and in the catheter tip. The two preparations were not significantly different in mean reduction in bacterial burden.</p> <p><u>Conclusion:</u> DuraPrep™ (PVP-I + alcohol) was more effective in limiting bacterial regrowth than PVP-I alone.</p>
MacMillan	1993	catheter site antiseptis	70% isopropyl alcohol	10%	<p>Area surrounding catheter is wiped with alcohol, followed by cleansing of the site and hub with 10% PVP-I for 2 min.</p>	<p><u>Results / Conclusion:</u> St. Michael's Hospital, Toronto's central TPN line-related infection rate is at a 7-year low of 1.5 per 10000 patient-days (1992 data).</p>

Authors	Year	Indication	% alcohol	% PVP-I	Method	Results/Conclusions
Felton	1996	catheter site antisepsis	70% ethyl alcohol	10%	<p>Subjects were 8 healthy volunteers with no known sensitivity to the antiseptics or dressing materials and with at least 10^2 recoverable bacteria per cm^2 skin surface on the arms and who refrained from the use of antibacterial soaps, shampoos, etc. for a period of 2 weeks prior to the study. Treatment sites on the arms of each subject were treated with one of the following:</p> <ul style="list-style-type: none"> - 10% PVP-I alone - 70% IPA alone - PVP-I + IPA (Persist™) - no treatment (negative control) <p>Persist™ was applied in a circular motion for 15, 30, 45 or 60 s, PVP-I for 60 s, and IPA for 30 s. In one group the PVP-I was wiped off with sterile gauze after application; in another group it was allowed to air dry. Sites were sampled with the detergent scrub technique at 10 min or 24 hr. For the 24 hr interval, the sites were covered with an OpSite® IV3000 dressing until sampling.</p>	<p>Results: Persist™ - treated sites had similar bacterial recovery to IPA alone and PVP-I alone- treated sites. There were no significant differences among the treatment groups, including application time for Persist and whether PVP-I was blotted or air dried. All treatments resulted in an average bacterial count ≤ 36 colonies/cm^2 of skin. This was true for both the 10 min and 24 hr sampling intervals. One subject had bacterial counts above the minimum quantifiable limit with the 15 s application time, although this was probably due to contamination.</p> <p>Conclusion: Persist™ catheter site preparation had the same level of antisepsis as either PVP-I or IPA with an application time of 30 s or more. This may increase compliance with catheter insertion site protocols.</p>

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
Felton & Wolosyn	1996	catheter site antisepsis	70% ethyl alcohol	10%	<p>Subjects were 8 healthy volunteers with no known immune dysfunction, sensitivity to the antiseptics or dressing materials and with at least 10² recoverable bacteria per cm² skin surface on the arms and who refrained from the use of antibacterial soaps, shampoos, etc. for a period of 2 weeks prior to the study.</p> <p>Treatment sites on the arms of each subject were treated with one of the following:</p> <ul style="list-style-type: none"> - 10% PVP-I alone - PVP-I + IPA (Persist™) - no treatment (negative control) <p>Persist™ was applied in a circular motion for 30 s, and PVP-I for 60 s. Sites were allowed to air dry before covering with an OpSite IV3000 or standard gauze dressing for 24, 48 or 72 hr. Sites were sampled at these intervals using the scrub-cup technique.</p>	<p><u>Results:</u> Persist™- treated sites had similar bacterial recovery to PVP-I alone- treated sites, regardless of dressing type. Additionally, the 72 hour time period had no effect on the recolonization rate.</p> <p><u>Conclusions:</u> Persist™ had similar antibacterial activity to PVP-I alone under OpSite or standard gauze dressings. The shorter application time required for Persist™ may enhance compliance with catheter-site preparation protocols.</p>

Authors	Year	Indication	% alcohol	% PVP-I	Method	Results/Conclusions
Felton & Wolosyn	1997	catheter site antiseptis	70% ethyl alcohol	10%	<p>Subjects were 8 healthy volunteers with no known immune dysfunction. Subjects did not use any antibacterial soaps, shampoos, etc. during the course of the study. After bacterial flora had stabilized, subjects' skin sites were treated with one of the following:</p> <ul style="list-style-type: none"> - PVP-I - 70% isopropyl alcohol - chlorhexidine gluconate - PVP-I + ethyl alcohol (Persist™) <p>Persist™ was applied to the skin in a circular motion from the mock puncture site outward for 30 s with a swabstick. All other treatments were applied for 1 min. The sites were allowed to dry completely, then covered with sterile OpSite® dressings. Samples were taken at 1, 5, 7 and 9 days post preparation using the detergent scrub technique.</p>	<p><u>Results / Conclusion:</u> All preparations showed high antiseptic efficacy and a similar bacterial recovery function (day 7 and 9 were significantly greater in CFUs than days 1 or 5). At no sampling interval were there any significant among-treatment differences. However, with a shorter application time, PVP-I + alcohol (Persist™) may result in better compliance with catheter-site preparation protocols.</p>

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
HillTop Research Group	1997	catheter site antisepsis	70% ethyl alcohol	10%	Persist™ was compared to Povidone-Iodine (PVP-I) on bacterial counts in the skin surface in a repeated measures design in 129 subjects.	<p><u>Results:</u> Persist™ and PVP-I exhibited significant efficacy relative to untreated control sites at 10 min, 24 hr, 120 hr and 168 hr. PVP-I was slightly but significantly more effective than Persist™ at 24 hr, but the two treatments did not differ at 10 min, 120 hr or 168 hr. No adverse events were reported during the study.</p> <p><u>Conclusion:</u> Persist™ is an effective an safe catheter site antiseptic agent.</p>

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
Schifman & Pindur	1993	venipuncture site antisepsis	70% isopropyl alcohol	10%	Compared "conventional" vs. PREP method for blood culturing in 1546 cultures from 988 patients. Conventional: wipe with two 70% isopropyl alcohol pads and one 10% PVP-I swab "PREP": 10% acetone/ 70% IPA scrub followed by PVP-I ampule. The PVP-I was allowed to dry at least 30 s prior to venipuncture with both methods.	<p><u>Results:</u> A reduced number of contaminants (including <i>S. epidermis</i>, <i>Staphylococcus</i>) was obtained using the PREP method (4.6% of cultures positive using conventional, 2.2% using PREP method).</p> <p><u>Conclusion:</u> IPA followed by PVP-I is more effective in reducing skin flora contamination than PVP-I followed by IPA.</p>

Authors	Year	Indication	% alcohol	% PVP-I	Method	Results/Conclusions
Lee, Ho, Chan, Mak, Hong & Lin	2002	venipuncture site antisepsis	70% isopropyl	10%	<p>PVP-I + isopropyl alcohol was compared to a standard scrub solution (Hibicet, 0.5% cetrimide + 0.05% chlorhexidine) in the preparation of blood platelet donors for venipuncture.</p> <p>The chosen antecubital venipuncture site was scrubbed thoroughly with scrub solution (PVP-I or Hibicet) for 30 s, after which any excess solution was removed with a sterile swab. Then 70% isopropyl alcohol was applied in a concentric spiral manner for another 30 s. The alcohol was allowed to dry completely before venipuncture was performed. Each study period was 9 months. Platelet concentrates were obtained from whole-blood collection (5 platelet samples pooled together) and cultured. 17,951 (Hibicet) and 17,855 (PVP-I + IPA) pooled samples were screened for bacterial contamination.</p>	<p><u>Results:</u> The contamination rate associated with cetrimide + CH + IPA was 0.072%, while the rate associated with PVP-I + IPA was 0.042%, which represents a relative risk reduction of 0.42. The majority of contaminants were <i>Bacillus</i> spp and coagulase-negative <i>Staphylococcus</i>. Differences in organisms isolated following the two preparations were not significant.</p> <p><u>Conclusion:</u> The authors propose that PVP-I + IPA be used on a routine basis for donor skin disinfection in order to better prevent venipuncture-associated contamination of platelet concentrates with skin flora.</p>

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
Calfee & Farr	2002	venipuncture site antiseptis	70% ethyl alcohol	10%	<p>This was a randomized, crossover, investigator-blinded trial of the following preparations:</p> <ul style="list-style-type: none"> - 10% PVP-I - 70% isopropyl alcohol - tincture of iodine - PVP-I + 70% ethyl alcohol (Persist[®]) <p>The venipuncture site was swabbed in a circular motion x3 with 3 swabsticks soaked in antiseptic. After the 3rd swab, the area was allowed to dry completely. Blood cultures were classified as positive or negative, and positive cultures were further classified as true-positive or contaminated.</p>	<p>Results: Contamination rates were very low and not significantly different among the groups, although Persist[™] had numerically the lowest contamination rate. PVP-I alone had the highest rate of contamination, both during a baseline period (it was the standard antiseptic used in the hospital) and during the study.</p> <p>Conclusions: Alcohol-containing antiseptics (Persist[™] and IPA alone) were more cost-effective and offered lower contamination rates. There was a significant decrease in contamination rates with alcohol-containing antiseptics compared to the baseline period, presumably due to their more rapid antimicrobial activity compared to iodophors.</p>

Authors	Year	Indication	% alcohol	% PVP-I	Method	Results/Conclusions
Lilly & Lowbury	1971	handwashing by hospital staff	70% ethyl alcohol	not specified	<p>Five subjects washed with each of the following preparations (one per day) in a Latin Square design:</p> <ul style="list-style-type: none"> - PVP-I + ethyl alcohol - alcoholic 0.5% CH - aqueous 1% cetrimide - 0.1% benzalkonium chloride <p>The control fluid was sterile water. The disinfectant was rubbed onto the whole surface of both hands and wrists with a gauze swab and reapplied as necessary to ensure that the skin was visibly wet for 2 min. Then hands were briefly rinsed under running warm water and dried on a sterile towel. Samples were taken immediately before and after the application of the disinfectant.</p>	<p>Results: PVP-I + EtOH and CH yielded comparable reductions in skin flora. Both of these agents were significantly more effective than cetrimide or benzalkonium chloride.</p> <p>Conclusion: PVP-I + EtOH and CH are effective and safe agents for antiseptic handwashing.</p>

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
Kawana, Matsumoto, Saito, Higuchi, Fujiwara, Takahashi, Yanagihara & Takahashi	1993	handwashing by hospital staff	83% ethyl alcohol	0.50%	<p>Subjects were 21 hospital workers who had refrained from using any antibacterial soap, shampoo, deodorant, etc. and any oral antibiotics and avoided handwashing as much as possible for 24 hours.</p> <p>Baseline samples were taken, and 3 days later both hands were washed with soap & water followed by HAD Hand Wash (0.50% PVP-I (Isodine[®]) + 83% ethyl alcohol). HAD Hand Wash was taken onto the palm and rubbed into the hands for 3 min until the solution dried. Samples were taken immediately from the right hand and at 30 min, 1 hr, 2 hr and 4 hr from the left hand in different subjects. All samples (including baseline) were taken using FDA's Glove Juice Technique.</p>	<p><u>Results:</u> Immediately after washing there was a reduction in bacterial cells counts of 75.4% compared to baseline. This tended to decrease over time, with reduction rates of 69.0% at 30 min, 71.9% at 1 hr, 35.8% at 2 hr and 27.6% at 4 hr. All of the bacteria that were detected were Gram-positive bacteria native to the sebaceous glands, sweat glands or skin surface.</p> <p>One case of roughening of the skin of the hand was observed immediately after use of the PVP-I + EtOH wash, but this improved by 2 hr and no other notable side effects were observed.</p> <p><u>Conclusion:</u> PVP-I & EtOH is a safe and effective agent for antiseptic handwashing.</p>

Authors	Year	Indication	% alcohol	% PVP-I	Method	Results/Conclusions
Kirita, Hamano, Ochi, Ihara et al	1993	handwashing by hospital staff	83% ethyl alcohol	0.50%	<p>HAD Hand Wash (PVP-I (Isodine[®]) + ethyl alcohol) was compared with the standard wash (Welpas[®], alkonium chloride alcohol lotion) at 6 sites along the surgical ward. Subjects were 30 medical staff with no abnormalities of thyroid function, no hypersensitivity to iodine, no dermatological disease of the hand or fingers and were not pregnant.</p> <p>For each washing, 3 ml of HAD Hand Wash was taken in the palm and rubbed for approx. 3 min until the solution dried. Each study period was 4 weeks, during which each subject washed with the test material 2-10 times daily. Specimens were taken using the palm-stamp method.</p> <p>Identification of bacterial spp and colony counts were made on the left hand before and after disinfection on the final day of the study period.</p>	<p>Results: The mean reduction rate of the number of colonies with PVP-I + ethyl alcohol (compared to Welpas[®]) was 86.9 +/- 21.2% for the first study day and 91.5 +/- 12.8% for the final study day. The most frequently isolated organism before disinfection was <i>S. epidermidis</i>, but after disinfection the number of subjects from which this organism was isolated was reduced by 83.3%. Similarly, the presence of <i>S. aureus</i> was reduced by 92.99%. <i>Bacillus</i> was reduced from 75.8-100%, probably due to spore formation; however, <i>Bacillus</i> is generally considered non-pathogenic and therefore did not pose a clinical problem.</p> <p>A transient feeling of dry skin was reported by 2 subjects which was considered attributable to the effect of ethyl alcohol. No other side effects were reported.</p> <p>Conclusion: PVP-I & EtOH is a safe and effective agent for antiseptic handwashing.</p>

<u>Authors</u>	<u>Year</u>	<u>Indication</u>	<u>% alcohol</u>	<u>% PVP-I</u>	<u>Method</u>	<u>Results/Conclusions</u>
Nagai, Ogase, Takechi, Kodata & Kumamoto	1993	handwashing by hospital staff	83% ethyl alcohol	0.50%	The antiseptic effect of PVP-I + EtOH (HAD Hand Wash) was evaluated in 40 subjects. Pre and post treatment bacterial counts assayed by "glove juice" method: Hand was washed with soap or HAD Hand Wash and inserted into a rubber glove filled with sampling solution. Hands were massaged in the solution and then the solution was decanted and smeared onto agar medium for determination of bacterial counts.	<p><u>Results:</u> Triple disinfection (3x washing) resulted in 95% disinfection, single washing resulted in 77% disinfection. ($p < .0001$). The maximal effects were seen 30-60 minutes after washing and lasted for up to 4 hours (52% with a single wash, $p < .05$). No adverse events were reported.</p> <p><u>Conclusion:</u> Disinfecting once with PVP-I + EtOH is sufficient for routine hygienic handwashing, while disinfecting 3 x is recommended for stricter antisepsis such as surgical handwashing.</p>

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Jarvis, Wynne, Enwright & Williams	1979	handwashing by hospital staff	not specified	10%	<p>Six hospital laboratory workers with no history of skin disease or infection washed with one of the following for a period of two minutes:</p> <ul style="list-style-type: none"> - PVP-I surgical scrub (Betadine®) - chlorhexidine surgical scrub (Hibiscrub®) - 95% alcohol, 0.5% CH & 0.1% glycerol - alcoholic PVP-I (Betadine®) solution - plain bar soap - Betadine® bar soap <p>Each subject used all agents in randomized order in a crossover design with a minimum of 10 days between agents. Each agent was dispensed in 10 ml aliquots and 2 aliquots were used per wash. Alcohol agents were allowed to evaporate after vigorous rubbing, and detergent solutions were rinsed and dried from the hands with sterile towels. Sterile surgical gloves were worn for 90 minutes after washing.</p>	<p>Methods continued: The effect of multiple washings was assessed by six washings (3/day) following wearing of surgical gloves for 90 min. Specimens were obtained by rinsing the hands with Ringer's solution, neutralizing residual antiseptic and plating the runoff.</p> <p>Results: Compared to regular bar soap, PVP-I + alcohol yielded the best mean reduction in flora immediately after hand washing (95.36%), followed by alcoholic CH (87.77%), PVP-I (87%), CH (61.98%) and PVP-I bar soap (54.67%). After the sixth wash, alcoholic CH and alcoholic PVP-I produced the greatest mean reduction in flora (97.78% and 93.34%), followed by PVP-I (85.78%), CH (78.12%) and PVP-I bar soap (58.33%). Results were similar after wearing gloves for 90 min. Alcoholic solutions were superior in disinfecting and preventing recolonization than detergent agents.</p> <p>Conclusion: PVP-I + alcohol was more effective immediately after handwashing compared to PVP-I, bar soap and CH. Alcoholic chlorhexidine was superior to the other agents at other time points.</p>

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King & Price	1963	handwashing by hospital staff	not specified	not specified	<p>Five subjects washed using the serial basin hand-scrubbing technique of Price (washing in a series of basins of sterile water, applying disinfectant, and washing in a second series of basins). Antiseptics tested were:</p> <ul style="list-style-type: none"> - Ioclide - Virac - Ioprep - Betadine <p>applied with gauze friction for 120 s.</p> <p>Simple alcoholic and aqueous solutions having approximately the same iodine content were tested in like manner. Bacterial counts of the washings were obtained.</p>	<p><u>Results:</u> 1% aqueous iodine solution applied for 2 min was less efficacious than the alcoholic solutions and was irritating to the eyes, nasal passages and skin. When plotted against data from other studies, the iodophors were more effective than bar soap but less effective than 1% iodine in 70% alcohol. Additionally, iodine + ethyl alcohol was found to be more effective than iodine + isopropyl alcohol.</p> <p><u>Conclusion:</u> Iodophors are intermediate in effectiveness between soap and water and tincture of iodine (TI) + alcohol.</p>

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Deshmukh & Kramer	1998	handwashing by hospital staff	62% ethyl alcohol	not specified	Five minute PVP-I only scrub of hands forearms and elbows, vs. 1 minute PVP-I scrub followed by application of EtOH foam onto hands, forearms and elbows. An additional group which did not scrub was examined for bacterial colonies as a control. Samples were taken from fingertips at 1 and 2 hours after scrub.	<p><u>Results:</u> Both scrub regimens resulted in significant reduction in the number of bacterial colonies. No difference between the two (5 min vs. 1 min).</p> <p><u>Conclusion:</u> PVP-I + EtOH was not superior, but equally as effective as PVP-I alone, and may be more cost effective and practical in situations where water is not available.</p>