

**TAB 8**

**Excerpt of comments from CTFA/SDA in regards to the log reduction performance criteria (75N-183H – CP7, Appendix C)**

## APPENDIX C PERFORMANCE CRITERIA

- A review of the published scientific literature and product brochures provides data supporting the surrogate endpoints proposed by the Industry Coalition.
- Many NDA preparations (containing Chlorhexidine gluconate) and OTC preparations containing Category I active ingredients (alcohol and povidone-iodine) do not meet the performance criteria proposed in the 1994 TFM.
- Neutralization of substantive active ingredients must be carried out in every step of the sampling procedure to insure accurate product evaluation.

### Introduction

Three *in vivo* tests are proposed to demonstrate the efficacy of topical healthcare antimicrobial products:

- ASTM E1174 Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations
- ASTM E1115 Standard Test Method for Evaluation of Surgical Hand Scrub Formulations
- ASTM E1173 Standard Test Method for Evaluation of a Pre-operative Skin Preparation.

These methods have been used for many years to evaluate efficacy. However, over the years certain modifications have been made by some users to improve the reliability and reproducibility of these tests. This makes comparison of data between tests difficult as the test conditions may vary. One of the most important modifications adopted in the last decade has been the incorporation of neutralizers at all steps in the sampling process. This is important because substantive topical antimicrobial agents are frequently removed from the skin during the sampling process and can continue to inhibit and/or kill bacteria during subsequent handling leading to a false measure of efficacy. This example underscores the importance of having standardized, defined, and peer-reviewed test methodology, as well as the necessity for having an easy mechanism to update methods when scientific evaluation determines a fundamental flaw.

For the purposes of full disclosure, rather than exclude studies that are scientifically weak, we are presenting in the tables of Appendices D and E all of the studies discovered in our literature search. In those tables, shading denotes that a result does not meet the performance criteria set forth in the 1994 TFM. In preparing the tables in this section examples were excluded where the sample

timings did not closely coincide with the recommended sample times, the concentration of active ingredient was omitted, or which involve antimicrobial impregnated implements. Each tally table provides the number of examples that passed or failed the criteria proposed by the SDA/CTFA Industry Coalition in the Healthcare Continuum Model (HCCM) proposal and the number that passed or failed the criteria proposed by the Agency in the 1994 TFM. The score is underlined where there is a difference in the number of examples that met the criteria between the HCCM proposal and the 1994 TFM.

The amount of product used, product forms, and many other parameters that may have affected the outcome of each test are noted in the tables found in Appendix D. With one exception, the impact of those differences on the reduction of bacterial loads was not considered in the development of the tally tables. Because the inclusion of neutralizers in all sampling fluids of substantive ingredients was viewed as vital to understanding the data presented its impact is briefly discussed under each method.

The following review proposes performance criteria for each category, primarily using data available in the literature for materials the FDA has recognized as being efficacious, i.e. NDA products containing Chlorhexidine and products containing alcohol and iodine (Category I ingredients). Many well-known and highly recommended products that contain Chlorhexidine, alcohol and iodine products do not meet the performance criteria for the methods provided in the 1994 TFM for three categories of products.

## HEALTHCARE PERSONNEL HAND PREPARATIONS

- Most products containing ingredients already known to be efficacious meet the performance criteria proposed in the HCCM for healthcare personnel hand preparations: 1.5 log<sub>10</sub> reduction after the 1<sup>st</sup> wash and a 2 log<sub>10</sub> reduction after the 10<sup>th</sup> wash.
- Many products containing ingredients already known to be efficacious do not meet the performance criteria set for healthcare personnel handwashes in the 1994 TFM: 2 log<sub>10</sub> reduction after the 1<sup>st</sup> wash and a 3 log<sub>10</sub> reduction after the 10<sup>th</sup> wash.
- Neutralization of all sampling fluids and media is critical for accurate evaluation of products with substantive active ingredients.

### Chlorhexidine Gluconate

Appendix D, Table 1 (Healthcare Personnel Hand Preparations – Chlorhexidine gluconate) is a compilation of data on Chlorhexidine gluconate (CHG) products using methods based on ASTM E1174 Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations (HCPHW). While Chlorhexidine gluconate is not an active ingredient under consideration for this monograph, it is an NDA approved OTC drug widely used as a Healthcare Personnel Handwash. Therefore, it should meet the performance criteria proposed for products to be regulated under this monograph.

The following sections compare the performance of Chlorhexidine gluconate formulations against the criteria proposed by the Industry Coalition in the HCCM and by FDA in the 1994 TFM. As Chlorhexidine gluconate is a substantive antimicrobial ingredient, the effect of neutralization on the performance of these products is discussed.

**HCCM Proposal:** In 1996 the Industry Coalition proposed a standard of 1.5 log<sub>10</sub> reduction after the first wash and a 2 log<sub>10</sub> reduction after the 10<sup>th</sup> wash for the Healthcare Personnel Preparation Category.

All but one example in the reported studies using Chlorhexidine gluconate formulations met those standards.

**1994 TFM:** The proposed performance criteria were a 2 log<sub>10</sub> reduction after the first wash and a 3 log<sub>10</sub> reduction after the 10<sup>th</sup> wash.

Thirty-three examples evaluated 4% Chlorhexidine gluconate formulations. Where neutralizer was incorporated only in the plating media, these formulations met the 1994 TFM efficacy standards after wash #1 in five of nine cases and after wash #10 in all nine cases (Bartzokas *et al.* 1987; Ciba-Geigy 1990; Purdue Frederick 1986; Steris 1998; Huntington 1994; Stiles & Sheena 1987; Ballard 1985). When neutralizer was incorporated in the glove for wash #10, these formulations met these efficacy standards after wash #1 in two of seven cases and after wash #10 in no cases (Ciba-Geigy 1995; Jampani *et al.* 1998; Billhimer *et al.* 1998; Sheena and Stiles 1983c).

Seven studies evaluated 2% Chlorhexidine gluconate formulations. Two of them incorporated neutralizer only in the plating media. One formulation met the 2 log<sub>10</sub> reduction after the first wash (Stiles and Sheena 1987). Another formulation met the 3 log<sub>10</sub> reduction after the 10<sup>th</sup> wash (Peterson *et al.*, 1978). Three examples incorporated neutralizer in the glove, and none met either of the surrogate endpoints set in the 1994 TFM (Johnson 1998a; Sheena and Stiles 1983c).

A single study evaluated a 0.75% Chlorhexidine gluconate formulation (Steris 1998). Neutralizer was incorporated only in the medium. The formulation met the established criteria after both the first and tenth washes.

**Neutralization:** These results clearly demonstrate the importance of neutralizer in the sampling fluids. If neutralizer is added to all sampling media, including that in the glove, the reduction seen from use of substantive ingredients is usually less than if neutralizer is incorporated only in the media. This is shown as a greater proportion of examples failing to meet the criteria when neutralizer is added to the glove than when neutralizer is added to the medium. As the scientific community has learned of the impact of antimicrobial agents carried into the sample fluids, they incorporated that knowledge into the most recent ASTM version of ASTM E1174, Standard Test Method for Evaluation of the Effectiveness of Health Care or Consumer Handwash Formulations, by incorporating neutralizers in all sampling media.

Tally Table: HCPHW Method – Chlorhexidine Gluconate

	1994 TFM		HCCM	
	1 WASH	10 WASHES	1 WASH	10 WASHES
	2 log <sub>10</sub>	3 log <sub>10</sub>	1.5 log <sub>10</sub>	2 log <sub>10</sub>
	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail
<b>4% CHG</b>				
Glove Neutralization	<u>2/5</u>	<u>0/4</u>	<u>6/1</u>	<u>4/0</u>
Other Neutralization <sup>1</sup>	<u>10/6</u>	<u>22/1</u>	<u>16/0</u>	<u>23/0</u>
<b>2% CHG</b>				
Glove Neutralization	<u>0/3</u>	<u>0/1</u>	<u>1/2</u>	<u>1/0</u>
Other Neutralization <sup>2</sup>	1/1	4/0	1/1	4/0
<b>0.75% CHG</b>				
Media only Neutralization	1/0	1/0	1/0	1/0

Other Neutralization includes studies where it is unknown where neutralizer was incorporated in the protocol or where it was added to the plating medium only.

<sup>1</sup> Gojo 1999, Peterson *et al.* 1978; Jampani *et al.* 1998; Paulson 1994; Sheena and Stiles 1983; Stuart Pharmaceuticals 1986; Dial Corporation Undated; Ciba-Geigy 1990; Ballard 1996; Bartzokas *et al.* 1987; Ciba-Geigy 1990; Purdue Frederick 1986; Steris 1998; Huntington 1994; Stiles and Sheena 1987; Bartzokas *et al.* 1987; Ciba-Geigy 1990; and Ballard 1985.

<sup>2</sup> Gojo 1999; Huntington 1992; Ballard 1998; Peterson 1978; Stiles & Sheena 1987.

*An underline indicates that there is a difference between the number of examples that meet the criteria of the HCCM and the criteria of the 1994 TFM.*

## Alcohol

Appendix D, Table 2 (Healthcare Personnel Hand Preparations -- Alcohol) is a compilation of data on alcohol-based products using HCPHW methods. Alcohol was accepted in the 1994 TFM as efficacious for use as a healthcare personnel hand preparation. The alcohol formulations evaluated contained between 60 and 70% Ethanol. Alcohol is not a substantive antimicrobial agent, and therefore the tally table is not broken down by neutralization method.

**HCCM Proposal:** The 1996 Healthcare Continuum Model proposed a standard of 1.5 log<sub>10</sub> reduction after the first wash and a 2 log<sub>10</sub> reduction after the 10<sup>th</sup> wash for the Healthcare Personnel Preparation Category.

All of the reported studies using alcohol formulations met the first wash standard and 15 of the 21 studies met the tenth wash standard.

**1994 TFM:** The proposed performance criteria were a 2 log<sub>10</sub> reduction after the first wash and a 3 log<sub>10</sub> reduction after the 10<sup>th</sup> wash.

60% Ethanol formulations met the performance criteria after wash #1 in 5 of 8 examples and after wash #10 in 1 of 6 examples (Johnson 1998; Jones *et al.* 2000; Johnson Wax Undated; SDA/CTFA 1995a).

When the concentration of ethanol was increased to 62%, all of nine examples met the performance criterion after wash #1. Only one of nine examples met the performance criterion after wash #10 (Johnson & Johnson Medical 2000; Kimberly-Clark 1999; Gojo 1999; Paulson *et al.* 1999; Dyer *et al.* 1998; Paulson 1994)

There are three examples evaluating 70% ethanol formulations (Huntington 1995; Dyer *et al.* 1998). All three met the criterion after Wash #1 and all three failed to meet the criterion after wash #10.

There are four additional examples using other alcohol examples. A study using 70% isopropyl alcohol showed that the product would not meet the performance criterion after wash #10 (Aly & Maibach 1980). A study using 80% ethanol showed that the product met the performance criterion after wash #1 and not after wash #10 (SDA/CTFA 1995). An alcohol foam product met the criterion after wash #10 (SDA/CTFA 1996). An example using an unspecified concentration of alcohol met the criterion after wash #1, but not after wash #10 (Kaiser *et al.* 2000).

**Neutralization:** Since alcohol evaporates from the hands after application, it does not carry over into the sampling fluid. Therefore, the incorporation of neutralizers in the glove does not have the same effect on the results as it has for substantive active ingredients.

Tally Table: HCPHW Method – Alcohol

	1994 TFM		HCCM	
	1 WASH	10 WASHES	1 WASH	10 WASHES
	2 log <sub>10</sub>	3 log <sub>10</sub>	1.5 log <sub>10</sub>	2 log <sub>10</sub>
	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail
<b>Alcohol</b>				
60% Ethanol	<u>5/3</u>	<u>1/5</u>	8/0	<u>6/0</u>
62% Ethanol	9/0	<u>1/8</u>	9/0	<u>7/2</u>
70% Ethanol	3/0	<u>0/3</u>	3/0	<u>1/2</u>
Other	2/0	1/3	2/0	2/2

An underline indicates that there is a difference between the number of examples that met the criteria of the HCCM and the criteria of the 1994 TFM.

### Povidone-iodine

Appendix D, Table 3 (Healthcare Personnel Hand Preparations -- Povidone-iodine) is a compilation of data on iodine-containing products using the HCPHW method. Povidone-iodine is recognized in the 1994 TFM as being efficacious as a healthcare personnel hand preparation. Povidone-iodine products are sometimes used as handwashes. Povidone-iodine is a substantive antimicrobial ingredient.

**HCCM Proposal:** The 1996 Healthcare Continuum Model proposed a standard of 1.5 log<sub>10</sub> reduction after the first wash and a 2 log<sub>10</sub> reduction after the 10<sup>th</sup> wash for the Healthcare Personnel Preparation Category. Sheena and Stiles (1983) studied the use of washes over the range of 25 ppm to 7500 ppm available iodine. The 7500 ppm available iodine sample met the HCCM proposed criteria for the healthcare category after a single wash. In 1985 Stiles and Sheena evaluated the efficacy of PVP-I formulations over the range of 0.01 to 0.75% PVP-I. All formulations containing 0.01% PVP-I or greater met the performance criteria after the first wash when the baseline contamination met 3.7 log<sub>10</sub>. When the baseline contamination was less than 2.5 log<sub>10</sub>, none of the formulations met this criterion. In a subsequent study Stiles & Sheena (1987) evaluated iodine washes over the range of 200 to 7500 ppm available iodine. All met the proposed criteria after a single wash. A 7.5% PVP-I formulation met the 2 log<sub>10</sub> reduction criteria after the tenth wash (Peterson *et al.* 1978), while another 7.5% PVP-I formulation met the 1.5 log<sub>10</sub> reduction criteria after the first wash (Rotter 1984). In a study where the concentration of active ingredient was unspecified, the formulation met the criteria at both wash samplings (Kaiser *et al.* 2000).

**1994 TFM:** The proposed performance criteria were a 2 log<sub>10</sub> reduction after the first wash and a 3 log<sub>10</sub> reduction after the 10<sup>th</sup> wash. After a single wash none of the samples met the 2 log<sub>10</sub> reduction criteria in the Sheena and Stiles (1983) study (0.0025-0.75% available iodine), however all three examples met the criterion in the 1987 Stiles and Sheena study (0.02-0.75% available iodine). In the 1983 Sheena and Stiles study, only the 0.75% PVP-I example using a baseline of > 3.8 log<sub>10</sub> met the performance criterion after one wash. Peterson *et al.* (1978) conducted a healthcare personnel handwash study using a 7.5% PVP-I formulation. This formulation met the 3 log<sub>10</sub> reduction criterion after wash #10. Rotter (1984) showed a 7.5% PVP-I formulation to meet the 2 log<sub>10</sub> reduction criterion after a single wash. Kaiser *et al.* (2000) presented an iodine formulation of unspecified concentration that met both performance criteria.

No tally table is incorporated because of the limited data for povidone-iodine in this application.

## SURGICAL SCRUB PREPARATIONS

- Most products containing ingredients already known to be efficacious meet the performance criteria proposed in the HCCM: a 1 log<sub>10</sub> reduction after wash #1, a 1.5 log<sub>10</sub> reduction after wash #2, a 2 log<sub>10</sub> reduction after wash #11, and the flora should not exceed baseline levels 6 hours after use.
- Many products containing ingredients already known to be efficacious do not meet the performance criteria proposed in the 1994 TFM: a 1 log<sub>10</sub> reduction after wash #1, a 2 log<sub>10</sub> reduction after wash #2, a 3 log<sub>10</sub> reduction after wash #11, and the flora should not exceed baseline levels 6 hours after use.
- Neutralization of all sampling fluids and media is critical for accurate evaluation of products with substantive active ingredients.

### Chlorhexidine Gluconate

Appendix D, Table 4 (Chlorhexidine Gluconate – Surgical Scrub) is a compilation of data on Chlorhexidine gluconate products using methods based on ASTM E1115 Standard Test Method for Evaluation of Surgical Hand Scrub Formulations. While Chlorhexidine gluconate is not an active ingredient under consideration for this monograph, it is an approved OTC drug widely used as a Surgical Scrub. Therefore, it should meet any performance criteria proposed for products to be regulated under this monograph.

The following sections compare the performance of Chlorhexidine gluconate formulations against the criteria proposed by the Industry Coalition and by FDA in the 1994 TFM. As Chlorhexidine gluconate is a substantive antimicrobial ingredient, the effect of neutralization on the performance of these products is discussed.

**HCCM Proposal:** The 1996 Healthcare Continuum Model proposed performance criteria of 1 log<sub>10</sub> reduction after the first wash, a 1.5 log<sub>10</sub> reduction after wash #2 and a 2 log<sub>10</sub> reduction after wash #11 for preparations in the Surgical Scrub Category. To show persistence, the flora should not exceed baseline levels 6 hours after use.

The studies in which 4% Chlorhexidine gluconate preparations were evaluated using neutralizers only in the media include: Peterson *et al.* 1978; Huntington 1994; Purdue Frederick 1985; Aly & Maibach 1988; Mulberry *et al.* 2000; Loeb *et al.* 1997; Paulson 1994; Johnson and Johnson Medical 2000; and Rotter 1984. In those studies, the 4% Chlorhexidine gluconate preparations met the efficacy

standards set at washes #1, #2, and #11 in all but one case when the neutralizers were incorporated in the media only. In those studies where use of neutralizer was not indicated (Ballard undated; Jampani *et al.* 1998; Rosenberg *et al.* 1976; Stuart Pharmaceuticals 1986; Ciba-Geigy 1990; Johnson Wax, undated; Dial Corporation, undated), the 4% Chlorhexidine gluconate preparations met the efficacy standards in all cases but two. However where neutralizers are added to the glove during sampling, many more formulations failed to meet the proposed standards (Faoagali *et al.* 1995; Cremieux *et al.* 1989; Aly & Maibach 1983; Babb *et al.* 1991; Morrison *et al.* 1986; Larson *et al.* 1986; Butz *et al.* 1990; Hobson *et al.* 1998; Larson *et al.* 1987; Bendig 1990; Larson *et al.* 1987; Larson *et al.* 1990; Larson *et al.* 2001; Larson and Bobo 1992; Lowbury *et al.* 1974; Pereira *et al.* 1990; Rotter 1984; Reverdy *et al.* 1984; Sheena and Stiles 1983c; Larson and Loughon 1987). While the 1 log<sub>10</sub> reduction required after wash #1 was met in ten instances, it was not met in another eighteen examples. After wash #2, all three examples met the 1.5 log<sub>10</sub> reduction required; and after wash #11 three of six examples met the 2 log<sub>10</sub> reduction required.

Two studies evaluated 2% Chlorhexidine gluconate preparations using neutralizer only in the media (Paulson 1994; Huntington 1992). One preparation failed to meet the wash #1 efficacy criteria of a reduction of 1 log<sub>10</sub>, but met the efficacy criteria at the other two time points. The other preparation met the efficacy standards at all sampling times. When neutralizers were added to the glove (Jones *et al.* 2000; Larson *et al.* 1989; Sheena and Stiles 1983c; Larson and Loughon 1987), the reduction after wash #1 was met in one instance and not met in four others. In the one study carried out to wash #11, that 2% formulation met the efficacy criteria at all time points. In two examples (Ballard 1998, Johnson Wax undated) where neutralization was not indicated in the text, the 2% formulations met the efficacy criteria at all sampling points.

A 0.5% Chlorhexidine gluconate was evaluated in two studies (Lowbury *et al.* 1974; Stuart Pharmaceuticals 1986). The status of neutralization was not defined in the Stuart brochure. This preparation met the efficacy criteria after washes #1 and #2, but not after #11. In the Lowbury study (which included neutralizer in the glove), 0.5% Chlorhexidine gluconate did not meet the efficacy criteria after wash #1 when applied as a liquid or with gauze.

**1994 TFM:** The standard proposed was a 1 log<sub>10</sub> reduction after wash #1, a 2 log<sub>10</sub> reduction after wash #2, a 3 log<sub>10</sub> reduction after wash #11, and the flora should not exceed baseline levels 6 hours after use.

In studies of 4% Chlorhexidine gluconate preparations evaluated using neutralizers only in the media, the efficacy standards set at washes #1 and #2 are met in all but one case. However, three of the thirteen examples fail to meet the efficacy criteria of 3 log<sub>10</sub> reduction after wash #11. In those studies where use of neutralizer was not indicated all but two of the 4% Chlorhexidine gluconate

preparations met the efficacy standards after wash #1; eight of ten products met the efficacy standards after wash #2 and only six of the eleven products met the wash #11 standards. Where neutralizers were added to the glove during sampling, many more formulations failed to meet the proposed standards. While the 1 log<sub>10</sub> reduction required after wash #1 was met in ten instances, it was not met in another eighteen studies. After wash #2, only one of three examples met the 1.5 log<sub>10</sub> reduction required, and after wash #11 only two of six examples met the 2 log<sub>10</sub> reduction required.

Two studies evaluated 2% Chlorhexidine gluconate preparations using neutralizer only in the media. One preparation failed to meet the wash #1 efficacy standard of a reduction of 1 log<sub>10</sub>, but met the efficacy standards at the other two time points. The other preparation met the efficacy standards at wash #1 and wash #11, but not after wash #2. When neutralizers were added to the glove, the reduction after wash #1 was met in one instance and not met in four others. In the one study carried out to wash #11, the 2% formulation did not meet the efficacy criterion after washes #2 and #11. In the two examples where neutralization was not indicated in the reports, both formulations met the efficacy criteria after wash #1, one of two cases after wash #2, and both after wash #11.

A 0.5% Chlorhexidine gluconate was evaluated in two studies (Lowbury *et al.* 1974; Stuart Pharmaceuticals 1986). The status of neutralization was not defined in the Stuart brochure. This preparation met the efficacy criteria after wash #1, but not after washes #2 or #11. In the Lowbury study, 0.5% Chlorhexidine gluconate did not meet the efficacy criteria after wash #1 when applied as a liquid or with gauze.

**Neutralization:** These results clearly demonstrate the importance of neutralizer in the sampling fluids. If neutralizer is added to all sampling media including that in the glove, the reduction seen from use of substantive ingredients is usually less than if neutralizer is incorporated only in the media. This is shown as a greater proportion of examples failing to meet the criteria where neutralizer is added to the glove than when neutralizer is not added to the glove sampling fluid. As the scientific community has learned of the impact of antimicrobial agents carried into the sample fluids, they incorporated that knowledge into the most recent ASTM version of the Surgical Scrub method.

## Alcohol

Appendix D, Table 5 (Alcohol—Surgical Scrub) compiles data on alcohol products using the Surgical Scrub method. Alcohol is an approved OTC drug used for this application. Therefore, it should meet any standard proposed for products to be regulated under this monograph. Alcohol is not a substantive antimicrobial agent and therefore the tally table is not broken down by neutralization method.

There are six examples of surgical scrub studies using 60% Isopropyl alcohol preparations; twenty-one using 70% Isopropyl alcohol preparations; one example uses 60% Ethanol, another uses 70% “alcohol” and two more uses 70% Ethanol.

**HCCM Proposal:** The 1996 Healthcare Continuum Model proposed a standard of 1 log<sub>10</sub> reduction after the first wash, a 1.5 log<sub>10</sub> reduction after wash #2 and a 3 log<sub>10</sub> reduction after wash #11. To show persistence, the flora should not exceed baseline levels 6 hours after use.

All six of the 60% Isopropyl alcohol examples met the 1 log<sub>10</sub> reduction criteria after a single scrub (Morrison *et al.* 1986; Larson *et al.* 1986; Larson *et al.* 1987). Sixteen of twenty-one examples of 70% Isopropyl alcohol studies met the reduction criteria after a single wash (Larson *et al.* 1986; Babb *et al.* 1991; Aly & Maibach 1979; SDA/CTFA 1995; Reverdy *et al.* 1984; Hough Hoseason & Co. Ltd., Undated) while five did not (Morrison *et al.* 1986; Larson & Bobo 1992; Lowbury *et al.* 1974).

Three studies evaluated Ethanol using the Surgical Scrub procedure. Using 60% Ethanol (Jones *et al.* 2000) resulted in meeting the HCCM criteria at all three scrub times. Using 70% Ethanol, one example met the performance criteria after the first wash (Reverdy *et al.* 1984), while another example did not (Lowbury *et al.* 1974).

**1994 TFM:** The standard proposed was a 1 log<sub>10</sub> reduction after wash #1, a 2 log<sub>10</sub> reduction after wash #2, a 3 log<sub>10</sub> reduction after wash #11, and the flora should not exceed baseline levels 6 hours after the first wash.

All six of the 60% Isopropyl alcohol examples met the 1 log<sub>10</sub> reduction criteria after a single wash. Sixteen of twenty-one examples of 70% Isopropyl alcohol studies met the reduction criteria after a single wash while five did not.

Use of a 60% Ethanol preparation met the TFM criteria at all times except after wash #11 (Jones *et al.*, 2000). Using 70% Ethanol, one example met the performance criteria after the first wash (Reverdy *et al.* 1984), while another example did not (Lowbury *et al.* 1974).

Tally Table: Surgical Scrub Method -- Alcohol

HCCM			
	WASH #1	WASH #2	WASH #11
	1 log <sub>10</sub>	1.5 log <sub>10</sub>	2 log <sub>10</sub>
	Pass/Fail	Pass/Fail	Pass/Fail
60% IPA	6/0	0/0	0/0
60% Ethanol	1/0	1/0	<u>1/0</u>
70% IPA	<u>16/5</u>	<u>1/0</u>	0/1
70% Ethanol	1/1	0/0	0/0
TFM			
	WASH #1	WASH #2	WASH #11
	1 log <sub>10</sub>	2 log <sub>10</sub>	3 log <sub>10</sub>
	Pass/Fail	Pass/Fail	Pass/Fail
60% IPA	6/0	0/0	0/0
60% Ethanol	1/0	1/0	<u>0/1</u>
70% IPA	<u>15/4</u>	<u>0/1</u>	0/1
70% Ethanol	1/1	0/0	0/0

An underline indicates that there is a difference between the number of examples that met the criteria of the HCCM and the criteria of the 1994 TFM.

Where neutralizers were added to the glove, six examples met the surrogate endpoint at wash #1 (Aly & Maibach 1983; Faoagali *et al.* 1995; Hobson *et al.* 1998; Pereira *et al.* 1990; Larson *et al.* 1990; Kundsinn and Walter 1973), while four did not (Cremieux *et al.* 1989; Pereira *et al.* 1997; Babb *et al.* 1991, Larson and Bobo 1992). Following wash #2, only one example met the proposed standards; no examples met the 3 log<sub>10</sub> reduction after wash #11.

Six examples failed to detail the absence or inclusion of neutralizers. All six examples reduced the bacteria on the hands by 1 log<sub>10</sub> after wash #1. Two of five examples reduced the bacteria on the hands by 2 log<sub>10</sub> after wash #2. No examples met a reduction of 3 log<sub>10</sub> after wash #11.

**Neutralization:** These results clearly demonstrate the importance of neutralizer in the sampling fluids. If neutralizer is added to all sampling media including that in the glove, the reduction seen from use of substantive ingredients is usually less than if neutralizer is incorporated only in the media. This is shown as a greater proportion of examples failing to meet the criteria when neutralizer is added to the glove than when it is not added to the glove. As the scientific community has learned of the impact of antimicrobial agents carried into the sample fluids, they incorporated that knowledge into the most recent ASTM version of the Surgical Scrub method.

Tally Table: Surgical Scrub Method -- Povidone Iodine

HCCM			
	WASH #1	WASH #2	WASH #11
	1 log <sub>10</sub>	1.5 log <sub>10</sub>	2 log <sub>10</sub>
	Pass/Fail	Pass/Fail	Pass/Fail
<b>7.5% PVP-I</b>			
<b>Glove Neutralization</b>	6/4	1/2	<u>2/3</u>
<b>Other Neutralization</b>	12/0	<u>8/2</u>	<u>4/6</u>
TFM			
	WASH #1	WASH #2	WASH #11
	1 log <sub>10</sub>	2 log <sub>10</sub>	3 log <sub>10</sub>
	Pass/Fail	Pass/Fail	Pass/Fail
<b>7.5% PVP-I</b>			
<b>Glove Neutralization</b>	6/4	1/2	<u>0/5</u>
<b>Other Neutralization</b>	12/0	<u>5/5</u>	<u>1/9</u>

*An underline indicates that there is a difference between the number of examples that meet the criteria of the HCCM and the criteria of the 1994 TFM.*

included neutralizer in all sampling fluids (Aly *et al.* 1998). Of these only one of three examples met the performance criteria on the dry site (Vorherr *et al.* 1988), and one of two examples met the criteria on the moist site. A single example evaluated a 1% Chlorhexidine gluconate formulation (Leyden and Kligman 1981) and found it to meet the performance criteria for the dry sampling area. Neutralization status was not given.

**1994 TFM:** The performance criteria proposed were a 2 log<sub>10</sub>/cm<sup>2</sup> reduction on the abdomen; a 3 log<sub>10</sub>/cm<sup>2</sup> reduction on the groin; microbial count does not exceed the baseline 6 hours after use. For injections: a 1 log<sub>10</sub>/cm<sup>2</sup> reduction within 30 seconds of product use.

All five 4% Chlorhexidine gluconate examples where neutralization was not noted met the performance criteria for the dry and the moist sampling sites. Of the three examples where neutralizer was added to all sampling fluids, only one example met the performance criteria on the dry site (Vorherr *et al.* 1988), and one of two examples met the criteria on the moist site. A single example evaluated a 1% Chlorhexidine gluconate formulation (Leyden and Kligman 1981) and found it to meet the performance criteria for the dry sampling area. Neutralization status was not given.

**Tally Table: Chlorhexidine Gluconate – Pre-op Preps**

	Injections TFM & HCCM	HCCM		TFM	
	Dry Site	Abdomen	Groin	Abdomen	Groin
	1 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	3 log <sub>10</sub> /cm <sup>2</sup>
	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail
<b>4% CHG</b>					
Unknown Neutralization	-	5/0	5/0	5/0	5/0
Cup Neutralization	-	0/2	<u>2/1</u>	0/2	<u>3/0</u>
<b>1% CHG</b>					
Unknown Neutralization	-	1/0	-	1/0	-

exceed the baseline 6 hours after use. For injections: a 1 log<sub>10</sub>/cm<sup>2</sup> reduction within 30 seconds of product use.

All six examples that evaluated 60% or 70% IPA for use in the preparation of injection sites met the performance criteria (SDA/CTFA 1995; Gunderman *et al.* 1985; Gunderman *et al.* 1985).

Four examples evaluated IPA using the dry site (Gunderman *et al.* 1985; Leyden *et al.* 1996; Leyden & Kligman 1981). One 60% IPA and one 70% IPA example met the performance criteria of a 2 log<sub>10</sub>/cm<sup>2</sup> reduction on the abdomen, while one 60% IPA and one 70% IPA example did not. All three examples evaluating 60% Ethanol or 70% Ethanol on the dry site met the performance criteria (Jampani *et al.* 2000; Leyden and Kligman 1981).

Two examples evaluated 60% Ethanol using the moist site (Jampani *et al.* 2000). Only one met the criteria proposed by the 1994 TFM.

**Tally Table: Alcohol – Pre-operative Preparations**

	Injections TFM & HCCM	HCCM		TFM	
	Dry Site	Abdomen	Groin	Abdomen	Groin
	1 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	3 log <sub>10</sub> /cm <sup>2</sup>
	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail
<b>70% IPA</b>	5/0	1/1	-	1/1	-
<b>60% IPA</b>	1/0	1/1	-	1/1	-
<b>70% Ethanol</b>	-	1/0	-	1/0	-
<b>60% Ethanol</b>	-	2/0	<u>2/0</u>	2/0	<u>1/1</u>

An underline indicates that there is a difference between the number of examples that meet the criteria of the HCCM and the criteria of the 1994 TFM.

## **POVIDONE-IODINE**

Appendix D, Table 9 (Povidone-iodine – Pre-operative Preparations Studies) compiles data on Povidone-iodine (PVI) products using methods based on ASTM E1173 Standard Test Method for Evaluation of a Pre-operative Skin Preparation. PVI (5-10%) is approved for use as a patient pre-operative preparation and

**Tally Table: Povidone-Iodine – Pre-operative Preparations**

	Injections TFM & HCCM	HCCM		TFM	
	Dry Site	Abdomen	Groin	Abdomen	Groin
	1 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>	3 log <sub>10</sub> /cm <sup>2</sup>
	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail
<b>10% Povidone-iodine</b>					
Media Only Neutralization	1/0	0/1	-	0/1	-
Cup + Media Neutralization	1/0	2/0	2/0	2/0	2/0
<b>7.5% Povidone-iodine</b>					
Media Only Neutralization	-	0/1	0/1	0/1	0/1
Cup + Media Neutralization	-	0/1	-	0/1	-
<b>5% Povidone-iodine</b>					
Media Only Neutralization	-	1/0	-	1/0	-

**Neutralization:** These results do not demonstrate the importance of neutralizer in the sampling fluids for iodine in this method.