

**TAB 7**

**Excerpt of comments from CTFA/SDA in regards to the log reduction performance criteria (75N-183H – CP7, section 4)**

**SECTION 4  
PERFORMANCE CRITERIA**

- **The performance criteria proposed by the FDA in the 1994 TFM are overly stringent. Two Category I active ingredients (iodine and alcohol) and an NDA approved OTC ingredient (Chlorhexidine gluconate) do not meet the performance criteria proposed in the June 17, 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products Proposed Rule (TFM).**
- **The performance criteria proposed by the Industry Coalition provide an appropriate evaluation of topical antimicrobial products as efficacious products containing iodine, alcohol, and Chlorhexidine gluconate meet these criteria.**
- **The performance criteria proposed by the Industry Coalition are appropriate provided that ASTM Standard Methods are used.**
- **FDA should adopt performance criteria that are applicable to all product forms and active ingredients, for the defined use situations.**
- **All products used as Healthcare Personnel Hand Products, Surgical Hand Scrubs, and Patient Pre-operative Skin Preparations should be shown to be effective after a single use.**
- **The demonstration of cumulative effects from multiple applications is not appropriate for alcohols and potentially other active ingredients and should not be a requirement.**

### **Introduction**

In 1995 the SDA/CTFA Industry Coalition proposed performance criteria for six categories of products as part of their response to the 1994 TFM on Topical Antiseptic Drug Products. A comparison of the FDA and Industry Coalition performance criteria for healthcare personnel hand products, surgical hand scrubs, and pre-operative skin preparations can be seen in Table 4.

**Table 4**  
**Reductions Proposed as Performance Criteria**

		<b>HCCM</b>	<b>1994 TFM</b>
<b>Healthcare Personnel Handwash</b>	Wash 1	1.5 log <sub>10</sub>	2 log <sub>10</sub>
	Wash 10	2 log <sub>10</sub>	3 log <sub>10</sub>
<b>Surgical Hand Scrub</b>	Wash 1	1 log <sub>10</sub>	1 log <sub>10</sub>
	Wash 2	1.5 log <sub>10</sub>	2 log <sub>10</sub>
	Wash 11	2 log <sub>10</sub>	3 log <sub>10</sub>
	Flora should not exceed baseline 6 hours after use.		
<b>Patient Pre-operative Preparation</b>	Dry Site	2 log <sub>10</sub> /cm <sup>2</sup>	2 log <sub>10</sub> /cm <sup>2</sup>
	Moist Site	2 log <sub>10</sub> /cm <sup>2</sup>	3 log <sub>10</sub> /cm <sup>2</sup>
	Injections	1 log <sub>10</sub> /cm <sup>2</sup>	1 log <sub>10</sub> /cm <sup>2</sup>
	Flora should not exceed baseline 6 hours after use.		

As described in Section 2, a review of the published scientific literature and product support materials was conducted. Appendix D is a compilation of the data from the literature where methods similar to the ASTM methods were used to evaluate Chlorhexidine gluconate, alcohol or iodine products.

- **The performance criteria proposed by the FDA in the 1994 TFM are overly stringent. Two Category I active ingredients (iodine and alcohol) and an NDA approved OTC ingredient (Chlorhexidine gluconate) do not meet the performance criteria proposed in the June 17, 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products Proposed Rule (TFM).**
- **The performance criteria for Healthcare Personnel Hand Products, Surgical Hand Scrubs, and Patient Pre-operative Preparations proposed by the Industry Coalition provide an appropriate evaluation of topical antimicrobial products, as efficacious products containing iodine, alcohol, and Chlorhexidine gluconate meet these criteria.**

### **Healthcare Personnel Hand Products**

Table 5 summarizes the percentage of studies that met the criteria proposed for the Healthcare Personnel Hand Product Category using a method based on ASTM E 1174 Standard Test Method for Evaluation of Health Care Personnel or Consumer Handwash Formulations. The data were combined regardless of the type of neutralization carried out in the test method, the amount of product used, or the percentage of active ingredient incorporated into the product. Alcohol data include both ethanol and isopropyl alcohol.

**Table 5**  
**Percentage of Examples Meeting Performance Criteria**  
**Healthcare Personnel Hand Products**

		HCCM	1994 TFM
<b>Chlorhexidine Gluconate</b>	<b>Wash #1</b>	100%	57.7%
	<b>Wash #10</b>	100%	78.6%
<b>Alcohol</b>	<b>Wash #1</b>	100%	85.7%
	<b>Wash #10</b>	71.4%	14.3%

NDA-approved OTC Chlorhexidine gluconate containing products should be expected to meet the performance criteria for this category at both Wash 1 (immediate effect) and Wash 10 (cumulative effect) as Chlorhexidine gluconate is a persistent antimicrobial ingredient. The HCCM criteria are appropriate since FDA has recognized these products to be efficacious in the NDA approval process. The performance criterion proposed by the Industry Coalition in the HCCM is more appropriate than those proposed in the TFM as these products consistently meet the wash criteria. However, the FDA proposed performance criteria are too stringent as many examples of Chlorhexidine gluconate products fail to meet those criteria.

Alcohol is not a persistent antimicrobial ingredient, and repeated application does not provide a cumulative effect in this protocol. Alcohol is commonly used as a healthcare personnel hand rub/sanitizer and 100% of the examples met the Wash #1 performance criterion; fewer met the more stringent Wash #10 criterion. Significantly fewer examples of alcohol products met the criteria as proposed in the 1994 TFM. The HCCM criteria are more appropriate for alcohol than those of the TFM.

### **Surgical Hand Scrub**

Table 6 summarizes the percentage of studies that met the criteria proposed for the Surgical Hand Scrub Category using a method based on ASTM E 1115 Standard Test Method for Evaluation of Surgical Hand Scrub Formulations. The data were combined regardless of the type of neutralization carried out in the test method, the amount of product used, or the percentage of active ingredient incorporated into the product. Alcohol data include both ethanol and isopropyl alcohol.

**Table 6**  
**Percentage of Examples Meeting Performance Criteria**  
**Surgical Hand Scrubs**

		<b>HCCM</b>	<b>1994 TFM</b>
<b>Chlorhexidine Gluconate</b>	<b>Wash # 1</b>	56.9%	56.9%
	<b>Wash # 2</b>	96.3%	66.6%
	<b>Wash #11</b>	83.3%	63.3%
<b>Alcohol</b>	<b>Wash # 1</b>	82.8%	82.8%
	<b>Wash # 2</b>	100%	66.6%
	<b>Wash #11</b>	66.6%	33.3%
<b>Povidone-Iodine</b>	<b>Wash # 1</b>	81.8%	81.8%
	<b>Wash # 2</b>	69.2%	46.2%
	<b>Wash #11</b>	31.25%	6.7%

NDA-approved OTC Chlorhexidine gluconate containing products should be expected to meet the performance criteria for this category at Washes # 1 and 2 (immediate effect) and Wash #11 (cumulative effect) as Chlorhexidine gluconate is a persistent antimicrobial ingredient. A greater percentage of examples met the performance criteria proposed by the Industry Coalition in the HCCM. However, the FDA proposed performance criteria appear to be too stringent, since about one-third of the NDA-approved products did not meet the FDA proposed criteria. Therefore, the HCCM criteria are more appropriate than those of the TFM.

Alcohol is not a persistent antimicrobial ingredient, and repeated application does not provide a cumulative effect in this protocol. Alcohol is not commonly used in the United States as a surgical hand rub/sanitizer. Of the two examples available for Washes #2 and #11, only one met the HCCM criteria at those time points. The data for alcohol appear to support acceptance criteria for a single wash of 1 log<sub>10</sub> reduction, as was proposed in the 1994 TFM and the HCCM.

Povidone-iodine has some persistent properties and many formulations met the Wash #1 criteria proposed in the TFM and by the HCCM. More formulations met the HCCM criteria at Wash #2 than the TFM proposal. Even fewer formulations met the Wash #11 criterion for either standard proposal. This can be interpreted to indicate that the criteria as proposed for the cumulative effect are too stringent in both proposals.

### **Patient Pre-operative Preparation**

Table 7 summarizes the percentage of examples that met the criteria proposed for the Patient Pre-operative Preparation Category using a method based on ASTM E 1173 Standard Test Method for Evaluation of a Pre-Operative Skin Preparation. The data were combined regardless of the type of neutralization carried out in the test method, the amount of product used or the percentage of active ingredient incorporated into the product. Alcohol data include both ethanol and isopropyl alcohol.

**Table 7**  
**Percentage of Examples Meeting Performance Criteria**  
**Patient Pre-operative Preparations**

		HCCM	1994 TFM
<b>Chlorhexidine Gluconate</b>	<b>Dry Site</b>	71.4%	71.4%
	<b>Moist Site</b>	100%	87.5%
	<b>Injections</b>	-	-
<b>Alcohol</b>	<b>Dry Site</b>	75%	75%
	<b>Moist Site</b>	100%	50%
	<b>Injections</b>	100%	100%
<b>Povidone-Iodine</b>	<b>Dry Site</b>	42.9%	42.9%
	<b>Moist Site</b>	85.7%	85.7%
	<b>Injections</b>	100%	100%

The HCCM and the 1994 TFM agree on the criteria for evaluation of injection site preparations and for dry site evaluations. The sole difference is in the criteria for moist site. There were few examples in the literature detailing results of products using this method of evaluation at a moist site. Of the two examples using alcohol, one test result met the HCCM criteria of  $1.5 \log_{10}/\text{cm}^2$  reduction, but did not meet the 1994 TFM criteria of  $2 \log_{10}/\text{cm}^2$  reduction.

- **The performance criteria proposed by the Industry Coalition are appropriate provided that ASTM Standard Methods are used.**

As can be seen from review of the data in Appendix D, methods based on or identical to those proposed by ASTM are widely used to evaluate Topical Antimicrobial Products. Methods included in the Monograph should be appropriate for all product forms and types under that rulemaking. The methods must be reproducible and based on the most recent scientific data available in the published literature. The use of scientifically sound methodology will ensure that effective products are marketed under the auspices of the Monograph. The use of a voluntary consensus organization such as ASTM will provide for regular review and updating of the methods as needed.

- **FDA should adopt performance criteria that are applicable to all product forms and active ingredients, for the defined use situations.**

The performance criteria for a specific category must be uniform for all product forms and active ingredients. As can be seen in Appendix D, there are a number of different topical product forms that are available in each category, e.g. bars, liquids, dips, gels, lotions and foams. The test method must be flexible enough to allow for different types of topical product application and different dilutions of product (if any).

- **All products used as Healthcare Personnel Hand Products, Surgical Hand Scrubs, and Patient Pre-operative Skin Preparations should be shown to be effective after a single use.**
- **The demonstration of cumulative effects from multiple applications is not appropriate for alcohols and potentially other active ingredients and should not be a requirement.**

Topical antimicrobial products used as Healthcare Personnel Handwashes, Surgical Hand Scrubs and Patient Pre-operative Preparations should be effective with each and every use. The caregiver should not have to use the product repeatedly in order to obtain efficacy. The first patient of the day should benefit as well as the last.

In the past it appears that there has been a confusion of the terms persistent and cumulative antibacterial product activity.

Persistence is defined as the prolonged or extended antimicrobial activity that prevents or inhibits the proliferation or survival of microorganisms after application of the product. This may be demonstrated by sampling a site at some point several minutes or hours after application and demonstrating bacterial antimicrobial effectiveness over a baseline.

Cumulative effect is defined as a progressive decrease in the numbers of microorganisms recovered following repeated applications of a test material. This manifests itself in *in vivo* surrogate end point tests as an increase in the log<sub>10</sub> reductions of products following two or more applications. Cumulative effect should not be confused with persistence that is time dependent, rather than application dependent.

Products used in these three categories may be required to show persistent effects, i.e. a reduction below baseline 6 hours after use. That requirement for persistence is acknowledged in the performance criteria for Surgical Hand Scrub and Patient Pre-operative Preparations. Both substantive and non-substantive active ingredients can show a persistent effect if they lower the number of bacteria significantly during the wash period.

Historically, testing for cumulative effects was included in the Healthcare Personnel Hand Products and Surgical Hand Scrub categories (i.e. sampling after Wash #10 or #11). However, alcohol is not substantive, and does not show a cumulative effect in these tests. Alcohol was approved for use in both of these categories. Therefore, cumulative testing should not be required because it has little relevance to effectiveness, when effectiveness is defined as ability to mitigate risk of disease transmission.

## **Summary**

The performance criteria proposed by the SDA/CTFA Industry Coalition for Surgical Hand Scrubs, Pre-operative Skin Preparations, and Healthcare Personnel Hand Preparations are supported by the data found in the scientific literature. These criteria provide an appropriate measure of efficacy that can be related to a significant incremental benefit from the use of such topical antimicrobial products.