

C T F

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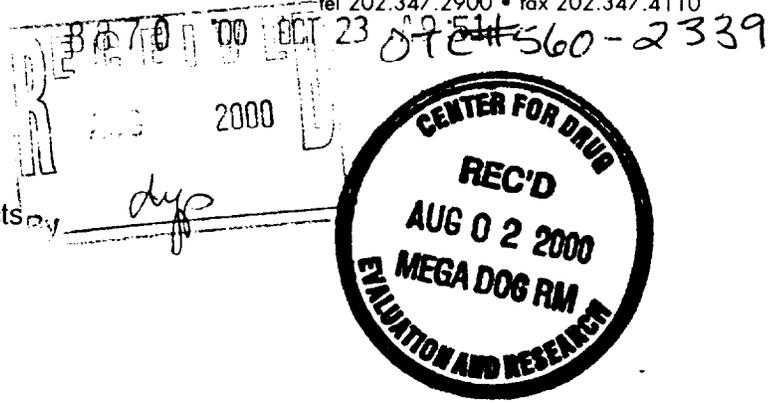
THE SOAP AND
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August 2, 2000

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane (HFD-560)
Rockville, MD 20857



Re: Tentative Final Monograph for Health-Care Antiseptic Drug Products; Healthcare Continuum Model; Materials Relating to Test Methods; Docket 75N-183H

Dear Dr. Ganley:

On July 29, 1998 the FDA convened a meeting of the Nonprescription Drugs Advisory Committee to discuss effectiveness testing for OTC topical antimicrobial products. The agenda included a number of presentations given by FDA-invited and Industry-sponsored speakers, with a particular emphasis on the suitability of the methods proposed in the June 17, 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) for establishing product performance expectations.

One of the Industry-sponsored speakers, Ms. Rhonda Jones, discussed "Performance Expectations: Linkage of Laboratory and Clinical Studies". Ms. Jones reviewed the outstanding issues associated with the TFM testing methodology, and illustrated the methodological difficulties with performance data for five topical antimicrobial formulations. Following the presentation the Chairman, Dr. Eric Brass, requested that summary tables of test characteristics and study results for the topical antimicrobial formulations which were referenced in Ms. Jones' presentation be provided to FDA.

An executive summary of the July 1998 presentation, together with the requested summary tables are provided under cover of this letter. These data demonstrate that:

- A standardized neutralization technique should be included in the proposed TFM test methods.
- Regardless of the neutralization procedure, chlorhexidine gluconate formulations (NDA products) and povidone-iodine formulations (Category I products), do not meet the proposed TFM performance criteria for topical antimicrobial formulations.

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CTFA is the national trade association representing the cosmetic, toiletry and fragrance industry. Founded in 1894, CTFA has an active membership of approximately 300 companies that manufacture or distribute the vast majority of finished personal care products marketed in the United States. CTFA also includes approximately 300 associate member companies, including manufacturers of raw materials, trade and consumer magazines, and other related industries.

The Soap and Detergent Association is the non-profit trade association representing some 120 North American manufacturers of household, industrial and institutional cleaning products; their ingredients; and finished packaging. SDA members produce more than 90% of the cleaning products marketed in the U.S.

Based on these data, the Industry Coalition concludes that there is a necessity to re-evaluate details of the methods described in the TFM, as well as the performance standards which have been proposed for topical antibacterial formulations.

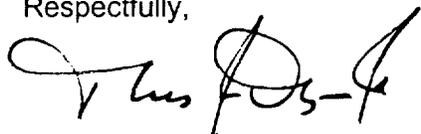
As discussed during the July 29, 1998 Nonprescription Drugs Advisory Committee, and the subsequent November 3, 1999 FDA feedback meeting on finished product efficacy testing, the Industry Coalition maintains that:

- valid and reproducible test methods are needed before performance criteria can be established;
- the outcome of testing will be dependent on both the finished product tested, and specific details of the testing protocol.

In order to advance the establishment of methodology for inclusion in the final Monograph, we request that the Agency take full account of the data provided with this letter, together with the Industry proposal on finished product testing submitted on September 29, 1999.

Please feel free to contact us if you have any questions. Please also note that copies of this document are being provided to the Dockets Management Branch for inclusion in the public record.

Respectfully,



Thomas J. Donegan, Jr.
Vice President - Legal & General Counsel
The Cosmetic, Toiletry, and Fragrance Association



Jenan Al-Atrash, Dr.PH
Director, Human Health & Safety
The Soap and Detergent Association

attachments

cc: L. Katz (HFD-560)
D. Lumpkins (HFD-560)
Dockets Management Branch

“Performance Expectations: Linkage of Laboratory Tests and Clinical Outcome Data”¹

Executive Summary of R. Jones presentation on behalf of SDA/CTFA of 7/98

- A process for development of the final monograph test methodology and performance criteria was proposed: 1) achieve method standardization via the ASTM peer review consensus process, 2) perform method validation studies, and 3) establish statistical and performance criteria.
- The need for standardized, defined, and peer-reviewed test methodology to encourage reliability, reproducibility, and comparability of test results was emphasized. The FDA modifications to the test methodology presented in the TFM were not supported by historical data nor were they a part of the existing ASTM published methods. The changes in test parameters were not well defined and thus the methods may not elucidate the appropriate product attributes. In addition, use situations may not be reflected by the proposed methodology and performance criteria may not be linked to clinical data.
- The principal efficacy attributes for topical antimicrobial products were defined as spectrum of antimicrobial activity, speed of kill, persistence, and *in vivo* effectiveness against transient and resident flora. Specific test methods used to measure or assess each attribute were outlined as well as the outstanding issues surrounding the conduct of the key test methods. These issues require resolution prior to proceeding with method validation.
- *In vivo* efficacy data, such as that required by the Healthcare Continuum Model or the FDA Tentative Final Monograph, collected from five formulations was presented to confirm the need to revisit the TFM methodology and performance expectations (Tables 1-9). Through the use of these examples, it was clearly shown that formulations with demonstrated clinical outcomes, NDA approval, and Over-the-Counter Drugs with Category I safety and efficacy status, fell short of the current performance criteria proposed in the TFM. Thus, these effective formulations would not be available as surgical scrubs or health care personnel handwashes under the current TFM.
- The importance of immediate neutralization (e.g. neutralization in the glove massage fluid) was illustrated with studies on chlorhexidine gluconate and povidone iodine (Table 1-3). Delayed (e.g. neutralization in subsequent growth media or dilution fluid) neutralization allowed for an extended contact time between the test material and the test organisms thus allowing an exaggeration of the activity of a formulation. The studies showed that with proper and immediate neutralization that NDA products such as CHG wash products and Category 1 Over-the-Counter Ingredients such as povidone iodine do not meet the efficacy criteria proposed in the TFM.
- Chlorhexidine gluconate (CHG) formulations were presented as an example of topical formulations requiring New Drug Application approval which includes an extensive review of safety, efficacy, chemistry, and manufacturing processes prior to marketing.

¹ Presentation by R. Jones, FDA Nonprescription Drugs Advisory Committee Meeting, July 29, 1998.

Chlorhexidine formulations are considered by many to be among the most effective products available for healthcare professionals to prepare surgical sites, to prepare the OR team for surgery, and to reduce nosocomial infection. There is an extensive database of *in vitro*, *in vivo* and clinical data to demonstrate the efficacy of these formulations. Data was presented on multiple 4% CHG formulations in simulated surgical scrub and healthcare personnel handwash studies comparing the change in reported efficacy with immediate and delayed neutralization techniques (Tables 1-2). When effective and well respected chlorhexidine NDA formulations are properly and immediately neutralized, they do not pass the performance criteria proposed in the 1994 TFM for surgical scrubs or healthcare personnel handwashes.

- Well respected by healthcare professionals for clinical effectiveness, povidone-iodine scrubs (7.5%) are over-the-counter drugs classified as Category I for safety and effectiveness by FDA. The impact of the lack of test standardization and neutralization was shown using a single formulation tested in multiple laboratories in the ASTM E1115 Surgical Scrub Method (Table 3). The data presented illustrated the need to strive toward greater standardization of the methodology to improve reproducibility and comparability of effectiveness between laboratories. However, regardless of the neutralization technique, formulations with a Category I ingredient such as povidone-iodine do not meet the proposed criteria for Over-the-Counter healthcare antiseptic drug products.
- FDA classifies triclosan as a Category III (safety and effectiveness) over-the-counter drug for healthcare personnel handwashes. A variety of clinical reports documenting positive clinical experiences concomitant with the introduction and use of two triclosan formulations, a 0.3% and 1.0% product, were reviewed. The performance of these formulations in healthcare personnel handwash studies with proper neutralization was presented (Tables 4-5). These studies allow a correlation of suggested clinical effectiveness to the performance criteria proposed in the TFM. With the inclusion of a 2.0% CHG control formulation, the 1% triclosan formulation was shown to exhibit comparable *in vivo* effectiveness to a chlorhexidine NDA formulation when CHG was properly neutralized (Table 4). The studies show that neither the NDA nor the clinically effective triclosan formulations pass the TFM requirement.
- Two recent studies demonstrating statistically significant reductions in *S. aureus* associated with atopic dermatitis using a 1.5% triclocarban (TCC) bar soap were discussed (Table 6). Although this formulation is an NDA, triclocarban is an over-the-counter drug classified as a Category III ingredient at levels up to 1.5% for effectiveness and Category 1 for safety for handwashing. Additional data was presented from a Cade multiple basin wash test (Table 7), a healthcare personnel handwash test (Table 8), and a cup scrub study (Table 9). The studies utilized plain soap or placebos as controls. These studies allow a correlation of suggested clinical improvement against *S. aureus* in atopic dermatitis cases to a range of tests proposed in the Healthcare Continuum Model. In addition, the data clearly show a statistically significant benefit of the formulation over plain soap and water against transient and resident flora for immediate and persistent antimicrobial activity.

“Performance Expectations: Linkage of Laboratory Tests and Clinical Outcome Data”¹

Executive Summary Tables

¹ Presentation by R. Jones, FDA Nonprescription Drugs Advisory Committee Meeting, July 29, 1998.

Table 1: Chlorhexidine Gluconate – Healthcare Personnel Handwash Studies

Formulation	Test Subjects	<i>S. marcescens</i> (ATCC 14756)				Wash Vol.	Wash Time	Rinse Time	Massage Time	Neutralization	Statistical Signif. vs. baseline	Log Reduction (Versus Baseline)			
		Baseline (log ₁₀ /hand)	Vol.	Rub Time	Dry Time							Wash No.			
												1	4	7	10
1994 TFM	-	-	-	-	-	-	-	-	-	-	-	2.0	-	-	3.0
4% CHG ¹	12	6.63	2.5mL ⁶ + 2.5mL	45sec	1min	3mL	30sec	30sec	1min	Media ⁷	-	2.61 ±0.33 p<0.1	3.41 ±0.37 p<0.01	3.95 ±0.29 p<0.01	4.15 ±0.34 p<0.05
4% CHG ²	12	7.07	2.5mL + 2.5mL	45sec	1min	3mL	30sec	30sec	1min	Media	n/a	2.51 ±0.26	3.09 ± 0.13	3.37 ±0.18	3.92 ± 0.28
2% CHG ³	36	8.07	n/a	n/a	n/a	5mL	15sec	n/a	n/a	Media	n/a	n/a	n/a	n/a	5.49
4% CHG ⁴	12	8.46	5mL	45sec	2min	5mL	15sec	30sec	n/a	Wash 1: Media Wash10: Glove ⁸	p<0.05	1.97 ⁹	2.88	3.46	2.77 ⁹
4% CHG ⁴	12	8.32	5mL	45sec	2min	5mL	15sec	30sec	n/a	Wash 1: Media Wash10: Glove	p<0.05	2.16	2.56	3.04	2.93 ⁹
4% CHG ⁵	9*	n/a	5mL	45sec	Air dry	5mL	15sec	30sec	1 min	Wash 1: Media Wash10: Glove	p<0.05	1.92 ⁹	n/a	n/a	2.84 ⁹

1 Bartzokas et al., Inf. Control, 1987, 8:163-167.

2 Ciba-Geigy Corporation, Document 2513E, 1990.

3 Peterson, Surg. Gynec. Obstet., 1978; 146:63-65.

4 Ciba-Geigy Corporation, FDA Public Docket 75N-183H, 1995.

5 Hanuman et al., Abs. Natl. Mtg. APIC, 1998.

6 The indication "2.5mL + 2.5mL" indicates that two additions of test material were used to reduce the loss through the subject's fingers.

7 The term "Media" indicates that the neutralizers were incorporated into the dilution and plating media only.

8 The term "Glove" indicates that the neutralizers were incorporated into the sampling fluid in the glove.

9 Performance falls below the requirements proposed in the 1994 FDA Tentative Final Monograph for Healthcare Antiseptic Drug Products.

Table 2: Chlorhexidine Gluconate – Surgical Scrub Studies

Formulation	Test Subjects	Resident Flora Baseline (log ₁₀ /hand)	Scrub Vol.	Scrub Time	Massage Time	Neutralization	Regrowth Below Baseline	Log Reduction (Versus Baseline)		
								Scrub 1/ Day 1	Scrub 2/ Day 2	Scrub 11/ Day 5
1994 TFM	-	-	-	-	-	-	-	1.0	2.0	3.0
4% CHG ¹	36	6.38 6.41	5ml ⁵ + 5mL	3min ⁵ + 3min	n/a	Media ⁶	Below at 6hrs	3.64	3.89	4.11
4% CHG ²	33	n/a	5ml + 5mL	3min + 3min	1min	Glove ⁷	Below at 3hrs	1.06±0.58 p<0.05	n/a	1.40±1.11 ⁸ p<0.05
4% CHG ³	6	n/a	5ml + 5mL	3min + 3min	1 min	Media	Below at 6hrs	1.50	2.07	2.95 ⁸
4% CHG ⁴	35	Day 1: 6.51±0.58 Day 2: 5.44±0.46 Day 5: 5.06±0.57	5ml + 5mL	1 min + 3min	5 min	Glove	n/a	0.76±0.53 ⁸ p=0.896	1.75±0.48 ⁸	2.39±0.58 ⁸ p=0.002

1 Peterson et al., Surg. Gynec. Obstet. 1978; 146:63-65.

2 Faogali et al. AJIC, 1995; 23:337-343

3 Huntington Laboratories, Inc., FDA Public Docket 75N-183, 1995.

4 Cremieux et al., App. Env. Micro.; 1989, 55:2944-2948.

5 The indication "5mL + 5mL" indicates that an initial volume of test material was used to scrub the hands for the time indicated followed by a subsequent addition of test material and scrub.

6 The term "Media" indicates that the neutralizers were incorporated into the dilution and plating media only.

7 The term "Glove" indicates that the neutralizers were incorporated into the sampling fluid in the glove.

8 Performance falls below the requirements proposed in the 1994 FDA Tentative Final Monograph for Healthcare Antiseptic Drug Products.

Table 3: Povidone Iodine – Surgical Scrub Studies

Formulation	Test Subjects	Resident Flora Baseline (log ₁₀ /hand)	Scrub Vol.	Scrub Time	Massage Time	Neutra l- ization	6 Hour Persistence	Log Reduction (Versus Baseline)		
								Scrub 1/ Day 1	Scrub 2/ Day 2	Scrub 11/ Day 5
1994 TFM	-	-	-	-	-	-	Below Baseline	1.0	2.0	3.0
7.5% PVP-I ¹	7	5.544	5ml ⁶ + 5mL	5 min ⁶ + 5 min	n/a	Media ⁷	Below Baseline	1.97	1.95 ⁹	1.82 ⁹
7.5% PVP-I ²	36	6.37	5ml + 5mL	3min + 3min	n/a	Media	Below Baseline	2.24	2.46	2.76 ⁹
7.5% PVP-I ³	33	n/a	5ml + 5mL	5 min + 5 min	1min	Glove ⁸	Below Baseline	1.10±0.52 p<0.05	n/a	0.43±0.60 ⁹ p<0.05
7.5% PVP-I ⁴	25	n/a	5ml + 5mL	5 min + 5 min	n/a	n/a	Below Baseline	1.0	n/a	1.0* ⁹
7.5% PVP-I ⁵	49	Day 1: 6.48±0.98 Day 2: 5.69±1.01 Day 5: 5.50±0.78	5ml + 5mL	1 min + 3min	5 min	Glove	Below Baseline	0.70±0.79 ⁹ p=0.001	1.26±0.62 ⁹	1.39±1.03 ⁹ p=0.0005

* This data was collected on Day 4 from Scrub 10.

1 Huntington Laboratories, Inc. FDA Public Docket 75N-183, 1995.

2 Peterson et al., Surg. Gynec. Obstet. 1978; 146:63-65.

3 Faogali et al. AJIC, 1995; 23:337-343.

4 Kubista, Lusskin. DKT 75N-183, C00104.

5 Cremieux et al., App. Env. Micro.; 1989, 55:2944-2948

6 The indication "5mL + 5mL" indicates that an initial volume of test material was used to scrub the hands for the time indicated followed by a subsequent addition of test material and scrub.

7 The term "Media" indicates that the neutralizers were incorporated into the dilution and plating media only.

8 The term "Glove" indicates that the neutralizers were incorporated into the sampling fluid in the glove.

9 Performance falls below the requirements proposed in the 1994 FDA Tentative Final Monograph for Healthcare Antiseptic Drug Products.

Table 4: 1% Triclosan – Healthcare Personnel Handwash Study

Formulation	Test Subjects	<i>S. marcescens</i>				Wash Vol.	Wash Time	Rinse Time	Massage Time	Neutra- l- ization	Statistical Signif. vs. baseline	Log Reduction (Versus Baseline)	
		Baseline (log ₁₀ /hand)	Vol.	Rub Time	Dry Time							Wash 1	Wash 10
1994 TFM	-	-	-	-	-	-	-	-	-	-	-	2.0	3.0
1.0% Triclosan	8 ¹	8.46±0.28	5mL	45sec	Air dry	5mL	15sec	30sec	1 min	Wash 1: Media ³ Wash10: Glove ⁴	p<0.05	2.13±0.38	2.14±0.47 ⁶
	12 ²	9.04	2.5mL + 2.5mL	45sec	2 min	5mL	30sec	30sec	1 min	Media	p<0.05	2.28	2.79 ⁶
2.0% CHG	9 ¹	8.40±0.25	5mL	45sec	Air dry	5mL	15sec	30sec	1 min	Wash 1: Media Wash10 : Glove	p<0.05	1.92±0.52 ⁶	2.84±0.4 ⁶

1 Johnson & Johnson Medical, Data on File, March 12, 1997.

2 Johnson & Johnson Medical, Data on File, June 10, 1997.

3 The term "Media" indicates that the neutralizers were incorporated into the dilution and plating media only.

4 The term "Glove" indicates that the neutralizers were incorporated into the sampling fluid in the glove.

5 The indication "2.5mL + 2.5mL" indicates that two additions of test material were used to reduce the loss through the subject's fingers.

6 Performance falls below the requirements proposed in the 1994 FDA Tentative Final Monograph for Healthcare Antiseptic Drug Products.

Table 5: 0.3% Triclosan – Healthcare Personnel Handwash Study

Formulation	Test Subjects	<i>S. marcescens</i>				Wash Vol.	Wash Time	Rinse Time	Massage Time	Neutra l- ization	Statistical Signif. vs. baseline	Log Reduction (Versus Baseline)			
		Baseline (log ₁₀ /hand)	Vol.	Rub Time	Dry Time							Wash No.			
												1	4	7	10
1994 TFM	-	-	-	-	-	-	-	-	-	-	2.0	-	-	3.0	
0.3% Triclosan ¹	6	8.49	5mL	45sec	2 min	5mL	60sec	30sec	1 min	Media ²	n/a	1.74 ³	1.98	1.93	1.93 ¹

1 Huntington Laboratories, Inc., FDA DKT 75N-183, 1995.

2 The term “Media” indicates that the neutralizers were incorporated into the dilution and plating media only.

3 Performance falls below the requirements proposed in the 1994 FDA Tentative Final Monograph for Healthcare Antiseptic Drug Products.

Table 6: 1.5% Triclocarban – Atopic Dermatitis Studies

Trial	Test Materials	Test Subjects ¹	Wash Out Period	Test Material Use: Duration	Test Material Use: Frequency	Evaluation	Evaluation Frequency	Dermatological Score (Global Improvement)	<i>S. aureus</i> Log Reduction (Versus Baseline)
Pilot Study ²	1.5% TCC Bar	28	7 day	4 weeks	At least once per day	-Microbial Sampling – both elbow creases, lesion and non-lesion sites -Product Use Diary -Derm. Evaluation – severity -Derm. Evaluation – Extent -Derm. Global Improvement Grade -Self Evaluation Questionnaire	0,14,28 day	2.2 (p=0.02)	0.3 (p=0.02)
	Plain Soap							1.5	0.0
Clinical Study ³	1.5% TCC Bar	50	7 day	6 weeks	At least once per day	Microbial Sampling – both elbow creases, lesion and non-lesion sites -Product Use Diary -Derm. Evaluation – severity -Derm. Evaluation – Extent -Derm. Global Improvement Grade -Self Evaluation Questionnaire	0,14,28,42 days	2.1 (p<0.01)	1.9 (p=0.02)
	Plain Soap							1.3	1.3

1 Subjects exhibited mild to moderate atopic disease with active dermatitic lesions.

2 The Procter & Gamble Company, Data on File, 1995.

3 Brenemen et al. Abst. Ann. Mfg. Am. Acad. Derm., 1998.

Table 7: 1.5% Triclocarban – Cade Handwash Study

Formulation	Test Subjects	Wash Out Period	Test Material Use: Duration/Frequency	Resident Flora Baseline (log ₁₀ /hand)	Wash Vol.	Wash Time	Rinse Time	Neutralization	Fifth Basin Log ₁₀ Reduction (Versus Baseline)
1.5% Triclocarban ¹	25	1 week	5 days/3/day	>10 ⁶	1L.	60sec	30sec	yes	1.2
Placebo/Plain Soap	25	NA	5 days/3/day	>10 ⁶	1L	60sec	30sec	NA	0.0 – 0.2

¹ The Procter & Gamble Company, Data on File, Average of 8 studies 1976-1991.

Table 8: 1.5% Triclocarban – Healthcare Personnel Handwash Study

Formulation	Test Subjects	<i>S. marcescens</i>				Wash Volume	Lather Time	Rinse Time	Massage Time	Neutralization	Log Reduction (Versus Baseline)	
		Baseline (log ₁₀ /hand)	Vol.	Rub Time	Dry Time						Wash No.	
											1	10
1994 TFM	-	-	-	-	-	-	-	-	-	-	2.0	3.0
1.5% Triclocarban ¹	16	7.60	4.5ml.	30 sec.	0	Bar	30 sec	15sec	1min./hand	yes	2.8	n/a
Water Rinse ²	6	8.00	5mL	15 sec	5min.	n/a	n/a	15sec	1min./hand	n/a	0.53	n/a

1 The Procter & Gamble Company, Data on File, 1994.

2 The Procter & Gamble Company, Data on File, 1993.

Table 9: 1.5% Triclocarban – Cup Scrub Study¹

Formulation	Test Subjects	<i>S. aureus</i> (ATCC27217) ²			Use Period	No. of Washes	Neutra l- ization	Log Reduction (Versus Placebo)		
		Baseline (log ₁₀ /hand)	Vol.	No. of sites ⁴				Contact Time (Hours)		
								0.5	2	5
1.5% Triclocarban*	20	5.75	10ul.	1 site/ contact time	3 Day	7	Yes ⁵	0.5±0.42 p<0.001 ³	1.4±0.55 p<0.001 ³	1.5±0.87 p<0.003 ³
Placebo	20						Yes	-	-	-

1 The Procter & Gamble Company, Data on File, 1995.

2 ATCC 27217 is a penicillin-sensitive, tetracycline-resistance pigmented strain.

3 Wilcoxon Signed Rank Test (a non-parametric paired difference T-test).

4 Following inoculation, sites were occluded with a Hill Top Chamber® patch. The William and Kligman cup scrub technique was used to recover the surviving bacteria.

5 Triton X + Lethen

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

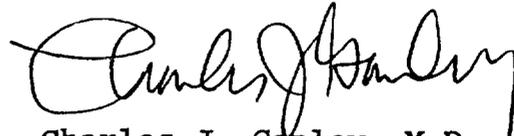
DATE: *Oct. 18, 2000*

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. *75N-183H*

TO: Dockets Management Branch, HFA-305

- The attached material should be placed on public display under the above referenced Docket No.
- This material should be cross-referenced to Comment No. _____


Charles J. Ganley, M.D.

Attachment