TOPICAL DERMATOLOGIC CORTICOSTEROIDS IN VIVO BIOEQUIVALENCE STUDY SUMMARY TABLES AND SAS TRANSPORT FORMATTED TABLES FOR DATASET SUBMISSION

I. Pre-Study Method Validation

Table 1. Chroma Meter Validation

Reading	Chroma Meter 1	Chroma Meter 2	Chroma Meter 3	Chroma Meter n
Date of testing				
Replicate 1				
Replicate 2				
Replicate 3				
Replicate 4				
Mean				
% CV				
Inter-Chroma Meter, Mean				
Inter-Chroma Meter, % CV				

Table 2. Skin Site Validation

Reading	Site 1	Site 2	Site 3	Site n
Date of testing				
Replicate 1				
Replicate 2				
Replicate 3				
Replicate 4				
Mean				
%CV				
Inter-Site, Mean				
Inter-Site, %CV				

Table 3. Intra-Subject and Inter-Site Validation

Reading	Subject 1	Subject 2	Subject 3	Subject n
Date of testing				
Site 1				
Site 2				
Site 3				
Site 4				
Mean				
% CV				
Inter-Subject, Mean				
Inter-Subject, % CV				

Table 4. Operator Validation

Reading	Operator 1	Operator 2	Operator 3	Operator n
Date of testing				
Site 1				
Site 2				
Site 3				
Site 4				
Mean				
%CV				
Inter-Operator, Mean				
Inter-Operator, %CV				

II. Summary of Studies

Table 5. Summary of the Pilot Dose Duration-Response Study

Study Ref. No.	Study Objective	Study Design	Treatment(s) (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameters		Study Report Location
					Emax	ED_{50} (minutes)	

Table 6. Summary of the Pivotal Bioequivalence Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameter	Study Report Location
					Negative AUEC (n=# 'evaluable' subjects)	
					Test:	
					Reference:	

Table 7. Summary of the Pivotal Bioequivalence Study

Treatment Dose: XX per site: Occlusion/Non-Occlusion Pharmacodynamic Parameters, Area Under the Effect Curve, Point Estimates and 90% Confidence Intervals (Locke's Method)					
Pivotal (Vasoconstrictor Study), Study No.					
Method	Number of Subjects	$AUEC_{(0\text{-}24hr)}$		Point Estimate	90% C.I.
		Test	Reference		
Calculated by Firm					

Table 8. Listing of Relevant Standard Operating Procedures for Pre-Study Method Validation and Pilot Dose Duration-Response and Pivotal BE Studies

SOP No.	Effective Date of SOP	SOP Title

III. Pilot Dose Duration-Response Study

Table 9. Study Information

Study Number	
Study Title	
Clinical Site (Name & Address)	
Principal Investigator	
Dosing Dates	
Were the subjects dosed in more than group?	Yes/No (If Yes, then answer the rest of the questions in this section)
If Yes, specify the screening dates for each group	
If Yes, specify the dosing dates for each group	
If specify, specify whether the same clinical sites were used for each group	

Table 10. Product Information

Product	**Reference**
Treatment ID	
Product Name	
Manufacturer	
Batch/Lot No.	
Expiration Date	
Strength	
Dosage Form	
Potency	
Homogeneity	If applicable
Dose Administered	(e.g. 5.0 µL/cm^2 (20µL total/4-cm^2 site))(e.g.)
Route of Administration	

Table 11. Demographics Profile of Subjects Completing the Pilot Dose Duration-Response Study Product Information

Study #		
		Treatment Groups
		Reference Product N=
Age (years)	Mean ± SD Range	
Age Groups	< 18 18 – 39 40 – 64 65 – 75 > 75	
Sex	Male Female	
Hispanic or Latino Race	N A B I W	
Not Hispanic or Latino Race	N A B I W	
BMI	Mean ± SD Range	
Other Factors		

Table 12. Dropout Information, Pilot Dose Duration-Response Study

Study #				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**

Table 13. Study Adverse Events, Pilot Dose Duration-Response Study

Body System/Adverse Event	**Study #**
	Reference Product N=
	n (%)

Table 14. Protocol Deviations, Pilot Dose Duration-Response Study

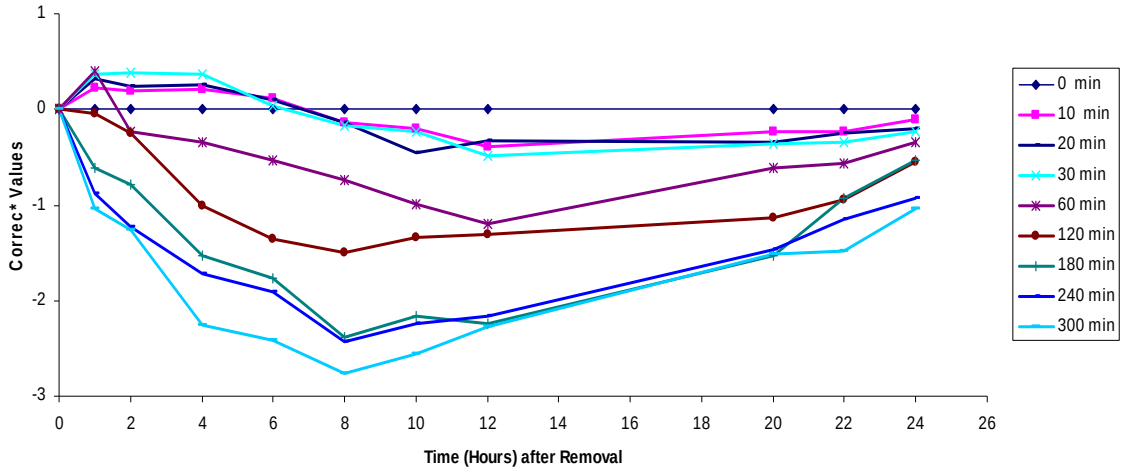
Study #	
Type	**Subject #s**

Table 15. ED_{50} and Emax Values Calculated

Model	**Software Used**		**Assumption of Distribution (ED_{50}) (Normal/Log Normal)**		
Initial Population Parameter Estimates		**Final Population Parameter (Model Derived) Estimates**			
ED_{50}	**Emax**	**ED_{50}**	**Emax**	**Maximum Likelihood**	**Akaike Criteria Value**

Figure 1. Graphical Representation of Time After Drug Removal versus Mean Corrected Values

Example:



IV. Pivotal Bioequivalence Study

Table 16. Study Information

Study Number	
Study Title	
Clinical Site (Name & Address)	
Principal Investigator	
Dosing Dates	
Were the subjects dosed in more than group?	Yes/No (If Yes, then answer the rest of the questions in this section)
If Yes, specify the screening dates for each group	
If Yes, specify the dosing dates for each group	
If specify, specify whether the same clinical sites were used for each group	

Table 17. Product Information

Product	**Test**	**Reference**
Treatment ID		
Product Name		
Manufacturer		
Batch/Lot No.		
Manufacture Date		
Expiration Date		
Strength		
Dosage Form		
Bio-batch Size		
Production Batch Size		
Potency		
Homogeneity	If applicable	If applicable
Dose Administered	(e.g. 5.0 µL/cm^2 (20µL total/4-cm^2 site))(e.g.)	(e.g. 5.0 µL/cm^2 (20µL total/4-cm^2 site))(e.g.)
Route of Administration		

Table 18. Demographics Profile of Subjects Completing the Pivotal Bioequivalence Study

Study #			
		Treatment Groups	
		Test Product N=	Reference Product N=
Age (years)	Mean ± SD Range		
Age Groups	< 18 18 – 39 40 – 64 65 – 75 > 75		
Sex	Male Female		
Hispanic or Latino Race	N A B I W		
Not Hispanic or Latino Race	N A B I W WB		
BMI	Mean ± SD Range		
Other Factors			

Table 19. Dropout Information, Pivotal Bioequivalence Study

Study #				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**

Table 20. Study Adverse Events, Pivotal Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups		
	Study #		
	Test Product A: N=	Reference Product B: N=	Not Assignable N=
	n (%)	n (%)	n (%)

Table 21. Protocol Deviations, Pivotal Bioequivalence Study

Study #		
Type	Subject #s (Test)	Subject #s (Ref.)

Table 22. Area Under the Effect Curve and 90% Confidence Intervals

Name of Drug Product Dose: [XXX µL per site – Non Occluded/Occluded, ___ minutes] Pharmacodynamic Parameters, Area Under the Effective-Dose Curve, Point Estimates and 90% Confidence Intervals (Locke's Method)				
Pivotal (Vasoconstrictor Assay) Study (Study No.)				
Number of Subjects[1]	$AUEC_{(0\text{-}24h)}$		Point Estimate	90% CI
	Test	Reference		

Table 23. Test Product Formulation

Ingredient	Function	% W/W

[1] Number of subjects who meet the criterion of the D2 response/D1 response ≥ 1.25

V. SAS Transport Formatted Tables for Data Submission for Pilot Dose Duration-Response Study and Pivotal Bioequivalence Study

Definitions:

Variable Name	Variable Label	Variable Type	Notes
DD	Dose Duration	Numeric (minutes)	A dose measured as the duration of exposure of the drug to the skin over a specified time period
ED50	Half-Maximal Effect Dose	Numeric (minutes)	The dose duration at which half-maximal skin blanching effect occurs
D1	Shorter Dose Duration Calibrator	Numeric (minutes)	The dose duration equal to one-half of the ED50
D2	Longer Dose Duration Calibrator	Numeric (minutes)	The dose duration equal to two times the ED50

Note: From Tables 24 to Tables 31, please refer to the Guidance for Industry – Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, finalized June 2, 1995, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm

V.1 Pilot Dose Duration-Response Study Data Submission Format

Table 24. Chroma Meter Raw Data

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	DD1	DD2	DD3	DDn
1	Baseline (pre-dose)*					
1	0					
1	0.5					
1	1					
1	n					
2	Baseline (pre-dose)					
2	0					
2	0.5					
2	1					
2	n					
n	Baseline(pre-					

	dose)					
n	0					
n	0.5					
n	1					
n	n					

*Baseline reading is within one hour prior to drug application

Example:

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	DD1	DD2	DD3	DDn
1	Baseline (pre-dose)	9.86	10.36	9.59	9.34	9.43
1	0	9.99	9.89	8.77	8.66	9.6
1	0.5	10.10	10.38	9.35	8.53	9.99
1	1	9.52	10.32	9.27	8.04	9.93
1	n	9.65	10.04	9.82	9.82	10.23
2	Baseline (pre-dose)	10.12	8.89	9.18	9.24	9.15
2	0	10.28	8.28	9.61	9.54	9.24
2	0.5	10.25	8.36	9.30	10.24	10.52
2	1	10.68	7.89	8.92	10.34	10.78
2	n	11.21	8.03	10.61	11.40	10.89

Table 25. Baseline-Adjusted, Chroma Meter Raw Data

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	DD1	DD2	DD3	DDn
1	0					
1	0.5					
1	1					
1	n					
2	0					
2	0.5					
2	1					
2	n					
n	0					
n	0.5					
n	1					
n	n					

Table 26. Baseline-Adjusted, Untreated Site-Corrected Chroma Meter Raw Data

Subject	Time after drug removal (hours)	DD1	DD2	DD3	DDn
1	0				
1	0.5				
1	1				
1	n				
2	0				
2	0.5				
2	1				
2	n				
n	0				
n	0.5				
n	1				
n	n				

Table 27. Area Under Effect Curve Data, All Subjects at Each Dose Duration

Subject	DD1	DD2	DD3	DDn
1				
2				
n				

V.2 Pivotal Bioequivalence Study Data Submission Format

Table 28. Chroma Meter Raw Data

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	D1	D2	ED50 (T)	ED50 (R)
1	Baseline (pre-dose)					
1	0					
1	0.5					
1	1					
1	n					
2	Baseline (pre-dose)					
2	0					
2	0.5					
2	1					
2	n					

n	Baseline(pre-dose)					
n	0					
n	0.5					
n	1					
n	n					

Table 29. Baseline-Adjusted, Chroma Meter Raw Data

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	D1	D2	ED50 (T)	ED50 (R)
1	0					
1	0.5					
1	1					
1	n					
2	0					
2	0.5					
2	1					
2	n					
n	0					
n	0.5					
n	1					
n	n					

Table 30. Baseline-Adjusted, Untreated Site-Corrected, Chroma Meter Raw Data

Subject	Time after drug removal (hours)	D1	D2	ED50 (T)	ED50 (R)
1	0				
1	0.5				
1	1				
1	n				
2	0				
2	0.5				
2	1				
2	n				
n	0				
n	0.5				
n	1				
n	n				

Table 31. Area Under Effect Curve Data, All Subjects at Each Dose Duration

Subject	D1	D2	ED50 (T)	ED50 (R)
1				
2				
n				