Determination of Water Vapor Transmission Rate for Various High Barrier Blister Packs

Executive Summary

Water Vapor Transmission Rate (WVTR) testing was performed to construct weight gain profiles due to moisture ingress of formed and sealed blisters (PVC, PVDC, Aclar Ultrx 2000 and cold form foil) when stored at 23°C/75% and 40°C/75% RH. The purpose of the test was to determine the potential to improve USP <671> by determining the time needed to reach steady state, the duration, and number of data points needed for WVTR calculation, the variability in data due to samples and testing labs, and to determine if empty blisters (i.e. "controls") are needed for accurate WVTR determination. This report summarizes the data collected from four testing labs - Merck, Pfizer, sanofi-aventis and Abbott Labs. Mean WVTR results determined by linear regression without zero time point is given in the following table:

Table 1
WVTR Means (mg/cavity/day)

Condition	Site	PVC	PVdC	Ultrx	Cold
23C/75%RH	AB	1.215	0.185	0.029	0.005
	MK	.	0.138	0.028	0.003
	PF	1.223	0.127	0.028	-0.001
	SA	1.280	0.142	0.028	-0.004
40C/75%RH	AB	2.978	0.789	0.136	0.011
	MK	.	0.791	0.137	0.003
	PF	3.183	0.882	0.152	0.008
	SA	3.019	0.841	0.144	-0.007

The primary findings are as follows:

- Steady state appears to be established after the second time point (first time point after initial) with the exception of PVC.
- The recommended time duration for testing is 2 days for PVC and 35 days for barrier blisters[1].
- The recommended number of test points is 2 for PVC and 5 time points for barrier blisters.
- The controls have little effect on the WVTR and can be safely eliminated.
- Some blister types and the controls show a higher increase in moisture from the first time point (at time '0') to the second time point than over the remaining time points.
- There is noticeable curvature in the PVC weights over time.
- There is no change over time in cold form blisters.
- For each blister type, site slopes are similar.

[1] Throughout this paper, blisters formed from PVdC, Aclar, and cold form foil are referred to as barrier blisters, as distinguished from PVC blisters.

- Both conditions of 23C/75%RH and 40C/75%RH discriminate between the blister types with better discrimination at the higher temperature.

Based on the results of this study, we recommend:

- The use of 40ºC/ 75% RH storage condition based on reduced variability as measured by RSD.
- The use of the ASTM E 96 calculator to ensure a constant partial moisture vapor pressure differential, determine the required number of blisters and balance sensitivity to ensure data precision and accuracy. Refer to **Appendix 1**.
- A test duration of 2 days for PVC and 35 days for barrier blisters at 40ºC/ 75% RH.
- The use of 2 time points for PVC at initial and day 2 and the use of 5 (weekly) time points for barrier blisters beginning at day 7. Eliminate the initial time point (time '0') for barrier blisters.
- Eliminate the use of empty controls when using non-paper backed lidding foil.
- The use of linear regression for calculating WVTR for barrier blisters.
- Report results in mg/day/blister cavity and eliminate reference to blister classification to enable comparison with other container closure systems (e.g. bottles).

Introduction & Objectives

The purpose of this study was to assess the opportunity to improve USP <671> by constructing the weight gain profiles, due to moisture ingress, of formed and sealed blisters when stored at 23°C/75% and 40°C/75% RH. The profiles were used to determine the time needed to reach steady state, the duration, and number of data points needed for Water Vapor Transmission Rate (WVTR) calculation, the variability in data due to samples and testing labs, and to determine if the empty blisters (i.e. the "control") are needed for accurate WVTR determination. The origins of this study also lie in part in a previous publication[1] that provided a theoretical basis for using WVTR per unit dose as a means to compare different container-closure systems.

Materials & Methods

Blisters were formed and filled with an appropriate amount of desiccant (or without desiccant in the case of controls) determined using the ASTM E 96 calculator described in Appendix 1, and sealed to a heat sealable foil lid structure according to established procedures. Subsequently, the blister samples were stored in environmental chambers controlled at 40±2°C/75±5%RH or 23±2°C/75±3%RH. Each individual container (blister pack or set of blister packs) was weighed at various time points throughout the study according to a study protocol as summarized in Appendix 2. The weights of the blisters were tabulated for statistical analysis and for determination of WVTR (in mg per day per blister cavity) for the specific blister types (material & cavity design) at the two testing conditions. A linear line of best fit was applied to the weight data for each container using linear regression. The slope of each line is the WVTR.

Four blister types were used in the study: (1) 200 µ PVC, (2) 200 µ PVC/ 60 gsm PVdC, (3) 200 µ PVC/ 51 µ Aclar, and (4) cold form foil. The lidding foil was 20 µ Push-Thru, without paper or supporting film. Details on test duration, weighing intervals, amount of desiccant, number of cards, number or replicates, etc are given in Appendix 2. The blisters were formed on a Pentapak CT1200 using toolings designed to accommodate a size '0' capsule. Four labs performed the WVTR testing: Merck (MK), Pfizer (Pf), sanofi-aventis (SA), and Abbott (AB).

Results/Discussion

A number of containers (n=17 of a total 300 blister cards) were removed from the analysis due to holes found in the blisters. All of these containers contained desiccant. Merck did not perform the PVC testing. Storage conditions were reversed for the Abbott blisters during days 15-17.

As can be seen in Appendix 2, the number of blister packs was not consistent across the four blister types. To compare across blister types, results were converted to mg/cavity. Note that for PVC, AB performed two runs of 5 containers apiece denoted AB1 & AB2 in the figures.

Summary

The weight and the calculated WVTR for each blister type are given in the following subsections (A-D). Each subsection consists of two figures followed by a slope summary table.

Figure descriptions:

Figure #1: Mean weight (mg/cavity) of 10 containers with desiccant at each time point by lab. Blisters were stored at 23C/75%RH.

Figure #2: Mean weight (mg/cavity) of 10 containers with desiccant at each time point by lab. Blisters were stored at 40C/75%RH.

Slope Summary Table Description

For each container type, there are two sets of results within the slope summary table. Each set provides the number of slopes (containers) used in the calculation, the mean, standard deviation, and RSD(%) of the slopes as well as the minimum and maximum slope for each site and condition. The two sets are: 1) Containers with desiccant and 2) Containers with desiccant after adjusting for the mean of the empty controls (i.e., At each time point, the mean of the empty controls (usually n=10) was subtracted from the weight of each container containing desiccant prior to fitting the linear regression line to determine the WVTR).

A) PVC

Figure A1
23°C/75% RH

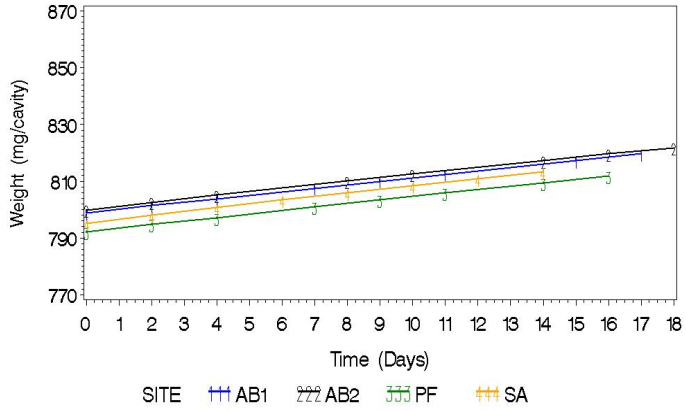


Figure A2
40°C/75%RH

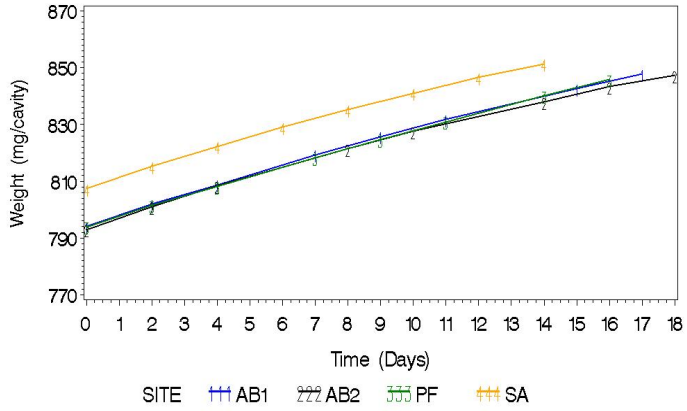


Table A
PVC Blisters
Slope Summary Statistics

Set 1 - As Is			Mean	Std Dev		Minimum	Maximum
Condition	Site	N	(mg/cavity/day)	(mg/cavity/day)	RSD(%)	Slope	Slope
23C/75%RH	AB	10	1.2230	0.0103	0.8402	1.2086	1.2371
23C/75%RH	PF	10	1.2313	0.0167	1.3552	1.2107	1.2690
23C/75%RH	SA	10	1.2943	0.0088	0.6803	1.2840	1.3074
40C/75%RH	AB	10	3.0820	0.0973	3.1586	2.8903	3.2236
40C/75%RH	PF	10	3.2391	0.0387	1.1957	3.1858	3.2951
40C/75%RH	SA	9	3.1387	0.0919	2.9282	2.9230	3.2429

Set 2 (Adjusted for Controls)			Mean	Std Dev		Minimum	Maximum
Condition	Site	N	(mg/cavity/day)	(mg/cavity/day)	RSD(%)	Slope	Slope
23C/75%RH	AB	10	1.2241	0.0101	0.8279	1.2090	1.2375
23C/75%RH	PF	10	1.2256	0.0167	1.3615	1.2049	1.2633
23C/75%RH	SA	10	1.2901	0.0088	0.6826	1.2798	1.3032
40C/75%RH	AB	10	3.0807	0.0966	3.1368	2.8899	3.2213
40C/75%RH	PF	10	3.2297	0.0387	1.1992	3.1763	3.2856
40C/75%RH	SA	9	3.1330	0.0919	2.9335	2.9174	3.2372

B) PVdC

Figure B1
23°C/75% RH

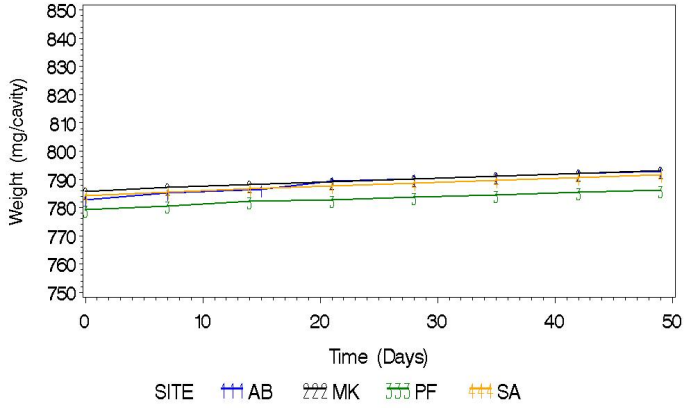


Figure B2
40°C/75%RH

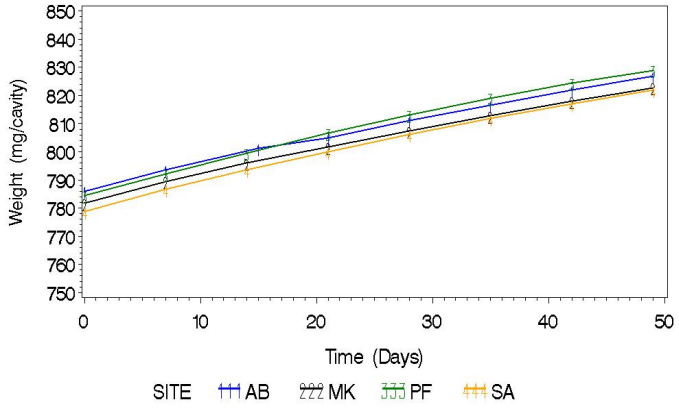


Table B
PVdC Blisters
Slope Summary Statistics

Set 1 - As Is Condition	Site	N	Mean (mg/cavity/day)	Std Dev (mg/cavity/day)	RSD(%)	Minimum Slope	Maximum Slope
23C/75%RH	AB	10	0.2067	0.0307	14.855	0.1869	0.2671
23C/75%RH	MK	10	0.1448	0.0010	0.674	0.1425	0.1458
23C/75%RH	PF	10	0.1366	0.0078	5.736	0.1150	0.1407
23C/75%RH	SA	10	0.1464	0.0006	0.435	0.1453	0.1472
40C/75%RH	AB	10	0.8207	0.0137	1.663	0.7887	0.8366
40C/75%RH	MK	10	0.8277	0.0161	1.948	0.7906	0.8475
40C/75%RH	PF	10	0.9146	0.0102	1.117	0.8953	0.9284
40C/75%RH	SA	10	0.8764	0.0091	1.034	0.8592	0.8901

Set 2 - Adjusted for Controls Condition	Site	N	Mean (mg/cavity/day)	Std Dev (mg/cavity/day)	RSD(%)	Minimum Slope	Maximum Slope
23C/75%RH	AB	10	0.1929	0.0307	15.9124	0.1731	0.2534
23C/75%RH	MK	10	0.1316	0.0010	0.7420	0.1293	0.1325
23C/75%RH	PF	10	0.1288	0.0078	6.0823	0.1072	0.1329
23C/75%RH	SA	10	0.1347	0.0006	0.4731	0.1337	0.1356
40C/75%RH	AB	10	0.8096	0.0137	1.6862	0.7775	0.8255
40C/75%RH	MK	10	0.8158	0.0161	1.9765	0.7787	0.8357
40C/75%RH	PF	10	0.9031	0.0102	1.1317	0.8838	0.9169
40C/75%RH	SA	10	0.8667	0.0091	1.0455	0.8495	0.8804

C) Ultrx 2000

Figure C1
23°C/75% RH

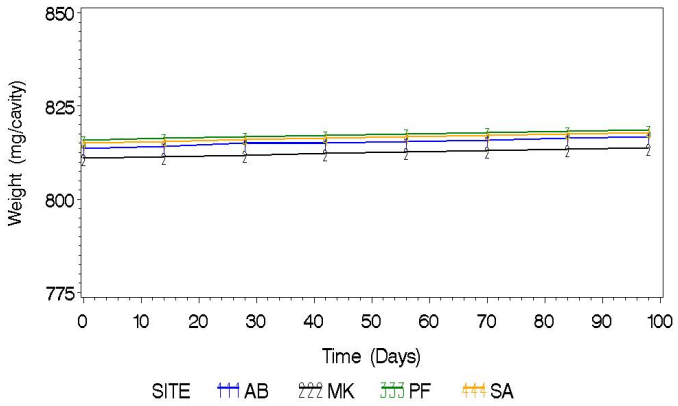


Figure C2
40°C/75%RH

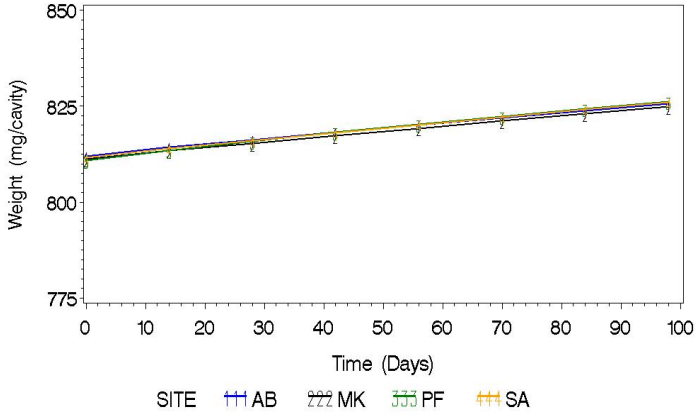


Table C
Ultrx 2000 Blisters
Slope Summary Statistics

Set 1 - As Is			Mean	Std Dev		Minimum	Maximum
Condition	Site	N	(mg/cavity/day)	(mg/cavity/day)	RSD(%)	Slope	Slope
23C/75%RH	AB	10	0.0306	0.0104	33.891	0.0240	0.0562
23C/75%RH	MK	10	0.0289	0.0038	13.027	0.0262	0.0366
23C/75%RH	PF	10	0.0287	0.0064	22.428	0.0252	0.0452
23C/75%RH	SA	7	0.0283	0.0008	2.830	0.0276	0.0296
40C/75%RH	AB	10	0.1389	0.0020	1.465	0.1355	0.1423
40C/75%RH	MK	7	0.1387	0.0012	0.857	0.1377	0.1407
40C/75%RH	PF	10	0.1563	0.0204	13.080	0.1396	0.1928
40C/75%RH	SA	10	0.1463	0.0017	1.185	0.1430	0.1479

Set 2 - Adjusted for Controls			Mean	Std Dev		Minimum	Maximum
Condition	Site	N	(mg/cavity/day)	(mg/cavity/day)	RSD(%)	Slope	Slope
23C/75%RH	AB	10	0.0289	0.0104	35.9286	0.0222	0.0544
23C/75%RH	MK	10	0.0264	0.0038	14.2965	0.0237	0.0341
23C/75%RH	PF	10	0.0267	0.0064	24.0997	0.0232	0.0432
23C/75%RH	SA	7	0.0258	0.0008	3.1073	0.0251	0.0271
40C/75%RH	AB	10	0.1363	0.0020	1.4935	0.1329	0.1397
40C/75%RH	MK	7	0.1360	0.0012	0.8746	0.1350	0.1379
40C/75%RH	PF	10	0.1543	0.0204	13.2463	0.1376	0.1909
40C/75%RH	SA	10	0.1437	0.0017	1.2061	0.1404	0.1453

D) Cold Form

Figure D1
23°C/75% RH

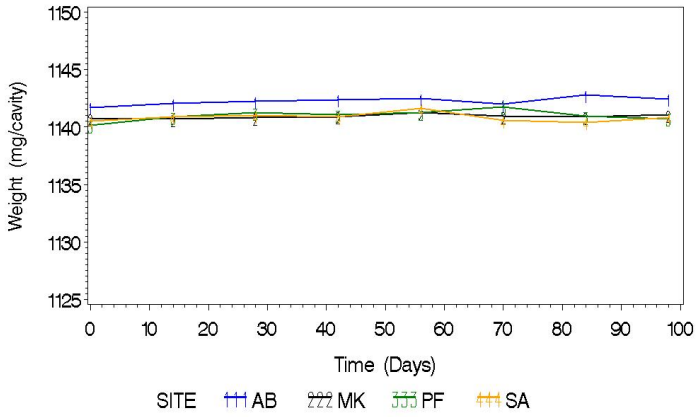


Figure D2
40°C/75%RH

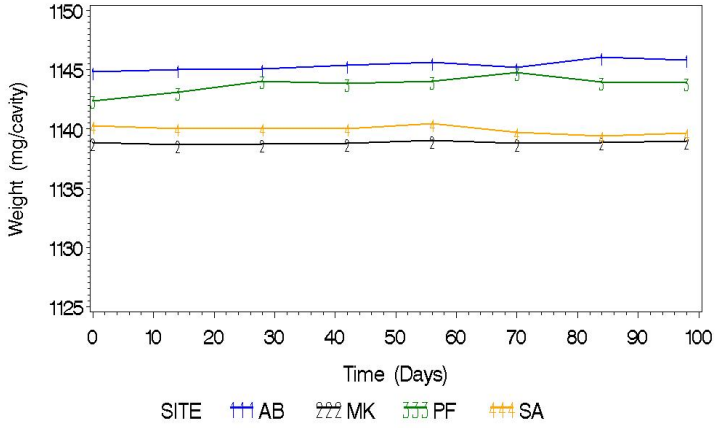


Table D
Cold Form Blisters
Slope Summary Statistics

Set 1 - As Is			Mean	Std Dev		Minimum	Maximum
Condition	Site	N	(mg/cavity/day)	(mg/cavity/day)	RSD(%)	Slope	Slope
23C/75%RH	AB	9	0.0069	0.0160	231	-0.0030	0.0443
23C/75%RH	MK	8	0.0031	0.0007	23	0.0023	0.0044
23C/75%RH	PF	10	0.0051	0.0154	301	-0.0040	0.0364
23C/75%RH	SA	8	-0.0006	0.0111	-1896	-0.0057	0.0265
40C/75%RH	AB	10	0.0110	0.0240	218	-0.0064	0.0575
40C/75%RH	MK	6	0.0020	0.0058	296	-0.0012	0.0134
40C/75%RH	PF	10	0.0146	0.0218	149	-0.0085	0.0423
40C/75%RH	SA	9	-0.0069	0.0032	-46	-0.0089	-0.0008

Set 2 - Adjusted for Controls			Mean	Std Dev		Minimum	Maximum
Condition	Site	N	(mg/cavity/day)	(mg/cavity/day)	RSD(%)	Slope	Slope
23C/75%RH	AB	9	0.0081	0.0160	198	-0.0019	0.0455
23C/75%RH	MK	8	0.0002	0.0007	433	-0.0007	0.0014
23C/75%RH	PF	10	0.0093	0.0154	166	0.0002	0.0406
23C/75%RH	SA	8	0.0051	0.0111	219	-0.0001	0.0322
40C/75%RH	AB	10	0.0173	0.0240	138	-0.0001	0.0638
40C/75%RH	MK	6	0.0040	0.0058	144	0.0009	0.0154
40C/75%RH	PF	10	0.0237	0.0218	92	0.0006	0.0514
40C/75%RH	SA	9	0.0017	0.0032	185	-0.0002	0.0079

The following table summarizes the observations from the figures and tables.

Table 2 Findings Summary for Blister Types and Test Sites

	Blister Type			
	PVC	**PVDC**	**Ultrx 200**	**Cold Form**
Curvature over time?	40°C/75%RH - Yes 23°C/75%RH - No	40°C/75%RH - Some 23°C/75%RH - No	No	No
Adjusting for Controls	Little effect (< 0.01 mg/cavity/day) Does not remove curvature.	Little effect. (< 0.014 mg/cavity/day)	Reduces slope slightly. (<0.003 mg/cavity/day)	No effect
Control Profile	Slight increase from initial to first time point after initial at 40°C - then no increase to final time point. PF has higher intercept.	Slight increase from initial to first time point after initial at 40°C - then no increase to final time point.	Slight increase from initial to first time point after initial - then no increase to final time point. MK controls have higher intercept than other sites.	No increase over time.
Intercepts (Blisters with desiccant)	SA has higher intercept at 40°C.	Site intercepts similar.	Similar at 40°C. Slight differences at 23°C/75.	Similar intercepts at 23°C. Some variation at 40°C.
Slopes (Blisters with desiccant)	Site slopes similar to one another. 40°C slopes higher than 23°C slopes. Within run standard deviations around regression line similar. Possible run to run slope and standard deviation around regression line variation based on Abbot data.	Site slopes similar to one another. 40°C slopes higher than 23°C slopes. Standard deviations about regression lines at 23°C vary from container to container for PF.	Site slopes similar to one another. 40°C slopes higher than 23°C slopes. Standard deviations about regression lines at 40°C vary from container to container for PF.	All slopes close to zero.

As noted in the overview, the formed blisters were sealed with 20 µ Push-Thru lidding foil without paper or supporting film. It is thought that avoiding a hygroscopic paper layer contributed to the negligible difference between WVTR calculated with and without the use of controls. Therefore use of non-paper backed foil is regarded as a necessary condition to eliminate the use of controls.

Comparison of Blisters and Labs

Table 3 and Figures 1 & 2 show the average slope for each blister type by site combination. Notice that site results are similar for each blister type with the blister type slopes decreasing as the blister barrier increases. Table 4 shows the standard deviation of the slopes for each combination.

Table 3. Comparison of WVTR for Blister Types and Test Sites (Mean, mg/cavity/day)

Condition	Site	PVC	PVdC	Ultrx	Cold
23C/75%RH	AB	1.2230	0.2067	0.0306	0.0069
23C/75%RH	MK	.	0.1448	0.0289	0.0031
23C/75%RH	PF	1.2313	0.1366	0.0287	0.0051
23C/75%RH	SA	1.2943	0.1464	0.0283	-0.0006
40C/75%RH	AB	3.0820	0.8207	0.1389	0.0110
40C/75%RH	MK	.	0.8277	0.1387	0.0020
40C/75%RH	PF	3.2391	0.9146	0.1563	0.0146
40C/75%RH	SA	3.1387	0.8764	0.1463	-0.0069

Table 4. Comparison of Standard Deviation of WVTR for Blister Types and Test Sites (Mean, mg/cavity/day)

Standard Deviations (mg/cavity/day)

Condition	Site	PVC	PVdC	Ultrx	Cold
23C/75%RH	AB	0.0103	0.0307	0.0104	0.0160
23C/75%RH	MK	.	0.0010	0.0038	0.0007
23C/75%RH	PF	0.0167	0.0078	0.0064	0.0154
23C/75%RH	SA	0.0088	0.0006	0.0008	0.0111
40C/75%RH	AB	0.0973	0.0137	0.0020	0.0240
40C/75%RH	MK	.	0.0161	0.0012	0.0058
40C/75%RH	PF	0.0387	0.0102	0.0204	0.0218
40C/75%RH	SA	0.0919	0.0091	0.0017	0.0032

Figure 1

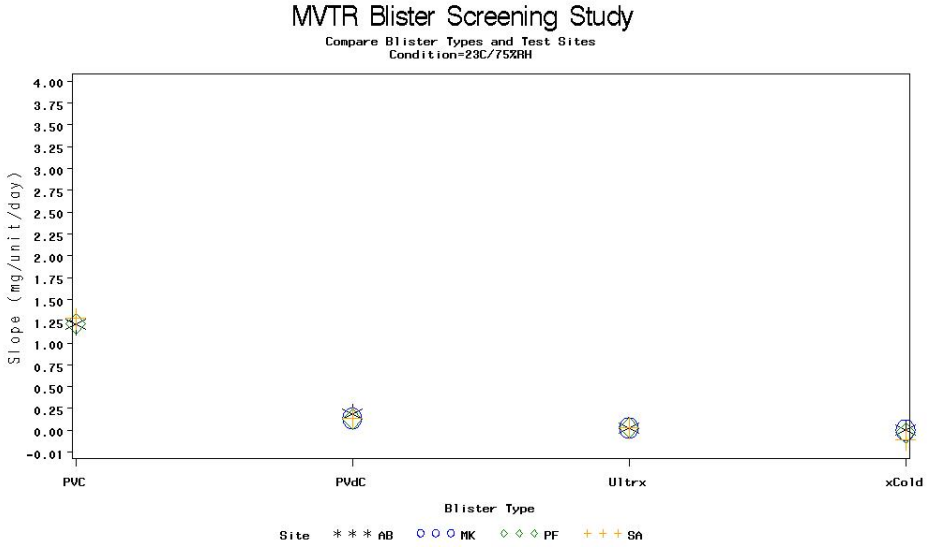
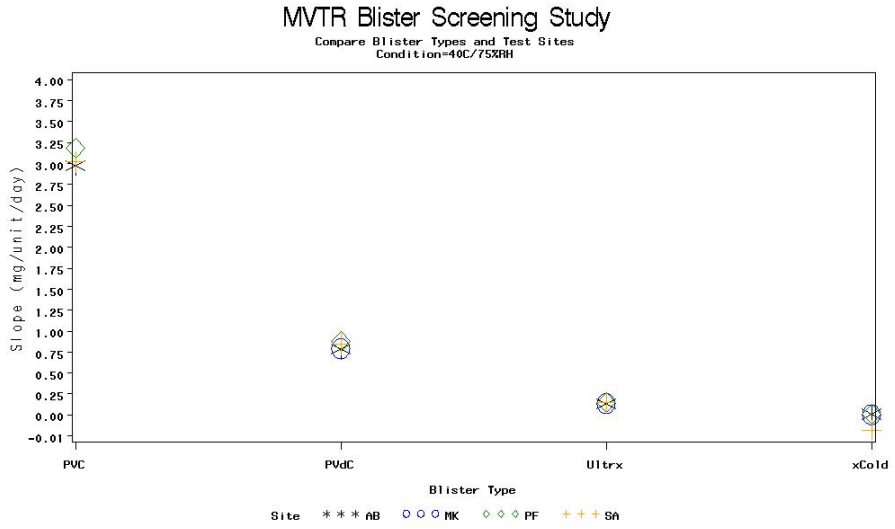


Figure 2



The above analysis uses a linear regression of the weights over time. A test that would just require using two time points to determine the slope would be easier than running a regression. In the screening study, there were 8 time points for each blister type. Table 5 shows the mean slope across the containers using four different slope calculations: 1) Slope using the 5th and 2nd time point, 2) slope using the 8th and 5th time point, 3) slope

using the 8th and second time point, and 4) slope using a linear regression. For the linear regressions, the initial was left out of the analysis to remove any effect that may take place between the initial and the second time point.

The effect of the curvature can be evaluated using this table by comparing the D5_2 which estimates the slope from the 2nd to 5th time point to the D8_5 slopes which measures the slope from the 5th to 8th time point. Notice that in general the slopes based on the 5th and 2nd time point are similar to the linear regression slope. The differences between sites appear much smaller than differences between the blister types.

Table 5:
WVTR Blister Screening Study
Compare Blister Types and Test Sites
Slope's Computed using Linear Regression
5th - 2nd, 8th - 5th, and 8th-2nd time points
(Initial removed)

Condition	Site	Slope Method	PVC	PVdC	Ultrx	Cold
23C/75%RH	AB	D5_2	1.2391	0.2422	0.0319	0.0100
	AB	D8_5	1.1816	0.1260	0.0312	-0.0004
	AB	D8_2	1.2101	0.1841	0.0316	0.0048
	AB	reg	1.2153	0.1852	0.0290	0.0048
	MK	D5_2	.	0.1391	0.0290	0.0125
	MK	D8_5	.	0.1376	0.0272	-0.0043
	MK	D8_2	.	0.1383	0.0281	0.0041
	MK	reg	.	0.1385	0.0282	0.0032
	PF	D5_2	1.2390	0.1419	0.0301	0.0082
	PF	D8_5	1.1946	0.1260	0.0258	-0.0122
	PF	D8_2	1.2168	0.1340	0.0280	-0.0020
	PF	reg	1.2234	0.1271	0.0279	-0.0011
	SA	D5_2	1.3270	0.1470	0.0295	0.0179
	SA	D8_5	1.2370	0.1365	0.0261	-0.0194
	SA	D8_2	1.2820	0.1417	0.0278	-0.0007
	SA	reg	1.2796	0.1415	0.0278	-0.0042
40C/75%RH	AB	D5_2	3.3583	0.8263	0.1379	0.0139
	AB	D8_5	2.6091	0.7567	0.1341	0.0056
	AB	D8_2	2.9732	0.7915	0.1360	0.0098
	AB	reg	2.9785	0.7889	0.1362	0.0109
	MK	D5_2	.	0.8472	0.1381	0.0089
	MK	D8_5	.	0.7375	0.1348	-0.0012
	MK	D8_2	.	0.7924	0.1364	0.0038
	MK	reg	.	0.7913	0.1370	0.0032
	PF	D5_2	3.3216	0.9978	0.1638	0.0218
	PF	D8_5	3.0281	0.7580	0.1420	-0.0030
	PF	D8_2	3.1749	0.8779	0.1529	0.0094
	PF	reg	3.1827	0.8820	0.1517	0.0080
	SA	D5_2	3.3239	0.9245	0.1488	0.0096
	SA	D8_5	2.7048	0.7570	0.1394	-0.0187
	SA	D8_2	3.0144	0.8408	0.1441	-0.0046
	SA	reg	3.0186	0.8414	0.1442	-0.0073

While 23ºC/ 75% RH provides the best storage condition for PVC blisters, 40ºC/ 75% RH was selected as the preferred storage condition based on reduced variability of WVTR of the barrier blisters as measured by RSD. PVC blisters saturate relatively quickly at 40ºC/ 75% RH, and use of the initial weight and day 2 weight to

calculate WVTR provided the highest slope and the best estimate of WVTR compared with, for example, WVTR calculated using the day 2 to day 4 weights as shown in Table 6.

Table 6:
WVTR Blister Screening Study
Compare PVC Slopes (Day 2 - Initial) vs (Day 4 - Day 2)

Condition	Site	Slope Day 2 - Initial	Slope Day 4 - Day 2
23C/75%RH	AB	1.317	1.218
	PF	1.327	1.185
	SA	1.371	1.368
40C/75%RH	AB	3.982	3.526
	PF	3.747	3.348
	SA	3.932	3.544

Use of the 40ºC/ 75% RH storage condition also allows manufacturer's to correlate results with stability data generated at the 40ºC/ 75% RH ICH storage condition.

Recommendations

Based on the results of this study, we recommend:

- The use of 40ºC/ 75% RH storage condition based on reduced variability, as measured by RSD, and ability to correlate with an ICH stability test condition.
- The use of the ASTM E 96 calculator to determine a constant partial moisture vapor pressure differential, the number of blisters and balance sensitivity to ensure data precision and accuracy.
- A test duration of 2 days for PVC and 35 days for barrier blisters at 40ºC/ 75% RH.
- The use of 2 time points for PVC at initial and day 2 and the use of 5 (weekly) time points for barrier blisters beginning at day 7. Eliminate the initial time point (time '0') for barrier blisters.
- Eliminate the use of empty controls when using non-paper backed lidding foil.
- The use of linear regression for calculating WVTR for barrier blisters.
- Report results in mg/day/blister cavity and eliminate reference to blister classification to enable comparison with other container closure systems (e.g. bottles).

The recommendations are made with pharmaceutical manufacturer's needs and capabilities in mind to provide a platform for meaningful comparison between container closure systems, and to enable determination of a WVTR performance space in which the stability of a solid oral dose form can be ensured.

Appendix 1

Reason for use of E- 96 Calculator

During design of the blister study, it was necessary to account for a number of simultaneous random variables. The following questions arose:

1. How to assure that there was enough desiccant in the package to carry the test to completion?
2. How to assure that steady state would be reached within the time of the test?
3. How to verify that steady state had been reached?
4. How to minimize variability resulting from limited sensitivity of the balance used?
5. What should be the duration of the test?
6. What weighing intervals should be used?
7. What desiccant should be used?

Each attempt to fix any one of the variables above resulted in uncertainty about the others. It was obvious that the questions were inter-related, but the solution was not obvious.

A literature review on the subject of steady state water vapor transmission revealed an ASTM method that provided an answer. The method is ASTM E96 – 00, "Standard Test Methods for Water Vapor Transmission of Materials". The method provides for control of the following test parameters, calculations and analyses:

1. Balance sensitivity < 1% of weight change during the period of steady state
2. Weights shall be accurate to 1% of weight change during the steady state period.
3. Weigh often enough to provide 8 or 10 data points during the test
4. Record time to 1% of time span between successive weighings.
5. Terminate the test if the total change in weight exceeds 10% of the initial weight of the desiccant.
6. The method specifies anhydrous calcium chloride, dried at 400 F (200 C), as a desiccant
7. The method specifies use of a blank for low transmission rates
8. Periodic weight change equals or exceeds 20% of (100 x scale sensitivity)
9. For graphic analysis, plot weight against time. Six points determines the straight line fit to determine the slope. Or,
10. For numerical analysis, use least squares regression analysis of weight as a function of time.

To design this experiment required an estimation of the value of water vapor permeation for the materials to be tested. This was done using values obtained during previous measurements of water vapor permeability.

Four steps were taken.

1. An iterative program was written in Virtual Basic to calculate outcomes for various scenarios among the parameters. The program used the guidelines provided in E-96 for the variable parameters.
2. Silica gel was chosen as the preferred desiccant for blisters. This choice was made on the basis of previous laboratory experience with several desiccants, including silica gel.
3. The estimated WVTRs were used to determine the expected uptake of water. This amount was compared with the water sorption isotherm for silica gel to establish the minimum amount of silica gel required to avoid saturation of the desiccant before the end of the experiment. It was determined that the amount of desiccant in the package must be enough to maintain RH of not more than 10% within the headspace of the package.
4. Test duration was chosen to allow for 8 data points, including zero time.

To ensure linearity of the weight gain vs. time data, one needs to keep the driving force for water-vapor permeation as nearly constant as possible during the testing period. Since the external water activity (i.e. RH) is maintained constant at 75% at either test temperature, this means that one would aim to keep the internal water activity as nearly constant as is practically feasible. We recommend placing sufficient desiccant in the container to ensure that the internal headspace RH does not exceed 10%. This way, the driving force would stay reasonably constant, between 75% and 65% RH, throughout the testing period.

Literature search suggests that a typical silica gel desiccant absorbs about 7% to 10% by mass of water at 40ºC/10% RH. Thus, in the proposed test method, one must place sufficient amount of desiccant in each cavity such that the total cumulative mass increase per mass of desiccant stays below 7% to 10% wt. To be on the conservative side, we chose 7% for our recommendation. The following table was generated to help determine the minimum amount of desiccant needed in each blister cavity according to the expected WVTR range of the material under test.

Anticipated Maximum WVTR, mg/cavity/day at 40C/75% RH	Recommended Test Duration, Days	Maximum Amount of Moisture Entering the Cavity, mg	Target Maximum Amount of Moisture in Desiccant at End of Test, wt% (corresponding to ~10% RH in the Moisture Sorption Isotherm of Silica Gel)	Minimum Amount of Desiccant Per Cavity, mg
0.1	35	3.5	7%	50
0.5	35	17.5	7%	250
1	35	35	7%	500
4	2	8	7%	114

Appendix 2 shows the results of calculations for amount of desiccant, weighing intervals and duration of test applied for the experiment reported here.

Appendix 2

PQRI Experiment for WVTR Test Method
Unit Dose Packages (Blisters)
Test Intervals, and Weight Gain
ASTM E 96 Calculator Information

(Size 0) PVC blisters,
Desiccant: Silica gel

Balance Sensitivity 0.1 mg, Conditions 23 °C/75% RH
Estimated WVTR= 0.5 mg/day/cavity at 23 °C/75% RH

	Sealed blisters
Duration of Test, days	**14**
Weighing Interval, days	**2 (total 7 points)**
Estimated Wt Gain/Interval/10-cavity, mg	10 mg
Amount Desiccant Required/cavity, g	**1**
No of Blister Cards (cavity/card) for each weighing	**1(10)**
Number of Replicate Weights	**10**
Total Number of Blister Cards for 4 labs	**40**

Balance Sensitivity 0.1 mg, Conditions 40°C/75% RH
Estimated WVTR= 1.2 mg/day/unit at 40 °C/75% RH,

	Sealed blisters
Duration of Test, days	**14**
Weighing Interval, days	**2 (total 7 points)**
Estimated Wt Gain/Interval/10-cavity, mg	24 mg
Amount Desiccant Required/cavity, g	**1**
No of Blister Cards (cavity/card) for each weighing	**1(10)**
Number of Replicate Weights	**10**
Total Number of Blister Cards for 4 labs	**40**

(Size 0) PVdC /60 gms blisters,
Desiccant: Silica gel

Balance Sensitivity 0.1 mg Conditions 23 °C/75% RH
Estimated WVTR= 0.065mg/day/cavity at 23 °C/75% RH

	Sealed blisters
Duration of Test, days	**49**
Weighing Interval, days	**7 (total 7 points)**
Estimated Wt Gain/Interval/20-cavity, mg	9.1
Amount Desiccant Required/cavity, g	**1**
No of Blister Cards (cavity/card) for each weighing	**2(10)**
Number of Replicate Weights	**10**
Total Number of Blister Cards for 4 labs	**80**

Balance Sensitivity 0.1 mg Conditions 40°C/75% RH
Estimated WVTR= 0.47mg/day/unit at 40 °C/75% RH,

	Sealed blisters
Duration of Test, days	**49**
Weighing Interval, days	**7 (total 7 points)**
Estimated Wt Gain/Interval/10-cavity, mg	32.9
Amount Desiccant Required/cavity, g	**1**
No of Blister Cards (cavity/card) for each weighing	**1(10)**
Number of Replicate Weights	**10**
Total Number of Blister Cards for 4 labs	**40**

(Size 0) Ultrx 2000 blisters,
Desiccant: Silica gel

Balance Sensitivity 0.1 mg Conditions 23 °C/75% RH
Estimated WVTR= 0.018mg/day/unit at 23 °C/75% RH

	Sealed blisters
Duration of Test, days	**98**
Weighing Interval, days	**14 (total 7 points)**
Estimated Wt Gain/Interval/30-cavity, mg	7.6
Amount Desiccant Required/cavity, g	**1**
No of Blister Cards (cavity/card) for each weighing	**3(10)**
Number of Replicate Weights	**10**
Total Number of Blister Cards for 4 labs	**120**

Balance Sensitivity 0.1 mg Conditions 40°C/75% RH
Estimated WVTR= 0.085mg/day/unit at 40 °C/75% RH,

Duration of Test, days	**98**
Weighing Interval, days	**14 (total 7 points)**
Estimated Wt Gain/Interval/10-cavity, mg	11.9
Amount Desiccant Required/cavity, g	**1**
No of Blister Cards (cavity/card) for weighing	**1(10)**
Number of Replicate Weights	**10**
Total Number of Blister Cards for 4 labs	**40**

(Size 0) Coldform Alu/alu blisters,
Desiccant: Silica gel

Balance Sensitivity 0.1 mg Conditions 23 °C/75% RH
Estimated WVTR< 0.01mg/day/unit at 23 °C/75% RH

	Sealed blisters
Duration of Test, days	**98**
Weighing Interval, days	**14 (total 7 points)**
Estimated Wt Gain/Interval/30-cavity, mg	<1
Amount Desiccant Required/cavity, g	**0.6**
No of Blister Cards (cavity/card) for each weighing	**5(6)**
Number of Replicate Weights	**10**
Total Number of Blister Cards for 4 labs	**200**

Balance Sensitivity 0.1 mg Conditions 40°C/75% RH
Estimated WVTR<0.01mg/day/unit at 40 °C/75% RH,

Duration of Test, days	**98**
Weighing Interval, days	**14 (total 7 points)**
Estimated Wt Gain/Interval/30-cavity, mg	<1
Amount Desiccant Required/cavity, g	**0.6**
No of Blister Cards (cavity/card) for each weighing	**5(6)**
Number of Replicate Weights	**10**
Total Number of Blister Cards for 4 labs	**200**

[1] Barry J, Bergum J, Chen Y, Chern R, Hollander R Klein D, Lockhart H, Malinowski D, McManus R, Moreton C, Mueller A, Nottingham L, Okeke C, O'Reilly D, Rinesmith K, and Shorts S, (PQRI Container-Closure Working Group), Basis for using Moisture Vapor Transmission Rate pre Unit Product in the evaluation of Moisture-Barrier Equivalence of Primary Packages for Solid Oral Dosage Forms, Pharmacopeial Forum, (2005), 31, (1) Jan.—Feb., 226 – 269.