DuPont™ Tyvek® Medical Packaging Transition Project

7-Year Accelerated Aging Industry Summary Report

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EXECUTIVE SUMMARY

7-Year Accelerated Aging package testing results for 11 cells in the Medical Packaging Transition Project ("**MPTP**") by third-party Nelson Laboratories indicate **Functional Equivalence** between current Tyvek® and Transition Protocol material. Specific test data to support this conclusion includes:

- Seal Strength (ASTM F88): 12 out of 12 instances of **Functional Equivalence**
- Microbial Barrier (ASTM F2638): 11 out of 11 instances of **Non-Inferiority**
- Package Integrity (ASTM F1929): 198 out of 198 instances of **No Dye Penetration**

Additional details are provided in the Tables and Figures that follow.

MEDICAL PACKAGING TRANSITION PROJECT ("MPTP") OVERVIEW SUMMARY

The **Pre-Sterilization and Post-Sterilization Industry Summary Report (November 2014; Corrected April 2015)** provides an extensive overview of MPTP. It can be found in the **"Medical Packaging Transition Project Industry Reports"** section of the www.areyouready.tyvek.com website. Important points to re-emphasize include:

- **Functional Equivalence** means that attributes of Transition Protocol material meet functional and performance requirements.
- The **U.S. FDA Transition Protocol** is a study plan based on sound principles of experimental design and statistical analysis for generating data to prove Functional Equivalence by comparing Transition Protocol material and Current Tyvek® using 60 different device/package combinations ("**cells**") with a validated design and a validated forming, sealing and assembly process. Table 1 summarizes all 60 U.S. FDA Transition Protocol cells.

Table 1. Sixty Cell U.S. FDA Transition Protocol Matrix

		Style	Pouches and Bags						Form-Fill-Seal						Rigid Trays								
EO	Coated	1073B	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
EO	Uncoated	1073B	22	23	24	25	26	27															
Gamma	Coated	1073B	28		29		30		31		32		33		34		35		36		37		38	39
Gamma	Uncoated	1073B	40		41		42																
Electron-beam	Coated	1073B							43		44		45										
Electron-beam	Uncoated	1073B	46		47		48																
EO	Coated	1059B							49		50		51										
EO	Uncoated	1059B	52	53	54	55	56	57	58		59		60										

- The **Phantom Protocol** involves the creation and testing of 18 additional sterilized medical device/ package combinations ("**cells**") that are outside the scope of the U.S. FDA Transition Protocol but have been requested by the industry to support risk assessments. Table 2 summarizes all 18 Phantom Protocol cells.

Table 2. Eighteen Cell Phantom Protocol Matrix

		Style	Pouches and Bags		Form-Fill-Seal	Rigid Trays		
EO	Coated	1073B	x74		X75	X71	X78	
EO	Uncoated	1073B	X61					
Gamma	Coated	1073B				X62	X63	
Gamma	Uncoated	1073B						
Electron-beam	Coated	1073B						
Electron-beam	Uncoated	1073B						
EO	Coated	1059B						
EO	Uncoated	1059B	X77					
Steam	Coated	1073B				X65	X66	X67
Steam	Uncoated	1073B	X69	X70				
Dry Heat	Coated	1073B				X68		
Low Temp. H_2O_2	Coated	1073B	X76					
Low Temp. $C_2H_4O_3$	Coated	1073B				X64		
Gamma	Coated	1059B			X72			
Electron-beam	Coated	1059B			X73			

- Eleven of the 78 combined U.S. FDA Transition and Phantom Protocol cells were tested under 7-Year Accelerated Aging conditions. Cell descriptors for these 11 cells, two of which were similar constructs, are as follows:
  - ✓ **Perfecseal® SBP2000 EU coated 1073B, 28 mil (700 micron) PETG tray, EO sterilized**
  - ✓ **Perfecseal® CR27 coated 1073B, Perfecflex® 35791-E 48-gauge (12 micron) PET/1.5 mil (38 micron) PE film, gamma sterilized pouch**
  - ✓ **Perfecseal® CR27 coated 1073B, Amcor Flexibles Inc. 12 mil (305 micron) EVA/Ionomer/EVA forming film, gamma sterilized FFS flexible blister**
  - ✓ **Perfecseal® CR27 coated 1073B, 50 mil (1270 micron) PETG tray, gamma sterilized**
  - ✓ **Perfecseal® HCW CR27 coated 1073B, 40 mil (1016 micron) PETG tray, gamma sterilized**
  - ✓ **Amcor Flexibles Inc. coated 1073B, 40 mil (1016 micron) PETG tray, gamma sterilized**
  - ✓ **Oliver-Tolas® SealScience® TPT-0260 coated 1073B, 25 mil (640 micron) PETG tray, gamma sterilized**
  - ✓ **Perfecseal® CR27 EU coated 1073B, 0.5 mil (12 micron) PET/2.0 mil (50 micron) PE film, low temperature oxidation sterilized pouch**
  - ✓ **Uncoated 1073B, 48-gauge (12 micron) PET/2 mil (51 micron) LDPE film, EO sterilized pouch**
- 7-Year Accelerated Aging conditions were nominally 50 °C and 23% RH; aging times were calculated based on an ambient temperature of 25 °C, which is the nominal temperature for real-time aging
- Paired data sets (Transition Protocol material vs. Current Tyvek®) for each cell were generated and analyzed from the following tests:
  - ✓ Seal Strength: ASTM F88
  - ✓ Microbial Barrier: ASTM F2638
  - ✓ Package Integrity: ASTM F1929
  - ✓ Visual Inspection: ASTM F1886M (***Only*** reported for Pre-sterilization and Post-sterilization time points; no ***aging*** visual inspection results will be reported)

This Industry Summary Report summarizes the 7-Year Accelerated Aging data for the 11 cells. Industry Summary Reports for other aging time points will be published as data generation and analysis are completed. More detailed and comprehensive reports than Industry Summary Reports will be prepared and submitted to the U.S. FDA and other regulatory bodies under Confidentiality Agreements.

TESTING and RESULTS OVERVIEW

Data were analyzed for the three different attributes detailed in the approved study design for 7-Year Accelerated Aging: seal strength, microbial barrier, and package integrity. In the following sections, a brief overview of the study design and associated statistical methods is provided, followed by a high-level summary of the results.

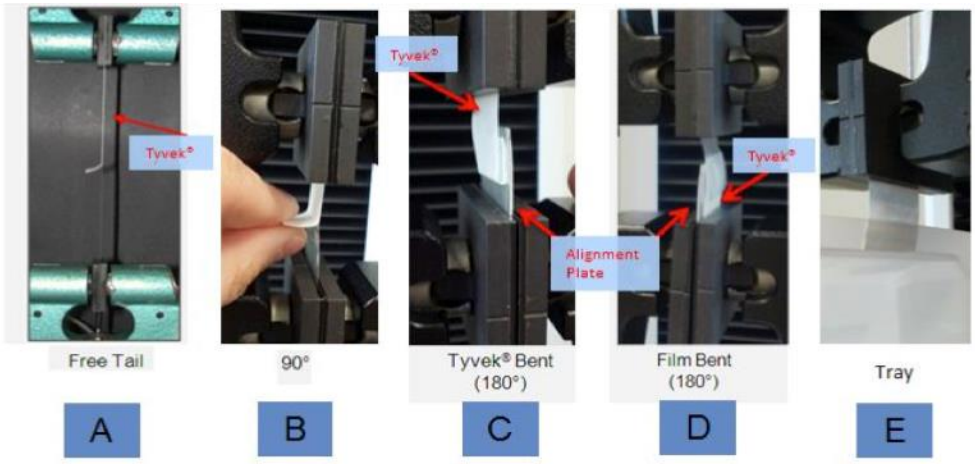
It should be noted that for the Pre-sterilization and Post-sterilization time points, three sealing conditions across the sealing window were tested for both the Test Material (also called Test or Transition Protocol material) and the Control Material (also called Control or Current Tyvek®). These three sealing conditions were denoted as Lower, Nominal, and Upper sealing conditions. However, for accelerated and real-time aging time points, only ***one*** sealing condition across the sealing window was tested. This sealing condition was specified by the Medical Device Manufacturers (**"MDMs"**) for each cell, and was based on the sealing condition used by the MDMs for their original stability testing during package qualification.

For the majority of cells, test packages for aging time points were manufactured with Nominal sealing conditions, while Lower sealing conditions were used for the remainder. No Upper sealing conditions were used for any aging time points.

Seal Strength (ASTM F88)

Seal strength was assessed via ASTM F88 in accordance with metric details specified by the MDMs. These metric details include a designation of either Maximum Load or Average Load as the response, as well as the testing apparatus/material orientation used. See Figure 1 for a visual description of the different seal strength methods/techniques employed in the study.

Figure 1. Description of Seal Strength Methods/Techniques



Technique	Tail Holding
A	Unsupported ("Free Tail", angle can vary throughout test)
B	Supported 90° (Fixed angle by hand or other)
C	Tyvek® Bent (Supported 180°) "TYVEK UPPER"
D	Film Bent (Supported 180°) "TYVEK LOWER"
E	Free Tail Tyvek® Upper Bent 180°

At the chosen sealing condition, 48 samples were tested for both Test Material and Control Material. For most cells, this consisted of 4 test strips cut from each of 12 packages. However, some packages were too small to obtain 4 samples per package so either 1 or 2 test strips were cut per package resulting in a total of 48 and 24 packages per condition, respectively.

Functional Equivalence was assessed by calculating the appropriate 90% confidence interval on the Difference in the Means (Test-Control) for each cell at the chosen sealing condition. If this interval was contained within the Functional Equivalence bounds, then the Seal Strength was declared Functionally Equivalent. While the Transition Protocol material must satisfy the Functional Equivalence criteria, Transition Protocol material packages must also meet or exceed Current Tyvek® package performance with respect to achieving minimum seal strength requirements, as defined by the MDMs.

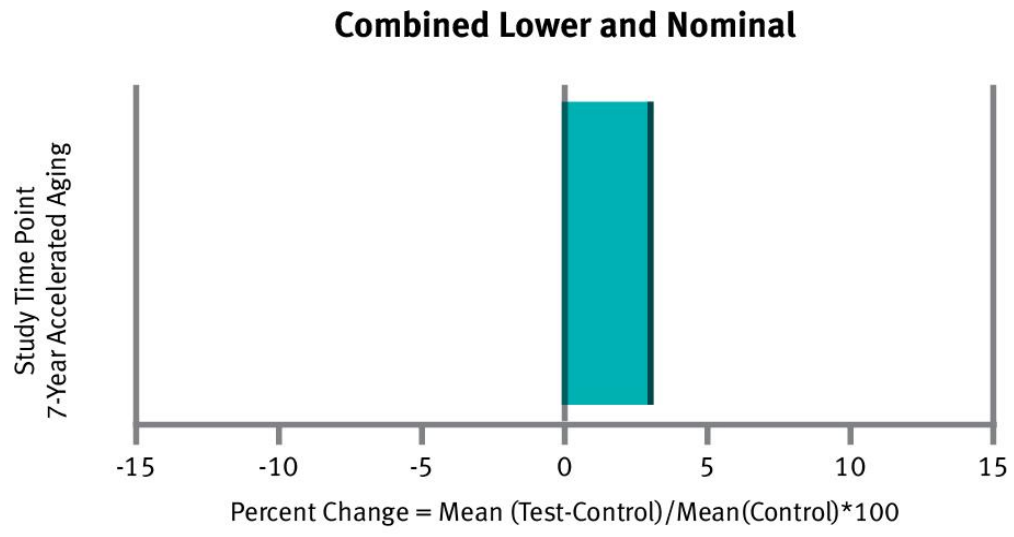
In the two figures that follow, the Average Percent Change in Seal Strength relative to the Control is calculated and presented in Figure 2 for all cells designated as Maximum Load. Figure 3 details the results for Average Load cells. Note this Average Percent Change is computed by calculating individual cell percent changes:

$$\text{Percent Change} = \text{Mean (Test-Control)}/\text{Mean (Control)}*100$$

and then taking the average of the individual cell percent change values. Average Percent Changes for Maximum Load cells for 7-Year Accelerated Aging are ~3%, which are in-line with Pre- and Post-sterilization, 1-Year Real-Time Aging, and 1-, 3- and 5-Year Accelerated Aging results (~4-6%). Average Percent Changes for Average Load cells for 7-Year Accelerated Aging are ~5%, which are also in-line with Pre- and Post-sterilization, 1-Year Real-Time Aging, and 1-, 3- and 5-Year Accelerated Aging results (~2-9%).

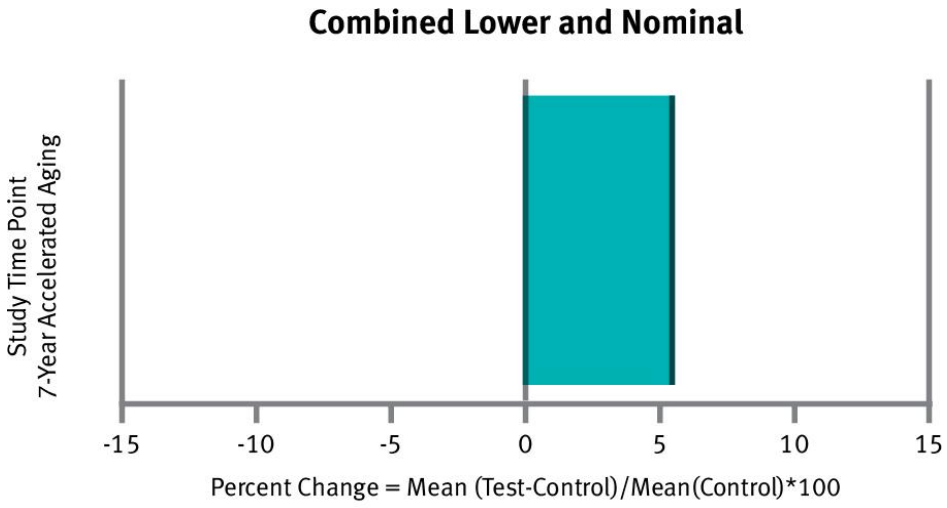
In creating the Maximum and Average Load Figures, two cells were double packages and both the inner and outer seal strength data were included. Peelable seal strength assessments made for this time point include: N=6 (Maximum Load) + N=7 (Average Load) totals N=13, determined from 11 cells + 2 cells (double). However, for 7-Year Accelerated Aging, only 12 seal strength assessments are actually being reported because for one Average Load cell, the majority of the package seal failures in both the Transition Protocol and Control materials were due to a failure mode other than peeling of the seal (as seen previously at the 3- and 5-Year Accelerated Aging time points). Hence, N=6 Average Load assessments.

Figure 2. Avg. Percent Change in Mean Seal Strength (Test-Control) for Maximum Load Cells; N=6



Test=Transition Protocol Material
Control=Current Tyvek®

Figure 3. Avg. Percent Change in Mean Seal Strength (Test-Control) for Average Load Cells; N=6



Test=Transition Protocol Material
Control=Current Tyvek®

A high-level summary of the results tested for each package configuration, material and sterilization combination is shown in Table 3. **There are 12 instances of Functional Equivalence for 7-Year Accelerated Aging. All cells with peelable seals met the Functional Equivalence criteria**.

Table 3. Summary of Seal Strength Functional Equivalence Results

Industry Summary: MPTP Test Results after 7-Year Accelerated Aging, Pass/Fail Summary for Seal Strength — ASTM F88

Tyvek® Style	Coating Type	Sterilization Type	Pouches and Bags		Form-Fill-Seal		Rigid Trays	
			Pass	Fail	Pass	Fail	Pass	Fail
1073B	Coated	EO					1	0
		Gamma	2	0	1	0	4**	0
		Electron-beam						
		Steam						
		Dry Heat						
		Low Temp. H_2O_2	1	0				
		Low Temp. $C_2H_4O_3$						
	Uncoated	EO	1	0				
		Gamma						
		Electron-beam						
		Steam						
1059B	Coated	EO						
		Gamma						
		Electron-beam						
	Uncoated	EO						

THERE ARE NO CELLS IN THIS CATEGORY BEING TESTED AFTER 7-YEAR ACCELERATED AGING

THERE ARE NO CELLS IN THE MPTP FOR THIS CATEGORY

**For one of the 5 cells total for this configuration, Transition Protocol material and Current material exhibited a majority of seal failures that were not peel failures; thus the seal strength results for this one cell were not included in the final analysis.

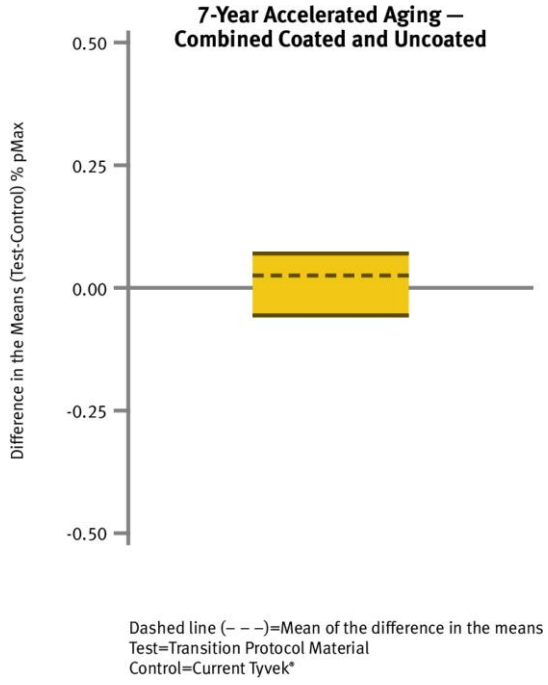
Microbial Barrier (ASTM F2638)

Microbial barrier performance was tested using ASTM F2638. The % pMax value for three Test samples and three Control samples from each cell was determined; a **lower/smaller** % pMax value indicates better microbial barrier performance. A statistical test of non-inferiority was performed to indicate the Test material does not underperform Control material. A 95% student's t upper confidence bound was calculated and compared to the pre-established non-inferiority criteria from the study design.

The Difference in the Means (Test-Control) for % pMax was calculated for each cell. These differences were then combined for Coated (N=10) and Uncoated (N=1) cells. The **endpoints** of the bar shown in Figure 4 represent the highest and the lowest Difference in the Means (Test-Control) observed for % pMax. A **0.00** value for the Difference in the Means indicates that the Transition Protocol material Mean and the Current Tyvek® Mean are the same. The **dashed line** in the bar represents the Mean of the Difference in the Means. **All 11 cells pass the Microbial Barrier Non-Inferiority Criteria for 7-Year Accelerated Aging, representing 11 instances of Functional Equivalence.**

It should be noted that the vertical scale in Figure 4 are *extremely* small numbers and represent minimal differences in the Means. Moreover, due to the outstanding microbial barrier performance of Tyvek®, **individual** % pMax values used in calculating differences were very small as well.

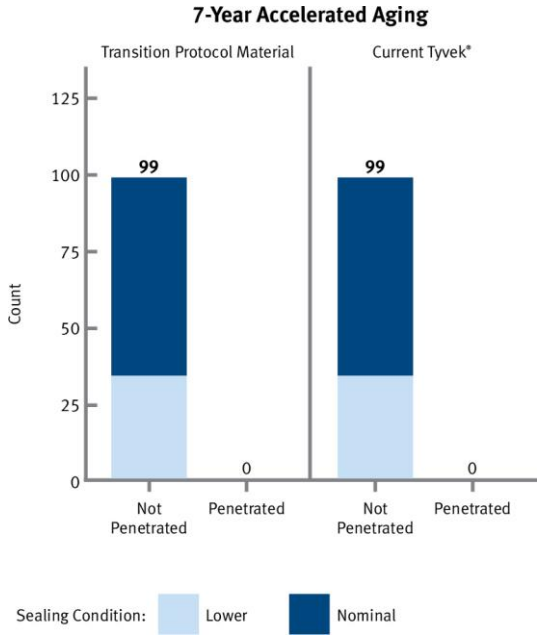
Figure 4. Range of Differences in % pMax Mean (Test-Control) for All 11 Cells



Package Integrity Testing (ASTM F1929)

ASTM F1929 was applied to assess package integrity via a dye penetration test. In the 7-Year Accelerated Aging phase of the study, package integrity testing was performed at the Lower or Nominal sealing condition, whichever was defined by the MDM for the cell. Nine Transition Protocol material packages and nine Current Tyvek® packages were tested for each cell; Figure 5 shows a summary of the data. There are 99 instances of no dye penetration in Transition Protocol material and 99 instances of no dye penetration in Current Tyvek® for a total of 198 instances of no dye penetration. **Package Integrity indicates Functional Equivalence because it passes the criteria set forth in the study design.**

Figure 5. Package Integrity Testing Summary



CONCLUSIONS

In summary, 7-Year Accelerated Aging testing indicates:

- 12 out of 12 instances of seal strength **Functional Equivalence**
- 11 out of 11 instances of microbial barrier **Non-Inferiority**
- 198 out of 198 instances of **No Dye Penetration**

These results continue to overwhelmingly support declaring **Functional Equivalence** between Current Tyvek® and Transition Protocol material.

Note: In previous reports for other study time points, Category Results were presented in an Appendix. Due to the limited number of cells tested after 7-Year Accelerated Aging, no such results will be presented.