DuPont™ Tyvek® Medical Packaging Transition Project

Industry Executive Summary Report

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INTRODUCTION

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.

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.

Additional **Protocol** details can be found in the www.areyouready.tyvek.com website.

This **Industry Executive Summary Report** summarizes **Industry Summary Reports** for the following study time points:

- Pre-sterilization and Post-sterilization (November 2014; Corrected April 2015)
- 1-Year Accelerated Aging (February 2015; Corrected April 2015)
- 3-Year Accelerated Aging (June 2015)
- 5-Year Accelerated Aging (July 2015)
- 1-Year Real-Time Aging (August 2015)

RESULTS SUMMARY

Package testing results for the 78 cells in the Medical Packaging Transition Project ("**MPTP**") by third-party Nelson Laboratories indicate **Functional Equivalence** between Current Tyvek® styles 1073B and 1059B and Transition Protocol material styles 1073B and 1059B. Specific test data to support this conclusion includes:

- Seal Strength (ASTM F88): 796 out of 798 instances of **Functional Equivalence**
- Microbial Barrier (ASTM F2638): 468 out of 468 instances of **Non-Inferiority**
- Package Integrity (ASTM F1929): 14,039 out of 14,040 instances of **No Dye Penetration**
- Visual Inspection (ASTM F1886M): 114,726 out of 114,729 instances of **No Material Defects**

Additional details are provided in the content sections that follow. Note that the data represents more than 50,000 seal strength tests and 2,500+ microbial barrier tests.

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										

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			

TESTING and RESULTS OVERVIEW

Data were analyzed for the four different attributes detailed in the approved study: seal strength, microbial barrier, package integrity, and visual inspection. In the sections that follow, brief summaries of the results are given for each attribute tested.

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.

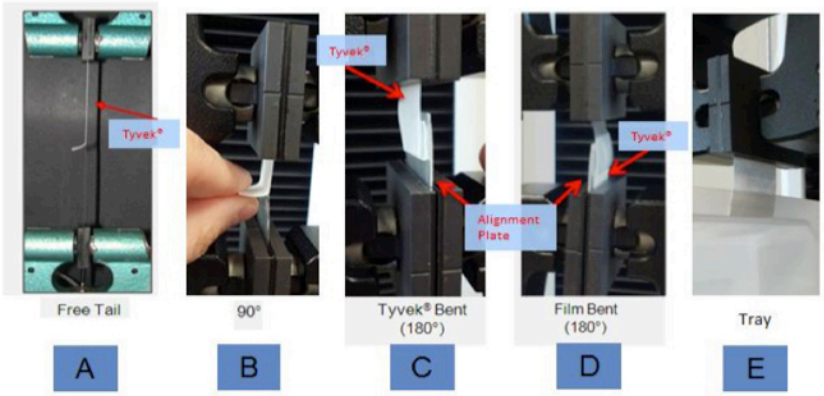
For the majority of cells, test packages for aging time points were manufactured with Nominal sealing conditions, while Lower sealing conditions were used for the remainder. No Upper sealing conditions were used for any aging time points.

Accelerated Aging conditions were nominally 50 °C and 23% RH; aging times were calculated based on an ambient temperature of 25 °C. Real-Time Aging conditions were nominally 25 °C and monitored ambient relative humidity.

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°

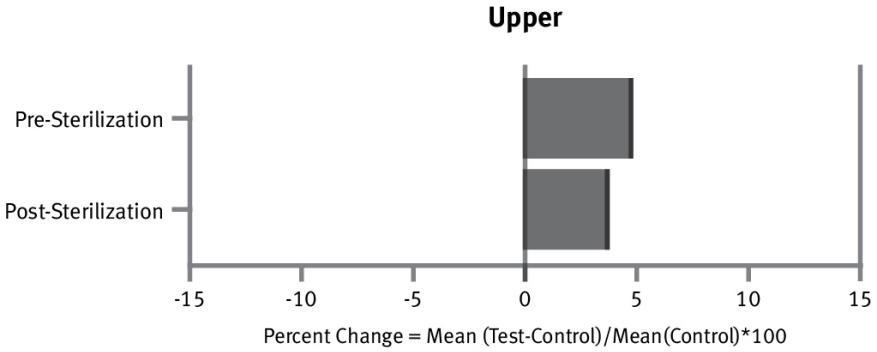
Functional Equivalence was assessed by calculating the appropriate 90% confidence interval on the Difference in the Means (Test-Control) for each cell at the chosen sealing condition. If this interval was contained within the Functional Equivalence bounds, then the Seal Strength was declared Functionally 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 six figures that follow, the Average Percent Change in Seal Strength relative to the Control is calculated and presented in Figures 2a, 2b and 2c for all cells within each time point designated as Maximum Load. Figures 3a, 3b and 3c detail the results for Average Load cells. Note this Average Percent Change is computed by calculating individual cell percent changes:

Percent Change = Mean (Test-Control)/Mean (Control)*100

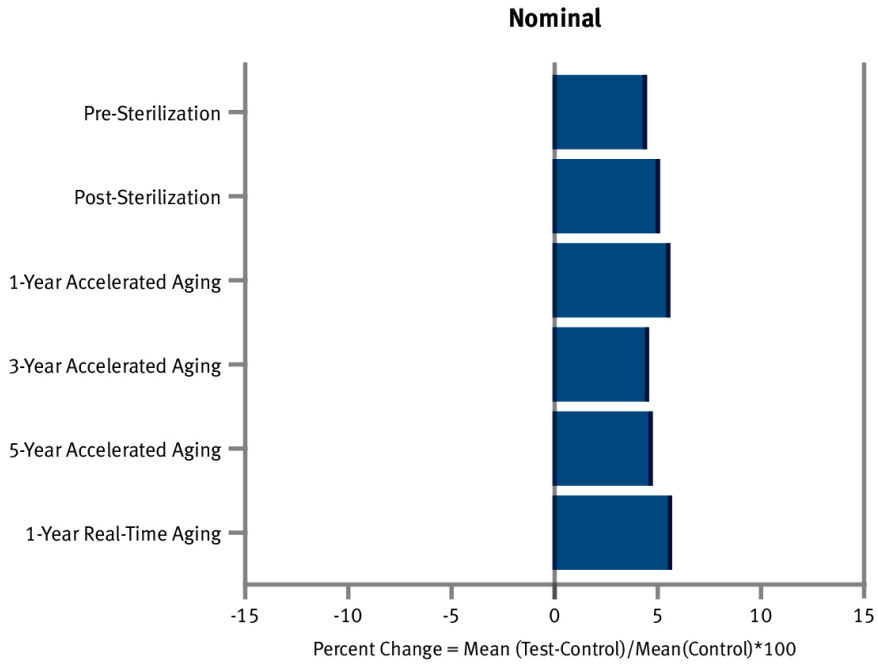
and then taking the average of the individual cell percent change values. Overall, Average Percent Changes for Maximum Load cells were ~4-6%, while Average Percent Changes for Average Load cells were ~2-9%.

Figure 2a. Avg. Percent Change in Mean Seal Strength (Test-Control) for Maximum Load Cells; Upper Sealing Condition



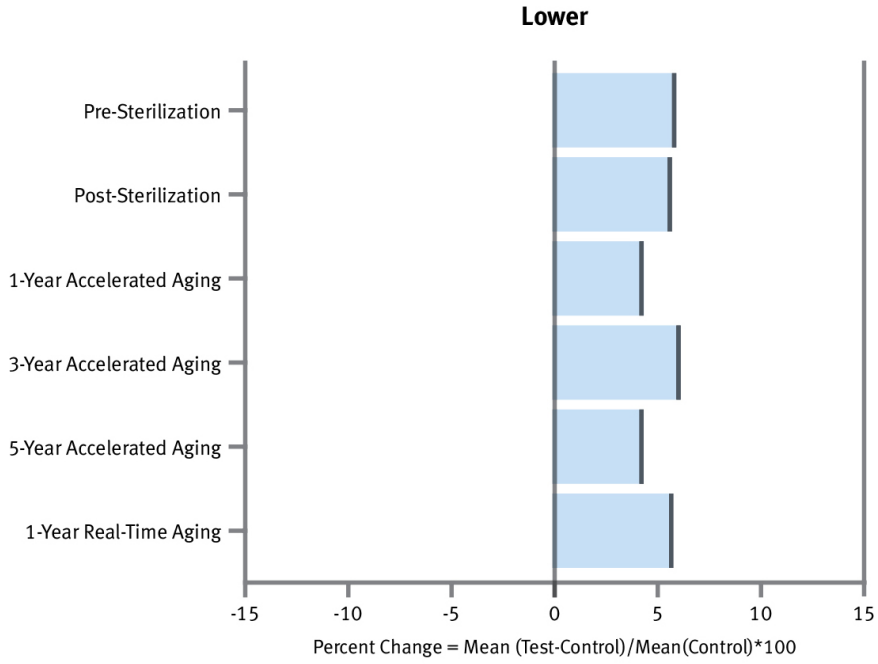
Test=Transition Protocol Material
Control=Current Tyvek®

Figure 2b. Avg. Percent Change in Mean Seal Strength (Test-Control) for Maximum Load Cells; Nominal Sealing Condition



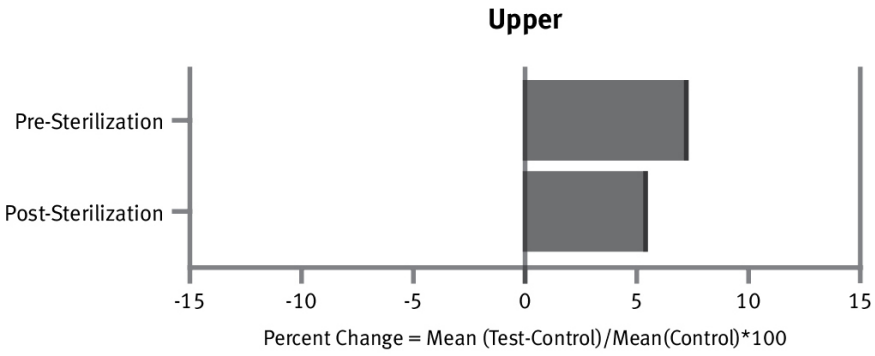
Test=Transition Protocol Material
Control=Current Tyvek®

Figure 2c. Avg. Percent Change in Mean Seal Strength (Test-Control) for Maximum Load Cells; Lower Sealing Condition



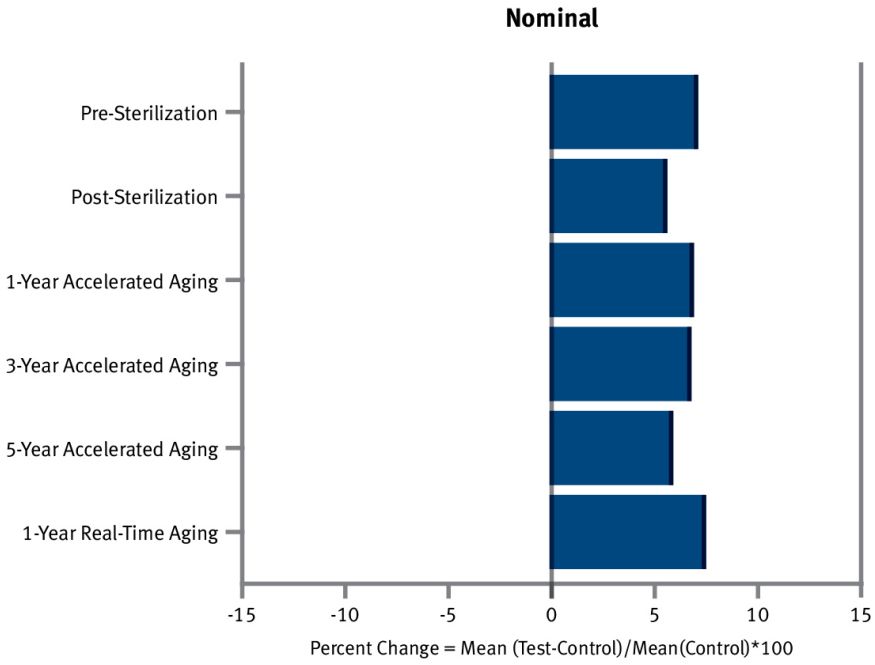
Test=Transition Protocol Material
Control=Current Tyvek®

Figure 3a. Avg. Percent Change in Mean Seal Strength (Test-Control) for Average Load Cells; Upper Sealing Condition



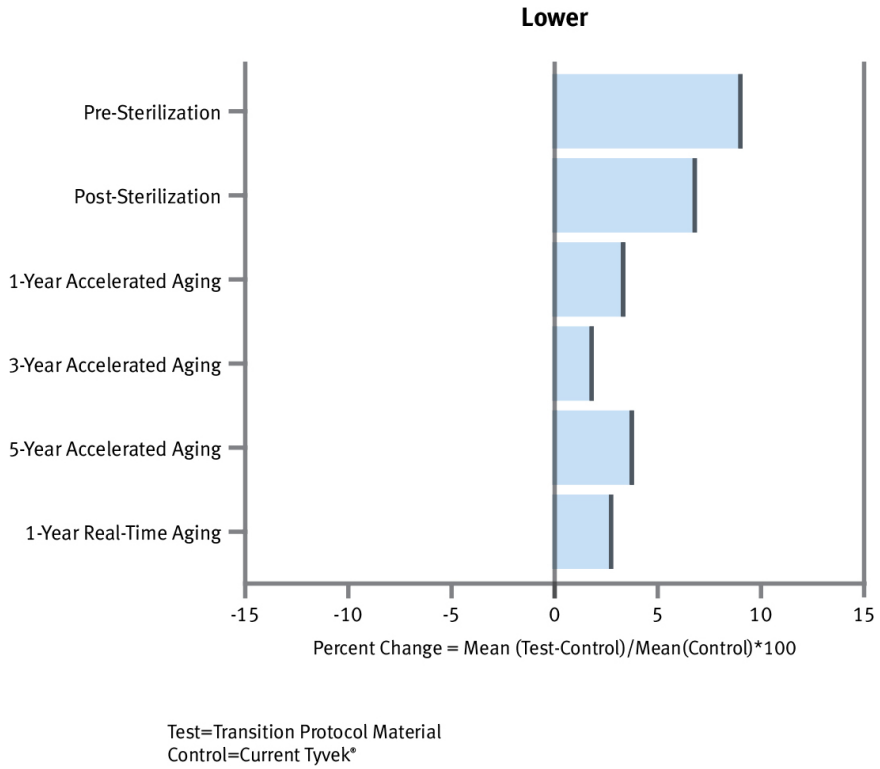
Test=Transition Protocol Material
Control=Current Tyvek®

Figure 3b. Avg. Percent Change in Mean Seal Strength (Test-Control) for Average Load Cells; Nominal Sealing Condition



Test=Transition Protocol Material
Control=Current Tyvek®

Figure 3c. Avg. Percent Change in Mean Seal Strength (Test-Control) for Average Load Cells; Lower Sealing Condition



Packages from three cells in the study contained non-peelable seals due to their constructions as vent, Kwikbreathe™ True Header, or weld seal bags. Because non-peelable seals were outside the scope of the study, these packages were not included in the Percent Change calculations. Moreover, in creating the Maximum and Average Load Figures, five cells were double packages and both the inner and outer seal strength data were included. Eighty peelable seal strength assessments were reported in the majority of reports: N=58 (Maximum Load) + N=22 (Average Load) totals N=80, determined from 78 cells – 3 cells (design) + 5 cells (double). For two time points however (3-Year and 5-Year Accelerated Aging, Average Load) for one Average Load cell, only 79 seal strength assessments were reported because the majority of the package seal strength failures for this cell in both the Transition Protocol and Control materials were due to a failure mode other than peeling of the seal. For these two time points, N=21 Average Load assessments.

A high-level cumulative summary of the seal strength results for each package configuration, material and sterilization combination is shown in Table 3. **Overall, there were 796 out of 798 instances of Functional Equivalence.**

Table 3. Cumulative Summary of Seal Strength Functional Equivalence Results*

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	Pre-Sterilization	11	0	13	0	24	0
		EO	35	0	35	0	55	0
		Gamma	15	0	15	0	38**	0
		Electron-beam			15	0		
		Steam					15	0
		Dry Heat					5	0
		Low Temp. H_2O_2	5	0				
		Low Temp. $C_2H_4O_3$					5	0
	Uncoated	Pre-Sterilization	14	0				
		EO	34	1***				
		Gamma	15	0				
		Electron-beam	15	0				
		Steam	5	0				
1059B	Coated	Pre-Sterilization			5	0		
		EO			15	0		
		Gamma			5	0		
		Electron-beam			5	0		
	Uncoated	Pre-Sterilization	5	0	2	1****		
		EO	25	0	15	0		

THERE ARE NO CELLS IN THE MPTP FOR THIS CATEGORY

* At all time points, vent bag, Kwikbreathe™ True Header bag and weld seal bag seal strengths are not included; the failure modes were non-peelable seals. (3 cells)

** For one Cell at two time points, Transition Protocol material and Current material exhibited a majority of seal failures which were not peel failures; thus the seal strength results were not included in the final analysis.

*** For one Cell at one time point, the package configuration exceeded the upper end of the equivalence limit by 0.06 lb/in., implying that the Transition Protocol material seal strength was stronger than the Current material.

**** For one Cell, the package configuration exceeded the upper end of the equivalence limit by 0.05 lb/in. at the upper sealing condition, implying that the Transition Protocol material seal strength was stronger than the Current material.

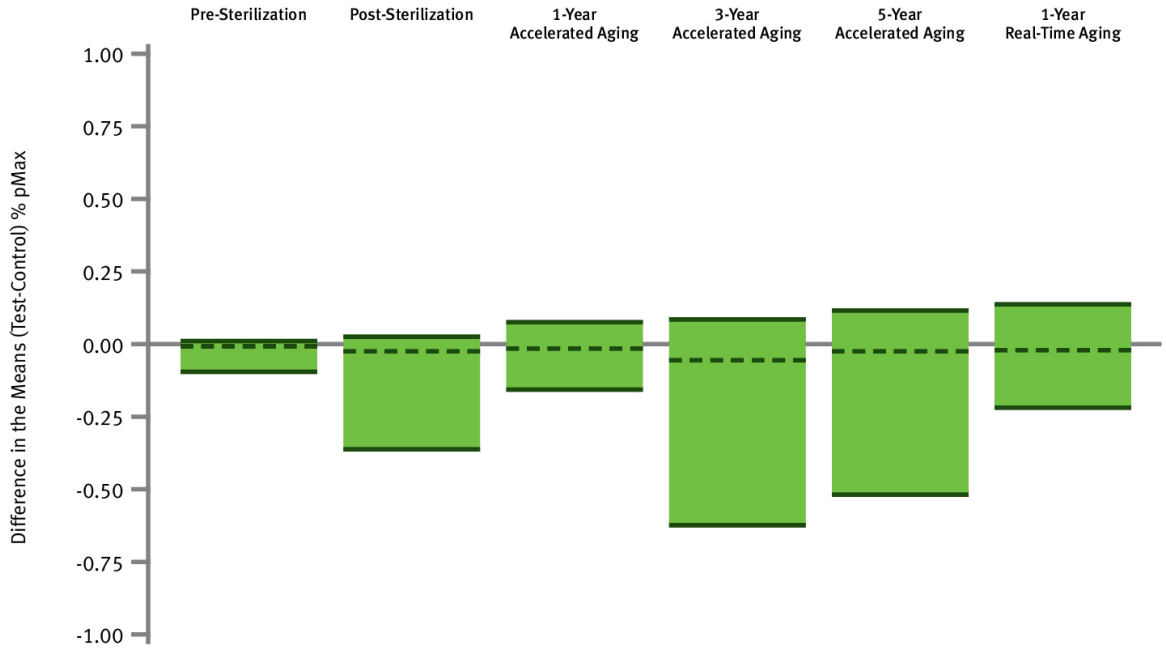
Microbial Barrier (ASTM F2638)

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 sorted according to Tyvek® style (1073B or 1059B) and coating status (coated or uncoated). The **endpoints** of each of the bars shown in Figures 4a, 4b, 4c and 4d 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 each bar represents the Mean of the Difference in the Means for each group. **Dashed lines** which fall below **0.00** (i.e. negative values) indicate the Transition Protocol material had a lower/smaller Mean than Control material (and thus better barrier)**. Overall, there were 468 out of 468 instances of Non-Inferiority, indicating Microbial Barrier Functional Equivalence.**

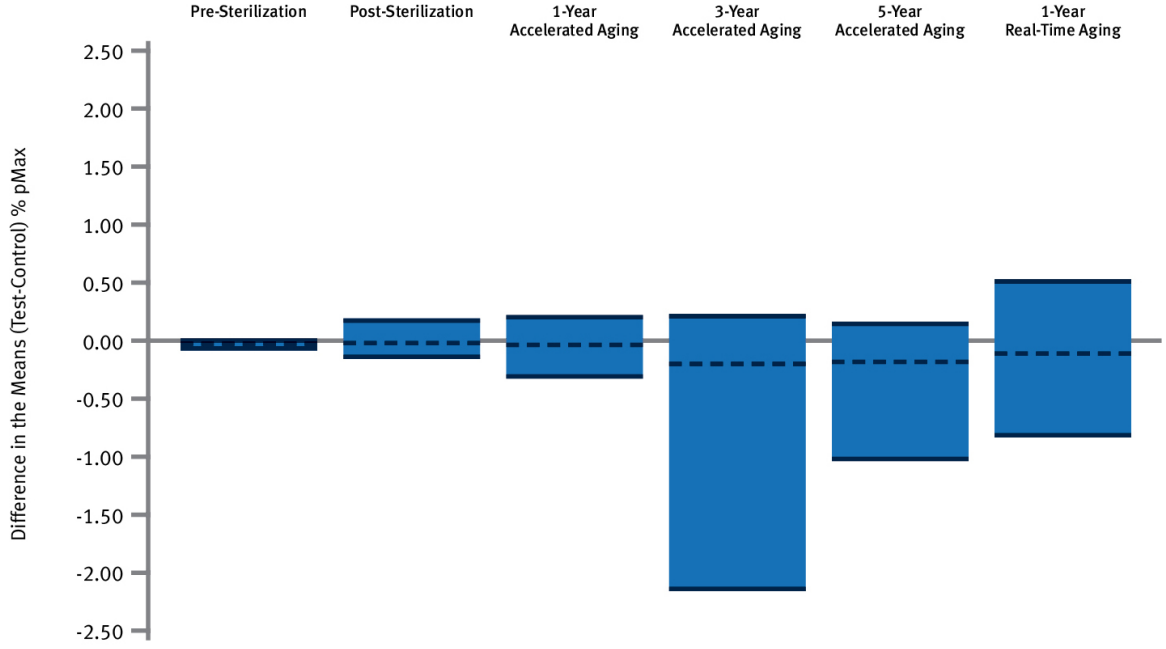
It should be noted that the vertical scales in Figures 4a-4d are fairly small numbers and represent minimal differences in the Means. Moreover, due to the outstanding microbial barrier performance of Tyvek®, individual % pMax values used in calculating differences were small as well.

Figure 4a. Range of Differences in % pMax Mean (Test-Control) for Coated 1073B Cells



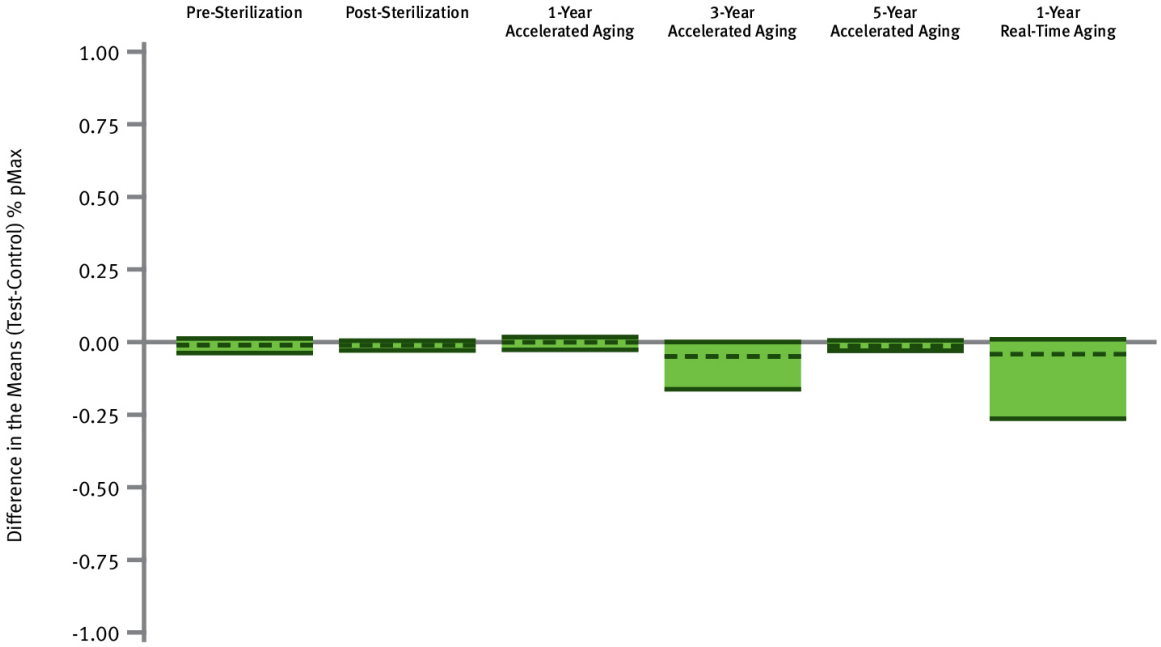
Dashed line (– – –)=Mean of the difference in the means
Test=Transition Protocol Material
Control=Current Tyvek®

Figure 4b. Range of Differences in % pMax Mean (Test-Control) for Uncoated 1073B Cells



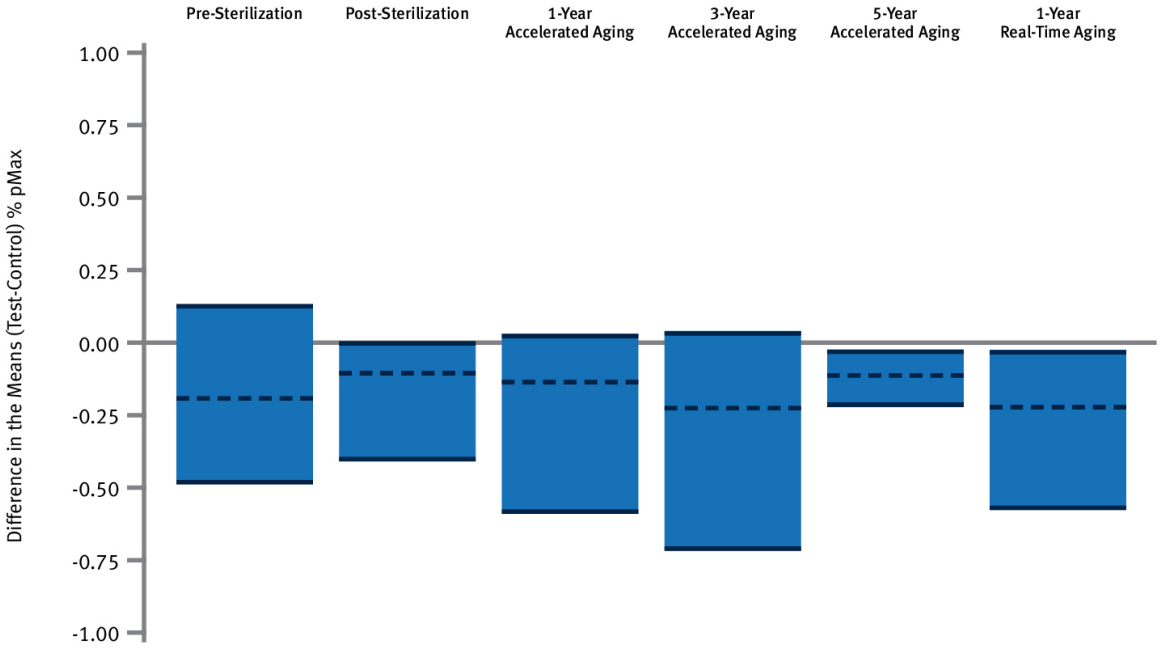
Dashed line (– – –)=Mean of the difference in the means
Test=Transition Protocol Material
Control=Current Tyvek®

Figure 4c. Range of Differences in % pMax Mean (Test-Control) for Coated 1059B Cells



Dashed line (– – –)=Mean of the difference in the means
Test=Transition Protocol Material
Control=Current Tyvek®

Figure 4d. Range of Differences in % pMax Mean (Test-Control) for Uncoated 1059B Cells



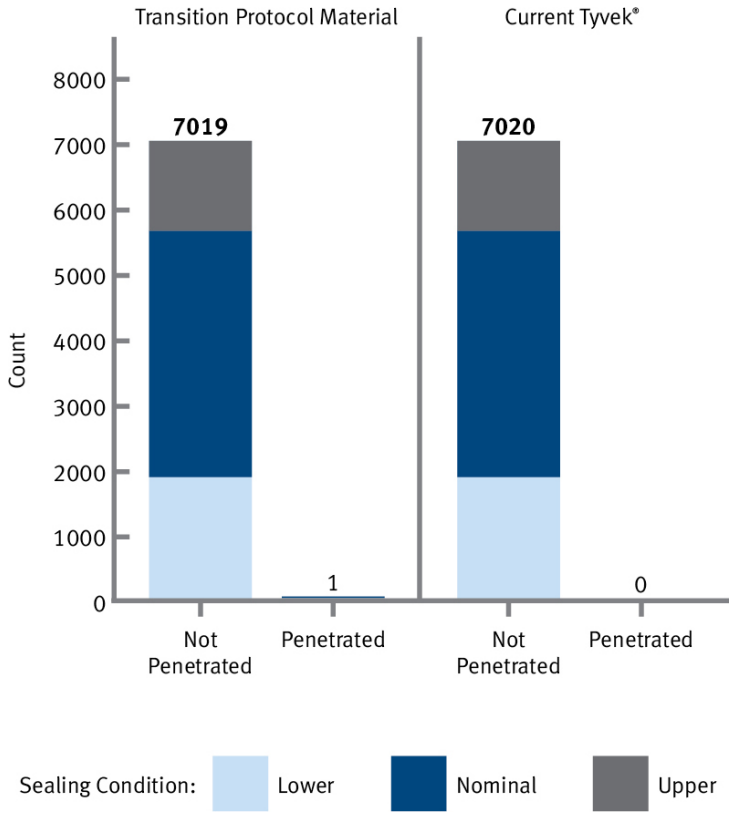
Dashed line (– – –)=Mean of the difference in the means
Test=Transition Protocol Material
Control=Current Tyvek®

Package Integrity Testing (ASTM F1929)

ASTM F1929 was applied to assess package integrity via a dye penetration test. Nine Transition Protocol material packages and nine Current Tyvek® packages were tested for each cell. All dye penetrations are subjected to root cause investigations and classified as either a material related defect or a non-material related defect as per the study procedure. Only dye penetration due to a Tyvek® material related defect is considered consequential.

To-date, a total of 14,040 packages were tested for dye penetration: 7,020 made with Current Tyvek® and 7,020 made with Transition Protocol material. There were no material related dye penetrations in Current Tyvek® packages and only one in Test packages, which is well within the established pass/fail criteria of the study. Figure 5 shows a summary of the data. **Package Integrity indicates Functional Equivalence because it passes the criteria set forth in the study design.**

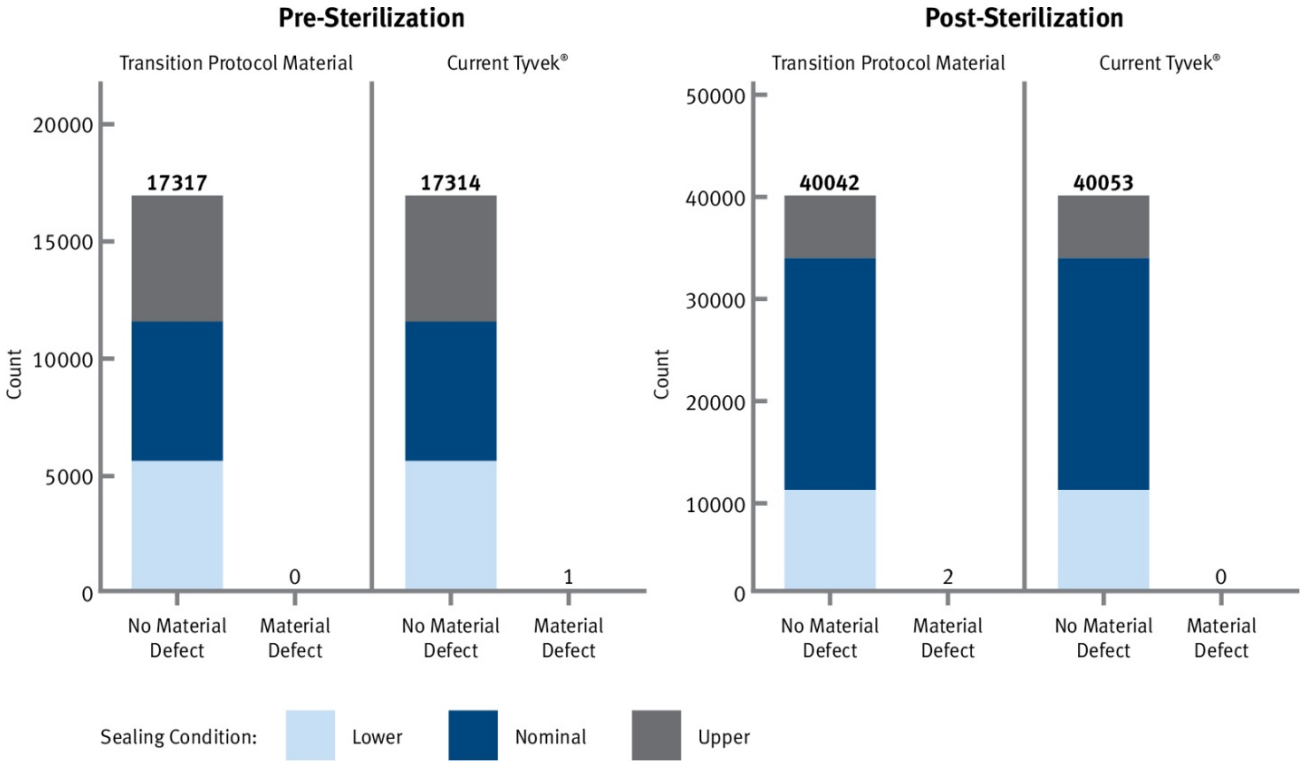
Figure 5. Package Integrity Testing Summary



Visual Inspection (ASTM F1886M)

All packages in the Pre-sterilization and Post-sterilization time points were visually inspected as per ASTM F1886M. A material related defect is defined in the Protocol as an anomaly in Tyvek® extending 50% or more across the width of the seal; the 50% criteria was established for the purposes of an operational definition. Note however that the presence of a defect such as this does not necessarily affect package integrity. Figure 6 depicts 114,726 instances of no material defects, and only one material related defect in Current Tyvek® and two material related defects in Transition Protocol material. This is well within the established pass/fail criteria of the study. The defects were veins or raised areas in the material that extended more than 50% across the width of the seal, defects that did not appear to affect the integrity of the package (per the Package Integrity results). **Visual Inspection indicates Functional Equivalence because it passes the criteria set forth in the study design.**

Figure 6. Visual Inspection Summary



EXCEPTIONS

For the six time points to-date, there were six exceptions, none of which preclude **Functional Equivalence**:

- **Three Visual Inspections**
- **Two Seal Strengths**
- **One Package Integrity**

A brief description and analysis of each exception follows.

Visual Inspections

A material related defect is defined in the Protocol as an anomaly in Tyvek® extending 50% or more across the width of the seal; the 50% criteria was established for the purposes of an operational definition. Note however that the presence of a defect such as this does not necessarily affect package integrity.

There was one Pre-sterilization material related defect in Current Tyvek® and two Post-sterilization material related defects in Transition Protocol material. The defects were veins or raised areas in the material that extended more than 50% across the width of the seal, defects that did not appear to affect the integrity of the package (per the Package Integrity results). These defect counts were well within the established pass/fail criteria of the study; hence **Functional Equivalence** was concluded by DuPont for Visual Inspections.

Seal Strengths

One uncoated 1059B FFS package failed the seal strength **Functional Equivalence** criteria by 0.05 lb/in. on the upper side of the criteria for the Upper sealing condition in the Pre-sterilization phase of the study. This implies the Transition Protocol material produced higher seal strength than the Control. The nature of this non-equivalence should not compromise one of the overarching goals of the study — package integrity; rather it should improve it.

This package, a Sterile Fluid Path product, was formed on equipment comprised of multiple cavities. A Root Cause Failure Analysis ("**RCFA**") identified potential causes related to unequal sampling among the cavities and/or execution errors in package labeling/testing; however, these causes could not be eliminated or assigned. Note that this anomaly was not observed at any other time point for this Cell. Also note a retest was performed using sample retains on both the Pre-sterilization and Post-sterilization packages with as much equal representation from cavities as possible. Twice the number of data points were tested on the Upper sealing condition to gain a better understanding of package sealing behavior. The anomaly was not replicated in the retest; the Test and Control material were found to be equivalent indicating **Functional Equivalence**.

One Phantom Protocol cell, an uncoated 1073B pouch package, failed the seal strength **Functional Equivalence** criteria by 0.06 lb/in. on the upper side of the criteria in the 3-Year Accelerated Aging phase of the study. This implies the Transition Protocol material produced higher seal strength than the Control material. As stated above, the nature of this non-equivalence should not compromise one of the overarching goals of the study — package integrity; rather it should improve it.

An **RCFA i**dentified a phenomenon denoted as “Tail Flipping”, which increased the variability of the Maximum Load measurement designated for the cell, as the root cause of the non-equivalence. A thorough analysis of contributing factors showed that sterilization type, Tyvek® style and coatings could be discounted as sources of variability causing “Tail Flipping”. The investigation concluded less stiff, lighter gauge film systems, and to a lesser extent Tyvek® fiber orientation with respect to the seal, were the key influences in conjunction with seal strength testing Technique “C” and Maximum Load measurements.

Higher Test material seal strength and the **RCFA** results leads to the logical juxtaposition of statistical and physical evidence and leads DuPont to conclude seal strength **Functional Equivalence**.

Package Integrity

Dye penetrated one Test package in the 5-Year Accelerated Aging phase of the study. All dye penetrations are subjected to **RCFA** investigations and classified as either a material related defect or a non-material related defect as per the study procedure. Unfortunately, the dye penetration sample was inadvertently discarded prior to the completion of an **RCFA**. Since DuPont was not able to confirm the origin of dye penetration, a conservative approach was adopted and it was classified as a material related defect.

Note that this defect count is well within the established pass/fail criteria of the study; hence **Functional Equivalence** was concluded by DuPont for Package Integrity. Also note that procedural changes were instituted at the third-party lab to mitigate the risk of lost packages requiring an **RCFA** in the future.

CONCLUSIONS

In summary, MPTP testing to-date contains a very small number of exceptions relative to the volume of testing for seal strength, package integrity and visual inspection. The nature and magnitude of the exceptions do not negatively influence overall conclusions regarding **Functional Equivalence**.

MPTP data to-date represents more than 50,000 seal strength tests and 2,500+ microbial barrier tests. In summary, the data indicates:

- 796 out of 798 instances of seal strength **Functional Equivalence**
- 468 out of 468 instances of microbial barrier **Non-Inferiority**
- 14,039 out of 14,040 instances of **No Dye Penetration**
- 114,726 out of 114,729 instances of **No Material Defects**

These results, in conjunction with EO residual documentation provided by MDMs showing MDM requirements were met, overwhelmingly supports declaring **Functional Equivalence** between Current Tyvek® and Transition Protocol material for styles 1073B and 1059B.