



DuPont™
Tyvek®
Medical
Packaging
Transition
Project

3-Year Accelerated
Aging
Industry Summary
Report

June 2015

A handwritten signature in black ink, reading "Bruce Allen Yost".

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EXECUTIVE SUMMARY

3-Year Accelerated Aging 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): 78 out of 79 instances of **Functional Equivalence**
- Microbial Barrier (ASTM F2638): 78 out of 78 instances of **Non-Inferiority**
- Package Integrity (ASTM F1929): 1,404 out of 1,404 instances of **No Dye Penetration**

Additional details are provided in the Tables and Figures that follow, including those in Appendix A, where results are presented by category.

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 ₂ O ₂	Coated	1073B	X76					
Low Temp. C ₂ H ₄ O ₃	Coated	1073B				X64		
Gamma	Coated	1059B			X72			
Electron-beam	Coated	1059B			X73			

- 3-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 3-Year Accelerated Aging data for all 78 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. After submission of the 1-Year Real-time Aging Report to the U.S. FDA, a letter affirming Functional Equivalence is expected (~3Q2015).

TESTING and RESULTS OVERVIEW

Data were analyzed for the three different attributes detailed in the approved study design for 3-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.

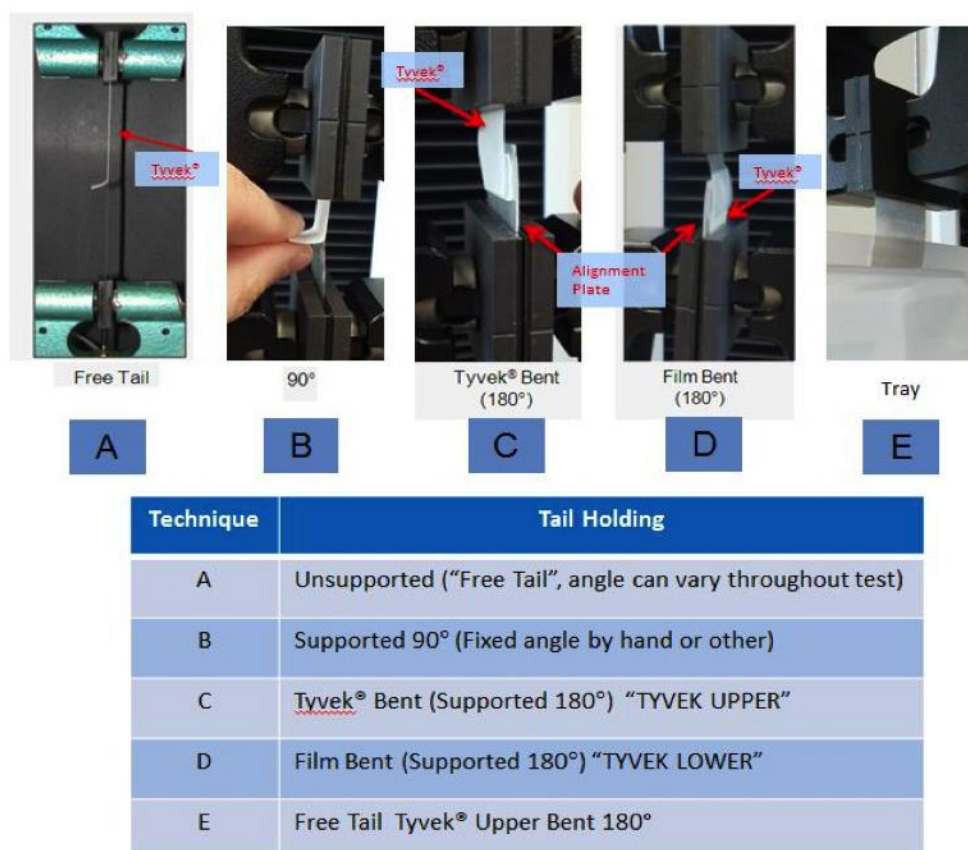
It should be noted that for the Pre-sterilization and Post-sterilization time points, three sealing conditions across the sealing window were tested for both the Test Material (also called Test or Transition Protocol material) and the Control Material (also called Control or Current Tyvek®). These three 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



At the chosen sealing condition, 48 samples were tested for both Test Material and the 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 3-Year Accelerated Aging are similar to the results for Pre-sterilization, Post-sterilization, and 1-Year Accelerated Aging cells (~4-6%), while Average Percent Changes for Average Load cells for 3-Year Accelerated Aging are ~2-7%, which are in-line with 1-Year Accelerated Aging results (~3-7%) and approximately two percent less than Pre- and Post-sterilization results (~5-9%).

As noted in the **Pre-Sterilization and Post-Sterilization Industry Summary Report**, 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 have been reported in previous time points: N=58 + N=22 totals N=80, determined from 78 cells – 3 cells (design) + 5 cells (double). For 3-Year Accelerated Aging, only 79 seal strength assessments are being reported because for one cell, the majority of the seal failures in both the Transition Protocol and Control materials were due to a failure mode other than peeling of the seal.

Figure 2. Avg. Percent Change in Mean Seal Strength (Test-Control) for Maximum Load Cells; N=58

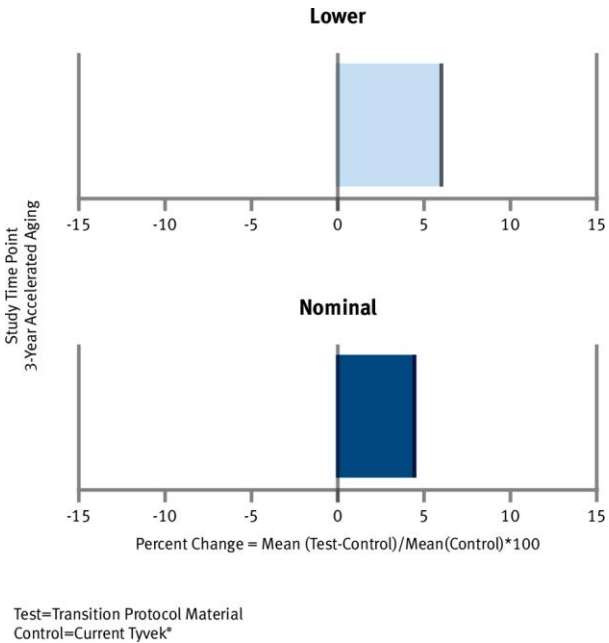
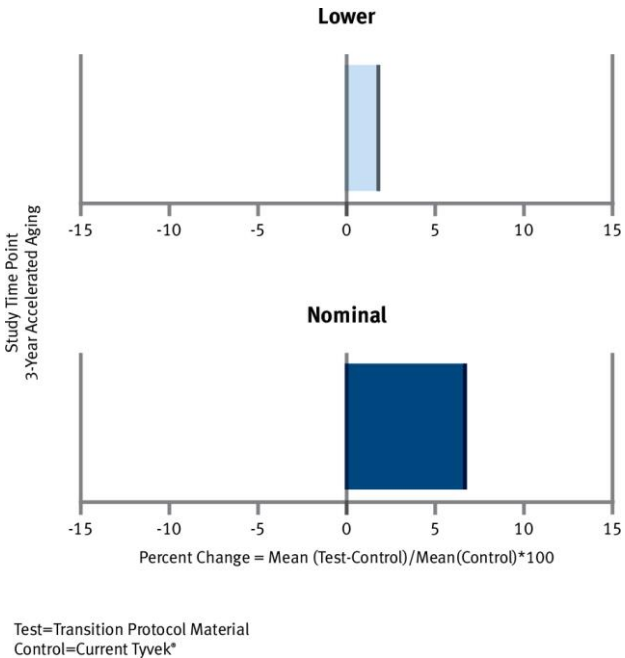


Figure 3. Avg. Percent Change in Mean Seal Strength (Test-Control) for Average Load Cells; N=21



A high level summary of the results tested for each package configuration, material, and sterilization combination is shown in Table 3. There are 78 instances of Functional Equivalence for 3-Year Accelerated Aging. All cells with peelable seals met the Functional Equivalence criteria with the exception of one Phantom Protocol cell – an uncoated 1073B pouch. This cell failed the Functional Equivalence criteria by 0.06 lb/in. on the upper end of the equivalence limit, indicating the Transition Protocol material produced higher seal strength than the Control material.

Table 3. Summary of Seal Strength Functional Equivalence Results*

Industry Summary: MPTP Test Results after 3-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	7	0	7	0	11	0
		Gamma	3	0	3	0	7**	0
		Electron-beam			3	0		
		Steam					3	0
		Dry Heat					1	0
		Low Temp. H ₂ O ₂	1	0				
		Low Temp. C ₂ H ₄ O ₃					1	0
	Uncoated	EO	6	1***				
		Gamma	3	0				
		Electron-beam	3	0				
		Steam	1	0				
1059B	Coated	EO			3	0		
		Gamma			1	0		
		Electron-beam			1	0		
	Uncoated	EO	5	0	3	0		

THERE ARE NO CELLS IN THE MPTP FOR THIS CATEGORY

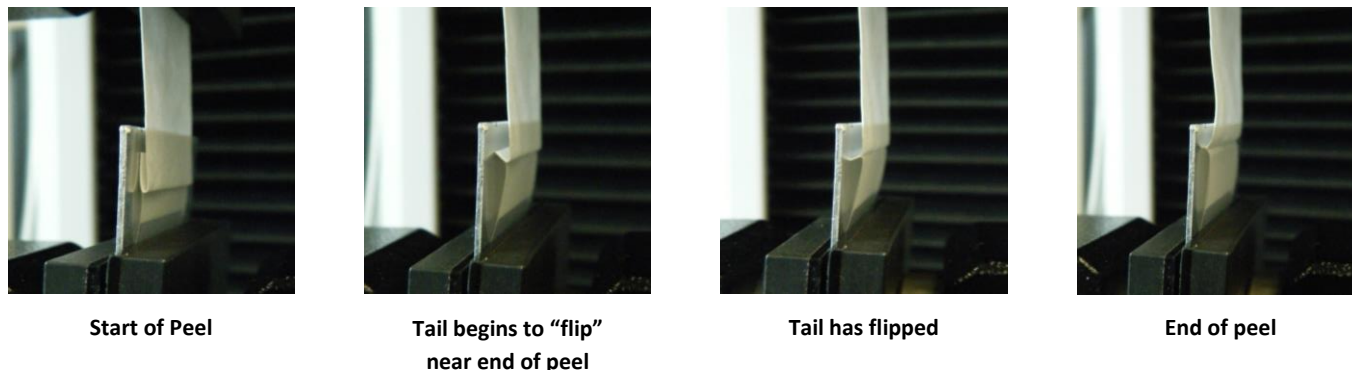
*Vent bag, Kwikbreathe™ True Header bag and weld seal bag seal strengths are not included; the failure modes were non-peelable seals. (3 cells)

**Transition Protocol material and Current material exhibited a majority of seal failures that were not peel failures; thus the seal strength results were not included in the final analysis. (1 cell)

***One 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. (1 cell)

A Root Cause Failure Analysis (“RCFA”) identified 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. “Tail Flipping” is pictured in Figure 4 and has only been observed for seal strength testing Technique “C”. Sources of variability **discounted** as causes of “Tail Flipping” include sterilization type, Tyvek® style and coatings. The investigation concluded that less stiff, lighter gauge film systems, and to a lesser extent package fiber orientation, were the key influences in conjunction with Technique “C” and Maximum Load measurements. However, the higher Test material seal strength should not compromise package integrity; rather it should improve it. Thus, the logical juxtaposition of statistical and physical evidence leads DuPont to conclude seal strength Functional Equivalence.

Figure 4. “Tail Flipping” Phenomenon



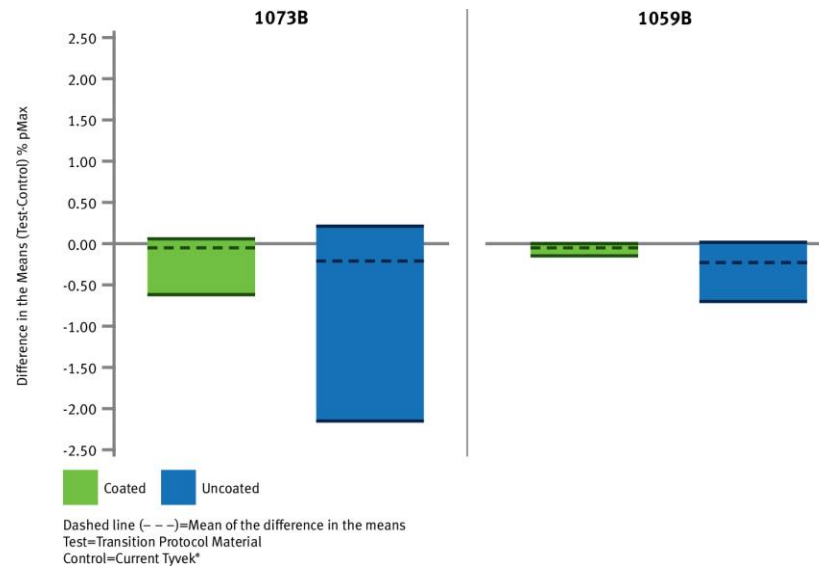
Microbial Barrier (ASTM F2638)

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 (1059B or 1073B) and coating status (coated or uncoated). The **endpoints** of each of the bars shown in Figure 5 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). **All 78 cells pass the Microbial Barrier Non-Inferiority Criteria for 3-Year Accelerated Aging, representing 78 instances.**

It should be noted that the vertical scale in Figure 5, as well as vertical scales on microbial barrier graphs in the Appendix, are very 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.

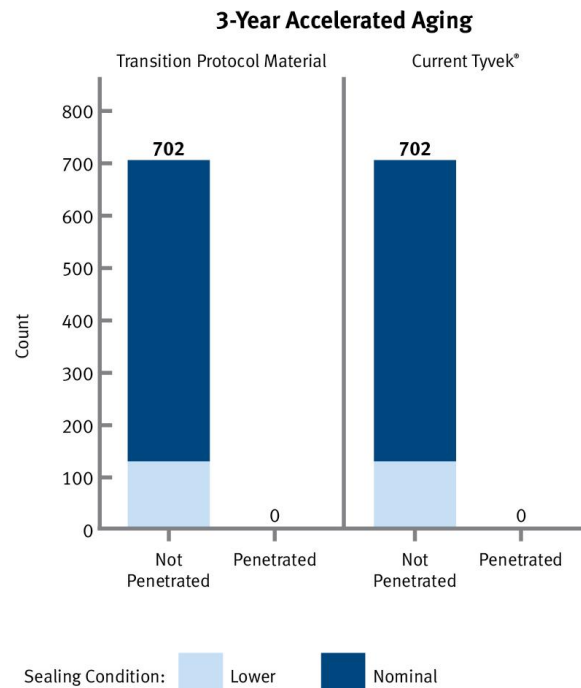
**Figure 5. Range of Differences in % pMax Mean (Test-Control)
for All Cells by Tyvek® Style, Time Point, and Coating Status**



Package Integrity Testing (ASTM F1929)

ASTM F1929 was applied to assess package integrity via a dye penetration test. In the 3-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 6 shows a summary of the data. No package failed the dye penetration test due to a material defect in Tyvek®; there are 702 instances of no dye penetration in Transition Protocol material and 702 instances of no dye penetration in Current Tyvek® for a total of 1,404 instances of no dye penetration. Due to the discrete nature of this data, the pass/fail criteria for package integrity will be assessed at the conclusion of the study.

Figure 6. Package Integrity Testing Summary



CONCLUSIONS

In summary, 3-Year Accelerated Aging testing indicates:

- 78 out of 79 instances of seal strength **Functional Equivalence**
- 78 out of 78 instances of microbial barrier **Non-Inferiority**
- 1,404 out of 1,404 instances of **No Dye Penetration**

The one 3-Year Accelerated Aging Phantom Protocol cell that did not meet the seal strength Functional Equivalence criteria exhibited higher seal strength in the Test material than Control material, which should not compromise package integrity. This was attributed to increased variability of the Maximum Load measurement due to a phenomenon denoted as “Tail Flipping”, which has only been observed with seal strength testing Technique "C". Ultimately, the juxtaposition of statistical and physical evidence for seal strength in conjunction with the microbial barrier results leads DuPont to conclude Functional Equivalence. Package integrity results will be assessed at the conclusion of the study but show no material related defects thus far.

APPENDIX A: CATEGORY RESULTS

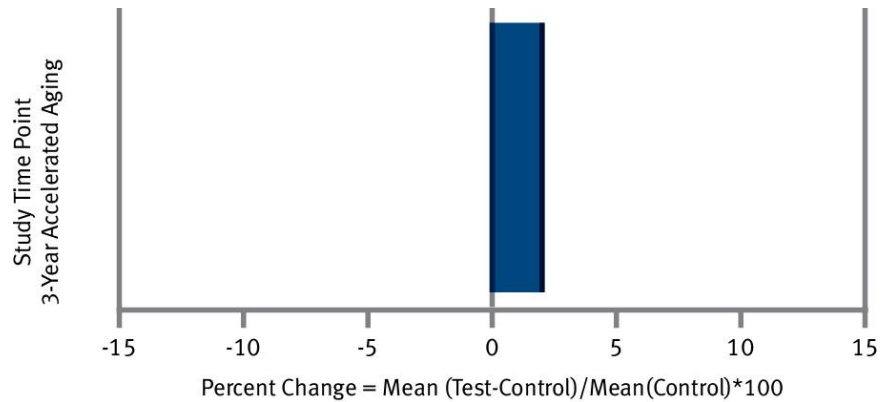
3-Year Accelerated Aging overall testing results were presented in the previous section. Appendix A presents the data in a different format, i.e. by category, where it is broken down in further detail to help facilitate industry risk assessments. As evaluations are done, be cognizant of the number of cells represented by each Figure.

A set of 3-Year Accelerated Aging Seal Strength, Microbial Barrier and Package Integrity results are shown for each of the following categories:

- **Coated 1073B Pouches/Bags**
- **Coated 1073B Form-Fill-Seal**
- **Coated 1073B Lids/Rigid Trays**
- **Uncoated 1073B Pouches/Bags**
- **Coated 1059B Form-Fill-Seal**
- **Uncoated 1059B Pouches/Bags**
- **Uncoated 1059B Form-Fill-Seal**

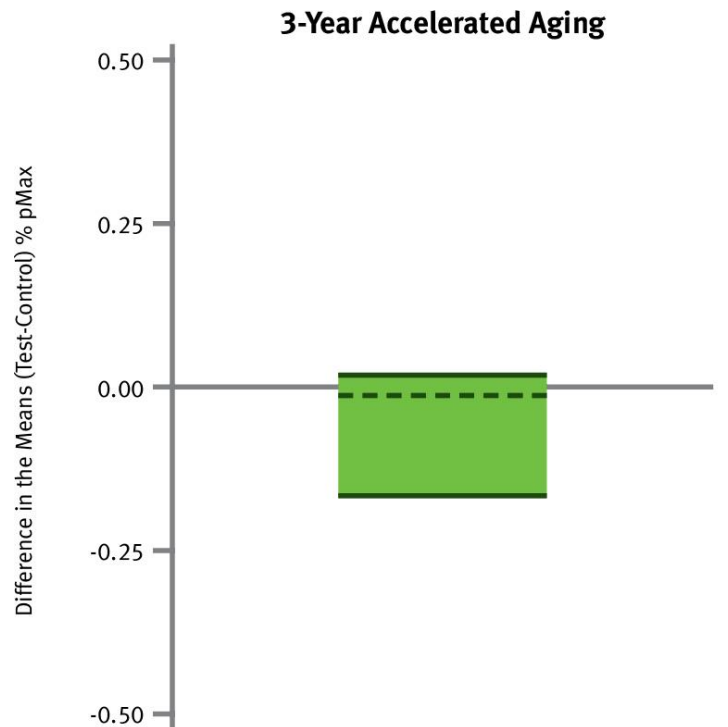
Coated 1073B Pouches/Bags

Figure A1. Avg. Percent Change in Mean Seal Strength (Test-Control) for Coated 1073B Pouches/Bags



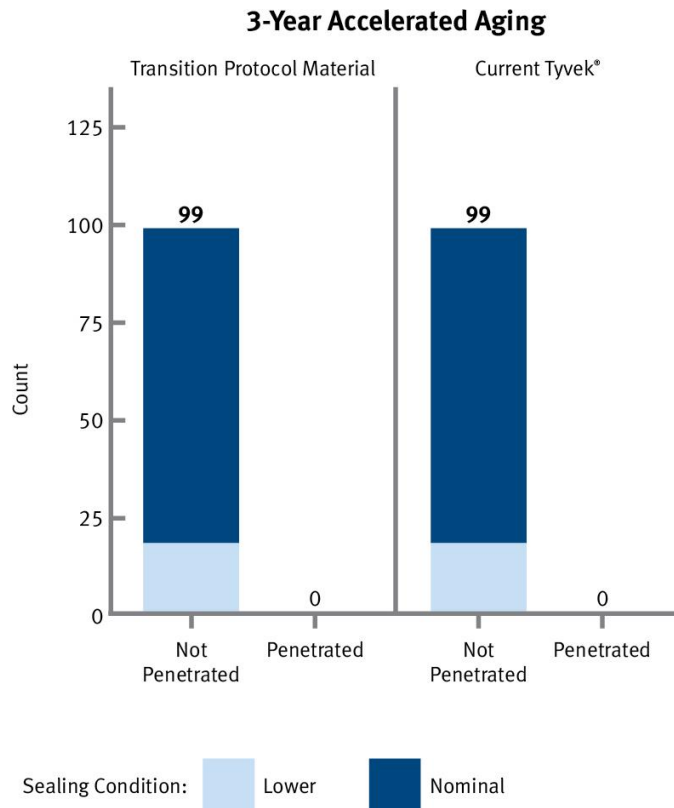
Test=Transition Protocol Material
Control=Current Tyvek®

Figure A2. Range of Differences in % pMax Mean (Test-Control) for Coated 1073B Pouches/Bags



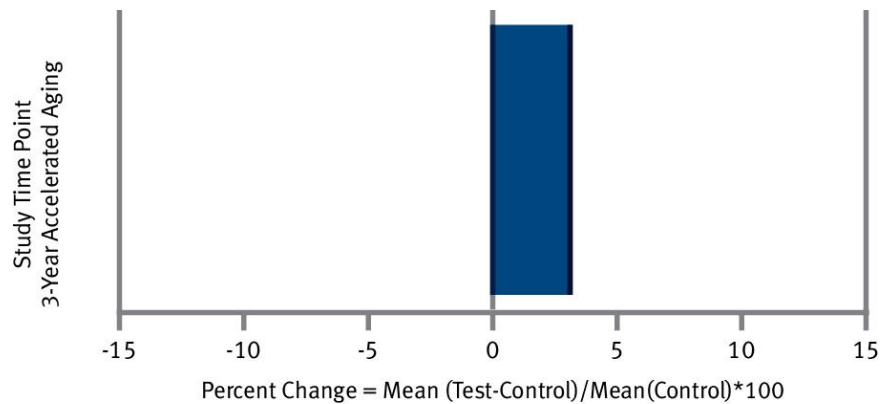
Dashed line (---)=Mean of the difference in the means
Test=Transition Protocol Material
Control=Current Tyvek®

Figure A3. Package Integrity Summary for Coated 1073B Pouches/Bags



Coated 1073B Form-Fill-Seal

Figure A4. Avg. Percent Change in Mean Seal Strength (Test-Control) for Coated 1073B Form-Fill-Seal



Test=Transition Protocol Material
Control=Current Tyvek®

Figure A5. Range of Differences in % pMax Mean (Test-Control) for Coated 1073B Form-Fill-Seal

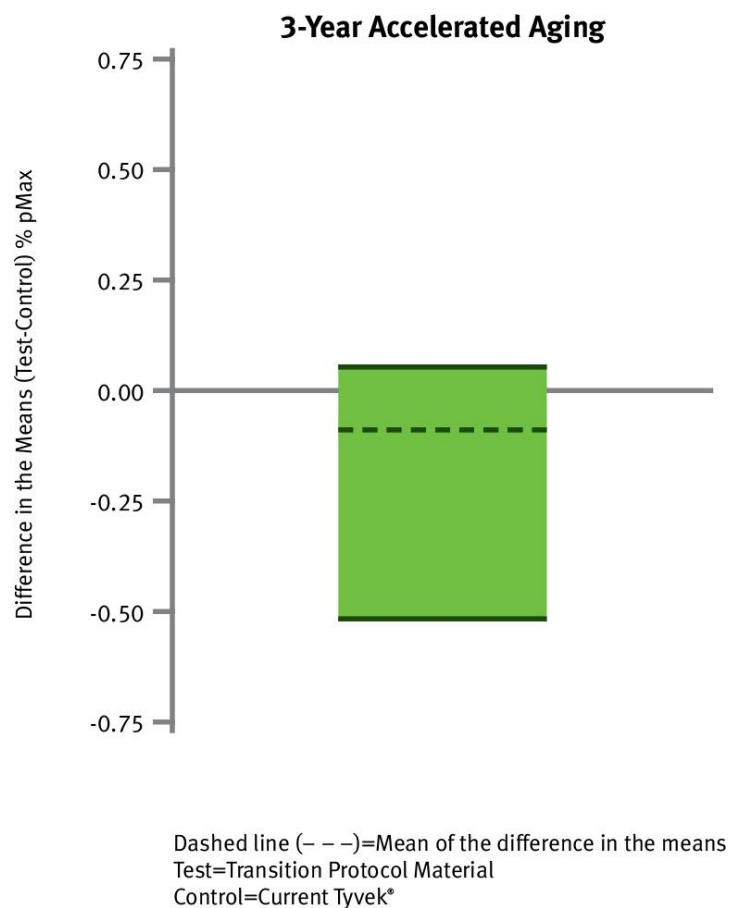
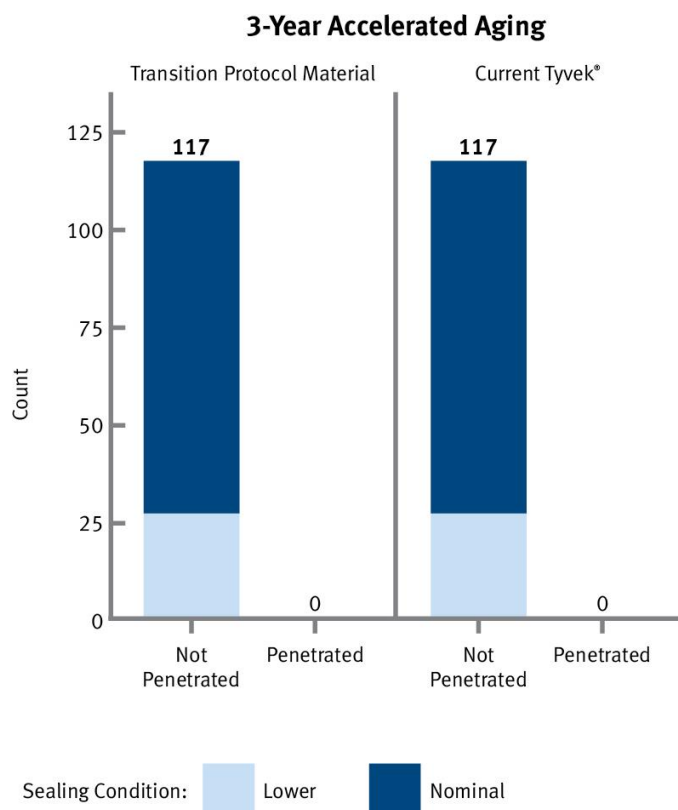
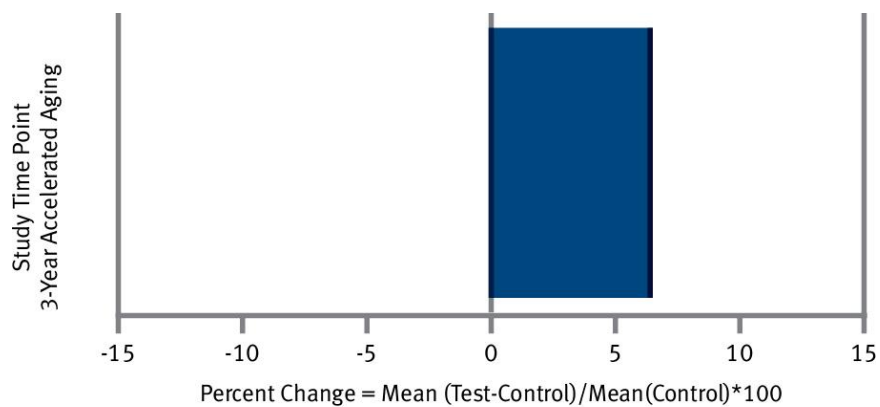


Figure A6. Package Integrity Summary for Coated 1073B Form-Fill-Seal



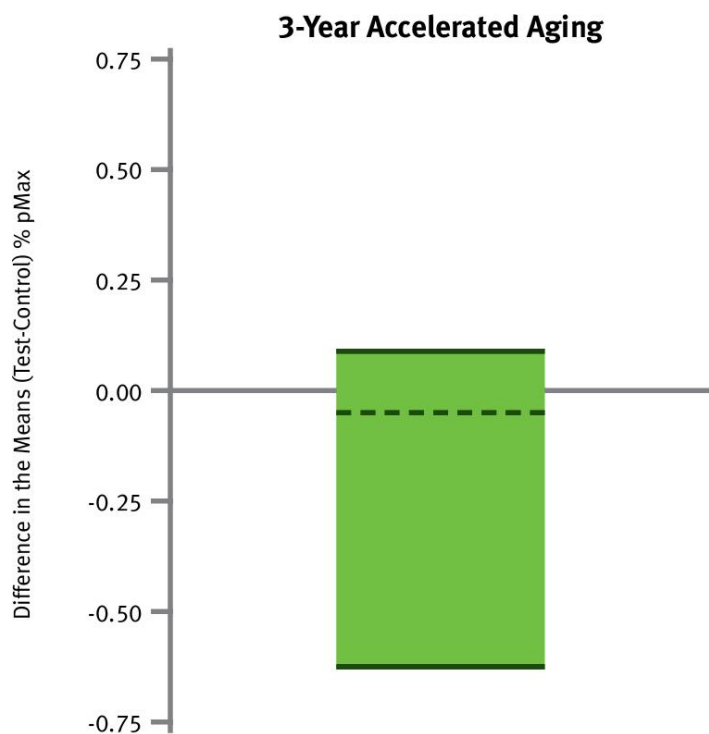
Coated 1073B Lids/Rigid Trays

Figure A7. Avg. Percent Change in Mean Seal Strength (Test-Control) for Coated 1073B Lids/Rigid Trays



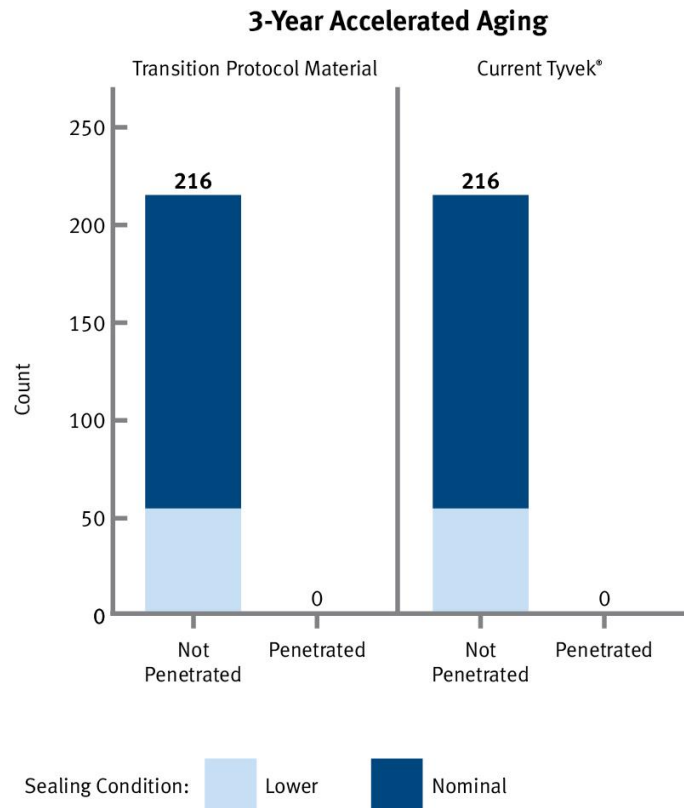
Test=Transition Protocol Material
Control=Current Tyvek®

Figure A8. Range of Differences in % pMax Mean (Test-Control) for Coated 1073B Lids/Rigid Trays



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

Figure A9. Package Integrity Summary for Coated 1073B Lids/Rigid Trays



Uncoated 1073B Pouches/Bags

Figure A10. Avg. Percent Change in Mean Seal Strength (Test-Control) for Uncoated 1073B Pouches/Bags

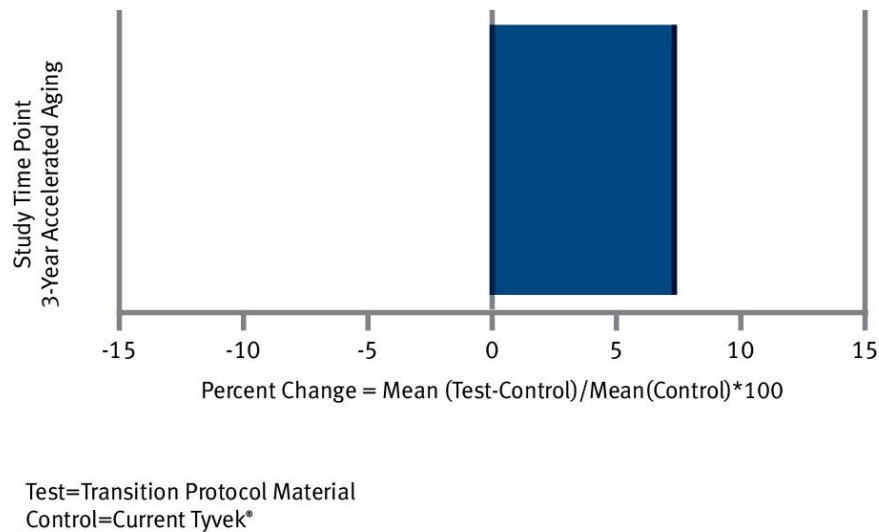


Figure A11. Range of Differences in % pMax Mean (Test-Control) for Uncoated 1073B Pouches/Bags

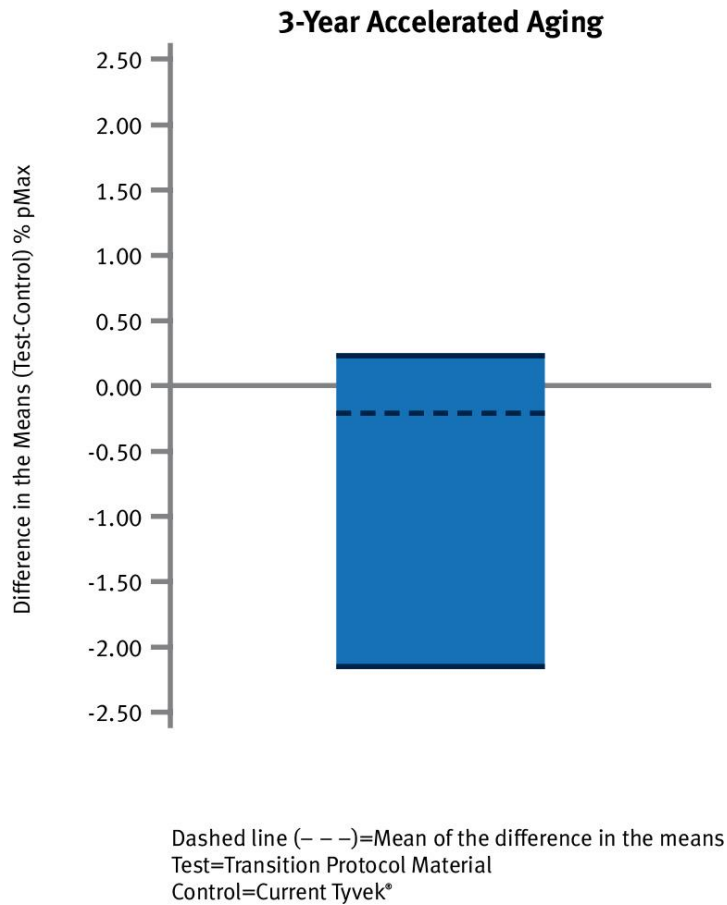
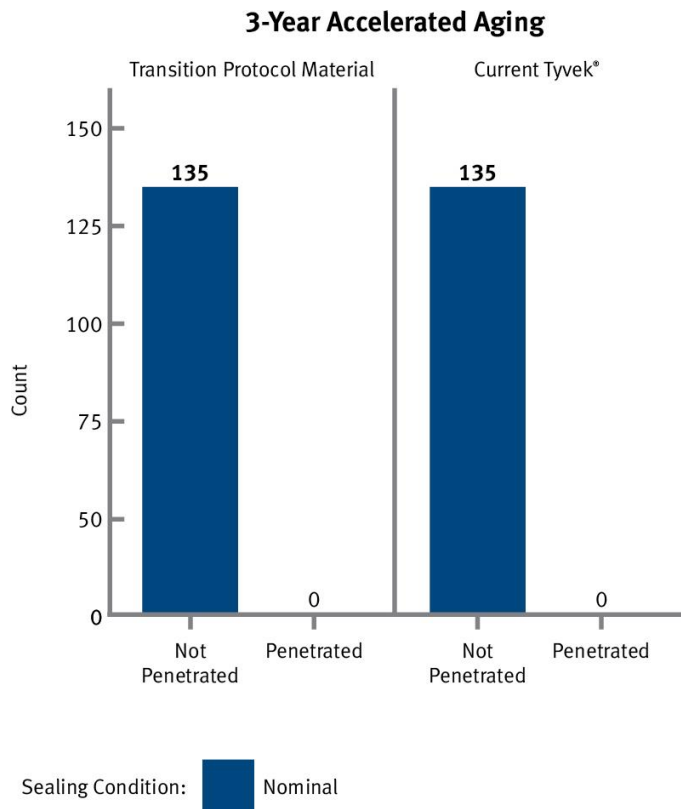
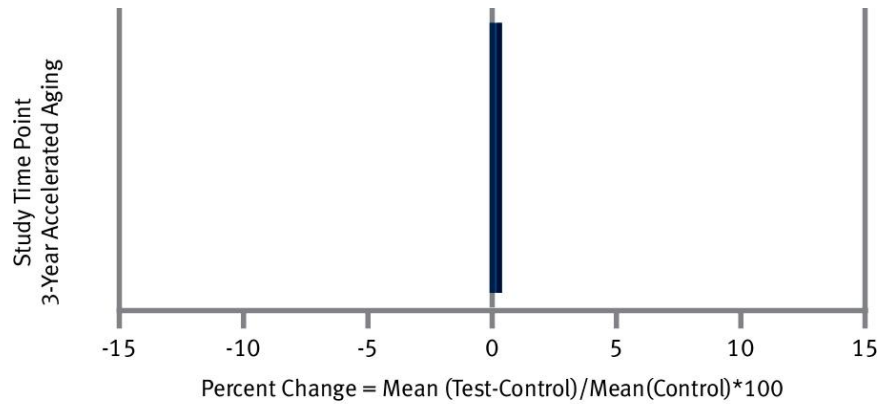


Figure A12. Package Integrity Summary for Uncoated 1073B Pouches/Bags



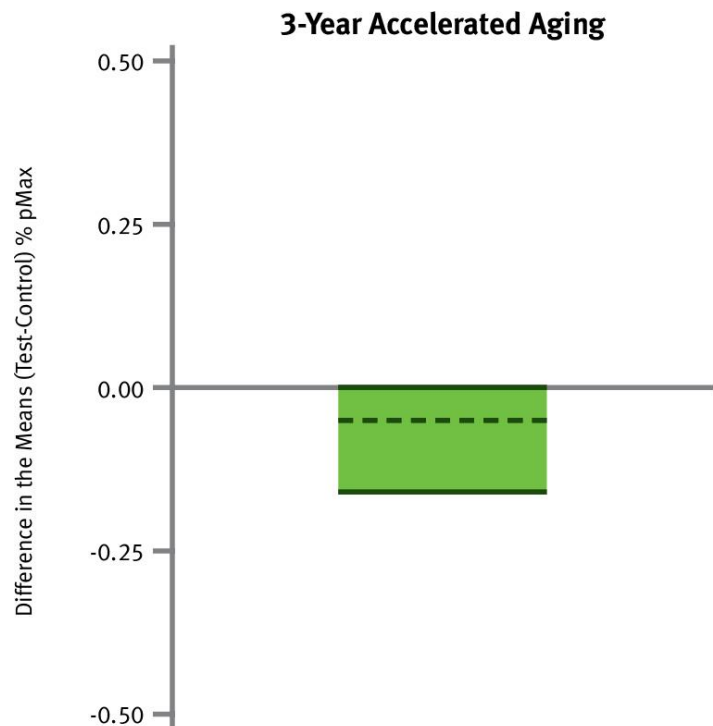
Coated 1059B Form-Fill-Seal

Figure A13. Avg. Percent Change in Mean Seal Strength (Test-Control) for Coated 1059B Form-Fill-Seal



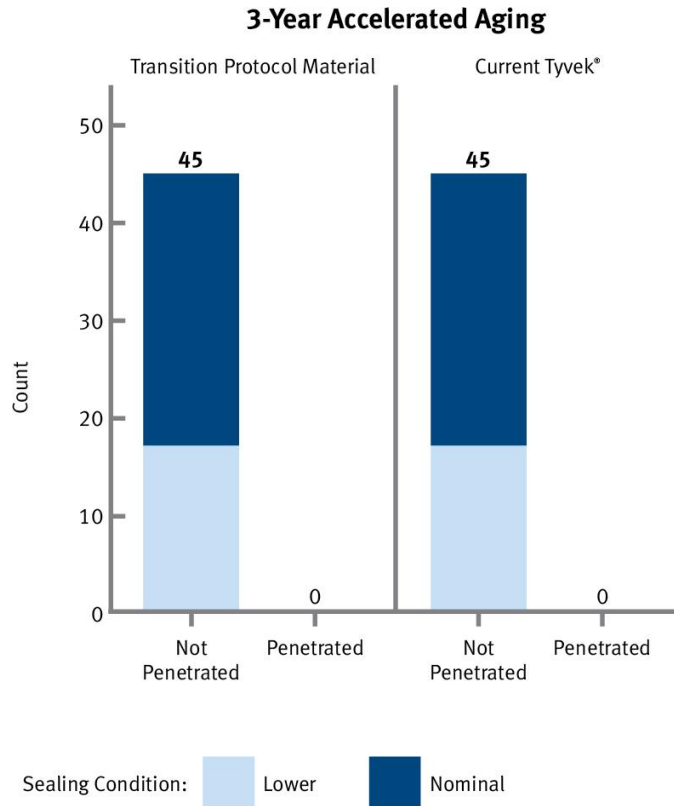
Test=Transition Protocol Material
Control=Current Tyvek®

Figure A14. Range of Differences in % pMax Mean (Test-Control) for Coated 1059B Form-Fill-Seal



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

Figure A15. Package Integrity Summary for Coated 1059B Form-Fill-Seal



Uncoated 1059B Pouches/Bags

Figure A16. Avg. Percent Change in Mean Seal Strength (Test-Control) for Uncoated 1059B Pouches/Bags

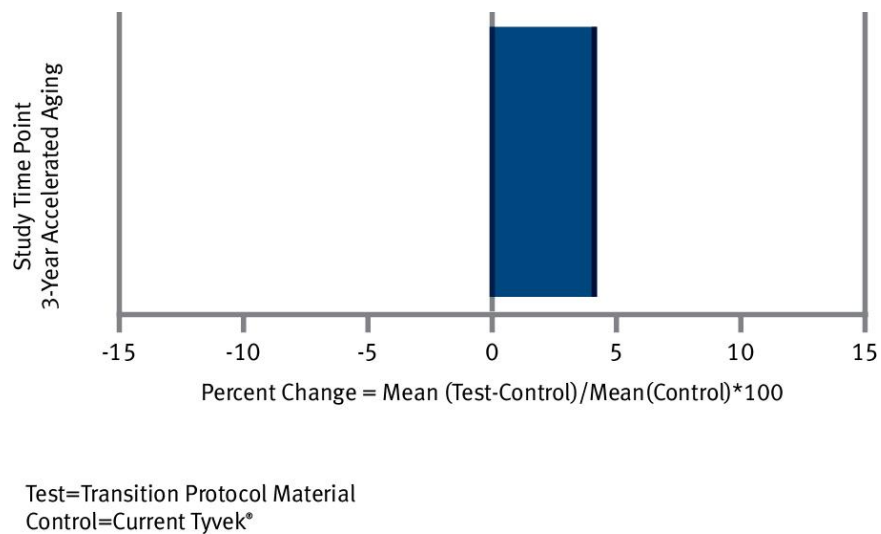


Figure A17. Range of Differences in % pMax Mean (Test-Control) for Uncoated 1059B Pouches/Bags

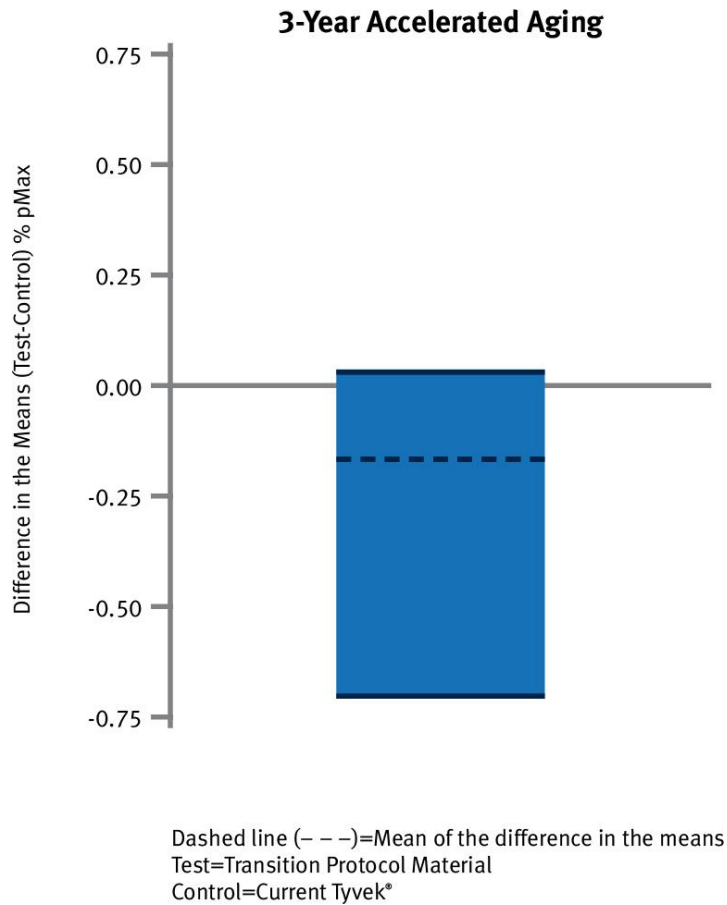
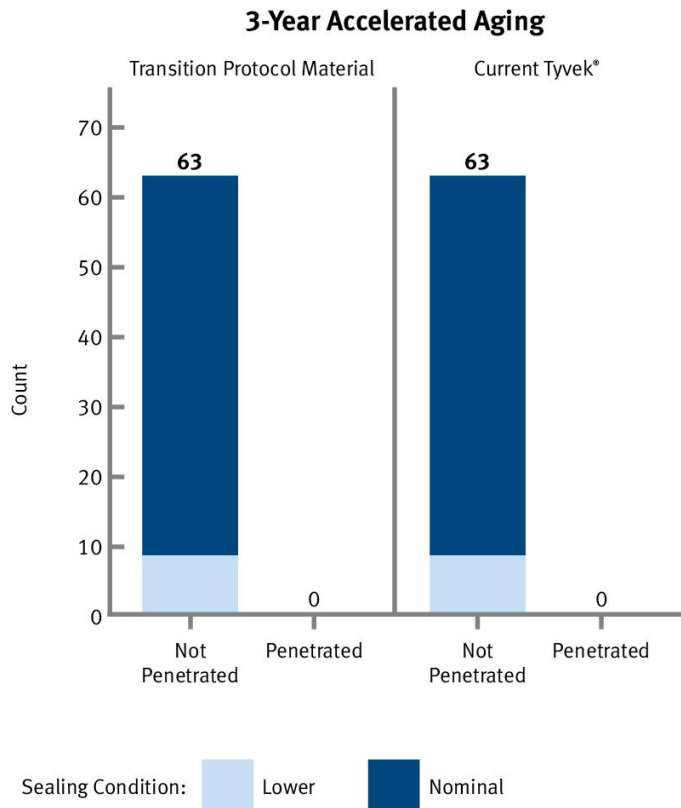
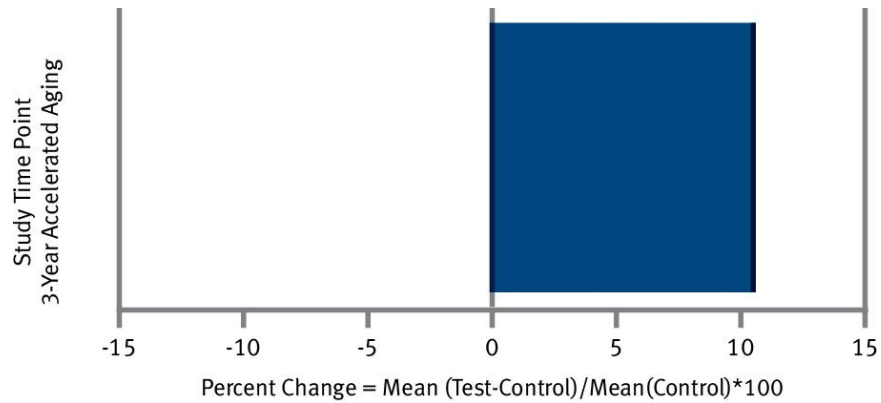


Figure A18. Package Integrity Summary for Uncoated 1059B Pouches/Bags



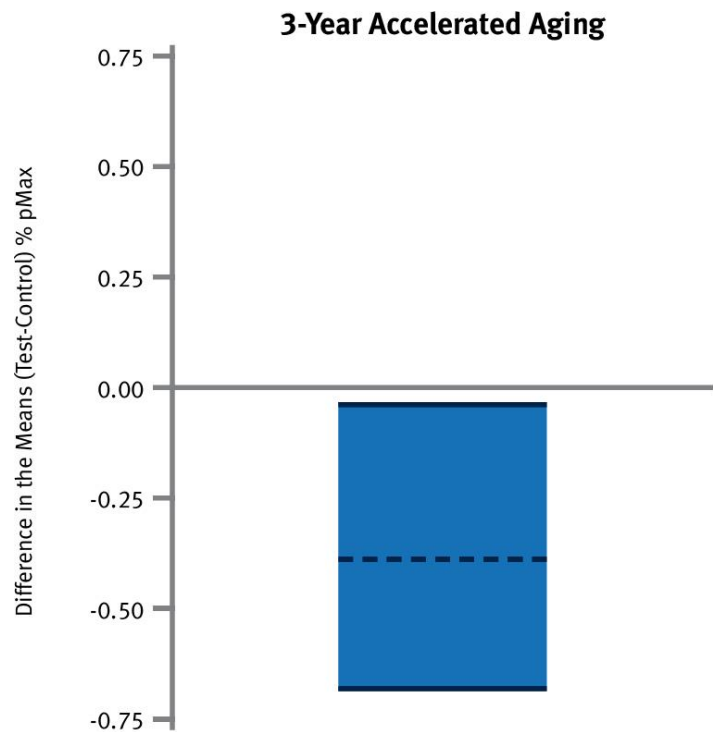
Uncoated 1059B Form-Fill-Seal

Figure A19. Avg. Percent Change in Mean Seal Strength (Test-Control) for Uncoated 1059B Form-Fill-Seal



Test=Transition Protocol Material
Control=Current Tyvek®

Figure A20. Range of Differences in % pMax Mean (Test-Control) for Uncoated 1059B Form-Fill-Seal



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

Figure A21. Package Integrity Summary for Uncoated 1059B Form-Fill-Seal

