Repligen ProConnex® RG-V Film

Validation Report

Introduction

Repligen ProConnex RG-V Film is a single-ply, multi-layer film that is 14 mils thick. The film structure contains a flexible gas barrier layer for long-term storage, and a polyester elastomer outer layer for optimal durability The product contact layer is an inert polyethylene plastomer. All film layers are I-168 free and animal origin free. ProConnex RG-V Film is produced in an ISO-7 cleanroom environment.

ProConnex RG-V Film Features

- Low coefficient of friction outer layer for enhanced durability and ease of installation
- Excellent flex durability
- High puncture resistance
- Entire film structure is animal-derived component free
- Customized modular bag port design
- Extractables testing completed per BPOG 2020 standards (post gamma irradiation >45 kGy)
- Sterilization method:
    - Gamma irradiation up to 45 kGy
- Produced in bag sizes from 50 mL to 3000 L
- ProConnex RG-V Film is produced in an ISO-7 cleanroom

Table 1. Mechanical Properties of ProConnex RG-V Film

Test	Standard	ProConnex RG-V Film
Tensile Strength @ Break (psi)	ASTM D-882	2636
Tensile Strength @ Yield (psi)	ASTM D-882	1007
Tensile Elongation (%)	ASTM D-882	738
Young's Modulus (psi)	ASTM D-882	30,450
Abrasion Resistance (Cycles @ 400g)	ASTM F-3300	3839
Puncture Resistance (lbf)	ASTM F-1306	16
Coefficient of Friction (MD/TD)	ASTM D-1894	0.36, 0.41
Flex Crack Resistance (900 Cycles)	ASTM F-392	0 pinholes
Haze (%)	ASTM D-1003	72

Table 2. Physical Properties of ProConnex RG-V Film

Test	Standard	ProConnex RG-V Film
Oxygen Transmission Rate (cm^3 / m^2 /day)	ASTM F-1307	0.30
CO_2 Transmission Rate (cm^3 / m^2 /day)	ASTM F-2476	<1
Water Vapor Transmission (cm^3/ m^2/day)	ASTM F 1249	0.48
Min Temperature, °C	Internal	-80
Max Temperature, °C	Internal	60

Layer	Material	Thickness
Product Contact	PE (polyolefin plastomer)	10.0 mil
Tie Layer	PE based	1.0 mil
Gas Barrier	EVOH	1.0 mil
Tie Layer	PE based	1.0 mil
Outer Layer	Polyester	1.0 mil

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Biocompatibility and Extractables Testing Summary of ProConnex RG-V Film

Extractables Summary

ProConnex RG-V Film was tested for extractables per the April 2020 Biophorum (formerly BPOG) document, "Extractables Testing of Polymeric Single-use Components used in Biopharmaceutical Manufacturing." Repligen submitted 8" x 10" 2D bag irradiated to 40 – 47 kGy per BPOG guidance to facilitate a worst-case scenario. Four (4) extraction solvents were used in this study.

Table 3. Extraction Solvents

Extraction Solvent	Description
WFI	Water for injection, Reagent Grade or higher
0.5 N NaOH	0.5 N sodium hydroxide solution, Reagent Grade or higher
0.1 M H_3PO_4	0.1 M phosphoric acid in water, Reagent Grade or higher
50% EtOH	50:50 ethanol: water (v/v), HPLC Grade or higher

Table 4. Timepoints

Timepoint
1 day (24 hours)
21 days
70 days

Table 5a. Reporting Thresholds Per Solvent & Timepoint

Solvent	Time Point	Organic			Inorganic	
		µg/mL	µg/cm²	µg/g	ng/mL	µg/cm²
WFI	24 hour	0.100	0.017	0.408	20.000	0.003
	21 day	0.100	0.017	0.412	20.000	0.003
	70 day	0.100	0.017	0.408	20.000	0.003
0.1 M H_3PO_4	24 hour	0.100	0.017	0.410	20.000	0.003
	21 day	0.100	0.017	0.407	20.000	0.003
	70 day	0.100	0.017	0.414	20.000	0.003
0.5 N NaOH	24 hour	0.100	0.017	0.409	20.000	0.003
	21 day	0.100	0.017	0.410	20.000	0.003
	70 day	0.100	0.017	0.412	20.000	0.003
50% EtOH	24 hour	0.100	0.017	0.410	20.000	0.003
	21 day	0.100	0.017	0.412	20.000	0.003
	70 day	0.100	0.017	0.414	20.000	0.003

Table 5b. Limits Of Detection Values For Headspace GC-MS Analysis For Volatile Organic Extractables

Analyte	Time Point	WFI		0.1 M H_3PO_4		0.5 N NaOH		50% EtOH	
		µg/cm²	µg/g	µg/cm²	µg/g	µg/cm²	µg/g	µg/cm²	µg/g
Methyl ethyl ketone	24 hour	0.007	0.176	0.007	0.177	0.006	0.154	0.013	0.309
Toluene		$6.244e^{-4}$	0.015	$6.472e^{-4}$	0.016	$7.371e^{-4}$	0.018	0.002	0.047
Octamethylcyclotetrasiloxane		0.002	0.058	0.017	0.411	0.128	3.077	$9.005e^{-4}$	0.022
Dodecane		0.002	0.056	0.003	0.068	0.003	0.080	0.002	0.038
Methyl ethyl ketone	21 day	0.007	0.178	0.007	0.175	0.006	0.155	0.013	0.311
Toluene		$6.244e^{-4}$	0.015	$6.472e^{-4}$	0.015	$7.371e^{-4}$	0.018	0.002	0.048
Octamethylcyclotetrasiloxane		0.002	0.059	0.017	0.408	0.128	3.085	$9.005e^{-4}$	0.022
Dodecane		0.002	0.056	0.003	0.067	0.003	0.080	0.002	0.038
Methyl ethyl ketone	70 day	0.007	0.176	0.007	0.179	0.006	0.155	0.013	0.313
Toluene		$6.244e^{-4}$	0.015	$6.472e^{-4}$	0.016	$7.371e^{-4}$	0.018	0.002	0.048
Octamethylcyclotetrasiloxane		0.002	0.058	0.017	0.416	0.128	3.102	$9.005e^{-4}$	0.022
Dodecane		0.002	0.056	0.003	0.068	0.003	0.081	0.002	0.038

Note: *A cell shaded in light blue indicates that the LOD was determined to be at a level above the reporting threshold.*

Table 5c. Limits of Detection Values for the Direct Injection GC-MS APCI Analysis for Semi-volatile Organic Extractables

Analyte	Time Point	WFI		0.1 M H_3PO_4		0.5 N NaOH		50% EtOH	
		µg/cm²	µg/g	µg/cm²	µg/g	µg/cm²	µg/g	µg/cm²	µg/g
n-Octane	24 hour	0.017	0.413	0.013	0.311	0.029	0.690	0.009	0.208
Octamethylcyclotetrasiloxane		0.004	0.107	0.013	0.323	0.018	0.430	0.003	0.068
Butylated hydroxytoluene		0.006	0.153	0.006	0.136	0.013	0.306	0.007	0.175
n-Octane	21 day	0.017	0.418	0.013	0.309	0.029	0.692	0.009	0.209
Octamethylcyclotetrasiloxane		0.004	0.108	0.013	0.321	0.018	0.431	0.003	0.068
Butylated hydroxytoluene		0.006	0.154	0.006	0.135	0.013	0.307	0.007	0.176
n-Octane	70 day	0.017	0.413	0.013	0.315	0.029	0.696	0.009	0.210
Octamethylcyclotetrasiloxane		0.004	0.107	0.013	0.327	0.018	0.433	0.003	0.069
Butylated hydroxytoluene		0.006	0.153	0.006	0.138	0.013	0.309	0.007	0.177

Note: *A cell shaded in light blue indicates that the LOD was determined to be at a level above the reporting threshold.*

Table 6. Summary Count of Extractables

Extraction Solvent	Volatile Organic Extractables	Semi-volatile Organic Extractables	Non-volatile Organic Extractables	Inorganic Extractables
WFI	2	2	1 (APCI); 0 (ESI)	0
0.5N NaOH	0	0	0; 0	0
0.1M H_3PO_4	1	2	0; 0	2
50% EtOH	3	4	2 (APCI); 23 (ESI)	N/A

The extractions were performed by incubating at 40 ± 3°C with continuous agitation at 50 rpm. Each solvent, water for injection (WFI), 0.1 M phosphoric acid solution (0.1 M H_3PO_4), 0.5 N sodium hydroxide solution (0.5 N NaOH) and 50% ethanol solution (50% EtOH), was added to a bag. The extracts were evaluated at the following time points: 24 ± 4 hours, 21 ± 1 days, and 70 ± 3 days.

The sample extracts were analyzed for volatile organic extractables by headspace gas chromatography with mass spectrometry (HS-GC/MS), semi-volatile organic extractables by direct injection GC-MS, non-volatile organic extractables by ultra-performance liquid chromatography with photodiode array (UPLC-PDA) and quadrupole time-of-flight mass spectrometry (GC/Q-TOF, APCI and ESI), and inorganic extractables by inductively coupled plasma mass spectrometry (ICP-MS). Ethanol extracts were excluded from ICP-MS.

Sample and Control Extraction:

Bags were extracted by filling them with 150 mL of extraction solvent and incubating at 40 ± 3°C with continuous agitation at 50 RPM for 24 ± 4 hours, 21 ± 1 days, and 70 ± 3 days. The surface area-to-solvent ratio of 6 cm^2 of internal bag surface area per milliliter of extraction solvent was achieved. Following the extraction, the sample extracts were found to be clear and colorless, with no particulates observed. The control extracts were prepared by storing a portion of extraction solvent in a Teflon vial with Teflon cap. The controls were stored with the samples during the extraction.

Table 7. Volatile Organic Extractables Summary (Headspace GC-MS) Above Limit of Detection

Solvent	RT, Min	Identification	Cas #	µg/cm²		
				24 Hr.	21 Day	70 Day
WFI	5.44	Pentanal	110-62-3	<LOD	<LOD	0.025
	7.41	Hexanal	66-25-1	0.018	0.021	0.027
0.1 M H_3PO_4	7.41	Hexanal	66-25-1	<LOD	0.020	0.027
50% EtOH	4.07	Tetrahydrofuran	109-99-9	<LOD	0.051	0.069
	4.19	Cyclohexane	110-82-7	<LOD	<LOD	0.084
	5.66	1,1-Diethoxyethane	105-57-7	<LOD	<LOD	7.601

Table 8. Semi-volatile Organic Extractables Summary (Direct Injection GC-MS APCI Analysis) Above Limit of Detection

Solvent	RT, Min	Identification	Cas #	µg/cm²		
				24 Hr.	21 Day	70 Day
WFI	4.85	Pentatonic acid	109-52-4	<LOD	<LOD	0.053
	6.36	Hexanoic acid	142-62-1	<LOD	0.07	0.111
0.1 M H_3PO_4	4.82	Pentatonic acid	109-52-4	<LOD	0.048	0.049
	6.36	Hexanoic acid	142-62-1	<LOD	0.085	0.092
50% EtOH	3.33	Unknown, (likely containing oxygen)	N/A	<LOD	<LOD	0.475
	9.79	Unknown alkane	N/A	<LOD	<LOD	0.038
	12.55	Unknown alkane	N/A	<LOD	<LOD	0.037
	15.00	Unknown alkane	N/A	<LOD	<LOD	0.024

Table 9. Inorganic Extractables Summary Above Limit of Detection

0.1M H_3PO_4			
Inorganic Extractable	**24 Hour**	**21 Day**	**70 Day**
Zinc (Zn)	0.018	<LOD	<LOD
Calcium (Ca)	0.009	<LOD	<LOD

Customer Service

Repligen Corporation
41 Seyon Street
Building 1, Suite 100
Waltham, Massachusetts 02453

customerserviceUS@repligen.com

(781) 250-0111