Aramus™ Single-Use 2D Bag Assemblies

High-grade, gamma-stable fluoropolymer film providing higher purity and greater reliability

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SECTION 1: INTRODUCTION

The Aramus™ single-use 2D bags are made of a high-grade, gamma-stable fluoropolymer, providing higher purity, greater compatibility, and increased safety for critical process fluids and final products. With a new single-layer technology that contains no curing agents, antioxidants, plasticizers, or adhesives, the number of potential contaminants is greatly reduced. These subassemblies offer the widest operating temperature range of bags currently available, making them more durable in frozen applications (-85° – 40°C [-121° – 104°F] or lower) without negatively affecting the film. This guide pertains only to Aramus gamma stable fluoropolymer 2D pillow style assemblies.

SECTION 2: REGULATORY OVERVIEW

Entegris has a long history of environmental compliance in countries of operation/distribution. Entegris actively reviews products for compliance and conformance with government and customer requirements affecting raw materials/substances that may be used in manufacturing processes. The certification of compliance (see pages 2-3) is an overview of regulatory compliance for Aramus single-use bags.

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LIFE SCIENCES

Aramus™ Single-Use Bag and Assemblies[1]: Certificate of Compliance[2]

Country of Origin: USA

Compliance Statements:

BIOLOGICAL REACTIVITY	STANDARD	STATEMENT
Biological Reactivity – *In Vitro*	USP <87>	Representative Aramus single-use bags and assemblies have been tested and meet these biological reactivity standards.
Biological Reactivity – *In Vivo*	USP <88>	
	USP Class VI	
Endotoxin	USP <85> and EP 2.6.14	
Hemolysis	ISO 10993-4	
PARTICULATES		
Particulate matter in single-use components and assemblies	USP <788> and EP 2.9.19	Representative Aramus single-use bags and assemblies have been tested and meet the particulate requirements established in USP <788> and EP 2.9.19.
FOOD CONTACT		
Indirect Food Additives – Polymers	21 CFR 177	Fluoropolymer resin used to manufacture the film and fitment comply with the requirements set forth in FDA specification 21 CFR.177.1550.
ANIMAL ORIGIN		
ADCF	Free of animal derivatives	Based on information provided by suppliers, no bovine or animal derived materials are used in the manufacture of the Aramus product fluid path raw materials. The Aramus fluid path materials are not intentionally exposed to animal content during the Entegris manufacturing process.
TSE/BSE Statement	TSE/BSE	Non fluid path peripheral items such as clamps and packaging either do not contain added animal derivatives or meet TSE/BSE treatment and manufacturing requirements defined in EMEA/410 rev 3; therefore, these items are not considered at risk for transmitting BSE/TSE as certified by the supplier.

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EXTRACTABLES		
Physiochemical Container Test	USP <661>	Representative Aramus single-use bags have been tested and meet the requirements established in USP <661>.
ENVIRONMENTAL IMPACT		
RoHS	Directive 2011/65/EU	Entegris has a long history of environmental compliance in countries of operation/distribution. Entegris actively reviews products for compliance and conformance with government and customer requirements affecting raw materials/substances that may be used in manufacturing processes.
REACH	Regulation EC/1907/2006	
	Directive 2006/122/EC3	

Manufacturing Environment: Quality & EHS Management Systems: Certified to ISO 9001:2008 and ISO 14001:2004

General: The information in this overview is provided for the purpose of communicating regulatory compliance for Aramus single-use bags and assemblies as shipped from an Entegris location. Entegris relies on the compliance testing and analysis performed by our raw material suppliers as the foundation for the listed regulatory statements, and Entegris makes no representation or warranty with regard to any such testing and analysis. Entegris makes no warranty, express, implied or statutory, with regard to the product(s) described in this overview, including, without limitation, the implied warranties of merchantability and fitness for a particular purpose. Ultimately, the customers must determine that use of this product is safe, lawful, and technically suited for their intended application and purpose, and Entegris assumes no liability for any loss or injury which may result from the use of the information contained in this overview.

Endnotes:

1. Aramus single-use bag assemblies include the Aramus bag and welded fitment along with components that have been connected to the bag such as tubing and fittings. These are components that come into contact with the process/product. In the case of components not manufactured by Entegris certificates of regulatory compliance have been acquired from our suppliers.
2. This statement of Regulatory Compliance applies to standard cataloged Aramus single-use bags and assemblies. Custom single-use bags and assemblies may not meet or may not have been tested to some or all of these regulatory requirements. Contact Entegris for details.

SECTION 3: CERTIFICATE OF ANALYSIS

Aramus Assemblies will be shipped with Certificate of Analysis and Gamma Irradiation Certificate (if product is irradiated).

SECTION 4: MANUFACTURING ENVIRONMENT

Aramus single-use assemblies are manufactured in an ISO Class 5 cleanroom. Entegris certifies each batch has been manufactured and tested according to approved procedures and specifications under a Quality System certified to ISO 9001.

SECTION 5: MATERIALS OF CONSTRUCTION

The Aramus single-use 2D subassembly bags are made of a high-grade, gamma-stable fluoropolymer. The Aramus film is an 8 mil fluoropolymer film that was selected for use in the Aramus product line of single use bags designed for the biopharmaceutical industry. The material features excellent chemical compatibility, low temperature performance, and gamma radiation stability.

Materials testing table

	TEST	SPECIFICATION	PRE-GAMMA[1]	POST-GAMMA
Mechanical testing	Puncture resistance	ASTM F1306	9.3 lbf	9.6 lbf
	Tensile test – MD[2]	ASTM D882	7880 psi	6450 psi
	Tensile test – TD	ASTM D882	7940 psi	7440 psi
	Elongation – MD	ASTM D882	677%	597%
	Elongation – TD	ASTM D882	590%	602%
	Elastic modulus – MD	ASTM D882	90.4 ksi	N/A
	Elastic modulus – TD	ASTM D882	99.0 ksi	N/A
	Seal strength[3]	ASTM F88	32.3 lbf	32.0 lbf
Temperature testing	Glass transition	ASTM D3418-12	N/A[4]	N/A
	Seal strength @ 40°C	ASTM F88	26.5 lbf	N/A
	Seal strength @ -20°C	ASTM F88	25.7 lbf	N/A
	Seal strength @ -85°C	ASTM F88	22.5 lbf	N/A
	Seal strength @ -196°C	ASTM F88	39.5 lbf	N/A
Permeability testing	CO_2 permeability	Proprietary	1082 cc/(m²*day)	864 cc/(m²*day)
	H_2O permeability	ASTM F1249	0.81 g/(m²*day)	0.70 g/(m²*day)
	O_2 permeability	ASTM D3985	234 cc/(m²*day)	219 cc/(m²*day)
Optical testing	Haze	ASTM D1003	11.7%	14.2%
	Luminous transmittance	ASTM D1003	92.7%	92.7%
	Diffuse transmittance	ASTM D1003	10.8%	13.1%

[1] Pre- vs Post-Gamma testing was performed on a different set of samples from the main testing and thus the values listed may differ slightly from those presented in the main text where applicable.

[2] MD: Machine Direction, TD: Transverse Direction

[3] Seal strength test samples failed by cracking or tearing and are thus not truly measures of seal strength. This is discussed in the report text.

[4]The Aramus material did not evince a glass transition temperature but rather performed as a fully crystalline structure.

SECTION 6: COUNTRY OF ORIGIN

The Aramus product was developed and is manufactured in the USA.

SECTION 7: ANIMAL DERIVATIVE CONTENT AND TSE/BSE RISK

Based on information provided by suppliers, no bovine or animal derived materials are used in the manufacture of the Aramus product fluid path raw materials. The Aramus fluid path materials are not intentionally exposed to animal content during the Entegris manufacturing process. Non-fluid path peripheral items such as clamps and packaging either do not contain added animal derivatives or meet TSE/BSE treatment and manufacturing requirements defined in EMEA/410 rev 3; therefore, these items are not considered at risk for transmitting BSE/TSE as certified by the supplier.

SECTION 8: U.S. FOOD AND DRUG ADMINISTRATION

The material used to produce the Aramus subassembly wetted surface meets FDA 21 CFR 177.1550 food contact requirements. Where silicone tubing is used on the Aramus assembled product, our supplier certifies the tubing meets the FDA requirements outlined in the Code of Federal Regulations 21 CFR 177.2600(a) and (b). This conformance includes all ingredients used in the product formulation. These ingredients are compliant to their specific regulations and 21 CFR 177.2600(c). This product can be used for food contact applications with food types I, II, IV B, VI, VII-B, and VIII of Table 1 and under conditions of use C through I-I of Table 2 in 21 CFR 176.170(c).

SECTION 9: SHELF LIFE

Aramus has been assigned a two-year shelf life. Shelf life study design includes real-time and accelerated studies using aging factors and calculations per ASTM F1980.

SECTION 10: GAMMA STERILIZATION

A VDmax^{25} radiation validation was performed per ANSI/AAMI/ISO 11137-2; Sterilization of Health Care Products – Radiation – Establishing the sterilization dose – Method VDmax, to substantiate Entegris' minimum exposure of 25 kGy provides a Sterility Assurance Level (SAL) of 10^{-6}. Triplicate dose mapping studies were performed using packaged product to validate that the dose of 25 kGy can consistently be achieved.

SECTION 11: STERILITY TESTING

During the VDmax^{25} radiation validation, bacteriostasis and fungistasis testing was performed prior to sterility testing to ensure the product did not adversely affect the outcome of the sterility test. The product did not exhibit any bacteriostatic or fungistatic activity and units tested post gamma verification dose passed ANSI/AAMI/ISO 11137-2 requirements.

SECTION 12: USP <87> BIOLOGICAL REACTIVITY TESTS, *IN VITRO*

Cytotoxicity testing assesses the potential of a given material to have a toxic effect on living cells.

Test: Samples of Aramus subassembly were tested by Toxikon in accordance with USP 40, NF 35, 2017; <87> Biological Reactivity Tests, In Vitro.

The test article sample was extracted in 10% Fetal Bovine Serum for 24 hours at 37 ±1°C, negative and positive controls were prepared similarly. Samples were placed directly onto mammalian monolayers of L929 mouse for 48 hours. Cultures were monitored for cellular degeneration and malformation and rated on a scale of 0 (No Biological Reactivity) to 4 (Severe Biological Reactivity).

Results: The test article samples scored a Grade 0 for Biological Reactivity after 48 hours. The negative and positive controls confirmed system suitability. The test samples were deemed to meet USP <87> criteria and not considered cytotoxic.

SECTION 13: USP <88> BIOLOGICAL REACTIVITY TESTS, *IN VIVO*, CLASS VI TEST

The USP Class VI testing assesses the potential toxicity of extracts from the Aramus subassembly into live animal models. Dosing is performed systemically, intracutaneously and implanted. Test animals are monitored for irritation or toxicity.

The post-gamma sterilized test article was exposed at a ratio of 120 cm2 product per 20 mL extract medium which included USP 0.9% Sodium Chloride for injection, Cotton Seed oil, 1:20 Ethanol in Sodium Chloride and Polyethylene Glycol 400 at 50°C ±2°C for 72 hours under dynamic conditions. These extracts were injected intracutaneously in rabbits and systemically in mice, and animals were observed for a biological response. Test article implantation into the paravertebral muscles of rabbits were observed for seven days for signs of irritation or infection.

Results: Aramus products meet criteria established per USP guidelines for Class VI Plastics 50°C.

SECTION 14: USP <85> BACTERIAL ENDOTOXINS TEST, EP, JP

Endotoxins are lipopolysaccharide complexes found in Gram-negative bacterial cell walls. They can cause fever in humans.

The testing was performed by Pace Analytical per the Kinetic Endotoxin Test method. The test article fluid path was flushed with sterile Water for Injection (WFI) at 37° – 40°C. A positive product control was prepared using the test article extract and the endotoxin standard. Sterile WFI and LAL Reagent water (endotoxin-free) were used as negative controls. LAL reagent was added to all test and control samples, which were then incubated and read via a plate reader.

Results: Based on the positive control, negative control and positive product control data; the system was suitable and the product did not interfere with the test system. The endotoxin level was determined to be below the limit of detection of the standard curve and reported as <0.0050 Eu/mL.

SECTION 15: USP <661.2> PHYSIOCHEMICAL TEST, PLASTIC PACKAGING SYSTEM FOR PHARMACEUTICAL USE

Physiochemical testing is performed to assess the safety aspects of a packaging system based on appropriate chemical assessments.

The test article was immersed in USP Purified Water at 70°C for 24 hours. The extract was then tested for Appearance, Absorbance, Acidity, or Alkalinity and Total Organic Carbon (TOC) per USP <661>.

Results: The Aramus products meet the requirements of USP 40, NF 35, 2017, USP <661.2>.

SECTION 16: ISO 10993-4 HEMOLYSIS: DIRECT CONTACT

The Hemolysis test examines the potential for contact of a product sample with blood to cause the rupture of erythrocytes (red blood cells).

Test: Samples of Aramus subassembly were tested by Toxikon in accordance with ISO 10993-4, 2002, Biological Evaluation of Medical Devices — Part 4: Selection of Tests for Interactions with Blood and ATSM F756.

Phosphate Buffered Saline (PBS) was added to the test article at a ratio of 6 cm2, incubated with rabbit blood for 3 hours, and then incubated at 37°C ±2°C, in triplicate.

Results: The percent hemolysis resulting from direct contact of the product with rabbit blood was 0.26% above the negative control. Per ISO 10993-4, a test article is considered nonhemolytic if its percent hemolysis is <5.0% above the negative control. The test article was therefore deemed nonhemolytic.

SECTION 17: ISO 10993-4 HEMOLYSIS: INDIRECT CONTACT

The Hemolysis test examines the potential for indirect contact of a product sample with blood to cause the rupture of erythrocytes (red blood cells).

Test: Samples of Aramus subassembly were tested by Toxikon in accordance with ISO 10993-4, 2002, Biological Evaluation of Medical Devices — Part 4: Selection of Tests for Interactions with Blood and ATSM F756.

The test article was extracted with Phosphate Buffered Saline (PBS) for 24 hours ±2 hours at 70°C ±2°C, and then the extract was incubated with rabbit blood for 3 hours at 37°C ±2°C, in triplicate.

Results: The percent hemolysis resulting from direct contact of the product with rabbit blood was 0.19% above the negative control. Per ISO 10993-4, a test article is considered nonhemolytic if its percent hemolysis is <5.0% above the negative control. The test article was therefore deemed nonhemolytic.

SECTION 18: EXTRACTABLES

An extractables study was performed by an independent laboratory following BPOG guidance. Please contact Entegris for additional information.

SECTION 19: DESIGN VALIDATION

Design validation was executed to demonstrate product adherence to functional requirements. All bags tested were exposed to a minimum gamma radiation dose of 42 kGy, as a worst case, prior to design testing. The design validation included the following testing:

- Leak test
- Tensile test
- Freeze thaw cycles
- Volume capacity test
- Hanging test
- Drainability test
- Burst test

Please contact Entegris for additional information.

SECTION 20: LEAK TESTING

The test aligns with ASTM F 2095-01; Standard Test Method for Pressure Decay Leak Test for Nonporous Flexible Packages with and without Restraining Plates. Aramus Assemblies are 100% leak tested. The detection limit on the Aramus bags is 30 micron.

SECTION 21: BIOBURDEN

Final routine assemblies are sampled prior to sterilization. Total bioburden is determined by summing the aerobic and yeast/mold counts. Testing performed in accordance with ISO 11737 and ISO 11137.

Subassemblies bioburden shall not exceed 25 CFU/mL and final assemblies shall not exceed 250 CFU/mL.

SECTION 22: PROCESS VALIDATION

Manufacturing equipment was validated as a system to provide evidence that the process, as defined using equipment specified, can consistently make product that meets final specifications. Process parameters where variation may impact product quality were identified and challenged. Intensified PQ (Performance Qualification) sampling included visual, leak, and burst testing. All IQ/OQ/PQ testing met protocol acceptance criteria.

SECTION 23: PACKAGING – SHIPPING VALIDATION

The standard product packaging was tested during shipping validation to ensure the designed packaging properly protects the Aramus bag and the Aramus assembled product. The packaged boxes were stress tested per ISTA 2A Testing for Packaged Products.

LIMITED WARRANTY

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