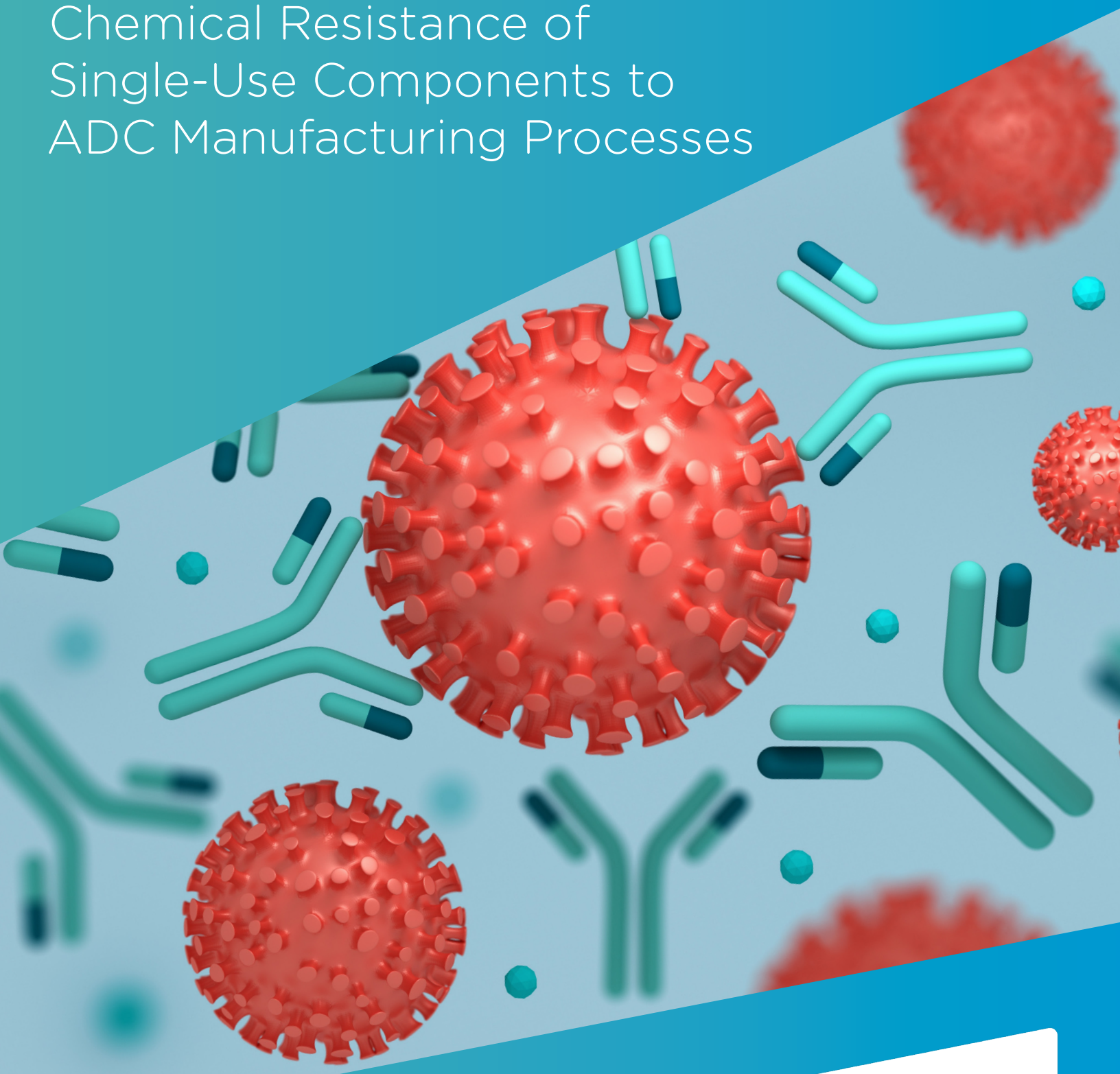
WHITE PAPER 0132

Chemical Resistance of Single-Use Components to ADC Manufacturing Processes



BIOPROCESS SOLUTIONS | LIFE SCIENCES

SAINT-GOBAIN

Haiyan Hong
Sr. Manager
Saint-Gobain Life Sciences
Research & Development

Laurent Rodriguez
Technical Services Manager
Saint-Gobain Life Sciences

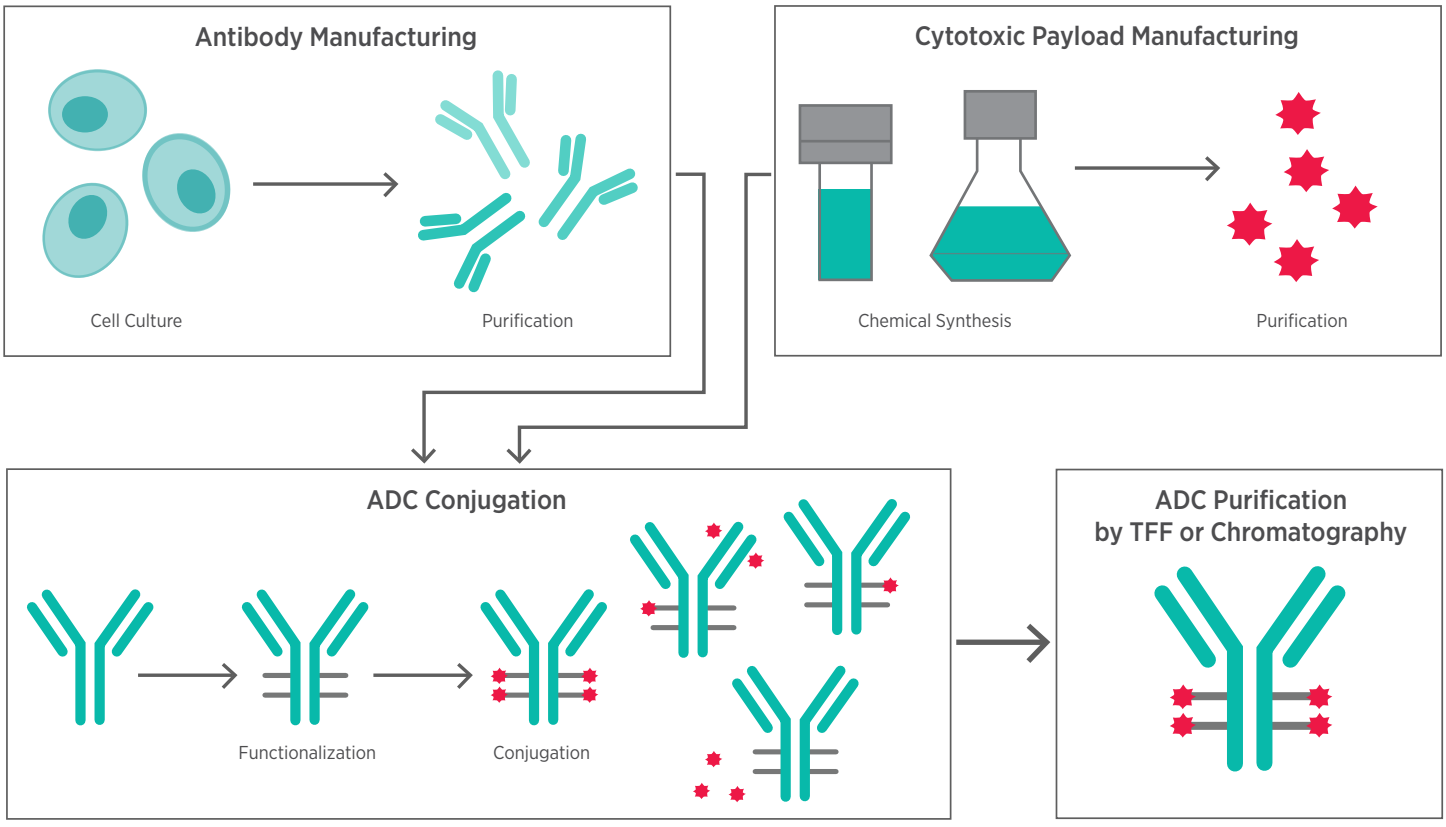
INTRODUCTION

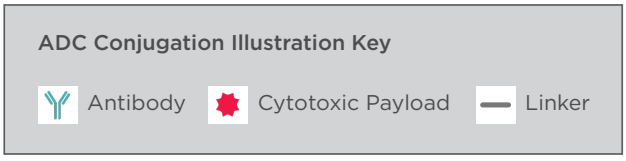
Antibody-drug conjugates (ADCs) are highly effective therapeutics created by combining monoclonal antibodies (mAbs) with cytotoxic, highly potent small-molecule drugs (cytotoxic linker-payload).

The adoption of single-use technologies, including overmolding technology, is becoming increasingly common among ADC manufacturers, as these technologies not only resolve typical challenges like cleaning validation and cross-contamination in biopharmaceutical production but also enhance safety and containment during the handling of cytotoxic linker-payload molecules used in ADC processes.

In the production of ADCs, organic solvents play a critical role in specific steps, particularly during the cytotoxic payload manufacturing and ADC conjugation phases.

DETAILED BREAKDOWN OF ANTIBODY CONJUGATION SOLVENT-INTENSIVE STEPS:





1. Linker-Payload Synthesis

Role of Solvents:

Organic solvents such as Dimethyl Sulfoxide (DMSO), Dimethylacetamide (DMAc), or acetonitrile are often used to dissolve hydrophobic payloads and facilitate chemical reactions.

Solvents also play a role in purification steps, where payload or linker by-products are removed.

Key Steps:

Reaction Medium: The payload and linker are synthesized in an organic solvent-based reaction medium to achieve the desired chemical structure.

Purification: Solvent-based extraction, crystallization, or chromatographic techniques may be used to isolate the pure linker-payload.

2. Antibody Conjugation

Buffer Preparation:

The mAb is prepared in an aqueous buffer suitable for the conjugation reaction, but organic solvents may be required to ensure the linker-payload's solubility and facilitate efficient conjugation.

Conjugation Reaction:

Solvent Use: DMSO or DMAc are often added to the reaction mixture to solubilize the linker-payload and to help it react with the antibody.

Controlled Conditions: The reaction is conducted under tightly controlled pH, temperature, and solvent concentrations to ensure specificity and minimize side reactions.

Quenching and Solvent Removal:

After the conjugation is complete, the reaction is quenched, and solvents are removed or diluted to prepare for purification.

The use of single-use technologies in Antibody-Drug Conjugate (ADC) manufacturing faces a significant hurdle: ensuring compatibility between components, bags, and assemblies, and the harsh solvents employed, including DMSO, DMAc, and acetonitrile. To address this, Saint-Gobain Life Sciences conducted a chemical compatibility study evaluating our single-use products with these solvents and their aqueous mixtures.

TEST DESIGN

The goal of the chemical compatibility studies was to check the function of the single-use assemblies and the individual components they are comprised of after exposure to relevant ADC manufacturing process. In addition, an extractables study is in the plan to characterize extractables profiles.*

Chemical compatibility studies were completed using the two designed single-use systems with tubing, filter, connector, overmolds and bags. The test conditions, including test solvents and exposure temperature/duration, were designed according to the ADC process conditions understood from customers, and summarized in the table on page 4 as "Process condition".

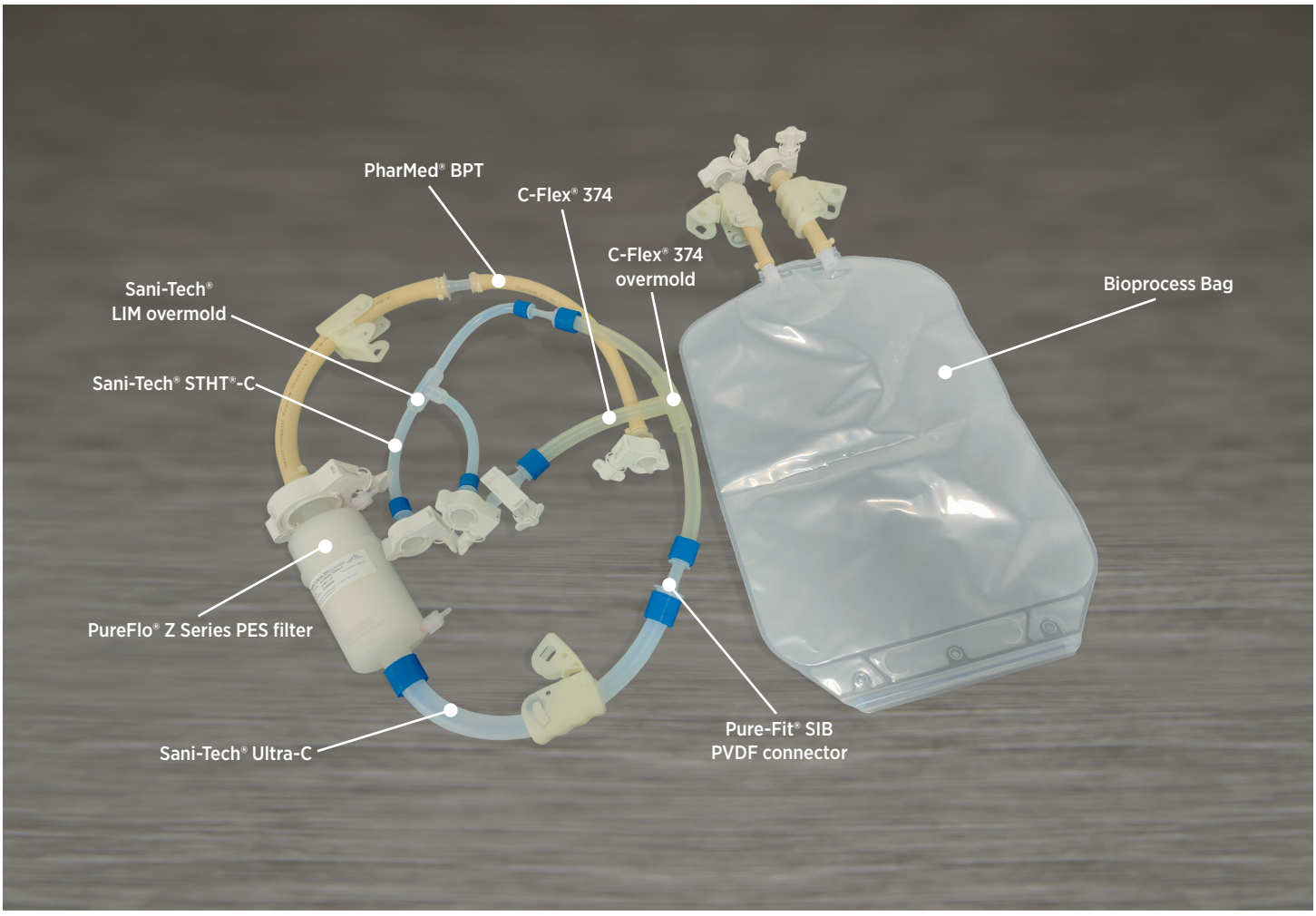
**The extractables data will be published sepereately at a later date.*

Table 1. Study design parameters

	Solvent	Temperature	Contact Time
Process condition 1	100%	Room temperature	1-2 h
Test condition 1	100%	30 ± 2°C	7 h
Process condition 2	15% to 30%	Room temperature	6-8 h
Test condition 2	30%	30 ± 2°C	7h for all components except Bags (24 h for bags)

Test conditions 1 : 100% Dimethyl Sulfoxide (hereafter: 100% DMSO), 100% Dimethylacetamide (hereafter: 100% DMAc) and 100% acetonitrile (hereafter: 100% ACN) have been used to address the processes where pure organic solvents were used.

Figure 1. Test assemblies



MATERIALS AND METHOD

Test system A samples were autoclaved at 121°C for 30 minutes with 1 cycle, test system B samples were gamma-irradiated at 27.5 - 45kGy. And then each test system was exposed to one of the test solvents at 30 ± 2°C using a shaker with a speed of 50 rpm. During exposure, additional clamps were used to close all open ends.

Table 2. Materials in wetted parts and their exposure duration

Assembly	Component	Product	Material of Construction	Treatment	Exposure Duration
A	Tubing	PharMed® BPT	TPE	Autoclave	7 hours
A	Tubing	C-Flex® 374	TPE	Autoclave	7 hours
A	Tubing	Sani-Tech® Ultra-C	Silicone	Autoclave	7 hours
A	Tubing	Sani-Tech® STHT®-C	Silicone	Autoclave	7 hours
A	Filter	PureFlo® Z Series PES filter	PES/PP/PET/Nylon	Autoclave	7 hours
A	Connector	PureFit® SIB PVDF connector	PVDF	Autoclave	7 hours
A	Overmold	C-Flex® 374 overmold	TPE	Autoclave	7 hours
A	Overmold	Sani-Tech® LIM overmold	Silicone	Autoclave	7 hours
B	Tubing	PharMed® BPT	TPE	Gamma-irradiation	7 hours
B	Tubing	C-Flex® 374	TPE	Gamma-irradiation	7 hours
B	Tubing	Sani-Tech® Ultra-C	Silicone	Gamma-irradiation	7 hours
B	Tubing	Sani-Tech® STHT®-C	Silicone	Gamma-irradiation	7 hours
B	Filter	PureFlo® Z Series PES filter	PES/PP/PET/Nylon	Gamma-irradiation	7 hours
B	Connector	PureFit® SIB PP connector	PP	Gamma-irradiation	7 hours
B	Overmold	C-Flex® 374 overmold	TPE	Gamma-irradiation	7 hours
B	Overmold	Sani-Tech® LIM overmold	Silicone	Gamma-irradiation	7 hours
B	Bag	Bioprocess Bag	LLDPE/EVOH/Nylon	Gamma-irradiation	24 hours

After the predetermined exposure duration, the assemblies were drained and flushed with deionized water, and then inspected visually for any signs of cracking, deformation, decomposition, swelling solubility, or leakage. Filters were removed from the assemblies and used for separate integrity tests and pressure hold tests. Bags were checked for pressure decay leak test and drop test. The acceptance criterion for each test can be found in Table 3.

The component will be concluded as compatible with the exposure condition when all the acceptance criteria listed below are met.

Table 3. Tests and acceptance criteria

Test	Test component	Acceptance criteria
Solvent exposure	All	Test temperature and duration should be within the pre-determined parameter ranges.
Visual inspection	All	The components or assemblies should show no signs of cracking, deformation, decomposition, swelling, solubility, or leakage.
Post-exposure integrity test	Filter	The filter should pass the integrity test including bubble point and diffusion flow test when wetted with standard reference liquid.
Post-exposure pressure hold test	Filter	The filter should pass the pressure hold test under 3.0 bar.
Post-exposure leak test	Bag	The bag should pass the pressure decay leak test.
Post-exposure drop test	Bag	The bag should show no sign of water leakage when dropped from six different directions with a drop height of 381 mm.

Table 4. Summary of results on autoclaved components

Autoclaved, 121°C for 30 minutes, 1 cycle								
	Tubing[1]				Connector[1]	Overmold[1]		Filter[1]
	PharMed® BPT	C-Flex® 374	Sani-Tech® Ultra-C	Sani-Tech® STHT® -C	Pure-Fit® SIB PVDF	C-Flex® 374 overmolds	Sani-Tech® LIM overmolds	PureFlo® Z Series PES filter
30% DMSO	OK	OK	OK	OK	OK	OK	OK	OK
30% DMAc	OK	OK	OK	OK	OK	OK	OK	OK
30% ACN	OK	OK	OK	OK	OK	OK	OK	OK
100% DMSO	OK	OK	OK	OK	OK	OK	OK	NR[2]
100% DMAc	OK	OK	OK	OK	NR[2]	OK	OK	NR[2]
100% ACN	OK	OK	OK	OK	OK	OK	OK	NR[2]

Notes:
[1] Test temperature: 30 ± 2°C, test duration: 7 hours; [2] NR- not recommended

Table 5. Summary of results on gamma-irradiated components

Gamma-irradiated, 27.5 - 45kGy									
	Bag[1]	Tubing[2]				Connector[2]	Overmold[2]		Filter[2]
	Bioprocess Bag	PharMed® BPT	C-Flex® 374	Sani-Tech® Ultra-C	Sani-Tech® STHT®-C	Pure-Fit® SIB PVDF	C-Flex® 374 overmolds	Sani-Tech® LIM overmolds	PureFlo® Z Series PES filter
30% DMSO	OK	OK	OK	OK	OK	OK	OK	OK	OK
30% DMAc	OK	OK	OK	OK	OK	OK	OK	OK	OK
30% ACN	OK	OK	OK	OK	OK	OK	OK	OK	OK
100% DMSO	OK	OK	OK	OK	OK	OK	OK	OK	NR[3]
100% DMAc	OK	OK	OK	OK	OK	OK	OK	OK	NR[3]
100% ACN	OK	OK	OK	OK	OK	OK	OK	OK	NR[3]

Notes:
[1] Test temperature: 30 ± 2°C, test duration: 24 hours; [2] Test temperature: 30 ± 2°C, test duration: 7 hours; [3] NR- not recommended.

CONCLUSION

Our bioprocess bags, tubing, connectors, and filters are designed to withstand the harsh chemical environments required for successful ADC production:

• All tubing, bioprocess bags, and overmolds passed all six solvent conditions after gamma-irradiation and after autoclave.

• Pure-Fit® SIB® PVDF fitting passed all solvent conditions except for DMAc 100% after autoclave.

• PureFlo® Z Series PES filter passed all solvent conditions except for ACN 100%, DSMO 100%, and DMAc 100% after gamma-irradiation and after autoclave.*

SUPPLEMENTARY NOTES

All the tests were completed without consideration of additional pressure generated from downstream or upstream. Process and product-specific validation tests might be needed to consider compatibility under higher temperature, longer exposure duration, and/or additional pressure, etc. in specific customer application situations.

** Testing with other filters is planned and will be published at a later date*

About

Authors

Haiyan Hong
Sr. Manager
Saint-Gobain Life Sciences
Research & Development

Haiyan has a Ph.D in polymer physics and chemistry from Shanghai Jiao Tong University. She has spent 17 years in the Life Sciences industry. She has worked for Saint-Gobain Life Sciences in Research & Development since 2015 and is currently leading an R&D and analytical team focusing on application, analytical testing, and product development.

Laurent Rodriguez
Technical Services Manager
Saint-Gobain Life Sciences

Laurent has a Professional Master in Biology and Biochemistry from the University of Grenoble, France.
He has been working in the Bioprocess field since 1994, holding various sales and product marketing positions. In 2022, he joined Saint-Gobain Life Sciences.
In his current technical role, Laurent is dedicated to supporting Saint-Gobain Life Sciences' Bioprocess customers in Europe.

Saint-Gobain Life Sciences

The Bioprocess Solutions business of Saint-Gobain Life Sciences is an industry-leading provider of materials science-based solutions for single-use fluid management, including TPE and silicone tubing, connection and flow control components, bioprocess and cell culture bags, filtration products, sensors, and over-molded technology, all available in customized assemblies that are produced in 20 manufacturing facilities located around the world. To find out more about Saint-Gobain Life Sciences and to learn how we can assist you with your application needs, visit our website.