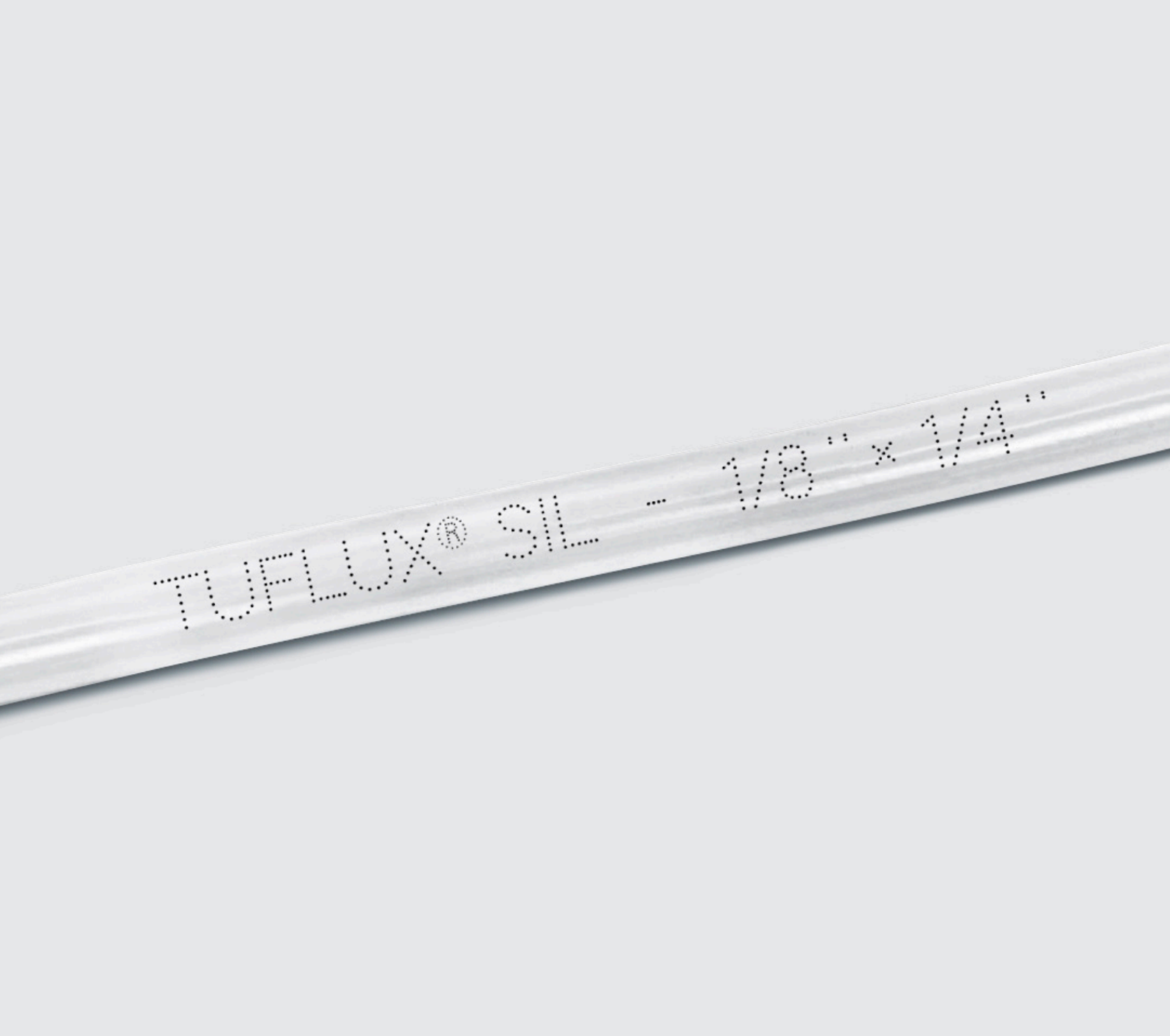

Tuflux® SIL Tubing (Sartorius) vs Pharma-50 (Dow Corning)

Comparability Guide

SARTORIUS

Applicable to:
Tuflux® SIL tubing used for the manufacture of Flexboy®, Flexel® and Cultibag®, as well as standalone coils and all other bag systems manufactured by Sartorius.

The results shown in this Comparability Protocol and Equivalency Test Report are indicative and do not constitute product specifications.

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1. Introduction

Sartorius bags and systems are widely used in biopharmaceutical processes for a variety of unit operations of the commercial production of drug products such as vaccines, recombinant proteins and monoclonal antibodies and for the development of future biomolecules in clinical phases.

Buffers and media are increasingly formulated, sterile filtered and stored in single-use Fluid Management Systems (FMS) that involve Flexel® and Flexboy® bags integrated with filters, impeller mixers, tubing, connectors and monitoring tools. Product intermediates are also filtered and stored between UF | DF and chromatography purification steps in gamma sterile fluid management systems.

Fluid management systems are also adopted for the formulation, filtration and aseptic processing of final drug products. From buffer media preparation, cell culture operations, purification operations up to final formulation, filtration and transfer, the silicone tubing Tuflux® SIL is a key element for the successful implementation of disposable manufacturing processes.

The Tuflux® SIL, Sartorius silicone tubing, is qualified, manufactured and released according to stringent product validation protocols and quality control testing, to offer safe and robust single-use processes to the end users of the biopharmaceutical industry.

This Validation Guide is to show comparability and variances between patinum cured silicone tubing from different suppliers (e.g. Raumedic and Dow Corning).

Tuflux® SIL will be the Sartorius standard tubing and replace the Dow Corning Pharma-50 in all new fluid management systems.

2. General Features

Physical Properties

The following values are determined on standard test specimens punched from a press plate.

	Color	Hardness Shore A	Operating Temperature Range	Ultimate Tensile Strength (according to ISO 527)	Elongation at Break (according to ISO 527)
Tuflux® SIL (Sartorius)	Translucent	60 ± 5	-60 °C to +200 °C (-76 °F to +392 °F)	> 8 MPa	> 600 %
Pharma-50 (Dow Corning)	Translucent	50 ± 5	-51 °C to 232 °C (-60 °F to 460 °F)	> 6.9 MPa	> 650 %

Material Hardness:

Purpose and Test Method

A measure of the indentation resistance of elastomeric or soft plastic materials, based on the depth of penetration of a conical indentor. Hardness values range from 0 (for full penetration) to 100 (for no penetration).

Tensile Properties:

Purpose and Test Method

A tensile test consists of applying an elongation to a tubing specimen and measuring the resulting strength. Mechanical properties can then be defined from the stress-strain curve.

Ultimate Tensile Strength (UTS):

The maximum stress a material can withstand is calculated by dividing the maximum load by the original cross sectional area of the specimen. The tensile strength test is performed with a tensile machine in stretching or elongation mode.

Elongation at Break:

The elongation is recorded at the moment of specimen rupture and often expressed as a percentage of the original length. Materials with high elongation at break withstand a high deformation before rupture. A high elongation at break often means high flexibility.

	Printing of ID and OD Dimensions on the Tubing	Coils Wrapped in Double Packaging	Low-Tack	Post Curing	Sterilization Resistance
Tuflux® SIL (Sartorius)	Yes	Yes	Yes	Yes	γ-irradiation Autoclave ETO
Pharma-50 (Dow Corning)	Not for Sartorius	Yes	No	Unknown	γ-irradiation Autoclave ETO

Tubing Printing

"a | b × c | d" where a | b is the internal dimension and c | d the outer dimension of the tubing in inches.

The innocuity of the ink is proven on printed tubing by the tests performed according to ISO 10993-5.

Low-Tack

The surface is coated in a plasma process. This coating provides a less sticky surface of these silicone tubing (low-tack) in comparison with common non-coated silicone products.

3. Biocompatibilty

Silicone tubing meets the requirements of the following biocompatibility tests:

	E.P. 3.1.9	USP <88> Class VI	USP <87>	USP <85>	Other ISO
Tuflux® SIL (Sartorius)	Yes	Yes	Yes	Yes	ISO 10993-4 ISO 10993-5
Pharma-50 (Dow Corning)	Yes	Yes	Yes	Yes	ISO 10993-4 ISO 10993-5

Purpose and Test Method

Biocompatibility tests are performed to demonstrate that the tubing is biocompatible and meets or exceeds the current USP and ISO requirements.

Tests are carried out on tubing samples before and after gamma irradiation (50 kGy). The tubing samples were supplied to an independent testing facility for evaluation under the current USP <88> and ISO 10993-5 biocompatibility standards.

USP <88> Class VI

Tubing material is implant tested, it meets the requirements of implant test to USP <88> Class VI, as well as the intracutaneous test and the acute toxicity test to USP <88> Class VI. This means that biological neutrality has been proven via these animal experiment tests on sterile and gamma or autoclave sterilized samples. The following tests were performed on samples with and without ink: cytotoxicity test, intracutaneous test, systemic injection test and implantation test (seven days).

Test Results of USP <88> Class VI

All materials used in the construction of the silicone tubing meet or exceed the requirements of the USP <88> Class VI– 121 °C plastics tests and are considered as non-cytotoxic and non-haemolytic.

USP <87> in vitro compared to USP <88> in vivo

Physico-Chemical Test

All testing presented in this comparability guide have been performed on gamma irradiated tubing at 50 kGy, that represents the maximum doses. If different, the tubing conditions will be specified.

European Pharmacopoeia: 3.1.9

Purpose and Test Method

With regard to their basic material, additives and properties, tubing in silicone rubber has been tested in compliance with the recommendations and guidelines on health assessment of plastics within the scope of the Food and Drug Act, sections A XV and B II XV, European Pharmacopoeia (E.P.) 3.1.9. as well as FDA regulation 21 CFR, § 177.2600.

Test Results

Tubing in silicone rubber meets the requirements of the European Pharmacopoeia 3.1.9. and regulation 21 CFR, § 177.2600.

The test methods, limits and results are those described by the E.P. monograph and listed in the table below.

Test Description	E.P. 3.1.9 Limits
Appearance of solution	Colorless
Acidity	≤ 2.5 mL NaOH 0.01M
Alkalinity	≤ 1.0 mL HCl 0.01M
Reducing substances	< 1 mL
Substance soluble in hexane	< 3 %
Volatile matter	< 2 %
Mineral oils	< 1 ppm
Platinum	< 30 ppm

4. Physico-Chemical Properties

	USP <381> Compliant	USP <661> Compliant	ADCF	REACH Compliant	FDA 21 CFR 177.2600 Compliant
Tuflux® SIL (Sartorius)	Yes	Yes	Yes	Yes	Yes
Pharma-50 (Dow Corning)	Yes	Yes	Yes	Yes	Yes

USP <381>
Elastomeric Closures for Injections

Purpose and Test Method

Elastomeric closures for containers are made of materials obtained by vulcanization (cross-linking) polymerization, polyaddition or polycondensation of macromolecular organic substances (elastomers). Elastomeric closures shall conform to biological, physico-chemical and functionality requirements. The tests are performed according to USP <381> recommendations.

Test Description	USP <381> Limits
Chearlessness	
Reducing substances	0
Lead	0 ppm
pH value change	5–7
Dry residue	< 2 mg

USP <661>

Containers, Physico-Chemical Tests – Plastic Purpose

Physico-chemical tests are designed to determine physical and chemical properties of Tuflux® SIL tubing and their extracts. They are performed on Tuflux® SIL samples before and after irradiation and accelerated aging conditions.

Test Method

Tubing samples were cut in small portions, previously gamma irradiated (50 kGy) and extracted (ratio of 30 g per 150 mL) in ultrapure water at 70 °C (158 °F) for 24 hours. The tests are conducted in order to determine physical and chemical properties of the test article and its extracts. The same test have been performed on tubing gamma irradiated (50 kGy) and stored during a period corresponding to a shelf life of three years (accelerated conditions).

Test Results

The silicone tubing Tuflux® SIL meets the USP <661> requirements when sterilized at 50 kGy with and without aging conditions corresponding to a shelf life of three years.

Test Description	USP <661> Limits
Non-volatile residue	< 15 mg
Residue in ignition	< 5 mg
Heavy metals	< 1 ppm
Buffering capacity	< 10 mL

ADCF Certified

Tubing Material does not contain any animal derived components.

REACH

Tubing material is free from any substances defined as SVHC – Substances of Very High Concern – by the European REACH regulation.

21 CFR, § 177.2600

With regard to their basic material, additives and properties, tubing in silicone rubber is in compliance with the recommendations and guidelines on health assessment of plastics within the scope of the Food and Drug Act, sections A XV and B II XV, as well as is FDA regulation 21 CFR, § 177.2600 compliant.

5. Barrier Properties to Water

The aim of this test is to evaluate the permeability of silicone tubes irradiated at 50 kGy to WFI at 60 °C (140 °F) for two, seven and 14 days, representing one, three and six months respectively, in normal room temperature conditions.

Tube	Mass Loss at 60 °C [%]			pH (calculated*)		Conductivity [µS/cm] (calculated*)	
	t = 2d	t = 7d	t = 14d	t = 14d (blank)	t = 14d	t = 14d (blank)	t = 14d
Tuflux® SIL (½" × ¾")	5.4	19.0	38.0	7.4	3.5	4.6	190.1
Pharma-50 (½" × ¾")	6.5	21.0	40.9		3.8		70.6

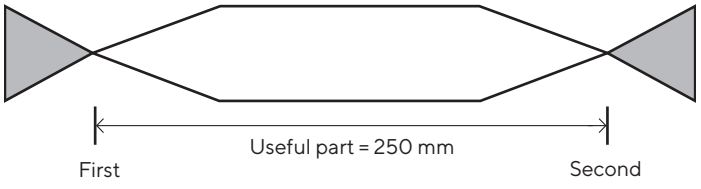
Note: *means that samples have been diluted three times before pH and conductivity measurements were taken. Therefore, pH and conductivity have been extrapolated -"calculated"- to their initial values, taking into account the dilution.

Barrier Properties to Water Vapor

The mass of each assembly is controlled at the start and after two, seven and 14 days of the samples being stored at 60 °C (140 °F). The percentage of mass loss is calculated from the weight at start of the test, compared to the weight after storage time.

pH and Conductivity

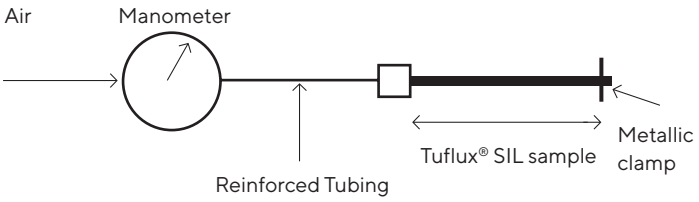
pH and conductivity are measured at t = 0 and after 14 days of storage at 60 °C (140 °F).



6. Pressure Resistance

Purpose
The goal of the burst pressure test is to assess the pressure resistance of the tubing depending on the tubing dimensions (inside and outside diameter).

Test Method
The test method is described in the scheme below. Three measurements of the pressure were taken for each tubing reference on gamma sterilized samples at 50 kGy at burst.



Pressure Resistance Results:
Pressure at which tubings inflate up to 10 % of their initial dimensions

Dimension ["] (ID | OD)	Dimension [mm]	Tuflux® SIL Air Pressure Limit Resistance [bar]	Pharma-50 Air Pressure Limit Resistance [bar]
⅛" × ¼"	3.2 × 6.4	4.5	3.8
¼" × ⅜"	6.4 × 9.6	3.1	2.4
¼" × 7/16"	6.4 × 11.1	3.5	3.3
⅜" × ⅝"	9.6 × 15.9	4.0	3.6
½" × ¾"	12.7 × 19.1	4.6	2.4
¾" × 1"	19.1 × 25.4	3.1	1.8
¾" × 1⅛"	19.1 × 28.6	4.7	2.4

7. Pumping Life Time

Purpose
The goal of the pumping life time test is to assess the mechanical resistance of the tubing under pumping conditions.

Test Method
The tubing is placed in a Watson Marlow series 720 peristaltic pump and speed is set up to maximum (> 300 rpm). The tubing was pumping water at an ambient temperature between two tanks, mimicking recirculation conditions.

The test was stopped and the time measured at which the tubing break resulted in a leak.

Tubing	Pumping Life Time [h]
Tuflux® SIL	> 70
Pharma-50	> 55

8. Flow Rates

Purpose

The objective of this test was to assess the maximum flow rate of some Tuflux® SIL dimensions.

Test Method

The time to transfer 100 L of water at room temperature with non-sterile tubing using a peristaltic pump set up at the maximum speed (310 rpm) was measured in duplicates.

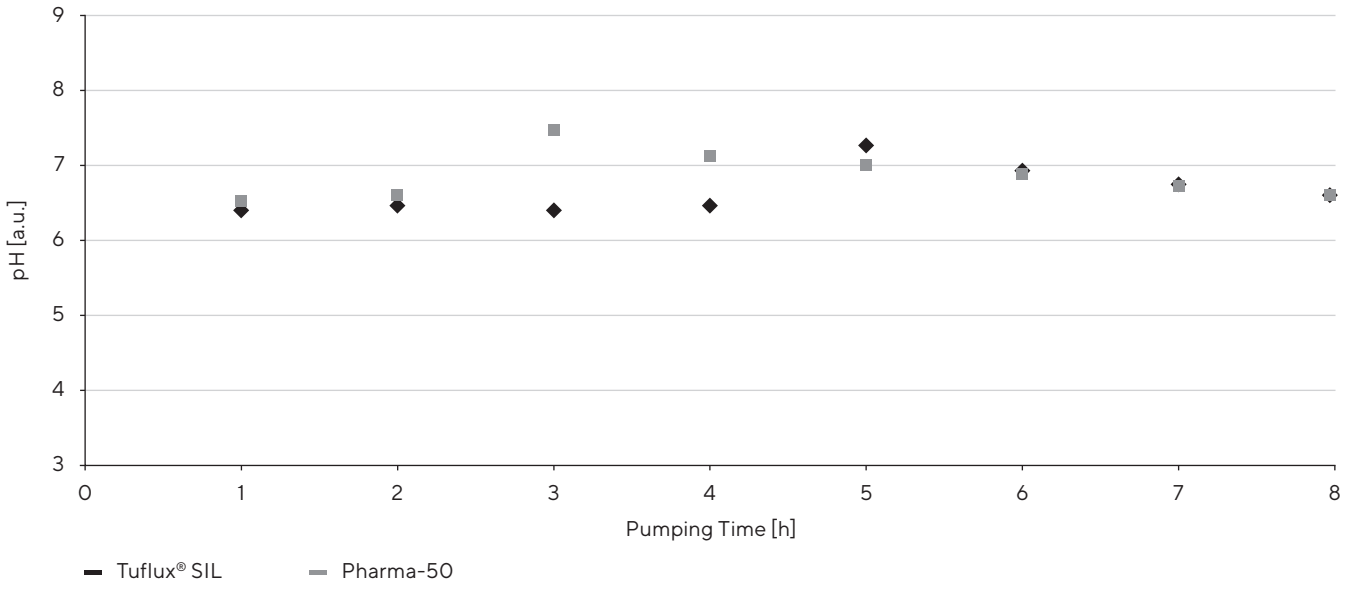
Tubing Size (ID × OD)	Tubing Material	
	Tuflux® SIL	Pharma-50
⅛" × ¼" 3.2 × 6.4 mm (WT 1.6 mm)	> 0.3 L/min	
⅜" × ⅝" 9.5 × 15.9 mm (WT 3.2 mm)	> 6.0 L/min	> 4.9 L/min
½" × ¾" 12.7 × 19.05 mm (WT 3.2 mm)	> 8.9 L/min	> 8.0 L/min

9. Tubing Benchmarking After Recirculation

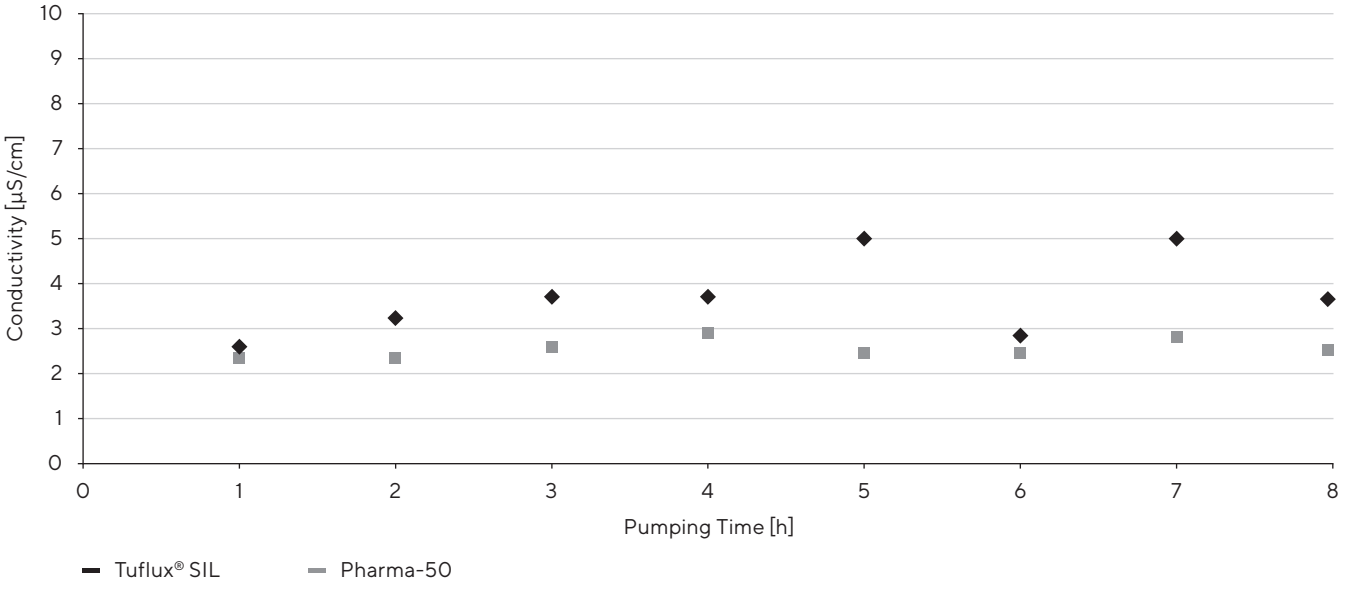
The goal of this test is to compare tubes irradiated at 50 kGy with the influence of the pumping time on pH, conductivity, particulates, UV | Vis and TOC.

Tests Conditions:
- Tube length: 2 m of ½ × ¾" tubing
- Volume WFI: 3 L
- Glass flask + plastic tube
- Rotation speed of the pump: 310 rpm
- Samples are taken at t = 0 and after x hours of pumping (x = 1, 2, 3, 4, 6, 8, 10)

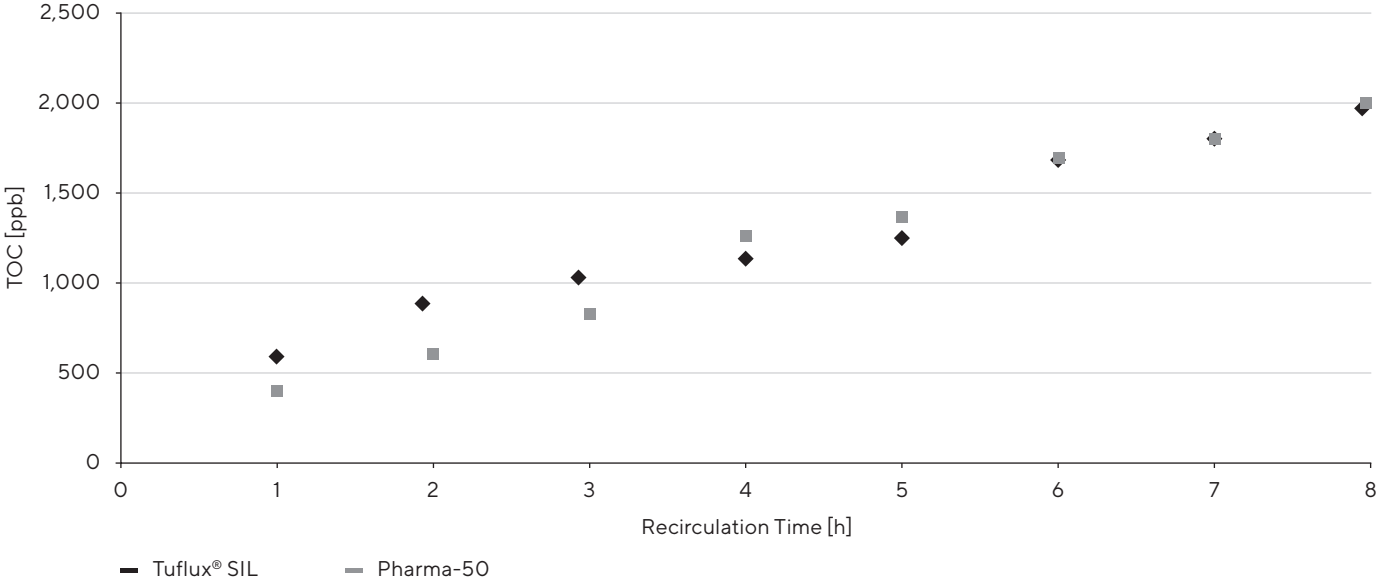
9.1 Pumping Time vs pH



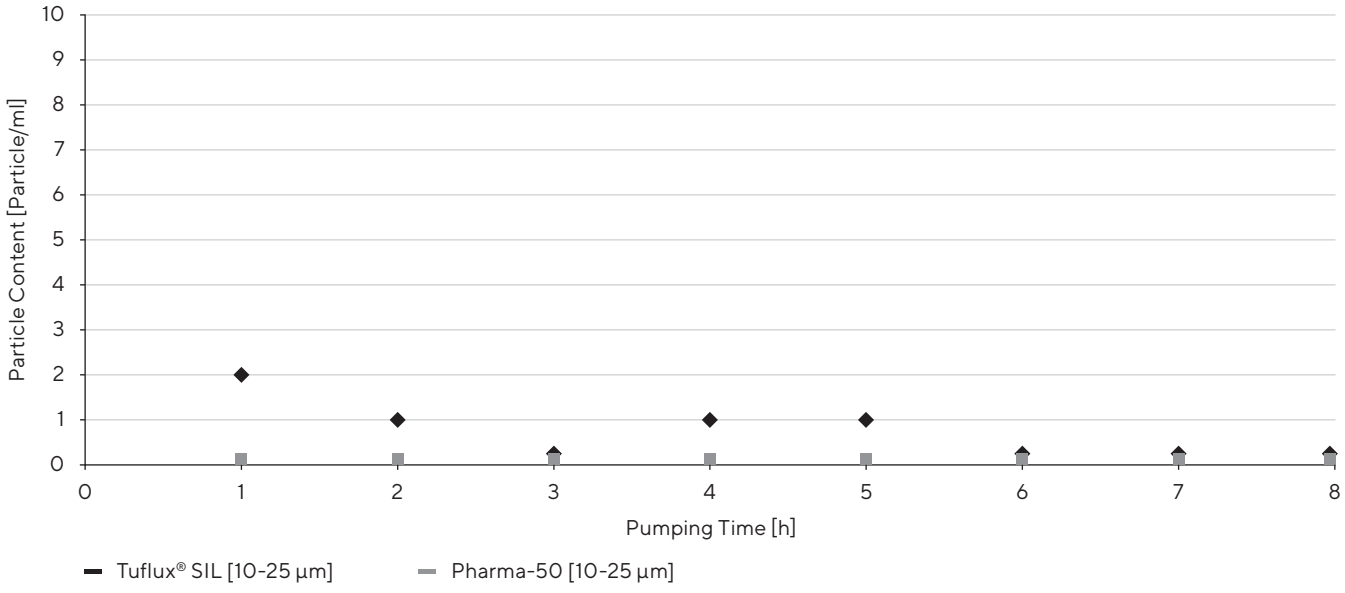
9.2 Pumping Time vs Conductivity



9.3 Pumping Time vs TOC Content



9.4 Pumping Time vs Particle Content

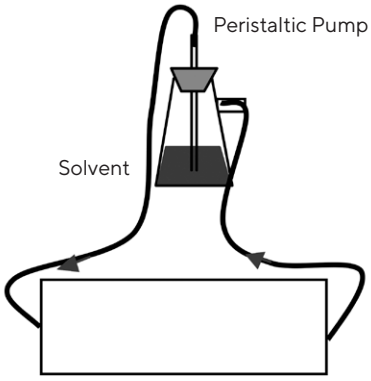


10. Extractable Studies

The comparison of tubing materials has been performed by solvent recirculation in tubing at room temperature:

- With EtOH for 2H-
- With 1M-HCl, 1M NaOH, WFI for 10H

→ Experiments as follow:



Purpose
Extractables are substances that can be extracted from a bioprocessing containment, such as a tubing, using extraction solvents and conditions that are more aggressive than the usual conditions of use. The goal of this extractable profile test is to supply worse-case extractable data to support process developers and toxicologists in their validation studies.

Reporting Limits for the Different Analytical Methods:
- Volatile Compounds (HS-GC | MS):
  Reporting limit: 0.01 µg/mL

- Non Volatile Compounds (LC | MS):
  Reporting limit: 0.01 µg/mL (for WFI only)

- Metal Analysis (ICP-MS | OES):
  Reporting limit: 0.1 µg/mL

- Semi-Volatile Compounds (GC | MS):
  Reporting limit: 0.05 µg/mL

The data shown below represents cleaned data.

Only values which are three fold above the blank are reported.

10.1 Results From Exposure of Silicone Tubing to WFI Solution

10.1.1 Volatiles by Headspace-GC | MS

Analytes	Quantification [µg/mL]	
	Tuflux® SIL	Pharma-50
Ethanol	0–0.05	0–0.05
Dichloromethane	0.05–0.1	0–0.05

Ethanol and dichloromethane are surely cross contaminant chemicals during sample preparation.

10.1.2 Semi-Volatile Compounds (GC | MS)

Analytes	Quantification [µg/mL]	
	Tuflux® SIL	Pharma-50
None		

10.1.3 Metal Analysis (ICP-MS | OES)

Solvent	Analytes	Quantification [µg/mL]	
		Tuflux® SIL	Pharma-50
WFI	Phospharus	0.1–0.5	0.1–0.5
	Silicone	0.1–0.5	0.1–0.5
	Sodium	1–5	1–5

10.2 Results From Exposure of Silicone Tubing to NaOH 1M Solution

10.2.1 Semi-Volatile Compounds (GC | MS)

Analytes	Quantification [µg/mL]	
	Tuflux® SIL	Pharma-50
Aromatic hydrocarbon	0	0

10.2.2 Metal Analysis (ICP-MS | OES)

Solvent	Analytes	Quantification [µg/mL]	
		Tuflux® SIL	Pharma-50
NaOH 1M	Aluminium	1–5	N.D.
	Boron	5–10	N.D.
	Silicone	50–100	50–100

N.D. = Not detected

10.3 Results From Exposure of Silicone Tubing to HCl 1M Solution

10.3.1 Semi-Volatile Compounds (GC | MS)

Analytes	Quantification [µg/mL]	
	Tuflux® SIL	Pharma-50
None	–	–

10.3.2 Metal Analysis (ICP-MS | OES)

Solvent	Analytes	Quantification [µg/mL]	
		Tuflux® SIL	Pharma-50
HCl 1M	Calcium	0.1–0.5	0.1–0.5
	Magnesium	0.1–0.5	0.5–1
	Silicone	1–5	1–5
	Sodium	0.5-1	N.D.
	Zinc	1–5	5–10

N.D. = Not detected

10.4 Results From Exposure of Silicone Tubing to EtOH Solution

10.4.1 Semi-Volatile Compounds (GC | MS)

Analytes	CAS Number	Quantification [µg/mL]	
		Tuflux® SIL	Pharma-50
Octamethyl Cyclotetrasiloxane NaOH 1M	[566-67-2]	0.5-1	N.D.
Decamethyl Cyclopentasiloxane	[541-02-6]	1-5	5–10
Dodecamethyl Cyclohexasiloxane	[540-97-6]	1–5	10–50
Tetradecamethyl Cycloheptasiloxane	[107-50-6]	1–5	10–50
Hexadecamethyl Cyclooctasiloxane	[556-68-3]	10–50	10–50
Octadecamethyl Cyclononailoxane	[556-71-8]	1–5	10–50
Other Siloxanes	-	1–50	100–250

10.4.2 Metal Analysis (ICP-MS | OES)

Solvents	Analytes	Quantification [µg/mL]	
		Tuflux® SIL	Pharma-50
Ethanol	Silicone	50–100	100–250
	Zinc	0.1–0.5	N.D.

Solvents = Ethanol
N.D. = Not detected

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