Emprove® Advanced Qualification Dossier

Custom documentation to support qualification and patient safety

MIX

Not appropriate for regulatory submission as active pharmaceutical ingredient. The use of this dossier shall be subject to the terms of use that can be found at **www.sigmaaldrich.com/emprove**

Millipore®

Preparation, Separation, Filtration & Testing Products

Contents

General Information

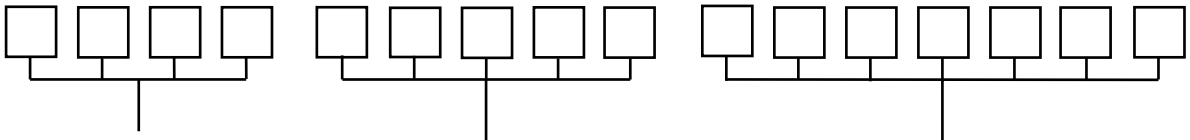
Catalog Numbers

This document supports the catalog number listed in this table.

Assembly Description	Mobius®, Silver,
Catalog Number	MIX
Assembly Revision Number	2
Certificate Level	Silver

Catalog Numbering System

Mobius® Single-Use Mixer Assemblies



Assembly Type
MIX = Mixer Assemblies
PMIX = Power Mixer Assemblies

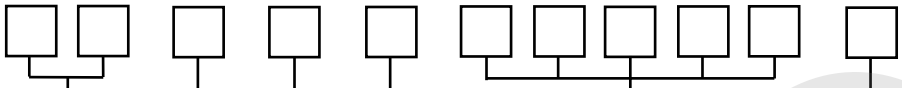
Bag Volume
(e.g. 0010L = 10 liters)

Assembly Serial Number
Unique assembly identification number (up to 7 digits long)

Lot Numbering System

Our lot numbering system is used to identify the manufacturing batch for each product. The batch records and device serialization records provide full traceability of the raw materials and components used in each product.

Danvers, MA, USA and Molsheim, France



Plant Code
L = Danvers, MA
FM = Molsheim, France

Year Code
0 = 2020
1 = 2021
2 = 2022
3 = 2023
4 = 2024
etc.

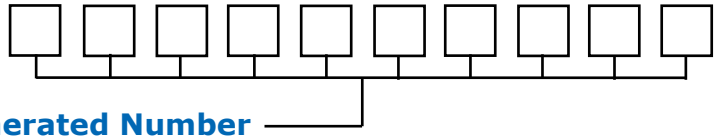
Month Code
A = January
B = February
C = March
D = April
E = May
H = June
J = July
K = August
M = September
N = October
P = November
S = December

Decade Code
A = 1
B = 2
C = 3
D = 4
E = 5
H = 6
J = 7
K = 8
M = 9
N = 0

Shop Order Number
5-digit sequential number

Sub-lot Code (Optional)
A = First sub-lot
B = Second sub-lot
C = Third sub-lot
etc.

Wuxi, China



10-digit Autogenerated Number

Product Description

The Mobius® single-use mixing solutions deliver advanced technology for mixing pharmaceutical ingredients from intermediate to final drug products and for the preparation of process solutions, such as buffers and media. Unlike traditional stainless-steel mixers, single-use mixers reduce downtime due to CIP, SIP, cleaning validation, and process engineering.

The mixing system includes a carrier, control box, motor, and power cord. The Mobius® Mixer assembly used in the system is a single-use device equipped with a magnetically driven impeller. This assembly typically consists of a bag with inlet and outlet tubing fastened to connectors as well as sampling port(s) and/or probe port(s).

Assembly Component Information

The following is a detailed breakdown of the assembly, outlining the individual components or devices. All components used in the assembly, which may come in contact with the product, have been evaluated for extractables data. When available, the Extractables Report for each tested component can be found in the 'Test Summaries and Results' section linked by the Report ID. Additional information for the components, such as the material of construction, supplier details, and surface areas for scaling purposes, are also provided.

Mobius Assembly Information

Part Number	Component Description	Comp. Type	Comp. Qty.	Fluid Path	Material of Construction	Surface Area (cm^2)	Supplier Name	Supplier Item Number	Report IDs
MIX	-					-			
	CONN-LUER FEMALE SMARTSITE NEEDLESS VALVE								
				No					
		RM							N/A
- 00106888PU-017									
					Stainless Steel				

Part Number	Component Description	Comp. Type	Comp. Qty.	Fluid Path	Material of Construction	Surface Area (cm^2)	Supplier Name	Supplier Item Number	Report IDs
		RM	1	No					N/A
- 00108135PU-3					Polypropylene	1.2			
						8.51			
- 00114016PU-10					LDPE	N/A			
			1	Yes		7.03			
- 00114151PU									
-						7.03			
- 00114209PU						N/A			N/A

Part Number	Component Description	Comp. Type	Comp. Qty.	Fluid Path	Material of Construction	Surface Area (cm^2)	Supplier Name	Supplier Item Number	Report IDs
	PACKAGING - COLLAR FOR 4" TC PORT	RM				N/A			N/A
- 00115734PU					White Expanded 3.5 PCF Polyethylene Foam				
	O-RING-PH PROBE PORT					1.2			
- 00125144DR									
- 00130238DR					Polypropylene	3.35			
				No					
						N/A			
- 1439003212				No					

Part Number	Component Description	Comp. Type	Comp. Qty.	Fluid Path	Material of Construction	Surface Area (cm^2)	Supplier Name	Supplier Item Number	Report IDs
					Platinum-Cured Silicone	N/A			N/A
- 2037001621						12.4			
									Contact Supplier For Data
- 6237001601									
- 6245081201	PLUG-MPC MALE POLYSULFONE	RM	1	Yes					
			1	Yes					
- - 7485040801PU-18						---			
				Yes		20.3			
- - 7486040801PU-14	TUBING-PHARMA 50 (1/2"ID X 3/4"OD)								

Part Number	Component Description	Comp. Type	Comp. Qty.	Fluid Path	Material of Construction	Surface Area (cm^2)	Supplier Name	Supplier Item Number	Report IDs
		SA	2	Yes					
- - 7486040801PU-14	TUBING-PHARMA 50 (1/2"ID X 3/4"OD)								
- 7486040801-6-6			1	Yes					
					Silicone	---			
- DISPC0Q2TP									N/A
- M0BGAMMALB		SA				N/A			N/A
		RM				N/A			
		RM	1	No					
- P88073						N/A			
- PKG-BAG									N/A
									N/A
	Mobius Generic Packaging Foam Placeholder								N/A

Part Number	Component Description	Comp. Type	Comp. Qty.	Fluid Path	Material of Construction	Surface Area (cm^2)	Supplier Name	Supplier Item Number	Report IDs
									-
- - 00018476PU-4	PORT PLATE – 1/2”HB								
						N/A			N/A
- - 00119250DR	MIXER-IMPELLER ASSEMBLY 67MM								
- - 00119251DR						96.7			
	PORT-4" TC								
						20.6			
- - 00130220DR									
				Yes					

FG: Finished Good
SA: Sub-Assembly
RM: Raw Material

Packaging Materials

The product's packaging meets our packaging integrity requirements after being subjected to the ISTA 2A standard testing procedure. Packaging is determined during build based on the quantity of assemblies ordered.

Component	Material(s) of Construction
Inner Bag	
Outer Bag	
Bubble Wrap	
Blue Cap*	
Pinch Clamp Cover*	
Foam Wrap*	
Foam Collar*	
Foam Pouch*	
Foam Sheet*	
Foam Roll*	
Pallets	

*Use of component depends on assembly design.

Component	Part Number*	Material(s) of Construction
Danvers, MA, U.S.A.		
Carton		
Complete Packaging Set	20201139	The set includes a box attached to a pallet, a urethane foam pad, a glued foam base assembly, a glued side assembly, and two foam collars. Each set comes assembled with the polyethylene foam components double bagged inside the box for use in the clean room and the urethane foam pad outside of the double bags.
Carton		
	20356973PU-02	Corrugated board: 275 # C Flute1
Molsheim, France		
Carton	PF20334	
Wuxi, China		
Carton		Corrugated carton: DW Kraft, B/C Flute

*The part number can be found printed on the bottom of the carton.

Carton Dimensions

Component	Part Number*	Outside Dimensions, in. (mm)		
		Length	Width	Height
Danvers, MA, U.S.A.				
Carton				
Complete Packaging Set	20201139	19 (482.6)	31 ½ (800.1)	47 ½ (1206.5)
Carton				
	P89809X2	20 ¾ (527.1)	14 ¼ (362.0)	28 (711.2)
Molsheim, France				
Carton	PF20333			
		30.83 (783)		
		47.24 (1200)		
Wuxi, China				
Carton				
				11 ¼ (285.8)
	CN00106807PU-08			

*The part number can be found printed on the bottom of the carton.

User Guide

A User Guide is not available for this custom product. To view our general Mobius® handling instructions and installation procedures, please visit our website: Mobius® Safe Handling. For Mixer and Power Mixer Assembly information, please visit our Mobius® Single-use Mixing Systems website: Mobius® Single-use Mixing Systems.

Drug Master File

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. Our company does not maintain DMFs for Mobius® single-use assemblies, because submitting a DMF is not a regulatory requirement nor a confirmation of compliance of our products. Instead, the same information that is typically included in the DMF can be found in this Dossier and the Quality Management Dossier for Mobius® single-use assemblies. If additional information is required, (e.g., Sterilization Validation, Quarterly Dose Audits etc.), please make this request through our Quality Services Department. The data may then be directly included in submissions [e.g., Abbreviated New Drug Application (ANDA), Biological License Application (BLA), etc.] to the FDA.

Safety Data Sheet

This product does not require a Safety Data Sheet (SDS) under the Occupational Health and Safety Administration Standard entitled “Hazard Communication” 29 CFR 1910.1200 for the United States of America.

This product is not a hazardous substance and does not contain hazardous ingredients or substances with European Community workplace exposure limits or substances of very high concern (SVHC) above their respective disclosure limits. This product does not require a safety data sheet according to Regulation (EC) No. 1907/2006 (REACH).

This product does not meet the criteria of a Workplace Hazardous Materials Information System (WHMIS) classification of a controlled product. This product does not require a WHMIS Material Safety Data Sheet in Canada.

Shelf Life

Millipore®

www.sigmaaldrich.com

EMPROVE® Material Qualification Dossier
Shelf Life Information Data Sheet
Mobius® Silver Assemblies

Shelf Life Information

Shelf Life:

Expiration

Shelf Life Supported Storage Conditions:

Mobius® Silver single-use assemblies have Not all assemblies undergo stability testing to determine their shelf lives. The design of the stability schedule is such that representative, individual components of the assemblies are tested to determine the assembly's holistic shelf life.

Specific lots of a Mobius® Silver single-use assembly from the date of manufacture. The assembly's overall expiration date is equivalent to the shortest remaining shelf life of any one component within that assembly. The expiration date designates the time prior to which the product will remain within the shelf life specification if stored under the defined conditions, and after which it must not be put into use.

Shelf Life Specialist
Separations and Instruments Technology Cluster

Storage and Handling

To ensure successful deployment of single-use technologies, it is vital that customers provide training to all personnel handling or working with single-use assemblies. Excess handling of assemblies at a customer's site could increase the risk of damage to an assembly. Customers should strive to reduce unnecessary handling of assemblies from receipt of product through application. A summary of our recommended handling practices for single-use assemblies are described below.

Warehouse and Storage Area

Upon receipt of single-use assemblies, the following steps should be taken:

Step	Description
1	Visually inspect the outer boxes for damage and report any damage if observed. It is recommended to establish an internal procedure with pre-defined escalation pathways.
2	To maintain the product integrity, store all single-use assemblies in the original packaging under controlled temperature conditions.
3	Open boxes using a shallow cutting tool with a controlled cutting surface, such as the tool shown below. Be careful not to damage the inner packaging. 
4	If placing internal labels on each assembly, the assemblies should NOT be removed from the original boxes. Packaging should be moved aside, and stickers placed on one corner of each assembly. Once complete, the packaging should be replaced, and assemblies stored as received until requested from the applicable production area.

Storage of Assemblies Outside Original Shipping Boxes

When storing assemblies, freezing and extreme heat (> 40 °C) should be avoided. The original sealed bag must be kept intact to protect the product from foreign matter and high levels of moisture. Additional storage recommendations must be considered:

Recommendation	Description
1	It is recommended that assemblies are stored inside of the original shipping boxes for as long as possible. Minimize the time assemblies are stored outside of corrugated boxes, as assemblies are more susceptible to damage in this state.
2	Storage surfaces must be clean, smooth, and free of sharp edges.
3	Storage surfaces should be no smaller than the footprint of the assembly. Assemblies should be stored flat. No part of the assembly should hang over the edge of the storage surface: 
4	For all carts used for storage, ensure the sharp corners and edges are capped off or covered appropriately to prevent damage to the assembly: 
5	Storage shelves should be placed in a location where nothing heavy can fall on top of the assemblies; this will help decrease the chances of damage due to impact from a foreign object.
6	Assemblies should not be stacked higher than they were in the original boxes.

Transport of Assemblies

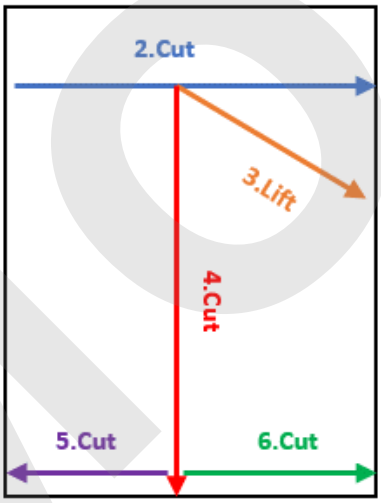
The following recommendations must be considered with respect to the transportation of assemblies:

Recommendation	Recommendation Description
1	Transport Mobius® assemblies in the original packaging.
2	Do not drop or bump the assemblies.
3	Do not fold bags for transport or storage.
4	Transport surfaces must be clean, smooth, and free of sharp edges.
5	Transport surfaces should be no smaller than the footprint of the assembly. No part of the assembly should hang over the edge of the transport surface.
6	Assemblies should not be stacked or transported on top of other products during transportation (See photo below). 

Opening Assemblies

The following steps should be taken for properly opening your assemblies in a controlled/isolated environment per your local aseptic transfer procedures:

Step	Description
1	When receiving our products, wipe down the outer containment bags / packaging bags (if applicable) using low lint /or non-shedding cleanroom wipes, prior to opening
2	Carefully cut across on the top of the outer bag, taking care not to cut across the processing bag using blunt tipped scissors or shallow safety cutter (Recommended).
3	Carefully lift the top of the bag away from the assembly.
4	Carefully cut down the center of the outer packaging bag only (See diagram).
5	From the bottom of the new center cut, carefully cut towards the outside of the package on the left side of the cut (See diagram).
6	Repeat Step 4, carefully cutting towards the outside of the package on the other right uncut side (See diagram).
7	Open the outer packaging bag and lift out of the inner bag.
8	Repeat steps 2 - 7 for the inner bag.
9	The assembly can then be lifted out of the inner packaging bag and placed on a smooth cart large enough to fit the footprint of the assembly, or directly install the assembly into a prepared bin or mixer carrier located nearby. **NOTE:** Sliding the assembly out of the inner packaging is not recommended as it could damage unprotected PureFlex® film causing abrasion



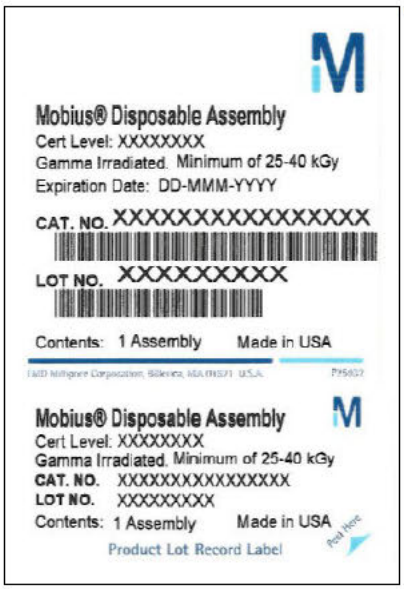
Preparation and Installation

Step	Description
1	Visually inspect and wipe down the inside of the bin, mixer, or carrier using a clean, lint-free wipe. Check to ensure the bin, mixer, or carrier is clean and dry and free off burrs, particulates, and sharp edges. Remove any residual debris (cable tie ends, powder, etc.) that may be present from previous use.
2	Report any damage to the bin, mixer, or carrier and remediate before installing the assembly.
3	Place the cart containing the assembly close to the bin, mixer, or carrier.
4	If the bin, mixer, or carrier has an appropriately sized door, install the assembly through the door itself prior to removing the additional packaging.
5	If the bin, mixer, or carrier does not have a door or the door is not large enough to load the assembly through, carefully remove the outer packaging and lift the assembly and install through the top of the carrier.
6	Carefully feed tubing through the correct ports to ensure tubing, clamps, and connectors do not contact the film surface during loading.
7	IMPORTANT! Secure any heavy objects (filters, heavy connectors, or clamps) located on the top of the assembly to ensure they do not drop into the carrier and onto the film surface.
8	After the assembly is loaded into the carrier, check the fit of all tubing. At no point should tubing be stretched, as this will cause unnecessary strain on connections and may lead to a leak.
9	Remove any remaining protective foam from the assembly after the assembly is properly installed in the bin, mixer, or carrier. To maintain the product's integrity, store all single-use assemblies in the original packaging under controlled temperature conditions. Freezing and extreme heat (> 40 °C) should be avoided.

Labeling

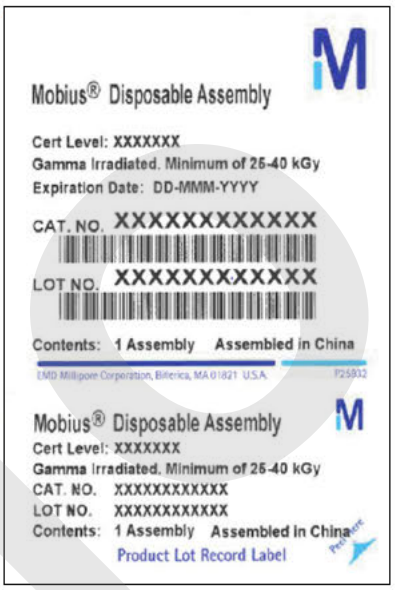
Primary Packaging (bag) Label

Manufactured in Danvers, MA, U.S.A.

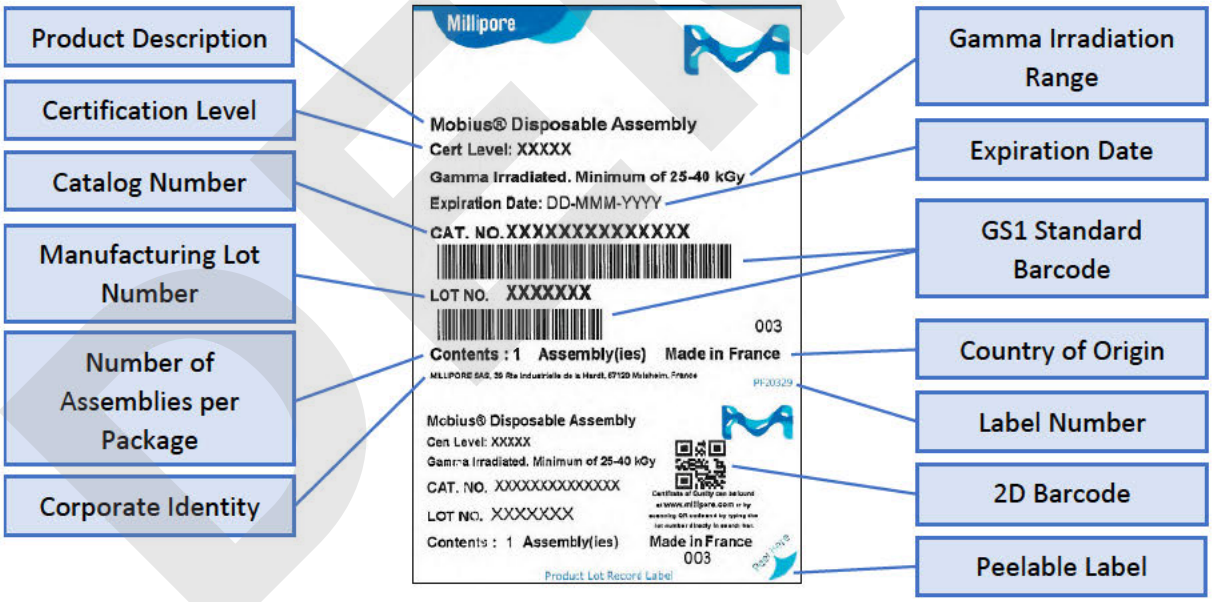


Manufactured in Molsheim, France

Assembled in Wuxi, China

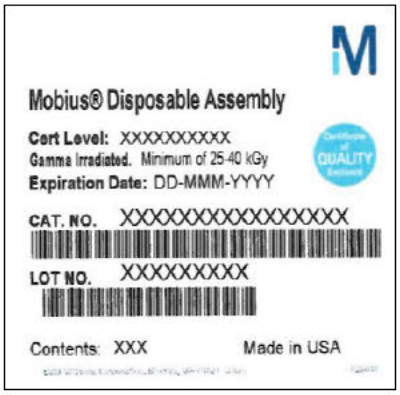


Primary Identification

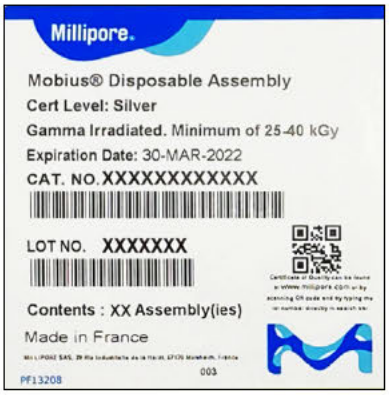


Secondary Packaging (carton) Label

Manufactured in Danvers, MA, U.S.A.

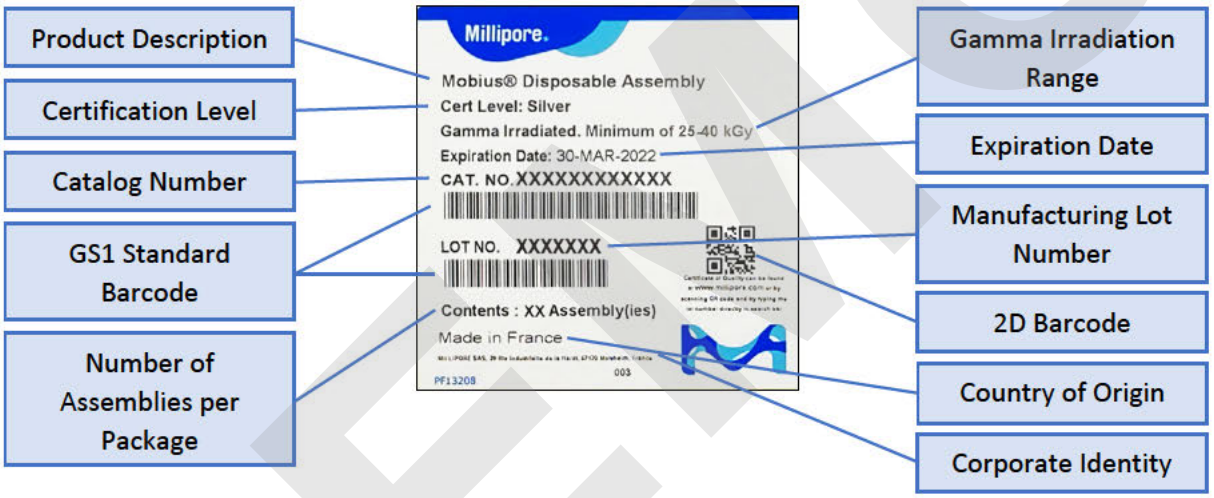


Manufactured in Molsheim, France



Assembled in Wuxi, China

Primary Identification



Handling Instructions Label

Handling Instructions

Do not drop or bump the assembly. Guard the connections and folds from impact. Lay the assembly flat and do not stack for transport and storage.

Do not stack anything on top of assembly.

Surfaces that contact the assembly must be clean, smooth, and free of sharp edges. Areas used for unpacking and transport should be no smaller than the footprint of the folded assembly.

Remove inner packaging bag from the outer one by cutting off the end with blunt-tipped scissors, taking care not to cut the assembly. Gently remove inner bag. Cut the end off in the same way. Cut the inner bag lengthwise down the center in order to lift the product up and out of the packaging.

Avoid impact, pulling, dragging, or stretching of the assembly's film. Abrasions to the film may cause leaks.

Protective packing materials should remain in place until unit is installed.

Filters and other components on tubing should be secured outside the bin or mixer carrier.

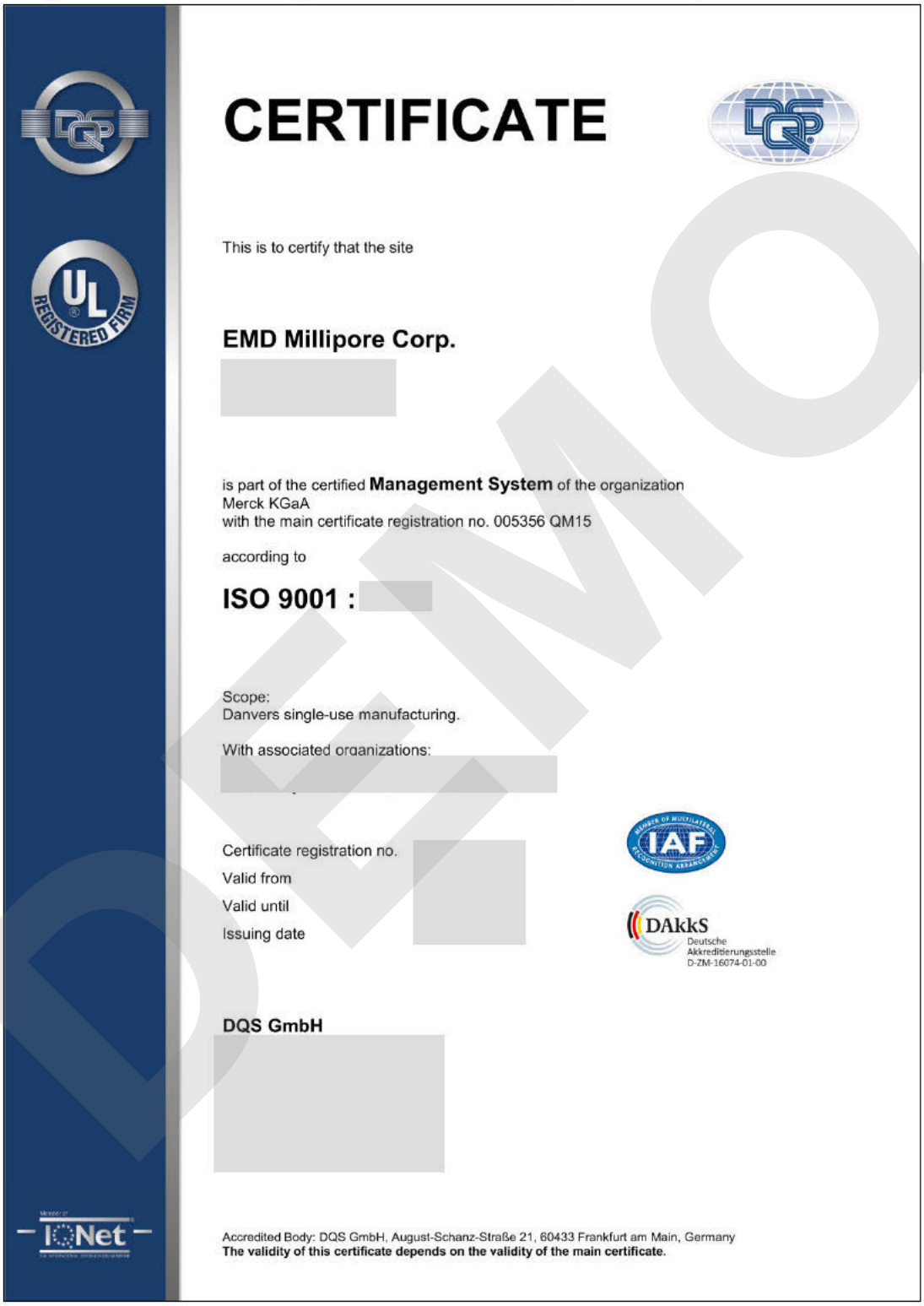
Tubing and fittings should not hang or pull on the assembly.

For more information, please scan the code below

www.millipore.com/singleuse

20192474PU, ver. 1.0

Manufacturing Regulatory Compliance (Danvers, MA, U.S.A.)



CERTIFICATE

This is to certify that the site

EMD Millipore Corp.

is part of the certified **Management System** of the organization
Merck KGaA
with the main certificate registration no. 005356 QM15

according to

ISO 9001 :

Scope:
Danvers single-use manufacturing.

With associated organizations:

Certificate registration no.
Valid from
Valid until
Issuing date

DAkkS Deutsche Akkreditierungsstelle D-ZM-16074-01-00

DQS GmbH

Accredited Body: DQS GmbH, August-Schanz-Straße 21, 60433 Frankfurt am Main, Germany
The validity of this certificate depends on the validity of the main certificate.

Manufacturing Regulatory Compliance (Molsheim, France)

CERTIFICATE

This is to certify that the site

Millipore S.A.S.

is part of the certified **Management System** of the organization
Merck KGaA
with the main certificate registration no. 005356 QM15

according to

ISO 9001 :

Scope:
Development, manufacturing, distribution and after sales support of devices, equipment, media, for fluid analysis and purification.
Engineering, Manufacturing, distribution and after sales support of systems, technical solutions and single use components for fluid storage, filtration, separation, and water purification systems for laboratories.
Scientific, commercial, technical and validation support to customers.

Certificate registration no.
Valid from
Valid until
Issuing date

DAkkS
Deutsche
Akkreditierungsstelle
D-ZM-16074-01-00

DQS GmbH

Accredited Body: DQS GmbH, August-Schanz-Straße 21, 60433 Frankfurt am Main, Germany
The validity of this certificate depends on the validity of the main certificate.

Manufacturing Regulatory Compliance (Wuxi, China)

CERTIFICATE

This is to certify that the site

Sigma-Aldrich (Wuxi) Life Science & Technology Co., Ltd.

is part of the certified **Management System** of the organization
Merck KGaA
with the main certificate registration no. 005356 QM15

according to

ISO 9001 :

Scope:
Packaging of bio-chemical reagent products (non-medicinal) and manufacture of disposal bio processing bags.

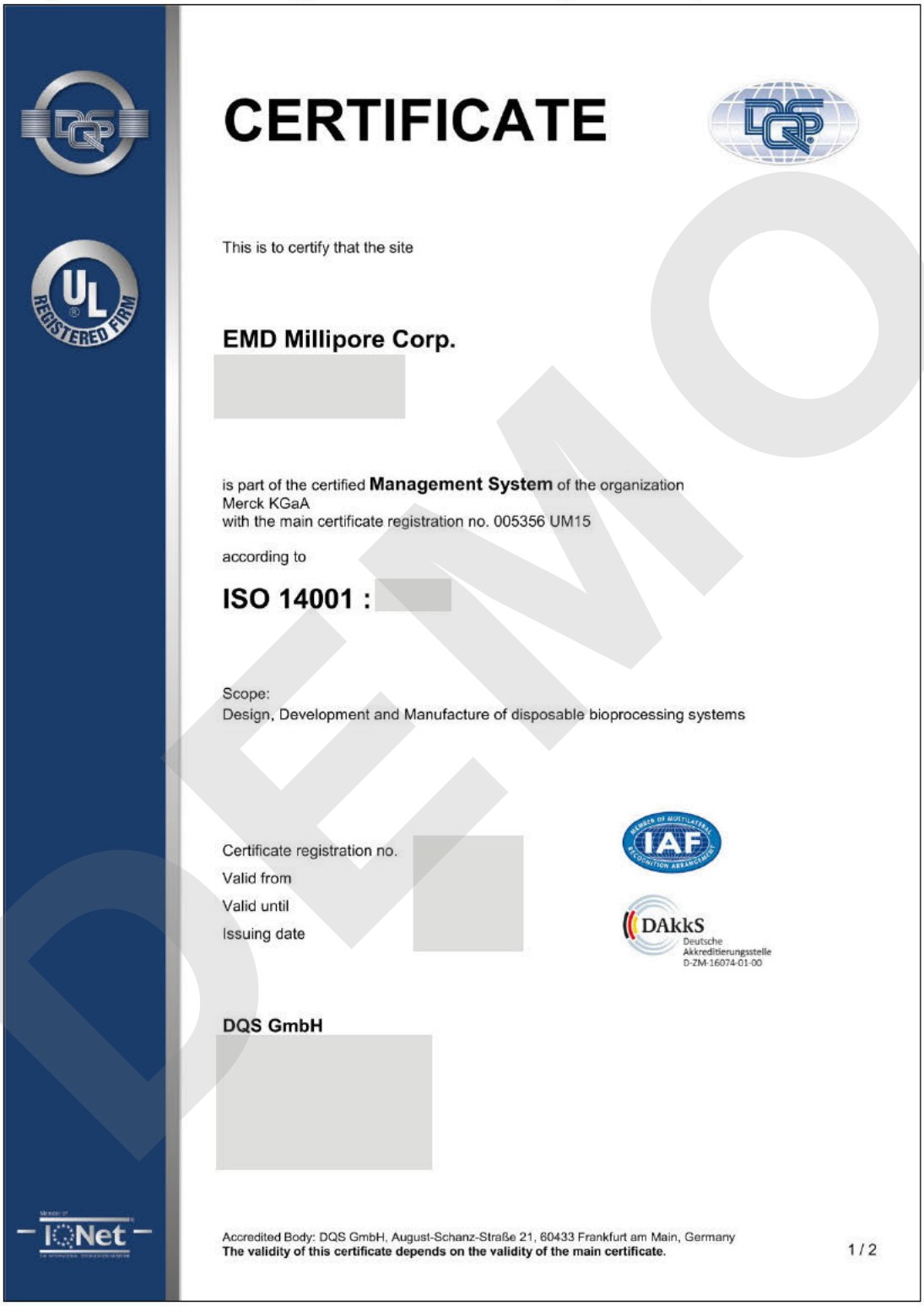
Certificate registration no.
Valid from
Valid until
Issuing date

DAkkS Deutsche Akkreditierungsstelle D-ZM-16074-01-00

DQS GmbH

Accredited Body: DQS GmbH, August-Schanz-Straße 21, 60433 Frankfurt am Main, Germany
The validity of this certificate depends on the validity of the main certificate.

Environmental Management Compliance (Danvers, MA, U.S.A.)



CERTIFICATE

This is to certify that the site

EMD Millipore Corp.

is part of the certified **Management System** of the organization
Merck KGaA
with the main certificate registration no. 005356 UM15

according to

ISO 14001 :

Scope:
Design, Development and Manufacture of disposable bioprocessing systems

Certificate registration no.
Valid from
Valid until
Issuing date

DAkkS
Deutsche
Akkreditierungsstelle
D-ZM-16074-01-00

DQS GmbH

Accredited Body: DQS GmbH, August-Schanz-Straße 21, 60433 Frankfurt am Main, Germany
The validity of this certificate depends on the validity of the main certificate.

1 / 2

Annex to certificate
Registration No.

EMD Millipore Corp.

with associated organizations:

This annex (edition: is only valid in connection with the above-mentioned certificate.

2 / 2

Environmental Management Compliance (Molsheim, France)

CERTIFICATE

This is to certify that the site

Millipore S.A.S.

is part of the certified **Management System** of the organization
Merck KGaA
with the main certificate registration no.

according to

ISO 14001 : 2015

Scope:
Manufacturing of devices and media for fluid analysis and purification.
Manufacturing of water purification systems for laboratories.
Engineering of filtration equipment.
Validation and scientific support to users.

Certificate registration no.

Valid from

Valid until

Issuing date

DAkkS
Deutsche
Akkreditierungsstelle
D-ZM-16074-01-00

DQS GmbH

Accredited Body: DQS GmbH, August-Schanz-Straße 21, 60433 Frankfurt am Main, Germany
The validity of this certificate depends on the validity of the main certificate.

Environmental Management Compliance (Wuxi, China)

CERTIFICATE

dqs

This is to certify that the site

Sigma-Aldrich (Wuxi) Life Science & Technology Co., Ltd.

is part of the certified **Management System** of the organization
Merck KGaA
with the main certificate registration no.

according to

ISO 14001 :

Scope:
Packaging of bio-chemical reagent products (non-medicinal) and manufacture of disposal bio processing bags.

Certificate registration no.
Date of revision
Valid from
Valid until
Issuing date

IAF

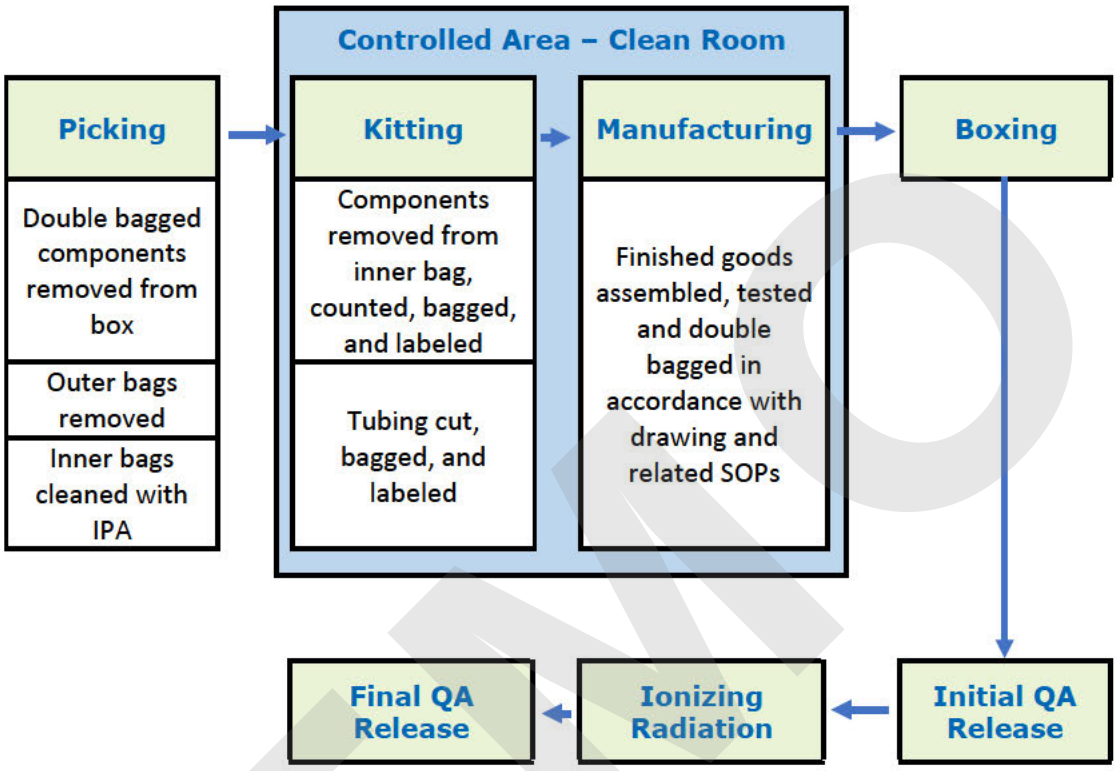
DAkkS
Deutsche Akkreditierungsstelle
D-ZM-16074-01-00

DQS GmbH

DQS IS A MEMBER OF
IQNET

Accredited Body: DQS GmbH, August-Schanz-Straße 21, 60433 Frankfurt am Main, Germany
Responisble Office: DQS AP Ltd.,906-907, Waterfront Place Block E, No.31,Lane 168, Daduhe Road, Putuo District, Shanghai, China, Post Code: 200062
The validity of this certificate depends on the validity of the main certificate and can only be verified by the QR-code.

Manufacturing Process Flow Diagram



Certificates of Quality

Each product is supplied with a Certificate of Quality which assures that each lot of assemblies is manufactured, tested, and released to the specifications presented on the certificate. This certificate provides the quality characteristics and acceptance criteria for each assembly. Each certificate lists the catalog and the lot number of the assembly as well as the test criteria for release. Contact Technical Service for Certificates of Quality.

Sample Certificate of Quality

Danvers, MA, USA

Disposable Assembly with Mobius® Technology, Silver

Catalogue Number: SAMPLE
Lot Number: SAMPLE
Expiration Date: SAMPLE
Drawing Revision: SAMPLE

Good Manufacturing Practices
This product was manufactured in an EMD Millipore facility which adheres to Good Manufacturing Practices.

ISO® 9001 Quality Standard
This product was developed in an EMD Millipore facility whose Quality Management System is approved by an accredited registering body to the appropriate ISO 9001 Quality Systems Standard.

Validated Production Process
This Product was fabricated using a validated manufacturing process. Principles of statistical process control and determinations of process capability have been applied to critical process variables. In-process controls are used to assure stability of the process.

Quality Assurance Lot Release Criteria
Each assembly of this manufacturing lot was tested and released to the following characteristics:

Critical Dimensions
Measurements are taken on assemblies to assure dimensional compliance with EMD Millipore specifications and tolerances.

Leak Integrity Testing In Manufacturing
In-process testing was performed on this lot to ensure leak integrity using a pressure decay method.

Appearance and Cleanliness
Each assembly has been visually inspected with an unaided eye per manufacturing work instructions and test specifications. The assembly meets the Quality Assurance release criteria.

Gamma Irradiation
Each assembly has been sterilized using a validated gamma irradiation level of 25-40 kGy.

Validation of Product Design
A risk based approach was utilized in the design and manufacture for this configured product to meet the following specifications.

Sterility
Quarterly dose audits are performed on representative samples to AAMI guidelines to ensure a Sterility Assurance Level (SAL) of 10^{-6} for assembly fluid path.

USP Bacterial Endotoxin
Quarterly performance review of extracts from representative samples of assemblies contain less than 0.25EU/mL per USP <85> as determined by the Limulus Amebocyte Lysate (LAL) test.

Particulates
Quarterly performance review of extracts from representative samples of assemblies that have been tested per USP <788>.

Component Materials Toxicity
Family component materials were tested post gamma irradiation and meet the criteria for the USP <88>, Biological Reactivity Test for class VI plastics. This product also meets USP <661> for Physico-chemical tests for plastic containers.

Shipping Test
Representative assemblies were tested and passed the ISTA Integrity-Plus Test Procedure 2A standard.

Stability Study
Studies support a shelf life of 2 years for functionality and sterility.

Molsheim, France

Millipore®

www.sigmaaldrich.com

Certificate of Quality

Disposable Assembly with Mobius® Technology, Silver

Catalogue Number : SAMPLE
Lot Number : SAMPLE
Expiry Date : DD-MMM-YYYY
Drawing Revision : X

We certify that the product described herein meets the following criteria.

Good Manufacturing Practices

This product was manufactured in a Millipore SAS facility which adheres to Good Manufacturing Practices.

ISO® 9001 Quality Standard

This product was developed in a Millipore SAS facility whose Quality Management System is approved by an accredited registering body to the appropriate ISO 9001 Quality Systems Standard

Validated Production Process

This Product was fabricated using a validated manufacturing process. Principles of statistical process control and determinations of process capability have been applied to critical process variables. In-process controls are used to assure stability of the process.

Quality Assurance Lot Release Criteria

Each assembly of this manufacturing lot was tested and released to the following characteristics:

Critical Dimensions

Measurements are taken on assemblies to assure dimensional compliance with Millipore SAS specifications and tolerances.

Leak Integrity Testing in Manufacturing

In process testing was performed on this lot to ensure leak integrity using a pressure decay method.

Appearance and Cleanliness

Each assembly has been visually inspected with an unaided eye per manufacturing work instructions and test specifications. The assembly meets the Quality Assurance release criteria.

Gamma Irradiation

Each assembly has been sterilized using a validated gamma irradiation level of 25-40 kGy.

Validation of Product Design

A risk based approach was utilized in the design and manufacture for this configured product to meet the following specifications.

Sterility

Quarterly dose audits are performed on representative samples to AAMI guidelines to ensure a Sterility Assurance Level (SAL) of 10^{-6} for assembly fluid path.

USP Bacterial Endotoxin

Quaterly performance review of extracts from representative samples of assemblies contain less than 0.25 EU/mL per USP <85> as determined by the Limulus Amebocyte Lysate (LAL) test.

Particulates

Quaterly performance review of extracts from representative samples of assemblies that have been tested per USP <788>.

Component Material Toxicity

Family component materials were tested post gamma irradiation and meet the criteria for the USP <88>, Biological Reactivity Test for class VI plastics. This product also meets USP <661> for Physico-chemical tests for plastic containers.

Shipping Test

Representative assemblies were tested and passed the ISTA Integrity-Plus Test Procedure 2A standard.

Stability Study

Studies support a shelf life of 2 years for functionality and sterility.

According to the above results, the product complies with Millipore SAS's acceptance criteria and is released.

This document has been produced electronically and is valid without a signature

Head of Mobius Quality, Molsheim France

N° ManGo template 20341412 Version 3.0 / N° ManGo certificate 20575992 Version 1.0

Disposable Assembly with Mobius® Technology, Silver

Catalogue Number:
Lot Number:
Expiration Date:
Drawing Revision:

Good Manufacturing Practices
This product was manufactured in an EMD Millipore facility which adheres to Good Manufacturing Practices.

ISO® 9001 Quality Standard
This product was developed in an EMD Millipore facility whose Quality Management System is approved by an accredited registering body to the appropriate ISO 9001 Quality Systems Standard.

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This Product was fabricated using a validated manufacturing process. Principles of statistical process control and determinations of process capability have been applied to critical process variables. In-process controls are used to assure stability of the process.

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Critical Dimensions
Measurements are taken on assemblies to assure dimensional compliance with EMD Millipore specifications and tolerances.

Leak Integrity Testing in Manufacturing
In-process testing was performed on this lot to ensure leak integrity using a pressure decay method.

Appearance and Cleanliness
Each assembly has been visually inspected with an unaided eye per manufacturing work instructions and test specifications. The assembly meets the Quality Assurance release criteria.

Gamma Irradiation
Each assembly has been sterilized using a validated gamma irradiation level of 25-40 kGy.

Validation of Product Design
A risk based approach was utilized in the design and manufacture for this configured product to meet the following specifications.

Sterility
Quarterly dose audits are performed on representative samples to AAMI guidelines to ensure a Sterility Assurance Level (SAL) of 10^{-6} for assembly fluid path.

USP Bacterial Endotoxin
Quarterly performance review of extracts from representative samples of assemblies contain less than 0.25EU/mL per USP <85> as determined by the Limulus Amebocyte Lysate (LAL) test.

Particulates
Quarterly performance review of extracts from representative samples of assemblies that have been tested per USP <788>.

Component Materials Toxicity
Family component materials were tested post gamma irradiation and meet the criteria for the USP <88>, Biological Reactivity Test for class VI plastics. This product also meets USP <661> for Physico-chemical tests for plastic containers.

Shipping Test
Representative assemblies were tested and passed the ISTA Integrity-Plus Test Procedure 2A standard.

Stability Study
Studies support a shelf life of 2 years for functionality and sterility.

20348244 Version 5.0

Specifications

Design Criteria

Sterility	Quarterly dose audits are performed on representative samples to AAMI guidelines to ensure a Sterility Assurance Level (SAL) of 10^{-6} for assembly fluid path.
USP Bacterial Endotoxin	Quarterly performance review of extracts from representative samples of assemblies contain less than 0.25 EU/mL per USP <85> as determined by the Limulus Amebocyte Lysate (LAL) test.
Particulates	Quarterly performance review of extracts from representative samples of assemblies that have been tested per USP <788>.
Component Material Toxicity	Family component materials were tested post gamma irradiation and meet the criteria for the USP <88>, Biological Reactivity Test for Class VI Plastics. This product also meets USP <661> for Physico-chemical tests for plastic containers.
Shipping Test	Representative assemblies were tested and passed the ISTA Integrity-Plus Test Procedure 2A standard.
Stability Study	Studies support a shelf life of 2 years for functionality and sterility.

Release Criteria

Critical Dimensions	Measurements are taken on assemblies to assure dimensional compliance with EMD Millipore specifications and tolerances.
Leak Integrity Testing in Manufacturing	In-process testing was performed on this lot to ensure leak integrity using a pressure decay method.
Appearance and Cleanliness	Each assembly has been visually inspected with an unaided eye per manufacturing work instructions and test specifications. The assembly meets the Quality Assurance release criteria.
Gamma Irradiation	Each assembly has been sterilized using a validated gamma irradiation level of 25-40 kGy.

Manufacturing Information

Country of Origin	U.S.A.	China	France
Manufacturing Location	Danvers, MA	Wuxi	Molsheim
Standard Warranty	The applicable warranty for the products listed in this publication may be found on our website within the "Terms and Conditions of Sale" applicable to your purchase transaction.		
Change Notification	Our worldwide Change Management procedure assures that our customers are notified in a timely manner of change(s) that might impact an end-user's process, procedure, product, or documents. A Change Notification policy, using a risk-based approach, considering the declared end use of the product, is industry best-practice. A customer notification is provided to customers who opt-in to receive notifications on customer-defined critical raw material.		

Test Summaries and Results

Component Material Toxicity

The following tests were performed on representative components to support Mobius® Silver assemblies.

USP <88> Biological Reactivity Tests for Class VI Plastics

Test Summary

Systemic and intracutaneous extract injections as well as intramuscular implantations were performed by an independent laboratory to determine the toxicity of Silver Single-use components and their suitability for contact with parenterals. Representative components of Silver Single-use Assemblies were gamma irradiated to >40 kGy then submitted for USP Class VI testing. These studies were conducted based on the USP <88> Biological Reactivity tests, In Vivo.

Results

All components of Silver Single-use Assemblies are non-toxic per USP Class VI biological tests for plastics.

Independent laboratory certificates can be viewed during a scheduled audit.

USP <661> Physicochemical Testing for Plastic Containers

Test Summary

Family component materials for Silver Single-use Assemblies were tested by a qualified contract laboratory per USP <661> for Physicochemical testing to determine physical and chemical properties. Representative components of Silver Single-use Assemblies were gamma irradiated to >40 kGy then submitted for USP <661> testing.

Extracts were tested for the following under USP <661>:

- Heavy Metals: to detect and identify the presence of metals in the extract.
- Buffering Capacity: to measure the alkalinity or acidity of the extract.
- Non-Volatile Residue: to measure the organic/inorganic residues soluble in the extract.
- Residue on Ignition: to measure the weight of residual substances not volatilized after the extract is ignited.

Results

Silver Mobius® Single-use components pass the requirements of USP <661>.

Independent laboratory certificates can be viewed during a scheduled audit.

Appearance and Cleanliness

Visual inspection is performed on all Mobius® assemblies during manufacturing.

Test Summary

Inspection is performed without magnification and with adequate lighting, i.e. normal room lighting, a light table and also a black inspection background. Inspect the assembly at a distance of 12 to 18 inches (standard arm's length), using the unaided eye. For general inspection, scan the entire surface of the object being inspected. Average inspection time is 5 to 20 sec per square foot.

Quality Assurance Release Criteria

Visual Acceptance Criteria - Manufacturing

Visual acceptance release criteria in manufacturing includes the following specific to hair, loose particles, embedded particles, and gels. Particle matter is measured using TAPPI Standard 0109 DIRTT (size estimation chart).

Particle Type	Maximum Quality Limit
Hair	0
Loose particles on the device or in packaging	0

Embedded Black, Brown, White or Gray Particle Matter (no other colors are acceptable) and Gel Pellets or Gel Spots

Article or Assembly Bag Size (L)	Maximum Number of ≤1.50 mm^2 Particles	Maximum Number of ≤1.50 mm^2 Pellets*
Tubing assemblies without an assembly bag	2	2
≤ 10	2	2
11 – 50	3	3
51 – 199	5	5
200 – 499	7	7
500 – 999	9	9
1000 – 3500	11	11

*Gel Pellets: Any quantity under 1 mm^2 is acceptable for all bag sizes.

Visual Acceptance Criteria – Customer Returns

Since returned assemblies are handled outside of cleanroom areas, the below visual acceptance criteria are used for customer returns. Particle matter is measured using TAPPI Standard 0109 DIRTT (Size estimation chart).

Particle Type	Maximum Quality Limit
Hair	0

Embedded Black, Brown, White or Gray Particle Matter (no other colors are acceptable) and Gel Pellets or Gel Spots

Article or Assembly Bag Size (L)	Maximum Quality Limit	
	Maximum Number of ≤1.50 mm^2 Particles	Maximum Number of ≤1.50 mm^2 Pellets*
Tubing assemblies without an assembly bag	2	2
≤ 10	2	2
11 – 50	3	3
51 – 199	5	5
200 – 499	7	7
500 – 999	9	9
1000 – 3500	11	11

*Gel Pellets: Any quantity under 1 mm^2 is acceptable for all bag sizes.

Loose Particles

Article or Assembly Bag Size (L)	Maximum Quality Limit	
	Loose ≤ 0.40 mm^2 particles in the fluid path	Loose ≤ 1.5 mm^2 particles outside the fluid path
Tubing assemblies without an assembly bag	2	2
≤ 10	2	2
11 – 50	3	3
51 – 199	5	5
200 – 499	7	7
500 – 999	9	9
1000 – 3500	11	11

Additional Guidance on Visual Observations

Upon inspection of our single-use assemblies, end-users may identify visual observations. Our classification of these observations aligns with BioPhorum's 'Single-Use system (SUS) Visual Observation Library'.

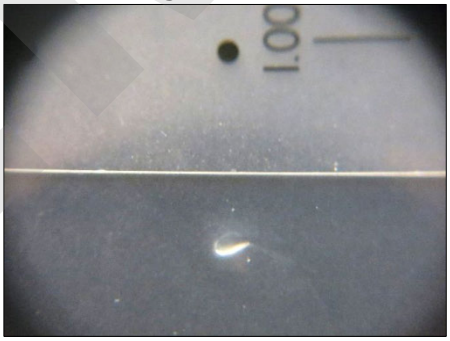
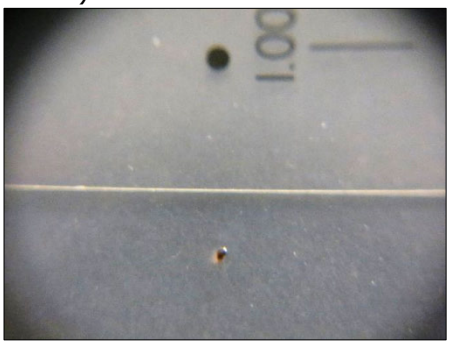
Note: This section is only meant to provide guidance to end users. It is not meant to serve as visual inspection acceptance criteria.

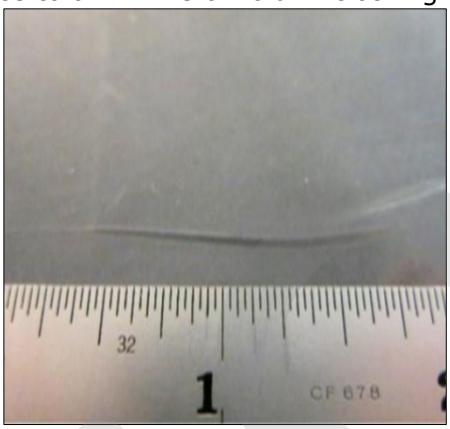
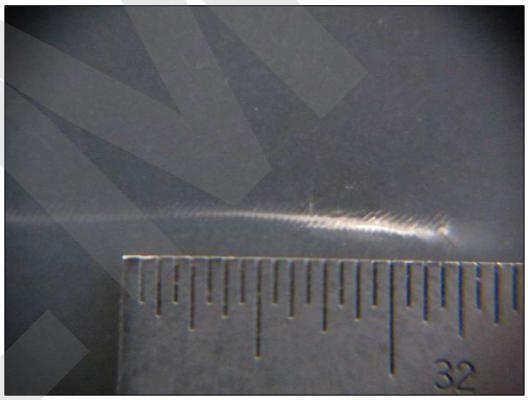
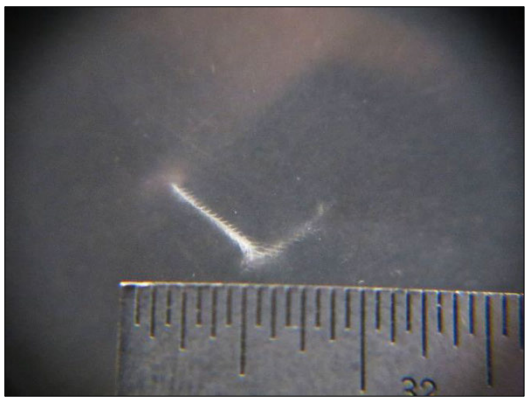
Film Observations

Film markings, created typically during film manufacture, assembly, or during customer handling/use, do not impact the assembly's performance. The table below outlines primary examples of film observations.

Inspections of the assembly should only be performed when deemed necessary, as a result of the customer's risk assessment. Increased handling of the assembly has been shown to increase the risk of damage and the presence of markings to the film significantly. Only a quick and careful inspection is recommended as the assembly is being loaded into the carrier/bins/Mixer to reduce handling.

In the event a specific film marking causes concern, please reach out to your local Single-Use Technical Application Specialist for assistance.

Observation Type	Potential Originating Cause	Definition and Photo
Gel Pellets	During film manufacture	A spot of unmelted resin embedded within the film. Clear in appearance; can feel like a raised bump, sometimes with a rough surface texture  *Gel Pellet Example. Camera Image Taken Through a 5X Eye Loupe.*
Embedded Particles	During film manufacture	Any colored material contained within the film that cannot be dislodged. Appears colored, usually black, brown, or grey; can feel raised to the touch (not a smooth surface)  *Brown Embedded Particle Example #1. Camera Image Taken Through a 5X Eye Loupe*

Observation Type	Potential Originating Cause	Definition and Photo
Creases	During film manufacture	A line that spans across the film. Similar appearance to a wrinkle or fold in clothing 
Zipper/Chevron Marks	During assembly or customer handling/use	A straight, curved or V-shaped line in the film consisting of a host of smaller angled lines, giving the film marking a zipper-like appearance. May be raised to the touch  *Zipper Example. Camera Image Taken Through a 5X Eye Loupe.*  *Chevron Example. Camera Image Taken Through a 5X Eye Loupe.*

Observation Type	Potential Originating Cause	Definition and Photo
Scratch	During assembly or customer handling/use	Score or mark on the film surface with a sharp or pointed object. smooth or rough edges dependent on origin of the scratch; may be tactile 

Leak Integrity Testing in Manufacturing

Test Summary

In-process samples from each lot of Silver Assemblies are leak tested using a pressure decay method. The assemblies are pressurized at a set pressure for a stabilization time, both of which are based on assembly volume. The detectable defect size is based on the total internal volume of the assembly. For example, if there are (3) 5L bags in an assembly, then the total internal volume is 15L and the detectable defect size would be 1000µm. The final pressure of the assembly, at the end of the test cycle, must meet the acceptance criteria.

Total Assembly Volume (L)	Detectable Defect Size (µm)
Non-bag assemblies	50
1 – 9	150
10 – 999	1000
1000 and above	2000

Results

All released assemblies met specifications. Data is within the lot record of the released product and may be viewed during a scheduled audit.

Bacterial Endotoxin

Test Summary

As part of component validation, representative components of Single-use assemblies were gamma irradiated to ≥ 40 kGy then submitted for testing at an approved independent laboratory per USP <85>. The Assembly must contain less than 0.25 EU/mL per USP <85> as determined by the Limulus Amebocyte Lysate (LAL) test.

As part of product release for Mobius® Silver assemblies, quarterly performance review of extracts from representative samples of assemblies must contain less than 0.25 EU/mL per USP <85> as determined by the Limulus Amebocyte Lysate (LAL) test.

Milli-Q® water is added to the assembly fluid path and held for 60 minutes. The assembly is agitated at the beginning and end of the holding period to ensure that water reaches all surface areas of the container. If the assembly is a tube set, the entire fluid path is filled. If the assembly includes a bag, 10% of the bag's volume is added. After the holding period, the water is drained from the assembly and saved as the extract for testing.

Solutions of assembly extracts were mixed with Limulus Amebocyte Lysate. A reaction at different dilutions indicates the maximum level of endotoxins present. The test results determine the level of endotoxins contained within the assembly.

Results

Extracts met the specification of < 0.25 EU/mL.

For each representative component, a validation report is on file and a summary of the report may be viewed during a scheduled audit.

Quarterly performance review data is on file and may be viewed during a scheduled audit.

Particulates

Test Summary

As part of component validation, representative components of Silver Single use assemblies were submitted for testing at an approved independent laboratory per USP <788>.

As part of product release for Mobius® Silver Assemblies, quarterly performance reviews of extracts from representative samples meet the particulate specification per USP <788>.

Milli-Q® water is added to the assembly fluid path and held for 60 minutes. The assembly is agitated at the beginning and end of the holding period to ensure that water reaches all surface areas of the container. If the assembly is a tube set, the entire fluid path is filled. If the assembly includes a bag, 10% of the bag's volume is added. After the holding period, the water is drained from the assembly and saved as the extract for testing.

Method 1 is routinely performed, and particle counts are conducted assuming a sample extraction volume. Method 2 is used only if results from Method 1 are inconclusive.

Method 2 particle count tests are conducted on a filter membrane through which a sample extraction volume is filtered. The sample must meet one of the following criteria.

USP <788> Specification

Method	Particle Size Range (µm)	Maximum Particles/Sample
Method 1	≥ 10	6000
	≥ 25	600
Method 2	≥ 10	3000
	≥ 25	300

Results

Extracts met the requirements of USP <788> Particulates.

A validation report is on file for each component and a summary of the report may be viewed during a scheduled audit.

Test results of representative Mobius® Gold Assemblies are leveraged for our Mobius® Silver assemblies based on quarterly performance reviews of extracts using Method 1 and are summarized below. Samples meet the particulate specification per USP <788>.

Catalog Number	Lot Number	Average Particles per Sample	
		≥ 10 µm	≥ 25 µm

Extractables Data

Introduction

The Extractables data presented in this section establishes a basis for risk assessment of the Mobius® Single-Use Assembly, by providing information on the compounds that may be extracted during usage. Each of the reports identified in the 'Assembly Component Information' section provides information on the tested component, including the study design, combined organic extractables results and elemental impurities. The estimated concentrations represent the highest concentration observed per model solvent across all lots.

The test methods employed in these studies are based on best practices per BioPhorum's best practices guide 'Extractables testing of polymeric single-use components used in biopharmaceutical manufacturing (2020)'[1] and the USP chapter <665> 'Polymeric Components and Systems Used in the Manufacturing of Pharmaceutical'[2].

The end user is responsible for interpreting this data to determine what additional studies may need to be conducted based on their installation.

In addition to these results, the Operational Excellence Dossier for the individual filters, connectors and films can be accessed through an Emprove® Suite subscription, with results reported per each analytical method.

[1] BioPhorum best practices guide, Extractables testing of polymeric single-use components used in biopharmaceutical manufacturing (2020)
[2] U.S. Pharmacopeia <665>, (2021). Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products.

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	
Analytical methods	**Comment**
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, 0.5 N NaOH, H_2O

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O						LC-UV-MS				
H_2O										0.061
H_2O						LC-UV-MS				
H_2O		-	7.37							
0.1 M H_3PO_4		N/A				LC-UV-MS				
0.5 N NaOH										0.094
0.5 N NaOH	Octadecanol								ND	0.066
0.5 N NaOH										
0.5 N NaOH										
50% EtOH						DI-GC-MS				
50% EtOH	Palmitic acid	57-10-3								1.0
50% EtOH										
50% EtOH							0.016			
50% EtOH							0.016	ND	0.17	0.31
50% EtOH	Unknown	-								

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1			
Cadmium	Cd	1		ND	ND
Mercury	Hg	1	3.3E-03		
Lead	Pb	1			ND
Cobalt	Co	2A		ND	
Nickel	Ni	2A	3.3E-03		
Vanadium	V	2A			
Silver	Ag	2B			ND
Gold	Au	2B	3.3E-03		
Iridium	Ir	2B		ND	
Osmium	Os	2B			ND
Palladium	Pd	2B	3.3E-03		
Platinum	Pt	2B			
Rhodium	Rh	2B			ND
Ruthenium	Ru	2B	3.3E-03		
Selenium	Se	2B			ND
Thallium	Tl	2B		ND	
Barium	Ba	3	3.3E-03		ND
Chromium	Cr	3		ND	
Copper	Cu	3			

Lithium	Li	3			ND
Molybdenum	Mo	3	3.3E-03		
Antimony	Sb	3		ND	
Tin	Sn	3			
Aluminum	Al	N/A		ND	
Calcium	Ca	N/A	0.032		ND
Iron	Fe	N/A	0.018		
Germanium	Ge	N/A			
Magnesium	Mg	N/A		0.0112	
Manganese	Mn	N/A	3.3E-03		
Titanium	Ti	N/A		ND	
Zinc	Zn	N/A			
Zirconium	Zr	N/A			ND

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	
Analytical methods	**Comment**
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O
NVR	
pH	0.1 M H_3PO_4, 0.5 N NaOH, H_2O

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)		
							RL	30 minutes	24 hours
H_2O		151-41-7						1.6	
H_2O	Trimethylsilanol			T					
H_2O						LC-UV-MS			0.71
H_2O						HS-GC-MS			0.66
H_2O			0.38		External		0.25		
H_2O	Unknown			U		LC-UV-MS			
H_2O	Acetone	67-64-1	3.46	T					0.30
0.1 M H_3PO_4					External			2.2	
0.1 M H_3PO_4	Trimethylsilanol		6.65			HS-GC-MS	0.25		12
0.1 M H_3PO_4			19.86	T					
0.1 M H_3PO_4	Unknown				External				
0.1 M H_3PO_4			3.46			HS-GC-MS		ND	
0.5 N NaOH	Bisphenol A			I	Authentic				
0.5 N NaOH			6.66	T					36
0.5 N NaOH	Hexamethyldisiloxane	107-46-0			Internal				

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1			ND
Cadmium	Cd	1	7.9E-03		
Mercury	Hg	1		ND	
Lead	Pb	1	7.9E-03		
Cobalt	Co	2A			ND
Nickel	Ni	2A			
Vanadium	V	2A	7.9E-03		ND
Silver	Ag	2B			
Gold	Au	2B	7.9E-03		
Iridium	Ir	2B			ND
Osmium	Os	2B	7.9E-03		
Palladium	Pd	2B			
Platinum	Pt	2B		ND	
Rhodium	Rh	2B	7.9E-03		
Ruthenium	Ru	2B		ND	
Selenium	Se	2B	0.079		ND
Thallium	Tl	2B			ND
Barium	Ba	3	7.9E-03		
Chromium	Cr	3			
Copper	Cu	3	7.9E-03		ND

Lithium	Li	3	7.9E-03		
Molybdenum	Mo	3			
Antimony	Sb	3			ND
Tin	Sn	3		ND	
Aluminum	Al	N/A	7.9E-03		ND
Calcium	Ca	N/A	0.79		
Iron	Fe	N/A	0.16		
Germanium	Ge	N/A			ND
Magnesium	Mg	N/A			
Manganese	Mn	N/A	7.9E-03		
Titanium	Ti	N/A	0.079		ND
Zinc	Zn	N/A			
Zirconium	Zr	N/A			ND

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
pH 10 Buffer	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	

Analytical methods	Comment
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O, pH 10 Buffer
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, 0.5 N NaOH, H_2O, pH 10 Buffer

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O					Internal					1.8
H_2O	Unknown PEG	-				LC-UV-MS				
H_2O				U	Internal		0.016			
H_2O	Unknown (m/z 148)	-				LC-UV-MS			0.37	0.62
H_2O						LC-UV-MS				0.40
H_2O					Internal			0.030		0.35
H_2O							0.016	ND		
H_2O					Internal	LC-UV-MS				ND
H_2O	Unknown PEG					LC-UV-MS	0.016			
H_2O	Unknown	-	0.91	U	Internal					
H_2O	Unknown (m/z 206)									
H_2O						LC-UV-MS				ND
H_2O	Unknown (m/z 162)	-	1.93	U					ND	0.084
H_2O					Internal					0.060
H_2O	Unknown siloxane					DI-GC-MS			ND	0.054

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1	3.4E-03		
Cadmium	Cd	1			
Mercury	Hg	1			ND
Lead	Pb	1		ND	
Cobalt	Co	2A	3.4E-03		
Nickel	Ni	2A			ND
Vanadium	V	2A	3.4E-03		
Silver	Ag	2B			
Gold	Au	2B	3.4E-03		ND
Iridium	Ir	2B		ND	
Osmium	Os	2B	3.4E-03		ND
Palladium	Pd	2B		ND	
Platinum	Pt	2B			
Rhodium	Rh	2B	3.4E-03		ND
Ruthenium	Ru	2B			ND
Selenium	Se	2B		ND	
Thallium	Tl	2B	3.4E-03		
Barium	Ba	3			ND
Chromium	Cr	3			
Copper	Cu	3			0.0213

Lithium	Li	3	3.4E-03		
Molybdenum	Mo	3			ND
Antimony	Sb	3	3.4E-03		
Tin	Sn	3		ND	
Aluminum	Al	N/A			0.041
Calcium	Ca	N/A	0.033		
Iron	Fe	N/A			0.0622
Germanium	Ge	N/A	NA		
Magnesium	Mg	N/A			
Manganese	Mn	N/A	3.4E-03		
Titanium	Ti	N/A			ND
Zinc	Zn	N/A	3.4E-03		
Zirconium	Zr	N/A			ND

Table 4. Revision History

Section	Change Description

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
pH 10 Buffer	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	
Analytical methods	**Comment**
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O, pH 10 Buffer
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, H_2O

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O							0.017	ND		
H_2O	Tetrahydrofuran				Internal	HS-GC-MS				
H_2O										0.018
0.1 M H_3PO_4	Unknown									
0.5 N NaOH						DI-GC-MS			ND	0.052
0.5 N NaOH	Acetone					HS-GC-MS				
pH 10 Buffer	Palmitic acid					DI-GC-MS				0.42
pH 10 Buffer					Internal					0.36
pH 10 Buffer	(E)-9-Octadecene									
pH 10 Buffer	3-[1-Hydroxy-3,5-bis(2-methyl-2-propanyl)-4-oxo-2,5-cyclohexadien-1-yl]propanoic acid									
pH 10 Buffer				U	External					0.018
50% EtOH	(E)-9-Octadecene					DI-GC-MS				
50% EtOH				I	Internal				0.18	0.26
50% EtOH	Stearic acid				Internal					

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1			ND
Cadmium	Cd	1	3.3E-03		
Mercury	Hg	1			ND
Lead	Pb	1	3.3E-03		
Cobalt	Co	2A			ND
Nickel	Ni	2A		ND	
Vanadium	V	2A	3.3E-03		
Silver	Ag	2B			ND
Gold	Au	2B	3.3E-03		
Iridium	Ir	2B			ND
Osmium	Os	2B	3.3E-03		
Palladium	Pd	2B			ND
Platinum	Pt	2B		ND	
Rhodium	Rh	2B		ND	
Ruthenium	Ru	2B			
Selenium	Se	2B	4.2E-03		
Thallium	Tl	2B			ND
Barium	Ba	3		ND	
Chromium	Cr	3	3.3E-03		
Copper	Cu	3			ND

Lithium	Li	3			ND
Molybdenum	Mo	3	3.3E-03		
Antimony	Sb	3		ND	
Tin	Sn	3	3.3E-03		
Aluminum	Al	N/A		ND	
Calcium	Ca	N/A	8.3E-03		ND
Iron	Fe	N/A			0.00465
Germanium	Ge	N/A	3.3E-03		
Magnesium	Mg	N/A		0.00566	
Manganese	Mn	N/A	3.3E-03		
Titanium	Ti	N/A			ND
Zinc	Zn	N/A	4.2E-03		
Zirconium	Zr	N/A		ND	

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
70 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	

Analytical methods	Comment
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, 0.5 N NaOH, H_2O

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O				T						0.32
H_2O										
H_2O					Internal					0.12
H_2O							0.016			
H_2O	Unknown Siloxane									
H_2O	Unknown (m/z 184)					LC-UV-MS				
H_2O									ND	0.030
H_2O	Ethoxytrimethylsilane					HS-GC-MS	0.016			
H_2O										
H_2O									ND	ND
H_2O										
H_2O									ND	0.025
0.1 M H_3PO_4					Internal					
0.1 M H_3PO_4	Unknown (m/z 383,300,255)					DI-GC-MS				
0.1 M H_3PO_4	Methoxytrimethylsilanol				Internal	HS-GC-MS				

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1			ND
Cadmium	Cd	1	3.4E-03		
Mercury	Hg	1			ND
Lead	Pb	1		ND	
Cobalt	Co	2A			ND
Nickel	Ni	2A	3.4E-03		
Vanadium	V	2A		ND	
Silver	Ag	2B			
Gold	Au	2B	3.4E-03		ND
Iridium	Ir	2B	3.4E-03		
Osmium	Os	2B			ND
Palladium	Pd	2B		ND	
Platinum	Pt	2B			
Rhodium	Rh	2B		ND	
Ruthenium	Ru	2B	3.4E-03		
Selenium	Se	2B			ND
Thallium	Tl	2B		ND	
Barium	Ba	3			ND
Chromium	Cr	3	3.4E-03		
Copper	Cu	3			ND

Lithium	Li	3			ND
Molybdenum	Mo	3	3.4E-03		
Antimony	Sb	3		ND	
Tin	Sn	3	3.4E-03		ND
Aluminum	Al	N/A		ND	
Calcium	Ca	N/A	0.027		ND
Iron	Fe	N/A			ND
Germanium	Ge	N/A	NA		
Magnesium	Mg	N/A			ND
Manganese	Mn	N/A		ND	
Titanium	Ti	N/A	3.4E-03		ND
Zinc	Zn	N/A		ND	
Zirconium	Zr	N/A			

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
pH 10 Buffer	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	

Analytical methods	Comment
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O, pH 10 Buffer
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, 0.5 N NaOH, H_2O, pH 10 Buffer

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O									ND	0.11
H_2O	Pentanoic acid									
H_2O										
H_2O	Heptanoic acid									0.024
0.1 M H_3PO_4			0.76	U	Internal					
0.1 M H_3PO_4		142-62-1							0.061	0.13
0.1 M H_3PO_4		109-52-4	12.03	T	Internal					0.077
0.1 M H_3PO_4										0.024
0.1 M H_3PO_4		111-14-8								
0.5 N NaOH		111-27-3								0.022
0.5 N NaOH										
pH 10 Buffer	1-Hexanol				Internal					
pH 10 Buffer				U			0.017			0.018
50% EtOH	Erucamide		9.61	I			0.017			ND
50% EtOH				U						

50% EtOH							ND
50% EtOH	Pentanoic acid				DI-GC-MS	0.017	
50% EtOH	Hexanoic acid						
50% EtOH						0.017	
50% EtOH	3,5-Di-tert-butyl-4-hydroxyphenylpropionic acid	20170-32-5	7.49				0.028
50% EtOH			7.42				0.028
50% EtOH					DI-GC-MS	0.017	0.027
50% EtOH		565-60-6				0.017	0.019
50% EtOH	2-Octanone					0.017	0.018
50% EtOH			9.82	T			<RL

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1			ND
Cadmium	Cd	1	3.4E-03		
Mercury	Hg	1		ND	
Lead	Pb	1	3.4E-03		ND
Cobalt	Co	2A			
Nickel	Ni	2A		0.00442	
Vanadium	V	2A		ND	
Silver	Ag	2B	3.4E-03		ND
Gold	Au	2B	3.4E-03		
Iridium	Ir	2B			ND
Osmium	Os	2B		ND	
Palladium	Pd	2B			
Platinum	Pt	2B	3.4E-03		
Rhodium	Rh	2B		ND	
Ruthenium	Ru	2B			ND
Selenium	Se	2B	3.4E-03		
Thallium	Tl	2B			ND
Barium	Ba	3		ND	
Chromium	Cr	3	3.4E-03		ND
Copper	Cu	3			

Lithium	Li	3			
Molybdenum	Mo	3	3.4E-03		
Antimony	Sb	3			ND
Tin	Sn	3		ND	
Aluminum	Al	N/A	3.5E-03		0.00418
Calcium	Ca	N/A		0.0928	
Iron	Fe	N/A			
Germanium	Ge	N/A			ND
Magnesium	Mg	N/A		ND	
Manganese	Mn	N/A	3.4E-03		
Titanium	Ti	N/A			ND
Zinc	Zn	N/A	3.4E-03		
Zirconium	Zr	N/A			ND

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
pH 10 Buffer	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	
Analytical methods	**Comment**
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O, pH 10 Buffer
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, 0.5 N NaOH, H_2O, pH 10 Buffer

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O										
H_2O							0.017			
H_2O						LC-UV-MS	0.017			
H_2O					Internal					
H_2O					Internal	LC-UV-MS	0.017			
H_2O	7,9-Di-tert-butyl-1-oxa-spiro[4.5]deca-6,9-diene-2,8-dione			T						
0.1 M H_3PO_4							0.017			
0.1 M H_3PO_4						LC-UV-MS	0.017			0.038
0.5 N NaOH										0.99
0.5 N NaOH							0.017			
0.5 N NaOH	7,9-Di-tert-butyl-1-oxa-spiro[4.5]deca-6,9-diene-2,8-dione					LC-UV-MS	0.017			0.062
pH 10 Buffer					Internal					
pH 10 Buffer								ND		ND
50% EtOH										0.80
50% EtOH	7,9-Di-tert-butyl-1-oxa-spiro[4.5]deca-6,9-diene-2,8-dione								0.031	

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1		ND	ND
Cadmium	Cd	1	3.4E-03		
Mercury	Hg	1			ND
Lead	Pb	1		ND	
Cobalt	Co	2A	3.4E-03		
Nickel	Ni	2A			0.0107
Vanadium	V	2A		ND	
Silver	Ag	2B	3.4E-03		
Gold	Au	2B			ND
Iridium	Ir	2B		ND	
Osmium	Os	2B	3.4E-03		
Palladium	Pd	2B		ND	
Platinum	Pt	2B	3.4E-03		ND
Rhodium	Rh	2B			
Ruthenium	Ru	2B		ND	
Selenium	Se	2B	3.4E-03		ND
Thallium	Tl	2B			ND
Barium	Ba	3		ND	
Chromium	Cr	3			ND
Copper	Cu	3	3.4E-03		

Lithium	Li	3	3.4E-03		
Molybdenum	Mo	3			ND
Antimony	Sb	3		ND	
Tin	Sn	3	3.4E-03		
Aluminum	Al	N/A		0.0829	
Calcium	Ca	N/A		0.0564	0.0621
Iron	Fe	N/A	0.019		
Germanium	Ge	N/A			ND
Magnesium	Mg	N/A	0.024		
Manganese	Mn	N/A	3.4E-03		
Titanium	Ti	N/A			ND
Zinc	Zn	N/A			0.00433
Zirconium	Zr	N/A			

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
pH 10 Buffer	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	

Analytical methods	Comment
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O, pH 10 Buffer
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, 0.5 N NaOH, H_2O, pH 10 Buffer

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O							0.017	ND	ND	0.063
H_2O	Unknown (m/z 134)									
H_2O									ND	0.029
H_2O				U						
H_2O						LC-UV-MS				
H_2O							0.017			0.019
H_2O										ND
0.1 M H_3PO_4						LC-UV-MS	0.017			
0.1 M H_3PO_4		-								0.060
0.1 M H_3PO_4										
0.1 M H_3PO_4							0.017			0.031
0.1 M H_3PO_4			5.86							
0.1 M H_3PO_4	7,9-Di-tert-butyl-1-oxaspiro(4,5) deca-6,9-diene-2,8-dione				Internal					
0.1 M H_3PO_4					Internal				ND	0.019
0.5 N NaOH	Unknown (m/z 210)				Internal					

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1			ND
Cadmium	Cd	1	3.4E-03		
Mercury	Hg	1	3.4E-03		ND
Lead	Pb	1		ND	
Cobalt	Co	2A	3.4E-03		
Nickel	Ni	2A			ND
Vanadium	V	2A		ND	
Silver	Ag	2B	3.4E-03		
Gold	Au	2B			ND
Iridium	Ir	2B		ND	
Osmium	Os	2B	3.4E-03		
Palladium	Pd	2B			ND
Platinum	Pt	2B		ND	
Rhodium	Rh	2B			
Ruthenium	Ru	2B	3.4E-03		ND
Selenium	Se	2B	3.4E-03		
Thallium	Tl	2B			ND
Barium	Ba	3		ND	
Chromium	Cr	3	3.4E-03		
Copper	Cu	3			ND

Lithium	Li	3	3.4E-03		
Molybdenum	Mo	3			ND
Antimony	Sb	3	3.4E-03	ND	
Tin	Sn	3			ND
Aluminum	Al	N/A	3.6E-03		0.00761
Calcium	Ca	N/A	0.033		
Iron	Fe	N/A		ND	
Germanium	Ge	N/A			
Magnesium	Mg	N/A		ND	
Manganese	Mn	N/A			ND
Titanium	Ti	N/A			
Zinc	Zn	N/A		ND	
Zirconium	Zr	N/A		ND	

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Gamma irradiation	
Gamma Irradiation (per lot) (kGy)	
Time between gamma irradiation and extraction (Requirement is ≤ 8 weeks) (Days)	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
pH 10 Buffer	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	
Analytical methods	**Comment**
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O, pH 10 Buffer
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, H_2O

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O										
H_2O	Unknown									
0.1 M H_3PO_4						DI-GC-MS				
0.1 M H_3PO_4							0.017			
0.1 M H_3PO_4	Irgafos 168									
0.1 M H_3PO_4						LC-UV-MS	0.017			
0.5 N NaOH	2,4-Di-tert-butylphenol									
0.5 N NaOH						DI-GC-MS				
0.5 N NaOH	2,4-Di-tert-butylphenol				External					ND
NaOH										
0.5 N N										
0.5 N H	2-Methyl-2-propanol					HS-GC-MS	0.016			0.050
0.5 N Na										
	Unknown	-								
p Buffer						LC-UV-MS	0.017			0.021

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1			ND
Cadmium	Cd	1		ND	
Mercury	Hg	1	3.4E-03		ND
Lead	Pb	1	3.4E-03		
Cobalt	Co	2A			ND
Nickel	Ni	2A		ND	
Vanadium	V	2A			
Silver	Ag	2B	3.4E-03		ND
Gold	Au	2B		ND	
Iridium	Ir	2B	3.4E-03		
Osmium	Os	2B			ND
Palladium	Pd	2B		ND	
Platinum	Pt	2B	3.4E-03		
Rhodium	Rh	2B		ND	
Ruthenium	Ru	2B			ND
Selenium	Se	2B			
Thallium	Tl	2B	3.4E-03		
Barium	Ba	3		ND	
Chromium	Cr	3	3.4E-03		
Copper	Cu	3			ND

Lithium	Li	3			ND
Molybdenum	Mo	3		ND	
Antimony	Sb	3	3.4E-03		
Tin	Sn	3			ND
Aluminum	Al	N/A		0.00558	
Calcium	Ca	N/A			<RL
Iron	Fe	N/A	3.4E-03		
Germanium	Ge	N/A		ND	
Magnesium	Mg	N/A			
Manganese	Mn	N/A	3.4E-03		
Titanium	Ti	N/A			<RL
Zinc	Zn	N/A	3.4E-03		
Zirconium	Zr	N/A		ND	

Extractables Component Report R23

Table 1. Study Design

Test item information	
Test article name	
Test article part number	
Test article lot number(s)	
Pretreatment of test article	**Value(s)**
Other	
Other	
Extraction solvents	**Average Solvent loss (%)**
0.1 M H_3PO_4	
0.5 N NaOH	
50% EtOH	
H_2O	
Time Points	**Extraction temperature (°C)**
30 minutes	
24 hours	
21 days	
70 days	
Test Article Extraction Conditions	**Value(s)**
Extraction method	
Solvent start volume (mL)	
Solvent contact surface area (EFA for filter) (cm^2)	
Surface area to volume ratio (cm^2/mL)	
Description of extraction procedure	

Analytical methods	Comment
DI-GC-MS	
HS-GC-MS	
IC	
ICP	0.1 M H_3PO_4, H_2O
LC-UV-MS	0.1 M H_3PO_4, 0.5 N NaOH, 50% EtOH, H_2O
NVR	50% EtOH, H_2O
pH	
TOC	0.1 M H_3PO_4, 0.5 N NaOH, H_2O

Table 2. Grand summary of organic extractables, ranked by abundance per solvent

Solvent	Compound	CAS	RT (min)	ID Type	Standard used for Quantification	Method and Detection Mode	Highest result of all lots tested (µg/cm²)			
							RL	30 minutes	24 hours	21 days
H_2O										
H_2O		105-60-2								
H_2O							0.017			
H_2O	Unknown (m/z 280)			U						
0.1 M H_3PO_4										
0.1 M H_3PO_4						LC-UV-MS	0.017			
0.5 N NaOH									0.051	0.12
0.5 N NaOH						LC-UV-MS			ND	0.043
0.5 N NaOH	Unknown (m/z 252)					LC-UV-MS				
0.5 N NaOH						DI-GC-MS				0.056
0.5 N NaOH	2,4-Di-tert-butylphenol									
0.5 N NaOH										0.061
0.5 N NaOH					Internal					
0.5 N NaOH	1,2-Cyclohexen-oxide						0.017			
0.5 N NaOH				U						

Table 3. Grand summary of extractable elements

Notes: “-” indicates < 20 µg/L; "n.a." indicates not analyzed, "N/A" indicates ICH class is not applicable

Element	Symbol	ICH Q3D Class		Highest result of all lots tested (µg/cm²)	
			RL	H_2O	0.1 M H_3PO_4
Arsenic	As	1		ND	
Cadmium	Cd	1	3.3E-03		
Mercury	Hg	1			
Lead	Pb	1			ND
Cobalt	Co	2A	3.3E-03		
Nickel	Ni	2A		ND	
Vanadium	V	2A			ND
Silver	Ag	2B			
Gold	Au	2B		ND	
Iridium	Ir	2B	3.3E-03		
Osmium	Os	2B			ND
Palladium	Pd	2B		ND	
Platinum	Pt	2B	3.3E-03		
Rhodium	Rh	2B			ND
Ruthenium	Ru	2B			
Selenium	Se	2B	3.3E-03		
Thallium	Tl	2B		ND	
Barium	Ba	3		0.0133	
Chromium	Cr	3			
Copper	Cu	3	3.3E-03		

Lithium	Li	3	3.3E-03		
Molybdenum	Mo	3			ND
Antimony	Sb	3		ND	
Tin	Sn	3	3.3E-03		ND
Aluminum	Al	N/A		0.00467	
Calcium	Ca	N/A	0.032		0.75
Iron	Fe	N/A	0.019		
Germanium	Ge	N/A			ND
Magnesium	Mg	N/A	0.024		
Manganese	Mn	N/A		ND	
Titanium	Ti	N/A			
Zinc	Zn	N/A	3.3E-03		
Zirconium	Zr	N/A			ND

Regulatory Information

Animal Origin Declaration

Animal Origin Declaration

MIX Mobius®, Silver,

To the best of our knowledge and based on the information which we have received from our suppliers, we declare that tallow derivatives have been used during production of the above-mentioned product.

The processing conditions of the tallow derivatives comply with the "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMA/410/01 Rev. 3).

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Bisphenol A (BPA) Statement

Bisphenol A (BPA) Statement

MIX Mobius®, Silver,

Bisphenol A (BPA, CAS# 80-05-7) is a key component in the production of polycarbonate, epoxy resins, polysulfone and polyetherimide. For pharmaceutical applications, there are no specific requirements or guidelines that regulate the use of BPA, since the regulatory focus has been human exposure by food contact.

We declare that raw materials of the above-mentioned product are constructed from polysulfone and polycarbonate. The polysulfone and polycarbonate materials are manufactured using Bisphenol A (BPA).

As indicated by government agencies, the materials of concern for BPA in food and beverage containers are solely polycarbonate and epoxy resins.

We provide this information to the best of our knowledge and based on the information which we have received from our suppliers, but without obligation or liability. Customers remain responsible for complying with all applicable laws, and for determining the suitability of our products for the customer's intended purpose.

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DEHP Statement

DEHP Statement

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To the best of our knowledge and based on the information which we have received from our suppliers, we declare that raw materials used to manufacture this product may contain di(2-ethylhexyl)phthalate (DEHP) not above 0.1 %.

We point out that we do not perform any testing on di(2-ethylhexyl)phthalate (DEHP) in the above-mentioned product.

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

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Elemental Impurities

To whom it may concern

Elemental Impurities for filters and single use products

The ICH Q3D (R2) guideline outlines a process to assess and control elemental impurities in the drug product. Elemental impurities in drug products can arise from a number of different sources, including leaching of elemental entities that are present in the drug product's manufacturing systems. Thus, knowledge about the presence, level, and likelihood of leaching of elemental entities in manufacturing systems is relevant to understanding how these systems contribute to a drug product's total elemental impurity burden.

The ICH Q3D (R2) guideline considers a risk assessment approach to control elemental impurities based on scientific knowledge and principles of risk management as described in ICH Q9. Supporting information for this risk assessment includes but is not limited to data generated by the drug manufacturer, supplier information and/or data available in published literature. For biotechnologically derived products the ICH Q3D (R2) guideline considers that the risk of elemental impurities is low as typical biopharmaceutical purification schemes have the capacity to clear elements introduced in cell culture/fermentation steps or from contact with manufacturing equipment to negligible levels.

Reviews of the available literature on elemental entities in pharmaceutically relevant polymers have shown that in most cases, levels of extracted elemental entities and leached elemental impurities in the materials assessed are low and are unlikely to significantly contribute to the elemental impurity profile of a final drug product (1, 2).

Millipore filters and Mobius® single-use assemblies are not tested for the presence of elemental impurities for release. However, we request to indicate the potential presence of elemental impurities as mentioned in the ICH Q3D guideline based on supplier questionnaires.

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Elemental Impurity testing have been conducted following BioPhorum recommendations for some products. If available, the Extractable results including elemental impurities are in the Emprove® Operational Excellence Dossier.

Sincerely,

Janmeet Anant
Global Regulatory Management

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Date:

References:

1. Jenke, D.R., et al. Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: A Literature Review. *PDA J Pharm Sci and Tech* 2015, **69**: 1-48.

2. Jenke, D.R. Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: An Updated Literature Review. *PDA J Pharm Sci and Tech* 2020, **74**: 324-347.

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GMO Statement

GMO statement

Filters & Single-Use devices

The European Regulations (EC) 1829/2003 and (EC) 1830/2003 concern the labelling and traceability of genetically modified organisms (GMO) and of food and feed produced from GM organisms.

Filters and Single-Use devices are not intended to be used as food or feed nor consist of genetically modified organisms. Hence, to the best of our knowledge, above-mentioned regulations are not applicable for Filters and Single-Use devices. Customers remain responsible for complying with all applicable laws, and for determining the suitability of our products for the customer's intended purpose.

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Burlington, MA 01803, USA
Phone + 1 (781) 533-6000

Natural Rubber Latex Statement

Natural Rubber Latex Statement

MIX Mobius®, Silver,

Information on Natural Rubber Latex with respect to the FDA Guidance for Industry: "User Labeling for Devices that Contain Natural Rubber (21 CFR 801.437)" (published April 2003).

The above-mentioned product is not considered to be within the scope of the FDA Guidance mentioned above because the product is not a medical device nor packaging for medical devices.

In addition, to the best of our knowledge, the product is not made with natural rubber latex. We point out that we do not perform testing on natural rubber latex for this product.

Disclaimer: Only materials in direct fluid contact of the above-mentioned product were considered in the scope of this statement.

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Melamine Statement

Melamine Statement

Filters & Single-Use devices

The fraudulent addition of melamine to food raw materials with intent to simulate a higher nitrogen content has come to the attention of the relevant authorities. In August 2009 the US FDA published a Guidance for Industry "Pharmaceutical Components at Risk for Melamine Contamination". The scope of the FDA guidance refers to pharmaceutical components containing nitrogen in the chemical formula and materials derived from milk.

For the purpose of this guidance, FDA uses the term "at-risk component" to mean those ingredients or raw materials that rely on a test for nitrogen content for their identity or purity or strength, and that contain nitrogen in amounts greater than 2.5 percent.

Filters and Single-Use devices are not components in the sense of the guidance, as they are not intended to be added directly to, or to become a component of the drug product.

Based on FDA's definition of at-risk components, we consider Filters and Single-Use devices not to be in the scope of this guidance. Customers remain responsible for complying with all applicable laws, and for determining the suitability of our products for the customer's intended purpose.

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Nitrosamine Risk Evaluation

Nitrosamine Risk Evaluation

RE: Mobius® Single-Use Assemblies, including Single-Use Filters

Based on European Medicines Agency's information on nitrosamine impurities and guidance on EMA's website (Nitrosamine impurities, Guidance for marketing authorization holders) and the US FDA Guidance for Industry (Control of Nitrosamine Impurities in Human Drugs), Marketing Authorization Holders (MAHs) are requested to evaluate the risk of the presence of nitrosamine impurities in human medicinal products containing chemically synthesized APIs. MAHs should ensure that they and the holder of the manufacturing authorization have access to relevant information from the API manufacturers concerning potential formation of nitrosamine impurities and the potential for cross-contamination.

Polymeric and membrane materials, utilized as materials of construction for Mobius® single-use assemblies and associated single-use filters from our company, are not in the scope of the above-mentioned regulatory notice. Therefore, we do not test for specific nitrosamine impurities in these products.

Our company is aware of nitrosamines and other chemicals of concern for the pharmaceutical industry; therefore, these types of chemicals are not purchased for manufacturing of single-use assemblies, including all filter device and other components. To the best of our knowledge, nitrosamines are not present, nor would they be expected to be present in any polymeric materials of construction. Our company is aware of the responsible nitrosating agents and derivatives of amines used in rubber compounding, which may react to form nitrosamines. None of these rubber materials are utilized for fluid contact materials of construction. Nitrosamines may also be present in latex materials; our company does not use any latex materials in our Mobius® single-use products.

We provide this information to the best of our knowledge and based on the information which we have received from our suppliers, but without obligation or liability. Customers remain responsible for complying with all applicable laws, and for determining the suitability of our products for the customer's intended purpose.

Sincerely,

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Residual Solvents

To whom it may concern

Residual Solvents for Millipore® filtration systems and Mobius® single-use assemblies

The scope of the guideline ICH Q3C (R8) is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

According to the guideline ICH Q3C it is our understanding that the topic of reporting residual solvent applies to drug substances or excipients or in the preparation of drug products. This guideline does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

ICH Q3C does not apply to pharmaceutical manufacturing equipment, including single- use assemblies and filtration systems, due to the inherent low level of residual solvent contribution. During an extractables evaluation, volatile and semi-volatile compounds including identification and quantification of residual solvents is performed. If available, the Extractable results are in the Emprove® Operational Excellence Dossier and have been conducted following BioPhorum and USP <665> recommendations.

Sincerely,

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Plant/Vegetable Origin Declaration

Plant / Vegetable Origin Declaration

MIX Mobius®, Silver,

To the best of our knowledge and based on the information received from our suppliers, we declare that raw materials used to manufacture the above-mentioned product are of plant or vegetable origin.

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Date of Evaluation:

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Appendix I: Assembly Drawings

Millipore®

Preparation, Separation,
Filtration & Testing Products

For additional information,
please visit

www.sigmaaldrich.com/emprove

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

Rev: 0.1
NOT APPROVED