Repligen Custom Polypropylene Bottles Validation Report

Introduction

Purpose of this validation report

The Validation Report presents product information for Custom Polypropylene (PP) Bottles from Repligen. As an engineer, scientist, or manufacturer, you may need this information to guide your validation activities, including process development, writing validation protocols, and scaling up systems.

This Validation Report covers all Custom PP Bottles from 1 L to 50 L.

Repligen is committed to providing all relevent technical, manufacturing, and quality information, however, only non-confidential information is presented in this document. Confidential details may be made available upon request through a formal confidentiality agreement or as part of a supplier audit.

Where to get help

If you need to know more about the bottles, contact the technical support team at Repligen. The technical support team includes scientists and engineers that can:

a. Answer your technical questions.
b. Assist in the in the selection of bottles.
c. Provide user training programs.

To obtain support, contact your local Repligen sales representative or our customer support team.

Quality documentation

Quality policy

Copies of the Repligen quality policy and ISO certificate can be found at repligen.com/resources.

To meet the needs of GMP manufacturing, these products are manufactured in the USA under the following quality standards:

- Repligen maintains an ISO 9001-compliant Quality Management System that is currently certified by TUV Americas and BSI, a copy of the current ISO certifications can be downloaded from repligen.com/resources.
- All materials in with direct fluid contact meet USP Class VI, and USP <88> requirements for *in vivo* Biological Reactivity.
- All fluid contact components are free from materials of animal origin or compliant with EMA 410/01 Rev 3.

Animal byproduct free

Repligen Custom Bottles are manufactured using materials for production that do not include ingredients of animal origin. Our products do not come in contact with animal product during storage and transportation.

ISO and USP Class VI statements

ISO Statement: Product is manufactured in compliance with Repligen ISO 9001 certified Quality Management System.

USP Class VI Statement: All fluid path materials meet USP Class VI biosafety requirements.

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Product information

Repligen Custom PP Bottles are designed to handle fluids in a variety of bioprocessing applications and offer a safe, clean, and durable solution for fluid transfer. Sterilization methods include gamma irradiation and autoclaving. Testing includes USP Class VI and extractables per the April 2020 Biophorum (formerly BPOG) document, "Extractables testing Of Polymeric Single-Use Components Used In Biopharmaceutical Manufacturing".

Product features

- Sizes from 1 – 50 liters
- Animal-derived component free
- Certified to meet:
    1. USP Biological Reactivity Tests, In Vivo USP Class VI.
    2. ISO 10993-11 guidelines for the Systemic Injection Test.
    3. ISO 10993-10 guidelines for the Intracutaneous Reactivity Test.
    4. Classified as nonreactive according to the ISO 10993-6 guidelines for the Implantation Test.
    5. Non hemolytic per ISO 10993-4, ASTM F756.
    6. All analytical testing conducted post-gamma irradiation > 45 kGy.
- Tested for extractables per the April 2020 Biophorum (formerly BPOG) document, "Extractables testing Of Polymeric Single-Use Components Used In Biopharmaceutical Manufacturing." (Post gamma irradiation > 45 kGy)
- Sterilization methods:
    1. Gamma irradiation up to 45 kGy
    2. Autoclave 121° C for 60 minutes

Ordering information

To place an order for Repligen Custom Bottles, explore the Custom Showcase and contact your local FSE for assistance.

Typical applications

- Single-use assemblies
- Buffer and media preparation
- Mixing applications
- Fluid sampling
- Pharmaceutical production

Raw material and manufacturing environment

Repligen conducts extractables testing to the most current industry standards available at the time of sample submission. Repligen Custom PP Bottles submitted in Q3 2021 were tested for extractables per the April 2020 Biophorum (formerly BPOG) document, "Extractables testing Of Polymeric Single-Use Components Used In Biopharmaceutical Manufacturing."

Plastic materials have been used in the manufacturing of therapeutics for many decades. Over the last 15 years, focused product development by vendors and biotechnology companies resulted in a plethora of single-use technologies. During this time, the industry witnessed the development and adoption of critical disposable and single-use technologies like mixers, bioreactors, filters, and connectors. As a result, standards and best practices for evaluating component safety have been set for the selection and qualification of plastics. In general, plastics used in biopharmaceutical manufacturing have low defined extractables and have been determined to be non-toxic at equivalent therapeutic doses. Many base standards used for guidance have been set by regulatory publications, including USP, CFR 21, and EMEA. These basic standards have been elaborated on by industry organizations like the Bio-Process Systems Alliance (BPSA) and Parenteral Drug Association (PDA) as well as product manufacturers through the publication of best practices of testing and assessment of data. In addition, end-user therapeutic manufacturers have become more

demanding in their analytical requirements, assessment of data, determination of risk, and minimum threshold for meeting internal standards.

Repligen is sensitive to the demands of the industry and will therefore supply relevant and applicable information about the plastics used in the product contact components of Repligen Custom Polypropylene Bottles

Extractables: Chemical compounds that migrate from any product-contact material when exposed to an appropriate solvent under exaggerated conditions of time and temperature.

Leachables: A subset of extractables that migrate into a drug formulation from any product contact material because of direct contact under normal process conditions.

There is a consensus that it is the responsibility of the product technology vendor to provide an extractable data package. Recently, there have been efforts to standardize the testing procedures for extractables; wherever possible. Repligen complies with standardization efforts. Additionally, in compliance with CFR 21, Part 211.65, Repligen Custom PP Bottles are designed such that all product contact materials are not reactive, additive, or absorptive which would alter the safety, identity, strength, quality, or purity of the drug product beyond established requirements.

Using the BPSA guidance as a backdrop, Repligen has designed an extractables program to produce a robust data package by conducting extractables testing using four solvents as well as exaggerated time and temperature conditions. Leachables, however, are considered process specific and the responsibility of the end user to define within specific process parameters.

Biocompatibility & extractables testing summary of Repligen Custom PP Bottles

For biocompatibility & extractables testing, Repligen submitted 1 L bottles irradiated to > 45kGy to facilitate a worst-case scenario for surface area-to-volume ratio and irradiation level. Repligen Custom PP Bottles were tested for extractables per the April 2020 Biophorum (formerly BPOG) document, "Extractables testing Of Polymeric Single-Use Components Used In Biopharmaceutical Manufacturing."

Biocompatibility testing; all passed:

- USP Biological Reactivity Tests, In Vivo (USP Class VI)
- ISO 10993-11 Systemic Injection Test
- ISO 10993-10 Intracutaneous Reactivity Test
- ISO 10993-6 Implantation Test
- Non hemolytic per ISO 10993-4, and ASTM F756

The purpose of the extractables study was to generate a supplier-sponsored extractables profile for Repligen Custom PP Bottles, specifically for the conditions established in this study. Such an assessment includes the detection, identification and quantitation of compounds or entities that can be extracted from the bottles under the conditions presented. The bottles were extracted by filling the sample with one of four extraction solvents (Table 7) and incubating at 40 ± 3°C for 24 ± 4 hours, 21 ± 1 days, and 70 ± 3 days. The sample extracts were analyzed for volatile organic extractables by headspace gas chromatography (GC) with mass spectrometry (MS), semi-volatile organic extractables by direct injection GC-MS, non-volatile organic extractables by ultra-performance liquid chromatography (UPLC) with photodiode array (PDA) and quadrupole time-of-flight (QToF) detectors, by both APCI and ESI, and inorganic extractables (except 50% EtOH extracts) by inductively coupled plasma (ICP) with MS detection. The analytical techniques employed provide a comprehensive strategy for establishing an extractables profile of Repligen Custom PP Bottles. The organic extractables discovered with estimated concentrations above the reporting threshold are summarized (Table 9, Table 10).

Table 1. Extraction solvents

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

Timepoints

- 1 day (24 hours)
- 21 days
- 70 days

Table 2. Count of extractables at or above reporting threshold per solution

Extraction solvent	Volatile organic extractables	Semi-volatile organic extractables	Non-volatile organic extractables	Inorganic extractables
WFI	0	0	0	2
0.5 N NaOH	1	0	0	2
0.1 M H_3PO_4	0	0	0	0
50% EtOH	0	2	3	14

Table 3. Volatile organic extractables summary

Solvent	RT, minutes	Identification	Cas #	ug/cm^2		
				24 Hr.	21 Day	70 Day
WFI	N/A					
0.5 N NaOH	2.49	Acetone	67-64-1	< LOD	0.217	0.325
0.1 M H_3PO_4	N/A					
50% EtOH	N/A					

Table 4. Semi-volatile organic extractables summary

Solvent	RT, minutes	Identification	Cas #	ug/cm²		
				24 Hr.	21 Day	70 Day
WFI	N/A					
0.5 N NaOH	N/A					
0.1 M H_3PO_4	N/A					
50% EtOH	2.92	Unknown siloxane	N/A	< LOD	< LOD	0.114
	20.39	1-Hexadecanol	36653-82-4	< LOD	0.872	< LOD

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