Flexicon
Liquid Filling

Validation summary guide

PEI Nozzles

WATSON MARLOW Fluid Technology Solutions

Executive Summary

This is the summary validation guide for disposable PEI nozzles. Full test methods and results are available in the full validation guide, by filling in a request form on the website: https://www.wmfts.com/en/validation/request/

Contents

1. Introduction 3
2. Conditions of use 3
3. Chemical compatibility 3
4. Validation testing 3
   4a. Summary table 3
   4b. USP <85> Bacterial endotoxins 4
   4c. USP <87> Biological reactivity tests, *in vitro* 4
   4d. USP <88> Biological reactivity tests, *in vivo* 4
   4e. USP <788> Particulate matter in injections 4
   4f. ISO 10993-5 Biological evaluation of medical devices, *in vitro* cytotoxicity 4
   4h. Nitrosamines 5
   4i. X-ray equivalency 5
5. Validation testing services 5
6. Conclusions 6

1. Introduction

Filling nozzles – disposable PEI 1000 are manufactured by Voss Industry and Medical A/S, Denmark for use in WMArchitect filling assemblies. These WMArchitect filling assemblies are made to optimized specifications (specific to Flexicon systems) at our BioPure manufacturing facility in Havant, UK.

This guide relates to filling nozzles – disposable PEI 1000 which from this point will be referred to as PEI nozzles.

2. Conditions of use

PEI nozzles are suitable for use according to the conditions in Table 1.

Table 1. Conditions for manufacturing, sterilisation, working and storage.

Manufacturing	Sterilisation	Working	Storage
Polyetherimide	Gamma irradiation 25–45 kGy	10°C–35°C (24.8°F–104°F)	10°C–30°C (14°F–86°F)
ISO 9001 quality management system			Dry environment, away from direct sunlight
			No exposure to chemicals or stress

Original packaging must be retained and stock rotated on a first in, first out (FIFO) basis. The performance of components cannot be assured beyond use by date or when not stored according to recommendations above.

3. Chemical compatibility

There is no data available on the chemical compatibility of the finished PEI nozzles with regards to how they perform in the presence of different solvents. As such, it is advisable for PEI nozzles to be tested under actual process conditions (see section 5 validation testing services).

4. Validation testing

PEI nozzles were autoclaved or gamma irradiated and subjected to the tests summarised in Table 2.

4a. Summary table

Table 2. Testing summary of evaluated standards.

Test	Description	Result
USP <85>	Bacterial endotoxins test	PASS
USP <87>	Biological reactivity tests, *in vitro*	PASS
USP <88>	Biological reactivity tests, *in vivo*	PASS
USP <788>	Particulate matter in injections	PASS
ISO 10993-5	Biological evaluation of medical devices, Tests for *in vitro* cytotoxicity	PASS

Test	Description	Result
BioPhorum Operational Group (BPOG)	Analysis of extractables	REPORT
Food and Drug Administration (FDA) guidance	Nitrosamines	REPORT

4b. USP <85> Bacterial endotoxins

Limulus Ameobocyte Lysate (LAL) gel clot test detects and quantifies endotoxin levels in samples. Test samples, negative control and endotoxin standards were extracted in LAL reagent water at room temperature for 60 minutes. LAL was added to samples and incubated at 37°C (98.6°F).

Results: *<0.005 EU/mL (irradiated), 0.005 EU/mL (autoclaved) <0.25 EU/mL (endotoxin limit of water for injection). Passing <USP 85> requirements.*

4c. USP <87> Biological reactivity tests, *in vitro*

USP <87> determines the biological reactivity of cell cultures in response to samples. Test, positive and negative control samples were prepared at 37±1 °C (98.6±33.8 °F) for 2 days. Biological reactivity was rated on a scale from Grade 0 (no reactivity) to Grade 4 (severe reactivity).

Results: *No reactivity or cytotoxicity, passing USP <87> requirements.*

4d. USP <88> Biological reactivity tests, *in vivo*

USP <88> assesses the toxicity of test articles systemically, intracutaneously and through implantation. Samples were immerged in: USP 0.9% NaCl, cottonseed oil, 1 in 20 ethanol in NaCl, and polyethylene glycol 400 at 121°C (249.8°F) for 0.1 hours. Injection sites were monitored for 72 hours.

Results: *No toxicity, passing USP <88> requirements.*

4e. USP <788> Particulate matter in injections

This test determines the number of particulates measuring ≥10 µm and ≥25 µm present in the fluid pathway. Samples were flushed with low particulate water, extraction fluid recovered and particles measured.

Results: *128 particles/device ≥10 µm and 7 particles/device ≥25 µm, passing USP <788> requirements.*

4f. ISO 10993-5 Biological evaluation of medical devices, *in vitro* cytotoxicity

The biological reactivity of a cell culture, in response to samples was determined. Test, positive and negative control samples were prepared at 37±1°C (98.6±33.8°F) for 2 days. Biological reactivity was rated on a scale from Grade 0 (no reactivity) to Grade 4 (severe reactivity).

Results: *No cytotoxicity, passing ISO 10993-5 requirements.*

4g. BPOG extractables

Samples were subjected to extraction in multiple solvents at controlled temperatures. The solvent extracts were analysed using:

- High Pressure Liquid Chromatography- Diode Array Detector-Mass Spectrometry (HPLC-DAD/MS) to detect the presence of non-volatile and UV active compounds
- Direct injection Gas Chromatography-Mass Spectrometry (DI-GC/MS) to detect semi-volatile compounds
- Headspace Gas Chromatography-Mass Spectrometry (HS-GC/MS) to detect volatile compounds

- Inductively Coupled Plasma-Mass Spectrometry (ICP/MS) to identify elemental impurities

Results: *Extractables were indicative of materials of construction. Validation testing services can provide further information in the evaluation of extractable data for risk assessment purposes, please see section 5.*

4h. Nitrosamines

Test samples were analysed for the following using DI-GC-MS:

- N-Nitrosodimethylamine (NDMA)
- N-Nitrosomethylethylamine (NMEA)
- N-Nitrosodiethylamine (NDEA)
- N-Nitrosodipropylamine (NDPA)
- N-Nitrosodibutylamine (NDBA)
- N-Nitrosopiperidine (NPIP)
- N-Nitrosopyrrolidine (NPYR)
- N-Nitrosomorpholine (NMOR)

Results: *Nitrosamines were undetectable.*

4i. X-ray equivalency

There is a foreseeable shortage of gamma irradiation capacity. BioPhorum and Bio Process Systems Alliance (BPSA) committees have steered supply chain representatives to adopt X-ray irradiation to mitigate this risk. The mechanism of X-ray irradiation is very similar to gamma.

WMFTS has chosen to qualify X-ray for irradiation. Testing was conducted as follows:

- Extractables (Reduced BPOG)
- Cytotoxicity (USP <87> / ISO 10993-5)
- Hydrostatic Pressure testing
- Dimensional measurement

Results: *Validated to be irradiated with Gamma or X-ray irradiation.*

5. Validation testing services

Our Validation Testing team will design your validation studies using the most up to date industry recognized standards alongside fully qualified testing partners. We will provide a bespoke results assessment to ensure you meet your specific quality assurance requirements.

Testing protocols cover a wide range of industry recognised validation tests for one-off or lot-release testing. These include but not limited to:

- Bioburden
- Particulates
- Endotoxin
- Leak testing
- Extractables and Leachables
- Sterility assurance
- Nitrosamines
- Chemical compatibility

Contact Validation.WMArchitect@wmfts.com or your WMFTS representative for more information.

6. Conclusions

Filling nozzles- disposable PEI 1000 have passed testing standards as summarised in this guide.

For more information on quality and compliance information not stated in this guide, please contact your WMFTS representative or WMFSales.flexicon@wmftg.com.

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