WATSON MARLOW Fluid Technology Solutions

AFLEX HOSE

SUMMARY VALIDATION GUIDE

Biotechnology and pharmaceutical products. Bioflex Ultra, Pharmaline N and Pharmaline X

Executive Summary

This is a validation guide for Aflex Hose products suitable for the pharmaceutical and biotech industries. The guide contains instruction in section 8 on how to obtain the detailed test procedures and supporting test reports.

Contents

1. Introduction

Aflex Hose is based in West Yorkshire, UK, and manufactures PTFE lined hose products. The facility manufactures from raw materials (e.g. PTFE granulated powder, braid wire, stock bar) to produce end-products in the form of hose assemblies. Aflex Hose is known for its excellent quality and innovative products that provide superior flexibility, kink resistance, cleanability and PTFE lined end fittings.

Products that are intended for high purity applications are:

- **Bioflex Ultra**
- **Pharmaline N**
- **Pharmaline X**

The PTFE liners are available in both natural PTFE and anti-static (static dissipative) versionS and are manufactured from materials compliant with FDA CFR 21 177.1550 and FDA CFR 21 178.3297 and USP VI <88>. Similarly, external rubber covers are compliant with USP VI <88>. All products are suitable for autoclave sterilisation. Aflex Hose operates an ISO 9001 quality management system.

Hose assemblies have the following features:

- **Individual build serial number for full traceability of materials of construction and manufacturing processes.**
- **PTFE raw materials are free from PFOA and PFOS.**
- **PTFE liners have extremely low extractable results, are non-toxic and free from animal derived content.**
- **Both PTFE lined and standard non-lined fittings are available. Lined fittings have superior cleanability and smooth flow to connecting pipework.**
- **PTFE exhibits outstanding chemical resistance and cleanability due to the hydrophobic nature of the material.**
- **High temperature resistance and good vacuum resistance**
- **Kink resistance.**
- **Excellent flexibility**

2. Conditions of use

Full details of the usage conditions are available within the product brochure.

3. Chemical compatibility

PTFE exhibits superior chemical compatibility over many polymer, ceramic and metallic materials. Aflex Hose can provide support to assess specific applications. Some chemicals can permeate through PTFE, such as Halides (chlorine / bromine / fluorine containing media are typical) and could corrode external components such as stainless steel braid. Contact Aflex Hose for more application specific information.

4. Materials, manufacturing and regulatory compliance statements

4a Materials of construction

Hose liners are smooth bore and externally convoluted to provide flexibility. The liner is manufactured from PTFE in compliance with FDA CFR 21 177.1550. Anti-static PTFE liners contain high purity furnace black in compliance with FDA CFR 21 178.3297 and 3A 62-02 requirements.

The liner has an outer stainless steel 316 helix wire wound into the external convolutions to provide additional hoop strength and kink resistance.

Metallic support braid is stainless steel 316. A polypropylene braid is available for the Bioflex Ultra product, but this cannot be supplied with a cover.

External covers are platinum-cured silicone or blue EPDM both are compliant with USP VI <88>.

End fittings are stainless steel 316L, unless otherwise specified.

4b Manufacturing environment

Aflex operate an ISO 9001 quality management system. Additionally, Aflex are certified to ISO 14001 and ISO 45001. If applicable hoses can be CE marked to the European Pressure Equipment Directive.

4c Country of origin

Aflex hose and fittings are manufactured in the UK. Assemblies may be put together in other countries – please consult the local supplier of assemblies for further information.

4d Compliance declaration summary

Named substance/compliance statement	Raw material	Manufacturing process	Final product
Animal Derived Content	–	–	–
Conflict materials (tin,tantalum, tungsten, gold) which are sourced from DRC or adjoining countires.	–	–	–
Gluten	–	–	–
Bisphenol A	–	–	–
Melamine	–	–	–
Latex/Dry Natural rubber	–	–	–
Phthalates	–	–	–
Nitrosamines or Nitrosamine precursors	–	–	–

'–' denotes not present or not added

4e REACH legislation

All raw materials, compounds used in the manufacturing process and the final Aflex Hose products comply with the REACH regulations. None of the chemicals used in the manufacture of Aflex Hose products are on the candidate list or the list of substances of very high concern (SVHC).

4f RoHS

In compliance with the restriction of hazardous substances (RoHS) directives, no listed substances are used in the manufacture of Aflex Hose products.

4g Material certification to EN10204-3.1

Material certification to EN10204-3.1 is available upon request.

Storage conditions

The storage periods quoted assume that all components are stored in a manner to optimise the storage periods.

a) Products must be fully protected from contact with all chemicals, including any incidental contact – e.g cleaning fluid

b) All products must be protected against physical damage including abrasion, kinking and crushing.

c) Temperature does not exceed 25C

d) Humidity of the atmosphere does not exceed 70%

e) Protected from direct sunlight and UV exposure

f) Protected from all sources of ionising radiation

g) Protected from exposure to ozone.

Material certificates are retained by Aflex Hose Ltd for 10 years from receipt of material.

5. Compendial and non compendial testing

5a Summary table

Table 2 contains a summary of all the compendial testing and ISO qualifications that Aflex Hose PTFE liners and cover materials have been evaluated for. Full test methods and results are available upon request.

Test samples

PTFE hose liner tests were carried out on both Natural and Anti-static materials. The tubing was internally smoothbore and externally convoluted and representative of the liner used throughout the size range and construction of the hose products relevant to this document.

EPDM (blue) and platinum cured silicone (white and clear) hose rubber cover testing were carried out on samples of fully cured material that followed the manufacturing processes associated with hose manufacture.

Table 2: List of compendial and non compendial testing performed

Test reference	Test Description Samples are PTFE (Natural & AS), EPDM, Silicone	Result
USP VI <87> L929 MEM	Biological reactivity test, *In Vitro*	PASS (Not including EPDM Blue)
ISO 10993-5 L929 MEM	Biological reactivity test, *In Vitro*	PASS (Not including EPDM blue)
USP VI <88>	Biological reactivity test, *In Vivo*	PASS
ISO 10993–6	Biological evaluation of medical devices, Local effects after implantation.	PASS
ISO 10993–10	Biological evaluation of medical devices, irritation and skin sensitization.	PASS
ISO 10993–11	Biological evaluation of medical devices, systemic toxicity	PASS

5b USP VI <87> Biological reactivity tests, *In Vitro*, samples: Hose liners PTFE Natural and AS; Hose covers silicone white and clear

USP <87> determines the biological reactivity of a cell culture in response to a given test article. Samples were tested in accordance with USP 41, NF 36, <87>, Biological Reactivity Tests, In Vitro. Negative control (High Density Polyethylene) and positive control (Natural Rubber) articles were prepared at 37°C (98.6°F) for 24 hours. Biological reactivity was rated on a scale ranging from Grade 0 (no reactivity) to Grade 4 (Severe reactivity).

Results: Based on the criteria of the protocol the USP <87> guidelines, the test articles meet the requirements of the test and is not considered to have cytotoxic potential.

5c ISO 10993-5 Biological evaluation of medical devices - part 5: tests for in vitro cytotoxicity. Samples: Hose liners PTFE Natural and AS; Hose covers silicone white and clear

The biological reactivity of a cell culture, in response to extracts from test articles was determined. The maintenance medium on the cell cultures was replaced by extracts of test articles or control article. The cell cultures were incubated for 48 hours at 37±1C (98.6F±/1.8F).

Results: Based on the criteria of the protocol the ISO 10993-5 guidelines, the test articles meet the requirements of the test and is not considered to have cytotoxic potential.

5d USP VI <88> Biological reactivity test, In Vivo, samples: Hose liners PTFE Natural and AS; Hose covers EPDM, silicone white and clear.

USP Class VI Plastics Test assesses the potential toxicity of a given test article systemically, intracutaneously and through implantation

Samples were tested in accordance with USP 40, NF 35 <88>, Biological Reactivity Tests, In Vivo. In addition the testing covers ISO 10993-6, -10, -11 and -12. This included the immersion of test articles in the following solutions: USP 0.9% sodium, chloride, cottonseed oil, 1 in 20 ethanol in NaCl and polyethylene glycol 400. PTFE hose liner samples were immersed at 121°C for 1 hour. EPDM and Silicone hose cover samples were immersed at 70°C for 24 hours.

Results: The test articles did not produce a biological response and meet the requirements of USP VI <88>, ISO 10993-6, -10, -11 and -12.

5e ISO 10993–6 Biological evaluation of medical devices, local effects after implantation. Samples: Hose liners PTFE Natural and AS; Hose covers EPDM, silicone white and clear

Solid material samples in direct contact with living tissue are evaluated. The test sites were examined for inflammation, encapsulation, necrosis, haemorrhage and discolouration macroscopically..

Results: No effects observed.

5f ISO 10993–10 Biological evaluation of medical devices, irritation and skin sensitisation. Samples: Hose liners PTFE Natural and AS; Hose covers EPDM, silicone white and clear

The intracutaneous test is designed to evaluate local responses to the extracts of test articles following intracutaneous injection. Test articles are extracted using 0.9% sodium chloride for injection, cottonseed oil, 1 in 20 ethanol in NaCl or polyethylene glycol 400 at 121°C for 1 hour (PTFE hose liner) or 70°C for 24 hours (EPDM, Silicone hose covers).

Results: No effects observed.

5g ISO 10993–11 Biological evaluation of medical devices, system toxicity. Samples: Hose liners PTFE Natural and AS; Hose covers EPDM, silicone white and clear

The purpose of the systemic injection study is designed to screen test articles extracts for potential toxic effects as a result of a single dose systemic injection. The test articles were extracted using 0.9% sodium chloride for injection, cottonseed oil,1 in 20 ethanol in NaCl or polyethylene glycol 400 at 121°C for 1 hour (PTFE hose liner) or 70°C for 24 hours (EPDM, Silicone hose covers).

Results: No signs of toxicity.

6. Extractables on natural and anti-static PTFE hose liner.

An extractables study is carried out using a range of solvents covering both USP <661.1>, BPOG and draft USP <665>. Extraction conditions were 40°C over 21 days and agitated. Additionally, specific analysis to confirm an absence of Perfluorooctanoic acid (PFOA) and Perfluorooctanesulfonic (PFOS) was conducted. Specific analysis for the modifier Perfluoro Propyl Vinyl ether (PPVE) added to manufacture modified PTFE. Analytical techniques are Gas Chromatography Mass Spectrometry (GC-MS) headspace and Liquid Chromatography using Ultra-Violet Mass Spectrometry (LC-UV-MS).

Elemental impurities analysis and sample preparation is according to USP <661.1> using solution S3, with 37 metals analysed to ICH-Q3D class I, IIa, IIb, III, Ph. Eur. 5.20, EMEA/CHMP/SWP/4446 and USP<231>, USP <661.1>.

Results: No volatile, semi-volatile or non-volatile were observed in any extract solutions. No PFOA or PFOS were detected as expected. No PPVE was detected as expected. TOC results were below LOD or USP<661.1> limits. Elemental impurities are significantly below ICH-Q3D inhalation concentration limits and results are available for end user toxicological assessment.

Additional statements

7. EN 16643:2016 Hose specification standard for non-adhesives bonded PTFE hose.

Aflex hose and hose assemblies meet the requirements of EN 16643:2016 Rubber and plastics hoses and hose assemblies — Non-bonded fluoroplastic lined (e.g. PTFE) hoses and hose assemblies for liquid and gaseous chemicals — Specification. The term “non-bonded” relates to the hose layer construction, where adhesives are not used to bond adjacent layers of the construction.

Electrical properties of the hose and hose assembly are specified within EN 16643 and measured in accordance with the methods in EN ISO 8031:2009 for both electrical continuity between end fittings and static dissipative properties.

Electrical continuity (EC) is measured on assemblies only and between the metallic end fittings. EC assemblies are marked “M” grade and the electrical resistance between end fittings is less than $10^2\Omega$ (100Ω). The M-grade must be appropriate for the assembly construction. The following are not EC:

- Bioflex Ultra tube only (TO)
- Pharmaline X
- Any assembly with non-EC fittings (e.g. Polypropylene fittings)

Anti-Static quality (AS) or static dissipative hose assemblies have an electrical resistance between $10^3\Omega$ to $10^8\Omega$ (1KΩ to 100MΩ), when measured between the liner or outer cover and the opposite end fitting.

Fire-proof and fire-resistant properties

The Bioflex Ultra BK (Black Anti-static rubber cover) assembly has fire resistant and fire proof properties, depending upon the assembly construction. Assemblies are fire resistant (5min) with no protection over the end fitting and ferrule, but fire proof (15min) with DRC cover protecting the ferrule at each end of the assembly. The fire compliance conforms with BS5173 section 103.13 part 6.2, TRbF 131/2 and EN 16643.

Electro polished end fitting requirements

Assemblies that include an electro polished Tri-clamp (or Tri-clover) non-lined stainless steel 316L fitting, or similar electro polished fitting, are electropolished and passivated to a surface finish of ≤15µin Ra (≤0.4 µm).

Standard	Aflex Statement
Design and manufacture	Aflex hose and hose assemblies are compliant with BS EN 16643:2016
Fireproof	Bioflex Ultra BK (Black anti-static rubber cover) Compliant with BS5173 section 103.13 part 6.2 Compliant with TRbF 131/2 Compliant with EN 16643 Fire resistant (5min) with no protection over the end fitting and ferrule Fire proof (15min) with DRC protecting the ferrule Note: The black anti-static EPDM cover does not have USP <87>, <88> validation

8. Links to test reports

Section	Validation guide section	Test report reference
5	USP <87> ISO 10993-5, -12	PTFE tube Natural 18-04239-G1 PTFE tube Anti-static 18-04246-G1 Platinum-cured silicone (White) 18-04248-G1 Platinum-cured silicone (Clear) 18-04176-G1
5	USP <88> ISO 10993-6, -10, -11, -12 (For PTFE Natural and AS the ISO 10993-6, -10, -11 -12 are confirmed in the certificate attached to the main report)	PTFE tube Natural 18-04239-G4 PTFE tube Anti-static 18-04246-G4 Platinum-cured silicone (white) 18-04248-G2 Platinum-cured silicone (clear) 18-04176-G2 EPDM (Blue) 19-01963-G2
6	Extractables Extractable heavy metals	PTFE tube Natural and Anti-static 18-453 PTFE tube Natural 1906136 PTFE tube Anti-static 1906137

Please contact your Watson-Marlow representitive for full access to test reports.

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BFXU/PHANX/25.04.22/Rev 2