Third Silicone Line equivalency study

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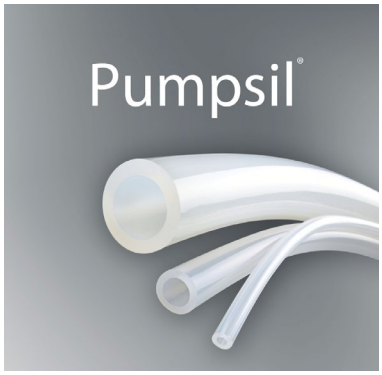

Executive summary

To meet the growing demand for our high performance silicone tubing product, Pumpsil®, Watson-Marlow Fluid Technology Group (WMFTG) has added a third extrusion line to our clean room at Falmouth, UK. This will also ensure additional capacity and security of supply over the coming years. The new extruder is from the same manufacturer and of equal design and capacity to the other line currently in operation. The operators are the same for all the extrusion lines, the raw materials remain unchanged and are from the same storage location. For these reasons WMFTG expects there to be no significant differences between the new extrusion line and the original line of this design.

In order to validate the new line and prove equivalency with the original line WMFTG has undertaken a full IQ-OQ-PQ and tubing extruded from the new and existing extruders has been tested to prove functional equivalence.

Introduction

Watson-Marlow Pumpsil® series tubing is a high purity platinum cured silicone which is USP Class VI and ISO 10993 compliant. It is manufactured in an ISO 14644-1 class 7 cleanroom which is temperature and humidity controlled, thereby providing a stable extrusion environment.

Manufacturing equipment and processes on the 3rd silicone line have been validated to a version of the industry recognised; Installation Qualification, Operational Qualification, Performance Qualification, henceforth defined as IQ–OQ-PQ. Performance of the finished Pumpsil product has also been evaluated. Equivalence measures in this study are: dimensional / physical attributes, peristaltic performance and an extractables profile.

Scope

This report details the outcomes of the process used to qualify the manufacturing process of the newly installed 3rd extrusion line (Ø105mm) in Watson Marlow Falmouth's silicone extrusion clean room. Performance of product manufactured from the newly installed extrusion equipment was assessed against the performance of product manufactured on the existing equipment.

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Outline of study

The validation was split into the three main stages:
IQ:-commissioning activity intended to verify that all required processes, equipment and resources that are used to supply the tube, are defined, available and functioning correctly.

OQ:-"challenge the manufacturing process" by exploring the process limits and determining and understanding the effect on the quality of the extruded tube.

PQ:-simulate a production scenario and provides quality assurance that the stipulated process settings/parameters derived in IQ & OQ deliver the product to specification.

Installation Qualification

The following table shows the check sheet of the actions that were completed under IQ.

Action	Completed
Verify cleanroom capability & certification & maintenance plan	✓
Verify equipment and tool identification (serial number)	✓
Verify extrusion equipment certification & maintenance plan	✓
Trial extrusion process with new equipment	✓
Complete ISIR	✓
Identify metrology equipment and processes	✓

IQ Acceptance Conclusion

All equipment, systems and processes were in place and functioning.
Tube was manufactured to drawing specification.
Tube was free from damage, draw marks, ribbing, contamination, excessive streaming and other general extrusion defects when inspected against the existing process SOP.
All features/dimensions specified on drawing were within tolerances.
The results demonstrate the capability of the new equipment to produce fully conforming tubing.

Operational Qualification

The following table shows the check sheet of the actions required under OQ.

Actions	Completed
Characterise extrusion equipment and tooling	✓
Extrusion process optimisation	✓
Capability (Cpk) study on critical dimensions	✓
ISIR	✓
Eventful conditions	✓
Results received and approved from the extractables study	✓
Peristaltic Test Samples manufactured	✓

Extractable analysis

Extractables testing has been used to show chemical equivalence between product manufactured on the new 3rd extrusion line and reference lines. The analysis was conducted on the largest tubing manufactured, 25.4 x 4.8mm. This size is deemed to be worst case from an initial curing perspective as it requires the largest throughput of raw material, has the greatest wall thickness and the largest internal surface area

Equivalence has been confirmed through an investigation of chemical extracts by Hall Analytical test services, an independent test house based in the UK, using the approach detailed in the Biophorum guidance paper "Extractables testing of polymeric single-use components used in biopharmaceutical manufacturing"[1]. The study compared both autoclaved and gamma irradiated samples from both extrusion lines and compared the chemical components after a 21 day extraction period using 50% Ethanol/WFI (water for injection) as per Biophorum guidelines. Gamma samples were irradiated to 40-55 kGy prior to extraction. This differs from the required 45- 55 kGy stated in the VMP due to the capability of the irradiation process. Both samples were irradiated during the same run and therefore are adequate for the equivalence study. Autoclaved samples were autoclaved at 121°C for 60 minutes prior to extraction. Analysis of the extracts was carried out using Headspace GC-MS, Direct Injection GC-MS and LC-DAD-MS reporting both the presence and estimated concentrations of known and unknown chemical entities against a set of five standards.

[1] https://www.biophorum.com/download/extractables-testing-of-polymeric-single-use-components-used-in-biopharmaceutical-manufacturing/

Experts at Watson-Marlow have determined after a thorough review that the extractables information provided between Pumpsil® manufactured on the two lines has minimal variation and identified extracts and concentrations are understood to be mainly siloxane related as would be expected. A minor variation was observed at 12.121 minutes for an unknown compound in the analysis of direct injection GC-MS for product manufactured on the 3rd line. This is likely to be due to normal variation in the tubing composition. The concentration of the extract is very low (< 1 µg/cm^2) and is the only quantifiable difference between the two lines.

In conclusion the 3rd line from an extractables perspective can be considered to have produced equivalent product.

OQ Acceptance Conclusion

The results demonstrate the capability of the new equipment to produce fully conforming tubing.

Capability analyses on bore and wall thickness have all shown Cpk indices above 1.33. To provide a better comparison of capability of the process across multiple batches the OQ samples will be combined with the results with PQ extrusion trials.

A thorough extractables analysis has demonstrated that product manufactured on both the existing and new lines can be considered equivalent.

Performance Qualification

The following table shows the check sheet of the actions required under PQ:

Actions	Completed
Production run of each tube size	✓
Capability (Cpk) study on critical dimensions	✓
Peristaltic Equivalence demonstrated	✓ (9.6 x 3.2mm)

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PQ Testing

Extractable analysis

The extractible analysis conducted at OQ remains valid for PQ. No changes have been made to the processing parameters for this size of tube since the preliminary optimisation work where samples had been extruded for the extractable analysis.

Peristaltic Life

Tests from five samples of three separate batches on each of the existing and new extrusion lines were required to provide data in support of the equivalence claims. In addition, both non gamma and gamma irradiated tube were tested to simulate customer applications.

Data from the tests were used to demonstrate the performance (mean life and flow drop) of tubing extruded on the new line is within two standard deviations of the performance of tubing produced on existing line (and vice-versa).

Two batches of tubing from the IQ/OQ runs combined with tubing manufactured in the PQ run yielded three separate batches for each size. Samples from each batch of tube were exposed to a gamma irradiation dose of 40-55 kGy.

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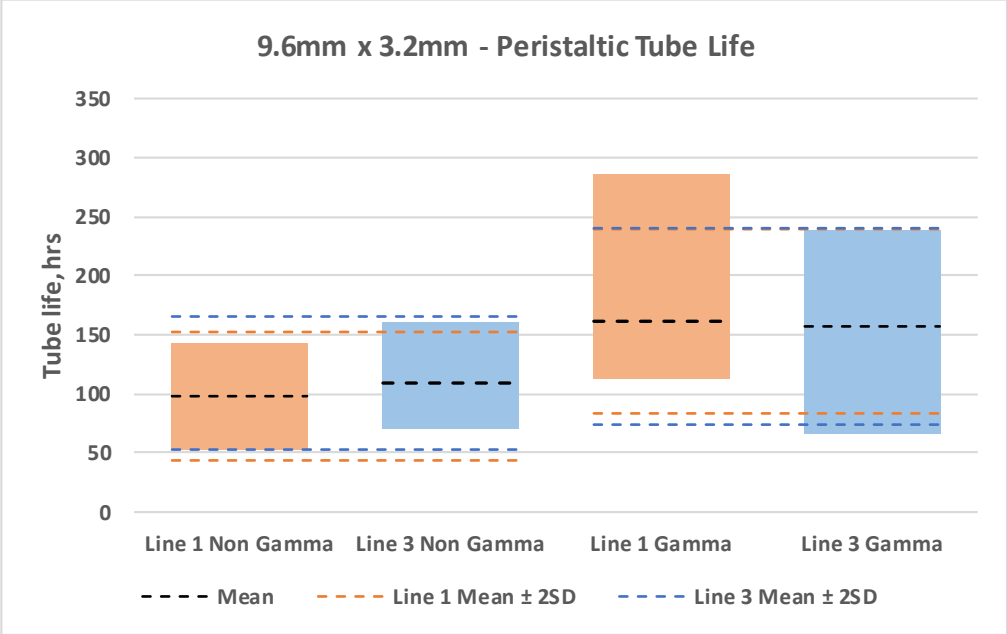
Peristaltic tests demonstrate that the average peristaltic tube life of the 9.6 x 3.2mm tubing extruded on Line 3 is within two standard deviations of the peristaltic tube life of product manufactured on existing Line 1 (and vice-versa).



Results using 9.6 mm bore x 3.2 mm wall tube tested in 620R Pump head running at 265rpm clockwise, no back pressure at room temperature. Results from three tube lots, five repeats per lot.

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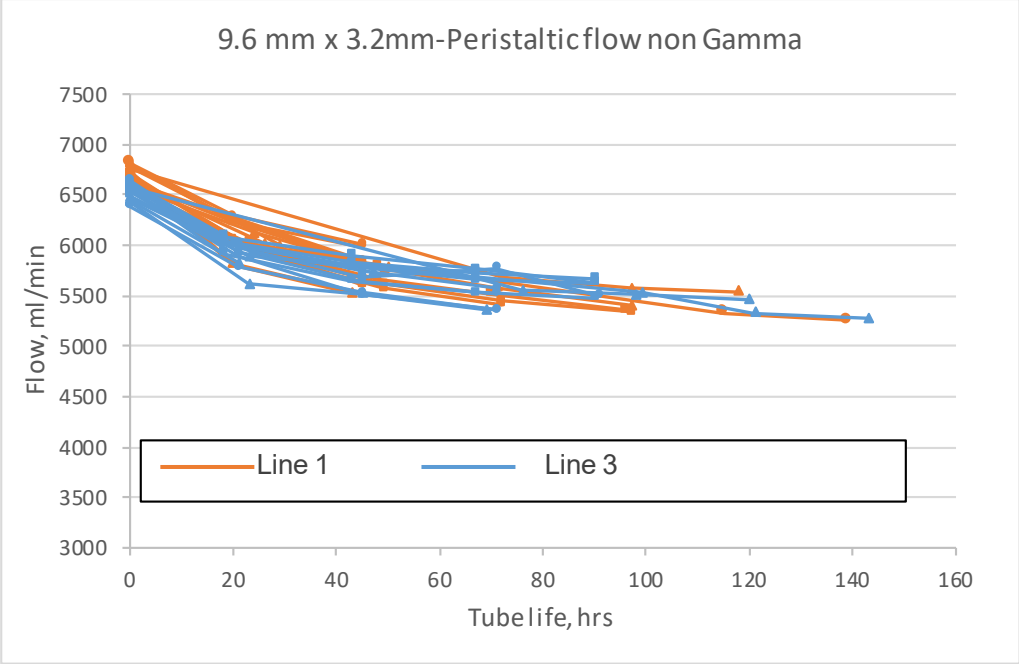
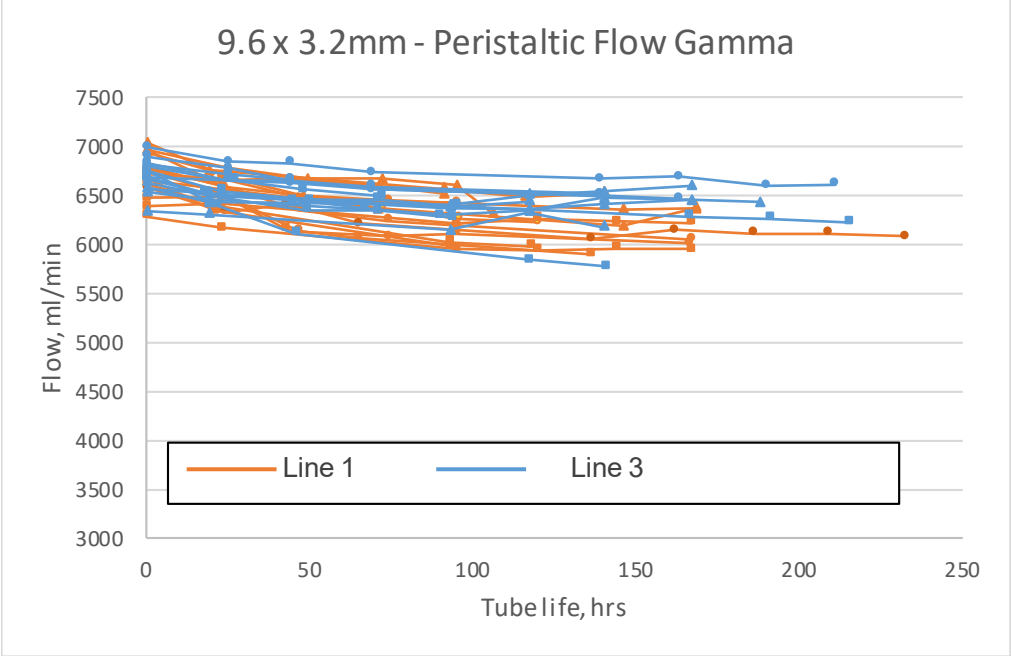
Peristaltic tests demonstrate the flow drop seen over time of the 9.6 x 3.2mm tubing extruded on Line 3 is equivalent to the tube extruded on line 1.



Results using 9.6 mm bore x 3.2 mm wall tube tested in 620R Pump head running at 265rpm clockwise, no back pressure at room temperature. Results from three tube lots, five repeats per lot.



Results using 9.6 mm bore x 3.2 mm wall tube tested in 620R Pump head running at 265rpm clockwise, no back pressure at room temperature. Results from three tube lots, five repeats per lot.

PQ Acceptance Conclusion

The trial extrusion runs, testing and analysis demonstrates that the New Line 3 is able to produce 9.6 x 3.2mm Pumpsil tubing that can be considered equivalent to that manufactured on the existing Line 1.

Capability analyses on bore and wall thickness have all shown Cpk indices above 1.33.

A thorough extractables analysis has demonstrated that product manufactured on both the existing and new lines can be considered equivalent.

Peristaltic testing and analysis has demonstrated that 9.6mm x 3.2mm Pumpsil® manufactured on both the existing and new lines can be considered to have equivalent performance.

Report Conclusion

This report details the outcomes of the process used to qualify the manufacturing process of the newly installed 3rd extrusion line in Watson Marlow Falmouth's silicone extrusion clean room. Performance of product manufactured from the newly installed extrusion equipment was assessed against the performance of product manufactured on the existing equipment and were found to be equivalent.

- The results demonstrate the capability of the new equipment to produce fully conforming tubing.
- An extractables analysis has demonstrated that product manufactured on both the existing and new lines can be considered equivalent.
- Peristaltic testing and analysis has demonstrated that 9.6 x 3.2mm product manufactured on both the existing and new lines can be considered to have equivalent performance.