WHITE PAPER 0128

Precision Final Fill Pump Tubing

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Precision Final Fill Pump Tubing

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In assessing the suitability of tubing for peristaltic pump filling processes, important performance parameters for examination are pump life, spallation, and effect on dosing accuracy. The influence of tubing selection on the filling process can be evidenced through operational reliability (range of pump life with filling equipment), impact to product being transferred (particulate shedding or spall), and the ability to hit dosing targets correctly and consistently.

Silicone tubing is often chosen for final fill pumping applications because of its compatibility with drug proteins, low extractables, and retention of physical properties over a wide temperature range (low compression set, flexibility, kink resistance, etc.). As silicone tubing differs in formulation and processing from supplier to supplier, differences can be expected in silicone tubing performance parameters as well. This paper focuses on the performance of five different platinum-cured silicone tubing products that are marketed for biopharma filling applications. The tests measure filling accuracy and precision, pump life, and the degree of spallation generation.

Saint-Gobain Sani-Tech® SPT-60L provides four times improvement in filling accuracy and two times improvement in precision over the closest performing competitor tubing.

Ⓐ Fill Precision and Accuracy (materials and methods)

Dispensed volume should correspond to the intended dose (accuracy) and be reproducible over time (precision). Providing the correct volume of drug product in the final container is critical for proper dose delivery aside from the cost impact of over/under filling (excess product, rejected containers).

SILICONE TUBING

Sani-Tech® SPT-60L was tested against four other silicone tubing products marketed for biopharma filling applications and tested for vial fill accuracy (dispensing target fill volume) and precision (repeatability of delivered volume). All silicone tubes were 1/16” x 3/16” ID x OD (1.6 x 4.8 mm). The silicone tubes and size were selected to represent tubing used in final fill drug manufacturing. Tubing was tested as non-irradiated and after gamma irradiation. Gamma irradiation was performed by STERIS (Libertyville, IL USA) at a delivered dose of average 42 kiloGray (kGy).

DATA COLLECTION

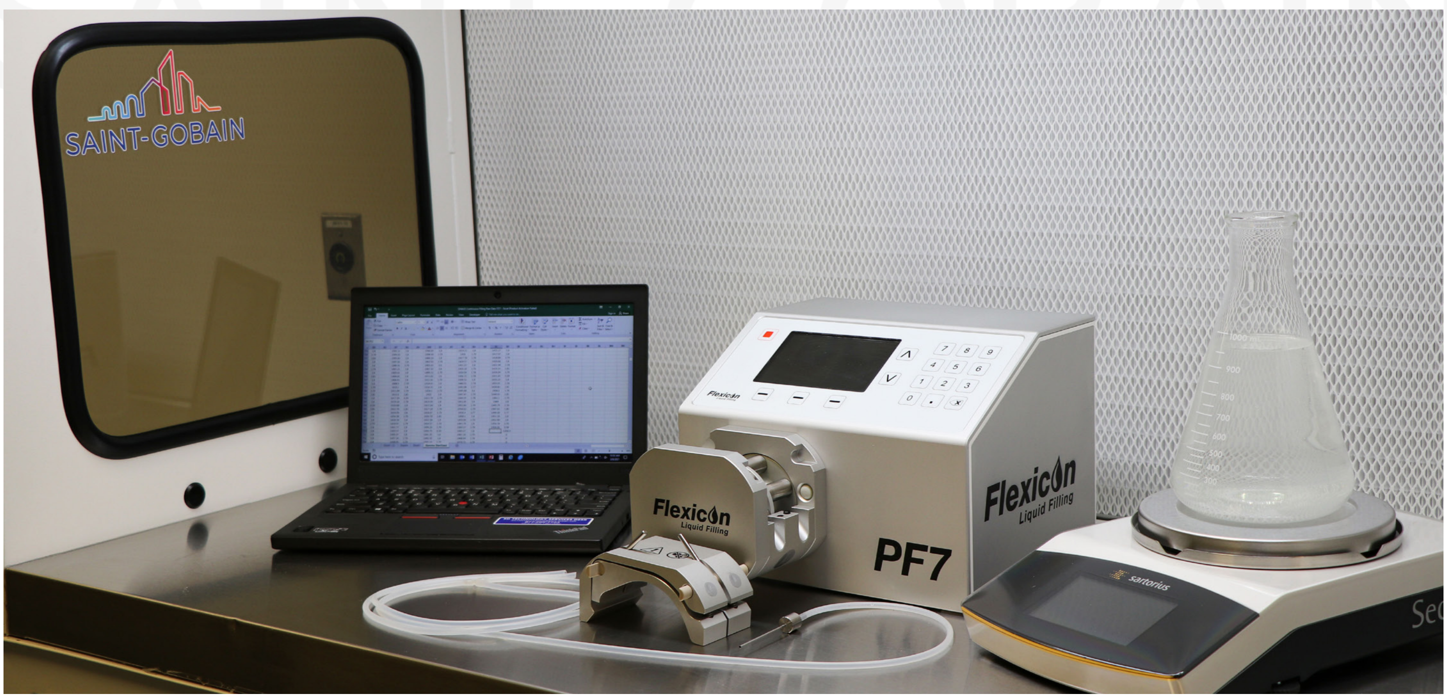
Vial fill precision and accuracy was automated with the OHAUS® Explorer® EX4202 electronic scale paired with Winwedge software for data collection of a RS232 instrument directly into Excel. Water was dispensed into a 2,000 ml flask with a mineral oil trap to avoid evaporation using a stainless steel AISI 316 L filling nozzle 30-030-016 (Watson-Marlow Flexicon A/S Ringsted, Denmark). The filling nozzle (1/16” ID (1.6 mm)) was chosen for the targeted fill volume of 1.8 ml.

BENCHTOP FILLER

A Flexicon® PF7 peristaltic filling machine by Watson Marlow was used in the study. Settings for the filling system were speed 300 and 400 RPM, acceleration of 100, deceleration of 100, and 10 sec fill delay. The fill delay was to allow time for the scale to stabilize between readings. Gamma irradiated tubing was tested at both 300 and 400 RPM with the same 1.8 ml targeted fill volume. All other settings remained the same.

METHOD

Two 24” lengths (610 mm) of the pump tubing to be evaluated were attached to a wye-connector (PVDF) and loaded into the pump head. An additional length of tubing (SPT-60L, 36” (914 mm)) was added behind the dispensing head and was terminated with a stainless steel filling nozzle to complete the pumping assembly. The filling nozzle was held above the end water height in the 2,000 ml collection flask. The pump was primed and calibrated following the pumps operating procedure. The pump was set-up to perform 1,000 vial fills. The scale would automatically read and record every 10 seconds. This test was performed in duplicate with two new pieces of pump tubing.



Saint-Gobain Life Sciences’ lab test environment

RESULTS

NON-IRRADIATED VS GAMMA IRRADIATED TUBING

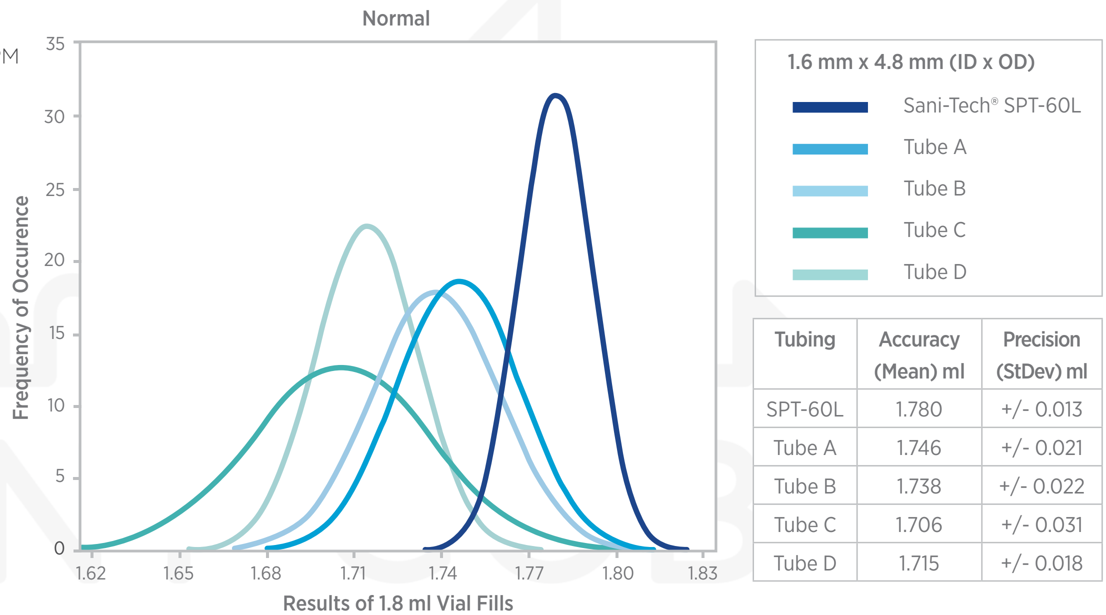
A histogram fit shows the results of 1,000 vial fills performed in duplicate for both non-irradiated and irradiated pump tubes.

The histograms allow for visualization of the accuracy (target fill) and precision (repeatability) of filling performance at 400 RPM for the 1.8 ml target volume.

A.1 Histogram Fit for 5 Different Non-Irradiated Platinum-Cured Silicone Tubes

Test Conditions:
Targeting 1.8 ml vial fill at 400 RPM

All tubes were calibrated to hit the target of 1.8mL on the first dispense. The deviation from the target and the deterioration of the tubing is measured here.

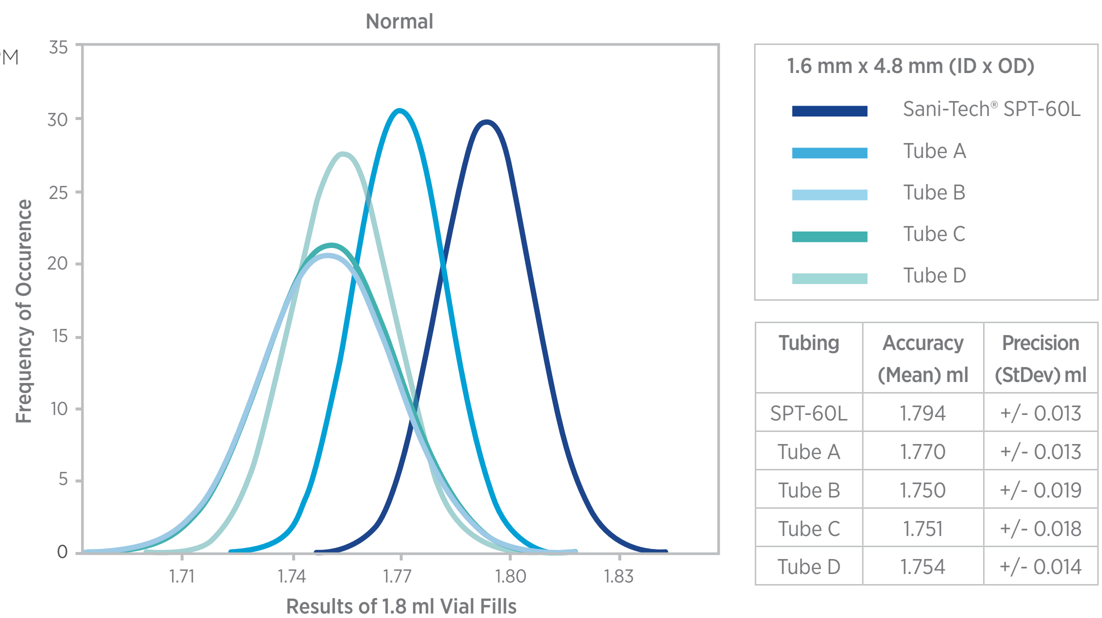


Tubing	Accuracy (Mean) ml	Precision (StDev) ml
SPT-60L	1.780	+/- 0.013
Tube A	1.746	+/- 0.021
Tube B	1.738	+/- 0.022
Tube C	1.706	+/- 0.031
Tube D	1.715	+/- 0.018

A.2 Histogram Fit for 5 Different Gamma Irradiated Platinum-Cured Silicone Tubes

Test Conditions:
Targeting 1.8 ml vial fill at 400 RPM

All tubes were calibrated to hit the target of 1.8mL on the first dispense. The deviation from the target and the deterioration of the tubing is measured here.

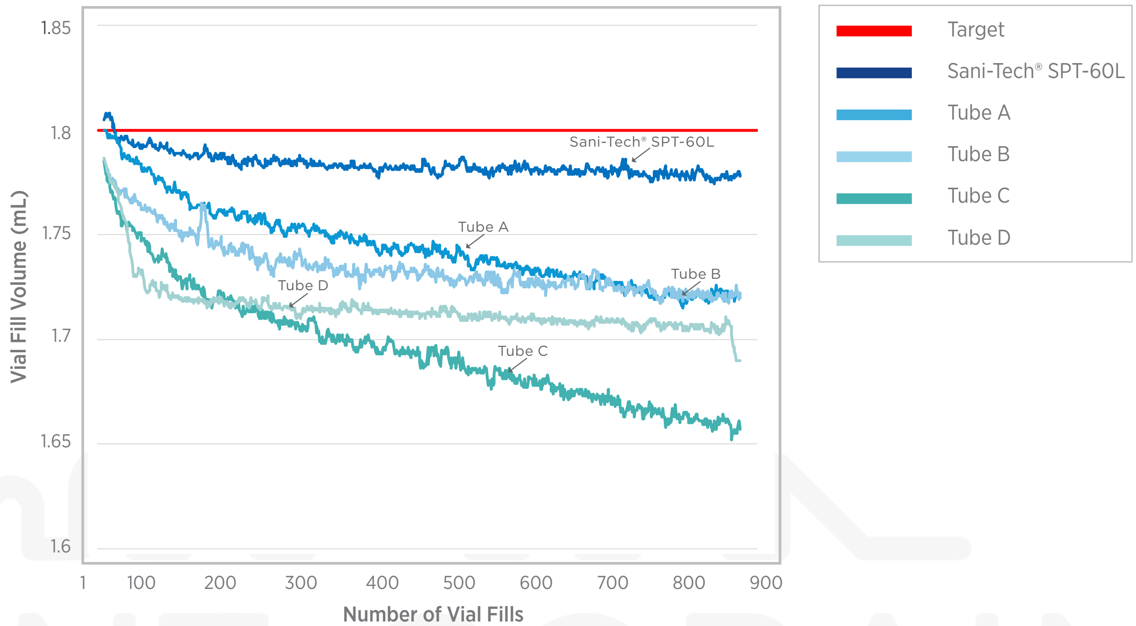


Tubing	Accuracy (Mean) ml	Precision (StDev) ml
SPT-60L	1.794	+/- 0.013
Tube A	1.770	+/- 0.013
Tube B	1.750	+/- 0.019
Tube C	1.751	+/- 0.018
Tube D	1.754	+/- 0.014

A.3 10 Point Moving Average for Individual Vial Fill Readings Targeting 1.8 ml Using Non-Irradiated Tubing Samples

A 10 point moving average represents the trend in data. It smooths out data by averaging subsets of 10 data points (for example, 1-10, 2-11, 3-12, 4-13, etc.).

All tubes were calibrated to hit the target of 1.8mL on the first dispense. The deviation from the target and the deterioration of the tubing is measured here.



Discussion

Sani-Tech® SPT-60L was the most accurate tubing for vial fill accuracy.

When gamma irradiated tubes were tested, Sani-Tech SPT-60L and Tube A had similar results for both accuracy and precision at 300 RPM (not shown), but at 400 RPM Sani-Tech SPT-60L had improved accuracy compared to Tube A. Better accuracy at higher pumping speeds can allow for shorter filling campaigns. Sani-Tech SPT-60L shows a clear advantage over other platinum-cured silicone tubes.

Sani-Tech SPT-60L has been tested to provide best-in-class accuracy and precision with at least a 4x improvement in filling accuracy and 2x improvement in precision when compared to competitive silicone pump tubing marketed for filling applications. The increased accuracy and precision provides additional assurance that vials are filled to the target volume and reduces the potential for costly over/under fills resulting in rejected vials.

Saint-Gobain Life Sciences' Sani-Tech® SPT-60L Tubing

B Pump Life (materials and methods)

Extended pump life provides assurance that tubing will deliver continued performance under a variety of pump conditions without rupturing.

Pump life was tested via an internal test method for determining the life of tubing until failure on non-irradiated tubing. This procedure used a Cole-Parmer® Masterflex® L/S® drive with a Masterflex® L/S® standard pump head (3 rollers) or an Easy-Load® II (4 rollers) pump head. Three different test conditions were used as shown in table (B.1) below.

In Test Condition #1, a Masterflex® L/S® standard pump head was operated at 300 RPM with 10 psi of backpressure. Backpressure is formed by flow-restriction of the tube with an inline pressure gauge. The tubing was tested until failure. Failure is determined by a leak sensor that automatically stops the pump when moisture is detected and records the number of hours. Pump life is defined as the length of time before tube failure/rupture.

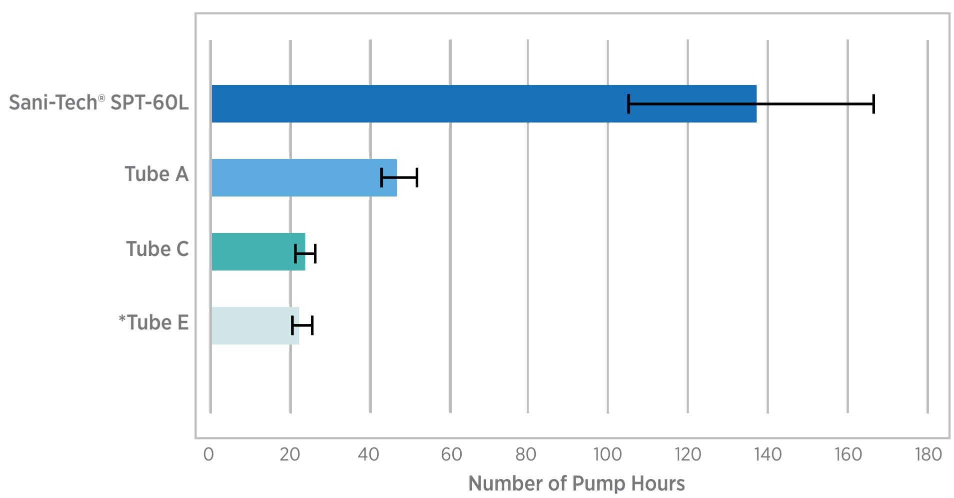
B.1 Tubing Test Conditions for Pump Life Studies

Testing Parameters	Test Condition 1	Test Condition 2	Test Condition 3
Tubing ID x OD	1/4" x 3/8" (6.4mm x 9.5mm)	1/4" x 3/8" (6.4mm x 9.5mm)	1/16" x 3/16" (1.6mm x 4.8mm)
Treatment	Non-Irradiated		
RPM	300	400	400
Backpressure (psi)	10	0	0
Pump Drive	Cole-Parmer® Masterflex® L/S® Standard Digital Drive 07522-20		
Pump Head	Masterflex® L/S® Standard Model 7017-21		Masterflex® L/S® Easy-Load® II Model 77200-60
Sample Size	8	5	5

B.2 Number of Pump Hours for Four Different Silicone Tubings

Test Condition 1:
Pump life of Sani-Tech® SPT-60L with 300 RPM and 10 psi of backpressure on a standard Masterflex® L/S pump head.

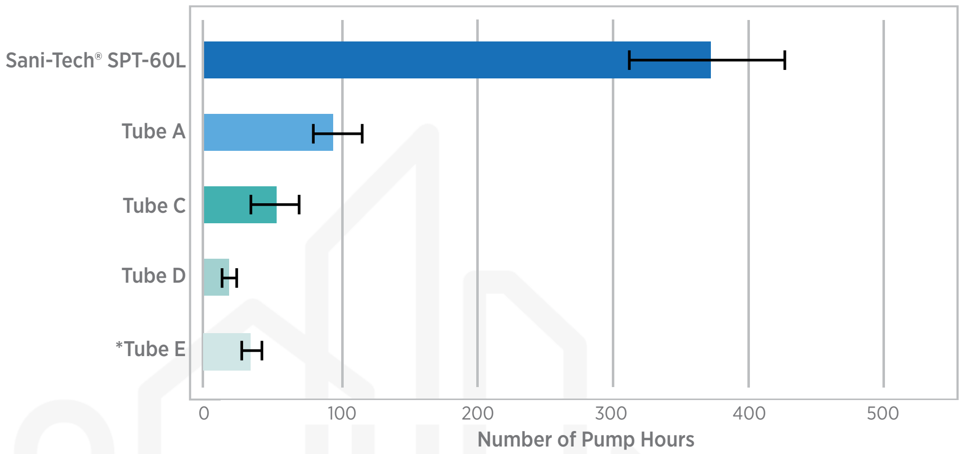
*Tube E was only available in 1/4" x 3/8" ID x OD for our testing. For this reason, we could not include it in Test Condition 3.



B.3 Number of Pump Hours for Five Different Silicone Tubings

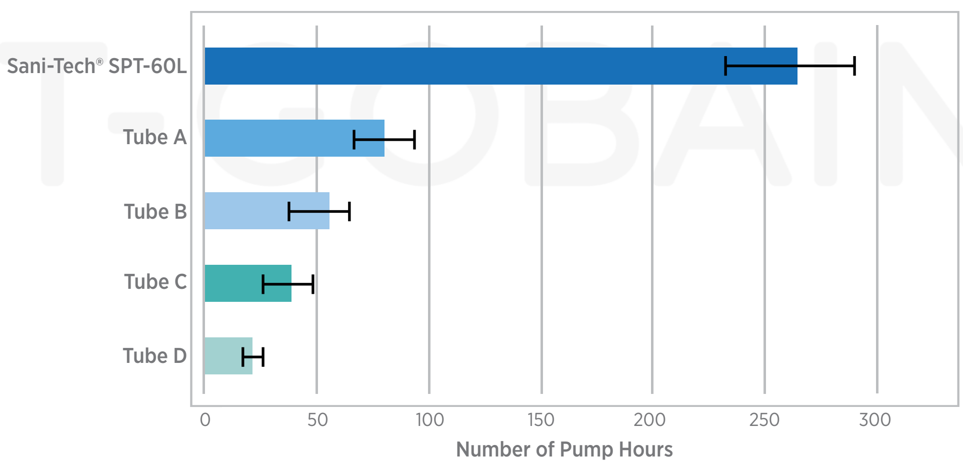
Test Condition 2:
Pump life of competitive silicone tubing and Sani-Tech® SPT-60L with 400 RPM and no backpressure on a standard Masterflex® L/S pump head.

*Tube E was only available in 1/4" x 3/8" ID x OD for our testing. For this reason, we could not include it in Test Condition 3.



B.4 Number of Pump Hours for Five Different Silicone Tubings

Test Condition 3:
Pump life of competitive tubing and Sani-Tech® SPT-60L with 400 RPM and no backpressure on a Masterlfex® L/S Easy-Load® II pump head.



Discussion

Sani-Tech® SPT-60L was tested against competitive silicone tubing for pump life on a Cole-Parmer® Masterflex® L/S® drive with either a Masterflex® L/S® standard pump head (3 rollers) or an Easy-Load® II (4 rollers) pump head under different test conditions.

Sani-Tech SPT-60L was shown to have longer pump life over other platinum-cured silicone tubing. Sani-Tech SPT-60L's long pump life provides customers with assurance that the tubing will provide continued performance under a variety of pump conditions.

C Spallation (materials and methods)

Spallation (or particle shedding) results from the shear-compression force in a peristaltic pump causing the release of particles from tubing. For injectable products, industry guidance provides the target of drug products that are 'essentially free' of particles, while current regulations establish the number and size of particles allowable per volume. Selecting a peristaltic pump tubing for final filling with low spallation is critical because the filling operation occurs after the final sterile filtration step.

SILICONE TUBING

Five different silicone tubes that are used in biopharma were selected to evaluate spallation. All silicone tubes were 1/16" x 3/16" ID x OD (1.6 x 4.8 mm). The silicone tubes and size were selected to represent tubing used in final fill drug manufacturing. Tubing was tested as non-irradiated and after gamma irradiation. Gamma irradiation was performed by STERIS (Libertyville, IL USA) at a delivered dose of average 42 kiloGray (kGy).

FLOW MICROSCOPY

Spallation was analyzed using imaging flow cytometry (IFC). FlowCam™ 8000 (Fluid-Imaging Technologies Scarborough, ME) is a flow imaging cytometer (particle counter) and particle analyzer that is paired with image analysis software VisualSpreadsheet® Particle Analysis Software Version 4. A flowrate of 5 ml/min was used at a magnification of 4x. No size filter and an auto image rate of 50 frames/second was used. The flow cell (FC300FV) had a 300 µm flow cell depth and a 1500 µm flow cell width.

BENCHTOP FILLER

A Flexicon® PF7 peristaltic filling machine by Watson Marlow was used in the study with a speed of 300 RPM, acceleration of 100, and deceleration of 100 with a fill delay of 1 second. Targeted fill volume for this study was 1.8 ml. The benchtop filler, along with the IFC, was placed in an Air Science® LF Series laminar flow cabinet to avoid contamination. Water was dispensed from a Milli-Q® IQ 7000 (Millipore Sigma) Ultrapure Lab water system setup with a 0.22 µm filter.

METHOD

SURFACE ROUGHNESS

Surface roughness was examined along the cross-section of the tube before pumping, using a Nanovea 3D Surface Profilometer (white light chromatic aberration technique). One area was scanned on the surface of each tube, two tubes for each sample.

SEM

A Zeis Merlin SEM was used to take high resolution images of the cross-section of the tubes that was within the pump head before and after pumping. Samples were prepped with a Quorum Q Series 150T ES sputter coater to deposit a thin layer of conducting Au material on the specimen surface.

SPALLATION

Spallation measurement methods typically sample a small amount of recirculated fluid (<10%) during pump tests (1-3). This methodology was not chosen because it was found that the particles that come off are not homogeneous in the fluid. In this study, small differences between silicone tubes were being investigated. After 1,000 cycles there may only be 1-5 large particles (>100 µm) in the entire fluid (100 ml) that was recirculated. It was important to be able to count these particles when they come off the tube to be able to make an accurate analysis.

To provide a more accurate representation of the particles generated over time, a modified method was created to compare the silicone tubes. 25 ml of UltraPure water was run through the FlowCam® 8000 as a blank first. Tubing was loaded on the Flexicon® PF7 pump and the first 3 vial fills of 1.8 ml was discarded to rinse the tubing of any contamination. The test was done without a needle at the end of the tubing. 100 ml of Ultrapure water was recirculated through the pump for 1,000 cycles at 300 RPM. The entire flask of 100 ml of recirculated (pumped) water was sampled through the IFC at a rate of 5 ml/min and at a magnification of 4x. This was repeated for 1,000 cycles and then another 1,000 cycles, each time with new 100 ml of UltraPure water. The IFC sampled the entire fluid pumped for the first 1,000, second 1,000, and third 1,000 cycles of vial fills. The tubing was not touched during the entire test to complete a total cycle of 3,000 vial fills. This test was done in duplicate for all 5 of the silicone pump tubes that were selected.

After 1,000 cycles there may only be 1-5 particles > 100 µm in the entire fluid (100 ml) that was recirculated.

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1. Cheng Her, L. M. (2020). Effects of Tubing Type, Operating Parameters, and Surfactants on Particle Formation During Peristaltic Filling Pump Processing of a mAb Formulation. *Journal of Pharmaceutical Sciences*, 1439-1448.
2. Romansky, S. M. (2002). Spalling and Sorption of Tubing for Peristaltic Pumps. *Pharmaceutical Development and Technology*, 317-323.
3. Verena Saller, J. M.-P.-C. (2014). Particle Shedding from Peristaltic Pump Tubing in Biopharmaceutical Drug Product Manufacturing. *Pharmaceutics, Drug Delivery and Pharmaceutical Technology*, 1440-1450.

Benchtop filler in Saint-Gobain Life Sciences' lab test environment

RESULTS

SURFACE ROUGHNESS

The surface roughness parameters of the tubes before pumping for non-irradiated tubing were very similar. Tube A had the highest surface roughness parameter, but little difference was observed between platinum-cured silicone tubing, indicating that they all have a relatively similar smooth bore on the ID.

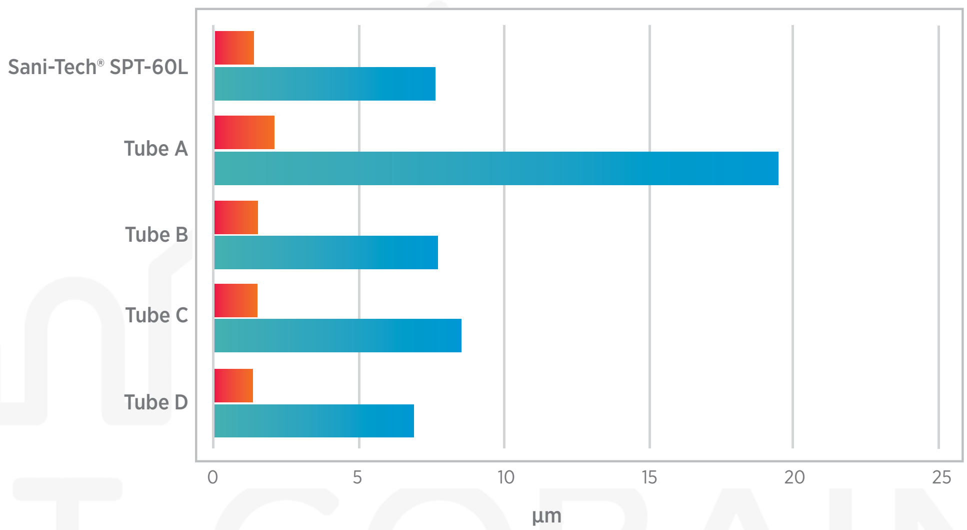
C.1 Average Surface Roughness of the ID Before Pumping

Sa (µm)

The arithmetical mean height most commonly used to evaluate surface roughness

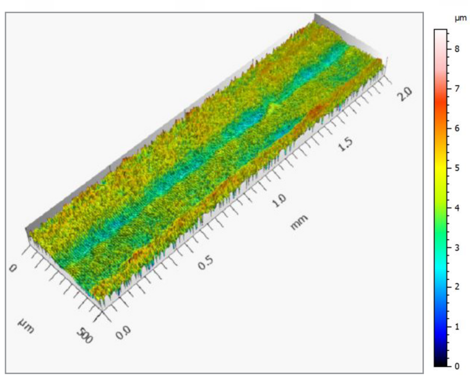
Sz (µm)

The maximum height from the lowest point to the highest point

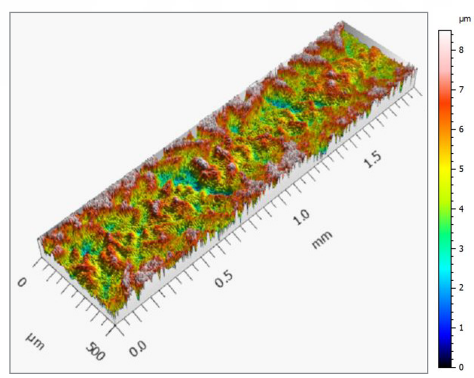


C.2 3D Surface Scans of Tubing

Imaging Conditions:
Surface Scan = 130 Micron Pen at 300Hz
Area Scans = 0.5 mm x 2.0 mm
Step Size = 5 µm for both “X” and “Y” Axis



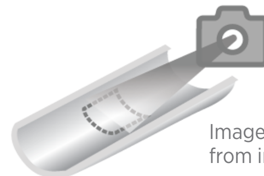
Sani-Tech® SPT-60L 3D height parameter



Tube A 3D height parameter

SEM

Images were taken of non-irradiated tubes before and after pumping of Sani-Tech® SPT-60L and Tube C. The surface roughness values above and the SEM images show little difference before pumping; however, after pumping, Tube C is shown to have visual deterioration of the surface. Sani-Tech SPT-60L shows little change in the surface morphology by SEM. This is further illustrated in the spallation data.

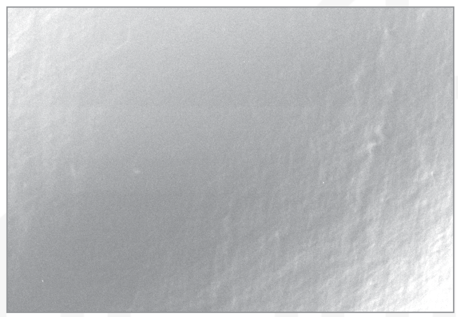


Images C.3 - C.5 were taken from inside the tubing.

C.3 Before Pumping

Imaging Conditions:
EHT = 4.00 kV
WD = 7.0 mm
Sample ID = Before pumping
Signal A = InLens
Width = 500.0 µm

Sani-Tech® SPT-60L (left) and Tube C (right) before pumping.



Sani-Tech® SPT-60L before pumping. The image represents the inner surface of the tubing.

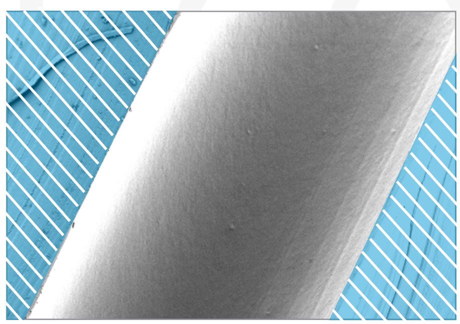
Tube C before pumping. The image represents the inner surface of the tubing.

C.4 After Pumping 3,000 Vial Fills

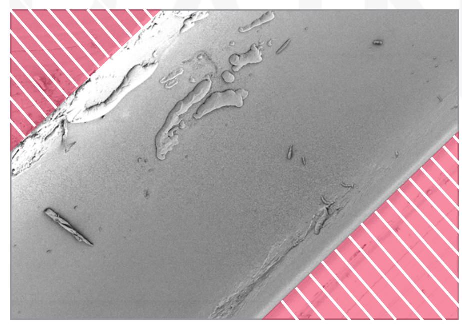
Imaging Conditions:
EHT = 4.00 kV
WD = 8.2 mm
Sample ID = After pumping
Signal A = HE-SE2
Width = 2.500 mm

Sani-Tech® SPT-60L Tube Wall

Tube C Wall



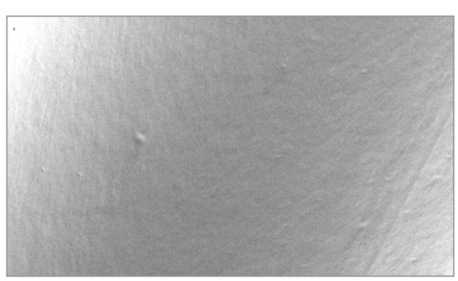
Sani-Tech® SPT-60L after pumping. The center of the image is the inner surface of the tubing.



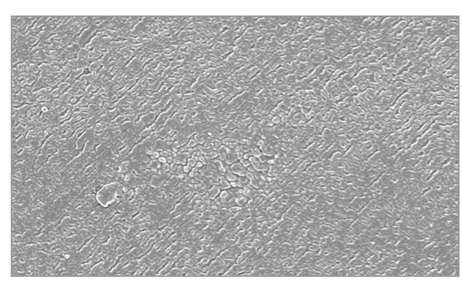
Tube C after pumping shows material shedding from the tubing. The center of the image is the inner surface of the tubing.

C.5 Zoom on Tube C Inner Surface Deteriorated

Imaging Conditions:
EHT = 4.00 kV
WD = 8.0 mm
Sample ID = After pumping
Signal A = InLens
Width = 100.0 µm



Sani-Tech® SPT-60L inner surface after pumping.

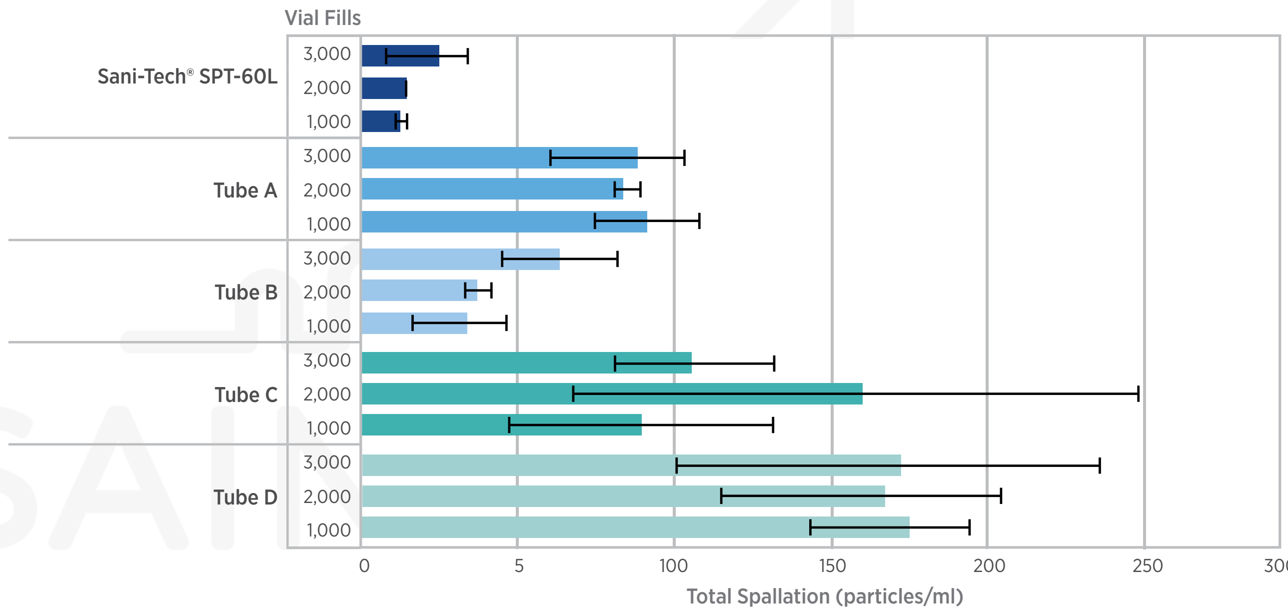


Tube C after pumping shows material deterioration at higher magnification.

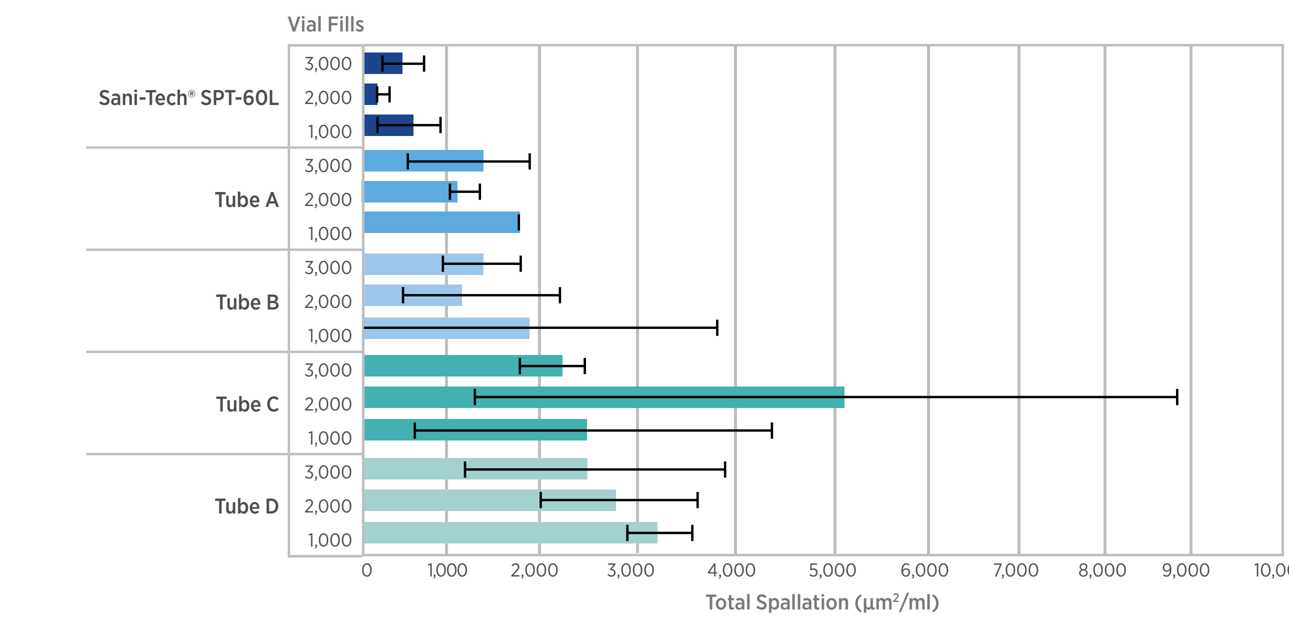
SPALLATION OF NON-IRRADIATED TUBING

Spallation is represented by particles/ml and by area of total spallation/ml (µm²/ml). These two parameters illustrate both total particles that are produced in the fluid path by tubing and the relative size of particles. Sani-Tech® SPT-60L non-irradiated has both the least amount of particles/ml and total area, showing that Sani-Tech SPT-60L is not releasing any large particles (>25 µm). The spallation amounts are independent of each 1,000 vial fills, with no trend in spallation observed. Tube D has the highest particles/ml, but when compared to the total area produced, it is mostly smaller particles because Tube C has the highest area of spallation produced.

C.6 Non-Irradiated: Total Spallation, Particles >2 µm (particles/ml) for Silicone Tubes



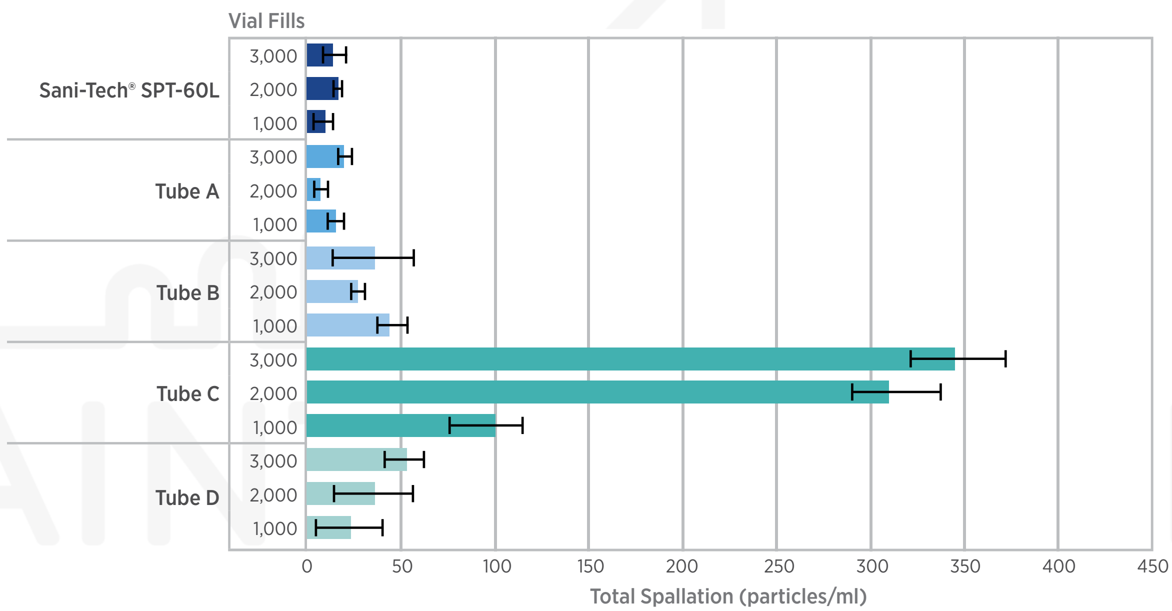
C.7 Non-Irradiated: Total Spallation Area (µm²/ml) for Silicone Tubes



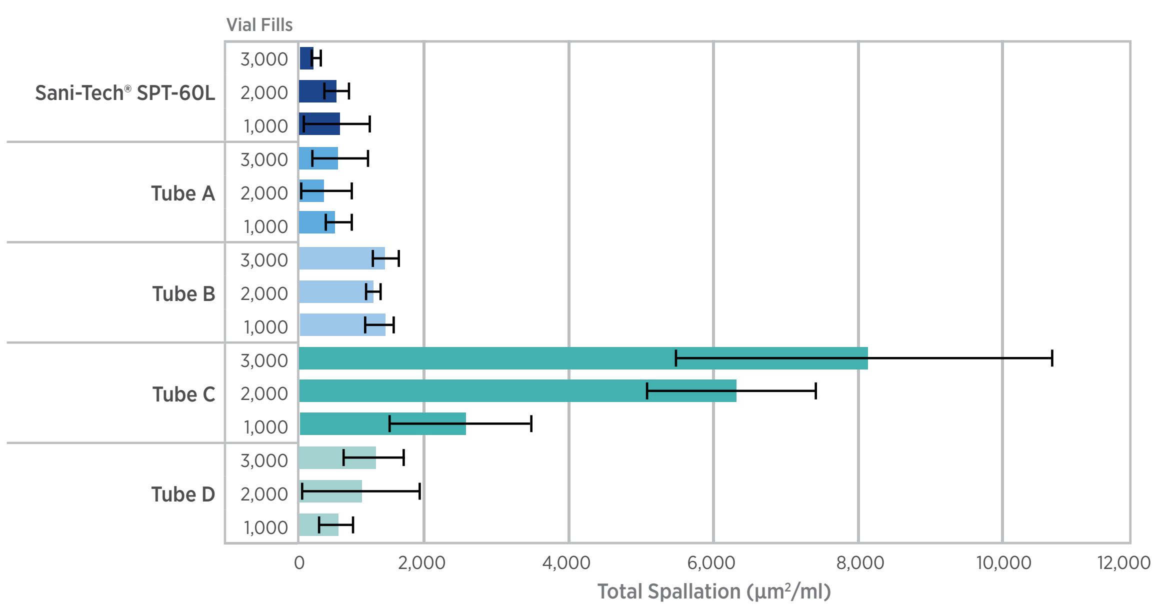
SPALLATION OF GAMMA IRRADIATED TUBING

The amount of total spallation produced after gamma irradiation does show a significant decrease in most silicone tubes, except for Tube C, which continues to have high spallation count. Sani-Tech® SPT-60L and Tube A have the least amount of particles/ml within all five samples. When comparing the size of the particles produced, Sani-Tech SPT-60L generates smaller particles than tube A when evaluating the area of the total spall produced.

C.8 **Gamma Irradiated: Total Spallation, Particles >2 µm (particles/ml) for Silicone Tubes**



C.9 **Gamma Irradiated: Total Spallation Area (µm²/ml) for Silicone Tubes**



C.10 FlowCam Particles (Examples from First 1,000 Vial Fills)

Top: Sani-Tech® SPT-60L particles from 10-25µm

Bottom: Tube D particles from 25-100µm

Discussion

Sani-Tech® SPT-60L was shown to have both similar surface roughness and SEM morphology images as other silicone tubes chosen in this study prior to pumping, but the SEM images and spallation after pumping show a significant difference between silicone pump tubes. Tube C showed clear abrasion of the surface that was consistent with spallation data. Non-irradiated Sani-Tech SPT-60L was shown to have both low spallation counts and total area of spallation released. After gamma irradiation, Sani-Tech SPT-60L and Tube A have a similar particle count, but the total area of particles released shows that Tube A released larger particles than Sani-Tech SPT-60L. Sani-Tech SPT-60L produced smaller particles, and Tube A produced larger particles. Tube C's spallation was the largest of all of the tubes and was visible in SEM images with clear deterioration of the surface after pumping. Sani-Tech SPT-60L produced low spall when compared to other silicone pump tubes, both before and after gamma irradiation.

Conclusion

Precise filling, long pump life, and low spallation generation has shown Sani-Tech® SPT-60L final fill tubing to be a superior final fill pump tubing when compared against other silicone tubing marketed for biopharma filling. With up to 250 hr pumping (depending on the fluid and pumping conditions), filling accuracy and precision was maintained over time with low spallation generation. Sani-Tech SPT-60L has been recommended by key filling equipment manufacturers for their customers based on these properties.

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About

Authors

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Heidi has her Master's in Materials Process Engineering from Worcester Polytechnic Institute and a BSE in Chemical Engineering from the University of Massachusetts in Amherst. She has spent 15 years specializing in silicone formulations and application specific testing. Her current research is focused on tubing used in final fill drug manufacturing.

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Heather has her MS in Biological Engineering from University of Missouri-Columbia. She has worked within in the single-use industry for 15 years serving in engineering, R&D, operations and marketing roles. Her product responsibilities include custom silicone assemblies with a focus on final fill applications.

Saint-Gobain Life Sciences

Saint-Gobain Life Sciences is an industry leading provider of material science based solutions for single-use fluid management including TPE and silicone tubing, connection and flow control components, bioprocess and cell culture bags, filtration products, sensors, and over-molded technology, all available in customized assemblies that are produced in 18 manufacturing facilities located around the world. To find out more about Saint-Gobain Life Sciences and to learn how we can assist you with your application needs, visit our website.

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