Opportunity to Mitigate Risk with Saint-Gobain ValPlus™ Certification

CONTAINMENT · FLUID TRANSFER · FILTRATION · CONNECTION & FLOW CONTROL · CLOSURE SYSTEMS · SINGLE-USE ASSEMBLIES

BIOPROCESS SOLUTIONS

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Opportunity to mitigate risk with Saint-Gobain ValPlus™ certification

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Saint-Gobain ValPlus™ provides pharmaceutical manufactures increased confidence in the cleanliness of the tubing products they use in critical applications.

The purpose of this paper is to describe the ValPlus™ testing protocols, share the results obtained, and illustrate the value it offers pharmaceutical manufacturers.

Single-use systems are becoming more common in bioprocessing operations due to their low capital requirements and lower validation costs. As this trend continues to develop, pharmaceutical manufacturers are requesting single-use system manufacturers to provide assurance that their single-use products are in compliance with current good manufacturing practices and do not alter the drug products beyond established regulatory requirements.[1]

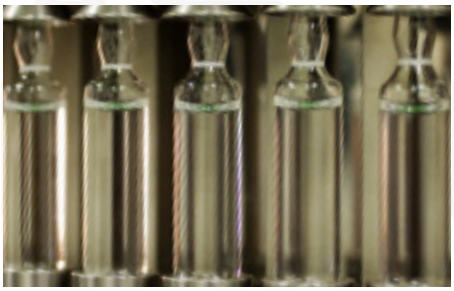
Certification of product cleanliness has become common for manufacturers of final packaging components such as vials and stoppers, but rarely are tubing products certified to meet endotoxin, bioburden, and particulate standards. In some cases, pharmaceutical manufacturers have taken their own risk-mitigation measures to reduce potential contamination such as rinsing tubing products with water for injection (WFI). However, these strategies are costly and in some cases, infeasible. Given the costs of this approach, the pharmaceutical manufacturing industry is primed for a change in the typical risk control strategy for tubing.

Saint-Gobain ValPlus™ - The Confidence of Validation

Saint-Gobain ValPlus™ provides pharmaceutical manufacturers increased confidence in the cleanliness of the tubing products they use in critical applications. Available with a variety of Saint-Gobain tubing brands such as C-Flex® and Sani-Tech®, ValPlus is a certification to USP <788> for particulate, USP <85> for bacterial endotoxin, and ISO 11737 for bacterial and fungal bioburden. This higher level of quality assurance is an industry-leading effort to quantify and reduce risks associated with fluid path contamination. The following white paper explains the methodology used to develop ValPlus and its advantages to the pharmaceutical manufacturer. In many cases, ValPlus certification may reduce risks related to validating fluid-path components, resulting in faster time to market and significant cost-savings.

Sampling Plan and Scope

A statistically sound sampling plan was created to test ValPlus™ certified products using industry standard ANSI Z1.4 (2008) with a general inspection level of II. Validated test methods were based upon standard compendial testing, namely USP <85>, <161>, <788>, and ISO 11737. The determined maximum batch size was taken to be 150 coils of tubing for most products. At an AQL of 1.0 per the Saint-Gobain Validation Master Plan, a minimum of 13 samples were tested. Products with a smaller maximum batch size, such as Sani-Tech® STHT®-C, required only 9 samples to be tested at an AQL of 1.0.



For each material, three extrusion campaigns were conducted under the normal process controls established for the manufacturing location. During each extrusion campaign, tube samples were manufactured with inner diameters specified by the bracketed experimental design. Samples were carefully collected at even intervals throughout the extrusion trial then labeled and controlled before submitting for testing. Particulate, endotoxin and bioburden testing was performed on the internal surface of the tube.

The tubing formulations tested and their size ranges are shown in Table 1.

[1] U.S Regulation 21 CFR 211.65 and "The rules governing medicinal products in the European Union" Eudralex Volume 4, Section 3.39

Table 1

Summary of formulations tested, location and sizes tested for ValPlus™ certification.

Tubing Formulation	Minimum Inner Diameter	Nominal Inner Diameter	Maximum Inner Diameter
C-Flex® 001	0.031" (0.8 mm)	0.125" (3.2 mm)	0.188" (4.8 mm)
C-Flex® 072	0.063 (1.6 mm)		
C-Flex® 374- Site 1	0.375" (9.5 mm)		
C-Flex® 374- Site 2	0.063" (1.6 mm)	0.374" (9.5 mm)	0.500" (12.7 mm)
Sani-Tech® STHT®-C	0.250" (6.4 mm)	0.375" (9.5 mm)	0.500" (12.7 mm)
Sani-Tech® STHT®-65	Rationale based on Sani-Tech(R) STHT(R)-C validation		
Sani-Tech® STHT®-R	0.250" (6.4 mm)	0.375" (9.5 mm)	0.500" (12.7 mm)
Tygon® 3350	0.063" (1.6 mm)		

Test Results - USP <788> Subvisible particulate

Samples were tested per USP <788> at an independent, ISO 17025 accredited test laboratory and registered with the US FDA. Samples were cut to 1 meter lengths and filled approximately 75% with low particulate water (LPW) with one end of the tube clamped. The other end of the tube was also clamped and the sample was inverted ten times to allow the fluid to fully contact the inner surface of the tube. The effluent was collected and analyzed via the light obscuration method using an HIAC Liquid Particle Counting System (LPC) Model 9703. Each sample was tested and results were not pooled. For smaller diameter tubes where inverting the sample was not feasible, the tubing was flushed with LPW ten times the interior volume and the effluent collected. All samples were within the acceptable limits specified by USP <788>: ≤12 particles/ml for particles >10 µm and ≤2 particles/ml for particles >25 µm. The average number of subvisible particles counted may be found in Figure 1 and Figure 2. Error bars represent the minimum and maximum number of particles counted for each trial.

Figure 1: Subvisible Particles >10 µm

Average number of subvisible particles >10 µm in various tubing formulations. Error bars represent maximum and minimum number of particles detected in each formulation.

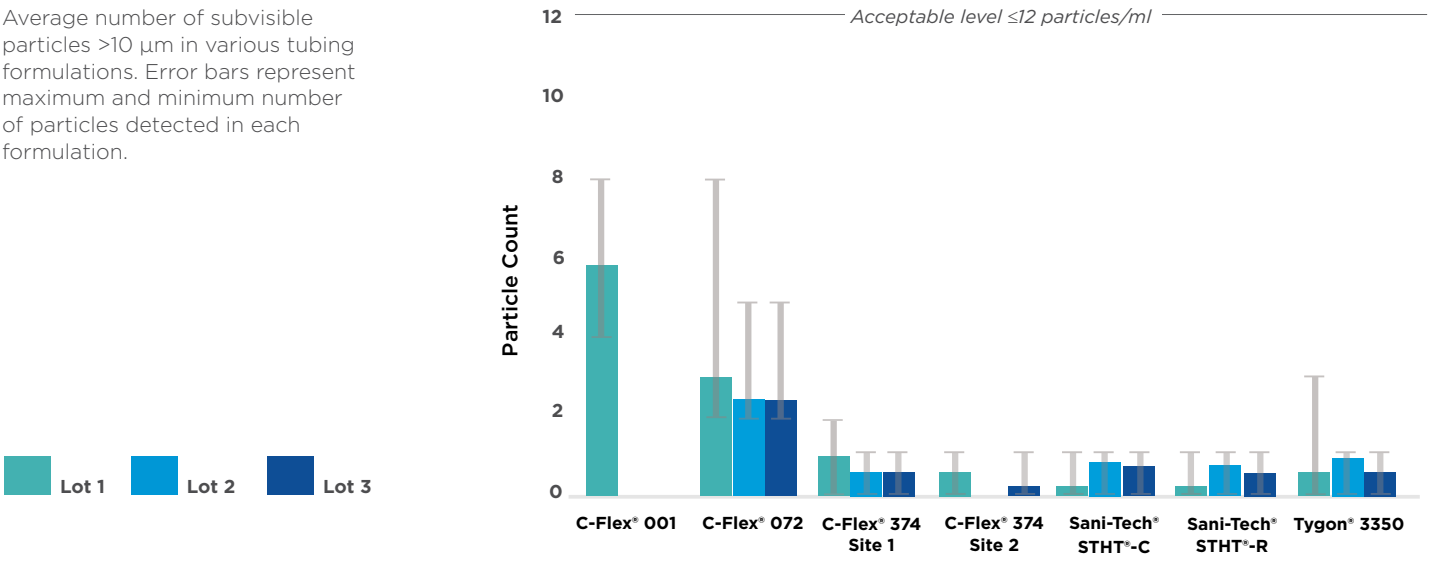
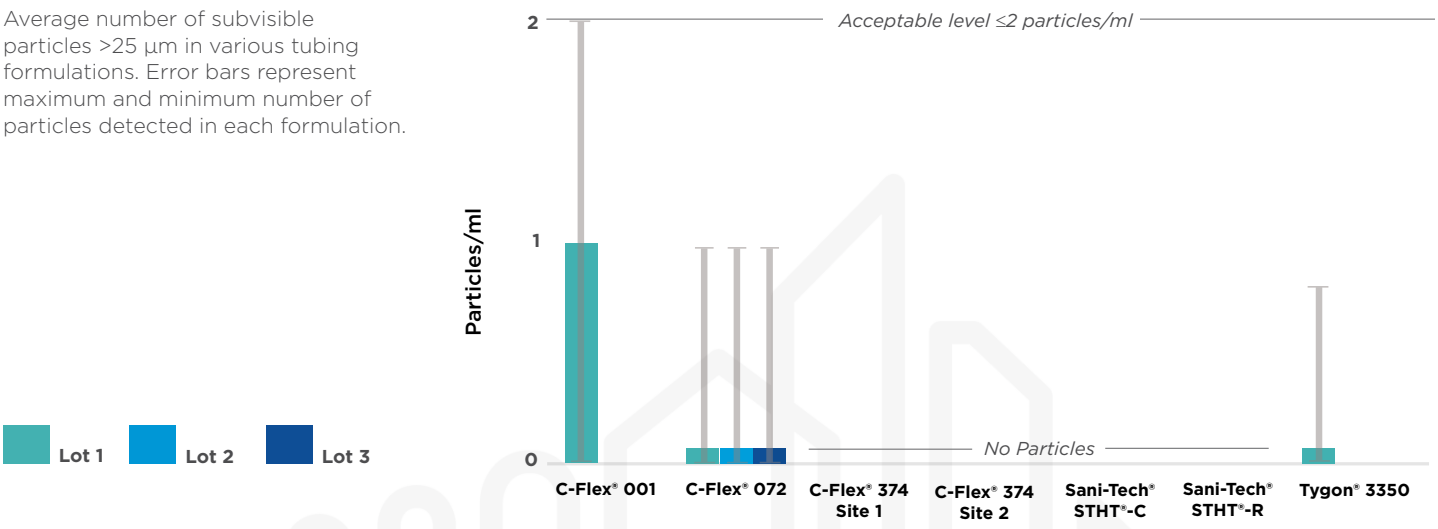


Figure 2: Subvisible Particles >25 µm

Average number of subvisible particles >25 µm in various tubing formulations. Error bars represent maximum and minimum number of particles detected in each formulation.



Test Results – USP <85> Bacterial Endotoxin

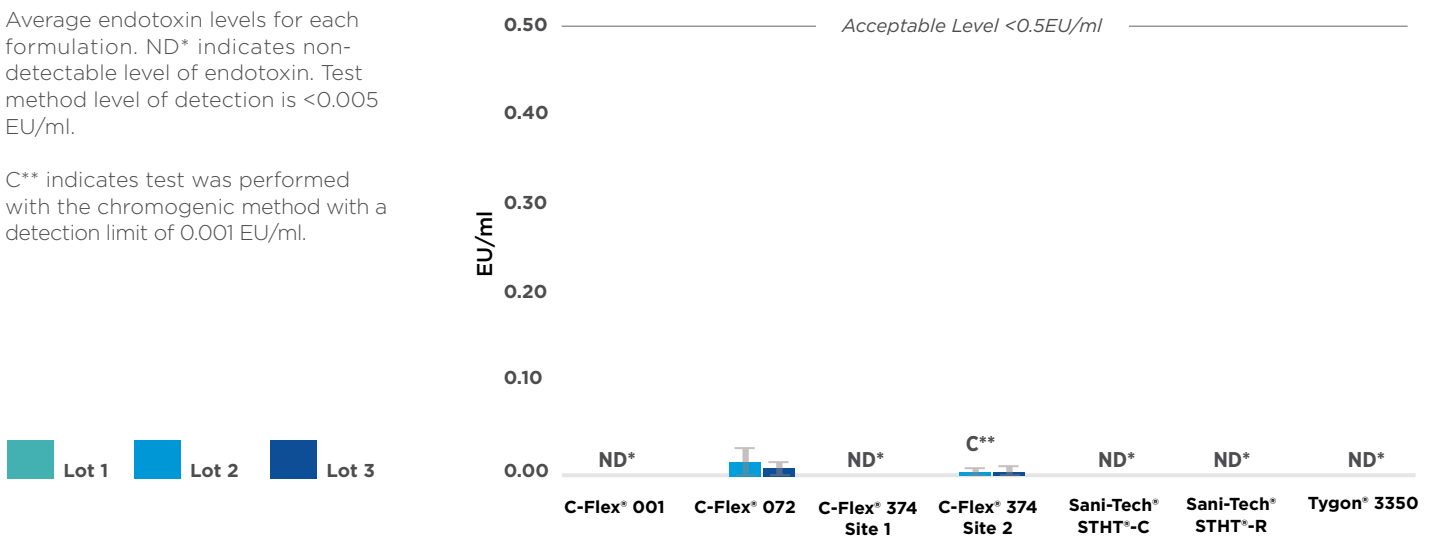
Bacterial endotoxin testing was undertaken at the same independent laboratory used for subvisible particulate quantification. Samples were cut to 1 meter lengths then filled to approximately 75% with water for Bacterial Endotoxins Test (BET) with one end of the tube clamped. After filling, the other end of the tube was clamped and the sample was inverted ten times to allow the fluid to fully contact the inner surface of the tube. The effluent was then collected and analyzed via the gel clot LAL method (limit of detection 0.005 EU/ml) or the chromogenic method (limit of detection 0.001 EU/ml). For rinsing volumes less than 40 ml, results must be below 0.5 endotoxin units (EU)/ml to be within acceptable limits. For rinse volumes greater than 40 ml, the 0.5 EU/ml limit must be upheld and there is a 20 EU/device limit.

Results in Figure 3 indicate that all formulations tested were significantly below the acceptable limits. Data was extrapolated to a 15 m length of tube and indicates that 15 m coils of tubing are below the 20 EU/device limit.

Figure 3: Average Endotoxin Levels

Average endotoxin levels for each formulation. ND* indicates non-detectable level of endotoxin. Test method level of detection is <0.005 EU/ml.

C** indicates test was performed with the chromogenic method with a detection limit of 0.001 EU/ml.



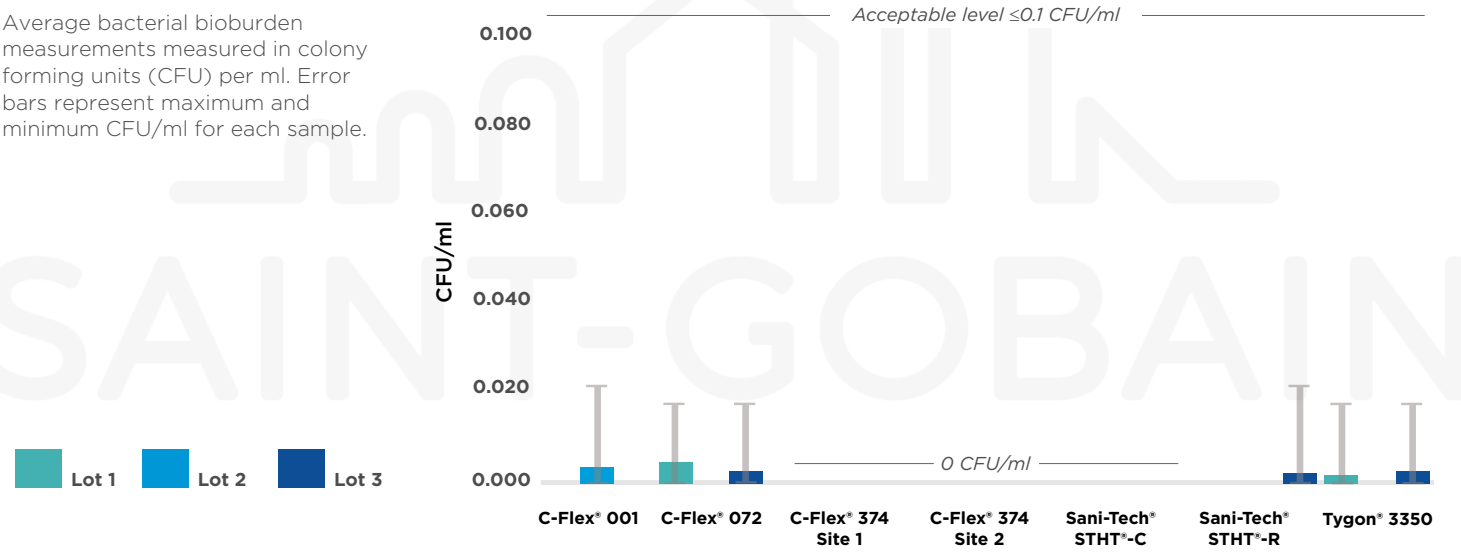
Test Results – ISO 11737 Bioburden

Bacterial endotoxin testing was undertaken using the same accredited and FDA registered independent laboratory. Bioburden testing was performed by cutting samples to 1 meter lengths, clamping one end and filling each tube with peptone tween (PEPB) leaving a small air bubble gap. Each sample was inverted ten times to contact the entire inner surface area of the tube.

Extract from each sample was swabbed on agar, then incubated for 7 days at 30-35 °C before being analyzed. Samples were not pooled. Figure 4 illustrates the average bacterial bioburden for each sample tested in colony forming units per milliliter (CFU/ml). Fungal bioburden was 0 CFU/ml for each sample tested. All samples were below the acceptable level of ≤0.1 CFU/ml.

Figure 4: Average Bacterial Bioburden

Average bacterial bioburden measurements measured in colony forming units (CFU) per ml. Error bars represent maximum and minimum CFU/ml for each sample.



Conclusion

During the manufacture of pharmaceuticals, it has become increasingly important to consider potential contamination risks caused by fluid path components.

The preceding results indicate that tube products certified with ValPlus™ are significantly below industry specifications for bioburden, endotoxin and particulate. This industry-leading certification allows the end-user to simplify their validation strategies for tubing products and reduce costs associated with other risk mitigation measures.

About

Authors

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Tony Perovsek is the Validation Manager for the Fluid Systems division of Saint-Gobain. His background includes 20 years in pharmaceutical and medical device validation for companies such as Boehringer Ingelheim and VWR.

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Nathan Klettlinger is a Product Manager for Bioprocess Solutions. He has a chemical engineering degree and a master's degree in business, bringing with him 10 years' experience in plastics and rubber including R&D and manufacturing engineering.

Saint-Gobain

The Bioprocess Solutions business unit of Saint-Gobain supplies the bioprocessing, pharmaceutical, cell therapy, and laboratory industries with high performance assemblies and fluid path components.

Its industry-leading product portfolio and material expertise provide customers with the answers and assurance they need when processing pharmaceutical products.

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