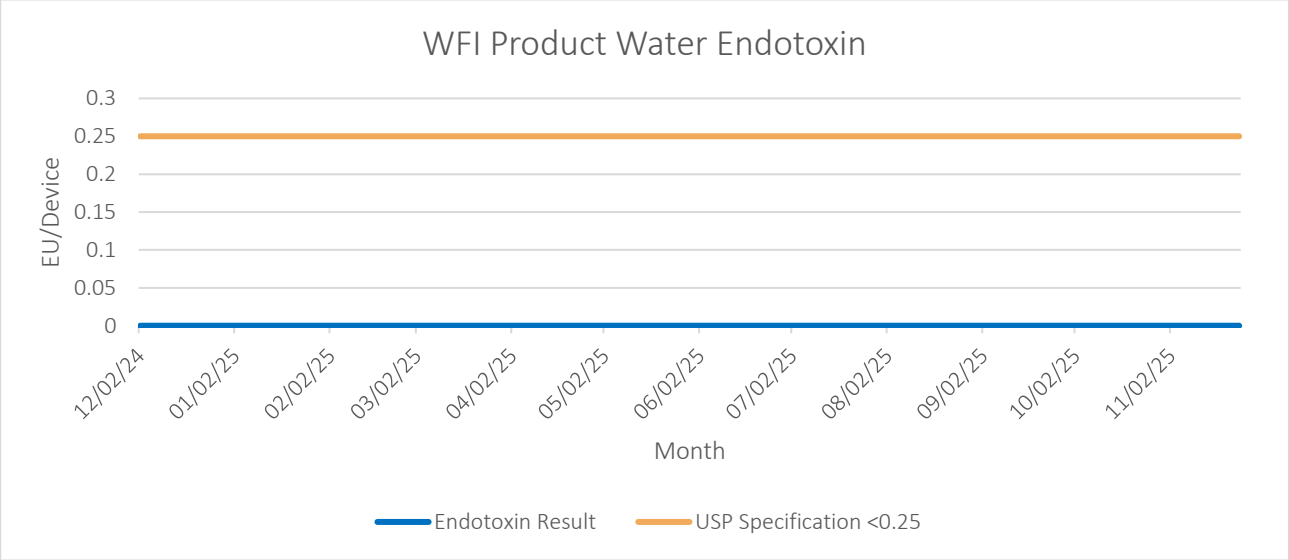
Comprehensive Endotoxin Program – Customer Notice

Endotoxins are the structural components found on the outer membrane of gram-negative bacteria. This endotoxin contamination can occur through raw materials, water, and equipment, such as tanks and their associated mixers, and even during handling and storage. The key to controlling endotoxin is to mitigate the risk of environmental endotoxins by implementing strict controls in the manufacturing facilities. These controls would include a strong cleaning program, regular environmental monitoring, and using endotoxin-free materials and equipment whenever possible. Implementing these controls in conjunction with utilizing the calculation derived per USP <85> for establishing endotoxin limits creates stability in the manufacturing process.

Aquabiliti utilizes the kinetic chromogenic assay as described in USP <85> to measure the color intensity related to the endotoxin concentration in the test samples of our bulk filled water. Acceptable endotoxin limits are set by USP <85> for injectable drugs, medical devices, and other products. For WFI, Sterile WFI, Sterile Purified Water, and Sterile Water for Irrigation, the allowable limit is less than 0.25 EU/mL (Endotoxin Units/mL).

Aquabiliti understands the importance of Endotoxin as it relates to parenteral therapies and monitors our WFI System weekly for endotoxin in addition to ensuring the finished product has a low endotoxin result as required by the customer. To demonstrate the stability of our water in regard to endotoxin levels, review the chart for the rolling calendar year for endotoxin results for our WFI Generation System.



Aquabiliti utilizes a test system primarily designed for aqueous solutions near a neutral pH, so it is ideal for use when evaluating our WFI. As indicated in the above chart legend, our samples are reported as <0.01 EU/mL, which reflects endotoxin levels below the detection limit of the test cartridge (0.01 EU/mL). These results confirm that the endotoxin concentration in the bulk filled water is too low to be quantified by the recommended method, supporting its suitability for use as Water for Injection (WFI) in parenteral therapies.

In addition to the routine endotoxin testing that is performed on the WFI Generation System, endotoxin testing is performed after the filling process to confirm that the final packaged product is free from endotoxins. This test ensures that the finished product is safe for use. Since Endotoxin is a final release test for the finished product, it will be reported on the Certificate of Analysis. Endotoxin Testing is conducted per USP <85> and the USP acceptance criteria / specification for the test is that the endotoxin levels be <0.25 EU/mL for the Bulk Packaged Water. Aquabiliti applies a tightened specification, limiting endotoxin to be $\leq$ 0.05 EU/mL.

At Aquabiliti, we ensure through routine monitoring of the WFI Generation System and through final release testing that the Bulk Water you are receiving as a critical raw material is not contributing to the introduction of endotoxin downstream in the manufacturing process.