Extractables Testing On Single-Use Connectors

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Over the last decade, the growing use of single-use technology (SUT) in the biopharmaceutical industry has transformed how drugs are developed and manufactured. Traditional methods using large stainless-steel bioreactors with costly clean-in-place and sterilize-in-place systems have been replaced, in most cases, by more efficient SUT bioreactors. Not only do SUT bioreactors reduce the costs associated with drug manufacturing, but they also offer more flexibility, allowing companies to streamline operations and increase productivity. However, as many benefits as there are to SUT, there is one critical issue drug companies must address when transitioning to plastic equipment, and that is the presence of extractables and leachables (E&L). E&L are defined by the Biophorum Operations Group (BPOG), an industry organization, as follows1:

- Extractables - A chemical entity that is extracted from a component of a process system into a solvent under controlled conditions that are usually more aggressive than normal operating conditions.
- Leachables - A leachable is a chemical entity that comes from single-use systems during normal use.

Testing for E&L and mitigating risks to a product—and more importantly, the patient who relies on it—are essential to being a trusted and reliable supplier in the single-use industry.

THE RISKS OF E&L

The presence of E&L during drug processing can contaminate the final drug product, resulting in reduced efficacy or even threats to a patient's safety. This has led to increased regulatory scrutiny about testing for the presence of these materials. Biomanufacturers submitting a biological license application must include E&L data to demonstrate overall product quality. Yet, specific testing requirements have not been provided by the FDA, leaving the industry with the responsibility to determine the most effective testing methods for ensuring an appropriate evaluation of materials.

A white paper written by members of BPOG titled Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing has become an industry guideline for extractables testing by single-use suppliers.2 While the FDA does not formally recognize the protocol as a regulatory requirement, 20 of BPOG's member companies have adopted it as best practice. The responsibility of testing for the presence of leachables often falls to the end user once product is available to test interaction between the drug and the single-use system. Leachable testing is also done to determine stability and safety of the drug product.

Prior to the creation of the BPOG protocol, there was not an appropriate guideline for reference when it came to extractables testing, leading to a lack of consistency from one supplier's data to another's. This made it difficult for customers evaluating equipment to determine the best fit for their product. The risk-based approach from BPOG drives harmonization and standardization across the industry. As the protocol states, "Integration of these proposals by SUS suppliers into their existing product lifecycle management processes would be highly beneficial to suppliers to ensure that a comprehensive and consistent set of extractables testing data are readily available to

biopharmaceutical end users."

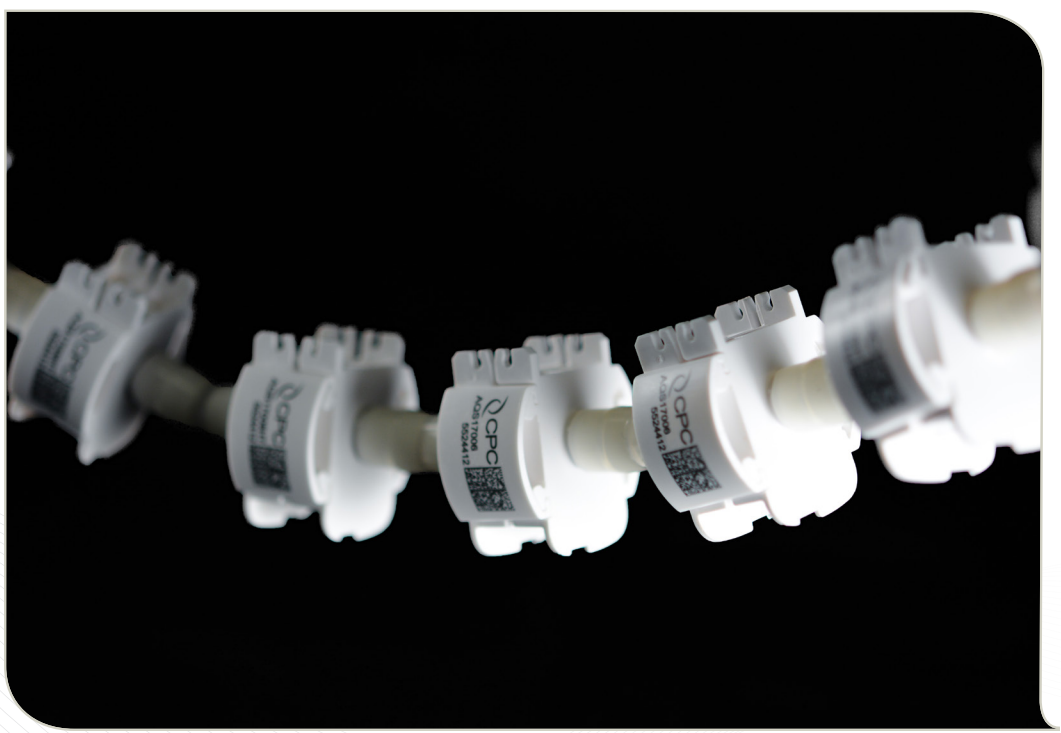
Partnering with a supplier that can demonstrate it has properly used BPOG testing and can provide the necessary data will also help avoid costly delays during the drug approval process. At CPC, it is important we execute the BPOG protocol properly on our single-use connectors, as they are a key component in maintaining sterility throughout processing of our customers' biopharma materials.

TESTING CPC CONNECTORS

To implement this approach in CPC's testing, a resource from BPOG was consulted to select a test lab and complete the evaluation. Testing the connectors became challenging, considering BPOG requirements for surface area to volume. Specifically, the guideline states the fluid used in testing a connector must have a 6:1 surface area to volume ratio. In other words, for every milliliter of fluid used, there must be six times as much square centimeters of surface area. With connectors being such small pieces of equipment, CPC had only one connector that met this requirement, which was its 3/8-inch HB AseptiQuik S. Nevertheless, since all of CPC's connectors are made from the same materials of construction, the results of the testing and accompanying data could simply be adjusted based on the different surface areas of other connectors.

Next, CPC had to determine how to create enough exposure to the connectors in the flow path during testing. Our team decided to create a daisy chain constructed of 20 connector halves (10 connected sets). Each connector had a small piece of PFA tubing attached to the hose between each connector, creating a long series of connectors (in Picture 1 below). The connectors also had to be pre-sterilized prior to connection.

BPOG's protocol recommends testing the connectors with six common extraction model solvents: water for injection (WFI), 0.1 M phosphoric acid (low pH), 0.5 NNaOH (high pH), 50 percent ethanol, 5 M NaCl (high ionic strength), and 1 percent polysorbate-80 (represents typical surfactant-containing aqueous solutions). The solvents had to be carefully poured in at an angle with breaks during filling to avoid trapping air in the tubing.



AseptiQuik S 3/8" hose barb connector used in testing, representing all AseptiQuik products made of the same materials.

Each solvent was then tested at three different time points (less than 30 minutes at 25° Celsius, 24 hours at 40° Celsius, and seven days at 40° Celsius). A population of connectors were exposed to gamma radiation, and a separate population was exposed to autoclaving. A total of 36 setups were used with 1,440 connectors used per setup. After exposure was complete, the test lab removed the solvents to examine the results and compiled a 120-page report. CPC then created a summary report to share with customers.

Visit the CPC website to request a copy of the report.

INITIAL DATA FINDINGS

After completing testing on its connectors, CPC discovered some key learnings, which included:

- The 4 other solvents did not find any other extractables that Ethanol and NaOH didn't identify.
- Ethanol had more readings at 24 hours than 7 days, which was not the case in the other solvents.
- When there was a unique result, it was typically a low concentration (<0.1 µg/cm2)
- The less than 30 min time point did not yield any valuable data.
- Many readings were very low (near the reporting limit).
- NaCl barely had any extractables.
- It was very hard to fit all of the daisy chain assemblies into the ovens at the same time.

While the study set-up was quite extensive and may be more than what is needed for a typical connector, it was a valuable exercise in that it did not show high levels of extractables. In fact, the levels of extractables that came from the connector were quite low, especially considering the testing is meant to be above and beyond the normal application conditions.

This data is intended to facilitate any future risk assessments performed by drug manufacturers when implementing a sterile connector. It also provides a better understanding of what these test conditions offer should there be any opportunities for improvements in future testing.

CONCLUSION

As the biopharma industry moves away from blockbuster drugs and toward a more targeted approach to drug development for smaller patient populations, SUT serves as a key tool in modern drug development. While the risk of E&L may present a potential obstacle in the adoption of certain single use components, working with a supplier that demonstrates its commitment to risk mitigation and compliance through appropriate BPOG testing is crucial to delivering safe and effective drugs

Though connectors can be considered a low risk item from an extractables point of view, due to their small surface area and short fluid contact time, CPC understands the value in creating comprehensive data for the industry. This data will prove valuable as the AseptiQuik connectors continues to become the standard single-use connection in the industry.

Reference

1. Biophorum Operations Group, Extractables and Leachables, https://www.biophorum.com/resource/extractables-leachables/#0
2. Ding, Weibing, et. al. (2014). Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing. Pharmaceutical Engineering. Vol. 34;6 https://www.biophorum.com/wp-content/uploads/2016/10/17_file.pdf

About CPC

CPC (Colder Products Company), the leader in single-use connection technology, offers a wide variety of bioprocessing connection solutions. Our innovative designs offer flexibility to easily combine multiple components and systems including process containers, tubing manifolds, transfer lines, bioreactors and other bioprocess equipment. AseptiQuik® Connectors provide quick and easy sterile connections even in non-sterile environments—a critical capability for biopharmaceutical and bioprocessing manufacturers. Featuring a wide range of options including 1/8- to 1-1/2-inch sizes and genderless and gendered connections, AseptiQuik connection technology delivers sterile, high-quality single-use connections and easy media transfer with less error risk. For additional information visit cpcworldwide.com or call +1-800-444-2474.

Confidence at every point of connection.