Bridging The Connectivity Gap Between Traditional Sensors And Single-Use Systems

By
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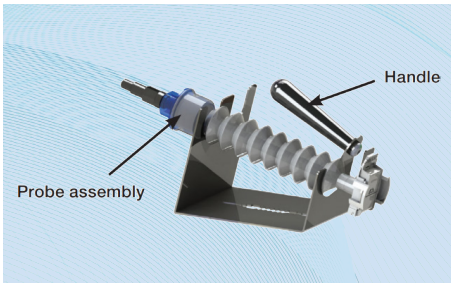

Figure 1
Probe assembly and autoclave tray[1]

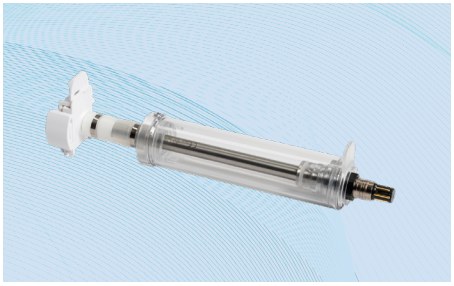

Figure 2
Assure Probe Sheath[2]

Critical process parameters (CPPs) are the key variables in the pharmaceutical manufacturing process that are most likely to affect the quality attributes of a biological product. CPPs must be monitored and controlled throughout the various stages of production. For example, in the production of recombinant proteins, the cell culture expansion and production steps require continuous real-time monitoring and control. Any deviations in CPPs from the historical data gathered during the process development steps could negatively impact cell growth and, therefore, product yield. They can also potentially affect the drug's overall safety and efficacy. The most common CPPs measured are pH, dissolved oxygen, capacitance, and biomass. Another example is in media or buffer preparation, where conductivity is used to measure and maintain the ionic strength of the solutions.

Sensors that measure pH, DO, capacitance, and biomass are traditionally made of glass or steel so that the sensor can be readily steamed in place when used in stainless steel bioreactors. When used in single-use (SU) bioreactors, the same sensors are sterilized by autoclaving inside of a closed system that is designed to attach to and insert the sensor into the single-use bioreactor without compromising the sterility of the sensor or the bioreactor (as shown in Figures 1 and 2). When used in single-use systems (SUS), conventional sensors come in many lengths. Traditionally, a sensor with a 12mm outer diameter (OD) is selected because the sensor conveniently fits within a standard ½-inch hose barb face port on the SUS. The widespread acceptance and adoption of single-use technology (SUT) across the industry has also driven increased demand for supporting equipment, such as SU sensors. While SU sensors offer all the benefits of SUT, their shortcomings have slowed adoption and impacted overall confidence in their performance.

The result is the continued use of traditional sensors, which can be used with both stainless steel and SUS. When using an SUS bioreactor, an aseptic connector is used to connect a traditional sensor that has been sterilized by autoclaving within a probe sheath that envelopes the sensor and maintains the sterility of the probe before insertion into the single-use bag. However, there are issues. For example, media may leak back into the probe sheath or the weight of the probe can bend/stress the seal in the traditional aseptic connector which breaks the sterile barrier around the sensor. This presents risks to the sterility and efficacy of the drug as well as to the costs of manufacturing. This also makes it critical to find a solution that can protect the investment for the lifetime of a product.

SINGLE-USE VS. TRADITIONAL SENSORS

Monitoring biological reactions occurring within bioreactors and fermenters is key in controlling these reactions as well as determining the optimal end point of the process. In mixed buffers and media solutions, pH and salt concentrations are essential for obtaining consistent manufacturing results. SU sensors provide the convenience of time (due to the elimination of autoclaving,

calibration, or probe maintenance). However, the technology of SU sensors is still evolving and, as a result, many drug manufacturers still rely on the stability, reliability, and reusability of traditional probes in an SUS. SU probes have shown their limitations when used in longer manufacturing operations, such as in perfusion/continuous cell cultures. There is also a risk of an "out-of-the-bag failure," where SU probes fail and the end user needs a redundant probe setup. In these cases, conventional sensors serve as backup in case the primary SU sensors fail.

SU sensors do not always cover the required measurement range with just one sensor, so two or more SU sensors must be used to measure the normal range of operations in a biological reaction. In addition, SU sensors are typically set at the factory and cannot be calibrated in line prior to use. SU sensors are then incorporated into an SUS, which is then sterilized using gamma radiation. Exposure to gamma radiation can impact the accuracy of the sensor, which affects the accuracy of the calibration data and the measurement during runs. If an SUS incorporating SU sensors is manufactured in January and gamma radiated in February but not used until months later, the system must be used knowing that sensor recalibration is not possible. Nevertheless, there may be considerable uncertainty about its accuracy. Another drawback of single-use probes is that they sometimes shorten the expiration date of a single-use bag, which can cause bags to be wasted if they cannot be used before the expiration date. This can result in thousands of dollars being thrown away.

Conversely, the historical accuracy of traditional sensors, backed by decades of data is a trusted tool for measuring critical process parameters. They also have a wider measurement range and could be reused, leading to lower long-term operating costs. Traditional sensors do face their own shortcomings, though. When used in a single-use system, traditional sensors must be aseptically inserted in a way that prevents leakage but maintains sterility. The assembly required to do so must be adaptable to allow the use of probes of varying lengths. An autoclavable probe sheath or bellows fits around the sensor to maintain sterility after autoclaving. A single-use aseptic connector sits on one end of the probe sheath/bellows and a probe adapter on the other where the conventional sensor screws into place. Incorrect assembly of the probe system can pose considerable risks to product loss, the sterility of a product, and measurement accuracy.

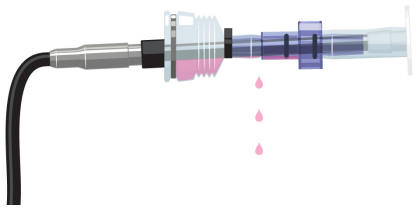

Figure 3
Traditional aseptic connector/probe assembly

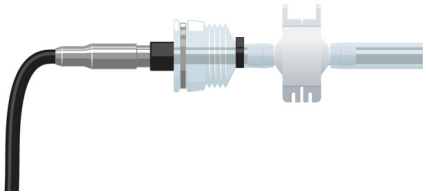

Figure 4
CPC AseptiQuik connector/probe assembly

SINGLE-USE CONNECTORS AND CONVENTIONAL PROBE INSERTION

As the industry continues to evolve and benefit from the advantages offered by SUT, there are two aspects of sensor technology that are important to highlight. Firstly, SU sensors have to evolve further to meet the increasing demands of the industry for robustness, reliability, and accuracy and to allow their use across the whole aspect of SUT. Secondly, for those manufacturers who use traditional sensors in an SUS, the universal availability of a reliable, genderless, SU aseptic connectors that allows the easy and intuitive connection of the sensor to the SUS is critical to give the manufacturer the confidence that their sensors are secure, do not leak, and function as designed.

An SUS needs secure, reliable, leak-free connections between various components and processes; SU connectors can be the first and last line of defense in an SUS. Even using the best bag, filter and tubing will prove futile without a reliable and robust connector. That is why it is critical to select a connector that is easy to use, robust, and does not require additional hardware to assemble. Some connectors are not easy to use because they require many assembly steps to make the final connection; the more steps there are for assembly, the higher the chance an operator will make an error. If the connector requires hardware not integral to the connector to secure the connection (e.g., tri-clover clamps), operators can misplace or forget to install the added components.

The sealing mechanism of the connector must be secure and robust. Small, thin O-rings can either roll out of the connector or roll into the flow path when pulling tabs. Some connectors can leak media outside of the connector because the weight of the probe distorts the connector seal, breaking sterility, and allowing media/buffer to leak outside the connector (known as side-load). CPC genderless connectors have larger, stronger gaskets that were designed not to roll out with the membrane pull and are more resistant to side-load than traditional aseptic connectors.

Figure 4
Steps for Aseptic probe insertion[1]

Step 1 - Connect the Aseptic Connector to the matching Aseptic Connector on the SUT

Step 2 - Connection of the probe to the SUT

Step 3 - Pull tabs and line up probe for insertion

Step 4 - Compress the bellows and probe to complete aseptic insertion

They are validated by using a test that hangs a 25-pound weight in four different directions on the connector after connection. The entire system is then tested from 5 to 75 psi to ensure there are no leaks from the connection while side loaded.

OVERCOMING THE SHORTCOMINGS OF TRADITIONAL SENSORS

Maintaining sterility, preventing leaks, and ensuring ease of use are the top user attributes and design priorities for any SU connector. Drug development is already a complex and expensive process, so providing manufacturers with tools that bring security, simplicity, and efficiency to their operations should be a key priority for today's equipment manufacturers. The AseptiQuik® G series of SU connectors from CPC does just that by offering a tool for making secure aseptic connections that are quick and easy to use, even in non-sterile environments. AseptiQuik G connectors are genderless and compatible with any bag or bioreactor design, which gives manufacturers more flexibility in vendor selection. The AseptiQuik G (AQG) with ½-inch hose barb tubing connection was specifically designed to meet the form, fit, and function demands of the industry for using traditional probes in SU assemblies, specifically:

- AseptiQuik G uses a simple, three-step "Flip, Click, Pull" robust connection process with an audible click to ensure secure engagement of the connector. There are no twisting/pushing/twisting multistep protocols required to engage the connector, and connections can be made quickly and efficiently in any location.
- The AseptiQuik G uses a robust compression seal in both halves of the connector so that the seal is made by two compressible surfaces being forced together under pressure. The seals are designed to fit traditional 12-mm OD autoclavable reusable probes to ensure a tight connection that prevents media from leaking back into the disposable probe sheath.

Figure 5
AseptiQuik G 1/2" hose barb genderless connector

- The AseptiQuik has a shorter body length, allowing you to use shorter probes.
- CPC has developed a four-direction side-load test to ensure the connectors do not leak even under excessive side-load conditions. Side load can occur when the weight of the probe and assembly puts sideways pressure on the seal of the connector. Under extreme conditions, this may compromise the sterile seal around the sensor/probe sheath, which can also cause media to drip out of the single-use assembly.
- Unlike some connectors, the AseptiQuik G does not require an external clamp or sealing mechanism to ensure and maintain a sterile connection.
- All AseptiQuik Gs are laser printed with part number, lot number, and a QR code for 100 percent product traceability, irrespective of which bag or bioreactor they are connected to. When the QR code is scanned, the user is provided

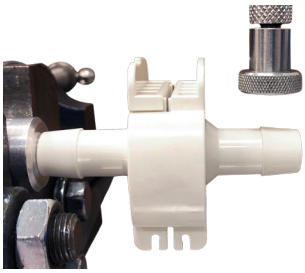

Figure 6
Extreme side-load testing on the AQG

the date of manufacture as well as a link to the CPC website that provides product specifications, best practices videos, and validation guides.

As the development and adoption of SUT continue to expand, there will be a growing demand for real-time, continuous measurement and monitoring of processes using both traditional and single-use sensors. The secure, leak-free connection of these sensors to the single-use assemblies is paramount in ensuring both the accuracy of the measurements taken and protection of the manufacture of expensive drug products.

REFERENCES

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[1] Probe connector images used with permission by Thermo Fisher Scientific.

[2] Assure probe sheath image used with permission by Cytiva

About CPC

Colder Products Company (CPC), a Dover company, the leader in single-use connection technology, offers a wide variety of solutions including sterile connect and sterile disconnect. Our innovative designs offer flexibility to easily combine multiple components and systems including process containers, tubing manifolds, transfer lines, bioreactors and other bioprocess equipment.

Robust single-use connectors maintain media sterility and integrity while improving production yields, decreasing time to market and reducing costs for biopharmaceutical manufacturers. Colder is ISO 13485 certified. We manufacture our products for bioprocessing applications in an ISO Class 7 certified cleanroom.

Founded in St. Paul, MN in 1978, CPC has more than 600 employees, operations in St. Paul, Germany, and China, sales offices in 10 countries, and more than 200 distributor partners around the globe.

For applications where reliability and sterility are a must, connect with Colder at cpcworldwide.com/bio

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Confidence at every point of connection.