Thermoplastic Tubing Welders and Sealers

Forging the Future of Disposable Technologies in the Biopharmaceutical Industry

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In an ongoing effort to control costs and improve time to market while still maintaining aseptic integrity, biopharmaceutical manufacturers have increasingly turned to disposable technologies such as "biobags" and LevTech's levitated impeller mixing system. That's with good reason. Recent studies have shown that by enhancing flexibility within the manufacturing process and reducing costs associated with validation and cleaning, disposables offer manufacturers operational as well as economic advantages (**1**).

However, as the trend toward disposables — or single-use process components — continues, many in the biopharmaceutical industry are turning their attention toward further enhancing the advantages they present. "The idea," explains Louis Zaczkiewicz, engineering director at Hyaluron Contract Manufacturing in Burlington, MA, "is not to settle for the value added by one or two disposable components, but to build an entire arsenal, or 'toolbox,' of technologies, which when implemented alongside disposable components facilitate greater customization and flexibility within the manufacturing process, while increasing efficiency."

Among the next generation of technologies for the manufacturer's "toolbox" are tubing welders and sealers. Used with thermoplastic tubing, welders and sealers facilitate aseptic connections and disconnections with little operator intervention and decreased dependence on Class A clean zones. Consequently, tubing welders and sealers offer end-users the ability to make quick and reliable in-process connections as well as a much higher level of sterility assurance for aseptic transfer applications and sampling.

"As you might imagine," Zaczkiewicz suggests, "the potential applications for this technology are numerous."

A 100-L disposable biobag (Sartorius AG in an aseptic suite at Hyaluron

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Thermoplastic Tubing

Recent developments in the use of thermoplastic resins have given rise to various types of heat-weldable Class VI tubing brands such as C-Flex (Consolidated Polymer Technologies, Inc., www.cflextubing.com), Pharmed (United States Plastic Corporation, www.usplastic.com), and Sanipure (Saint-Gobain Performance Plastics, www.medical.saint-gobain.com). Among the many advantages offered by these types of tubing for general fluid transfer in the biopharmaceutical industry is the ability to be fused and/or sealed when heated.

Typically, a formulation-and-fill process calls for several tubing connections and disconnections that allow operators to gain access to an otherwise closed system. Such connections facilitate fluid and gas transfer as well as sampling for the purposes of testing and monitoring. Making the requisite number of connections for each process can take valuable time and money both for customization and validation. And making in-process or "on-the-fly" tubing connections can also prove challenging. Additionally, each time a tube is disconnected (breached) there is an increased risk of contamination to the entire system. Mechanical clamps can fail, operator errors can occur, and valuable product can be compromised.

Because it can be heat-welded and -sealed, thermoplastic tubing offers end-users greater flexibility in customization and validation, particularly whenever customization is needed immediately. More important, this type of tubing mitigates process variations that can be brought on by discrepancies in technique, which decreases the potential for contamination and waste.

Welders and Sealers: To facilitate thermoplastic tubing connections and disconnections, end-users need tubing welders and/or sealers. As separate units, welders and sealers represent a worthwhile capital investment if you consider the costs that would otherwise be incurred from bag-vendor customization, validation, steam-in-place (SIP), Grade A operations, and/or loss of valuable products due to contamination.

Terumo Medical Corporation (www.terumomedical.com) was one of the first companies to enter the market for biomedical tubing welders and sealers. Although it is limited to use on tubing no larger than 0.25-in. OD and 0.125-in. ID, Terumo's sterile tubing welder has been widely used for low–fluid-flow applications as with bench-scale perfusion bioreactors and small-volume aseptic sampling.

Over time, end-user demand has given rise to welders and sealers that offer greater flexibility and ease of use. In recent years, several companies (including Wave BioTech, www.wavebiotech.com, and Sartorius) have introduced units capable of accommodating larger diameter tubing to allow for higher flow rates. They have also equipped their welders and sealers with more automated features to facilitate operation and monitoring of critical parameters such as temperature and the number of welds performed. For example, the BioWelder and BioSealer offered by Sartorius AG (www.sartorius.com) can handle 0.25-in to 0.75-in OD tubing, are fully automated, and can be monitored through a liquid crystal display (LCD) screen.

How (and Where) They Work

Although welders and sealers both work on the same principle, each operates independently and has its own advantages and unique function within the manufacturing process. The primary purpose of a tubing welder is to facilitate aseptic tubing connections, whereas the primary purpose of a tubing sealer is to facilitate disconnections.

Welders Facilitate Aseptic Connections: In more conventional formulation processes, the number of potential tubing connections within a system is somewhat limited by the number of ports on the vessel being used. Stainless steel tanks traditionally used have a fixed number of ports. In operations calling for several connections, repeated aseptic connections and disconnections must be conducted in Grade A zones or with the application of SIP.

Disposables (e.g., biobags) offer end-users the ability to tailor formulation vessels to their processes and thus better accommodate the number and type of connections needed. Vendor customization, however, can take a great deal of time and effort first in establishing consensus on a configuration and drawing, then subsequently validating the results. Once a design has been drawn up and approved, it can take up to 13 weeks to get a bag in place. And on-the-fly customization can be difficult, with such a custom-designed bag on which tubing extensions are dedicated to defined purposes.

With the advent of the tubing welder, however, manufacturers and end-users can conduct onsite and on-the-fly customization quickly and easily using a bag with just one or two extensions of weldable tubing. To begin this process, an operator would simply insert two tubes into a BioWelder's holding chamber along with a blade and then close the cover. Inside the welder, that blade cuts the tubing. The blade has been heated to 200 °C before insertion to depyrogenate it, then cooled to an optimal temperature for the particular type of tubing being welded. Next, the tube ends are held against the hot blade to soften them so they can be fused. Finally the welder slides the tubing into alignment along the edge of its blade, which then moves out of the way to allow those tubing ends to fuse together. In all, it takes only 60–90 seconds to produce a strong and reliable bond.

The BioWelder from Sartorius AG (www.sartorius.com) HYALURON CONTRACT MANUFACTURING (WWW.HYALURON.COM)

For still greater flexibility, end-users can order tubing extensions of varying ID dimensions that can accommodate small- and large-volumes and flow rates. This allows multiple connections and disconnections quickly and easily for sampling; addition of manifolds, air vents, and fluid filters; and many other in-process applications.

Consider the difference a tubing welder might make in the seemingly simple process activity of bulk pH adjustment. In an open mixing tank-and-liner application, sampling for pH and subsequent adjustments are easily accommodated. Numerous samples of varying sizes can be drawn with little mess or waste. But in closed mixing systems — such as those used for aseptic control, containment of cytotoxic and potent compounds, or gas overlay preservation as with the LevTech biobag — the process of pH adjustment can be much more difficult and inefficient.

With a closed system, an operator is limited to tubing extensions provided on the standard bag. The LevTech configuration, for instance, comes with two lengths of tubing extending from the top of the bag and one outlet/transfer tube extending from the bottom. Often, those extensions are no smaller than 0.25-in. ID and can be roughly two to three feet long. For an offline pH reading, the minimal volume needed is about 2 mL. However, given the relatively large inner diameter as well as the excessive length of the tubing provided, end-users typically lose significantly more

When implemented alongside single-use process components, thermoplastic welders and sealers IMPROVE flexibility and efficiency in biopharmaceutical manufacturing.

volume than that even when no leaks or errors occur.

Also, if any bulk fluid is left behind in such tubing after sampling (so-called tubing "dead legs"), then that fluid has to be flushed from the tubing before any subsequent sampling could be performed. If not, the later sample drawn would not truly represent the bulk formulation and thus would not adequately reflect its pH levels. Depending on the number of dead legs and the amount of flushing required, still more valuable bulk fluid could be wasted in an operation that really requires only a few milliliters.

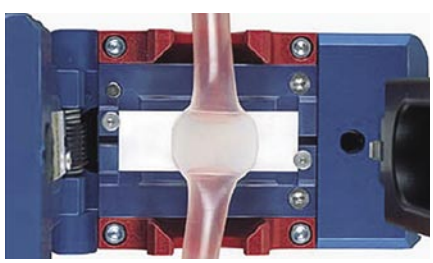
The process of pH adjustment can be made more efficient when a tubing extension of a considerably smaller inner diameter (0.125 in.) is used for extracting and delivering fluid. However, with more conventional connections (e.g., quick disconnects), repeated connections and disconnections significantly raise the potential for contamination as they become wetter and wetter.

Conversely, with a thermoplastic tubing welder, an end-user can add a 0.125-in. ID tubing extension of minimal length to the bag or existing tubing extension without experiencing the mess and waste that often accompanies more conventional operations. The smaller internal diameter and shorter length prevent waste when small samples are drawn. And the option of adding additional lengths of tubing quickly and easily, without breaching aseptic integrity, reduces the number of necessary connections — significantly decreasing the potential for contamination. This results in greater flexibility for the size and number of samples that can be drawn as well as increased efficiency in the handling of valuable bulk substances. More important, end-users can rest assured that aseptic integrity has been uncompromised throughout the process.

Sealers Facilitate Aseptic Tubing Disconnections: Tubing disconnections are those points in a manufacturing process at which an operator must disrupt fluid transfer in an otherwise closed system. Disconnections are often made, for example, to facilitate sampling for testing and monitoring. With both conventional systems and disposable bags, operators must rely on mechanical clamps to pinch tubing and stem the flow of fluid from a formulation vessel. Such clamps are often prone to failure, either due to faulty equipment or operator error. Once a clamp fails for any reason, leaks can expose an entire system and valuable product to contamination.

When using a thermoplastic tubing sealer, however, an operator no longer depends on mechanical clamps to make tubing disconnections. In fact, there is much less need for operator intervention altogether. Consequently, the potential for failures in operator technique and training is diminished, so a process becomes more robust and efficient overall.

To activate a BioSealer, an operator simply places an empty or liquid-filled length of thermoplastic tubing into the sealer's holding chamber. The tubing is then heated to between 120 °C and 160 °C and compressed between two ceramic heating elements. If any liquid is present, it is evacuated from the internal tube section, and the tube is then fused into a homogenous section that can be cut in two. The tubing below the fused section maintains its aseptic integrity, whereas the tubing above it can be fused again and cut away. In all, the process takes under five minutes to produce a bond that is stable and sterile. Although this sealer is used most frequently to irreversibly and aseptically seal tubing, it can also be used more creatively to generate fully intact and hermetically sealed samples for operations such as bioburden and/or sterility testing.



The BioSealer from Sartorius AG
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Traditionally, the process for retrieving a sample and transferring it to a sterile container requires several open-air manipulations performed in a Grade A clean zone. A sample is typically transferred or poured directly into a sterile test tube, which then needs to be tightly capped and sent to a laboratory for testing. Throughout such a process, the operator's sterile technique is very important. From collecting the sample to properly screwing the cap onto the container, the operator must be careful not to corrupt or compromise the sample in any way that could render a false positive.

With the BioSealer, on the other hand, an operator can deliver a sample that is truly representative of the process without any opportunity for introducing contaminants during open-air manipulation. A tubing extension that has been filled with fluid is inserted into the BioSealer, then heated and pressed. The action is repeated some distance up- or downstream from the initial seal, resulting in a fluid-filled section of tubing that is sealed in two locations. The operator can then cut that tubing at each of those sealed locations to produce a length of fluid-filled tubing that can then be submitted to the quality control group or a third-party testing facility. The end result is a tightly sealed sample that more accurately reflects the real number of viable microorganisms in the system.

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This also provides a much greater degree of confidence in the aseptic integrity of the entire system.

Providing Creative Solutions

As the trend toward disposables continues, the use of thermoplastic tubing welders and sealers will no doubt gain momentum as well. When implemented alongside single-use process components, these welders and sealers offer biopharmaceutical manufacturers greater flexibility and increased efficiency. With a tubing welder, an end-user can make quick and reliable tubing connections without absolute dependence on Class A clean zones. Consequently, end-users can conduct onsite customization, which reduces time-to-market as well as the costs associated with validation and cleaning. Additionally, with tubing sealers, end-users can conduct small-volume sampling with decreased risk of process variation due to lapses in operator technique and/or training. That translates to a much higher level of assurance for aseptic integrity.

In the years to come, disposable technologies — and the systems used to implement them, such as thermoplastic tubing welders and sealers — will continue to transform the biopharmaceutical industry and the way in which manufacturers meet its changing needs.

Reference

1 Craig J, Terentiev A. Levitated Single-Use Impeller in Disposable Mixing Systems: Manufacturing Platforms Benefit from Conventional Mixing in Single-Use Vessels. *BioProcess Int.* 2(9) 2004: S60–S63.

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