Closure and Stopper Systems: Getting Big Benefits from Small Components
Introduction

Protecting your liquid transfer processes—and your investment in biopharmaceutical materials—involves a multitude of components, from tubing and piping, to connectors and filters, to bioreactors and storage vessels. One of the easiest aspects of liquid transfer to overlook or take for granted is closure or stopper systems.

But all closure systems are not created equal, and specifying the right one for your application, made from the right materials, can be critical. The integrity of a large batch of processed fluids may depend on a simple-looking bottle stopper.

This document discusses the features and advantages the ideal closure system should offer and how you can realize sizable benefits from relatively small components.

The Challenges

All facets of a liquid transfer system or process must work together to minimize the risk of contamination, cross-contamination and the introduction of particulates. That includes all connections between tubing and storage vessels including stoppers, caps and inserts.

These connections are just as important to a secure, safe environment as any other element of a transfer system in the pharmaceutical, biotech or laboratory arena. And the unimposing closure between tubing and vessel is, in fact, carrying a sizable burden.

The challenges of these seemingly small components are many. Initially, they must be validated to meet demanding FDA, USP, ISO and other standards. This should include FDA CFR 177.2600, USP Class VI, ISO 10993, European Pharmacopoeia 3.1.9 and other industry benchmarks established over the years to ensure safety and purity.

A securely sealed bioprocessing system is crucial to the end product and ultimately patients.
Closures must demonstrate durability and long service life expectancy, especially in reusable transfer systems where they are repeatedly subjected to the passage of various chemicals. This factor, coupled with conditions such as temperature and humidity, has made problematic the use of certain rubber materials which are vulnerable to chemical and environmental deterioration.

The closures should enter service in a pristine state. For best results, this means assembly and packaging in ISO-certified clean rooms rated at Class 7 (Class 10,000) or better. The most effective closure systems should also be free of animal-derived materials to maximize biological safety and minimize contamination risk.

Versatility is another key challenge. Closure systems must be equally at home in pharmaceutical, biopharmaceutical, bench laboratory/chemistry and other environments. They can be applied to single or repeated use and sterilized through a variety of methods from autoclaving to gamma irradiation. Closure systems should match with processes using glass, metal or plastic containment.

Finally, closure systems should be available in a wide variety of styles including stoppers, caps, inserts (including True Unions and GL45s) and caps with tubing installed.

**Which System?**

Keeping all of the above in mind, which closure system should be specified? Your best plan is to look for a system that offers the following advantages:

- Meets the relevant USP, FDA CFR, ISO, EU and other industry standards
• Uses proven biologically safe materials such as platinum-cured silicone or biopharmaceutical grade TPE (thermoplastic elastomer) that incorporate no animal-derived substances or additives that are associated with the formation of agglomerates

• Satisfies requirements for chemical resistance, temperature usage, odor or taste transfer (specifically the lack thereof), validations and extractables

• Provides smooth sealing surfaces for a complete seal

• Offers adaptability to meet many different applications and systems. This includes:
  - pharmaceutical, biotech and laboratory environments
  - repeated or single use systems; note that repeated use should accommodate autoclave, and keep in mind that single use systems reduce cleaning requirements, MSDS bookkeeping and chemical storage, validation time and costs, while preventing cross-contamination
  - availability in a range of sizes and styles
  - resistance to microbial, chemical, physical (cracking) and environmental (extreme temperatures, particle migration) stresses
  - compatibility with a variety of identification and tracking solutions such as RFID

A range of standard bottle stopper sizes is available from many suppliers. Some can also provide stoppers with tubing already attached to speed installation, reduce multiple product inventories, and save labor costs.

Stoppers should be highly adaptable to meet the requirements of different systems and applications.
Additional Considerations

When biosafety cabinets are an essential part of your bench chemistry work, it’s important to note that sterile systems enabling users to collect and dispense processed fluids without going inside the cabinet itself are available.

And, while wrap paper offers an attractive initial cost advantage in dealing with biosafety cabinets, it brings long-term disadvantages as well. The dispensing of fluid requires going in the cabinet where a reusable dip tube is involved, and the potential rises for the introduction of particulates and contamination in the clean room.

Stoppers, caps and inserts require a slightly higher initial investment but are more reliable in the long run.

Conclusions

Like a chain, a biopharma transfer system depends on all of its links being strong enough to protect the integrity of the materials being transferred and prevent problems associated with contamination.

Closure and stopper systems are sometimes seen as small items, but choosing the right ones is vital. The impact of specifying the appropriate closure or stopper systems can be felt throughout an entire fluid transfer process.

BioClosure® container closures, offered in platinum cured silicone or biopharmaceutical grade TPE, are available from AdvantaPure®, a specialist in aseptic fluid flow systems.