# NEW TECHNOLOGY ADOPTION IN ASEPTIC FILLING: RISK AVERSION VS. CHANGE AVERSION

Source: Singota Solutions

*Singota® Solutions is a CDMO located in Bloomington, Indiana, USA that specializes in Parenteral, Early Phase Drug Development and Aseptic Filling projects.*

The drumbeat of continuous improvement programs and initiatives is a rhythm heard throughout the business world, and pharmaceutical companies are no exception in their embrace of pursuing improvements. More efficient and less error-prone processes, better employee training, and safer, more reliable equipment generally lead to improved products or services.

However, the scope of change necessary to drive such improvement often is a stumbling block for life sciences organizations. While incremental changes for the better are usually welcomed with enthusiasm, more profound shifts in technology or methodology can be stymied by an overabundance of caution. Certainly, caution is warranted when making products bound for patients, as their health is the primary goal. Yet, fear of the unknown may trigger the industry's deep-rooted sense of risk aversion, even when objective evidence demonstrates the innovation reduces risk.

It is imperative — for patient well-being as well as life science industry evolution — that pharmaceutical sponsors, manufacturers, and regulators are wary of being change-averse, versus risk-averse. A methodical evaluation that prioritizes verifiable data over hypothetical conjecture, the same scientific-minded approach that guides drug development and research, can quickly differentiate one from the other.

**Understanding Aseptic Filling Advances**

Aseptic filling is really just the transfer of a formulated bulk drug product into the final container that will be used to dose a patient, be it a vial, a syringe, or a cartridge. The product is typically rendered sterile by filtration and then transported to the units being filled through tubing, via a pump or pressure. Little occurs in the process with the potential to alter a product, so — alongside ensuring accurate fill volumes — contamination prevention is the key concern. This is because the parenteral medication (i.e., administered through routes other than the alimentary or respiratory tract) will bypass the body's normal defense mechanisms and be injected directly into a vein, a muscle, or subcutaneously.

The source in an aseptic filling operation with the most potential to contaminate the sterile drug product is the people doing the work. As 90% of the cells in a human body are not human, bioburden is much more likely to come from a person than anywhere else. Accordingly, numerous engineering controls exist to prevent that contamination: for example, work is performed in clean rooms with specialized HVAC systems filtering the air passing across the product, and operators are gowned/gloved/masked. A complex framework of environmental monitoring processes has grown up around these anti-contamination measures, intended to measure and demonstrate their efficacy.

These environmental monitoring standards, supported by regulatory guidelines, have existed for decades and have become well-embedded in our industry's quality practices, but they have not necessarily evolved alongside aseptic filling equipment improvements. Isolator technology, in use across the industry for quite some time, can effectively remove the human element from aseptic filling's contamination risk equation. Still, extensive monitoring of the manufacturing environment persists, even though isolator technology can establish an impenetrable barrier against the source of contamination.

Since a manufacturing isolator (essentially, a box housing the filling process, completely closed off to the outside environment) inherently prevents the drug product from becoming contaminated as it is being filled, calls for more sensitive environmental monitoring techniques to evaluate the technology are misguided. It should be noted that sterility assurance is dependent on statistics. Moreover, environmental monitoring mechanisms also use statistical samplings, not definitive evidence of safety for every unit. Obviously, if you tested every unit filled to be sure it was sterile, there would be no product left for the patients.

Unfortunately, misguided interpretation of the data based on historical norms can backfire. There have been cases where a contamination risk has been effectively engineered out of the equation, such that the monitoring data shows no failures, but the response has been to take even more samples in search of contamination that is no longer present. Indeed, the argument should be made that the intrusion into an isolator to perform unnecessary environmental monitoring introduces risk, rather than mitigates it.

Recognizing and Abstaining from Change Aversion
As is the case with any production equipment, aseptic filling providers are responsible for installation qualification, operational qualification, and performance qualification of their machines. Still, evidence-based arguments of efficacy can fall victim to "this is the way it's always been done" thinking. It is a convenient justification: do we really want to deviate from something that, in the past, the FDA has inspected (perhaps expected) and approved, even if it is demonstrably slower, costlier, or more prone to risk than existing technologies?

There is some validity to this argument. Regulatory guidelines seldom offer specificity, meaning a manufacturer's validation processes and procedures are open to at least some level of interpretation. However, the FDA has made a concerted effort towards solidifying a risk-based approach in its evaluations.

The agency's evolution has included optimized training and the hire of many new staff, resulting in inspectors who are more inquisitive and accepting of new technology and better able to evaluate its merit.

Still, there is a tendency within our industry to associate all risk with patient risk, and to even equate change itself with risk. Pragmatically speaking, if a manufacturer can demonstrate a new technology or a better methodology can reduce risk, it should be a good thing. Still, there seems to be a subset within our industry that remains dedicated to digging in its heels, offering unlikely hypotheticals to support its misgivings: "what if this and this and this and this?" – ending up in a situation wherein a dozen unlikely events would have to happen in a set order to fulfill this "gotcha" scenario.

In the objector's mind, the argument may be justified by the belief they are performing a public service in preventing that one-in-a-million instance. But, in the meantime, how does that risk compare with the risk of how things are currently done? Could we be standing in the way of patients receiving a more efficacious or safer therapy because we've created some beyond-rational reason why it could fail? These are not easy decisions to make, and this is why evidence-based evaluation and education of new technology and methodologies is vital, whether for the regulators or industry: executives, manufacturers, quality assurance, or regulatory affairs groups.

While seeing a well-established entity "take a chance" on a new technology with a limited-use record can sometimes positively influence other manufacturers to embrace the technology, that comfort threshold is elusive. How many companies have to successfully adopt a new technology, guiding it through product approval processes, before other organizations will trust it — 5? 10? 50? The answer likely is a blend of factors, including how much the new technology differs from current equipment and the name recognition of companies who have adopted the technology.

**Final Thoughts**

Advances in drug substance manufacturing — think cell culture, peptide synthesis, etc. — are the norm. Yet, at the end of that process, organizations continue to fall back on dated technology and processes to fill innovative new drugs into vials and syringes. However, particularly in the past decade, significant improvements have started to take place in the aseptic filling process.

Singota uses a technologically advanced, gloveless filling isolator workcell whose efficacy is well-supported by data from numerous clients and regulators. This system provides our clients with fast turnaround and shortened lead times while maximizing patient safety through gloveless robotic technology. We understand that disruptive methods and technologies inherently can raise red flags simply by being different. But evidence-based change for the better — be it incremental or disruptive — cannot be ignored by organizations that truly embrace continuous improvement.

Risk aversion is wise from a business standpoint and a patient perspective. Change aversion is a counterproductive way of thinking that ignores evidence based on negative past experiences or hypothetical scenarios to the detriment of both business and patients. Organizations that refuse to take a step forward because it is not yet perceived as perfect effectively take a step backward.

**Singota Solutions** is a US based CDMO in Bloomington, Indiana. Singota specializes in formulation development and aseptic fill finish for injectable projects. Once a formulation is established, Singota utilizes state of the art robotic filling technology and focuses on smaller batch size requirements. For more information, visit Singota.com to explore how Singota has established itself as a one-stop solution for all your developmental needs.

Contact **solutions@singota.com** to schedule a meeting with our business development team to further discuss your current or future projects.