Flexibility is not always best

Flexible containment is useful—but not for every application, argues one expert

Without doubt, flexible systems—single-use or multi-use, with disposable elements covering either individual components or entire systems—have many benefits. But there are inevitably problems too—problems which often seem to be being overlooked. So, is flexible containment really a panacea, as some people are trying to persuade us? Are its short-term benefits outweighed by less apparent drawbacks?

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Pictures: DEC

Engineers developing a pharmaceutical process should select the right equipment through quantitative risk assessments backed up by a sound knowledge of industry custom and practice. The pictures shows a flexible system with integrated tablet press.

There is a conflict over containment in the pharmaceutical industry. On one hand there is a growing requirement for higher levels of containment to match the increasing potency of pharmaceutical ingredients. Occupational exposure limits (OELs) for some active ingredients are now down to 5–10 ng/m³, equivalent to a grain of pollen in an average-sized living room. On the other hand is the rising demand for the benefits of flexible containment, which can be cost-effective, space-saving and easy to clean. Factor in the tendency for some compounds to be manufactured in very small quantities—down to less than 1 kg a year—and you have a difficult clash of priorities.

Engineers developing a pharmaceutical process should select the right equipment through quantitative risk assessments backed up by a sound knowledge of industry custom and practice. That means weighing established technologies, such as solid glove box isolators with rapid transfer ports, and glove box isolators designed for nanogram-scale operations, against flexible solutions. Outside the pharmaceutical industry the latter are also not new, having been used for many years in semiconductor manufacture, in space technology and for the removal of hazardous contaminants.

Flexible systems have many benefits. They can be single-use or multi-use, with disposable elements covering either individual components or entire systems. They may require less effort for cleaning, validation and qualification, although whether this effort can ever reach nanogram levels is debatable. Making an entire system disposable can reduce turnaround time, though only of course if there is no equipment inside. Speed of implementation can be another advantage, particularly in research and development applications where fast prototyping may be critical. There is no limitation on size or shape, and flexible systems are easier to retrofit to existing equipment that was never designed to be contained.

Then there are "halfway houses" in the form of semi-flexible systems. In the past such solutions have been recommended for micronizing systems in clinical trials. Semi-flexible systems have some of the benefits of solid containment, for instance allowing the use of "through-the-wall" mounting of process equipment and instrumentation, but retains the benefits of a flexible frontage.

But there are inevitably problems too—problems which often seem to be being overlooked.

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Key points for safe handling

- Always do a risk assessment.
- Always contain at source.
- Consider the full range of containment options.
- Transfers are a weak link, so their selection is key to successful containment.
- Avoid technique-dependent systems.
- Design for below the operator exposure limit.
- Remember ergonomics, cleaning, sampling, waste, and material compatibility.
- Always provide redundancy/secondary containment.
- Engineer out reliance on personal protective equipment.

Limits to flexibility

Think back to the toxins, carcinogens and mutagens that are so hazardous that they need to be contained at an OEL equivalent to a grain of pollen in your living room. How comfortable would you be with only a thin layer of plastic between yourself and such a material? With processes involving fine particles, like micronization, the consequences of containment failure can be very serious indeed, resulting in irremediable contamination of a building, and even lost lives.

Being susceptible to cuts and abrasion, flexible systems are more fragile than solid containment, and when they split or tear they "fail to danger". They have limited tolerance to pressure, vacuum and temperature, and potentially have Atex issues too. The risk of failure increases proportionately with the volume of material involved.

Other weaknesses include the effects of solvents, plasticizers, and antistatic agents, and quality issues: suppliers need to provide data to show that their containment materials meet regulations such as DMF number for NDA submittal and Certificate of Conformance. In-situ leak testing is more challenging to carry out on flexible systems. Even the environmental impact of disposal cannot be disregarded, with the potential for release of toxins when film material is incinerated.

Potentially high operating cost

Finally, a key element that is frequently overlooked (particularly by suppliers of flexible systems) is the potentially high operating cost. Yes, the initial outlay is low, but the repeated cost of replacement can in some cases be higher than that of a solid system.

This becomes highly significant when we consider equipment cleaning. Incineration costs for a simple flexible system are low, but if there is equipment inside that must be cleaned you face the same issues of dealing with waste contaminants as you would with a solid containment system.

Contained flexible granulator

Of course flexible containment has an important part to play in the industry, as long as all the potential downsides have been taken into account and a full risk assessment has been undertaken. Areas which benefit include research and development, where there are many unknowns, and small-scale production in clinical trials where equipment is not designed for containment, product changes are rapid, and cleaning can be difficult.

Conclusion

Implementing this technology on a broad scale, purely on cost grounds, is both dangerous and potentially, in the long term, more expensive. So it is much to be hoped that all process developers fully consider the pros and cons of flexible containment. Most important of all, understand and risk-assess your process.