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ACHEMA 2018: Containment in Process Engineering

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A paradigm change in solids production is underway in the chemical and pharmaceutical industries. The trend to increased specialization and higher-potency active ingredients creates the need for hermetically sealed process flows. Government regulations are also becoming stricter. To an increasing extent, the production process will have to be designed as a containment system.

No data – no market. This brief dictum from Brussels is a cause for serious concern at many companies in the process industry. It all stems from the EU REACH directive which requires prior registration for every substance produced or imported in volumes of 1 t/a or more. As marketing volumes increase, so too does the amount of data which a company must submit. This has a direct impact on the cost of the toxicological testing which is required. Testing costs an estimated 13,000 euros for volumes up to 1 t/a, but that figure can rise to more than 900,000 euros for volumes of 1,000 metric tonnes a year or more. Expensive as it is, registration is not some sort of modern-day sale of indulgences. It is actually only the first step. ECHA or a national regulatory authority then reviews the documentation which has been submitted. The EU would prefer that substitutes are found for hazardous substances. Where this is not possible, plant operators must prove that they can safely handle highly active substances. A look at the statistics shows that more than just a few companies are effected by these policies. More than 50% of all NCEs (new chemical entities) are considered to be potent compounds (OEL < 10 µg/m^3). The magic answer for maintaining smooth production flows despite these developments is containment.

The need to fully understand the process

"Containment means protecting the operator from the product and also protecting the product from the operator," said Thomas Weingartner, CEO of Lugaia Deutschland in describing the central issue. Containment (at least in the pharmaceutical industry) is nothing new. It is actually a long-term trend. Nevertheless, expertise in this field is not evenly distributed, reported Richard Denk, Head of Containment Sales at Skan, which specializes in cleanroom equipment, and founder of the Containment Expert Group at ISPE, the International Society for Pharmaceutical Engineering. "In 2004, we began putting containment on the agenda by offering training courses and seminars in Germany, Switzerland and Austria. 13 years have passed in the meantime, and I still have the feeling that we have only reached the tip of the iceberg. A lot of uncertainty remains. One reason why companies have such different levels of expertise on containment is undoubtedly the fact that the number of new products which are classified as extremely hazardous is increasing faster than the number of engineers and plant operators who are familiar with the issues involved. The knowledge deficit which has built up over the years is evident at conferences and training courses which are now attracting a large number of registrations and enrollments." The number of highly active substances has risen over the years, with the result that OEB level 5 is now often the standard. OEB stands for Occupational Exposure Band, and allocation to a band is based on the toxicological potency of a substance. OEB 5 means contamination of less than 1 µg/m^3. If this were scaled up to the size of the Empire State Building in New York, not more than one-twentieth of a teaspoon of the substance could be present in the entire building. There is naturally not just the "one solution" for achieving this. Instead, there are a number of different possible approaches. That is why, according to Claude Lefebvre, Director of Business Development at the milling equipment manufacturer Frewitt, one thing above all else is essential, namely a very good understanding of the process.

Human and product protection

The difficulties basically begin with the designations and definitions. Acceptance of the OEB classification is now widespread, but many pharmaceutical companies have their own standards which to some extent exceed the requirements of an OEB 5 solution. To cite only one example, the OEB 5 equivalent at Roche is called 3B. These are precisely the companies which are seen as major forces driving the containment solutions market. "In recent years, pharmaceutical mass production has relocated from Europe to Asia. In the industrialized countries, companies have been forced to concentrate more on the development of high-price products, e.g. for oncology," explained Iris Barnstedt, CEO of Brinox Deutschland which specializes in process systems. Working with these high-potency products has made it necessary to improve occupational safety standards. It soon became apparent that working in full-body protective clothing was a simple but uneconomic solution. People wearing this type of clothing can only work for relatively short periods at a time, and that drives up production costs. Moreover, clothing protects people, which of course always has priority, but not the product. Particularly in the pharmaceutical industry, the monetary value of a few grams of active ingredient can run into the hundreds or thousands of euros. David Johnson, containment expert at the pharmaceutical equipment manufacturer GEA , also stressed the need for an in-depth understanding of the process when the search for an optimal containment solution gets underway. "It is vital to realize that when determining the level of equipment needed and the containment performance, it is not enough to simply measure the product's Occupational Exposure Limit (OEL). This is a common misconception, and the result is a tendency in the industry for over-specification. If the solution chosen is too complicated, system operation, cleaning and maintenance become more difficult, and the procurement costs are obviously higher. Proving that a given solution is 'good enough' can be problematic but not impossible. If the reason why containment is necessary and the product are well understood and proper consideration is given to the operator and the equipment, it is possible to develop solutions which are more sophisticated and effective."

"Made in Germany" in demand

REACH may be forcing chemical producers to pay careful attention to occupational safety, but the number one market driver for containment solutions is the pharmaceutical industry, according to Fred Lonzer, Head of Sales and Marketing at the Müller Group which specializes in packaging and handling systems. Mass production is being replaced to an increasing extent with smaller batches and greater flexibility coupled of course with maximum safety. "We are working closely with isolator manufacturers in this segment to develop packaging units which have two interfaces. Reducing the number of interfaces makes the process safer," explained Lonzer. Fritz Martin Scholz, Product Manager at the Bosch Packaging Technology subsidiary Hüttlin, also reported that the pharmaceutical industry in particular (e.g. for cancer drugs) has been driving demand for containment systems in recent years. "For companies which have production operations in high growth regions, the active ingredient and the sales market are important considerations when decisions are made to produce with local or European equipment." Scholz is convinced that process systems "Made in Germany" offer leading-edge quality. "State-of-the-art systems offer features which are important for containment. They are able, for example, to detect possible faults and interruptions in the product flow and initiate corrective action without the need for manual intervention," said Scholz. It is often the small details which cause real problems. Plant operators tend to underestimate the problem potential and then find themselves confronted with unexpected situations. For example, where does the waste water go after cleaning? Then there is a crucial decision to make: Do I choose steel or single-use applications? Companies such as Hecht market isolator systems with disposable foil, but "throw-away" technology is not the solution of choice for some manufacturers. "Our emphasis is still on stainless steel systems. Naturally we are keeping a close watch on the market, and if there is demand for single use, we will react accordingly," reported Lonzer.

Containment alone is not enough

Plants operators have to clean all components which they will reuse. Again, there are two options/philosophies: removal of everything for cleaning or systems that can be cleaned in-line, in other words manual cleaning or CIP/SIP systems. Andreas Bürckert, design engineering team leader at the packaging machine manufacturer Bausch+Ströbel, explained the advantage of the latter approach: "With CIP/SIP, the process can be validated because the operations take place under machine control. The result is uniform cleaning quality and a defined time sequence." Also less manual intervention is needed by workers who would otherwise have to remove the components for cleaning by hand. There are fewer potential hazards and less time and effort are needed. Bürckert reports that for efficiency reasons, more and more plants operators are running their systems in parallel. While the CIP/SIP program is running on one system, production continues on the other system, and this reduces changeover time. If a plant operator decides to use automatic cleaning, this does not necessarily mean that the technology is deployed throughout the entire production line. "CIP/SIP can also be part of hybrid systems, where some of the equipment is cleaned and other equipment is single-use based."

Installation validation

However well-designed the solution is, no technical system provides 100% containment. Appropriate measurements must be taken prior to commissioning to assess compliance with the specified limits. The ISPE Good Practice Guide "Assessing the Particulate Containment Performance of Pharmaceutical Equipment" describes how users can measure the air concentration and surface contamination and compare them with the threshold value. Even on what is thought to be the best containment system in the world, caution is advised. Be confident, but check things anyway.

Outlook

It cannot be stressed often enough that containment is primarily about interfaces or, to be more precise, avoiding them. Any break in containment when moving the product from one process step to the next puts humans and the end product at risk. ISPE has obviously given serious thought to this, for example with the Pharma 2025 initiative which provides recommendations for future development: "It is essential that containment is integrated into the process and not adapted to the process. At the moment, in many cases process systems are not self-discharging and have to be opened, and that creates a break in containment. There is a need here for new, innovative solutions," said Denk. Another key question is what role humans will play in future production environments for highly-active substances. "The threshold values are now approaching the current limit of 1 ng/m^3. Current cancer therapeutics designed for targeted treatment, which contain substances that are extremely active, are getting closer and closer to the single-digit nanogram range. The specification for two new products recently introduced in the US is 0.1 ng/m^3. Measurement methods also continue to improve, and it is only a question of time before it is possible to detect such low threshold values. Finding suitable containment systems is likely to present the same challenges. Unattended, robot-controlled systems are one possible option."