Sterile manufacturing – current trends and developments

The pharmaceutical industry is currently in a state of flux. The introduction of classic blockbusters is diminishing. At the same time, biotechnology is just beginning to discover its potential. Gene therapy and personalized medicines are further forms of therapy which are showing signs of a promising future. Even now, this paradigm shift is showing a significant effect on automated sterile manufacturing processes.

Aseptic production and manufacturing of pharmaceuticals is per se expensive, and is only then used when either important reasons suggest it, or when it is mandated. Such reasons could include the specific application of the drug, or for reasons of formulation or shelf life.

The rationale for sterile manufacturing lies in the delivery of active ingredients into the human body. To achieve efficacy, many drug molecules need to circumvent some of bodies' natural defense mechanisms, including organs like the stomach. These types of drugs cannot be delivered orally. Parenteral delivery, however, circumvents many of the bodies' natural defenses. The body does not have a chance to keep any bacteria or viruses, which may be contaminating the drug, from directly accessing the (sensitive) circulatory system. Sterility of drugs administered directly into the blood stream is therefore of eminent importance, even in a healthy body.

personalized medicine

optical sensor technology

control stations

small lines

isolator technology

sterile processing

Protective concepts and monitoring

With the emergence of new drug types in the last few years, sterile manufacturing has also had to take into closer consideration some new aspects of working with these products.

New, toxic and highly potent active ingredients necessitate that the drug not only be protected from foreign particles, but also that the machine operators be protected from the product. Both requirements, protecting the product from the operator and vice-versa, have made increased use of cRABS and isolators as barrier systems. At the same time, the number of disposable dosing systems, consisting of product tanks, hoses, nozzles and even pumps, are seeing increased use. Pre-sterilized, single use product paths do not need to be cleaned or sterilized after a batch, so the risk of cross-contamination between batches is essentially zero. While the use of disposables reduces the up-front investment in costly CIP-SIP systems for machines, variable costs and cost of validation increase.

The human factor

Most of the isolated incidents of microorganisms found in filling and closing equipment have been proven to have originated from humans. It is therefore understandable that institutions such as the FDA and machine manufacturers strive to automate as much as possible and thereby remove the human factor as a potential source of risk of contamination. At the same time, automated process controls are broadened. Human intervention in a process is being reduced or completely eliminated in fully automated processes. Manual interventions are only then performed (or allowed) during a machine stoppage, and any product in process during the intervention is usually also automatically rejected.

Optical and sensoric inspection, weight monitoring, particle counting etc., are used to secure the pharmaceutical process during filling and closing, as well as in secondary packaging. If, for example, glass breakage is detected as soon as it occurs, the risk of contaminating the machine or an operator can be quickly mitigated. The possibility to electronically trace processes using

marking and codes is another example of securing the pharmaceutical process. Such data can be collected and operationally analyzed using ERP (Enterprise Resource Planning) software.

Smaller batches and high-value drugs

The pipeline for classic blockbuster drugs is thinning out. Biotech companies as well as small- to midsized pharmaceutical manufacturers see potential though, in progressive blockbusters and high value drugs. Lower output, a considerably expanded range of products and expensive, high-value drugs also require new technology and types of manufacturing equipment. This market constellation at the same time requires the presence of contract manufacturers. Whether a pharmaceutical company fills and finishes their product themselves, or has a contract manufacturer perform this work, the trend towards flexibility over output capacity remains the same.

Dosing technology has adapted to the new need for versatility, in which filling equipment is designed to operate with three different filling systems, such as rotary piston pumps, peristaltic pumps and time-pressure systems. The dosing systems are installed as interchangeable modules. Disposables work hand in hand with these modules by simplifying changeovers while ensuring the safe change in product. To make best use of this quick change of dosing system, and to reduce the turnaround time between batches, format changeovers have also been optimized.

Barrier technologies also ensure the safety of the product when different drugs are being manufactured. When equipment is not already placed in Class "A" cleanrooms, then the reduced operational costs of an isolator (over the lifetime costs vs. cleanroom), usually justify the use of an isolator. The isolators recently introduced at the ACHEMA 2012, with drastically reduced aeration times, are an important milestone in reducing the time between batches. Catalytic aeration allows one of the most time intensive phases of decontamination to be reduced by up to 50 %, as compared with normal aeration.

In the face of the trend to very expensive drugs, coupled with smaller batches, it is becoming more and more important to get every last drop of a batch into a saleable vial or syringe. The use of gravimetric IPC, from intermittent sampling IPC to 100 % IPC over the years has proven itself as an important basis for accurate filling and getting the most out of a batch of product. It is to be expected, that IPC systems will be used more often also in smaller machines.

Now or never – flexibility

Equipment manufacturers are trending more and more towards modular construction so as to be able to include a broad range of functions into a single machine platform. Some of these functions can also often be retrofitted at a later date. Machines to date were typically classified according to their output. Machines with the lowest output were often, even in a derogatory sense, classified as entry-level. Today though, even the smallest machines are equipped with some high-tech systems such as with isolators, or a range of other functions which can be added at a later date when required.

Biotech based drugs are often required to be freeze dried, as the shelf life would otherwise be too short to be practicable. Freeze drying is also per se expensive, and is only then used when required. The optimum integration of freeze drying into the filling and finishing process requires comprehensive planning. The increasing numbers of turn-key projects which are in process are witness to this.

flexibility | greater variety of products | turn-key lines

toxic and highly patent active ingredients | product protection

Conclusion

The pharmaceutical industry is in a profound state of flux. Cost pressures, higher safety requirements and a high demand on research are markers in this market. Equipment for filling and finishing of these products must take into account these important future developments.