
Photo: sanofi-aventis

Industrial-scale biotechnology is growing rapidly, but the full benefits of bioprocessing are achieved only in plants that are reliable, economical to build and, if necessary, flexible in operation. So, engineering know-how is in greater demand than ever.

Engineering know-how in demand

Processes based on biological transformations are fast gaining popularity as a way to make a wide variety of products. These range in scale from a few kilograms of cutting-edge pharmaceuticals to thousands of tons of fine chemicals, vitamins and proteins for animal feed. With predictions that within five years, half of all fine chemicals production will involve a biocatalytic step, bioprocessing is moving rapidly from a pharmaceutical specialty to a mainstream technique across many parts of the process industries.

Flexible plants for biopharmaceuticals

In the pharmaceutical industry, bioprocessing continues to increase in importance for the manufacture of enzymes, antibodies and other complex peptides.

The trend towards relatively fragile animal cells instead of bacteria, and the speed and uncertainties of the product development cycle, lead to some interesting engineering challenges. In spite of the sophistication of these cutting-edge biotech processes, almost all clients want plants that are multi-purpose rather than being dedicated to one particular product. A company with several promising drug candidates may need to start building a plant now, even though it may not know which products will be approved in three or four years' time, when production is ready to start. More ominously, the product originally planned for a plant may need to be withdrawn at short notice if it experiences problems at a late stage in clinical trials, or even after licensing.

One way for a company to reduce these risks is to develop a range of products based on a single "platform" such as, for instance, a certain type of yeast. This in turn favors the use of modular multi-product plants, which more closely resemble giant construction toys than conventional biotech plants. Multi-purpose plants have been familiar for many years in the conventional fine chemicals sector, but have been slow to catch on in biotech. Until recently the perception has been that bioprocesses are "special", requiring rigidly-designed plants that are each tailored for a particular product. More recently, companies have realized that this is not always so, and multi-product plants have become common.


Photo: Wacker Chemie

Biotech production of biological pharmaceutical actives under clean room conditions. Fermenters generate bacteria or yeasts, which are genetically engineered to secrete the desired active proteins.

Learning from fine chemicals

In contrast to the powders that typify conventional "small-molecule" pharmaceutical processes, biotech plants are primarily water-based. The fact that most biotech products are designed for injection ("parenterals") places stringent requirements on purity and sterility, but the use of liquids has several processing advantages. Like conventional chemical plants, biotech plants are increasingly using gravity flow to move materials through the process, starting at the top of the plant and finishing at the bottom. And compared to powders, operator safety is easier to achieve with liquid products.

Also recognizable from conventional chemical plants is the need for economies of scale. While fermenters for bulk enzymes and agricultural products may be several hundred cubic meters in size, 2–3 m^3 is a typical reactor size for biopharmaceuticals, and many plants are smaller. There is a definite trend to larger plants, however, and reactors of 20–30 m^3 for monoclonal antibodies are becoming relatively common. Larger plants will help to bring down product costs because product development, the use of aseptic techniques and stringent quality assurance are not only very expensive but also more or less independent of scale. And product costs certainly need to fall if biopharmaceuticals are to become widely used.

The yields of many biotech processes are currently low, so this is another focus of attention in the drive to increase throughput and cut costs. Much progress has already been made in improving the ability of the cell line to make the desired protein, and in increasing the amount of protein transferred through the cell wall into the growth medium. Growth media have improved greatly, and cell lines are also being made tougher, so that they

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can better withstand the stresses induced by crowding, mechanical agitation and air bubbles.

Better cells and better bioreactors

Better understanding of cell culture and improved reactor design has allowed fed-batch reactors up to 30 m^3 in volume to be used for biopharmaceuticals. In reactors of this size, issues such as lack of agitation and buildup of toxic carbon dioxide caused by hydrostatic pressure caused problems in the past. Now, however, reactor scale-up has been aided by better agitation and aeration, coupled with cell lines that can tolerate greater shear. In fact, agitators for cell culture reactors are moving away from low-shear marine impellers and back towards traditional medium-shear Rushton impellers, as used for bacteria and yeasts. At the same time, height-to-diameter ratios are increasing, from the 1:1 of a conventional cell culture bioreactor to the 2:1 or 3:1 used for fermenters. Perfusion systems, in which a membrane filter within the reactor is used to withdraw products or by-products, can allow bioprocesses to operate semi-continuously or even continuously.

Cleaning and sterilization of stainless steel equipment is a significant overhead in bioprocess plants. As a result, disposable vessels are finding increasing use, and now the concept is being used for bioreactors, too. Benefits include savings in equipment and chemicals for CIP and SIP; quicker batch turnaround; less effort needed for documentation; and perhaps improved product consistency. Current disposable vessels are limited to volumes of a few hundred liters, but future disposable reactors will be of a size of up to perhaps 5,000 liters.

Downstream processing

As well as the bioreactor itself, a complete bioprocessing plant also requires equipment and control systems to supply growth media and gas mixtures to the reactor, and to separate the product of interest from the culture medium or the cell mass. In older plants, the flow of material through the "downstream" separation stages often mimicked laboratory practices. New plants tend to be much more integrated, with a greater degree of continuous processing and closer links between the various stages, yet without losing flexibility. Modularization and effective project management are helping to cut the time needed to build complete bioprocess plants.

As with any plant construction, the key to cutting overall project times is to run several activities in parallel. This is a young industry and most of its best practices in project management will eventually come to be very similar to those in the chemical and petrochemical industries. One area in which pharmaceuticals and biopharmaceuticals are special, however, is in the issue of validation and qualification of processes and plants. Pharmaceutical manufacturers who are hard-pressed for resources are increasingly turning to engineering companies for help with process qualification (PQ). This reflects a general shortage of skilled people in this sector. ■