Front-End Engineering – A New Design Approach for Biopharmaceutical Facilities

Front-end engineering was developed to minimise design risks and optimise the overall project schedule in the planning and construction of biopharmaceutical plants – providing reliability of plans and decisions for both the client and the plant designer.

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"Products come from technologies." This sentence, from the 2003 Biotechnology Report by Ernst & Young, characterises the current status of the ‘red’ (medically-oriented) biotechnology industry in Germany and throughout the world. Biotechnology is continuing to develop at break-neck speed; biopharmaceuticals have already overtaken conventional chemically synthesised medicines in terms of new drug approvals. Construction of production plants must keep up with this development, and must not become the limiting factor in the introduction of innovative medicines to the market. The Front-End Engineering Approach developed by Linde-KCA embodies a concept that ensures the fastest and best planning and execution of high-tech projects in biotechnology.

A RELIABLE SCHEDULE

According to a study by Frost & Sullivan, biopharmaceuticals – medicines produced using biotechnological processes – achieved sales of $41.3 billion in 2002. This amounts to about 10 per cent of worldwide pharmaceutical sales. It is noteworthy that a significant portion of these sales (about $6 billion) is derived from medicines based
on EPO (erythropoietin), which are among the top-selling products worldwide.

The construction of production plants to keep up with this trend must not become a limiting factor for the introduction of new drugs to the market. 'Time to market' is a critical factor for the commercial success of innovative biopharmaceuticals. The consequence for the plant designer is that – in contrast to conventional plant construction projects – the engineering activities for biotech projects must usually start while the client’s product and process development are still going on and so must suffer from a great deal of uncertainty. The engineering conversion of a client’s particular production process is extremely complex, and must comply with strict regulatory requirements. Because of this, the plant designer must have a thorough understanding of the process, coupled with a knowledge of biotechnology, to be able to lead an interdisciplinary co-operation of engineers and scientists. This is best accomplished by teams into which the client’s experts are integrated.

Linde-KCA’s Front-End Engineering Approach was developed specifically to make possible a reliable evaluation of status, risks, costs and schedule in the early phase of biopharmaceutical high-tech projects with the goal of fast-track realisation. This can minimise risks and optimise the schedule for the planning and construction of plants. The result is reliability of plans and decisions, both for the client and the plant designer. The need for front-end engineering services has been identified on the route from the laboratory to production in both biotech companies and established pharmaceutical companies. It has been confirmed in reference projects.

FRONT-END ENGINEERING

After obtaining the existing process and project information from the client at the beginning of a project, a technology concept is generated and then a block layout is developed. The technology concept, together with the block layout, is the basis for an early estimate of the capital investment. In parallel with these activities, a process risk analysis is carried out in close co-operation with the client company; the results of this analysis flow back into the process development. The formulation of a preliminary project schedule completes the documentation of the front-end study.

Depending on the size and complexity of the project, such a study can be completed within three to six weeks. It gives the pharmaceutical company early information about costs, process and project status, and the schedule for the project. The documentation also makes up a reliable basis for the subsequent project phases – that is, for the conceptual and basic design.

GENERATION OF THE TECHNOLOGY CONCEPT

Know-how concentrated in the plant design company is a prerequisite for the fast and efficient generation of a technology concept (Figure 1). To ensure quick availability of the information required, this know-how is assembled in a library of plant unit models – for example, for bioreactors or centrifuges. This library contains functional descriptions as well as information about interfaces, procurement times and costs of the various units. It makes up the basis for generating a technology concept. Project-specific plant units are defined on the basis of the process
information from the manufacturer. With the help of identification parameters for each plant unit – such as the working volume of a bioreactor – a plant unit model can be selected from the library and adapted to the specific project. In this way, the entire process is described with project-specific plant units. This serves as the basis for developing the block layout and the cost estimate.

**BLOCK LAYOUT DEVELOPMENT**

A block layout brings together the preliminary space requirements for all the engineering disciplines such as process, process infrastructure, HVAC (heating, ventilation, air conditioning), electrical engineering and automation. The concept for development of a block layout is shown in Figure 2.

Specific tools – such as a layout library for plant units and a layout planning handbook – have been developed to ensure an efficient design approach. A typical layout for a plant unit shows the arrangement of the equipment, together with all the other space requirements for the unit – such as those for handling and logistics – in both a planar and side view.

Every project-specific plant unit is assigned a layout from the library, and is adapted to the specific project. At the same time, a functional programme and an initial layout arrangement are worked out on the basis of the layout planning handbook. With this information, the layouts can be assembled into a block layout.

**ESTIMATION OF CAPITAL INVESTMENT**

The total investment cost (TIC) can be estimated from the technology concept and the block layout by making use of benchmarking factors. The hardware costs for package units and other equipment are determined from the project-specific plant units. The hardware costs for the process control system are determined likewise – taking into account the complexity of the system. The complete technology costs are obtained by adding together the bulk and construction costs, estimated using benchmarking factors. The engineering costs can also be determined by using specific benchmarking factors for package units, equipment and process control systems.

The block layout also serves as the basis for the facility costs. It is used to determine the scope of the project for HVAC, cleanrooms and buildings. The hardware costs can then be determined from the HVAC volume factors and the area factors for cleanrooms and buildings. The engineering costs for the facility are also determined by means of benchmarking factors. As a rule, this route to an early estimate of the total investment cost allows for an accuracy of ± 30%.

**PROCESS RISK ANALYSIS**

Critical process steps and scale-up steps must be identified at an early stage for the plant design to be reliable. To accomplish this, an analysis of the developmental results and the process documentation is carried out with experienced biotechnologists and bio-process engineers. This includes a comparison of target and actual design data for the plant, and an initial determination of the principal requirements for qualification. In this way, it is possible to determine which stages of the process have attained the status required for starting conceptual design, and which require deeper analysis. For the latter case, shown in red in Figure 3, the measures necessary to reduce risk and to ensure scale-up are derived. They are documented in the form of a test programme for process development, synchronised with the requirements for further plant design.

Close interaction with the client manufacturer's experts is critical for the process risk analysis described. Only close co-operation can assure feedback of results to process development, so that the test programme is translated into action. This is the responsibility of the client.
The last step in a front-end study is to work out a preliminary project schedule. Figure 4 shows an example of such a schedule with a reduced project time, under the boundary conditions of a fast-track project for a small plant with modular design. The major project phases and their durations are stated and the finished front-end study forms a reliable basis for the fastest and technically best performance of the next project phases – the conceptual and basic design.

**CONCEPTUAL AND BASIC DESIGN**

The conceptual design should be strictly co-ordinated over all engineering disciplines simultaneously from the very beginning. This achieves high reliability for the technology, building size and cost estimate, and assures the fastest possible development of all the necessary planning documents. To comply with those requirements, Linde-KCA has developed a phase model for pharmaceutical and biotechnological projects which predefines the work and document-flow for each discipline and for the interfaces among the disciplines.

At the beginning of the conceptual design, a core team – together with experts from the manufacturer – checks the documents provided and evaluates the status of the project for the various engineering disciplines. This provides an early focus on the planning jobs that are critical for completing the conceptual design.

The conceptual design – which is worked out iteratively – should include all the relevant documents for the major disciplines, a detailed project schedule and a cost estimate that serves as a basis for the management decision on the investment. The conceptual design makes up the reliable base for beginning the basic design. In the latter planning phase, the phase model is also applied, as well as engineering tools tailored for the application to ensure error-free know-how transfer from the conceptual design and allow the fastest and best development of the basic design.

**INTERNATIONAL TECHNOLOGY TRANSFER**

Factors such as the demands of the global market, cost advantages and regulatory aspects have become decisive criteria for the selection of a production site for both pharmaceutical and biotechnology companies. As a result, new production plants are often built far from the centres of excellence for research and development, and engineering. This requires international technology transfer – often with a transatlantic dimension in view of the leading position of the USA in medically-oriented biotechnology, with all its consequences for the internal resources of the companies affected.

Linde-KCA supports such technology transfer projects with its know-how from front-end engineering, its experience in European plant design and construction, and its special knowledge about authorisation, engineering and commercial aspects for future production sites in Europe.

Front-end engineering – with its analysis of project and process status, risk, costs and schedules – is of special importance in technology transfer projects. The status analysis of a project – and especially of the process development – must also be performed at the site of the
process development, as must any additional required development tasks that are identified. However, on-site analysis at the selected site of the investment is preferred for costs and scheduling, due to the decisive influence of regional factors and requirements.

Complete and well-founded technology transfer documentation is the best basis for successful execution of a project at a selected site, utilising the proven engineering and contracting service spectrum from conceptual design to start-up and qualification. The success of a project can be assured by additional support in the search for potential financing and by co-operation in site evaluation.

CONCLUSION

Increased requirements on the pharmaceutical and biotechnology industries in recent years have fundamentally changed the demands for plant design and construction. Linde-KCA has developed know-how in front-end engineering and international technology transfer to support early-phase decisions about investments, to minimise design risks and to optimise the overall project schedule. This involves the following points in particular:

- Experience in assembling integrated project teams, as well as on-site planning
- Established methods for early and accurate estimation of capital investment
- Established capabilities and methods for process risk analysis
- Tools for the tailored adaptation of work-flow to a specific project
- International experience with highly varied projects
- Knowledge of the relevant laws and regulations of different countries

These capabilities and experiences allow for a very close co-operation with the experts from the client company in the earliest possible phase of the project. The objective is to offer capabilities tailored to the specific project, and thus assure the fastest, and best, planning and execution of high-tech projects.

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