Front-End Engineering

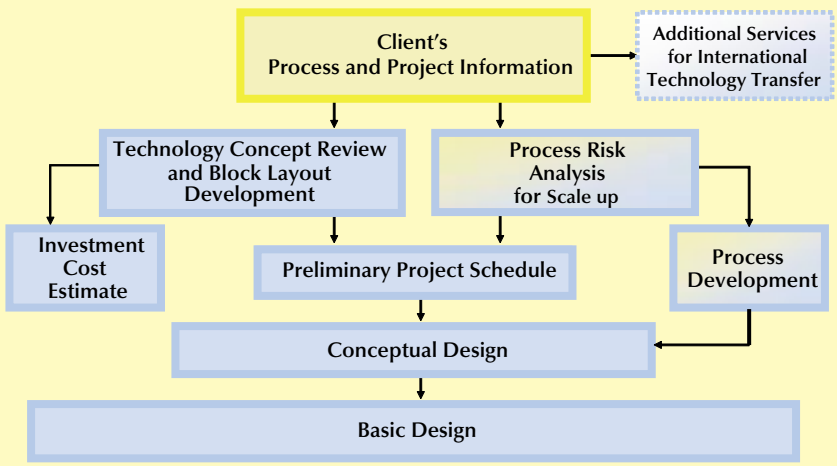
A New Design Approach for Biotechnology Projects

by Marc Reifferscheid and Karin Bronnenmeier

According to a study by Frost & Sullivan, medications produced using biotechnology reached sales of US$41.3 billion in 2002. That amounts to about 10% of worldwide pharmaceutical sales. A significant portion of those sales (about $6 billion) is from medications based on EPO (the hormone erythropoietin), which have gained the top rank in the "hit list" of the most-often-sold medications. EPO, used to treat anemia, is one of the most familiar biotech products. The potential of the biopharmaceutical industry becomes even more apparent from a glance at the product development portfolios of both pharmaceutical and biotech companies. The increasingly dominant class of biopharmaceutical APIs surpassed classical, chemically synthesized APIs as approved medications for the first time in 2002.

Because time-to-market is a critical factor for the commercial success of innovative biopharmaceuticals, construction of production facilities must not become a limiting factor for introducing new drugs. In contrast with conventional plant construction, engineering design activities for biotech projects usually start while a client's product and process development are still being defined and optimized, so they are subject to great uncertainties.

Figure 1: Linde-KCA's front-end engineering approach



The engineering conversion of a client's production process is a highly complex procedure, and it must comply with strict regulatory requirements. Facility designers must therefore thoroughly understand the nature of that process to ensure cooperation of an integrated team of engineers and scientists — including the client's experts.

Linde-KCA's front-end engineering approach was developed specifically to ensure reliable evaluation of status, risks, costs, and schedules in the early phase of biotechnology projects with the goal of fast-track realization. This approach minimizes risk and optimizes the schedule for facility planning and construction. Front-end engineering services can ease the route from laboratory to production in biotech companies as well as in established pharmaceutical companies.

Front-End Engineering

Figure 1 identifies the major services of front-end engineering. After a client provides existing process and project information, a technology concept is generated and a block layout developed. They form the basis for an early estimate of capital investment. In parallel with those activities, a process risk analysis can be carried out in close cooperation with the biopharmaceutical company. Its results flow back into process development. Creation of a preliminary project schedule completes the documentation of the front-end study.

Depending on the size and complexity of a project, such a study can be completed in three to six weeks. It gives the biopharmaceutical company early information about costs, process and project status, and the project schedule. The documentation also forms a reliable

basis for subsequent project phases (for the conceptual and basic design).

Generation of the Technology Concept

Figure 2 shows how knowledge and experience concentrated in a plant-design company are prerequisites for fast and efficient generation of a technology concept. To ensure quick availability of required information, this know-how is assembled in a library of plant unit models (bioreactors or centrifuges, for example). The library contains functional descriptions and information about interfaces, procurement times, and costs of various units. It forms the foundation for generating a technology concept. Project-specific plant units are defined on the basis of process information from the pharmaceutical manufacturer. Using 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. So an entire process can be described using project-specific plant units. This serves as the basis for developing a block layout and cost estimate.

Figure 2: Generation of the technology concept

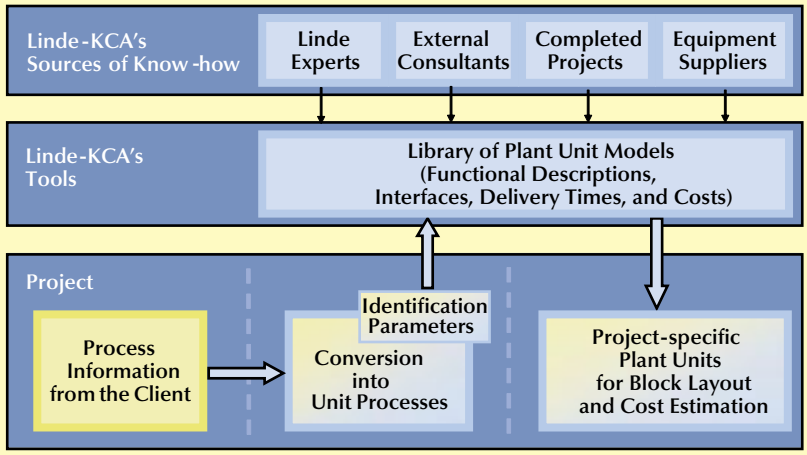
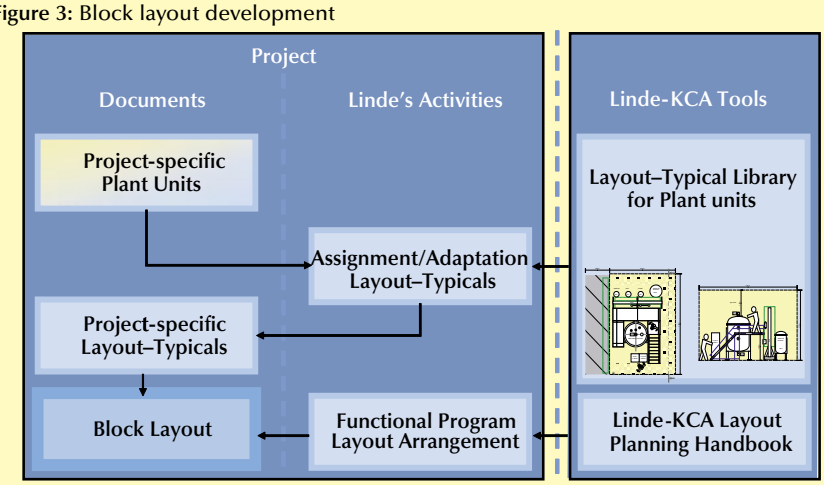


Figure 3: Block layout development



Block Layout Development

A block layout brings together the preliminary space requirements for all engineering disciplines such as process, process infrastructure, HVAC (heating, ventilation, air conditioning), electrical engineering, and automation. Figure 3 shows the Linde-KCA concept for development of a block layout.

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

Every project-specific plant unit is assigned a layout–typical from the library, which is then adapted to the specific project. At the same time, a functional program and initial layout arrangement are worked out on the basis of the layout planning handbook. That information allows layout–typicals to be assembled into a block layout.

Estimation of Capital Investment

Total investment cost (TIC) can be estimated from the technology concept and block layout by making use of benchmarking factors (Figure 4). Hardware costs for package units and other equipment are determined from the project-specific plant units. Hardware costs for the process control system are determined in the same way, taking the complexity of the specific project and process into consideration. The complete technology costs are then determined using benchmarking factors to estimate bulk and construction costs. Engineering costs can also be determined using specific benchmarking factors for package units, equipment, and process control systems.

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

Process Risk Analysis

For a reliable facility design, critical process and scale-up steps must be identified at an early stage. To accomplish that, experienced biotechnologists and bioprocess engineers analyze developmental results and process documentation.

Figure 4: Estimation of total investment cost using benchmarking factors

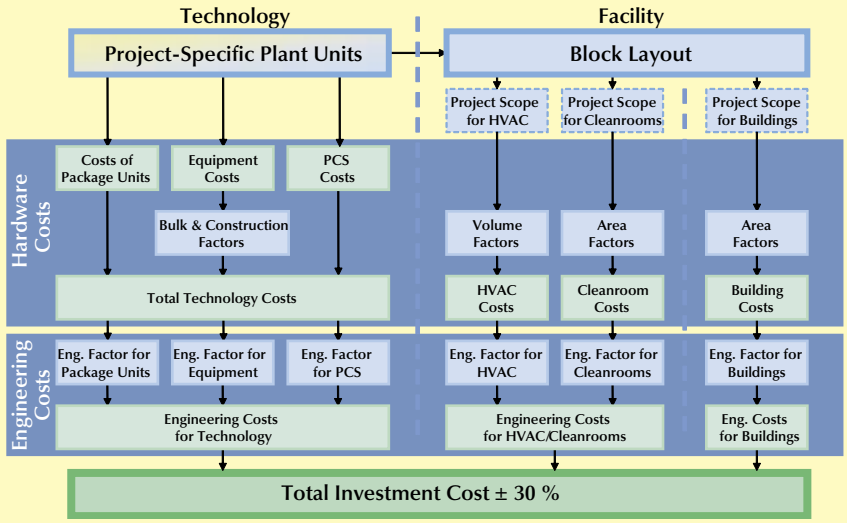
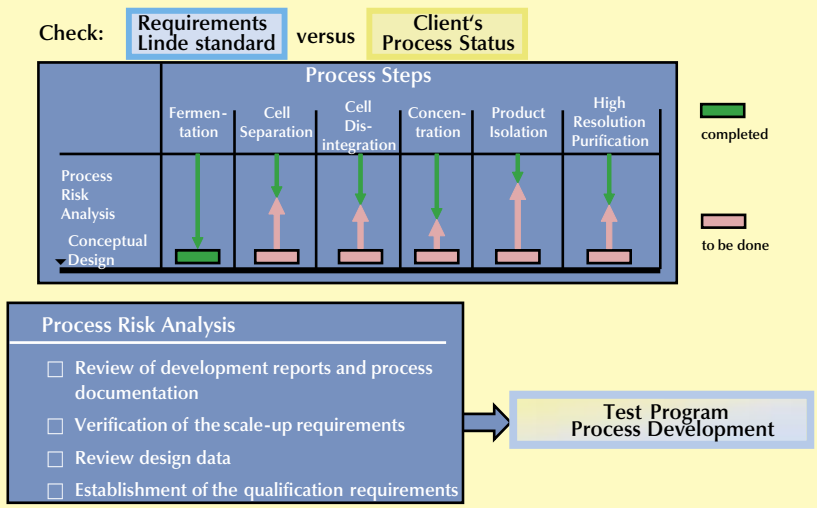


Figure 5: Process risk analysis



They compare target data with actual design data for the facility and make an initial determination of principal requirements for qualification. In this way they can determine which stages of the process are ready for conceptual design and which require deeper analysis. For the latter case, shown in red in Figure 5, measures are derived for reducing risk and ensuring scale-up. Those are documented in the form of a test program for process development and synchronized with the requirements for further plant design.

Close interaction with a pharmaceutical manufacturer's experts is critical for process risk analysis. Only close cooperation can ensure feedback of results to process development and translation of the test program into action. This is the client's responsibility.

Preliminary Project Schedule

The last step of a front-end study is to work out a preliminary project schedule. Figure 6 is an example of such a schedule for a fast-track project for a small, modularly designed plant. The major project phases and their durations are stated, from conceptual and basic design to start-up and qualification. The finished front-end study forms a reliable basis for the fastest and technically best performance of the following project phases, the conceptual and basic designs.

Conceptual and Basic Designs

The conceptual design should be a cooperative effort by representatives of all engineering disciplines from the very beginning. That achieves high reliability for the technology, building size, and cost estimate while assuring 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 biotechnology projects that predefines the work and document flow for each discipline and for the interfaces among the disciplines (Figure 7).

At the beginning of the conceptual design, a core team (together with the experts from the pharmaceutical 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, 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 management decision on the investment. The conceptual design forms a reliable base for beginning a basic design. In later planning, the phase model is applied and engineering tools are tailored to the application to ensure error-free knowledge transfer from the conceptual design and to allow the fastest and best development of the basic design.

International Transfer

Demands of the global market, cost advantages, and regulatory aspects have become decisive criteria for selection of a production site for pharmaceutical and biotechnology companies. As a result, new production plants may be built far from the centers of excellence for research, development, and engineering. That requires international technology transfer — often with a transatlantic dimension because of the leading position of the United States in biotechnology.

Technology transfer projects benefit from know-how in front-

end engineering, especially when combined with experience in European plant design and construction. Special knowledge about European authorities and commercial aspects is of particular advantage for projects with future production sites in Europe (Figure 8).

Front-end engineering, with 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 its process development, must be performed at the primary site, as must any additional required development missions. But on-site analysis at the selected site of investment is preferred for costs and scheduling because of the decisive influence of regional factors and requirements.

Complete and well-founded technology transfer documentation provides the best basis for successful execution of a project at a selected site using the proven engineering and contracting service spectrum from conceptual design to start-up and qualification. Success of a project can be assured by seeking additional support in the form of financing and site evaluation.

Supporting Early Decisions

Increasingly stringent regulatory requirements in the pharmaceutical and biotechnological industries are fundamentally changing the criteria for pharmaceutical plant design and construction. A front-end approach to engineering and international technology transfer supports early-phase decisions about investments, minimizes design risks, and optimizes the overall project schedule. The objective is to offer capabilities tailored to a specific project and thus to ensure the fastest and best planning and execution of high-tech projects through close cooperation with experts from the pharmaceutical company in the earliest possible phases of the project.

*Corresponding author **Dr. Karin Bronnenmeier** is a senior process biologist at Linde-KCA-Dresden GmbH, Bodenbacher Straße 80, 01277 Dresden, Germany, 49 3 51 250 3364, fax 49 3 51 250 4817, karin.bronnenmeier@linde-kca.com. She works there in business development for pharmaceutical plants emphasizing biotechnology. **Marc Reifferscheid,** Dipl.-Ing., is a senior process engineer at Linde-KCA-Dresden GmbH. He has been involved in planning and building of numerous pharmaceutical plants in Germany, Denmark, and Hungary.*

Figure 6: Preliminary project schedule

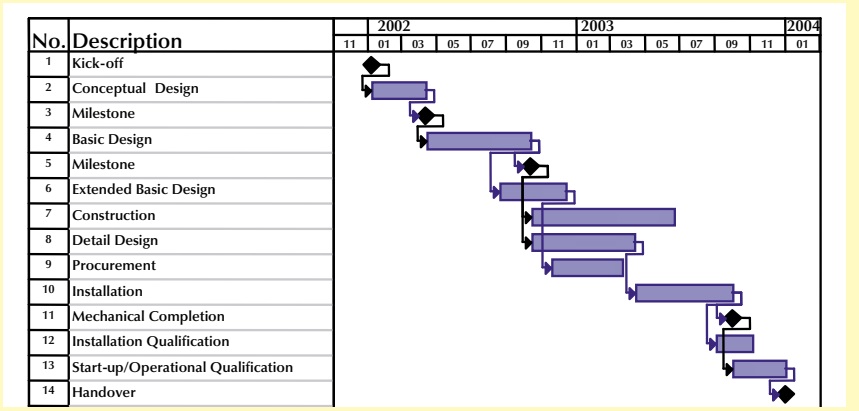


Figure 7: Conceptual design and basic design

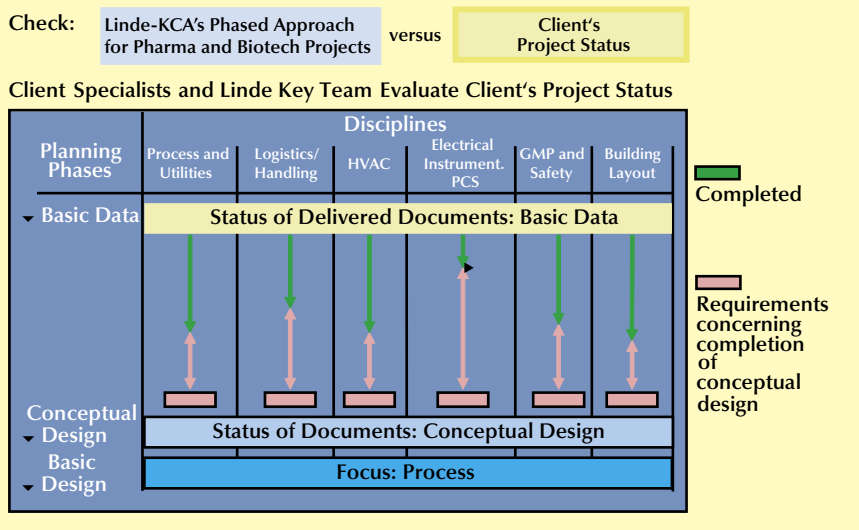


Figure 8: International technology transfer