Biotech Vision

The world of biotechnology is developing at an ever increasing pace. Pharmaceutical and Biotech companies are focused on new products with higher efficacy and technically more complex processes with higher productivity, which need to be brought to commercialization in an ever faster time frame.

This change in needs of the Pharmaceutical and Biotech industry has altered the fundamental requirements placed on the plant designer during the last few years. It makes great demands on the creative, technical and communicative skills and capabilities of companies and personnel.

To meet these demands engineering companies must take a lead in providing services on a partnering basis and in close cooperation with the Pharmaceutical or Biotech company. These services have to be tailored to the new needs for high tech projects performed on a Fast Track schedule.

Linde-KCA’s Mission

Linde-KCA’s highly motivated teams of skilled scientists, engineers and project managers, with expertise in the Pharmaceutical and Biotech industry, are dedicated to meeting the requirements of the clients in the dynamically developing market.

Linde-KCA’s Front End Engineering is a process driven design approach, starting in parallel to R&D or manufacturing upgrade. The main goals are a feasibility check by early total investment cost estimate, a process risk analysis and an early scheduling for the Fast Track project.

Linde-KCA’s key personnel work in an integrated team with the client’s R&D, manufacturing, quality assurance, and engineering teams. We provide all the necessary services and support at the client’s site to ensure the fastest, and technically best design approach. Additionally we have the capabilities to execute a Transatlantic Technology Transfer project, for clients with plans to build a new facility in Europe.

Linde-KCA’s Front End Engineering supports both large and small Pharmaceutical and Biotech companies in their move to design and build high tech facilities on a Fast Track schedule from the very beginning of a project.
Overview
Front End Engineering Services

Linde-KCA has developed a Front End Engineering approach for the Pharmaceutical and Biotech industry to allow our clients to make an informed early investment decision, and to minimize the overall project schedule. We typically include the services described in the following section in our definition of Front End Engineering. This scope is readily modified depending on the status of the project at inception of Front End Engineering, and also based on the client’s specific requirements.

Key issues that effect the client’s investment decision are the total investment cost (TIC) and uncertainties as well as risks in process and project development. To address these issues the principal deliverables of Linde-KCA’s Front End Engineering approach are the technology concept review and the block layout development, with a subsequent investment cost estimate, and a process risk analysis. Using benchmarking factors will ensure the speed and accuracy of the development of the cost estimate. The process risk analysis will be performed in conjunction with the client and includes a review of the R&D work underway and an evaluation of the risks associated with scale-up and implementation of new technologies. In this way critical process issues can be identified at an early point in the schedule to allow for a faster and technically superior process configuration.

With the block layout development and the process risk analysis completed, a first project execution plan can be generated. A coordinated and synchronized engineering approach by all disciplines then ensures the fastest possible Conceptual and Basic Design.
From the start of Conceptual Design, engineering work in all disciplines has to proceed in parallel, and in a strictly coordinated manner. This provides a high level of reliability for technology, building dimensions and cost estimate and ensures the fastest completion of all necessary engineering documents.

To meet this requirement Linde-KCA has developed a phased approach for Pharmaceutical and Biotech projects, with pre-defined work & document flows for each discipline. At the very beginning our key team evaluates the overall project status, together with the client, to determine the status of the engineering documents for the different disciplines, and to focus on those items critical for the completion of the Conceptual Design.

The iteratively engineered Conceptual Design consists of all necessary documents for the main disciplines, a project schedule and, at our client’s request, a more accurate cost estimate. The Conceptual Design forms the secure basis for the initiation of the Basic Design.

With focus on the process, the Basic Design is developed by our team of key specialists from each discipline, using the phased approach described above. With our sophisticated engineering tools, and our highly qualified technical teams, Linde-KCA ensures error-free know-how transfer from Conceptual Design, and the fastest and most accurate way to a complete Basic Design documentation.
Services for Transatlantic Technology Transfer

Increasingly US Pharmaceutical and Biotech companies are being driven by market demands, regulatory pressures, or because of regional economic incentives, to consider the erection of new production plants in locations that are remote from the companies’ centers of excellence, such as their central R&D departments and their in-house engineering support. Such an investment is very demanding on the company’s internal resources.

Within Linde-KCA’s Front End Engineering approach we offer additional services to support US Pharmaceutical and Biotech companies in Transatlantic Technology Transfer for production plants to be built in Europe. Depending on the status at the beginning of the project Linde-KCA adapts the Front End Engineering and evaluates the process and project, with a focus on regulatory compliance for a Transatlantic Technology Transfer. The needs for completion of Conceptual and Basic Design and the necessary scope of Technology Transfer documentation will be determined.

With Linde-KCA’s approach to Front End Engineering and Transatlantic Technology Transfer we are able to significantly reduce demands on our client’s internal managerial and technical resources. Additionally we offer financing support and a site evaluation with a focus on human resources, infrastructure and flexibility of regional authorities early in the project. For Technology Transfer projects to Europe our client also has access to Linde-KCA’s full range of engineering and contracting services including Detail Design, Procurement, Construction, Commissioning and Qualification.
Summary of Linde-KCA’s Front End Engineering Capacities

- Front End Engineering know how in-house
- Demonstrated capabilities in Transatlantic Technology Transfer management
- Experience in building integrated teams at client’s site
- Established methods for accurate early cost estimate
- Established in-house capabilities and methods for process risk analysis
- Staff and tools to customize the workflow for different design phases
- Transatlantic project experience, with multi-faceted projects
- Knowledge of legislative and regulatory issues on both sides of the Atlantic
- Successful Front End Engineering and Technology Transfer Project Records

With Linde-KCA’s skills, capabilities and experience we have the resources to be the best partner for Front End Engineering and Transatlantic Technology Transfer projects in the Pharmaceutical and Biotech industry. Furthermore, with our experienced teams, we can continue to work for the client as an extension of his in-house resources or, at the clients request, perform one or more of the execution stages of the project.

We are prepared to support you.
Selected References

**Plant for the production of recombinant blood coagulation factor VIII**
Client: Bayer AG, Leverkusen; Location: Germany, planned for Wuppertal-Elberfeld; 
Product: Recombinant blood coagulation factor VIII; Type of plant: Plant for the production of the pharmaceutical ingredient in high-cell-density perfusion cultures of BHK cells and purification of the glycoprotein; Scope of work: Know how and technology transfer from production and R&D into Design Basis; Conceptual design for all disciplines; Total investment: appr. 160 million EUR; Current status of project: Conceptual design finished; Planning period: December 2000 - June 2001

**Project LANTUS Insulin, Aventis Pharma**
Client: Aventis Pharma Deutschland GmbH; Location: Frankfurt/Main/Germany; Type of order: Plant for the production of the insulin derivative Insulin Glargine (trade name Lantus®); Product: Recombinant insulin derivative with depot effect achieved by engineered amino acid sequence; Production process: Biotechnological fermentation; Scope of work: Engineering “Lump sum” (appr. 25 million EUR); Basic and detail engineering, procurement (on behalf and on account), civil, construction, commissioning, qualification; Handover: 2002; Total investment: appr. 150 million EUR; Current status of project: Detail engineering, under construction

**Plant for the fractionation of human blood plasma**
Client: Aventis Behring GmbH; Location: planned for Marburg/Germany; Kind of plant: Plant for the fractionation of human blood plasma; Products: Basic fractions of human blood plasma and products of down stream processing; Volume: 160 million EUR; Scope of work: Concept and basic engineering for process, architecture, civil, infrastructure, IT (3,7 million EUR); Project status: Basic engineering finished; further planning depending on the final site decision

**Biotechnological Production of Hepatitis B Surface Antigen (HBsAg)**
Type of order: Process development; Partner and process supplier: Rhein Biotech, Düsseldorf/Germany; Scope of work: Concept for the transfer of the laboratory process to production scale; financing, planning und construction of the pilot plant; assistance during the runs of the pilot plant and in the preparation of the development report; concept of a production process in compliance with GMP; Capacity: 50 Liters per batch; equivalent to 15 million doses/a; Result: Marketable procedure; e.g. license contract issued to Pasteur-Merieux-Connaught; authorisation for Argentina; Completion: 1998

**Plant for production and packaging of Insulin**
Client: Biomed, Kiev; Plant location: Kiev/Ukraine; Kind of order: Construction of a complete factory as joint project of Linde-KCA-Dresden GmbH and Glatt GmbH Weimar, consisting of plants for - high resolution purification, - manufacture of solution, - filling and packaging of ultra-pure Insulin, as well as auxiliary and subsidiary facilities; Licensee: Hoechst AG, Frankfurt-Höchst; Product: Insulin of highest purity; Scope of work: Turnkey plant in compliance with GMP; Start-up: 1997

**Multi-purpose plant for the production of steroid agents**
Client: GEHE AG, Jenapharm GmbH; Plant location: Jena/Germany; Process: Jenapharm GmbH; fermentation, isolation, syntheses, cleaning, drying, micronization; Product: Steroid agents; Scope of work: Turnkey plant to GMP standards; general contractor, authority engineering, basic engineering, detail engineering, delivery, construction, installation, operational and performance qualification, start-up; Start-up: 1995
Locations and Contacts

Linde-KCA headquartered in Dresden, Germany, is the Pharmaceutical and Biotech Engineering Center of Excellence for the Linde Group. Linde is a major worldwide supplier of engineering services and industrial gases, and has a major presence in many countries. Linde-KCA, if required, draws on these additional engineering and management resources from the parent company in Munich and the affiliates in the United States and worldwide.

Within its engineering organization, Linde designs and builds Pharmaceutical, Chemical, Gas Processing, Gas Separation and Environmental Plants worldwide.

For further information about Pharmaceutical and Biotech Plants, please contact us under the following addresses:

**LINDE-KCA-DRESDEN GMBH**
Pharmaceutical Plants
Postal address:
Bodenbacher Straße 80
01277 Dresden, Germany
Phone: +49 (0)3 51 2 50-37 07
       +49 (0)3 51 2 50-35 42
Fax: +49 (0)3 51 2 50-48 14
christoph_kevelordes@lkca.de

**LINDE PROCESS PLANTS, INC. (LPP)**
Postal address:
8522 East 61st Street
Tulsa, Oklahoma 74133-1923
Phone: +1 918 250-85 22
Fax: +1 918 250-69 15
hans_kistenmacher@lindeppusa.com
http://www.lindeppusa.com