PRAXIS

A publication by Bioengineering AG

Portrait of Rentschler Biotechnologie GmbH, a globally active service company that supports its clients in the development, production, and registration of biopharmaceuticals. Bioengineering AG was responsible for the technical planning, construction, commissioning and qualification of the 500-liter GMP production facilities.

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Bioengineering –
Experience only specialists can have

Ulm. 7.23 p.m.

Rentschler Biotechnologie

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Company

Rentschler Biotechnologie GmbH is an independent, globally active service company that supports its clients in the development, production, and registration of biopharmaceuticals. Short development periods and the highest standards of quality and efficiency are ensured.

Headquarters

Rentschler Biotechnologie is headquartered in Laupheim, located in southern Germany. Here, at our facilities encompassing 5,500 m^2 in total surface area, the company manufactures and fills finished products in accordance with international quality standards.
Rentschler Biotechnologie also maintains a US sales office in New Providence, New Jersey, which was established to offer more extensive support to its North American clients and to expand its market presence in North America.

Facilities

The GMP certified production of active pharmaceutical ingredients (API) at Rentschler Biotechnologie is conducted at facilities featuring state-of-the-art technical equipment. It encompasses Upstream Processing (USP) as well as Downstream Processing (DSP).
Presently, eight independent GMP plants exist on a surface area of 4,500 m^2. They support small scale developmental projects and manufacture commercial scale products under cGMP. Currently, production on a scale of up to 500 liters is possible; however, by mid-2008, the capacity will be expanded from 8 to 10 production lines with a capacity of up to 2,500 liters.
Cell fermentation on different systems (stirred tank reactor, multi-tray) and cell clarification using different methods is done in the USP area. For over 30 years Rentschler Biotechnologie has been working successfully with cell cultures in the production of biopharmaceuticals. The product purification which is part of DSP takes place in separate parts of the plant, also equipped with state-of-the-art technology.
Besides the process development and the production of active pharmaceutical ingredients, the pharmaceuticals can also be formulated and packaged; furthermore, Rentschler Biotechnologie carries out analytics, quality control (QC), registration and quality assurance (QA) for its products.

Bioengineering AG was responsible for the technical planning, construction, commissioning and qualification of the 500-liter GMP production facilities.

Rentschler Biotechnologie GmbH today

The world market for therapeutic proteins and monoclonal antibodies continues to grow. Global revenues of up to 121 billion dollars are forecasted for 2010. Available production capacity needs to grow accordingly.

In 2006, Rentschler Biotechnologie GmbH launched an investment program of 50 million Euros to expand its production facilities. The company is expanding its production facilities and ancillary equipment to increase its capacity for the manufacture of products for clinical trials and commercial supply. Two fermentation lines with a total volume of 5,000 liters (2 x 2,500 liters) for commercial quantities and several smaller lines with a capacity of up to 500 liters for the manufacture of clinical study products are currently built and commissioned. In mid-2007 Rentschler Biotechnologie has already started up two new 500-liter GMP production lines thus completing stage one of its capacity expansion program.

Advanced service from Rentschler Biotechnologie GmbH

Rentschler Biotechnologie offers all services including market introduction of a new biotechnological product, all from one source. The company supports its clients in all the phases of product development – from the cell line to registration including process development, manufacture and Fill and Finish of the active pharmaceutical ingredient, as well as assistance with regulatory affairs. A time- and cost-intensive transfer of technology is thus unnecessary, which means success for our clients' projects and accelerated time-to-market.

GxP certified services:

Development of cell lines

When manufacturing a recombinant protein, the requirements of the FDA and the EMEA have to be met right from the outset, i.e. as soon as the cell line is selected and established. The cell lines produced at Rentschler Biotechnologie meet all the prerequisites for setting up an optimal production process.

Core competencies in the development of cell lines

- Development of serum and protein-free cell lines
- Production and storage of Master and Working Cell Banks (MCB/WCB)
- Characterization of Master and Working Cell Banks (MCB/WCB)

Process development for clinical and commercial production

Rentschler Biotechnologie possesses extensive specialist competence and state-of-the-art facilities for developing economical and robust upstream and downstream processes.

Core competencies in USP and DSP Development

- USP development and optimization of fermenter processes in stirred tank bioreactors at lab scale and scale-up to production levels
- Development and scale-up of multi-tray fermenter processes
- DSP development at lab scale and scale-up to pilot and production levels
- Process validation under GMP guidelines
- Validation of viral safety

API Production under GMP

At Rentschler Biotechnologie all the opportunities for the biotechnological production of active pharmaceutical ingredients in mammalian cells are available – from simple services for development and production to cooperative process development up to validated, GMP-compliant production.
The GMP certified production of APIs at Rentschler Biotechnologie is done in state-of-the-art facilities. They include upstream processing areas, and downstream processing.

Core competencies in GMP certified API Production

- Production for clinical trials Phases I-III in accordance with GMP guidelines
- GMP production for the market
- Stirred tank reactors: 30 to 500 liters, from mid-2008 up to 2,500 liters
- Multi-tray technology: Daily harvests up to 1,000 liters
- Cultivation methods: batch, repeated batch, fed batch, continuous methods (e.g. perfusion)

Fill and Finish

At Rentschler Biotechnologie, Fill and Finish encompasses every service – from galenic development and aseptic filling, the lyophilization in vials and pre-filled syringes, to the packaging of clinical samples. Rentschler Biotechnologie's galenic experts have years of experience in the development and optimization of galenic formulations, and also offers, amongst other things, the formulation of proteins for parenteral applications.
Through cooperation with a variety of European partners, Rentschler Biotechnologie also makes it possible to develop specialized forms of application.

Core competencies in Fill and Finish

- Proteins as formulated pharmaceutical medicines
- Aseptic filling of vials with/without lyophilization
- Production of up to 6,000 vials/h or 95,000 vials/batch
- Aseptic filling of pre-filled syringes
- Production of up to 20,000 syringes/batch
- Labeling, packaging, and shipping of clinical samples
- All methods meet the requirements of FDA and EMEA

Analytics and Quality Control

Rentschler Biotechnologie's experience of over 30 years in the field of biotechnological analysis and method development helps to provide effective, economical, and quick solutions to specific client requests.
All areas of chemical, biological, pharmaceutical and microbiological analytics and quality control have been audited and accredited in accordance with EU-GMP, US-CFR and ICH guidelines. In addition, Rentschler Biotechnologie also offers the transfer of already developed methods or the complete development and validation of analytic methods in accordance with international guidelines.

Core competencies in Analytics and Quality Control

- Chemical, biological, pharmaceutical, and microbiological analysis
- Protein structure analysis, identity and purity testing
- Glycoprotein characterization, oligosaccharide mapping
- Identification of Posttranslational Modifications (PTMS)
- Bioassays, SDS-PAGE, Western blots, and ELISA for the quantitative determination of proteins
- Residual analysis for DNA, host cell proteins and other processing chemicals
- BIAcore analytics
- Stability studies under ICH conditions

Registration approval consulting and implementation for biopharmaceutical substances

The Regulatory Affairs Team at Rentschler Biotechnologie has had decades of experience in national and international registration/approval processes. Thanks to its excellent contacts with European authorities and its expertise in pharmaceutical development and registration, clients can rest assured that the product development and corresponding documentation will meet the registration approval requirements.

Core competencies in Registration for biopharmaceutical substances

- Registration approval consulting and implementation of registration procedures during the course of product development
- Assurance of regulatory compliance from lab scale to commercial scale
- Compilation of registration approval dossier (market approval)
- Competent authority contacts
- Organization and implementation for regulatory submission
- Advice on biological/virological safety questions

Quality Assurance

The Quality Assurance department at Rentschler Biotechnologie monitors the in-house quality standards and adapts these standards to the requirements placed by the national and international authorities.

Core competencies in Quality Assurance

- Maintain quality standards during development
- Maintain EU and cGMP compliance
- Prepare, consult, and follow-up on process and method transfers
- Undertake GMP audits on behalf of the client
- Qualify suppliers and subcontractors
- Consult on the development and implementation of quality systems
- Assessment of documentation for GMP compliance of prior project phases

Corporate Project Management

At Rentschler Biotechnologie, all clients have a reliable, competent contact person who is responsible for project management. The project manager is solely responsible for planning and coordinating all activities across department boundaries, heads the interdisciplinary project team, and coordinates the contributions by each of the specialized departments. The project manager is also responsible for deadlines, the project budget as well as implementation monitoring.

Project Management services

- Corporate project management including planning and control
- Proactive communication (transparency of the project status)
- Monitoring of project goals as well as timelines and budget

Reception area. 9.12 a.m.

Left: Main production bioreactor, capacity 500 liters.
Rear: Inoculum bioreactor, capacity 20 liters.
Right: Prefermenter, capacity 100 liters.

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Main production bioreactor, capacity 500 liters.

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Complete plant: Main bioreactor, prefermenter,
inoculum bioreactor.

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Inoculum bioreactor with control cabinet, capacity 20 liters.

The success story of Rentschler Biotechnologie GmbH

Rentschler Biotechnologie GmbH had already begun developing vaccines for bacterial infections as early as 1947. Since the foundation of its own internal biotechnology department in 1974, the company has brought a large number of pioneering biopharmaceutical products to the market, among them the world's first interferon API.
Today, Rentschler Biotechnologie no longer develops its own pharmaceuticals. Instead, it makes its entire expertise available as a service to its clients.

1927 Founding of Dr. Rentschler & Co., development, manufacture and marketing of pharmaceuticals.
1947 Founding of a bacteriological and virological institute, development, manufacture and marketing of vaccines.
1974 Founding of Rentschler Biotechnologie; start developing and manufacturing Interferon
1979 Launch of recombinant cell technologies.
1983 World's first market approval for a natural IFN-β compound (Fiblaferon®).
1989 Approval gained for recombinant IFN-γ_ and topical IFN-β gel.
1993 All biotech activities are consolidated in Rentschler Biotechnologie GmbH.
1997 Focus on contract development and contract manufacture (CMO) of biopharmaceuticals.
2003 Commissioning of new facilities, tripling production capacity.
2005 Start expansion program for API Production (2 x 500-liter und 2 x 2,500-liter fermentation lines).
2006 Founding of the US company with a sales office in New Jersey.
2007 Commissioning of new 500-liter GMP production lines.
2007 Staff of about 450, approx. 310 in biotechnology.

Left: Main production bioreactor, capacity 500 liters. Rear: Inoculum bioreactor, capacity 20 liters. Right: Prefermenter, capacity 100 liters.

Prefermenter, capacity 100 liters.

Main production bioreactor, capacity 500 liters.

500-liter fermentation facilities with Bioengineering AG

When planning and constructing the new 500-liter fermentation facilities, Rentschler Biotechnologie GmbH chose Bioengineering AG as its partner because this company has great knowledge and experience in the field of plant construction for cell culture production.

Bioengineering AG components

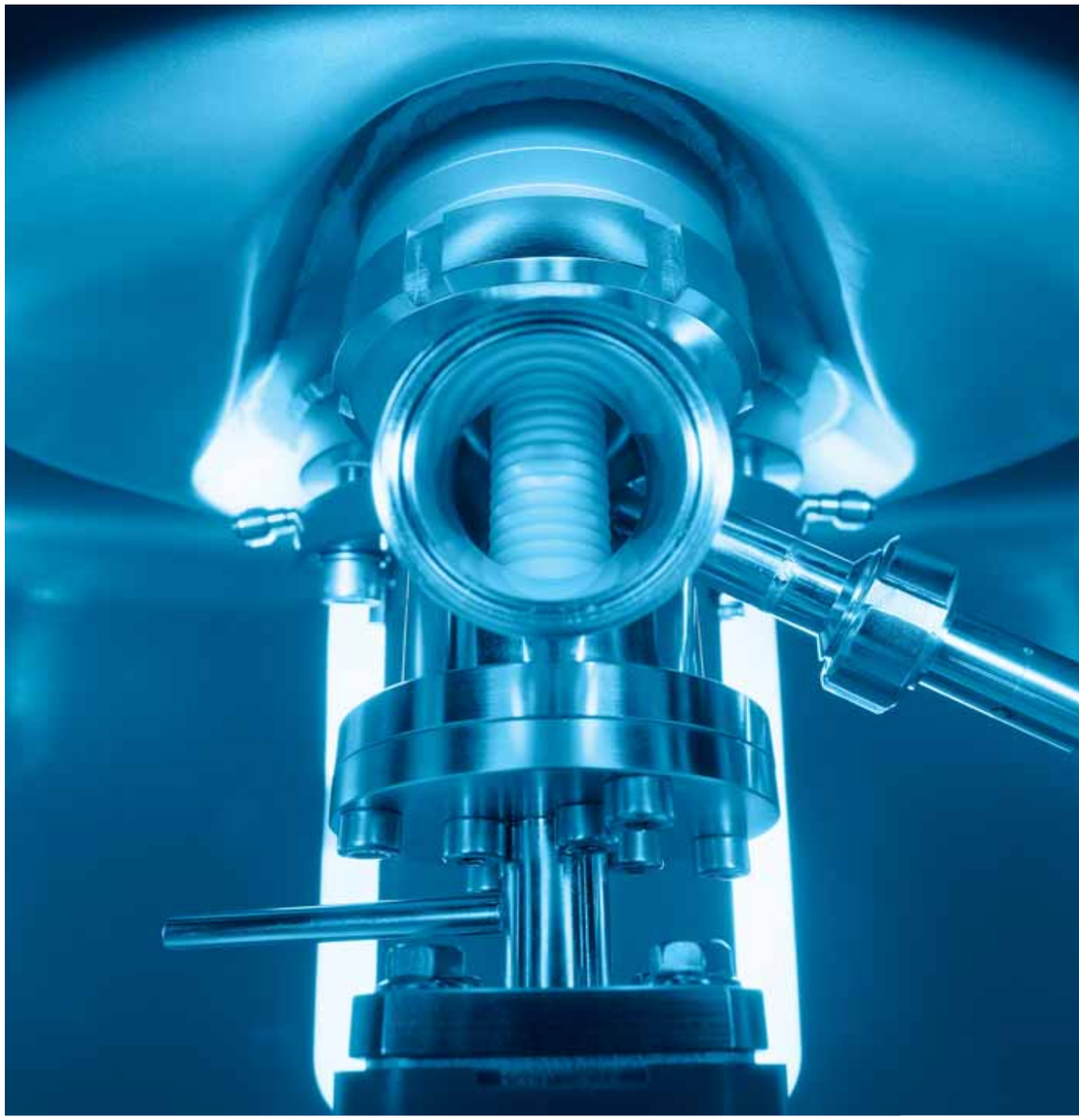
Bioengineering was responsible for the construction of two fermentation lines at Rentschler Biotechnologie, each with three fermenters. They have a maximum capacity of 20, 100 and 500 liters each and can therefore easily support varying product demands.
Bioengineering has constructed the reactors, implemented the bioengineering components and instrumentation, carried out the detailed engineering, and was responsible for IQ, OQ and the commissioning of the plant.

Fermentation

Since 2007, Rentschler Biotechnologie has introduced two new fermentation lines. Each line contains three sterilizing and fully-automated cell culture bioreactors with work loads of 20, 100 and 500 liters.

How Bioengineering AG did this

The work process was customized. Bioengineering received extensive user specifications from Rentschler Biotechnologie. Based on these documents, the engineers at Bioengineering worked constantly to further improve these concepts in order to ensure that all processing systems would be constructed in the optimal manner.
In all construction phases, Bioengineering examined and discussed new and innovative solutions together with Rentschler Biotechnologie before implementing the final concepts. The result of these studies was a diagram of the final piping systems and instrumentation as well as all other relevant technical documents.
The bioreactors, with a capacity of up to 500 liters, and all reactor framing were built in Wald, Switzerland and tested at the plant.
Experts from Bioengineering commissioned and qualified the facility in cooperation with production teams from Rentschler Biotechnologie and Biotech GmbH.



A promising future

By expanding its production facilities, Rentschler Biotechnologie GmbH will be adding 2,500 m^2 of GMP area. In the future, 10 independent GMP suites will be available for upstream and downstream processing with a total surface area of around 7,000 m^2.

Plans for mid-2008 call for the commissioning of the first of two new 2,500-liter multi-purpose fermentation lines. These facilities also have the capabilities to be used in perfusion processes. The expansion project as a whole comprises a new laboratory building, a central energy supply facility, an expanded logistics area as well as additional pilot facilities for sterile filling of syringes and injection vials.

By adding additional fermentation facilities, the Rentschler Group will strengthen and expand its biotechnology business through customer-tailored services, from cell line development to large-scale cGMP production, registration of drugs, and Fill and Finish. This will allow Rentschler Biotechnologie to offer its clients not only the development and manufacture of biopharmaceuticals for support of clinical studies in the future, it will also permit future production on a large scale for supply of commercial quantities.

A	C	T	Let us A.C.T. together:
Advanced Service. An integrated, custom-tailored offer of biopharmaceutical services from cell line to registration.	Competence. A biotech pioneer with over 30 years of experience in the development and production of biopharmaceuticals.	Time to Market. A competent partner that can turn your vision into a successful product quickly and reliably.	Rentschler Biotechnologie service is called A.C.T. – Advanced Service, Competence and Time to Market, which stands for a comprehensive range of services backed up by knowledge from more than 30 years of experience with biopharmaceuticals.

Complete plant: Main bioreactor, prefermenter, inoculum bioreactor.