

HEALTH – MADE IN GERMANY

# **German Biomanufacturing Guide**

MAY 2011

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## The export initiative for the German health care industry

Germany's Federal Ministry of Economics and Technology invites you to use this guide, which it is publishing as part of the "Export Initiative for the German Health Care Industry."

The "Export Initiative for the German Health Care Industry" is focused on supporting the industry's efforts to promote exports. Germany Trade and Invest is implementing the program on behalf of the Federal Ministry for Economics and Technology. The initiative creates, in particular, a network of existing measures to promote health care industry foreign trade.

The website [www.health-made-in-germany.com](http://www.health-made-in-germany.com) features publications, information about trade missions, and background facts relevant to export

that are easy to find because the website has been created with users from the health care industry in mind. Furthermore, the initiative is also active in marketing. In this context, the "Export Initiative for the German Health Care Industry" takes the entire health care industry into particular account through working groups that update and implement marketing measures. Working groups from the pharmaceuticals, medical technology, medical biotechnology and telemedicine/healthcare services sectors have already been established. The groups are composed of representatives from professional and specialist associations and companies, giving them particular insight into sector needs with respect to how Germany's health care industry can best serve its trading partners from abroad.

## Overview Biomanufacturing

Biomanufacturing – a booming branch

Germany's biomanufacturing sector is known worldwide as one of the industry's leaders. With a fermentation capacity of 675,000 liters, Germany leads Europe and is second only to the US in the production of biopharmaceuticals.

Biomanufacturing – production of effective ingredients in large fermenters – began in Germany in 1987. It started with the first commercial manufacture of an active substance for preventing blood clots called alteplase. This initiated the development of Germany into a locus for medical biotechnology. As the sector advanced, the first vaccine to protect women against the virus that causes cervical cancer was developed by Harald zur Hausen. In 2008, zur Hausen was awarded the

Nobel Prize for Medicine for his research. And in 2009, a German bio-tech-start-up-company had licensed a tri-functional antibody it developed to treat cancer-related ascites.

Due to favorable labor market conditions, Germany assumed a preeminent role in biotechnological research and development and is a trailblazing provider in the field of producing biotechnological active ingredients. Maintenance of the highest of technical standards as well as the corresponding regulatory requirements in production and quality control guarantee optimal product quality. Companies seeking reliable and safe manufacturing processes will discover there is no better place to find these conditions than in Germany.

### Medical biotechnology – Germany's strongest biotechnology discipline

Germany has become an international "hot spot" in the area of medical biotechnology. The country has the greatest number of biotechnology companies in Europe, top-flight research infrastructure, and is home to some of the world's most-renowned scientists.

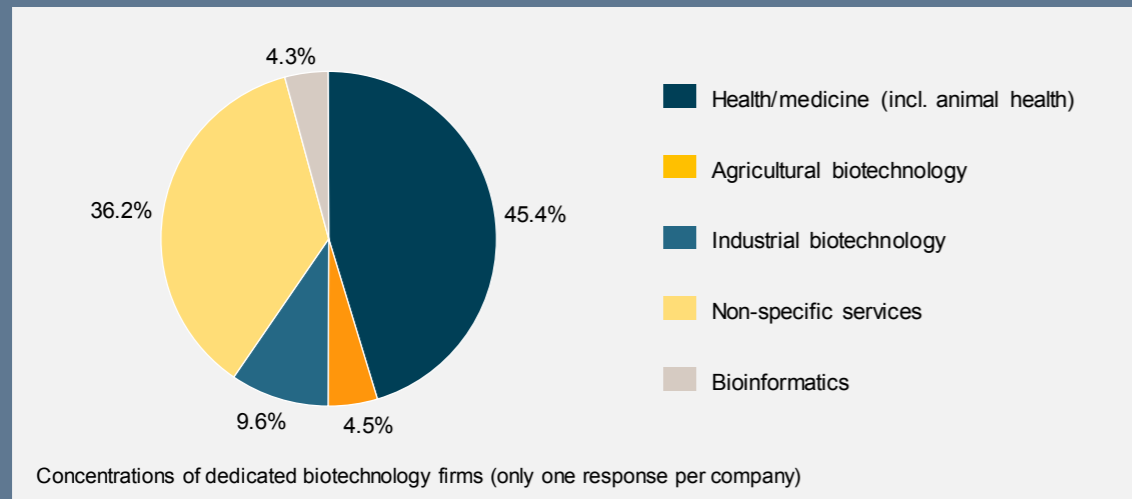
Some 45 percent of the biotechnology companies based in Germany develop new drugs or diagnostic methods in the areas of human and animal medicine. Medical use ranks among the most important applications of biotechnology. Some 36 percent of the remaining biotech firms do not focus on a specific area, or are active several application

areas. A significant number of these firms provide services for the biotechnology industry. Included in this category are companies that are contracted for production and do not have their own product development as such.

The rest of the companies are active in bioinformatics, agriculture and industrial biotechnology.

Small firms with only a few employees are characteristic of this industry. Most companies have less than 50 employees.

Source: biotechnologie.de



The German medical biotechnology sector is dominated by the production of biopharmaceuticals (e.g. antibodies), the manufacture of which is among the most demanding within the area of genetic technology. In addition to their use for making therapeutic drugs, DNA/RNA technologies also play a key role in genetic therapies and regenerative medicine as well as in medical biotechnology itself.

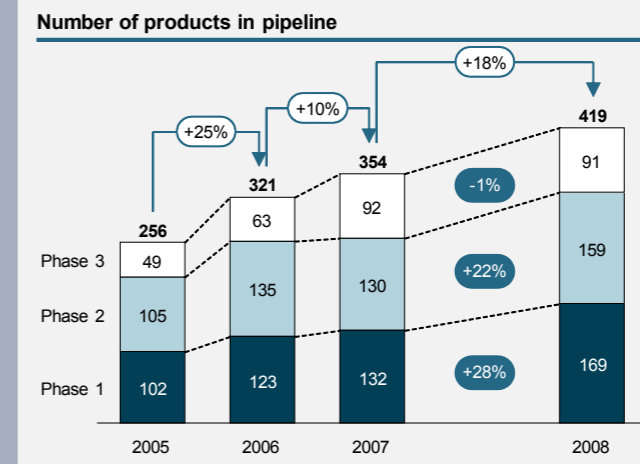
Medical biotechnology companies' sales rose nearly 40 percent from the years 2005 to 2009, to give the sector an annual growth rate of nine percent for that period. German medical biotech products and technology platforms are sought after abroad and

international demand is rising.

The German market for biopharmaceuticals had sales of EUR 4.4 billion in 2008, for an increase of nearly 10 percent on the preceding year.

In 2008, 419 biopharmaceuticals were in Phase I-III clinical trials. Of these, monoclonal antibodies dominated, with 162 projects. Most of these antibodies were for treating tumors. They accounted for a total of 30 percent of all new biopharmaceuticals then in a clinical trial stage or licensing process.

Biopharmaceutical product pipeline 2005-2008



Source: vfa and BCG, 2009

The German biopharmaceuticals' market grew by 18 percent in 2008. That makes Germany number two in biotechnologically manufactured drugs -- second in the world only to the USA. And other branches of biotechnology are growing continually as well. In 2009, 188 biopharmaceuticals were licensed

in Germany. Sales of biopharmaceuticals on the German pharmaceuticals market grew by five percent (2009 level) to EUR 4.7 billion and as a result, accounted for 16 percent of sales in the German pharmaceuticals market as a whole.

### Outlook – the biotechnology sector will continue to grow in importance

Biotechnological processes are coming into use in more and more economic areas – to make production more efficient and sustainable, for example. It has recently become apparent that the challenges of the future cannot be effectively met without the aid of processes incorporating biotechnology. Our future living standards will be founded on a knowledge-based bio-economy. Biotechnology is one of the cornerstones of this foundation.

There will be more companies that produce biotechnological goods and more people employed

in the sector. Sales will be stable. Top flight research and development that is highly respected internationally will continue. Without a doubt, Germany's biotechnology industry will go on gaining significance, both at home and abroad.

On the following pages, we would like to introduce you to German companies engaged in biomanufacturing. The companies listed in this directory provided the information it contains in response to a survey taken for the purposes of compiling this guide.

**Directory of Companies with Fermentation Capacity**



BAVARIAN NORDIC

## Bavarian Nordic GmbH

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### Existing co-operations:

- National Institute of Health, USA
- National Cancer Institute, USA
- Impfstoffwerk Dessau-Tornau, Germany

### Expressions system:

- Mammalian
- Microbial
- Other: manufacturing of live viral vaccines

**Fermenter capacity (volume in liters):** 5 L - 200 L

### Services offered:

Bavarian Nordic considers partnerships as essential part of our business model.

We are open to the full range of set-ups from in-licensing and out-licensing to sophisticated partnerships.

Bavarian Nordic owns a broadly applicable MVA-BN® vaccine platform technology, which can be applied to develop multiple vaccines across various disease areas, and has been tested in more than 3,400 persons.

We can offer out-licensing opportunities of our proprietary technologies and/or vaccine programs and we search for innovative technologies supplementing our in-house technologies and programs.

Bavarian Nordic is dedicated to two therapeutic areas, cancer and infectious diseases.

We are also interested in research collaboration with academic groups and biotech companies. We might be able to provide technologies and production know-how that your organization can use to explore scientific arenas that lay beyond the resources and skills available to you.

At our Berlin site we offer GMP-compliant contract services mainly for the manufacturing of Seed Stocks and Investigational Medicinal Products of live viral vaccines for use in preclinical and clinical trials.

## Company Profile:

Bavarian Nordic is a leading industrial biotechnology company developing and producing novel vaccines for the treatment and prevention of life-threatening diseases with a large unmet medical need. The company's clinical pipeline targets cancer and infectious diseases.

With operations in Denmark, Germany, the USA, and Singapore, Bavarian Nordic employs over 400 people.

Bavarian Nordic's patented technology, MVA-BN® is – as demonstrated in clinical studies – one of the world's safest, multivalent vaccine vectors for the development of vaccines against various infectious diseases such as smallpox, HIV/AIDS, as well as against breast and prostate cancer. Several MVA-BN®-based HIV, cancer and smallpox vaccines are in clinical Phase I and Phase II trials.

Bavarian Nordic has ongoing development contracts with the US government (awarded in June 2007, September 2004 and February 2003) to develop IMVAMUNE® as a safe third-generation smallpox vaccine. Bavarian Nordic's advanced clinical development program has been further expedited by the US government with the FDA's grant of "fast-track" status for IMVAMUNE®, the first-ever smallpox vaccine candidate to be given this designation.

Bavarian Nordic's pipeline currently includes a total of seven development program in cancer and infectious diseases.



## BIBITEC Gesellschaft für Prozessentwicklung mbH

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### Existing co-operations:

- University of Bielefeld
- University of Applied Sciences, Bielefeld
- Steinbeis-Transferzentrum, Mannheim

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):** 100 L stainless steel bioreactor

### Services offered:

- Cultivation of Mammalian cells (batch, fed-batch, perfusion)
- Upstream and downstream process development up to 100L scale
- cGMP-compliant production of APIs for use in clinical trials up to phase III
- Validation studies

### Company Profile:

BIBITEC GmbH specializes in the production of recombinant proteins, monoclonal antibodies and APIs for use in clinical trials up to phase III using Mammalian cells. The activities comprise the areas of development and optimization of production processes, protein analytics and quality assurance. The fermentation capacity in Mammalian cells is up to 100 L. Protein purification is located in clean rooms' class C. The company is GMP-certified and has recently completed the process development and optimization as well as GMP-compliant production of EPO for use in clinical trials. The entire production and purification process was successfully transferred to large-scale production and market supply. BIBITEC was founded in 2001 by internationally-recognized experts at the University of Bielefeld and has since then co-operated with various pharmaceutical and biotechnology companies.



## BIOMEVA GmbH

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### Existing co-operations:

BIOMEVA has served more than 30 customers worldwide.

References are available upon request.

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):** 10 L; 100 L; 1000 L working volume

### Services offered:

#### cGMP production of biopharmaceuticals

- Process development and optimization
- Cell Bank Manufacture of microbial MCBs and WCBs
- Cell Bank Characterization / Testing
- Cell Bank Storage (long-term) in the vapor phase of liquid nitrogen
- Development and validation of analytical methods
- Process validation

### Company Profile:

BIOMEVA GmbH, a reliable and experienced contract manufacturing organization (CMO) in the biopharmaceuticals' industry, is dedicated to meeting manufacturing needs for the production of microbially expressed protein products.

Since 1993, BIOMEVA has been producing more than 350 batches of cGMP-compliant material for pharmaceutical and biotech companies at the 1000 L scale. BIOMEVA has served more than 30 customers worldwide. Partners benefit from BIOMEVA's proven operational expertise in the transfer, development, optimization, scale-up and validation of cGMP processes.

BIOMEVA offers comprehensive services around cGMP manufacturing and processing of biopharmaceuticals using microorganisms (E. coli and yeasts), including process development and process optimization (High cell density fermentation, downstream processing and chromatographic purification). In its fully cGMP-compliant facility, BIOMEVA can manufacture at Biosafety Level I (BSL-1) and Biosafety Level II (BSL-2).

BIOMEVA houses classified laboratories for microbial cell bank production, testing, characterization and storage, and state-of-the-art production facilities (Class A, B, and C, D) for fermentation, chromatography, bulk filling, and quality control.

Chromatography purification steps can be performed at ambient or cold room (2-8°C) temperatures. A Class A/B filling suite is maintained for bulk drug substance filling.

BIOMEVA has been inspected by the German authorities and the EMA. A general manufacturing licence as well as a GMP certificate has been granted.

BIOMEVA is privately owned and centrally located in Heidelberg, Germany.



## BioPlanta GmbH

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### Existing co-operations:

- EU-Project SUPROGAL (University of Barcelona, Spain; Holland Biodiversity, Netherlands; Ludwig & Co, Netherlands; Vitroflora Labor, Poland; Bulphytoils, Bulgaria; Agrobioinstitute, Bulgaria)
- Instituto de Biotecnología de las Plantas, Cuba
- Fraunhofer-Institut für Zelltherapie und Immunologie, Germany
- VITA 34 AG, Germany
- Collaboration with pharmaceutical companies in Germany and Switzerland
- HHL - Leipzig Graduate School of Management, Germany

### Expressions system:

- Mammalian
- Microbial
- Other: Plant (*in vitro* culture, *ex vitro* culture in soil and hydroponics in greenhouse)

### Fermenter capacity (volume in liters):

- Bioreactor capacity from 250 ml to 40 l
- Production of 10.4 million plants in a 40 m<sup>2</sup>
- GMP production unit

### Services offered:

- In vitro production, breeding and selection of functional plants
- Biomass production in in vitro bioreactor systems for whole plants, shoots, roots and micro-tubers
- Platform technology for manufacturing of plant derived compounds, extracts and active substances (recombinant proteins)
- Development of phytotechnologies for treatment of water and soil (phytoremediation)
- Application of cryopreservation techniques for plant genetic resources
- R&D network

### Company Profile:

BioPlanta is one of the leading companies in applying biotechnical (engineered) approaches for discovery, development and commercialization of fine chemicals and pharmaceutical compounds. BioPlanta has developed a technology for *in vitro* production of differentiated plant organs using bioreactors. Thereby, the use of the Temporary Immersion System (TIS) is one of the main features of the BioPlant-System.

BioPlant-System is particularly suitable for manipulating plant metabolism to generate active compounds with higher value than field plants. The system is adaptable to the special requirements of different plant species and culture types, such as shoots, roots and micro-tubers. The control and variation of culture conditions leads to customized content and spectra of the specific compounds.

This innovative platform technology was installed to manufacture plant-derived chemical compounds for the pharmaceutical, flavorings and food-related industries. It allows the production of high-quality drugs, cost-effective scale-up, efficient screening of new active compounds and the design of novel drugs in compliance with European GMP guidelines. The entire production process takes place in GMP compliant clean rooms.

For this innovative technology, BioPlanta was awarded both the Leipzig Innovation Prize and the Innovation Prize of the Free State of Saxony. Furthermore, BioPlanta was the winner of the IQ-Innovation Award of Central Germany in the cluster Biotechnology - Life Science in 2009.

### The following services are provided by BioPlanta GmbH:

- Production of elite plants
- Search for biologically active plant ingredients (extracts for industry, active substances for pharmaceuticals)
- Specific and tailor-made spectrum of active agents
- Production of test batches for preclinical and clinical analysis
- Development of alternative resources
- Optimization of biological activity of extracts

The BioPlanta team consists of scientists, engineers, laboratory assistants and technicians from the field of environmental sciences, chemical engineering, process engineering, chemistry, biology and plant breeding.



## bitop AG

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### Existing co-operations:

- Merck KgaA, Germany
- Several undisclosed small to midsize biotech/pharmaceuticals' companies

### Expressions system:

- Mammalian
- Microbial
- Other bacteria, yeast, fungi, extremophiles

**Fermenter capacity (volume in liters): 1L– 3,500 L**

### Services offered:

Process development for natural compound manufacturing: small molecules, amino acids, sugars, secondary metabolites

- Fermentation optimization (Integration with strain optimization)
- Downstream processing: process development & optimization
- Manufacturing of biomolecules for health care and cosmetics from pilot scale to multi-tons
- EN ISO 13485 approved Quality Management System
- Markets: Pharmaceuticals (intermediates), Medical Devices, Cosmetics, Nutrition

### Company Profile:

bitop AG is a biotechnology company and specialist in the industrial production and use of natural protective molecules originating from extremophilic microorganisms. These unique molecules have been named Extremolytes by bitop AG.

The company has an in-house highly specialized process chain for the development, production and purification of high quality Extremolytes. Based on many years of experience, these processes are subject to constant optimization and secure sufficient manufacturing capacity while maintaining high quality.

The company offers a globally exclusive portfolio of ingredients and marketable product concepts with high innovative potential. Based on the distinct protective properties of Extremolytes like Ectoin® and Glycooin®, these are especially developed for use in the fields of Health e.g. Allergy, Dermatology, Respiratory, Cosmetics and Life Sciences.



## Boehringer Ingelheim

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### Existing co-operations:

- VTU Technology, Pfenex Inc.
- Fresenius Kabi, Xencor (Technology Cooperations)
- Amgen/Wyeth
- Merck Serono, MedImmune
- GSK, Bayer Schering, Genentech
- Lilly
- Genzyme, Intermune
- Nycomed
- 3Rivers
- Canyon
- Elan (incomplete list of customers)

### Expressions system:

- Mammalian
- Microbial
- Other Yeast

### Fermenter capacity (volume in liters):

**6x 15,000 L, 2x 12,000 5x 2,000 L (Mammalian GMP)**

2x 6,000L, 3x 300 L (microbial GMP)

### Services offered:

Boehringer Ingelheim offers its customers a one-stop-shop approach. This means we can provide everything starting from strain development (BI-HEX®, conCERT™, E. coli Genome Integration, Autoprotease Fusion), process development (up- and downstream), up-scaling, large scale manufacturing, analytical services, formulation development up to fill & finish and also regulatory support.

### Company Profile:

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 142 affiliates in 50 countries and more than 41,500 employees. Since it was founded in 1885, the family-owned company has been committed for 125 years to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine.

Today, Boehringer Ingelheim is one of the world's leading companies for contract development and manufacture of biopharmaceuticals. All types of services from Mammalian cell line or microbial strain development to final drug production can be delivered within a one-stop-shop concept. Boehringer Ingelheim delivers services for pre-clinical development up to global market supply with a strong commitment to its customers at its manufacturing facilities for Mammalian cell culture and microbial fermentation. Boehringer Ingelheim has brought 18 molecules to market and has many years of experience in multiple molecule classes such as monoclonal antibodies, recombinant proteins, interferons, enzymes, fusion molecules and plasmid DNA. Furthermore, high-titer platform technologies for new antibody mimetic formats such as scaffold proteins and antibody fragments are available for the manufacture of customer products.

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## Celonic GmbH

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### Existing co-operations:

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):** 20 L / 75 L / 300 L / 1000 L

### Services offered:

- Cell-Line Development for new biological entities and biosimilars
- Technologies for fast track development of high yield production cell-lines (CEMAX) and SEFEX technology for serum free cloning
- Process Development (Upstream&Downstream)
- GMP Production up to 1000 L scale for clinical phases and market supply
- Release of drug substance and product
- ICH conform stability studies
- GMP compliant protein analytics
- GLP compliant analytics to support preclinical and clinical studies

### Company Profile:

Celonic, established in 1998, is a Contract Manufacturing and Service Organization having operational sites in Jülich (Germany) and Basel (Switzerland). The company offers comprehensive services for the development and GMP-compliant production of biopharmaceuticals. These services cover the establishment of regulatory conformity, high-yield production cell-lines, the development and optimization of analytical, downstream and upstream processes as well as the GMP-production of biopharmaceutical proteins. The state of the art GMP facility located in Basel is certified by the Swiss authorities (SwissMedic) and offers production capacities from small scale up to 1000 L scale fermentation for the production of active pharmaceutical ingredients (API) for clinical phases and market supply.

Celonic additionally performs analytical studies in order to support preclinical safety studies and clinical trials and is certified by the German authorities to be compliant with Good Laboratory Practice (GLP). These analytical services include but are not limited to the quantification of drugs and anti-drug antibodies in serum.

In addition, the company built up its own pipeline of new, innovative biopharmaceutical proteins for the treatment of cancer and various types of immune diseases such as rheumatoid arthritis, morbus crohn and sepsis.

## Cevec Pharmaceuticals GmbH



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### Existing co-operations:

- Life technologies Inc., August 2010, on Co-development and Distribution of CAP-T cells as “research only” tool.
- Inno Biologics, August 2009 (R&D License)
- InVivo, September 2009, (R&D License)
- Aragen, March 2010, (R&D License)
- Numerous others, undisclosed

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters): 10 (2010), 50 (2011)**

### Services offered:

- Partnering, out-licensing and co-development of proprietary immortalized human cell lines, CEVEC Amniocyte Production system (CAP®) stable cell line, and CAP-T™ transient cell line
- Cell line development services, process development and scaling up
- Vaccine co-developments with proprietary vaccine production platform

### Company Profile:

**CEVEC is on track to become a leading solution provider for the production of biopharmaceuticals and vaccines.** CEVEC focuses on the development of high quality human cell expression systems combining the highest ethical standards with market leading performance. CEVEC's platform expression technologies CAP and CAP-T are based on specific, amniocyte-derived immortalized human cell lines that meet industrial standards. CAP and CAP-T are designed for stable and transient biopharmaceutical protein and virus/vaccine production. The use of both cell lines in the course of biopharmaceutical or vaccine drug development provides a unique advantage in retaining identical protein structures and authentic posttranslational modifications throughout the development process, from early discovery to bioproduction.

**CEVEC's management** has all the capabilities required to direct optimally all relevant research & development as well as marketing/business development activities.

**CEVEC's CAP cells are obtained in an ethical way.** In contrast to other suppliers CEVEC's Amniocytes do not originate from tumor cells nor had a miscarriage or pregnancy termination been involved. In 2004, the primary cells were obtained using methods that comply with the highest of ethical standards during an amniocentesis, a routine clinical prenatal examination.

**CAP and CAP-T technology combine unique benefits to customers:** The decisive USP of CAP and transient CAP-T technology are provided by the identical genetic origin of both the transient and the stable cell line. A key benefit of CAP cells is that they are able to produce highly glycosylated and complex, difficult-to-express proteins in unmatched high yields. CEVEC's growing customer base in Europe, Asia and the US favor the CAP cells due to their proven robustness to changing media and culture conditions, rapid growth in serum-free and chemically fully-defined media, and extreme protein and vaccine yields.

**CEVEC's business model** follows a two-pronged strategy: In therapeutic proteins and monoclonal antibodies the company is establishing a multichannel outlicensing model as we a) market the CAP T technology with our partner Life Technologies Corp in the non-commercial academic market, b) have our own worldwide sales force in place to non-exclusively market CAP and CAP T to commercial customers (Big Pharma, Biotech, CMO, CRO) and c) use our business development activities to exclusively market our bio better projects (recombinant human versions of alpha 1 antitrypsin, C1 inhibitor and alkaline phosphatase) to interested partners. In vaccines CEVEC is - together with its development partners - building up a proprietary pipeline of product candidates in high value indications (e.g. influenza, rota, RSV, etc.).

A recent case study has shown that CEVEC's CAP cells hold high promise as the best-in-class production system for Influenza vaccines and other virus vaccines. Compared to leading other cellular production systems (like MDCK) CAP demonstrated outstanding results in view of virus yield, extremely short production cycles and minimal media consumption. **CEVEC's CAP system is a suspension- based and serum free offering the best starting point for new vaccine production approaches with excellent upscaling possibilities.**

CEVEC has been operating since 2004. It is located in Cologne, Germany. Since late 2008, the company has been marketing its cell-based technology for protein and antibody production. The company has attracted EUR 10 million in venture capital.



## durakult GmbH

<b>Name of company:</b>	durakult GmbH
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### Existing co-operations:

- Due to our non-disclosure agreements we are not able to specify our cooperations at the moment.

### Expressions system:

- Mammalian
- Microbial
- Other

Fermenter capacity (volume in liters): 0.25 – 40 L

### Services offered:

- Strain optimization
- Strain development
- Research assignment
- Fermentation of starter cultures
- Strain maintenance
- Troubleshooting of microbial processes

### Company Profile:

The durakult Gesellschaft für biologische Technologien mbH develops and optimizes production strains and starter cultures for the biotechnological production of food and chemicals on the basis of biofilms. The underlying fundamental technology is the durakult®-bioreactorsystem (patent applied), which is able to avoid using methods of genetic engineering. In fact the durakult®-technology is making use of natural evolutionary mechanisms to adapt cells to the desired parameters for industrial production. Furthermore, we provide microbiological services, e.g. fermentation of starter cultures, research assignments, troubleshooting of microbial processes and strain maintenance.

The durakult GmbH is a spin-off from the Institute of Microbiology at the Freie Universität, Berlin (group of Prof. Mutzel) and was founded in 2009 by the two co-founders Dr. Claudia Keil-Dieckmann and Dr. Jens Baumgardt. The founding period was funded by the Federal Ministry of Economic Affairs und Technology (BMWi) with about half a million Euros. Since then we have been working on the campus of the elite university on problem-solving strategies for our several customers in the food and chemical industries. Research assignments range from the optimization of fermentation performance of production strains to the search for new microorganisms for biotechnological production of food and food ingredients. Currently the durakult GmbH employs 4 permanent staff members.



## Entelechon

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### Existing co-operations:

- PolyQuant: Subsidiary for protein analysis and production of QconCAT
- Plasmid Factory: Partner for upscaled plasmid production
- University of Liverpool/Manchester:
- Prof. Rob Beynon, Dr. Julie Pratt, Prof. Simon Gaskell as developer of the QconCAT-Technology and Advisory Board of PolyQuant

### Expressions system:

- Mammalian
- Microbial
- Other

Fermenter capacity (volume in liters): 100

### Services offered:

- Strain development E. coli
- Feasibility studies

### gene2protein service:

- Transient expression in HEK293/CHO cells (volume 1-10 L)
- Protein production (gram-scale) in
- E. coli
- S. pombe and S. cerevisiae
- Pichia pastoris
- Baculovirus
- Bacillus subtilis
- Expression of isotope-labeled proteins
- all services above are non-GMP

### Company Profile:

Entelechon, founded in 1999 as one of the first enterprises dedicated to synthetic biology, is a development lab for biotechnological and pharmaceutical projects. Our broad range of competences - from molecular biology to bioinformatics, protein expression, and quantitative proteomics – combined with an excellent service, are the keystones of our success.

Entelechon is a service-oriented company mainly focused on the production of optimized and customized artificial DNA sequences based on a highly flexible and efficient gene synthesis platform. Entelechon also provides proteome solutions and manufacturing of protein-based diagnostics with the innovative QconCAT technology. A highly-advanced bioinformatics platform completes the synthetic biology service in silico solutions.

#### Services:

- Gene optimization
- DNA synthesis
- Design and production of gene libraries
- Assay Development
- Development of Biomarkers
- Bioinformatics services
- Custom software development
- Protein expression and purification
- Production of peptides and antibodies
- Molecular Biology

#### Products:

- Leto gene optimization software

The company is privately funded and autonomous of VC.

#### Management:

Dr. Werner Deininger, Director, Co-Founder

Markus Fischer, Director, Co-Founder

## Glycotope Biotechnology GmbH



<b>Name of company:</b>	Glycotope Biotechnology GmbH
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### Existing co-operations:

- Becton Dickinson
- Biotest
- Sanofi Aventis
- Novartis
- Trigen
- Micromet
- Scintic Diagnostics GmbH
- Procorde

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):** 4x10, 2x50, 1x100, 2x250 in batch and perfusion mode

### Services offered:

- Strain development
- Process development
- Glyco-optimization
- GMP-manufacturing
- Fill and finish
- Cell banking
- Protein analytics
- Bioactivity and cellular assays
- Immunomonitoring

### Company Profile:

Glycotope Biotechnology is a contract manufacturer for active biopharmaceutical ingredients (bio APIs) such as proteins and antibodies using know-how in biotechnological recombinant protein production. We are located in Heidelberg, the hot spot of life sciences in Germany.

During the last two years, the GLYCOTOPE group, consisting of Berlin-based Glycotope GmbH, and its 100% affiliate, Heidelberg-based Glycotope Biotechnology GmbH, has developed into a fully-integrated biotech company, offering a complete portfolio of drug development from the gene to the drug ready to be administered in clinical trials. With currently 140 employees, it represents one of the largest biotech companies in Germany.

For more than 25 years, we have been a recognized partner in process development and GMP-manufacturing of antibodies and non-antibody biopharmaceuticals. We can produce purified batches for preclinical studies and GMP batches for clinical phases and commercial batches. Furthermore, we offer fill and finish for up to 500 vials/batch.

Using the proprietary GlycoExpress™ technology based on our proprietary human cell lines, we improve the glycosylation structures on biotherapeutics, leading to improved bioactivity, reduced side-effects and prolonged half-life time.

Upon client demand, Glycotope Biotechnology's is able to transform know-how from the workbench into process development and further up-scalable GMP production, e.g. by starting from a newly-generated cell line for the expression of a protein of medicinal importance.

These main activities also include contract research & development services in the fields of immunology, protein chemistry, and molecular biology, applied on novel, active pharmaceutical ingredients for the drug industry and on the development & production of diagnostics for immunological and hematological indications.

Glycotope Biotechnology is operating GMP compliant as defined by current ICH guidelines and has been certified according ISO 9001. The facilities are also approved according to the corresponding German laws for Gene Technology (GenTG), Control of Epidemics (IfSG, BioStoffV) and Protection against Radiation (StrlSchV). The manufacturing facilities are approved for bulk API production of proteins for pharmaceutical purposes.



## IDT Biologika GmbH

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### Existing co-operations:

- Max-Planck-Institute for Dynamics of Complex Technical Systems (Magdeburg) – Prof. U. Reichl (Bioprocess Engineering)
- Martin-Luther-Universität Halle-Wittenberg
- Otto-von-Guericke-Universität, Magdeburg

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):**1,150 L microbial, 2,000 L Mammalian

### Services offered:

Vaccines:

- strain development
- process development incl. fill-finish
- clinical trial material production incl. fill-finish
- market material production incl. fill-finish
- packaging services

### Company Profile:

IDT Biologika is a mid-sized biologics' specialist focused on vaccines' development and production services as well as parenteral fill-finish services for biologics. More than 850 employees create cutting-edge solutions for biologics from strain development to market supply packages. With more than EU 200 million invested in the last 10 years, we are proud to operate world class facilities that have been awarded also by the ISPE.

With successful audits from EMA, FDA, CFIA, KFDA, R.O.C., PAI, USDA and ANVISA, we serve nearly all the major markets and several governmental organizations.



## Miltenyi Biotec GmbH

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### Existing co-operations:

- Miltenyi Biotec is actively collaborating with numerous academic and industrial partners.

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):** currently up to 200 l, further expansion planned

### Services offered:

- Master cell bank (MCB) / working cell bank (WCB)
- Process development (USP / DSP)
- mAbs from protein free cultured hybridoma cells
- Recombinant proteins with procaryotic / eucaryotic cells
- Pharma production
  - » Fill and finish, lyophilisation, labelling and packaging
  - » Stability tests
  - » Dedicated equipment for small volumes
- Custom development and manufacturing of instruments, reagents and disposables for therapeutic aphaeresis and ex-vivo cellular therapies

### Company Profile:

Miltenyi Biotec, founded in 1989, is a premier provider of advanced products and services in the fields of stem cells, immune and cellular therapies as well as tissue regeneration. As a multinational corporation with more than 1100 employees in 18 countries worldwide, we develop, manufacture and commercialize state-of-the-art technologies and products for research and clinical applications. Our product and service offerings cover all areas of cell-based research and clinical development, from sample preparation, cell separation, cell culture, flow cytometric and molecular analysis, including gene expression profiling and DNA analysis, to clinical therapeutic applications and contract GMP manufacturing. Our research tools, analytical and preparative instruments, clinical-grade reagents and medical devices provide integrated translational solutions that meet the high demands and expectations that Miltenyi Biotec customers have come to expect from a leading biotechnology tool provider.



## PharmedArtis GmbH

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### Existing co-operations:

Country	Cooperation form	Cooperation partner
Germany	1,2,3,4,5,6,7	1,2,3
Netherlands	1,2,5,7	1,3
Switzerland	2,3	3
U.S.A	2,5,6	1,3
Argentina	2,3,4,5,6	2,3
Indonesia	2,4,6	2
India	1,3,4	2

#### Cooperation form:

1. R&D / 2. Product development / 3. Work contract (contracted production, contracted sale)  
4. Marketing/sale / 5. Licensee / 6. Licensor / 7. Funding

#### Cooperation partner:

1. Research institute, college, etc. 2. Pharmaceuticals, medical equipment 3. Bio-industry

### Expressions system:

- Mammalian
- Microbial
- Other Yeasts

**Fermenter capacity (volume in liters):** 2 x 500 L

### Services offered:

Feasibility studies (cloning, strain development, media adaptation) for the production of biopharmaceuticals in various systems:

- E. coli; yeasts (Hansula polymorpha and others), Mammalian cell lines
- Process development, up- and downstream (fermentation and purification) as to a GMP-compliant production (up to a 500 L scale), incl. formulation
- Consultancy on quality
- CMC documentation etc.

### Company Profile:

PharmedArtis GmbH, a German biotech firm, provides complete services from gene to recombinant protein. While focusing on biopharmaceuticals, we also develop for diagnostic applications. Using our proprietary strains of yeast we produce your proteins at high yields. We also accommodate other bacterial systems such as E. coli as well as Mammalian or plant-derived cells. As spin-off of Fraunhofer-IME we are able to produce API according to GMP regulation for clinical trials phase III in a state-of-the-art facility. Based on a strong patent portfolio we develop innovative immunotherapeutics against cancer, auto-immune diseases and inflammation. We seek partners on these and our Biosimilars.

PharmedArtis was founded by three researchers from the Fraunhofer Institute of Molecular Biology and Applied Oecology in Aachen and two experienced scientists each with more than 20 years of industrial background. Following the hybrid business model as a service provider as well as a developer of novel immunotherapeutics, much emphasis was placed on developing the proprietary CoMed system (first milestone in 2008) and pursuing first patent protection of the immunotherapeutic concepts (patent granted in 2008 for apoptotic agents). In 2009 the production license for the state-of-the-art GMP facility was granted. Over the years PharmedArtis has won several publicly-funded projects and works actively in the indications of prostate carcinoma, pancreatic tumors and inflammation.

Dr. Georg Melmer

CEO

PharmedArtis GmbH

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## Phyton Biotech GmbH



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### Existing co-operations:

- Bristol-Myers Squibb - (Taxol®)

### Expressions system:

- Mammalian
- Microbial
- Other : Plant Cell

**Fermenter capacity (volume in liters):** 220,000 Liters in total

### Services offered:

We provide our partners a unique package for commercial manufacturing and development of Active Ingredients via fermentation systems, most preferably plant cell fermentation:

- Large Scale Fermentation
- GMP compliant Analytics and Quality Control
- Cell Line Development
- Process Development
- Scale up

### Markets:

- Pharmaceuticals
- Cosmeceuticals
- Nutraceuticals
- Biopharmaceuticals

### Company Profile:

Phyton Biotech was founded in 1990 in Ithaca, NY with the objective of developing manufacturing solutions for complex plant-derived compounds through plant cell fermentation technology. In 1993, it was acquired by DFB Pharmaceuticals, a private Texas-based pharmaceutical company.

Phyton Biotech owns and operates the world's largest cGMP plant cell fermentation facility with bioreactors specifically designed to meet the needs of plant cells in culture as well as preformulation and quality control. The total fermenter capacity is 220,000 Litres.

A second fermenter line (Biosafety Level 1) with fermenters of up to 7,500 L including certain downstream equipment for separation, filtration and purification, has been set up in a physically separated area of the plant. This set up addresses the need for the production of recombinant proteins.

The supply of high active substances through plant-derived cell cultures offers enormous potential to produce hardly feasible complex molecules in a resource-friendly way and with permanently high quality at competitive prices. Phyton Biotech's expertise for the cultivation of plant cells both in laboratory and in large scale, allows the combination of development and production in an outstanding manner and to offer these services for industries using active plant derived substances.

The team of Phyton Biotech GmbH is dedicated to demanding, sophisticated large scale fermentation and pharmaceutical production. It offers many years of Manufacturing, Quality Management and Quality Control experience and has been expanded significantly to cover the needs of the extended Phyton Biotech GmbH business.

In 2009 Phyton acquired Natural Pharmaceuticals, Inc. (NPI) and offers full downstream production of paclitaxel and docetaxel Active Pharmaceutical Ingredients (API).



## PlasmidFactory GmbH & Co KG

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### Existing co-operations:

PlasmidFactory has a long-term co-operation with Entelechon GmbH (Regensburg) and CCS GmbH (Hamburg). The company is working in close co-operation with research institutions such as the German Cancer Research Center (DKFZ) in Heidelberg, the University of Munich, Bielefeld University, the Charité in Berlin, Imperial College, London, CNRS, Paris, and the Institut Pasteur, Paris, to name just a few.

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):** 5 – 300 L

### Services offered:

- PlasmidFactory offers contract manufacturing of plasmid and minicircle DNA in various Quality Grades meeting individual demands.
- The new High Quality Grade plasmid DNA is specially adapted for use in GMP applications such as virus or RNA production.
- In Stock products: various reporter-gene plasmids and minicircles, pDG plasmids for the AAV production as well as pEPI and pEpito plasmids with S/MAR elements.

### Company Profile:

PlasmidFactory - founded in 2000 - is Europe's leading contract manufacturer for plasmid DNA. In its laboratories in Bielefeld (Germany), the company is producing high-quality plasmid DNA from milligram to multi-gram scale meeting the individual requirements of the research scientist. Typical applications are transient gene transfer, production of viruses, viral vectors, RNA, antibodies and others.

Besides that, PlasmidFactory is also offering the production of *minicircle* DNA. These are minimal circular DNA molecules consisting almost exclusively of the "gene of interest" that have the desired (e.g. therapeutic) effect in target cells. The company holds the worldwide master patent for any *minicircle* technology.

PlasmidFactory offers a unique spectrum of services related to the production and application of plasmids. This includes gene synthesis and optimization as well as a wide range of analytical services, e.g. the CGE service, a powerful, fast and reliable method to detect and quantify plasmid topologies.

The so-called '*In Stock* products' complement the product portfolio. These plasmids and *minicircles* are always in stock and are usually shipped within 48 hours of order. Currently available from the *In Stock* service are various reporter gene plasmids and *minicircles* and AAV Helper & Packaging Plasmids and pEPI / pEpito plasmids containing S/MAR elements for long-term gene expression.

PlasmidFactory's research and development as well as its complete service branches are based in Germany. With various projects funded by the German Federal Ministry of Education and Research (BMBF), the German Ministry of Economics (BMWi) and European research co-operations, e.g. as partner in the European Network of Excellence CLINIGENE (FP 6), PlasmidFactory is the driving force in the development of innovative gene vectors.

## ProBioGen AG



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### Existing co-operations:

ProBioGen maintains a production alliance with Boehringer Ingelheim to provide for seamless process transfers to high volume production capacity.

Besides this, the company is a contract partner to numerous international pharmaceuticals and biotech companies, e. g.:

- Functional Genetics Inc.
- Life Technologies
- Novartis Vaccines & Diagnostics
- NovImmune SA
- Vakzine Projekt Management GmbH
- IDT Biologika GmbH
- Minapharm Pharmaceuticals
- Novartis Pharma
- Sanofi Pasteur
- Virdante Pharmaceuticals

### Expressions system:

- Mammalian
- Microbial
- Other: Avian

**Fermenter capacity (volume in liters):** 500 L, to be expanded;  
2,000 L -> 10,000 L at Boehringer Ingelheim

### Services offered:

#### Contract Development & Manufacturing Services

- Cell line engineering & GMP manufacturing

#### Expression with Proprietary Systems

- High yield CHO cell & media platform
- Novel AGE1® producer cell lines
- HN for human-identical posttranslational modifications
- CR for vaccine production

#### Improvement of Product Properties with Proprietary Technologies

- GlymaxX Technology to boost ADCC activity of MABs

#### Determination of Bioactivity with Cell-Based Assays

- Immune-activity based on the human Artificial Lymph Node technology
- Custom tailored systems for FSH, IFN, & many others

### Company Profile:

ProBioGen AG is an internationally operating Contract Development & Manufacturing Organization (CDMO), focused on cell line engineering, process development and GMP manufacturing of biopharmaceuticals (therapeutic proteins and vaccines).

More than 15 years of experience in Mammalian cell culture and biopharmaceutical manufacturing make ProBioGen a well-reputed and reliable contract partner. Its comprehensive technological skills and outstanding scientific excellence, reflected in a strong intellectual property base, qualify ProBioGen to master even the most challenging development and manufacturing projects.

The service portfolio of ProBioGen covers the entire drug development value chain, including regulatory support for IND-filing. All services and technologies are embedded in a total quality management system to assure compliance with international ISO and GMP standards (EMA/FDA).

A highly flexible capacity-planning system allows a rapid project start; the professional project management ensures that projects are completed strictly in-time and on-budget.

Besides state-of-the-art services based on a proprietary CHO cell line and medium platform, ProBioGen develops innovative technologies, such as:

- “GlymaxX”, a novel and simple, yet efficient Glyco-Engineering Technology to boost the ADCC activity of antibodies by minimizing their fucose content, which, notably, can also be applied to existing antibody-producer cell lines.
- AGE1® Producer Cell Lines for safe and cost-efficient production of glycoproteins and virus-based vaccines, as potent alternatives to existing platforms:
- > Human (“HN”) for human-identical posttranslational modifications;
- > Duck (“CR”) as replacement of primary chicken material for vaccine production.
- The unique Human Artificial Lymph Node technology to analyze drug & vaccine effects on the immune system in vitro (e.g. to identify potential adverse side effects), as part of a broad portfolio of qualified cell-based assays.

Founded in 1994, ProBioGen is located in Berlin, Germany and enjoys a global customer portfolio including small biotech firms as well as large pharmaceutical companies.



## Rentschler Biotechnologie GmbH

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### Existing co-operations:

- Preferred partnership agreement with Boehringer Ingelheim for a seamless project transfer to large-scale manufacturing of up to 15,000 L.
- Cooperation agreement with CELLCA GmbH aimed at the development, application and marketing of a high-level expression system for Mammalian cells.

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters): 30, 50, 250, 500, 1,000, 2,500 L**

### Services offered:

GMP certified services provided by Rentschler Biotechnologie:

- Cell Line and Process Development
- Production of Active Pharmaceutical Ingredients
- Aseptic filling in vials and pre-filled syringes:
- Analytics and Quality Control
- Marketing Authorization Application and Consulting
- Quality Assurance
- Corporate Project Management

### Company Profile:

Rentschler Biotechnologie GmbH is a global full-service contract manufacturer with more than 35 years of experience in the development, production and approval of biopharmaceuticals in compliance with international GMP standards (EMA/FDA). Rentschler Biotechnologie has nine GMP suites with volumes of 30, 50, 250, 500, 1,000 and 2,500 liters, allowing the production of material for clinical trials (phase I to III) and for market supply. Rentschler also provides regulatory advice, protein analytics, quality control, and the sterile filling of syringes and injection vials.

As a pioneer in the development and production of biopharmaceuticals, Rentschler was the first company in the world to gain market authorization for an interferon-containing drug. The long-term experience of Rentschler Biotechnologie combined with the range of comprehensive services ensures the success of any project - rapidly and reliably. Rentschler is flexible when it comes to services, capacity and products - for process development or production of materials for clinical trials and the market, whether low-dose cytokines or high-dose antibodies and biosimilars. The company is family-owned and independent and has currently about 600 employees.



## Richter-Helm

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## Company Profile:

Richter-Helm is a dynamic and expanding biotechnology company located in Hamburg, Germany. As one of the first biopharmaceutical enterprises in Europe, Richter-Helm has more than 20 years of experience in the development and GMP-compliant production of recombinant proteins, plasmid DNA and microbial vaccines. With more than 120 employees,

Richter-Helm is offering customized state of the art solutions for all steps in biopharmaceutical projects via contract development and manufacturing services in GMP facilities for microbial production (fermentation scale up to 1500L). Thus Richter-Helm is the ideal partner for biopharmaceuticals development by offering material from pre-clinical and clinical trials to market supply at a large scale.

On the other hand Richter-Helm is the platform of Gedeon-Richter and Helm AG for worldwide licensing options as well as partnerships for co-development and marketing of biopharmaceutical development projects.

## Existing co-operations:

As a CMO Richter-Helm is not allowed to disclose most of its customers. During the past 13 years Richter-Helm worked on more than 30 GMP manufacturing projects and additionally 28 development projects. Material was manufactured for phase I, phase II and phase III clinical trials for customers from EU, US and other territories. Currently 3 products are manufactured for commercial supply. Richter-Helm's customers are mainly small and mid-sized biotech companies as well as big pharmaceutical companies.

## Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):** 30L, 300L, 1500L

## Services offered:

- Strain development (own E.coli expression systems)
- Process development/process optimization (fermentation, primary recovery, refolding strategies, DSP)
- Cell banking (establishment, characterization, storage of MCBs and WCBs)
- Analytical Testing (development of methods for IPC and release testing, formulation studies, ICH stability studies, validation)
- Technology Transfer of processes at all stages, incl. comparability exercises
- GMP manufacturing of clinical trial supply (Phase I, II, III)
- Process Validation
- GMP manufacturing of commercial supply



## Sirion Biotech GmbH

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### Existing co-operations:

Cooperation with Helmholtz Zentrum Munich for development of gene therapy for B-cell lymphomas.

### Expressions system:

- Mammalian
- Microbial
- Other

**Fermenter capacity (volume in liters):** 10

### Services offered:

Sirion Biotech offers cell line engineering services (GLP)

- Cellular models for target validation
- Assay development, reporter gene assays
- Immortalization of primary cells

Sirion offers a service dedicated to increase yield and quality of production cell lines

- The service offered identifies cellular pathways which are relevant for quality and production. SIRION BIOTECH offers cell line engineering for proof-of-concept studies of increased yield and quality

## Company Profile:

SIRION BIOTECH GmbH is a biotech company that produces genetically modified cells and is a technology provider in the area of viral vector systems with more than 100 products and services. Having a strong expertise in cell line development, SIRION BIOTECH serves as a partner for development and optimization of cell lines for various applications. SIRION BIOTECH currently operates projects for most of the major pharmaceutical companies in Europe and USA and has ongoing collaborations with leading academic and governmental research institutes.

### Problem:

Genetically modified cell lines for screening and target validation require a high degree of standardization. Increased validity of results from screening and preclinical target validation is obtained from close-to-the-patient primary cell models. Availability of genetically modified primary cells for screening, biological assays and target validation in vivo is limiting pharmaceutical development.

### Solution:

Sirion Biotech offers standardized cell lines for target validation in vivo and screening with reliable expression or knockdown (RNAi). Unique gene delivery technology based on our own viral vector technology guarantees highest standards. Primary cell-derived cell lines with the potential to differentiate open a new horizon in screening and cell line development.

### Business:

- SIRION BIOTECH offers genetically modified cells ready-to-use for screening, biological assays, as fee-for-service. SIRION BIOTECH has developed products and patented the technology for viral gene delivery that are sold commercially as well as being used for scientific purposes.
- Virus vector technology for vaccine development is licensed to biotech and pharmaceutical companies.
- SIRION BIOTECH is seeking distributors in Israel and Middle East.

### Technology/ IP:

- SIRION BIOTECH is developing viral vector technology including serotype adenovirus vectors for vaccine development
- This technology was patented in 2008 and 2010
- Primary cell screening solutions are offered to pharmaceutical and biotech companies.

### Management Team:

Dr. Jürgen Flach: CEO

Dr. Christian Thirion: Founder & CSO

## Trenzyme GmbH



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<b>Website:</b>	www.trenzyme.com

### Existing co-operations:

Different biotechs and leading pharmaceutical companies from all over the world.

References on request.

### Expressions system:

- Mammalian
- Microbial
- Other

Fermenter capacity (volume in liters): 10 L

### Services offered:

- Fast screening of the best expression system: Cross organism expression platform
- High throughput screening for soluble target protein expression facilitating the upstream process development (E. coli)
- Development of stable Mammalian cell lines within 30 business days (target expression guaranteed)
- Development of assay cell lines according to needs of customer

### Company Profile:

Trenzyme GmbH is a privately-owned service-based company founded in 2000. The company is located in Konstanz (Germany) and operates a well-equipped, state-of-the-art laboratory building with more than 440 sqm. In the year 2008, Trenzyme introduced a sophisticated quality management system and was certified in accordance with DIN EN ISO 9001:2008.

### Mission

By providing innovative services to our customers from the life sciences' industry we are providing solutions to their demanding R&D challenges.

More than ten years of experience allow the company's highly-skilled, specialized technological experts to use their outstanding, state-of-the-art laboratory equipment to work in full tandem with our clients and partners to fulfill our mission of *servicing your innovation!*

### Technology

- ExoIN for development of stable homogeneous Mammalian cell lines
- Cross organism expression platform for fast screening of best expression system
- High throughput expression screen for fast upstream process development



## Wacker Biotech GmbH

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### Existing co-operations:

- Hans-Knöll-Institute (Jena, Germany): research cooperation on E. coli-based expression systems.
- Pieris AG (Freising-Weihestephan, Germany): collaboration on the use of Wacker's proprietary ESETEC® secretion system for the production of Pieris' Anticalins ® for clinical use.
- Morphosys AG (Martinsried, Germany): collaboration on the use of Wacker's proprietary ESETEC® secretion system for the production of antibody derivatives and therapeutic target molecules.

### Expressions system:

- Mammalian  
 Microbial  
 Other

**Fermenter capacity (volume in liters):** 300L (total fermenter volume)

### Services offered:

- Cell line development (microbial). Feasibility studies with ESETEC®, Wacker's proprietary
- E. coli secretory technology
- Cell banking
- Process & analytical development, transfer and optimization
- Process validation
- Qualification and validation of analytical methods
- Production of preclinical material
- GMP manufacturing and API release by Qualified Person
- Protein refolding: 1,250-2,500L tanks
- PEGylation
- Lot release and stability testing
- Regulatory support

### Company Profile:

Wacker Biotech GmbH is an experienced contract manufacturer of biopharmaceuticals in microbial systems. The company was founded in 1999 as a spin-off from the Hans-Knöll Institute in Jena and has been a 100% subsidiary of Wacker Chemie AG since 2005.

Wacker's integrated service portfolio covers molecular biology, process and analytical development and the GMP manufacturing of biologics for clinical trials and commercial supply. WACKER's state-of-the-art facility in Jena has been successfully audited by international customers and regulatory authorities, and operates in compliance with FDA and EMA requirements. Our clients range from large, internationally-operating pharmaceutical companies to biotech start-ups.

### Facilities

Wacker has segregated facilities for process development, cGMP production and quality control.

The process development department has 900-sqm dedicated lab space. Fermentation, downstream processing and analytical development are performed in separate labs. The lab equipment is highly-aligned with that for GMP production.

The state-of-the-art multi-product cGMP facility for contract manufacturing was recently renovated and expanded after an EUR 18 million investment. The 1,500-sqm cGMP unit has 3 clean rooms for fermentation, primary recovery and downstream processing.

The quality control department operates in 1,000-sqm dedicated labs and performs a broad variety of analytical methods for in-process controls and release testing.

### Technologies

Wacker offers cutting-edge proprietary technologies for the efficient and cost-effective production of biologics.

*ESETEC®: proprietary E. coli based secretion system:*

Wacker's secretion system allows the high-yield production of correctly folded proteins in the culture broth. It comprises an engineered *E. coli K12*-based host strain and a set of proprietary plasmids.

*DENSETEC®: proprietary technology for high-cell-density fermentation:*

Wacker holds IP for a high-cell density fermentation technology that allows optimal volumetric productivity in robust and highly reproducible fermentation regimes. High product amounts are reached.

### Track Record

Wacker Biotech has an established track record and more than 20 years of experience in process development and manufacturing of therapeutic proteins. Wacker holds a manufacturing license for the production of several recombinant proteins and has experience with a broad variety of bioprocesses from European and US-based customers. Wacker's experience includes projects from preclinical development to process validation and API delivery for clinical phase III.

**Directory of Companies with Strong Ties to Biomanufacturing**



## BioGenes GmbH

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### Existing co-operations:

Rentschler Biotechnologie Germany  
 Novartis Switzerland  
 Merckle Germany  
 Vivalis France

### Expressions system:

- Mammalian
- Microbial
- Other

### Services offered:

**Highly sensitive HCP assays are increasingly important for proving drug purity and finally drug approval. BioGenes has over 12 years experience in the development, validation and production of HCP assays covering a broad spectrum of antigens in different cell lines.** BioGenes offers the development, validation and production of HCP assays including:

- Adaptation of HCP assays to customer processes
- Project design and preparation of a project plan
- Antigen preparation and validation
- Development of suitable antibody pairs
- Development of HCP assay in the working matrix or matrices
- Validation of HCP assay according to customer requirements and ICH guidelines
- Production of the immunoassay
- Technology transfer to the customer – SOPs and training of the staff
- GMP compliant release tests
- Stability and performance tests according to the customer requirements
- Production of complete kits or assay components
- Documentation according to regulatory guidelines

### Company Profile:

Since 1992, BioGenes has been successfully offering immunological and protein biochemical services and has built strong expertise and reputation in the fields of antibody and immunoassay development. The strong commitment to quality and service as well as proactive project management makes BioGenes a reliable industry partner that provides customers with continuous updates on their project status to reach milestones and to keep deadlines. Successful long-term alliances with biotech and pharmaceutical companies prove that BioGenes is the partner of choice in the fields of protein analysis. BioGenes is certified to meet the international requirements and regulations of quality assurance and animal welfare.

**Immunoassay development, validation, and production:** From drug discovery and development to the manufacturing of clinical and commercial supplies, BioGenes supports customers with a whole range of GMP-compliant analytical services starting from feasibility assessments to complete immunoassay development, manufacturing, and implementation. BioGenes' repertoire comprises the design of sandwich and competitive assays for the qualitative and quantitative determination of antigens or antibodies, and the development, validation and production of generic or process-specific Host Cell Protein ELISAs for quality control.

**Routine and highly-sophisticated antibody development:** Biogenes has successfully developed monoclonal antibodies against all kinds of antigens: peptides, soluble proteins, membrane proteins, phosphorylated antigens, small organic molecules like haptens, oligo- and polysaccharides as well as highly toxic substances. Furthermore, BioGenes' scientists have developed antibodies that distinguish modified proteins and peptides from non-modified (e.g. phosphorylation, methylation etc.) as well as anti-idiotypic antibodies. Only 0.2 mg of purified protein is sufficient for complete monoclonal antibody development.

For universities, institutes and industrial research, BioGenes offers affordable routine antibody development. The services include custom production of polyclonal antisera and antibodies in rabbit, goat, mouse, guinea pig, and rat against all kinds of antigens e.g. proteins, peptides, haptens and toxins. Customers can use the BioGenes standard immunization protocol or order immunization according to their own immunization scheme. Premium quality polyclonal antibodies are delivered in 4 weeks.



## biosyn Arzneimittel GmbH

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### Existing co-operations:

- International cooperations with pharmaceutical companies as supplier of carrier molecules for the development of therapeutic vaccines.

### Expressions system:

- Mammalian
- Microbial
- Other Isolation and purification of bio molecules from natural, e.g. marine source

### Fermenter capacity (volume in liters):

### Services offered:

- Supply of carrier proteins for immune therapies and challenging agents for immunological tests, including technical and regulatory support.

### Company Profile:

biosyn Arzneimittel GmbH, Schorndorfer Strasse 32, D-70734 Fellbach is a privately-owned pharmaceutical company located in Fellbach near Stuttgart in the Federal Republic of Germany. It was founded in 1984. The company now has approx. 80 employees in Germany and in its subsidiaries in Austria and the USA.

biosyn Arzneimittel GmbH has specialized primarily in the fields of oncology and intensive care medicine. biosyn currently offers around 30 drugs approved in 18 countries worldwide

biosyn markets world-wide Pharmaceutical Products and Active Pharmaceutical Ingredients in the fields of trace elements, minerals, biologics and biotechnology, respectively.

biosyn Arzneimittel GmbH represents a classical pharmaceutical company with all the required expertise: manufacturing, regulatory affairs, marketing, distribution, finances. Furthermore the company operations are especially focused on R & D in product and clinical development.

The manufacturing of biosyn's proprietary active pharmaceutical ingredients takes place at their own production facility in Fellbach. biosyn's laboratories are also in Fellbach. The processes are GMP-certified.

biosyn Vertriebs AG in Balzers, Liechtenstein, and the biosyn Corporation in Carlsbad, California, USA, are subsidiaries of biosyn. biosyn also has a scientific office in Austria.



Biotype Diagnostic GmbH

## Biotype Diagnostic GmbH

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### Existing co-operations:

- Charité University hospital, Berlin
- University hospital, Dresden
- Technical University, Dresden
- University of Magdeburg
- Erasmus University Medical Center, Rotterdam
- DITABIS Digital Biomedical Imaging Systems AG
- Fraunhofer Institute for Material and Beam Technology
- Fraunhofer Institute for Applied Optics and Precision Engineering, IOF
- Max Bergmann Center of Biomaterials Dresden, biodresden e.V.

### Expressions system:

- Mammalian
- Microbial
- Other

### Services offered:

The Biotype Diagnostic GmbH is developing, producing and distributing biotechnological products in close collaborations with academic and clinical partners.

We provide multiplex PCR, and chip-based applications in the following area:

- Leukaemia (AML diagnostic, chimerism monitoring, minimal residual disease analysis)
- Dermatology (dermatophyte identification)
- Interior hygiene (mold detection)

### Company Profile:

Biotype Diagnostic GmbH is an innovative, dynamic and aspiring company with more than a decade of experience in developing, producing and distributing DNA-based technologies. Having developed under strict requirements for establishing high quality DNA-typing assays for forensic purposes, we demonstrate our competence by supplying these products to diverse medical jurisprudence facilities within Germany, Austria and Switzerland.

Supported by our wide ranging network and specific know-how we have gathered on DNA analytics, we are continuously transferring scientific knowledge into marketable molecular biologic applications. Hence our product portfolio is steadily expanding; we likewise meet the demands of human medicine. In this area, we strongly promote promising diagnostics and, thus, therapy-relevant proceedings.

On the basis of highly informative molecular markers we offer sophisticated multiplex PCR applications to monitor post-transplant chimerism status for leukemic diseases and non-malignant disorders that require stem cell transplantation. Moreover, for reliable diagnosis and subsequent elaborated therapy of acute myeloid leukemia we provide a solution that simultaneously detects 31 transcript variants that are most frequently observed within this disease pattern. Furthermore, we will soon have developed a highly sensitive molecular biological application that mediates reliable, robust and highly informative analysis of residual malignant leukemic cells (minimal residual disease, MRD analysis).

We further emphasise the field of dermatology. Just now our pipeline is loaded with a PCR-based dermatophytes detection kit for a more rapid, convincing and convenient diagnosis of dermatomycosis. An application to detect and identify molds is set up and will help to reduce the pathogenic load of indoor areas.

Experts in multiplex PCR applications, Biotype Diagnostic GmbH's work also spans chip-based technology. Our product-portfolio also includes a microarray detection kit for identification of 27 dry rot fungi. In the immediate future, we are aiming to additionally develop protein-based devices for fast, simple-to-use, routine-fit and reliable diagnostics.

We are thinking vertically, horizontally and laterally to inspire innovations and get science to markets. This consequently fosters our product variety. The broad point-of-care product-portfolio indicates Biotype Diagnostic GmbH as a well-situated, future-oriented and comprehensively-themed company. We support your visions while guaranteeing the highest quality standards.



## cellasys GmbH – R&D

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### Existing co-operations:

Various co-operations with national and international industry and academia

### Expressions system:

- Mammalian**
- Microbial
- Other: label free whole cell based assay technology

### Services offered:

- Quality control
- Cell culture media optimization
- Process optimization
- Consultancy

### Company Profile:

Cellasys offers system solutions for online analyses of living cells. These include services such as research and development, production and maintenance of cell based assays. Furthermore, we are consultant for development of applications, data analysis and data interpretation.

The cell-based assays monitor different parameters directly at living cells. These parameters are extracellular acidification (pH), cellular respiration (pO<sub>2</sub>) and morphology (impedance) of the cells.

The measurement is label-free, parallel, continuous and in real-time. With these cell- based assays one can e.g. determine the efficiency of a drug outside of humans (or animals) priors to the start of the therapy.

Another possible application is to continuously monitor the vitality of cells in a micro-fermenter.

## Heppe Medical Chitosan GmbH



<b>Name of company:</b>	Heppe Medical Chitosan GmbH
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### Existing co-operations:

Cooperation with:

- national and international medium-sized and large medicinal and pharmaceutical companies
- companies operating in the cosmetic field

### Collaboration with:

scientific institutes

universities

(references on personal request)

### Expressions system:

- Mammalian**
- Microbial
- Other

### Services offered:

#### Business & Services

- HMC produces and sells chitin, chitosan and their derivatives as well as chitosan specialties, such as nanoparticles, especially for the cosmetics and pharmaceutical industry under GMP conditions
- Process development and synthesis according to GMP, up-scaling and custom manufacturing
- Custom research and development (e.g. drug delivery and wound treatment)

## Company Profile:

### Problem

- Chitosan available on the market has very wide-ranged specifications
- Reproducibility of mode of action cannot be guaranteed due to fluctuating properties
- No GMP certified chitosans are available for the pharmaceutical industry
- There is no specialized supplier who produces chitosan derivatives on customer request

### Solution

- HMC+ offers a unique spectrum – both in quality and variety – of chitin, chitosan and their derivatives, with more than 100 standardized chitosans with very narrow and reproducible specifications.
- Unique technology for GMP-compliant production

### Market

- Market growth (worldwide) is approx. 27% p.a. This equals a global market volume of EUR 1.62 billion.
- Primary market: pharmaceutical industry and medical devices
- Aftermarket: biotechnology, cosmetics industry, university research
- The company is striving to establish itself on the European market by means of dealer networking and in-house sales. Expansion to North America will occur in the medium term.

### Technology/IP

- The biopolymer chitin can be found in crabs, shrimps, squids, fungi and insects.
- Chitosan is produced by chemical syntheses of chitin (by deacetylation)
- Company's own production technology enables narrow specified and reproducible final products
- Standard products as well as technology for production of nanoparticles have been established. They are offered to the pharmaceutical industry for processing and as drug delivery systems.
- Quality seal "Made in Germany"

### Management Team:

#### Katja Heppe – CEO (Dipl. Biotechnologist)

- 15 years of experience with chitosan
- Scientific studies:
- Drug delivery via chitosan through blood-intestinal and blood-brain barrier
- Application patent on "Chitosan as delivery system"
- 4 years experience as head of laboratory in biotechnology companies
- Founder of the company

#### Caterina Kästner - Head of Sales & Marketing (Dipl. Interpreter & translator)

- 8 years experience as manager, sales & marketing
- 5 years experience as key-account manager and project leader in pharmaceutical company

#### Torsten Richter – Head of QC & QA (Dipl. Chemical engineer)

- 10 years experience as Head of Production in biotechnological companies (production of biopolymers)
- 5 years experience as quality manager
- Experienced in technology transfer



## IKTM, Städtisches Klinikum Braunschweig gGmbH

<b>Name of company:</b>	IKTM, Städtisches Klinikum Braunschweig gGmbH
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### Existing co-operations:

- Helmholtz Centre for Infectious Research (Braunschweig) : adenoviral modified dendritic cells (human)
- Medizinische Hochschule Hannover (Hannover): lentiviral modified dendritic cells (human)
- Medizinische Hochschule Hannover (Hannover): isolation of CMV specific T-cells (human)

### Expressions system:

- Mammalian**
- Microbial
- Other: human cellular therapy

### Services offered:

#### Services currently offered by the infrastructure:

The GMP-facility offers possibilities for isolation  
genetic modification  
cultivation and cryo-preservation of human cellular products

Beside the GMP-platform ICTM offers an apheresis unit, an EFI accredited HLA-facility and has together with the Helmholtz Centre for Infection Research (HZI), possibilities for analyzing, functional testing and imaging of the cellular products manufactured.

### Company Profile:

#### GMP facility for cellular and gene therapy

##### Description of the infrastructure:

The clinical GMP facility is a joint venture of the Pharmacy and Transfusion Medicine Dept. (ICTM) of the Städtisches Klinikum Braunschweig (SKBS). In this facility, the ICTM is at this moment concentrating on GMP-production of cellular products like dendritic cells (DCs), human stem cells (HSCs) and specific cell subpopulations.

The facility is intended to serve the SKBS and researchers from HZI, but is also open to external clients.

##### Services currently offered by the infrastructure:

The GMP-facility offers possibilities for isolation, genetic modification, cultivation and cryo-preservation of cellular products. Beside the GMP-platform, ICTM offers an apheresis unit, an EFI-accredited HLA-facility and has in combination with HZI, possibilities for analyzing, functional testing and imaging of the cellular products manufactured.

##### Modality of access:

Access to the facility is on a client-service basis or through scientific collaboration. Bioprocess and analytical development can be performed in a joint approach/ collaboration between ICTM and partners, while GMP operation will have to be performed only by experienced ICTM-staff and on a service basis.

##### Reimbursement for use of the GMP-facility

Reimbursement for GMP operations will be calculated on the basis of use of staff and specific GMP-rooms. Consumables, like immunomagnetic beads kits for cliniMACS separations, will be charged for separately.



## SIRS-Lab GmbH

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### Existing co-operations:

#### Joint development and research projects include partnerships with:

- Analytik Jena AG, Pfizer Germany
- German Sepsis Society
- Hans-Knöll Institut Jena
- Many university hospitals throughout Germany and Europe
- 

### Expressions system:

- Mammalian**
- Microbial
- Other

### Fermenter capacity (volume in liters):

### Services offered:

Diagnostic Test Development, Assay Development, Gene Expression Service

### Company Profile:

Located in Jena, Germany, SIRS-Lab is a molecular diagnostic company which develops and commercializes unique and innovative products to identify and monitor life-threatening infections such as sepsis, one of the major causes of death in hospitals. In the year 2000, SIRS-Lab was founded as a university-spin off in the sepsis research hub of Jena, Germany. The company has developed its proprietary sample preparation technology LOOXSTER®, and applies it in VYOO®, its CE-marked diagnostic product for sepsis diagnosis. With its upcoming product SIQNATURE®, the company also plans to assess the body's immune response to infection by means of gene expression monitoring.



## Vibalogics GmbH

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### Existing co-operations:

#### Expressions system:

- Mammalian**
- Microbial
- Other:

#### Services offered:

- cGMP manufacturing of viruses, bacteria and derivatives thereof
- Process development
- Seed banking / cell banking
- Formulation
- Freeze-drying / Foam- / Vacuum-drying
- Fill and Finish Services
- Analytical testing (GMP compliant) such as HA, HIA, TCID50, EID50, PCR, ELISA, E.P. requested assays etc.
- Project management

### Company Profile:

Vibalogics is a partner for companies committed to developing innovative therapeutic and prophylactic vaccines and biologics. As a one-stop-shop, Vibalogics offers GMP-compliant manufacturing, formulating, filling, lyophilisation, and QC testing of drugs based on recombinant and wild-type viruses and bacteria. The drugs are predominantly used for vaccinations, treatment of life-threatening diseases, gene therapy and virotherapy. Four state-of-the-art production suites with cleanroom class A-D areas are operated under biosafety level 2. An experienced team is available for a successful transfer of drug and vaccine lead-candidates from laboratory to clinical trials.

Vibalogics specializes in Biopharmaceuticals such as live bacteria and viruses which are usually generated in a recombinant manner.

At Vibalogics bacteria are produced using fermenters and single-use bioreactors. The same is true for viruses if propagated on permanent or primary cell cultures. Production using cell factories or on eggs is well-versed, too. For downstream processing cross-flow filtration units, a continuous ultracentrifuge and chromatography systems are ready-to-use.

Drug substances (API) produced by Vibalogics or any third party can be formulated, filled into different vial formats and lyophilized. Product-fill simulations and media fills compliant with the ICH guidelines are performed as standards. Vibalogics assists their partners in their choice of vials, stoppers and seals to meet European requirements.

To complete Vibalogics' one-stop-shop, comprehensive quality control services are offered: numerous physico-chemical tests, biological as well as biochemical assays are standards.

## Fraunhofer Institute for Toxicology and Experimental Medicine

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### Existing co-operations:

- BRAIN - Biotechnology Research and Information Network AG, Zwingenberg, Germany
- MediGene AG, Martinsried, Germany
- Mologen AG, Berlin, Germany
- MBI Fermentas AB, Vilnius, Lithuania
- ZMBH - Zentrum für Molekulare Biologie der Universität Heidelberg, Germany
- DOMPE farmaceutici spa, L'Aquila, Italy
- Biogenerix AG, Mannheim, Germany
- Hexal AG, Holzkirchen, Germany
- Bioceuticals Arzneimittel AG, Bad Vilbel, Germany
- F. Hoffmann-La Roche Ltd; Basel, Switzerland
- SANUM-Kehlbeck GmbH & Co. KG, Hoya, Germany
- PolyPhag GmbH, Viersen, Germany
- University of Cologne, Institute for Biochemistry, Cologne, Germany

### Expressions system:

- Mammalian**
- Microbial
- Other

**Fermenter capacity (volume in liters):** up to 400 L

### Services offered:

- Development of expression systems for recombinant antibodies
- Development of CHO- and microbial cell lines for recombinant gene expression
- Development of microbial cells for plasmid DNA-processes
- GMP manufacture and storage of master and working cell banks
- Development and scale up of cultivation and purification processes
- GMP manufacture of recombinant plasmids and proteins
- Aseptic fill of investigational new drugs (infusion bags, ampoules and vials)

### Company Profile:

At its Braunschweig location, the Fraunhofer ITEM performs client-based development of manufacturing processes for active pharmaceutical ingredients based on biomolecules such as proteins, glycoproteins/antibodies, nucleic acids, virus-like particles, and even viruses and bacteriophages. Microorganisms (E. coli, B. megaterium), yeasts, and mammalian cell lines (CHO, BHK) are in use.

Services include the GMP-compliant manufacturing of master and working cell banks as well as the development of lab-scale API manufacturing processes, scale-up to pilot scale, validation of critical process parameters and analytical methods, GMP manufacture of clinical API lots in bioreactors up to 400 L, and finally the aseptic fill and finish of drug products for clinical trials.

For accelerated transfer of biopharmaceutical product candidates based on recombinant antibodies and DNAs into early phase-II clinical trials, platform technologies are established that each include chemically defined growth media (for CHO cell lines and E. coli), cultivation regimes, purification sequences and analytical methods for determination of purity, identity, content and activity. Even a proprietary CHO cell line for the over-expression of antibody genes is in advanced development.

In the field of biopharmaceutical product candidate development, the Fraunhofer ITEM covers the entire sequence of individual steps for the translation of biopharmaceutical product candidates into QP-released drug products ready to be used in clinical trials. The Fraunhofer ITEM offers this as a full service or in the form of single and defined service steps. Clients are medium and large pharmaceutical companies as well as biotech and even academic institutions.

The comprehensive technology portfolio from early process development to the manufacturing of final dosage forms for clinical trials is accompanied by a high level of competence, while guaranteeing a strict focus on individual goals of client projects with simultaneous adherence to technical feasibilities as well as regulatory needs.

## Imprint

### Publisher

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### Layout and Print

Yoni Advertising Productions (Y.A) Ltd. ISRAEL

### Notes

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### Order Number

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