

Our Experience - Your Advantage

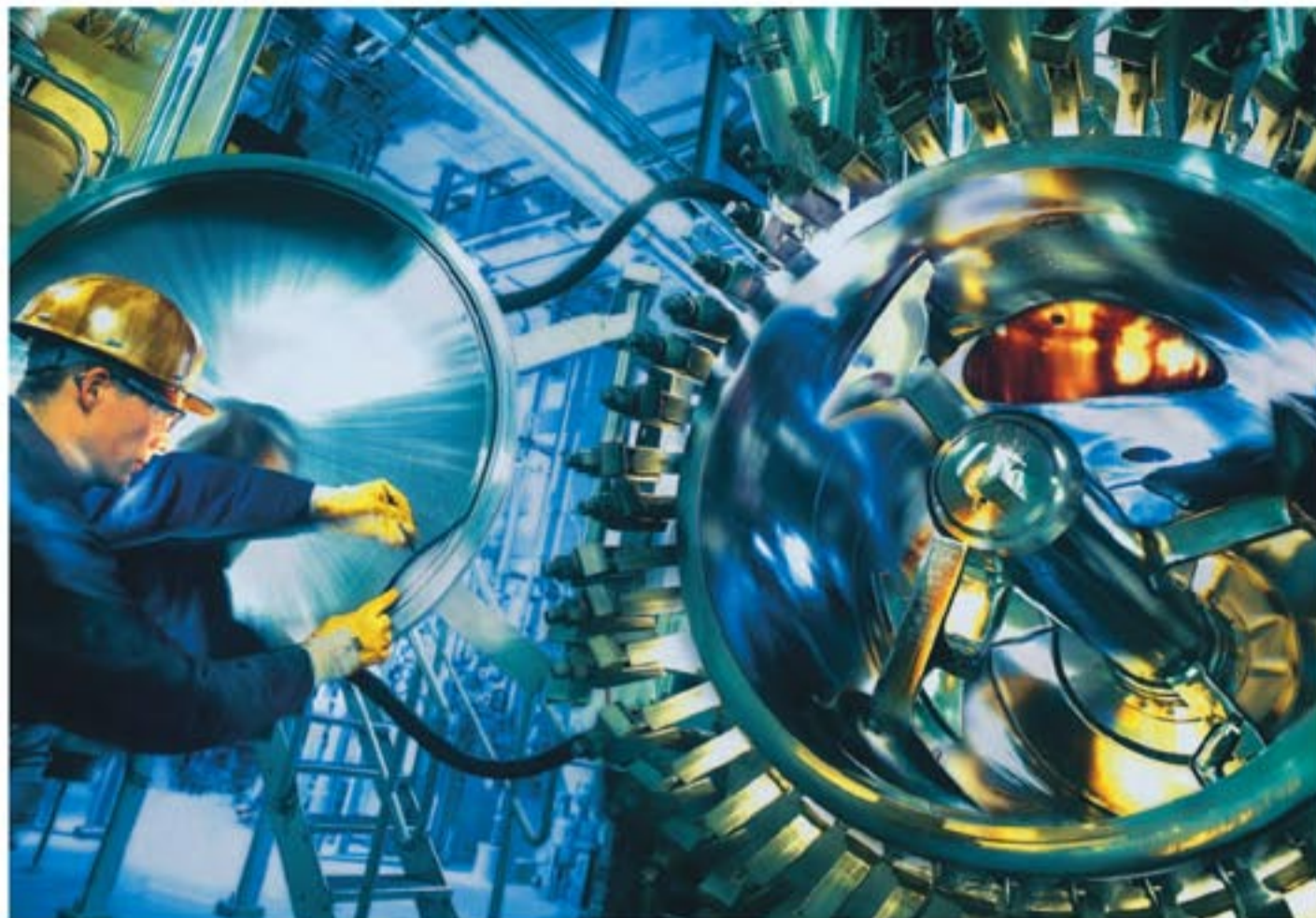
Bayer HealthCare – Your Partner in the Production and Development of Active Pharmaceutical Ingredients

More than 100 years of experience in the production of active pharmaceutical ingredients, 30 years of cutting-edge biotechnology, successful audits by national and international authorities at regular intervals, modern infrastructure for biological and chemical production and, as an extra plus, close proximity to departments with competence in development – having a partner with these credentials at your side, who needs more?

The site in Wuppertal is historically linked to great scientists. It was here that the chemist Felix Hoffmann synthesised aspirin in 1897 and then, about 50 years later, the Nobel Prize winner Gerhard Domagk developed sulfonamides for the treatment of infections. Other active ingredients followed and, more recently, the anti-cancer drug 'sorafenib' was yet another example of the pharmaceutical success story of Bayer HealthCare (BHC). Traditional production plants for Active Pharmaceutical Ingredients (Department of API-Production) are to be found in Wuppertal alongside the two other autonomous departments, Biotechnology and Chemical Development (see figure). Bayer HealthCare is committed to the principles of "Responsible Care" and "Sustainable Development". BHC also recognises the fact that the trust of the neighbouring community is something that has to be fostered and encouraged.

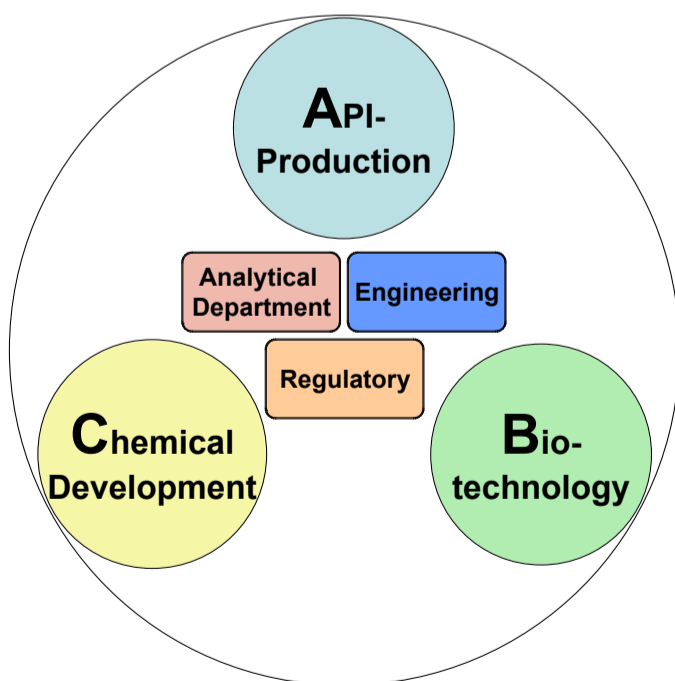
Customised Service...

Bayer HealthCare employees provide clients with a flexible and highly effective organisation, a complete pharma infrastructure and a comprehensive range of services in the three departments, "API Production", "Biotechnology" and "Chemical Development" (see small diagram); put another way, the "Wuppertal ABC" stands for a service programme that covers everything, from the very first gram of substance for toxicological studies through to the production of chemical and biological API in 100 ton amounts. The client benefits not only from the high level of innovation within the Bayer organisation but also from integration into the already established Bayer Quality Control System. This guarantees an excellent production quality, high delivery reliability and high standards with respect to occupational health and safety and protection of the environment. This platform not only ensures that clients can concentrate on their core business; it also gives them crucial advantages in the pharma market. Integrated operations that range from process research, through process development, to production of the active ingredient, especially when clustered, ensure optimal results. It is possible to be integrated into the pharmaceu-



tical development process at any point and at any time – stress-free, efficient and without any large investments. We even offer professional support during the approval process.

The networks within the global Bayer organisation encourage the exchange of ideas and knowledge and result in a continuous process of optimisation and creation of value for the external partner. For example, the Chemical Development department maintains a close cooperation with the pre-clinical disciplines of Formulation Technology, Toxicology, Regulatory Affairs and Isotope Chemistry. BHC uses these modules to build a complete concept that is tailored to the indi-



vidual requirements of the client; a concept not only for technical development or production of active ingredient samples for the clinic, but also for maintaining supplies to the market. The favourable conclusion of numerous inspections and audits by the FDA and European authorities, as well as by clients themselves and local authorities, is the reward for the dedication shown by BHC and is also a clear guarantee for success.

API production: over 100 years of experience...

When it comes to time-saving and cost-reducing production of active ingredients, a highly qualified team of employees and state-of-the-art facilities are ready to give all their support to the client. Over the last 25 years many satisfied contractors have used the opportunities provided by "Custom Synthesis", which range from contract manufacturing through to the sale of active ingredients. Originally conceived as a reliable source of pharmaceutical products for their own medicaments, Bayer has also acted as a contract manufacturer

and supplier of active ingredients since 25 years. In addition to the standard technologies, special facilities are also available for carrying out reactions that have more sophisticated requirements, and qualified systems as well. Clients are able to contract for single steps in the production process of registered active ingredients and intermediates, as well as for precursors. After an initial feasibility study, the plant is adapted for the product

and appropriate measures taken to ensure an adequate supply of raw materials. This guarantees a sustainable product quality – reliability is just as important for the external client as it is for members of the Bayer organisation. The Active Ingredient Production department coordinates every step of the production process at BHC and ensures that there is a constant feedback with the client. Highly complex processes are carried out according to the principles of the Green Chemistry Programme, using modern analytical technologies, and are carefully documented in accordance with cGMP regulations. Plant operations are controlled and monitored by a variety of modern process controls manufactured by well-known providers. The high degree of automation means that the client can profit from a cost-effective production and a trouble-free reproducibility.

Biotechnology: the full potential of modern biology...

Innovative biocatalysts, custom-made proteins, monoclonal antibodies or specialities for the fine chemical industry – all this is offered by the Biotechnology department that has been serving external clients from this site since 2003. This broad range of services is not only aimed at up-and-coming young biotech-companies, who are looking for a competent partner for their development project, but also at traditional companies from the pharmaceutical or speciality chemical industry who know that, when it comes to contract production, they can rely on the quality and reliability associated with the Bayer Cross logo. Bayer Biotechnology is more than just effective, as can be seen in the complexity of the fermentation process involved in the production of 'acarbose'. This is the active

ingredient contained in the anti-diabetic drug Glucobay®. The Wuppertal biotechnology experts also produce the monoclonal antibody involved in the purification of Kogenate® - the Bayer product for the treatment of haemophi-

and bulk products. Another advantage: the complete downstream processing unit has been designed to be explosion-proof, so that large-scale handling of organic solvents is also possible. Chemical Development: turning molecules into drugs... The technical development of an active ingredient is an important part of the development process as a whole. A development process that is optimized with respect to timelines, resources and quality not only ensures an optimal patent life for the active ingredient but also increases the sustainable value of the whole project. The Department of Chemical Development at BHC offers an integrated spectrum of services that addresses all the important technical aspects of the development of active ingredients. For example, Levitra®, which is the youngest Bayer medicament, was brought from pre-clinicals to the market in less than four years. This short development time is only possible when an efficient supply of high quality active ingredient for pre-clinical and clinical development is guaranteed from the very start of the project. In the subsequent phases of development, the most immediate questions concern the establishment a potent, economical and safe production process

Bayer HealthCare Services in Wuppertal

Bayer HealthCare is a partner for API-Production, Biotechnology and Chemical Development and offers the following services:

- Rapid access to clinical trials
- Reaction volumes for chemistry, extraction and fermentation: from 0.03 m3 to 80 m3
- Biotransformation, Secondary Metabolites, Recombinant Proteins, Bio-catalysts
- Explosion-proof areas in all three departments
- Genetically modified organisms (Bio-safety level 1)
- High standards of safety and environmental protection (ISO 14001)
- Production of highly active compounds and parenteral drugs

Special services:

- Low temperature reactions (-100°C)
- Separation of enantiomers by chromatography
- High vacuum distillation (10–5 mbar)

Additional services:

- Quality control, engineering, micronization, packaging, formulation
- Regulatory activities: complete or assistance in the preparation of official regulatory documents
- Ecology, safety, environmental monitoring

liacs. Over and above all this, the department has great experience in the production of genetically engineered proteins, the development of biotransformation processes and the production of food additives.

The Biotechnology Centre – one of the largest genetic engineering facilities in North-Rhine-Westphalia – is fitted out with modern equipment for production and development studies. Special techniques, from the classical genetic optimisation of micro-organisms, through modern genetic engineering procedures, to the newest methods of product analysis, are all used here. This enables not only technical process development, including scale-up from 10 litres to 40 m3, but also the production of intermediates

with a technical maturity that will extend into the very latest phase of production. That this process involves high standards of quality goes without saying. If required, BHC will prepare all the necessary documentation for submission to the authorities for its clients and partners. This means the customer can benefit from the many years of experience that Bayer HealthCare has had with registration and approval procedures.