SPECIAL I: FINE CHEMICALS

The impact of biotechnology on fine chemicals

Gunter Festel, Festel Capital, Hünenberg, Switzerland

Industrial biotech is an emerging field within modern biotechnology that uses living cells like moulds, yeasts, bacteria or mammalian cells as well as enzymes to produce a large variety of products including bulk chemicals, enzymes, vitamins and active pharmaceutical ingredients (APIs). This sector is expected to grow significantly during the next years by offering the chemical and life science industry more customer-suited products, quality improvements and a higher cost effectiveness in the process. Not only the established chemical and life science companies are actively agitating in this field, but also a significant number of start-ups or small and medium enterprises (SMEs) are contributing to the increase of influence industrial biotech will have in the coming years.

In 2015 about 15% of the chemical products with a sales volume of approximately 305 billion euros will be produced by biotechnological processes (Fig. 1). The highest potential for biotechnological processes is in the area of fine chemicals (mostly APIs) where 50% of the sales volume (approx. 50 billion euros) will be produced by biotech routes in 2015. This is expected especially for the production of complex chiral molecules, such as enantiomerically pure APIs with chiral centres, which can be produced by biotech routes. The increasing requirement for chirality results from parallel regulation-policies at FDA in the US and EMEA in Europe to accomodate the fact that usually only one out of two chemical enantiomers is active and beneficial. The "wrong" enantioner is regarded either as inactive or even as a potentially harmful entity that has to be removed. More than 50% of the top 100 drugs are based upon enantiomerically pure molecules and such drugs already today exhibit sales exceeding 100 billion euros. In addition, 60% of the new APIs in drug development Phases 2 and 3 are chiral and 90% of the new chiral substances are developed enantiomerically pure. Thus, biotransformation will be a key technology for the synthesis of new drugs.

Fig. 1: Market potential for industrial biotechnology

Technological aspects

Biotransformation (enzyme catalysis, whole-cell bioconversion) is the conversion of a specific substrate by stereospecific catalysis using isolated enzymes, cells or microorganisms. Enzymatic catalysis increasingly allows higher concentrations of educts and non-physiologic temperatures and conditions. Thus, both novel enzymatic systems and optimization with techniques such as molecular evolution have led to succesful applications of "biological" processes within the chemical industry. But a single enzymatic catalytic step does not necessarily lead to the desired product, so that the reaction has to be performed in multiple steps. The cell-free biotransformation will nevertheless widely replace fermentation for the production of small molecules.

The technical development has progressed at an enormous rate and will further boost the application potential of biotransformations. The increasing knowledge of enzyme reactions in non-aqueous solution will lead to a broadened spectrum of processes and a greater number of substrates. Due to new developments in reactor and process design, the process efficiency will be improved. The versatile application of extremophiles will enable more robust processes, thus increasing the diversity of process conditions and reducing reaction times. The common use of the directed evolution process leads to the development of tailor-made and high-performance enzymes particularly when using molecular scaffolds as starting points derived from the wealth of evolutionary diverse microorganisms. Organisms that are not cultivable can be accessed by molecular genetics via direct cloning of environmental DNA. This technological breakthrough has led to an enormous boost of the number of available enzymatic systems. The genetically engineered modification of microorganisms will thus result in the implementation of new enzymes and reactions and to new sustainable processes.

Business models and growth strategies

Most industrial biotech start-ups and SMEs are service-oriented companies, offering their particular know-how. The disadvantage of this concept lies in the fact that the intellectual property (IP) of the services provided afterwards belongs to the custom-

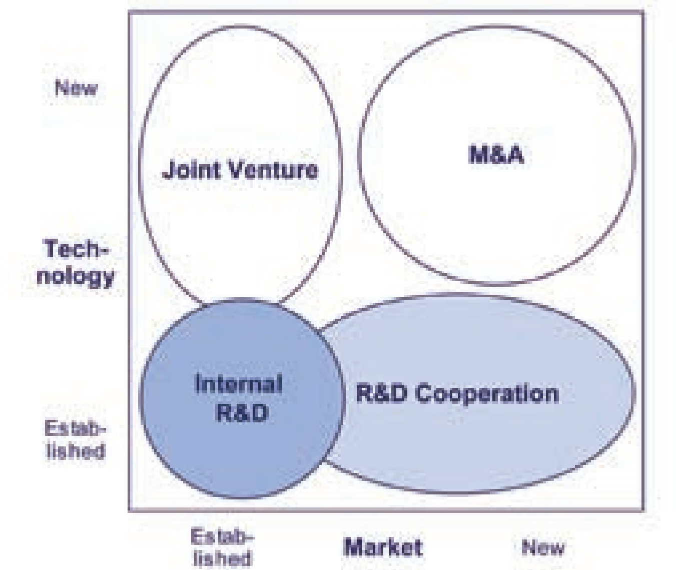


Fig. 2: Used growth strategies in the field of industrial biotechnology

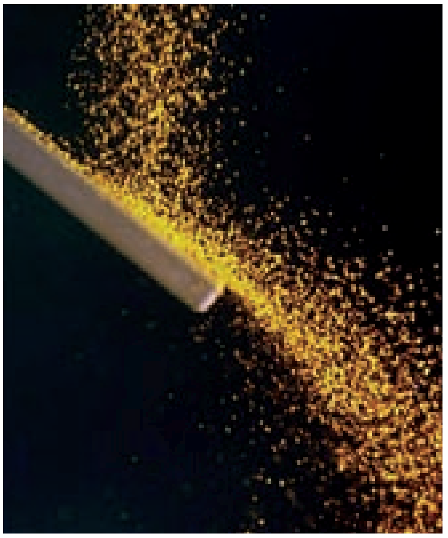
er. Therefore, the value-building potential through development and commercialization of own IP is very limited. The superior IP business model focuses on the development of own technologies and products, which are sold or out-licensed. With a suitable strategy and network the start-up or SME is able to achieve a stronger and steadier growth potential. As the IP business model offers substantial advantages, service-oriented companies increasingly focus their development and growth strategies on the aggregation of own IP.

Currently, most European industrial biotech start-ups and SMEs in the field of fine chemicals use a very limited set of growth strategies (Fig. 2). The preferred strategy is based on organic growth through the development of internal R&D for established markets and technologies. Most often this strategy originates from the fact, that industrial biotech start-ups and SMEs keep up very good relationships with universities and research institutes and thus have a very fast access to the latest research results. However, since the companies have to carry the entire costs of R&D activities, the number and size of projects that can be realized is very limited due to financial restrictions.

Another option of accessing new and emerging markets as well as financial resources can be seen in entering a partnership or cooperation with an already established company. Whereas start-ups avoid a time- and cost-consuming development of new markets, the established partner is able to incorporate innovative and state-of-the-art technologies from start-ups into the own product portfolio. Nevertheless, it is evident that the start-up loses much of its independence, which could possibly lead later into a complete merger and acquisition (M&A) process. In contrast, R&D cooperations or joint ventures between start-ups to realize synergetic effects on the technological as well as the market side are rare, originating from the fact, that there is strong competition between start-up companies to get funding from established companies for joint R&D programs.

Conclusion

Industrial biotech is of enormous importance for the competitiveness of the European chemical and life science industry. A decisive driving force for the transfer to biotechnological production processes is clearly the cost factor. As a rule, biotech routes have substantially lower capital and manufacturing costs and allow greater flexibility because the minimum economies of scale are much lower. In some industrial segments, such as the food industry, sometimes higher prices can be achieved for biotechnological products compared with their chemically produced counterparts. However, other factors than the production costs usually do not play a role in the choice of the production process. The restrictions of biotechnological production processes are therefore seen primarily on the economic side, e.g. operative costs, R&D costs and investments. The synthesis of existing products by chemi-



cal procedures is frequently so cheap, that the development of a biotechnological production process is generally not cost-efficient. Furthermore, production facilities for chemical syntheses already exist and can not be changed to biotechnological production without massive new investments. The notable number of successful implementations of biotech processes clearly shows that the European chemical industry is increasingly using the potential of molecular biology to sustain competitiveness especially with regard to US and Asian challenges.

But Europe is a long way from using the potential of industrial biotech as the start-up scene in that area is not properly developed. The further development depends on the ability to establish a prospering start-up scene in Europe. Long-term oriented financial support during the seed and growth phase is the key success factor to develop a prospering industrial biotech start-up scene in Europe. The establishment of a dedicated "European Industrial biotech Seed and Growth Fund" would be a suitable instrument to enable capital markets access and foster industrial growth in industrial biotech.

OECD STUDY

Belgium is a leading innovator

Paris – Belgium is one of the best performing countries in the biopharmaceutical sector. This is the result of an analysis of the Organization for Economic and Commercial Development (OECD), in which national reports prepared in the year 2000/2001 by Belgium, Finland, France, Germany, Japan, the Netherlands, Norway and Spain were compared with numbers from the United States, the UK and Japan. The study evaluated the countries' performance in two categories: scientific and industrial innovation developments.

Taken together Belgium shows the best overall performance beating even the United States and the UK. The country ranks third in scientific development measured by biopharmaceutical publications per million capita (105) and first in innovation and industrial performance assessed among other factors by patent applications. According to the report the country had applied for more patents per capita (13.2) than the US (11.3) and the Netherlands (9.6). The UK (7.6), Germany (7.4), Finland (5.4), Norway (5.3) and France (5.2) are still above the OECD average of (5.1) whereas Japan (4.8) and Spain (1.1) fare below.

The general scientific development is measured in the OECD study by the number of papers published per inhabitant. In this category Finland takes a firm lead with 144 papers per capita, followed by the Netherlands (122), Belgium (108), the UK (96), the United States (92), Norway (81), Germany (72), France (72), Japan (58), and Spain (44) that ranks below the averages of all countries in the EU (68) and the OECD (54). However, Spain is catching up its backlog showing the fastest annual growth (11.5%) in publications per capita between 1994 and 2001 followed by Germany (10.3%). The lowest growth rates, according to the report, have the United States (6.2%), Finland (5.9%) and France (5.9%).