Press Release

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New technologies beef up pharmaceutical production

- **Cost-optimized production**
- **Innovative diagnostic techniques and API formulations**
- **Demographic change drives growth**

In contrast to what was going on elsewhere, turnover in the pharmaceutical industry continued to rise even during the depth of the economic crisis in 2009, and there is no end to the upward trend in sight. IMS Health predicts that worldwide turnover will be in the region of $960 - $970 billion in 2012. The figure for 2011 was $955 billion, up 5.1% from the previous year. The higher incidence of age-related illness associated with demographic change and the increase in disease normally associated with modern civilization in the emerging countries are generally regarded as the biggest factors driving future growth.

The rating agency Standard & Poor´s (S&P) expects that annual growth rates will range between 12% and 15% in the emerging markets in the period 2012 - 2016. It estimates that the US market will expand by no more than 4% during the same period.

An increased prevalence of common diseases such as diabetes, high blood pressure and cancer is associated with rising affluence in emerging markets such as China and India. These illnesses used to be a health problem that mainly afflicted the US and Europe. China is now the largest market for diabetes medication and the second largest market for cancer therapy drugs. More than 2.2 million people contract cancer each year. Around 92 million people were suffering from diabetes in 2010. That number could increase to 130 million by 2030 according to S&P. Besides the increase in illnesses associated with modern civilization, population aging is another factor which could result in China becoming the world’s number two pharmaceutical market by 2015, second only to the US.

In the past, high corporate earnings, pricing autonomy and a well-stocked product pipeline were taken for granted. Today however companies are faced with higher R&D expenditure,

competition from generics which put pressure on earnings and a supply base which has growing market clout. To remain competitive in the global marketplace, the industry is addressing process and cost optimization with renewed energy. Innovative technologies as well as new therapeutic and diagnostic techniques are becoming increasingly significant.

Biopharmaceuticals extend the product portfolio

Advances in the life sciences are playing a key role in the development of new drugs. Based on a deepening understanding of the complex mechanisms in cell clusters and organs, researchers are now able to investigate how the illnesses originate at the level of the molecules which are actually involved. Using this information, the researchers can then go on to develop therapeutic agents and medication for personalized medicine.

The number of proteins and enzymes which are being used for their therapeutic or immunizing effect is currently increasing at a rapid rate. Boston Consulting Group (BCG) has reported that roughly 200 pharmaceuticals with around 110 APIs are currently approved for use in Germany. Biopharmaceuticals are drugs and vaccines which contain APIs that are produced with the aid of genetically modified organisms.

The worldwide market for biopharmaceuticals is growing. Turnover in 2010 was $107 billion and that figure is expected to rise to $167 billion by 2015 according to a forecast published by IMARC Research Inc. in its Global Biopharmaceutical Market Report (2012-2015). Biopharmaceutical market share in the emerging markets (Brazil, Russia, India, China, Mexico, Turkey and South Korea) will also increase. The figure is expected to rise from 5% in 2009 to more than 8% in 2015.

At a time when all signs point to growth in the international marketplace, turnover of biopharmaceuticals is stagnating in Germany. “A highly promising market segment with stunted growth potential,” commented Dr. Frank Mathias, President of vfa bio (a research-based pharmaceutical trade association) as he gave his perspective on the 2012 BCG report on medical biotechnology in Germany. There are plenty of products in the pipeline, but in contrast to the steady growth recorded in 2010, turnover of biopharmaceuticals remained flat at around 5.4 billion euros in 2011. The report cites political intervention in the market as the cause. The mandatory rebate was raised from 6% to 16% in August and a price moratorium is also in force.

In 1978, Arthur Riggs developed the first genetically engineered human insulin which was placed on the market as Humulin in 1982. In the intervening period, the pharmaceutical industry has gone through a period of very rapid growth. The market for biopharmaceuticals offers great potential for molecular biological and biochemical technologies. It is important to keep in mind however that the road which leads from basic research to a marketable therapeutic or diagnostic product is a very long one.

Government intervention, expiration of patent protection and promotion of biosimilars create significant challenges for biopharmaceutical producers. The ability to develop new forms of therapy holds the key to continued growth in the global market. Products currently in the development pipeline will have an important role to play. According to BCG and vfa bio, 46% of current API development is targeted at illnesses for which biopharmaceuticals are not yet available. The list includes Alzheimer's disease, skin cancer, prostate cancer, systemic lupus erythematosus and meningitis prophylaxis. The need for innovative biopharmaceuticals will continue to grow in the years to come, with demographic trends being one of the contributing factors.

Single-Use-Technologies on the rise

These developments caused that single-use-technologies have moved from niche markets into the mainstream in recent years. The number and variety of single-use systems available on the market for biopharmaceutical R&D and production applications has increased steadily over the past ten years. In the meantime there is a wide variety of products available. Most single-use products are found in processes where protein-based biotherapeutics made from mammalian cells are the target products. With the broad spectrum of components, sensors and single-use pumps which are available, complete single-use upstream processing for culture volumes up to 2 m^3 is now feasible. The range of options includes bioreactors which use wave motion to mix materials (GE Healthcare’s Wave Bioreactor and Biostat CultiBag RM from Sartorius Stedim Biotech) as well as single-use stirred bioreactors available in a variety of versions (e.g. rigid plastic tanks from Mobius CellReady, UniVessel SU and CelliGEN BLU and flexible bag systems from S.U.B., Biostat CultiBag STR and XDR Bioreactor). The size, the underlying principle of operation and mixing as well as the instrumentation vary on these systems, and they all have their own defined fluid dynamics. For repetitive steps (mixing, storage, material handling, inoculant production, fermentation and biomass separation), basic operation sets have been consolidated into process platforms. These platforms are technical implementations which combine a well-defined sequence of processes or process steps. A number of these platforms are now available for media production, fermentation and biomass separation. The size of the systems as well as the number and sequence of process steps vary.

There are technical limitations to the deployment of single-use technologies in upstream processing due to the plastics which are contained in the products. The list of limitations includes stability, applications spectrum, scale-up and handling. The current size limits from the user perspective are in the 1,000-2,000 liter range for bag volumes and 30 inches for filter cartridges, even if suppliers offer larger bag systems (up to 5,000 liters). Above these thresholds, users currently install multiple systems in parallel when they need to increase

capacity. Recent surveys by Aspen Brook Consulting indicate that 80% of users regard this approach as adequate.

Despite the fact that the increasing deployment of single-use systems in upstream processing has led to the development of similar systems for downstream processing, the latter are not as significant a factor as the upstream systems. The basic downstream processing steps used in the production of biopharmaceutical products include conventional filtration and chromatographic techniques as well as recent developments such as functional filtration/absorption and mixed-mode technologies. The term mixed-mode refers to a multiple retention mechanism which forms the basis for interactions between the target and the sorbent. In contrast, the filling process for the formulated end product in biopharmaceutical production normally involves conventional fluid transfer with or without final lyophilization. From the available set of basic operations, the most suitable methods for product isolation and purification are selected and combined to form a sequence. The sequence and quality of the methods chosen varies depending on the properties and quality requirements of the product which is being purified.

Growth in the market for disposable systems which are used in the production of protein-based therapeutic products can be expected to slow down. However if development work continues, the products needed for complete single-use production systems and the “single-use factory in a box” will become closer to reality. “There is already a vision for an SUS container-based vaccine factory which can be shipped anywhere in the world in a very short space of time to produce vaccine (assuming of course the availability of qualified staff),” reported Prof. Regine Eibl from Zurich University of Applied Sciences.

We will probably also see new applications of single-use bioreactors (1) in the production of microbial niche products, (2) for production methodologies involving algae and (3) for products in the pharmaceutical, food and cosmetics industries which are based on plant suspension cells, hairy root cultures and mesenchymal tissue. “A large number of 100 % SUS-based implementations of fermentation processes involving animal cell cultures are already established, and more are on the way“, said Detlef Eisenkrätzer from Roche. The latest generation of biotherapeutics will have a decisive influence on the future development of single-use technology. Eibl is convinced that personalized medicine, especially the production of cell therapeutics using stem and T cells, is likely to be one of the most promising future applications of single-use technology. Cell therapeutics are generally regarded as a major product segment in personalized medicine. Products for regenerative medicine (skin, cartilage and bone) have been making their way into the market since the 1990's, and the first customized (person-specific) vaccine for treating prostrate cancer received FDA approval in April 2010. Compared to established manufacturing techniques for protein therapeutics, cell therapy is still in its infancy. Innovative equipment and new technologies will be absolutely essential for commercial success. Given the product requirements and the way the products are used, there is no alternative to single-use systems. More than 200 cell therapeutics for

transplant medicine, cancer and aids therapy are currently at the clinical trial stage. This is a great opportunity not only for the medical field but also for single-use technologies.

The extensive status update published by the DECHEMA ad-hoc Single-Use-Technologies Working Group shows the options and limits of single-use-technologies. Among other things, the update provides manufacturer information along with a wealth of details about available products and components. This report is available for download: http://biotech.dechema.de/Publikationen