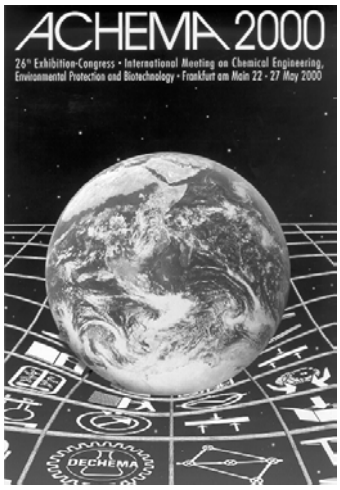

ACHEMA 2000
22. – 27. May 2000
Frankfurt am Main/Germany

The opening ceremony of the 26th ACHEMA was performed in the Congress Center at the Frankfurt Exhibition Grounds. From Monday, May 22, 2000 the gates to the world's biggest chemical engineering Exhibition–Congress and International Meeting on Chemical Engineering, Environmental Protection and Biotechnology was opened to the public for 6 days. The special trend reports of ACHEMA 2000 exibition (no 1–19) were prepared for publication by authorities from DECHEMA. In this issue of Chemical Industry JI. (Hemijska industrija) trends covering Pharmaceutical Technology, Trends in pharmaceutical industry, Genetic Engineering, and Industrial Biotechnology are prepared. Trends covering Proces Identification (PI), Process Instrumentation and Control, Process Safety, and Plant Engineering Tools were published in No 6 of Chemical Industry JI., while trends covering the Pumps and valves, Pumps, fitting and seals, Compressors, drives and seals, and Trends in Automation in No 7–8, Packaging: New Materials, new Technologies, Enviromental management, in No 10. Others informations of these type will be published in the next issues of Chemical Industry JI.

PHARMACEUTICAL TECHNOLOGY

For pharmaceutical processors, the journey from drug development to commercial introduction can take 10–15 years and cost $500 million. Only one of 5,000 new drug discovered will ever be administered to patients. Many of these products will be low–cost generics, while designer pharmaceuticals will be subject to intense pricing pressure. Against this backdrop, compound annual growth for the global pharmaceutical industry is estimated at 6%, with sales expected to reach $400 billion in 2001.

Focus on drug discovery

To ensure future competitiveness and profitability, drugmakers are streamlining operations and plowing resources identifying molecules that can be used to develop new drugs. Most of the major pharmaceutical companies have made equity investments or formed partnerships in combinatorial chemistry, a technique that allows researchers to make thousands of different compounds simultaneously. Using supercomputers and software to predict how individual molecules will behave in a specific process environment, drugmakers aim to cut the development time for new drugs to 6–9 years.

The pharmaceutical industry's growing reliance on combinatorial chemistry and high–throughput screening is expected to drive demand for laboratory automation technology and equipment, including organic synthesizers, automated solid–phase extraction apparatures, robotic stackers or arms, integrated robotic platforms, workstations and platforms, report market analysts at Strategic Directions International (Los Angeles). Demand for liquid handlers, the largest segment of the laboratory automation market, with global sales of $468 million in 1998, is expected to grow about 15%/year through 2003. However, the fastest growth is expected to come from cheminformatics software and integration automation software, which are expected to top 20%/year through 2003.

Merging assets, outsourcing production

Where pharmaceutical companies lack geographic or product strength, they are securing it through mergers and acquisitions or other strategic alliances. Some of the deals initiated or completed within the last year include: Merger of Astra AB and Zeneca Group Aventis, new company formed by merger of Rhone–Poulenc Rorer and Hoechst Marion Roussel Merger of Monsanto and Pharmacia & Upjohn Acquisition of ISIS Pharma by Alpharma Pfizer's agreement to acquire Warner Lambert Proposed merger of Glaxo Wellcome and SmithKline Beecham.

Production of pharmaceutical bulk actives and intermediates is being outsourced to facilities designed to meet the stringent standards of current Good Manufacturing Practices (cGMP), allowing drugmakers to quickly test and scale up drug production without having to make an initial investment in new plant and equipment.

Over the last three years, several companies in the U.S. and Europe have started up or expanded contract manufacturing, design, and engineering and construction services tailored to pharmaceutical, biotechnology and fine–chemical manufacturers. They include:

Huls's experSCience, which boasts a complete package, including research, pilot–plant testing and design of commercial–scale facilities Dow Chemical's contract manufacturing arm. Honeywell (formerly AlliedSignal), which expanded its cGMP pharmaceutical intermediates facility in Seelze, Germany Foster Wheeler's Steril AG unit in Basel Krupp Uhde and Herzog–Hart's strategic business unit, based in Bad Soden, Germany, to provide engineering, procurement and construction management services, ADP Marshall, a cGMP design/build service of Fluor Daniel Universal Pharma Technologies, a joint venture of UOP and Pharm–Eco Laboratories Francis, the Milan–based business of Laporte Fine Chemicals, upgrade of its cGMP contract manufacturing capabilities for bulk actives and intermediates.

When pharmaceutical companies are ready to make a capital investment, increasingly it is for construction of large multipurpose pilots plants. Until recently, construction costs for such projects was typically $10–50 million. Today, many are being built in the $300–million range. The pilot plants are usually owned by the drugmaker's research arm and are often as large as the final production plant.

There are several reasons for the for the increase in pilot–plant size:

New drugs are moving quickly and continuously through company pipelines. Prototype drugs are being produced in volume for large–scale clinical trails. The makeup of new drugs is changing – some are more toxic and require high–level containment Pharmaceutical companies are diversifying and are involved in obtaining approvals in many types of drugs at the same time – maximizing opportunities for revenue generation. Typically, large–scale pilot plants contain multiple suites and an assortment of process of equipment to produce a variety of drugs In the U.S., Japan and Europe, the regulatory approval process is being streamlined. Efforts by the International Standards Organization (ISO) and other governing agencies to harmonize pharmaceutical manufacturing standards are intended to allow drugmakers to serve global markets from centralized locations. This would lower the cost of pharmaceutical production and make innovative drugs more accessible.

Some processors of pharmaceuticals and intermediates have improved productivity and shortened time–to–market by implementing Six Sigma, a globally recognized measure of delivered quality that results in only 3.4 defects per million, or 99.99966% error–free performance.

Automated operation will reduce contamination and improve productivity

Automated manufacturing processes will reduce contamination, boost yields and improve productivity. As pharmaceutical manufacturers make the switch from traditional batch processing to continuous operation, they are driving demand for clean–in–place (CIP) and steam–in–place (SIP) systems. Long used in the dairy industry for cleaning tanks, CIP is becoming available for a wider range of equipment, reducing manual cleaning and saving downtime. CIP protocols expose material to corrosive cleaning fluids, often at elevated temperatures to 80°C and pressures to 414 kPa. The effective CIP cycle requires that contact materials be able to withstand repeated cycles of flush–rinse–drain, without softening, scouring, leaking or breaking.

Routine SIP cycles aid in maintaining a sterile environment. SIP cycles of 150°C at 359 kPa are common. Materials must have a smooth inner profile, and joints must be precisely aligned and tightly mated to ensure smooth passage of production and cleaning fluids, and to avoid crevices – microscopic hiding places for chemical or biological contaminants.

Here's a sampling of equipment designed for CIP–SIP, most of them were presented at ACHEMA 2000:

The Aeromatic Fielder Div. of Niro offers CIP for all of its fluid–bed dryers, granulators and coaters. The CIP system features a wash–liquid preparation unit that filters, preheats, mixes and pumps fluids. CPI is aided by an easy–to–clean air distributor for fluid beds. Tema Systems' sanitary TS–400 CPI decanter operates at 204° C. Heineken Filtering Systems is working with its customers to validate their CPI systems. The company has conducted test to validate its CPI systems on its HF inverting filter centrifuge. The test was performed using a fluorescing solution of riboflavin sprayed onto all areas of the unit that come into contact with product and allowed to dry. The wash fluid was dispensed through the spray nozzles and feed pipe. After washing, the machine was examined using an ultraviolet light. The CIP system brings the centrifuge to 98% clean. Flooding the CIP system with a solvent that the remaining product is soluble in, can clean the unit to less than 1 ppm. Equipped with fully automated CIP–SIP, the Powerfuge by Carr Separations can be steam–sterilized to 121° C at 1.9 bars in about 20 minutes. There is no disassembly of equipment, virtually eliminating the risk of worker injury or product exposure. Sweco markets a filter dryer designed for separating and vacuum drying product in a single machine. Designed to Class 100 cleanroom standards, PharmASep can process up to 25 kg of solids with particle sizes larger than 1 μm, on either a batch or semi–continuous basis. CIP is especially difficult to implement in valves, which must be self–draining to flush out the cleaning fluids. In a typical low–flow control valve, it can take hours for CIP fluids to pass through the small orifices. H.D. Baumann offers a family of aseptic, process control valves that allow for precise, low–flow control and high capacity for CIP. Waukesha Cherry–Burrell's mixproof valves permit dissimilar liquids, including CIP solution, to safely pass through the same valve body. CIP solution enters the valve from a tube connected to the valve seat cleaning line, which services all valves associated with that particular product line. The valves are available in one–piece or two–piece body designs Watson–Marlow Bredel Pumps offers a CIP–SIP option with its SP40 and SP50 hose pumps for metering and transfer applications

Materials of construction: stainless steel, glass and fluoropolymers

Selecting the right material of construction for high–purity equipment – including mixers and reactors, or pumps, valves, piping and tubing – is a strategic decision that ultimately affects the quality and yield of product to be made. The selection process can be simplified by separating the many considerations involved into four general areas: Process and service requirements, Size restrictions and mechanical requirements, Acceptable materials, Equipment cost.

Typically, the project manager or engineer will choose the most cost–effective and practical material of

construction. But the initial investment cost should not be the first consideration. A cost analysis should be one of the last considerations – after the performance requirements and acceptable materials of construction have been evaluated. In high–purity applications, matching the materials of construction to the mechanical, chemical and product demands of the process is critical.

For pharmaceutical production, Type 316L stainless steel is standard for mixers and vessels. This nickel–containing, or austenitic, stainless steel is temperature–tolerant, abrasion resistant and easy to clean. A practical and economical material for sanitary applications, stainless steel can be fabricated into vessels of virtually unlimited size and capacity. However, Austenitic stainless steels are suitable only for low concentrations of reducing acids. High levels of halogen ions, especially the chloride ion, can break down stainless steel's passive surface film, causing corrosion, particularly in the crevices of the vessel.

Glass–lined steels may be a safer choice for reactors and other equipment subjected to corrosive chemicals, especially at operating temperatures above boiling, often associated with reaction chemistry and distillation processes. Glass linings are oven–fired, fusing the glass to the internal surfaces of the vessel or the column that will contact process materials. The chemical resistance of glass linings will vary with the specific glass formulation used. The information, available from glass–lining manufacturers, is based on a combination of their own laboratory testing, customer testing and industry experience.

An exception to the acceptability of using stainless steel and glass–lined reactors is in applications that involve either solids or abrasive materials, e.g., powders, crystals, inert fillers, or naturally occurring corrosive organic acids, e.g. citric, lactic or tannic acids at or above boiling temperatures. One must consider all of the possible chemical interactions and byproducts as well as end products being made.

Fluoropolymers provide the highest degree of corrosion protection, but the engineer must take into consideration the nature of the chemistry and the effects, in any, of chemical permeation, vacuum or agitation. The cost of a fluoropolymer–lined vessel or column is about the same as a comparable–size glass–lined unit, which is about 1.5–2 times the cost of a stainless steel model. In pharmaceutical applications, fluoropolymers are often used to line connecting piping, valves, fittings, expansion joint and internals for vessels and columns – agitators, baffles, trays and packings.

In demanding operating environments – where wide temperature and pressure swings, corrosive process chemicals and cleaning fluids are present, fluoropolymers exhibit the best overall performance. Some, such as perfluoroalkoxy (PFA) and polytetrafluoroethylene (PTFE) are fully fluorinated; others, including polyvinylidine fluoride (PVDF) and ethylene chlorotrifluoroethylene (ECTFE), are partially fluorinated. Studies have identified stainless steel as the most difficult piping to clean, followed by polypropylene (PP), glass, machined PFA, rotationally molded PFA, silicone–coated glass and PVDF. Easiest to clean is injection–molded PFA.

Protecting products and personnel

Processing high–purity pharmaceuticals and intermediates requires tight control of particulate matter, to prevent cross–contamination of products as well as to protect operators from exposure. Manufacturers are motivated by market factors to achieve standards of product purity, but they also have an ethical and legal obligation to assure the health and safety of personnel.

Where there is a risk of exposure, either to the operator or to the product, regulations require the installation of systems to ensure the capture, containment and control of airborne particles. Central to an effective strategy for overall contamination control is air filtration and flow. A typical cleanroom may provide high levels of product integrity, but not necessarily ensure the operator's safety. Neither can protection from potentially harmful substances be assured by simply donning a gown, face mask and gloves.

A cleanroom with a low particle count may be the most–effective solution for providing a healthy environment, but it is increasingly difficult to achieve. Potent drugs can have exposure limits of less than 1$\mu m/m^3$ (8–hour total weighted average). Consider, for example, that a grain of table salt weight 150 μg. If an operator inhales 10 m^3 of air in 8 hours, that one grain of salt inhaled would be comparable to an exposure level of 15 $\mu g/m^3$! In such cases, the combination of a containment booth in a cleanroom offers the best protection for both products and operators. More economical, in some cases, are double–containment systems that minimize the risk of contaminants either entering or leaving the chamber.

An alternative to cleanrooms staffed with workers sheathed in sanitary garments – particularly in cases where high handling risk are present – is an isolation barrier. With such systems, commercialized for aseptic pharmaceutical production, unit operations are confined to small chambers filled with an environmentally friendly sterilant, such as gaseous hydrogen peroxide. In addition to saving space, labor and protective clothing, isolation barriers reduce energy costs by about 15%.

Isolation barriers that use hydrogen peroxide or other environmentally friendly sterilant avoid the handling problems associated with the chemicals typically used low–temperature sterilization, such as ethylene oxide, formaldehyde and glutaraldehyde. However, some manufacturers of these sterilants contend that hydrogen peroxide is no less hazardous, and as a sterilant, is inferior.

Controlling the flow of clean air during pharmaceutical manufacturing processes ensure that workers are protected from substances that can be extremely hazardous. The benefits of doing so are great, since industry regulations demand increasingly higher

levels of particle control, both to protect operators from the risk of exposure, and to maintain product integrity.

TRENDS IN PHARMACEUTICAL INDUSTRY

The increase in globalisation in recent years has made a mark on the pharmaceutical industry. This branch, which has been spared from economic crises for decades, felt the effect of turbulence for the first time. Both in research and production new ways of reining in the increasing costs are being sought.

In 1998 Europe was second only to the USA in terms of drug production. Whereas the market in Europe is relatively stagnant – in Germany, for example, growth of six percent is predicted – there is great potential in South–East Asia, Brazil, Argentina and Mexico. The reasons are, above all, an increase in the population and in particular in the affluence of the middle class. But the USA and Europe still remain the main research locations and therefore the most important production sites for drug manufacturers. In Japan, traditionally also one of the big research countries, economic problems have led to the reduction of funds for research.

Competition is tougher – price pressure is increasing

A common feature at all production sites is the increase in the intensity of international competition and the price pressure of the market. Two examples illustrate this:

Drugs, which are present at low concentrations in the pharmaceuticals, form the basis for the economic success of a pharmaceutical company. The search for a promising compound is like the proverbial search for a needle in a haystack, because the faster the systematic unraveling of the human genome progresses and the greater the advances in chemical synthesis, the greater the number of potential candidates for a drug. The question is how can the right compound be recognized? The search is not only laborious but also costly. It can take up to ten years before a drug is finally brought to market and the cost from the beginning of the search to the final registration of the drug is around US$ 350 million. Only one out of 5,000 compounds makes it to the marketplace.Whereas in the past only very few companies investigated a particular drug at any one times, today several companies will be searching simultaneously for promising compounds. This means that a drug has scarcely been brought to market before, within a short space of time, it has been copied and is being provided by other drug companies. The duration of the period of exclusive right to use is decreasing and the costs have to be recovered quicker. Thus the high research and development costs have to pay off within a short space of time.

Another example, the rise in the proportion of OTC (over the counter) products worldwide illustrates clearly the increasing price pressure. In Europe alone, the drugs market for self–medication grew by around 40 percent from 1990 to 1996. The price which the pharmaceutical industry has to pay is that OTC products are six times cheaper than prescription drugs.

How is the pharmaceutical industry fighting the spiraling costs? First of all, new markets are being sought. In addition to malaria or AIDS drugs, these are, above all, products which will have a big impact on the market, for example nutraceuticals. These are nutrient products which are designed to improve health, for example probiotic yogurts. This idea, which came from the USA, is becoming more and more popular in Europe.

Faster research thanks to modern biotechnology

On the other hand, one is trying to reduce costs in research and production. According to the motto "nip the problem in the bud", attempts are being made to reduce the time spent on research. Focal points are the areas genomics, proteomics and bioinformatics. The rapid decoding of the human genome offers the chance to understand many diseases at the molecular level and to isolate target proteins for pharmaceutical research. If a target protein is identified then the search for molecules which inhibit the activity of this protein, and thus have potential for the treatment of the disease, begins.

The computer–aided search for new drugs has become the key to successful and rapid identification of promising compounds. Although the computer cannot provide the answers to every question, its importance in drug research is increasing. It can be used to make a meaningful pre–selection from the huge number of possible drugs, and molecule libraries can be tailored to certain properties before the compounds are synthesized. Furthermore, with the aid of software, hypotheses can be made which enable further experiments to be planned more effectively. Modern computer technology has become an indispensable part of pharmaceutical research.

With the aid of automated combinatorial chemistry one hundred to a thousand more substances can be synthesized and tested when searching for a new drug than by the conventional method of single substance synthesis. HTS (high throughput screening) systems come to the aid of drug researchers. These systems run the test substances automatically through an array of internal tests. In this way, many substances can be tested simultaneously for their efficacy – in the past this was restricted to 96 samples per run. For the pharmaceutical industry this rate is no longer sufficient, the ambitious target is to be able to run and check the efficacy of 100,000 samples per day. To achieve this aim, sampling systems are required which not only run more samples but also reduce the sample volume at the same time. After all, the test substances are often very expensive to produce and must be used as efficiently as possible. At the ACHEMA Special Show Synthesis, Screening and Sequencing Machines and the symposium of the same name, the latest developments in this field were presented.

Faster decisions are required in production

In production tools are required which enable quick decisions to be made. Systems for supply chain management (SCM) or classic production planning are now in more demand than ever before. Coupled with optimization methods from production, these systems have considerable promise for the industry. This goes hand in hand with the realization that the key skills need to be redefined. For example, the actual production process is often passed on to highly specialised contract manufacturers.

The result of this new development is a great challenge, not only for process organisation but also for the plant engineer. Small batches with a more regular change of product are manufactured, as a result the setup times of the plant must be reduced. All surfaces and materials which come into contact with the product must be of high quality in order to be suitable for any task. This includes the simplification and acceleration of cleaning and sterilisation processes. Many manufacturers presented their new concepts for sterile technology at ACHEMA. Meanwhile, a considerable number of individual and national requirements in terms of material quality, proof of qualification, documentation of validation and production processes, etc., has resulted from the global orientation of the pharmaceutical industry. The increasingly comprehensive documentation of these processes is an additional burden to the daily workload of both plant engineers and operators.

More responsibility for the plant engineer

The plant supplier is taking a lot more responsibility for his plant than was the case a few years ago. He is advising pharmaceutical companies not only on technical aspects but also about how to achieve efficient production. More process steps in the plant are to be expected nowadays as is the automation of the process (including the logistics) and a material flow which is free from contamination. In addition to cost efficiency, the increasing demands placed on cleaning techniques have been a talking point in recent years.

Isolation technology, which has been implemented in only a few plants in Germany, will continue to be the predominant technology. Isolation technology is the systematic separation of man and process, whereby the sterile zone, for example, is reduced to a filling machine. The aim is to minimize the microbiological contamination of aseptically produced products by the environment. This concept has several advantages. For example, as a result of the smaller chamber volume, the air purification process is less laborious and the construction standard for filling chambers lower. Whereas with the conventional technology a large sterile room has to be cleaned, the smaller isolator is automatically disinfected with H_2O_2 and gassed daily. These precautions increase the level of sterility enormously. Examples of this technology were presented at ACHEMA.

Safety is foremost

A high level of safety is also paramount with the electronic fingerprint technology. A new procedure is now being used by the FDA (Food and Drug Administration) to inspect plants. Recently, electronic batch records have become compulsory, so that all production processes, which were previously recorded on paper, now have to be stored in electronic form. Since the electronic fingerprint has now become standard practice, systems such as the electronic fingerprint on chip cards are being used. However, these modern systems must be compatible with the programs currently in use. Tracking software, whether it is used for scales, mixers, or packaging lines, will be in demand in future. Exhibitors presented new solutions in this field at ACHEMA.

New demands for packaging

Pharmaceutical packaging now has to meet new requirements. Export to countries in the climate zones 3 and 4 has increased. As a consequence new demands are being placed on the barrier capability of packaging in terms of humidity, translucence and temperature resistance. The increase in counterfeit medication calls for new concepts from manufacturers of pharmaceutical packaging to prevent falsification, for example holograms. In addition to new drugs and packaging, manufacturers also presented new ways of preventing falsification of medication at ACHEMA.

Breaking down the barriers between medicine and process engineering

Process engineering will play an important part in future in new forms of therapy and in galenics. Two examples are tissue engineering and nanotechnology. Scientists have been working for some time on biological replacements for the liver so that in the case of acute liver failure the essential functions can be maintained until a transplantation can be performed. Whilst doctors ensure that the right biological conditions are available, the practical aspects are down to process engineering. The artificial liver is nothing but a bioreactor where the supply of nutrients, the temperature and other physiological conditions have to be controlled.

In similar spectacular fashion, nanoparticles have become the topic of conversation in medical technology. These particles are 10 to 1000 nm in size and made up of plastic or organic macromolecules. They can bind or enclose drugs and in this way transport them undetected into a cell. This transport system has special advantages, particularly in the case of polar drugs, substances with an electric charge or, compounds which, as a result of their bulk, cannot pass through the cell membrane. Other drugs can, with the aid of nanoparticles, be transported to their site of action in the body. An example is powder inhalers for asthma drugs, which enable very fine drug particles to be inhaled. The drug particles, which must reach the lungs, are bound to particles which are 50 to 200 micrometer in size. This

enables the flow and dispersion of the powder to be better regulated during inhalation. Nevertheless, large aggregates are often formed which are excreted in the buccal or pharyngeal cavity of the patient. If it were possible to coat drug particles with a size of 10 micrometer or less with even smaller, inert particles, the drug flow would be sufficient without carrier particles and the dose could be determined exactly.

Both examples illustrate that process engineering will have an important place in the pharmaceutical industry, and not only in classic procedures, such as mixing, drying or granulating. The pharmaceutical industry will, more than ever before, depend on process engineering in the areas of the future. The ACHEMA provided a platform for traditional processes and gave future technologies in pharmaceutical engineering added impetus.

GENETIC ENGINEERING

Biologists around the world are only months away from "cracking" the human genome, the genetic code that determines most, if not all, human characteristics. A "rough draft" of the genome is expected shortly, with a polished version within three years.

When this monumental project began in 1990 at nonprofit research laboratories – at the National Institutes of Health in the U.S., and global research institutes including the Max Planck Institute in Berlin and the Cancer Research Center in Heidelberg – it was expected to take another 15 to 20 years to complete. Even at the ACHEMA 97 trade fair, completion was not expected until 2005.

Automated gene sequencing, expression and discovery systems, genetic bioarrays, and databases have dramatically cut the time needed for genetic decoding, making it far less tedious and allowing research to accelerate at breakneck speed. At the same time, new companies – some less than one year old – centered mainly in California and Maryland in the U.S. – are working on human and other genomic projects. Their goal: even faster results, accessible, in some cases, via portals on the Internet, to the world's pharmaceutical and academic laboratories.

Until fairly recently, only simple genomes of viruses and bacteria had been decoded. Now, genomes of organisms ranging from baker's yeast, Saccharomyces cerevisiae, to roundworm Acenorhabditis elegans and the fruit fly, Drosophila melanogaster, are complete, or close to it.

Genomics fights diseases

Developments are proceeding rapidly. In September 1999, Iceland based Decode Genetics discovered the gene that causes pre–eclampsia, a disease of pregnancy. Subsequently, other breakthroughs were made: scientists in Australia and at Stanford University, have used genomics to identify genes that regulate the human immune system; researchers at Millennium Pharmaceuticals Inc. and Wyeth Ayerst Research used genomics to identify "potassium channel interacting proteins" that control the electrical signals of the brain; researchers at the University of Pittsburgh showed how a defective gene leads to certain forms of hereditary cancer; Curagen received U.S. patents 5,977,311 and 5,986,055 for discoveries mapping the protein interactions implicated in cancer cell proliferation.

Supercrops by Genomics

While it promises to usher in powerful new medical treatments, genomics is also allowing for the development of new "supercrops," with superior nutritional value and insect resistance. In summer 1999, scientists at the University of Freiburg and the Swiss Federal Institute of Technology developed a genetically modified rice, using a gene from a French bean to boost iron content, two genes from a daffodil and another from a bacterium to produce beta carotene, a source of vitamin A, and another gene that produces an enzyme to counteract phytic acid, which prevents the body's absorption of iron. The new rice would allow people who subsist mainly on rice to get nutrients normally found in other foods. Research funded by The Rockefeller Foundation in China has boosted rice yields by 15 to 25%, while another project in Mexico has added genes to rice and corn to help the plants tolerate high concentrations of aluminum, and an Indian research project has added genes to help rice plants tolerate long periods under water, a problem in parts of Asia.

How to explain individual's genetic differences?

An area of growing interest to genomic researchers is "single nucleotide polymorphisms (SNPs)," points at which different individuals' desoxyribonucleic acid (DNA) differ by a single base. SNPs are expected to help explain individuals' genetic differences, such as differing susceptibility to specific diseases. The Human Genome project is mapping SNPs, and, last year, a consortium of 10 global pharmaceutical companies, including Bayer Corp., Hoechst Marion Roussel, Hoffman La–Roche, and Novartis, together with the U.K.'s Wellcome Trust, started a $30–million project to find and map 300,000 common SNPs. New automation technology is also being developed for SNPs. Recently, Orchid Biocomputer, Inc. (Princeton, N.J.) commercialized SNPstream, an automated, high–throughput assay platform for industrial–scale SNP genotyping, and has since received three U.S. patents for genotyping technology. In February, Sequenom, Inc. (San Diego, Calif.) went public, offering technology based on its MassARRAY system for high–speed, high–throughput SNP analysis.

The number of patents is increasing

Although genetic engineering faces a backlash of negative public opinion in the short term, serious ethical issues must be grappled with in the long term. Patenting questions, for example, will decide how accessible new

gene technologies will be. Although gene–related patents have been issued by most countries for over 20 years, some critics are now calling for stricter barriers, particularly in light of the growing use of automation. A key question is how short a DNA sequence has to be to be patentable, and whether SNPs or promoters should be included. The U.S., which has issued over 1,800 patents on full gene sequences, mainly for plants, but more recently for animals and humans, is considering regulations that would limit the ability to patent genomics findings.

Questions of individual privacy also loom. How would data on each individuals' genetic makeup be accessed for medical treatment, yet be kept confidential to avoid job and other discrimination? In the U.S., where health insurance risks pose thorny problems, President Clinton recently issued an executive order banning discrimination against employees based on genetic records.

Given the novelty of gene therapies, risks and serious adverse events that occur during clinical trials of new genes must also be registered, and reporting guidelines established. In the U.S., the American Soc. of Gene Therapy recently suggested that data be reported to both the U.S. Food and Drug Admin. and the National Institutes of Health.

For now, researchers continue to battle the clock to wrest more secrets from human, animal and plant genomes. James Watson, who won the Nobel Prize for his role in determining the structure of DNA in the 1950s, is said to have dismissed automated genomics as "monkey work." By broadening R&D's emphasis from the micro to the macro level, from painstaking analysis and replication to discovery of larger patterns and correlations, and interactions between various genes, genomics companies are proving him wrong. As their stock prices approach those of e–commerce merchants, innovators are quickly staking claims to portions of the commercial genomics field and creating new, multimillion dollar markets.

Leading the pack in automated gene sequencing instrumentation is PE Corp. Formerly Perkin–Elmer, the California–based holding corporation is said to control over 80% of the world's sequencing market through its rights to polymerase chain reaction (PCR) technology and automated sequencers based on that technology. PCR, whose discoverer won the Nobel Prize for Chemistry in 1993, "unzips" the DNA molecule's double helix into two separate strands, using the enzyme, polymerase, to remove constituent bases and reconstruct a new DNA molecule from each strand.

In 1998, PE set up PE Biosystems Group, to sell analyzers, such as the Prism 3700, and to collaborate on new automation technology. The company sold $1.2 billion of instrumentation last year. At the same time, PE established Celera Genomics Group (Rockland, Md.) , to use the analyzers to offer genomic data on a subscription basis. The company, which went public at the end of last year, uses the analyzers to sequence repeating molecules in the helix, then analyzes results by supercomputer. The technique, "shotgun sequencing," was pioneered by Celera R&D director Craig Venter, previously head of the Institute for Genomic Research, and had only been tried on less complex genomes. Building up a 50–terabyte computer arsenal, the company claimed it would be able to sequence the human genome in three years, and for one–tenth the cost of the U.S. government's effort. By the start of this year, it had already tracked 90% of the genome, a year ahead of time.

Currently, pharmaceutical companies license Celera data for millions of dollars per year. The company is also developing a gene portal on the Internet, hoping to attract people who wish to learn more about their genomic makeup. Later this year, the company will offer sampling analyses to the public via the Internet.

Information technology and bioarrays speed up genomics research

Bioarrays are another key genomics research tool. The arrays grew out of the concept of "sequencing by hybridization," first developed in the 1980s by scientists from Yugoslavia, the U.K., and Russia, as an alternative to sequencing by gel electrophoresis.

Affymetrix, Inc. (Santa Clara, Calif.) commercialized the concept and now leads the market with its GeneChip technology, disposable DNA arrays containing gene sequences, reagents, a scanner and other instruments on a silicon chip, for analyzing human, murine, rat and yeast genomic data. Demand for such systems is growing rapidly. According to the U.K. based consulting firm, Frost & Sullivan, global demand for DNA microarray systems accounted for $130 million last year and will grow to $400 million by 2003. Affymetrix recently introduced a new human cancer array that enables over 1,700 genes related to cancer to be measured simultaneously. The company also introduced a Yeast Genome array that puts the entire yeast genome on a single chip, and offers a range of new SNP mapping arrays, screening services, diagnostic software, and therapies. Other leaders in the automated genomics race include Millennium Pharmaceuticals (Cambridge, Mass.), Human Genomic Sciences, Inc., Incyte Pharmaceuticals (Palo Alto, Calif.)., Rosetta Inpharmatics, Inc. (Kirkland, Wash.) and Curagen (New Haven, Conn.), which, last February, completed the first mapping of the yeast and fruit fly genomes. The company offers technologies for each step of the genetic decoding process; SeqCalling for gene and SNP sequencing; GeneCalling for automated gene expression; and PathCalling, a high–throughput sequencing technology and database, which identifies protein interactions within biochemical pathways, associating those proteins with disease related genes.

In the plant area, Agrinomics LLC (Portland, Ore), set up last summer, offers ACTTAG activation gene tagging. The company is now involved in a five–year, $7.5–million venture with the seed companies, Aventis S.A. and Agritope, Inc., to use the technique to develop bacterially resistant vegetable crops.

Newcomers are entering the genomics fray almost daily. Lynx Therapeutics, for example, is offering a new gene sequencing technology that attaches large sets of DNA molecules to micron–diameter plastic beads, allowing genes to be sorted, compared and sequenced. The technique is among those currently being used by DuPont's agricultural division.

In February, a relatively unknown company, Athersys (Cleveland), disclosed a new technology, Random Activation of Gene Expression for Gene Discovery (RAGE–GD), which uses radiation to break down the DNA molecule, then inserts a proprietary "promoter" to find a break in front of a gene, and switch it on. The technology would allow natural human proteins to be derived from specific genes, even when other information on those genes is not available. The company, which claims to be the first to have developed a synthetic human chromosome, has filed for 10,000 new genetic patents based on the technology. In contrast, Celera reportedly has 6,500 genomic patents pending; Human Genomic Sciences, 6,700 and Incyte, 6,300, of which 173 have been granted.

New software systems are being developed to keep pace with genomics research. InforMax, Inc., for example, recently released High–Throughput Research, including GenoMax, to provide analytical tools for genomics. The new system automates research by creating "virtual biologists" who can mine genomic and other data 24 hours/day, 7days/week, while facilitating collaboration and offering distributed processing. In February, Spotfire, Inc. (Cambridge, Mass) launched a new software system specifically for gene expression analysis, Array Explorer 2, which offers an open computing platform and connections to genomic databases. The system costs $1,000/year per user.

From single gene to genomics and proteomics

Researchers agree that they've only scratched the surface of genomics. After sequencing the human genome, they'll have to identify all genes, identify those expressed during key events. They'll also need to understand how gene regulatory systems function, identify proteomes and SNPs. Full scale commercialization of products based on genomics research is still over 10 years away, observers say. However, cell therapy markets are expected to grow by 40%/yr. over the next five years, Frost & Sullivan says. Last year, U.S. revenues alone stood at $77 million. Delivery systems will be critical for new gene therapies. In February, Genetronics Biomedical Ltd. (Toronto) moved into the field, offering electroporation for gene delivery. The technique applies pulsed electric fields directly to target tissues, facilitating uptake of genes into the cell's interior. So far, the company has licensed technology to Boehringer Ingelheim.

INDUSTRIAL BIOTECHNOLOGY

The prospects for biotechnology have never looked better. Breakthroughs in genomics, combinatorial and other lead optimization techniques, enhanced bioreactors and separations technologies, and improvements in laboratory computer platforms have combined to bring the science closer than ever to realizing its potential. ACHEMA 2000's exhibition and congress offered an international forum for presentation and discussion of these future–technologies.

Biotechnology market is booming – stocks are rising

In Europe, biotechnology revenues increased by 36% in 1998, to 3.7 billion Euros, according to the market research firm, Ernst & Young. In the U.S., biotechnology companies secured nearly $12 billion in funding while 22 biotechnology drugs and therapeutics were approved by the U.S. Food and Drug Administration. In fact, the total number of biotechnology drugs approved over the past five years is twice the total approved since 1987, according to U.S.–based Biotechnology Industry Association (BIO).

Biotechnology stock values have risen to heights more typically associated with e–commerce. In the U.S. last year, biotechnology stocks traded on the Nasdaq outperformed the overall composite index by 24%, and, early this year, BIO says, they outperformed those of Internet companies by over 17%. The number of initial public offerings has also grown – most recently, Iceland's DeCode Genetics decided to "go public" and seek a listing on the Nasdaq, the U.K.'s Times reported, in a move that would make it one of Europe's largest biotechnology companies. Driving improved efficiency are high–throughput screening technologies, demand for which, according to the analysts, HighTech Business Decisions (Moraga, Calif.), will approach $2 billion this year. "Pharmaceutical and biotechnology companies are under tremendous competitive pressure to find drug leads quickly," says company president, Sandra Fox. Throughputs for such systems, she says, are expected to jump from an average of 173,000 wells read per week to more than 500,000 by next year, while companies using the latest innovations, she says, are reading more than 1 million wells per week.

Biotechnological breakthroughs in drug therapies

Recent biotechnological breakthroughs run the gamut from drug therapies to the fields of environmental remediation, textiles, plastics, and agriculture. In drug development, researchers came one step closer to the "Holy Grail" of medical R&D: treatments for the virus causing human acquired immune deficiency syndrome (AIDS). In February, the first genetically derived treatment for the virus received FDA approval, while Human Genome Sciences, Inc. (Rockville, Md.) received a U.S. patent on a human gene producing a receptor thought to be the entry point for the AIDS virus. A number of companies, including Progenics Pharmaceuticals, Praecis Pharmaceuticals and the Schering–Plough Research Institute (Kenilworth, N.J.) are developing drugs that would block this receptor.

At the same time, positive clinical test results were seen for the blood substitute, Hemopure, designed as a replacement for people who needed blood transfusions during surgery. Developed by Biopure Corp. (Cambridge, Mass.), the compound contains a highly purified form of hemoglobin. The company's stock prices rose more than four fold after this news, a pattern that is becoming more common this year.

Edible vaccines expressed in plants, long a goal for biotechnology companies, also inched closer to reality in February, when successful clinical trials were concluded on swine for a plant derived vaccine. Developed by ProdiGene (College Station, Tex.), the vaccine uses recombinant proteins from genetically enhanced plants to treat transmissible gastroenteritis virus (TGEV) in livestock.

Industrial biotechnology business commercializes new products

Industrial biotechnology has also posted gains, as biocatalysis systems developed by such companies as Diversa, Inc. (San Diego, Calif.), Energy BioSystems (The Woodlands, Tex.), ThermoGen, Inc. (Chicago), Maxygen (Santa Clara, Calif.) and Mercian of Japan, made progress in chemical processes and environmental textile applications. Diversa, whose stock price rose four–fold at the beginning of this year, commercialized its first product last year. Halliburton Energy Services (Houston) is using the heat–resistant enzyme to reduce viscosity in its crude–oil–reservoir fracturing fluids. Diversa is also working with Dow Chemical to scale up production of a biocatalyzed polymer derived from epichlorohydrin, and also sealed a $12.5–million deal with Novartis.

Novo Nordisk, the leader in industrial enzyme development, plans to spin that $630–million business off this year, Forbes magazine reports, while Genencor has seen its industrial biotechnology business grow to over $300 million. "By 2002, a substantial number of companies will have supplemented metal and chemical catalysts with biocatalysts," predicts Frost & Sullivan analyst Adita Sapru. "Once they feel comfortable with the enzymes' catalytic abilities, they will incorporate biocatalysts into other areas of their processes."

Polymers and their building blocks are one focus of the new research. In Japan, Nitto Chemical Industries (Tokyo) has scaled up a biocatalytic process to make 35,000 m.t./yr of acrylamide, eliminating the need for platinum and palladium catalysts. In the U.S., DuPont has worked with Genencor to develop a biocatalyst that uses recombinant DNA technology to convert sugar into 1,3–propanediol. The new catalyst would eliminate the need for acrolein and ethylene oxide, as well as the metal catalyst recycling headaches. In addition, the company has licensed Nitto's A4–nitrohydroamylase biocatalyst to make adiponitrile into the herbicide, 5–cyanovaleramide without the use of manganese oxide.

Environmental applications are another goal. Energy BioSystems Corp. is developing biodesulfurization technology based on Rhodococcus flavin reductase, which can increase desulfurization rate ten–fold. One of the goals: a diesel fuel with sulfur content below the ppm range. The company has developed a new proprietary gene–shuffling technology to develop hybrid genes to improve this and other industrial processes.

New materials: biopolymers

Improved fermentation and separation are also bringing new materials closer to market. In the U.S., these traditional techniques are driving biopolymers from the fringe to the mainstream. DuPont is currently evaluating and fine–tuning separations techniques to improve production of spider silk, one of nature's strongest materials. Spider silk is stronger than steel, with twice the metal's tensile strength. It is biodegradable and can be made at room temperature, while its properties would make it an excellent choice for making such protective garments as bullet–proof vests. DuPont, however, is focusing on textiles that feel like silk, wear like polyester, and don't need dry cleaning. Evaluating soy and corn, the company has had the most success so far with Escherichia coli. The company is now working with two separation techniques. In one, the biosilk gene is designed to include code that will cap certain amino acid sequences onto the ends of the silk protein. A solvent or particle with affinity for these acids is then used to extract the silk. Other, more traditional separations, including precipitation, filtration and extraction are also being used to separate the material from the host microbes. The company has scaled its process up to 4,5 kg/batch, and plans to start a pilot plant, producing 45 to 450 kg/batch over the next three to five years. Taking a completely different approach to developing spider silk is Nexia Biotechnologies of Montreal Canada, which is growing the material in genetically engineered goats, which produce the silk in their milk.

However, spider silk is still far from commercial. Early this year, a biopolymer entered the commercial plastics arena. Developed using Natureworks, a process developed by joint venture partners, Cargill, Inc. (Minnetonka, Minn) and Dow, the process makes plastic from the dextrose produced by corn, wheat, sugar beets and other biomass. The plastic's properties are said to rival, or even surpass, those of hydrocarbon–derived polymers in packaging and fabrics. So far, they have attracted customers including the packaging companies Bimo Italia SpA, Germany's Autobar Group Ltd and Hoechst Trespaphan GmbH, Austria's Flexpack Europe B.V., Unifi, and Canada's Cascades, Inc.

Enabling the breakthrough was a proprietary distillation process, combined with a fermentation technique developed by CSM N.V.'s (Amsterdam) Purac division. Dow and Cargill will bring a plant onstream in Blair, Nebraska next year to process 1,4 mio L/d of corn into 136 mio kg/yr of polymer; a plant will be built in Europe by 2003, and the company plans to add new facilities at economically favorable locations around the

world, using indigenous feedstocks, every 18 to 24 months or so. The process offers environmental benefits, requiring between 30 and 50% less fossil fuels than conventional plastics processes; in addition, it should provide an attractive outlet for farmers, the company believes.

Biotechnology in Agriculture

Farmers in some parts of the world have embraced the use of biotechnology in agriculture, buying genetically modified, or "transgenic" seeds. Proponents see biotechnology further enhancing developments such as cross breeding that have boosted crop yields. According to BIO, the U.S. farmer can now feed 129 people, compared with 19 in 1940. As the world's population grows, genetic modifications to improve nutritional content, such as the "golden rice" developed by Swiss and German researchers last year, promise to help alleviate malnutrition.

Yet, agricultural applications for biotechnology are becoming more unpopular, and an obstacle to friendly trade. At the World Trade Organization meeting in Seattle last November, protests against genetically modified foods made the front covers of the world's newspapers; the public in the U.K. is increasingly skeptical of "Frankenfoods," and the European Union and nations such as Brazil, are becoming more reluctant to embrace agricultural biotechnology , particularly transgenic seeds.

In the U.S., agricultural biotechnology markets are further developed. In 1997, agricultural biotechnology products accounted for $875 million, roughly half of that for transgenic seeds, according to the market consulting firm, The Freedonia Group (Cleveland, Ohio), which expects 27%/yr growth for the next few years. By 2002, Freedonia analysts predict, U.S. sales should near $2.9 billion, with seeds accounting for $2 billion of that total. Yet, even in the U.S., public criticism is increasing. A study published in Nature magazine last Spring, which found that pest–resistant corn containing genes from the bacterium Bacillus thuringiensis may kill monarch butterflies, had a negative impact. Developers of B.t. corn are working to minimize environmental impact, but, even though the study's findings were later criticized and disputed, controversy over genetically modified foods has intensified.

In Europe, Greenpeace International has spearheaded efforts to slow the acceptance of genetically modified food. Last year, leading supermarket chains in the U.K., France, Ireland, Switzerland, Belgium, Austria and Italy formed a consortium that has agreed not to sell genetically engineered products. The European Union has reportedly blocked authorization of new genetically modified foods until around 2002. In Brazil, the national environmental protection agency and the soybean–growing state of Rio Grande del Sul sued Monsanto over approval of its genetically modified soybeans; the nation has also halted acceptance of transgenic crops.

One major issue is labeling. Consumer groups are calling for the mandatory labeling of genetically modified foods. U.S. producers, whose crops have already been reviewed by the FDA, feel this is unnecessary.

Another issue is patenting and market rights. "The aggressive pursuit of patents on varieties containing traits of special national importance, like basmati or jasmine, generates fear and animosity and is seen to threaten foreign exchange earnings by countries such as Thailand and Pakistan," says Gordon Conway of the Rockefeller Foundation in New York. He advocates that companies adapt a "plant variety protection" system with public breeding agencies in developing countries.

In Japan, the issue of market control has reportedly moved Japan's Agriculture Ministry to accelerate development of the nation's first genetically modified rice, which it intends to register this year. Observers say the impetus is to block foreign ventures from gaining the upper hand in a vital national market. Currently, the Japanese are against use of biotechnology in food. A survey of 600 consumers last November found 83% of them unwilling to buy genetically modified foods.

Scientists affirm safety of biotechnology

Leading scientists in the field of biotechnology, including James Watson, the "father" of the field, who helped unveil the structure of DNA, issued public statements early this year, affirming the safety of biotechnology, and groups such as BIO, in the U.S., are sending this message to legislators and the public. Companies are also taking a closer look at possible negative impacts of genetically modified organisms in agriculture, in particular, the impact on other species of plants, as well as on non–target insects, and taking steps to prevent impact.

As powerful new drugs and environmentally benign processes and products move from the drawing board to the market, the financial community is becoming more convinced of the need for biotechnology. The next step will be convincing the public at large. By improving communication, stressing the benefits that the technology allows, and addressing risks and ensuring their minimization, biotechnology companies hope to surmount this obstacle.

According to the press informations
Prepared by DECHEMA e.V.
Dejan U. Skala Editor–in–Chief