



## ACHEMA 2003 19 – 24 May 2003 Frankfurt am Main/Germany

*The opening ceremony of the 27th ACHEMA will be performed in the Congress Center at the Frankfurt Exhibitions Grounds. From Monday, May 19 2003 the gates to the world's biggest chemical engineering Exhibition / Congress and International Meeting on Chemical Engineering Environmental Protection and Biotechnology will be opened to the public for 6 days.*

*The special technical and trend reports of ACHEMA 2003 exhibition were prepared for publication and released by internet as press information by authorities from DECHEMA. In this issue of Hemijska industrija (Chemical Industry Journal) trends covering Supercritical Fluids, Pharmaceutical Engineering and Biotechnology and Bioprocessing are presented. Other trends reports are preparing to be published successfully in the next several issues of this journal in 2003.*

### SUPERCRITICAL FLUIDS – GREEN AND EFFECTIV

Supercritical fluids are increasingly finding application in the process industries, not only in extraction processes, but also as environmentally friendly solvents in synthesis techniques or in environmental technology. Numerous exhibitors will present new processes and trends at ACHEMA 2003 from 19 – 24 May 2003 in Frankfurt/Main.

A supercritical fluid is a substance which, when subjected to particular set of pressures and temperatures, exhibits a specific set of characteristics. Within these critical temperature and critical pressure zones, the distinction between the gaseous and liquid phases disappear, and the substance can only be described as a fluid with a unique – and often desirable – set of properties and characteristics related to compressibility, homogeneity, and solvency. These supercritical properties are characteristic of the critical pressure and temperature conditions inside the supercritical fluid region. In many cases, a relatively common substance, such as carbon dioxide, in its supercritical state, offers distinct advantages for some chemical process operations.

Carbon dioxide is widely used to produce supercritical CO<sub>2</sub>, thanks to its convenient critical temperature, its relatively low cost, chemical stability, non-flammability, and its non-toxicity. As a supercritical fluid, CO<sub>2</sub> is being increasingly applied as an environmentally friendly substitute for many organic solvents, thereby reducing atmospheric pollution and eliminating solvent residues in products. Used as a supercritical fluid, carbon dioxide is expected to eliminate some of the economic and environmental burden associated with the current global use of more 30 billion pounds/year of halogenated and other organic solvents.

In addition to replacing some of the solvents used today, supercritical fluid carbon dioxide (SFCO<sub>2</sub>) may reduce the demand for water used in chemical process applications, and the accompanying costs associated with wastewater treatment. By some estimates, the global semiconductor industry alone could save about

40 billion gallons of water per year by using SFCO<sub>2</sub> instead of water for various wet-processing operations.

Near-critical and supercritical CO<sub>2</sub> are already used for extraction and purification of many synthetic and natural substances. For instance, commercial-scale plants have been scaled up for the extraction and purification of caffeine from coffee and tea, as well as the extraction of biological products from herbs, spices and vegetables. For such applications, liquid CO<sub>2</sub> is compressed and heated before being transferred to a vessel for extraction. Solute-laden CO<sub>2</sub> is then fed into a separator, where the pressure and temperature are adjusted to reduce the dissolving power of the CO<sub>2</sub>, causing the extracts to be precipitated. Pressure adjustments can occur in several stages, allowing different extracts to be isolated. Low-density CO<sub>2</sub> is then fed to a refrigerated condenser and collected as a liquid.

### Simpler synthesis

Some traditional chemical reactions are also good candidates for SFCO<sub>2</sub>. Hydrogenation, for example, is ideal because hydrogen, which dissolves with difficulty in other solvents, dissolves much more readily in CO<sub>2</sub>. In February 2002, Thomas Swan & Co. (Consett, U.K.) started up a 1,000-m.t./year multipurpose plant that uses SFCO<sub>2</sub> as a solvent hydrogenation, as well as Friedel-Crafts alkylations and acylations, hydroformylations and etherification. The Swan-SCF process exhibits 100% and 100% conversion in a large number of reactions in a single pass. Initial production is trimethyl-cyclohexanone (TMCH), an acetone derivative used in styrene products.

The plant carries out continuous hydrogenation using a heterogenous Deloxan-type catalyst (Deloxan is a Degussa AG product) in SFCO<sub>2</sub> over supported platinum or palladium. Unlike conventional hydrogenation plants, which use volatile organic solvents that must be separated from products by distillation, the Swan plant removes CO<sub>2</sub> as a gas for recycle, simply by reducing its pressure to drive the supercritical CO<sub>2</sub> back to its gaseous phase.

Swan's process is based on research that the company initially sponsored at the University of Nottingham (U.K.). In 1995, chemistry professor Martyn Poliakoff first performed hydrogenation using SFCO<sub>2</sub> in a continuous flow system. This and other latest applications of supercritical CO<sub>2</sub> in chemical synthesis were presented at the International Conference "Green Solvents for Catalysis", organized by DECHEMA Society for Chemical Engineering and Biotechnology in Bruchsal/Germany in October 2003.

### Polymerization

Because CO<sub>2</sub> cannot be oxidized using conventional chemical means – it is already the product of complete combustion – it is completely nonflammable. This property instills a tremendous advantage for some traditionally hazardous chemical processes and reactions. For example, fluorinated vinyl monomers, such as tetrafluoroethylene (TFE), are rendered nonexplosive when mixed with CO<sub>2</sub>. In addition, highly reactive, free-radical polymerization of these monomers can be carried out directly in a SFCO<sub>2</sub> continuous phase reactor.

Expanding on this potential, DuPont Fluoroproducts (March 2002) commercialized Teflon polytetrafluoroethylene (PTFE) resins made from a polymerization process that uses SFCO<sub>2</sub> as the reaction media. Developed jointly by DuPont and scientists at the University of North Carolina, the technology eliminates the energy-intensive drying that is typically required when water is used to process PTFE and other polymers, such as polyvinyl chloride, polyvinylidene fluoride and polyacrylic acid. Called Process G, the new process is being used initially to make select melt-processible products for applications such as wire and cable insulation and jackets, flexible tubing, and industrial films. The process can also be used to make other melt-processible fluoropolymers for applications, such as high-purity fluid-handling systems.

### Microelectronics manufacturing

Of the 400–500 steps involved in typical semiconductor fabrication, about one third are related to cleaning and purification. As an alternative to the ultrapure water that is traditionally used, SFCO<sub>2</sub> offers an effective substitute that can be made readily available at the high purity levels that chipmaking operations require, says Joseph DeSimone, a chemistry and chemical engineering professor at the University of North Carolina. DeSimone, who directs the National Science Foundation's Science & Technology Center for Environmentally Responsible Solvents and Processes, is at the forefront of SFCO<sub>2</sub> technology. He says that other applications for SFCO<sub>2</sub> are emerging, including photolithography, where basic silicon wafers are transformed into integrated circuits (ICs), by the application of thin-film photoresists and other features.

SFCO<sub>2</sub> is a good solvent to use for the removal of various coating materials that are used in this process. Micell Technologies and SC Fluids, Inc. are among the

companies that are developing systems that use supercritical CO<sub>2</sub> to remove photoresist masks and to clean semiconductors during chipmaking operations. The technology is poised to make significant inroads over the next two to three years, as chip fabricators focus on producing integrated circuits (ICs) with line widths of 130 nanometers (nm) or less.

Most technologies used for the removal of photoresist masks use chemical solvents that have to be rinsed away with deionized water, and subsequently dried with isopropyl alcohol. At 130 nm, it will be difficult to get either chemicals or water into tiny crevices. By comparison, supercritical CO<sub>2</sub> has zero surface tension, so no feature size is too small for it to wet effectively.

### Waste remediation

SCFs are also proving effective for the remediation of different types of wastes. In nuclear waste remediation, for example, the use of SCFs "breaks the paradigm of using large volumes of water," says Robert Fox, a chemist for the Idaho National Engineering and Environmental Laboratory. At INEEL, which is operated by the U.S. Dept. of Energy, SCFs have been used successfully to remove organic contaminants from soil since the early 1990s. Several years ago, INEEL began investigating SCFs for the removal of radioactive metals, and continues to investigate this option through research that is sponsored by British Nuclear Fuels Group, an Idaho Falls-based unit of British Nuclear Fuels Ltd.

In the process, CO<sub>2</sub> and an added metal binder are mixed with soil that contains radioactive plutonium and americium, and then the entire mixture is heated and pressurized. As the supercritical CO<sub>2</sub> and metal binder passed through the soil, the highly solvent chemical agents capture the contaminants. As the CO<sub>2</sub> passes out of the soil, it is depressurized, and its radioactive load is captured in a vial before the CO<sub>2</sub> is returned to the atmosphere. The current state-of-the-art is about 83% removal of plutonium and about 95% of americium, says Robert Holmes, chief scientist for British Nuclear Fuels Group. In an industrial-scale setting, the CO<sub>2</sub> would be recycled. Efficiency can be improved, he says, by adding ethanol and different chemical agents, and further work on this continues.

The process is said to be as good or better than conventional processes for removing nuclear waste because it is not as harsh. For example, absorption using concentrated nitric acid (a conventional approach) dissolves about 25% of the soil. By comparison, supercritical CO<sub>2</sub> does not denature or destroy soil mass.

At the Japan Atomic Energy Research Inst., scientists have developed a method called Supercritical CO<sub>2</sub> Fluid Leaching (SFL) for removal and recovery of uranium from solid wastes. In experiments, sand containing 0.2 to 0.4 wt.% uranium is treated at temperatures of 40–60C and pressures of 100–200 bars. Uranium is removed to 0.01–0.001% of the original amount, and is then isolated and collected by evaporating the CO<sub>2</sub> under ambient temperature and pressure.

Meanwhile, a considerable investment is being made in developing processes that employ supercritical water for oxidizing waste and for generating power. In January, Chematur Engineering AB secured the first customer for its Aqua Critox process. Similarly, Johnson Matthey will use the supercritical water oxidation (SCWO) technology to recover platinum group metals from spent catalysts.

In tests sponsored by BOC (London) and six U.K. water suppliers, the feasibility of the Chematur's Aqua Critox process for destroying municipal sludge was tested over a 30-hour period in a pilot plant at Karlskoga Sweden. The plant was operated at a temperature of 570°C, pressures of 23.3 MPa and a flowrate of 230 kg/hour. The Aqua Critox was able to oxidize both raw and digested sewage sludges into three clean effluent streams – a gas phase consisting primarily of CO<sub>2</sub> and O<sub>2</sub>; an inert, inorganic solids fraction containing mainly Fe<sub>2</sub>O<sub>3</sub>, SiO<sub>2</sub>, P<sub>2</sub>O<sub>5</sub> and Al<sub>2</sub>O<sub>3</sub>; and a liquid phase containing low concentrations of NH<sub>4</sub><sup>+</sup> and some trace levels of low-molecular-weight volatile fatty acids, such as acetic acid.

Chematur and Johnson Matthey are collaborating in the development of a new technology based on Aqua Critox. Called AquaCat, the new process destroys practically all of the organic or carbonaceous components in spent catalysts, leaving a clean water stream with COD levels of less than 20 ppm. The precious metals in the spent catalysts are collected as an oxide that is free of organics and ready for chemical refining. The technology is said to be applicable for the treatment and recycling of chemical wastes, industrial sludge and municipal wastewater.

### Power generation

Once-through utility (OTU) supercritical boilers are already widely used in Europe and Japan, and Foster Wheeler Power Group, Inc. expects them to make a comeback in the U.S. for power generation based on coal combustion. Unlike drum-type boilers, OTU boilers do not rely on the density difference between steam and water to provide proper circulation and cooling of furnace enclosure tubes. As a result, these boilers can be operated at supercritical pressures (above 220 bars), says Steve Goidich, lead performance engineer, for Foster Wheeler. Current state-of-the-art steam conditions for OTU boilers are about 300<sup>o</sup>bars and 600°C, which provides about a three-percentage-point improvement in plant efficiency over drum-type boilers. The target for future development is to push steam conditions up to 350<sup>o</sup>bars and 700°C to further improve efficiency.

### Dry cleaning with near-critical CO<sub>2</sub>

Restrictions on emissions and exposure limits for perchloroethylene – a widely used solvent for dry cleaning garments – have spurred development of alternative dry-cleaning technologies based on the more environmentally friendly supercritical CO<sub>2</sub>. ICI and Linde Gas Group have jointly developed a new cleaning fluid,

called Washpoint, that combines CO<sub>2</sub> and a cleaning booster. The companies say recent advances in dry cleaning machine technology make it possible to use CO<sub>2</sub> under sufficient pressure to turn it into a fluid with good solvent properties.

Similarly, in the late 1990s, the University of North Carolina and Pacific Northwest National Laboratory developed a CO<sub>2</sub>-based dry-cleaning system, called Hangers, that is now marketed by Cool Clean Technologies. The Washpoint fluid developed by ICI and Linde is said to be compatible with the commercially available Hangers system.

## PHARMACEUTICAL ENGINEERING

*Budget reductions are affecting medical insurance organizations, and limited financial resources are placing constraints on ongoing operations and investment in new facilities in the pharmaceutical industry. To survive as a supplier to the pharmaceutical industry, a company must deliver high quality, but it must also keep a close watch on costs. Systems and equipment are used in a much more flexible manner today, and as a result the need for creativity during the development and design of pharmaceutical components is greater than ever.*

There are conflicting developments evident in the pharmaceutical industry. Business prospects are excellent. Life expectancy is rising, and older people need more medication to treat ailments such as Alzheimer's Disease and depression. The younger generation is also turning to new products, and there is strong demand for nutraceuticals in particular. Rising levels of affluence in Asia and South America are creating new markets for pharmaceutical companies. New active ingredients are raising the hopes of patients and pharmaceutical companies alike. However, funding in the government sector and in health insurance organizations worldwide is subject to increasing constraints. Not every medication is eligible for reimbursement, or there may be a requirement to prescribe only generics. Patent protection will soon expire for many blockbusters. This has all resulted in lower turnover for large pharmaceutical companies. Not only that, research on new active ingredients and medicines is becoming more difficult and costly. Increased expenditure and new gene technology projects have not increased the number of new active ingredients as much as the industry had hoped.

The German Association of Research-Based Pharmaceutical Companies (VFA) has reported that the number of new approvals in 2000 and 2001 was at the lowest level in ten years. This was the case despite the fact that the pharmaceutical industry is one of the most research-intensive industries. At 11.9 percent of turnover, R&D expenditure in the industry was nearly twice that of the electrical, chemical and automotive industries. Research in the pharmaceutical industry remains concentrated in the US and Europe. There has recently been a noticeable increase in research expenditure in the UK, while Germany is now in third place behind

France. Five years ago, Germany was number one in terms of R&D expenditure.

A geographical shift is taking place. It had been evident for some time that Europe is no longer the world's largest producer of medicines. It has lost its leadership position to the US. Information provided by the VFA indicates that the value of US production in 2000 was 121.3 billion euros compared to 112.4 billion euros for Europe. Although Germany, along with France and the UK, is still one of the largest producers of medicines in Europe, it has lost its position at the top. The number of new approvals of active ingredients reflects this trend. European countries were the leaders in new approvals until 1997, but since 1998 the US has accounted for 40 percent of new approvals. Europe lags significantly behind at 30 percent, followed by Japan at 20 percent. Only three active ingredients were approved in Germany in 2000.

### **The need for flexibility**

System and equipment producers are feeling the direct effects of these trends. As competitive and cost pressures increase on the international stage, pharmaceutical companies need to react faster and with greater flexibility to customer preferences. There is a need to manage smaller, more varied production quantities. Niche markets must be catered to. To reduce cost, many pharmaceutical producers are consolidating their production operations, producing medicines for different countries at one location. The presentation and size of the products and of the packaging varies, and lot sizes are becoming smaller. In parallel with these developments, the volume of custom business is rising. Machines must be used very efficiently to justify costly investment in new technology. Even pharmaceutical companies that in the past only produced their own medicines are now accepting contract work to achieve full machine utilization.

System and equipment producers must provide systems that offer absolute flexibility. It is no surprise that multi-product systems are now the solution of choice. However, designing these systems requires not only industry knowledge and experience, but also a much deeper process understanding, because many technical details have to be considered during the planning stage. Only high-grade materials are suitable for use in multi-product systems, because the system must be able to handle the entire spectrum of substances used in the industry. System manufacturers use standard connections, for example on pipelines and fixtures, so that these units can be replaced quickly. It is up to the specialists to determine whether or not automation can be used in these systems.

### **Sterile right from the start**

Regardless of whether a multi-product system or a standard system is used, sterile production is the most important requirement in medicine manufacturing. A number of aspects must be considered in order to

achieve a sterile production environment. The process of finding a solution begins with a well thought-out system concept, which handles pharmaceuticals and their ingredients flow, and it carries through to design of semi-aseptic equipment and a sophisticated cleaning process. A semi-aseptic environment at the beginning of the production process helps reduce sterilization times, and it contributes to more effective disinfection. However, special design features must be implemented to achieve a semi-aseptic environment.

To start with, the right materials and surface finish must be selected. Cr-Ni-Mo 1.4404/1.4435 (316L) stainless steel is normally used. However, even higher-grade materials (for example Hastelloy) are needed for certain media. When the manufacturing process has finished, surfaces that come into contact with the product are mechanically ground and polished and subjected to electro-chemical treatment as required by surface standards, which apply to defined sterility categories. Smooth surfaces reduce the adhesion of product residue and the build-up of coatings, thus enhancing cleaning effectiveness.

Membranes, bellows and seals used in these applications must be made using FDA approved materials. Seals present a particularly difficult problem. For one thing, seal materials are exposed to process conditions that are anything but straightforward. High temperature and pressure levels as well as aggressive cleaning agents and disinfectant solutions rule out all but a few materials. For another thing, many grades of elastomer cannot be used for toxicological reasons. The risk is too great that these materials will interact with process media and release impurities. Despite the difficulties involved, seals have been developed in recent years that can be used in these demanding environments. There will be ample opportunity at ACHEMA 2003 to talk with leading seal manufacturers.

A completely non-technical aspect has moved to the forefront in the development and design of new systems in recent years, namely validation. Costs solely related to documenting and preparing the system for validation now represent 10 to 15 percent of overall costs. Validation is normally performed by the operator, but the manufacturer cannot avoid a qualification process. Operators expect that a certain degree of preparatory work will have been completed. For the equipment manufacturer, this means building up know-how and staying informed about new laws issued by Japanese, European and US authorities. The exhibition and conference at this year's ACHEMA will once again offer the opportunity to keep up with unfolding events.

### **Segregation by system**

The zone concept is now commonly used throughout the production area. Different cleanroom classes are used to address different tasks. These areas are strictly separated into non-production space, production zones and specially controlled areas that contain operations such as packaging lines.

Gravity is used in today's production environments to drive material flows. This requires a fair degree of technical creativity on the part of equipment producers, particularly when modular systems are used for raw material supply. It is important that filling units, which can accommodate big bags, containers, sacks or drums, can be changed quickly without generating much dust. The same applies to discharging, and removal units must also fit into the low-dust concept. Even if totally automated material flow remains wishful thinking at many companies that have too many manual operations, equipment producers are already in a position to offer attractive material transport concepts, and some of these concepts will be presented at ACHEMA. They facilitate production automation for at least some products.

There is a general tendency to strictly separate technical infrastructure and products. Modern pharmaceutical facilities usually have a line where sterile production is performed, plus additional passageways where activities such as maintenance of non-sterile air-conditioning systems or other equipment can be performed. A number of equipment manufacturers, including producers of coaters and pill presses, have designed a separate unit to house motors, drive units and other technical equipment. This cabinet can be fitted into a wall to facilitate maintenance from the non-sterile side.

The dosage contained in modern pharmaceutical products today is normally significantly smaller than in older versions. Nevertheless, most medicines are now more effective. Handling these substances has become much more hazardous both for employees and for the environment. This is particularly true for toxic active ingredients, for example most cancer treatment agents. In order to protect personnel and the environment from these products, production methods must be introduced that strictly separate the substance from humans. Isolator technology is an adequate solution. However, the impression often arises that an isolator provides the answer to all aseptic problems, but this is only the case in some very specific situations. For one thing, handling is more cumbersome than in a traditional production environment. Also, the cost of an isolator can quickly overload the budget. Difficulties arise when product protection is counterproductive from the standpoint of GMP requirements.

The design of an isolator in general is quite elaborate, making it very inflexible. As manual intervention becomes more complicated, difficulties increase. The operator should also be aware of the fact that this technology almost always involves an insular solution, which contains very few standardized elements. Nevertheless, there are many cases where an isolator is indispensable. Precise harmonization between the isolator and the machine is critical for achieving reliable protection. Many equipment producers, including manufacturers of filling machines, will display their design at ACHEMA in Frankfurt including machines equipped with an isolator.

### **Cleaning validation remains difficult**

In regard to all of these items, there is one aspect that will have to be given even greater consideration in the future, namely the development of a cleaning process. Up to 20 percent of the current GMP violations and warning letters are related to this problem. Fluid, solid or viscous materials and even toxic product remnants often adhere to pill press tools, containers and laboratory devices. There must be a cleaning process, which removes these remnants without leaving any cleaning agent residue. Cross-contamination must be avoided at all costs, and there should be no particles introduced with dry air.

The process of cleaning equipment, pipelines and systems is a time- and cost-intensive operation. Fast, effective cleaning methods that do not tie down qualified personnel significantly increase efficiency. Validation actually represents more of a problem than cleaning. For this reason alone, the cleaning characteristics and specific design of cleaning equipment should ideally be discussed between the supplier, cleaning agent supplier and pharmaceutical manufacturer during acquisition of a production system.

### **Electronic documentation is not keeping up with legislation**

Few laws in recent years have made as much of a stir as 21 CFR Part 11. The law was created to place electronically managed quality-relevant records on equal footing with paper-based documentation. The problem is that there is now a much wider spectrum of systems and equipment that comes into the realm of computer validation. Affected items include laboratory devices, production equipment, autoclaves, chromatographs, process control systems and even AutoCAD drawings that contain product specifications. Introduction of electronic signatures led to even more stringent requirements.

Suppliers have gone down different paths in implementing this law. Some offer devices that conform to Part 11 or at least contain partial implementations of the technical requirements. Others are taking a wait-and-see attitude and are waiting for demand to come from pharmaceutical customers, but it is then usually too late to make significant changes. Here again, ACHEMA will offer ample opportunity to discuss the issue with manufacturers and to ascertain whether the new guidelines have been implemented to a sufficient degree.

There is now also a need for maximum creativity in the pharmaceutical packaging sector, which is essentially the last link in the chain. General trends include smaller runs, increased child safety features, low cost packaging materials, a highly efficient packaging process and increased machine flexibility. To create a common denominator which encompasses all of these characteristics is anything but easy. It has become increasingly common for packaging material producers, machine manufacturers and pharmaceutical companies to work closely together. The result is often not only safe

packaging, but sometimes also points the way to an innovative delivery system.

During the last ten years, work on new drug delivery systems has been more intensive than ever before. Development of an active ingredient is one thing, but getting it to the right place in the body is quite another matter. Many active ingredients are either relatively insoluble, have insufficient concentration or are adsorbed in the stomach. In some cases, legislators are pressing for new delivery systems. The banning of CFCs has expedited the development of dosing aerosols. Needleless injection systems, micro encapsulation, nanotaxis, transdermal bandages or new types of inhalers for respiratory disease are only a few of the areas where doctors, process engineers and the packaging industry are developing new ideas. ACHEMA will offer considerable stimulus to all those who are involved in these technologies.

## BIOTECHNOLOGY AND BIOPROCESSING

*Biotechnology-based processes typically use renewable feedstocks (such as corn, soybeans and alfalfa plants) instead of petroleum-derived feedstocks, and processes that rely on the natural metabolic activity of living organisms, to synthesize complicated molecules, such as chemicals, pharmaceuticals, plastics and cleaner-burning "biofuels." Compared to conventional, petroleum-based production routes, such biotechnology-based processes can often be carried out under less-extreme process conditions, and they often have reduced environmental impact, and lower capital and operating costs, as well. Meanwhile, additional research and development efforts are being used to develop and commercialize biocatalytic processes in which various natural enzymes are used instead of traditional metal catalysts during the production of pharmaceuticals and industrial chemicals.*

*Biotechnology and biotechnological equipment are ranked among the cornerstones of the ACHEMA. In 2003, for the first time the ACHEMA will be complemented by a world-class Biotechnology Conference.*

While biotechnology-based routes are often attractive from the standpoint of favorable operating conditions and reduced environmental hazards, the operation of biotechnology-based processes on a commercial scale poses unique technical and regulatory challenges, particularly as such processes are scaled up from pilot- and batch-scale demonstration units, to commercial-scale production. Despite the engineering challenges associated with these systems, biotechnology-based routes have a bright future throughout the chemical process industries, and the engineering community is avidly pursuing them.

### Engineering chemicals from crops

In recent years, the chemical process industries (CPI) have made substantial investments in the development of production routes that convert renewable plants and crops into chemicals and fuels, to reduce depend-

ence on petroleum-derived feedstocks, improve the safety and operating conditions of the process, produce more environmentally benign products, and reduce capital and operating costs.

In a biochemical process pioneered by DuPont Co., dextrose derived from wet-milled corn is the feedstock that is used to produce the monomer 1,3-propanediol (PDO). During the process, genetically engineered *Escherichia coli* bacteria metabolize the glucose and convert it to PDO.

The modified *E. coli* was developed by Genencor International, and it is said to have a 500-fold increase in bioprocessing productivity, compared to the microorganisms whose genes were extracted and incorporated into the modified bacteria.

DuPont is also working with Diversa Corp. to develop enzymes for use in a range of biotechnology-based processes that are currently under development by DuPont.

Meanwhile, Cargill Dow LLC – a joint venture of Cargill, Inc. (Minnetonka, Minn.) and Dow Chemical Co. (Midland, Mich.) – recently started up a commercial-scale, 140,000-m.t./yr facility to produce the polymer polylactide (PLA) using a corn-based route. In the process, unrefined glucose from wet-milled corn (up to 40,000 bushels/day) is fermented to produce lactic acid, which is then condensed to lactide. This lactide is purified and polymerized using a standard transesterification catalyst, in a solvent-free melt process. The company says this PLA resin can be used in consumer goods, including plastic fibers, bottles and films.

In a related development, the University of Wisconsin has developed a corn-based process to produce propylene glycol. In the process, lactic acid fermented from corn-derived glucose is mixed with excess hydrogen and vaporized at 80–220°C. The mixture is then converted to propylene glycol over a silica-supported copper catalyst. To date, however, the process has only been demonstrated at a laboratory scale. According to the researchers, further developmental work is needed to reduce costs prior to scaleup.

By genetically manipulating the leaves of alfalfa plants, researchers at the U.S. Dept. of Agriculture's Plant Science Research Unit have been able to produce the plastic polyhydroxybutyrate, which could be used as a copolymer in consumer products and medical devices. The group has taken three genes from *Ralstonia*, a bacterium that produces plastic naturally, and incorporated them into the alfalfa plant's tissue. While this plastic can be produced directly from bacteria using fermentation, that route is very expensive. By comparison, the researchers say the modified-alfalfa process has cost advantages, because alfalfa is a high-yielding, perennial plant that is inexpensive to grow.

In the area of consumer products and biopharmaceuticals, High Plains Corp. (Wichita, Kan.; [www.highplainscorp.com](http://www.highplainscorp.com)) has developed a process whose main feedstock is dry-milled sorghum or corn, and the company is using this process to produce glycerol, an ingre-

dient that is widely used in cosmetics, pharmaceuticals and other products.

Dow Chemical Co. to develop pharmaceutical proteins for therapeutic applications using lower-cost, plant-based production routes, instead of the conventional (but more costly) mammalian-cell culture manufacturing process. Specifically, the two companies are working together to produce glycan protein structures using transgenic plants. Glycans are specific sugar units that are an integral part of many complex therapeutic proteins, such as several blood-clotting proteins and monoclonal antibody drugs that are already on the market today.

### Helping crops to protect themselves

In another lucrative application for biotechnology, scientists and engineers at such companies as BASF AG, Monsanto, DuPont, Syngenta and Bayer CropScience – which recently acquired Aventis CropScience – continue to develop genetically engineered pesticides, fungicides and herbicides. By isolating certain genes from bacteria and expressing them directly in the plants themselves, such efforts give the plants greater resistance to insect damage. This reduces or eliminates the need for chemically derived pesticides that are dangerous to the environment, and known to cause cancer in humans.

### Biodiesel and ethanol

Another area of intense biotechnology activity is in the production of more environmentally friendly transportation fuels that are not derived from petroleum. These include ethanol, which is produced from corn and other grains, and biodiesel, which is produced from soybean and canola oil. Both of these plant-derived fuels perform comparably to conventional petroleum-derived fuels, such as gasoline and diesel, but produce significantly lower emissions.

### Biodiesel

Biodiesel is produced using transesterification. In this process, new or used vegetable oil (soybean oil is the most common), animal fat or grease is reacted with an alcohol, to produce chemical compounds known as fatty acid methyl esters. Glycerin, which is the main byproduct of biodiesel production, is removed, and this byproduct stream can often be sold for use in cosmetics and other consumer products.

Leading U.S. biodiesel producers include Biodiesel Industries, Griffin Industries, Stepan Co., World Energy Alternatives and Procter & Gamble Co.

Focusing on an interesting alternative to soybeans, the U.S. Dept. of Energy has developed a process to produce biodiesel fuel using spicy mustard seeds as the main feedstock. DOE feels that once this process is scaled up, it could add another 5–10 billion gallons to the current U.S. annual production of 1.9 billion gallons of biodiesel. Meanwhile, DOE notes that the byproduct

mustard meal (the seed that remains once the desired oil has been removed) has a potential market as a high-value pesticide, so its resale value is expected to help offset the anticipated commercial-scale costs associated with this new biodiesel fuel.

Part of the appeal of biodiesel is that it can be used on its own, or blended with petroleum diesel to create a biodiesel blend. Either way, biodiesel fuel can often be used as a direct substitute for petroleum-derived diesel fuel, since its use requires little or no modification of conventional compression-ignition engines. This allows operators of vehicles and fleets to switch to biodiesel and biodiesel blends without having to replace their vehicles, their spare-parts inventories, their refueling stations and their skilled mechanics.

In the U.S. alone, more than 200 commercial, vehicle fleets (including some operated by the U.S. Dept. of Energy, U.S. Dept. of Agriculture, and U.S. Postal Service, plus the school buses, garbage trucks, and public-utility vehicles used by many municipalities) already use biodiesel to meet strict emissions regulations.

The use of biodiesel in a conventional diesel engine results in substantial reduction of unburned hydrocarbons and nitrogen oxides (major smog-causing pollutants), and carbon monoxide and particulate matter, compared to emissions from diesel fuel. In addition, emissions of sulfur oxides and sulfates (major components in the production of acid rain) in biodiesel exhaust are essentially eliminated.

Notably, biodiesel emissions have significantly reduced levels of polycyclic aromatic hydrocarbons (PAH) and nitrated-PAH compounds (nPAH) – which have been identified as potential cancer-causing compounds – compared to traditional diesel fuel. Test results indicate PAH compounds are reduced by 75–85%, with the exception of benzo(a)anthracene, which is reduced by 50%. Certain nPAH compounds, such as 2-nitrofluorene and 1-nitropyrene, are reduced by 90%, and the rest of the nPAH compounds are reduced to trace residual levels.

Today, the main challenge facing large-scale production and commercial use of biodiesel are the production costs, which can be three times that of petroleum diesel. However, ongoing biotechnology research is underway to increase the oil content of canola and soybean crops.

Soybeans are the world's second-largest oil crop (surpassed only by palm oil), and the U.S. is currently the world's largest producer of soybeans (contributing 47% of the total global output). Other leading producers include Brazil, Argentina and China.

### Ethanol

Ethanol is also widely used as a clean-burning fuel and as an oxygenate additive in reformulated gasoline, and demand for this renewable fuel has grown significantly since the formerly dominant fuel oxygenate, methyl tert-butyl ether (MTBE), has fallen from grace. While adding MTBE to gasoline is widely recognized as

a way to reduce certain regulated air pollutants, the ether itself poses certain environmental hazards, particularly in terms of potential groundwater contamination, so in the U.S., many state regulatory agencies are phasing out MTBE use as an oxygenate additive in gasoline, or have banned its use altogether. This has created increased demand for ethanol as a more environmentally friendly alternative to MTBE.

In the U.S. alone, ethanol production in 2002 was expected to reach 2.2 billion gallons, up from 1.77 billion gallons in 2001, according to the Renewable Fuels Association. This steady growth in demand follows a 20% increase from 1999 to 2001. In the U.S. alone, six new ethanol plants came online in 2002, and more than a dozen more are under construction.

One drawback of ethanol is that unlike biodiesel, which can easily be used as a direct substitute for petroleum-derived diesel fuel in existing cars and trucks, ethanol is most often used as a relatively small part of an ethanol/gasoline blend (10 vol.% ethanol or less in the blend is the standard). Such blends can easily be used in existing autos and light trucks, but higher levels of ethanol would require engine modifications, and would not be compatible with the existing service-station infrastructure.

To boost ethanol yield from corn crops and bring down the associated production costs, researchers at companies such as Genencor International Inc., Novozymes Biotech, Inc. and Iogen Corp. are focusing their efforts in several areas:

- To develop corn crops that have a higher starch content
- To produce improved, genetically enhanced enzymes, yeasts and bacteria that can accelerate the fermentation process used to make ethanol
- To devise ways produce ethanol from virtually any type of plant, tree or agricultural wastes (for more information, refer to the Council for Biotechnology Information)

In another fuel-related biotechnology development, JGC Corp. has developed a biomass slurry fuel (BSF) that can be used as a boiler fuel. In the process, wood waste from eucalyptus trees is crushed to produce 0.3-mm chips, which are slurried in water. The slurry is processed in a hot-water drying reactor (an energy-efficient alternative to traditional evaporator drying units, says the company), under the subcritical conditions of 300°C and 120 bars for 30 minutes. The resulting deoxidized chips are then pulverized to 0.02-mm powder and a dispersant is added, to produce a biomass slurry fuel comprised of 70% powder and 30% water.

In bench-scale testing, JGC has converted eucalyptus chips into a BSF with a composition of 80% carbon, 14% oxygen and 6% hydrogen. This, notes the company, approaches the 83% carbon content of bituminous coal. The BSF has a calorific value of 5,000 Kcal/kg, and contains 0.01% sulfur and 0.2–1.0% ash. The company is currently building a 50–500-m.t./yr pilot plant for the process, and estimates that a 500,000-m.t./yr plant would be profitable.

## Biocatalysis using enzymes

The benefits of enzyme catalysis have been well-known for years. In many cases, naturally occurring enzymes outperform metal catalysts, both in their specificity and their environmental impact. However, for years, enzymes have been considered too fragile to work at the extreme temperatures, pressures and pH levels that are found in most industrial chemical processes.

However, in recent years, recombinant genetic-engineering techniques have helped process developers to overcome these limitations. For example, using so-called "bioprospecting" techniques, process developers have been able to identify and culture microbes that thrive under more-extreme process conditions. This continues to open up opportunities to use these hearty microbes for the production of pharmaceuticals and industrial chemicals.

According to the market-research firm Freedonia Group., U.S. demand for enzymes, primarily for pharmaceutical, industrial and biocatalysis use, will grow by 6.7%/yr through 2006, to reach a market value \$1.6 billion by then. In addition to Genencor and Novozymes mentioned above, other leading companies involved in enzyme-related research include Genentech, Genzyme, DSM, and Chr. Hansen A/S, Degussa AG, BASF Intermediates, Kyowa Hakko Kogyo Co. and Hayashibara Biochemical Laboratories.

## Challenges during scaleup and commercialization

Among the challenges faced by process developers is the fact that the naturally occurring metabolic reactions that take place inside a bioreactor vessel rarely occur under steady-state conditions; and, the environmental conditions within the reactor are constantly changing during metabolic processes. The difficulty of scaling up new biopharmaceuticals and other biologically derived products is most apparent during the cell-culturing steps (when the compound is produced) and during separation and purification (when the cell-culture-based pharmaceuticals and fermentation-derived end product must be isolated from impurities and other compounds in the product stream).

Adding complexity to this process is the fact that facilities employing any biotechnology-based processes face rigorous government regulations. U.S. operators, for example, must comply with the "Current Good Manufacturing Practices (cGMP)" established by the U.S. Food and Drug Administration, and bioprocessing guidelines set by the American Society of Mechanical Engineers. Meanwhile, the International Standards Organization, and many country-specific regulatory bodies, also set guide.

ACHEMA 2003 from 19 – 24 May 2003 in Frankfurt am Main/Germany provides a unique opportunity to take part in an outstanding biotechnology event and simultaneously to make the best use of the synergistic effects of ACHEMA as the world forum of the process industries, in which biotechnology is fast gaining ground.