PROCESS TECHNOLOGY

Plasma Recycling Process Debuts

Alcoa's Brazilian affiliate Alcoa Aluminio S.A (www.alcoa.com.br) has joined Tetra Pak (www.tetrapak.com.br), Klabin (www.klabin.com.br) and TSL Engenharia Ambiental (Sao Paulo, Brazil; www.tslambiental.com.br) to inaugurate a carton-packaging recycling (CPR) facility in Piracicaba, Brazil, that, for the first time, enables the total separation of aluminum and plastic components from each other and from the cartons. The enabling technology is a plasma treatment process developed by TSL Engenharia Ambiental. "It constitutes a significant enhancement to the current CPR process, which, up until now, separated the paper, but kept plastic and aluminum together," says Franklin Feder, president of Alcoa Latin America.

During operation, electrical energy is used to produce a jet of plasma at 15,000°C, which heats the plastic and aluminum mixture. Plastic is transformed into paraffin and the aluminum is recovered in the form of high-purity ingot. Alcoa, which supplies thin-gauge aluminum foil to Tetra Pak for aseptic packaging, uses the recycled aluminum to manufacture new foils. The paraffin is sold to the Brazilian petrochemical industry.

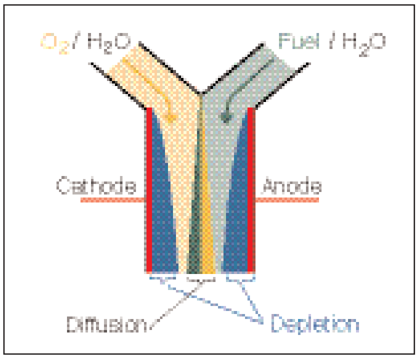
Paper that is extracted during the first phase of the recycling process is transformed into cardboard by Klabin. TSL Engenharia Ambiental is responsible for operating this new facility, which has the capacity to process 8,000 ton/yr of plastic and aluminum, corresponding to a recycle capacity of 32,000 ton/yr of aseptic packaging. Feder says that the emission of pollutants during material recovery is minimal and handled in the absence of oxygen without combustion, yielding an energy efficiency rate close to 90%.

Simplify Pharmaceutical Cleaning Validation

High-performance liquid chromatography (HPLC) or total organic carbon (TOC) are the traditional techniques used for cleaning validation in pharmaceutical manufacturing. However, both methodologies have substantial drawbacks. HPLC requires long setup and analysis times — often requiring one to two days of downtime before processing equipment can be certified for cleanliness. And while TOC offers faster processing times, clocking in at a quick three minutes per sample, the results they give back are non-specific, only indicating that a sample contains organic compounds. This could lead to a false positive and unnecessary cleaning.

Offering, speed, sensitivity and specificity is Smiths Detection's (Danbury, CT; www.smithsdetection.com) IONSCAN-LS, which uses ion mobility spectrometry (IMS) technology to quickly and simply detect low levels of organic compounds. "It is an accepted technology that is used in laptop swabs for explosives at airport security checkpoints, thus demonstrating its high-speed, accurate capabilities under some of the most challenging environmental operating conditions," says John Carroll, applications chemist at Smiths Detection. Compared to the traditional HPLC equipment, the IONSCAN-LS dramatically drops setup and analysis times, so that running a set of samples that may take more than a day using HPLC can be completed in just a few hours. It also overcomes the shortcomings of TOC testing by identifying the exact organic compound in ppm to ppb levels. "IMS technology is also economical. It costs just pennies per sample to analyze," says Carroll.

Smiths Detection, working in conjunction with the Dober Group (Midlothian, IL; www.dober-group.com), have developed IMS methods for Dober's Chematic pharmaceutical detergents. "Cleaning verification methods are generally based on the detergent component that is the most difficult to rinse or the 'last to leave'," notes Rebecca Brewer, director at the Dober Group. In this particular instance, surfactants, which make up about 0.5–10% of the detergent formulation, are the "last to leave." The surfactants are often mixtures of oligomers of different chain lengths. With IMS, they can be quantified and specified to very low levels, since they yield peaks in an IMS plasmagram.



In this fuel cell system, the fuel and oxidant are brought together as liquid streams in a microchannel, where they merge and flow laminarly between the catalyst-covered electrodes without mixing. The protons and electrons diffuse through the liquid-liquid interface.

Fuel Cell Takes a Microfluidic Route to Reducing Operating Costs

Researchers at the Univ. of Illinois (UIUC; Urbana-Champaign; www.uiuc.edu), working with INI Power Systems, Inc. (Cary, NC; www.inipowersystems.com), have designed a microfluidic fuel cell that operates without a solid membrane to separate the fuel from the oxidant (Figure, left). "Eliminating the membrane will not only reduce fuel-cell costs — typically the membrane accounts for 20–30% of the overall cost — but makes it possible for the fuel cell to operate with either alkaline or acidic chemistry," says Paul Kenis, professor of chemical and biomolecular engineering and project leader.

The microfluidic cell consists of a Y-shaped channel (1 mm high × 1 mm wide) in which two liquid streams containing fuel (1 M methanol or formic acid) and oxidant (1 M KOH or H_2SO_4 saturated with O_2) are merged, without mixing, into the 3-cm-long stem. Because of the microscale dimensions involved, the two fluids flow under laminar conditions, and thus remain separated. The redox reactions occur at the opposing walls of the stem, which are coated with catalyst-doped electrodes. For

Scalable Dendrimer-Based Platform Debuts

Dendrimers are sphere-shaped nanostructures that can be engineered to carry molecules (which add functionality or reactivity) by either encapsulating the compound in an interior cavity or by attaching it to a surface. The size and shape of the dendrimer is determined by the spherical shells, called generations, that possess these reactivities and are grown around the unit's core. To date, manufacturing methods have required dendrimers to reach a certain generation before other functions can be added to them. Dendritic NanoTechnologies, Inc. (DNT; Mount Pleasant, MI; www.dnanotech.com) has commercialized a family of dendrimer nanostructures that, for the first time, can be scaled in terms of function/reactivity. Designated Priostar Generation 3, they significantly improve upon the original PAMAM dendrimers that were invented 25 years ago by DNT president and chief technology officer Donald Tomalia while he was at The Dow Chemical Co. (Midland, MI; www.dow.com). Further, they can be manufactured in high volumes at costs that are 2–3 orders of magnitude lower than their PAMAM Generation 3 counterparts.

The PAMAM Generation 3 dendrimers are created in 8 steps and take 1 month of processing time. "In contrast, Priostar Generation 3 dendrimers require 3 steps and a few days, thanks to the use of faster, kinetically driven chemistry, combined with the use of polyfunctional branch-cell reagents to rapidly and precisely build dendrimer structures in a controlled way, generation by generation," says Tomalia. A unique aspect of production is the amplification procedure. Priostar dendrimers' surface groups increase by a factor of 3 for each succeeding generation (e.g., G1 = 12 surface groups, G2 = 36 surface groups, G3 = 108 surface groups). The PAMAM surface groups only increase by a factor of 2 for each succeeding generation (e.g., G1 = 8 surface groups, G2 = 16 surface groups, etc.). "This allows rapid building of surface functionality and molecular weight, therefore obtaining container properties in fewer generations than for PAMAM," notes Tomalia. The methodology also requires lower levels of dilution, thereby offering a higher-capacity method that is more easily scaled to commercial dimensions.

Another interesting characteristic of Priostar the introduction and control of six critical nanostructure design parameters that may be used to engineer over 50,000 different major variations of sizes, compositions, surface functionalities and interior nanocontainer spaces that are expected to offer novel properties for use in a wide variety of commercial applications, including drug delivery, sensors, catalysts, surfactants and medical imaging. These dendrimers also are more thermally stable (approximately 350°C for Priostar versus 130°C for PAMAM). Initially, Priostar dendrimers will not be made available to the research community. However, DNT plans to establish a limited number of business partnerships for commercial research that could lead to direct commercialization.

acid (or alkaline) conditions, proton (or OH^-) exchange takes place via diffusion through the liquid-liquid interface.

Work continues at UIUC to improve the performance of the cell, and to also increase the power by connecting multiple cells into a stack. Depending on the performance of each cell, about 100–200 cells would be required to operate a laptop computer, says Kenis. Meanwhile, INI Power — a spin-off company formed by Larry Markoshi, the co-inventor of the Laminar Flow Fuel Cell — has exclusively licensed the technology from UIUC and is working to commercialize products by the end of 2006.

Turning a Hydrate Problem into a Self-Serving Solution

Natural gas hydrates — crystal structures in which methane molecules are trapped in a lattice containing more than 85% water — often form in oil and gas pipelines under conditions of medium-to-high pressure (> 500 psig) and low temperature (< 20°F), causing blockages and holding up production. Conventional treatment methods, including the use of methanol and glycol to shift the conditions at which hydrates are stable, and kinetic hydrate inhibitors have been met with limited success. Now, scientists at Heriot-Watt Univ.'s Centre for Gas Hydrate Research (CGHR; Edinburgh, U.K.; www.hw.ac.uk) under the leadership of Bahman Tohidi, director of the GHRC, are proposing a completely different approach. Instead of trying to prevent hydrate formation, they encourage their crystallization into specially designed hydrates that can be transported as a stable, smoothly-flowing slurry.

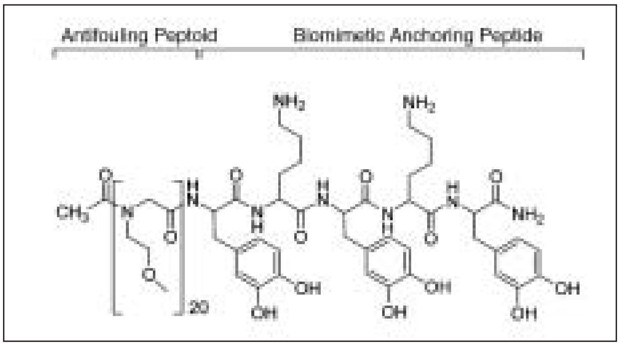
The patent-pending technology, borne out of a 3-yr, $685,000 project funded by the U.K. Dept. of Trade and Industry and four industry partners, comprises a family of proprietary chemicals that are added to the hydrocarbon fluid during transport to control the size of the crystals as well as their tendency to agglomerate. "This cold-flow approach will reduce the operating and capital cost of pipelines, decrease the operating pressure, and eliminate the need for insulation (to prevent hydrate formation)," says Tohidi.

Transporting gas as hydrates offers other advantages. "For one, when these structures form, methane molecules are held closer together than they are in their gaseous state, which increases pipeline capacity," Tohidi notes. The technique is also safer. "If a pipeline is attacked, hydrates burn slowly, but do not explode. And, if pipes rupture, large amounts of gas do not escape." The additive has been awarded funds for further testing and development.

BIOTECHNOLOGY

Novel Biopolymer Coating Boosts Fouling Resistance

Many of the biopolymers proven to be effective at preventing bacteria, cells and proteins in the body from accumulating on the medical devices coated with them do not last long *in-vivo*, falling prey to chemical degradation to the body's enzymes. Northwestern Univ. (Evanston, IL; www.northwestern.edu) researchers have developed a new class of synthetic antifouling macromolecules (Figure, above) that are mimics of polypeptides (these mimics are also known as peptoids) and demonstrate both robust, water-resistant anchorage to biomaterial surfaces and long-term resistance to fouling in a biological environment (*J. Am. Chem. Soc.*, May 13, 2005).



The molecule shown is an example of the new class of chimeric peptidomimetic polymers designed by Northwestern Univ. researchers. It consists of a short anchoring peptide that mimics an adhesive protein from marine mussels coupled to a chain of N-substituted glycine (peptoid) oligomer, which provides resistance to protein and cell fouling.

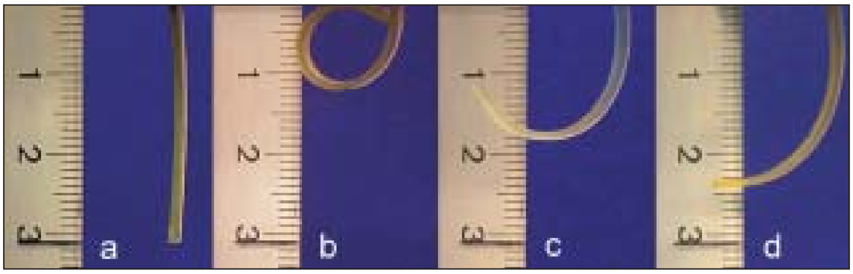
The general design of these chimeric peptidomimetic polymers is that of a short functional peptide for adsorption, coupled to a variable-length N-substituted glycine (peptoid) oligomer, which prevents biofouling. When tested on titanium dioxide substrates in environments with fresh serum and cells, the coatings warded off deposits for up to five months, which, according to Phillip Messersmith, professor of biomedical engineering and lead investigator in the study, is the longest successful *in-vitro* antifouling demonstration.

Messersmith expects *in vivo* testing of the new polymer to begin in about a year. The coatings are believed to hold promise for use on a variety of medical implants, including cardiac stents and biosensors, as well as on water-processing equipment, to prevent biofouling.

Edible Laser-Marking Wins Patent

Sherwood Technology (Widnes, Chesire, U.K.; www.sherwoodtech.com) has been granted a European patent for a method of laser marking edible products using its DataLase Edible color-change technology. This novel technique, for which Sherwood was also recently awarded a U.S. patent, features the deposition of DataLase — a non-toxic, white inorganic pigment that can be applied by most common coating and printing processes or as a masterbatch in the case of plastic molding — onto pharmaceutical and food products, such as tablets and fruits. The coating undergoes a safe color-change from white to black when exposed to the infrared energy from a low-power CO_2 laser, thereby creating a highly visible, stable image.

Previous methods of marking these substrates required a mechanical embossing or surface-printing technique, both of which resulted in a significant number of rejects due to damaged product, according to Andrew Jackson, the company's marketing manager. Sherwood's innovation is now available through licensing agreements and strategic partnerships.



A sample of "smart plastic" (a) is elongated and irradiated with ultraviolet light, forming a temporary shape (b). Photos (c) and (d) show the plastic recovering its original shape after exposure to UV light of a different wavelength. Scale is in centimeters. Photo courtesy of GKSS.

R & D UPDATE

Intelligent Plastics Change Shape with Light

A new family of polymers that change their shape when illuminated with ultraviolet (UV) light and return to their original shapes when exposed to light of specific different wavelengths has been developed by researchers at the GKSS Research Center (Teltow, Germany; www.gkss.de), Massachusetts Institute of Technology (MIT; Cambridge; www.mit.edu) and the Institute for Technology and Development of Medical Devices (Aachen, Germany), among others (*Nature* 2005, **434** (7,035), p. 879). The innovation may offer advantages over temperature-responsive, shape-memory polymers used in industrial and medical applications (*e.g.*, sutures that self-tie into a knot).

The shape-changing capability is imparted by photosensitive molecules that are grafted onto a copolymer backbone. When the photosensitive film is exposed to an external stress (*e.g.*, stretching) and illuminated with a specific wavelength of ultraviolet light, the molecules crosslink. After the light is switched off, the polymer maintains an elongated structure long after the stress has been released, even when the material is heated to 50°C.

Exposure of the polymer to light of another wavelength cleaves the new bonds, allowing the material to spring back to its original shape. "A corkscrew spiral can be created by exposing only one side of the stretched sample to light," notes Andress Lendlein, director of GKSS. Uses for the polymers' photosensitivity are being explored in minimally invasive surgery.

Environmentally Safer Catalyst Increases Hydrogen Deposition

Engineers at Ohio State Univ. (OSU; Columbus; www.osu.edu) have developed a chemical catalyst for water-gas shift reactions that increases hydrogen production by 25% at the same temperature and using the same amount of catalyst as required with iron-chromium alternatives, when tested on a feed mixture similar to that produced from coal gasification.

Chromium helps to maintain the pore structure of iron oxide and protect it from sintering during the reaction, speculates Umit Ozkan, professor of chemical and biomolecular engineering at OSU and project leader. This led the team to seek out the components that would have high thermal and chemical stability, such as aluminum, silicon, and titanium, to replace chromium.

"The specific way we prepare the catalyst is key to its superior performance and cost efficacy," notes Ozkan. "Both of the promoters are incorporated into the iron matrix using a modified sol-gel (MSG) technique, which can be thought of as a controlled inorganic polymerization." Traditional sol-gel techniques are based on alcoxides and rely on co-precipitation to prepare Fe-Cr catalysts. Ozcan's group uses an organometallic iron precursor, but the other metals are added in the form of

inorganic salts. The precursors used in MSG are also less expensive than the ingredients used in co-precipitation, notes Ozcan. “For example, Al is less costly than Cr. In addition, the use of nitrate salts is much less expensive than the use of alkoxides for all ingredients, which is typical of a sol-gel preparation,” she explains. The team plans to conduct tests to determine whether the catalyst works in the presence of sulfur.

Bridging the Superconductivity Gap

Superconductivity is a state of matter normally exhibited at temperatures below –450°F in which electrical current flows without resistance through a material as a result of the material’s electrons acting in pairs. A collaborative team of scientists from the Univ. of California (UCLA; Los Angeles; www.ucla.edu), Los Alamos National Laboratory (Los Alamos, NM; www.lanl.gov) and Chonnam National Univ. (Gwangju; South Korea; www.chonnam.ac.kr/english_home) have discovered that one material, a mixture of plutonium, cobalt and gallium ($PuCoGa_5$) derived its superconductivity from magnetic correlations, and exhibits this property at temperatures warmer than –427°F. “Even though that temperature seems low, $PuCoGa_5$ possesses the highest superconducting transition temperature among actinide based compounds found so far,” says researcher Nicholas Curro.

This new class of magnetically mediated superconductors might encompass materials ranging from metals to oxides that would be the basis for the dissipation-less flow of electric current through power lines. Magnetic fluctuations, rather than interactions mediated by tiny vibrations in the underlying crystal structure, are believed to be responsible for the electron pairing that generates the material’s superconductivity.

Shimmying Molecule Sheds Light on Cure for the Common Cold

A team of scientists at Purdue Univ. (West Lafayette, IN; www.purdue.edu) has determined why a prototype antiviral drug is showing so much promise as a means of neutralizing rhinoviruses that cause the common cold. Although these findings reveal a significant characteristic that antiviral compounds must possess in order to be successful, lead investigator, Carol Post, professor of medicinal chemistry and biological sciences at Purdue quickly points out that they are not likely to result in a cure for the common cold on their own.

The antiviral compound is called WIN (short for 2,6-dimethyl-1-(3-[3-methyl-5-isoxazolyl]-propanyl)-4-[4-methyl-2H-tetrazol-2-yl]-phenol). Its key feature, which is deemed an important characteristic for any anti-viral drug molecule, is a flexible structure that allows it to shimmy inside the virus' complex outer surface, thereby altering the virus to the point where it cannot complete the infection process.

The rhinovirus' outer surface is made up of proteins organized into pentagons that form an icosahedral capsid or protective shell. "Although our antibodies are designed to destroy viruses, the rhinovirus may mutate from a previous cold virus so that our antibodies can't recognize the new one," she explains. The viral shell also changes shape during the life cycle of a single rhinovirus particle. These shape changes seem to depend on a small, cigar-shaped cavity within the folds of a protein called VP-1 that forms around the capsid's axis of pentameric (5-fold) symmetry. Post observes that filling this cavity appears to stop the virus from changing shape. WIN is a prime candidate for the task.

Once the rhinovirus particle penetrates the infected cell, the capsid opens up, releasing RNA, which instruct the cell to reproduce the rhinovirus particles. "This change is possible because the capsid proteins, including VP-1, are flexible enough to allow the release of genetic material," notes Post. "Restricting the VP-1 protein motions would prevent the capsid from opening, thereby preventing the virus from releasing genetic material," she adds.

One reason why the WIN compound is so effective is that it can shimmy through a narrow hole into the cigar shaped cavity where VP-1 resides. "It's all part of the inhibition mechanism," explains Post. The wiggling part is important to get into the cavity. When WIN occupies the cavity, it has the long-distance effect of preventing the release of RNA by restricting motion at the 5-fold axis." Unable to come up with a scientific explanation, the team hypothesizes that "having a WIN compound in its cavity may be the VP-1 protein's equivalent of a person who has a full stomach not wanting to move around very much."

Post and her colleagues are planning additional computer simulations using the CHARMM molecular mechanics program running in parallel on fast Linux clusters to identify the underlying cause of the long-distance effects. By understanding WIN's locking mechanism, researchers may be able to design drugs that can lodge themselves into the virus' cavity without causing adverse effects.

REGULATORY UPDATE

U.S. Hunkers Down on Power Plants' Hg Emissions

On March 15, 2005, the U.S. became the first nation to regulate mercury (Hg) emissions from coal-fired power plants (CFPPs), as the Environmental Protection Agency (EPA; Washington, DC; www.epa.gov) issued its Clean Air Mercury Rule (CAMR) affecting utilities nationwide. The rule, which builds upon the agency's Clean Air Interstate Rule (CAIR), aspires to reduce utilities' Hg discharges from the current 48 ton/yr to 15 ton/yr (~70%) by 2018 by establishing standards of performance that limit Hg emissions from new and existing facilities, and by creating a market-based cap-and-trade program — modeled after EPA's Acid Rain Program — that reduces Hg emissions in two phases.

The first phase caps Hg discharges at 38 ton/yr by 2010, and will take advantage of co-benefit reductions — *i.e.*, Hg reductions achieved by reducing sulfur dioxide (SO_2) and nitrogen oxides (NO_x) emissions under the CAIR. In the second phase, due in 2018, an additional cap will reduce emissions to 15 ton/yr upon full implementation. New coal-fired power plants (those that started construction on or after Jan. 30, 2004) must meet stringent new-source performance standards, in addition to complying with the caps.

Under the cap-and-trade system, each state and the two affected tribes are assigned an Hg-emissions budget for all of their fossil fuel-fired electric utility steam generating units. Other types of entities not listed could be affected. To determine whether a facility, company, business, organization, etc., is regulated by the final rule, the owner or operator should examine the applicability criteria in 40 CFR 60.45a of the final New Source Performance Standards.

Each state must submit a state-plan revision detailing how it will meet this budget for its affected sources. The rule also includes a cap-and-trade program that states can adopt to achieve and maintain their Hg-emissions budgets. States may join the trading program by adopting the federal model trading rule into the state regulations. The states and tribes are not obligated to adopt the EPA administered cap and trade program. However, their emission budgets are permanent, regardless of growth in the electric sector.

In the cap-and-trade program, the government allots to each state and tribe a specific number of Hg allowances. A Hg allowance is equivalent to 1 oz of Hg. Each state allots a number of Hg allowances to the affected facilities within the state. Each affected facility must hold an allowance for each ounce of hg that the facility emits to the atmosphere. If the affected facility desires to increase its power output, then it must purchase Hg allowances from other facilities that have excess allowances, must install additional air-pollution-control equipment so as to maintain the same Hg emissions despite the increase in power output, or must come to an agreement with other affected facilities to decrease the emissions from those other facilities so that the overall Hg emissions do not increase.

EPA says the mandatory declining emissions caps in the CAMR, coupled with significant penalties for noncompliance, will ensure that the rule requirements are achieved and sustained. As with the Acid Rain Program, the flexibility of allowance trading should create financial incentives for CFPPs to seek new and low-cost ways to reduce emissions, and improve pollution-control-equipment effectiveness.

The final text of the Clean Air Mercury Rule may be found in the Federal Register of May 18, 2005, on pp. 28,605-28,700.

Regulatory Update is prepared by William A. Shirley, P.E., J.D., a chemical engineer and attorney in private practice in St. Louis, MO; Phone: (888) OSHA-LAW; E-mail: envtllaw@charter.net.

PATENT UPDATE

The Future of Drug Development

The Hatch-Waxman Act was passed by Congress to encourage pharmaceutical companies to develop new drugs, while allowing generic drug manufacturers to bring cheaper versions of drugs to market once patents expire. The Act includes a “safe harbor” provision [35 USC 271(e)(1)] that permits drug makers to perform the experiments necessary to obtain FDA approval without incurring liability for patent infringement, even if their activities infringe another’s patent rights. But the statute’s language is not clear as to which activities it shelters. It simply states that it is not an act of infringement to use a patented invention “solely for uses reasonably related to the development and submission of information under a federal law that regulates the manufacture, use, or sale of drugs.”

Until recently, the courts have broadly interpreted the language of the safe harbor provision. But in *Integra Lifesciences v. Merck,* the Federal Circuit took a much narrower view of the exemption. Merck hired a consulting research group that was working with certain compounds, called RGD peptides, that interact with specific receptors on cell surface proteins. The researchers were investigating the usefulness of the peptides as potential drug candidates. But Integra held a patent covering the peptides. At first, Integra offered to license their use to Merck, but when Merck rejected the proposal, Integra sued for patent infringement. Merck argued that its activities were exempt from infringement under the safe harbor provision.

In considering Merck’s argument, the Federal Circuit had to decide whether the safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in the future, be subject to FDA approval. The court reasoned that the focus of the exemption is the provision of information to the FDA, not the hunt for new drugs that may or may not undergo clinical testing for FDA approval. The court concluded that general biomedical research to identify new pharmaceutical compounds was not covered by the exemption, and ruled that Merck had infringed Integra’s patent. Merck appealed its case to the U.S. Supreme Court.

On June 13, 2005 in a unanimous decision, the Supreme Court set aside the Federal Circuit’s ruling. The Court reasoned that “the use of patented compounds in pre-clinical studies is protected as long as there is a reasonable basis for believing the experiments will produce the types of information that are “relevant” to the FDA approval of a future drug. The decision means that many types of early-stage research would be covered by the safe harbor provision, and pharmaceutical companies are presumably free to use patented technologies at no cost in drug development programs.

On one hand, since companies at least appear to have a lower cost of development, the cost to the consumer for an approved drug should also be lower. However, since the owners of the patented technologies, typically researchers and universities, are now faced with the shrinking value of their intellectual property, the loss of value could stunt innovation and lead pharmaceutical firms to perform the research themselves. This cost would have to be passed on to the consumer as higher prices for new drugs. The true effect that the Supreme Court decision will have on drug prices will only be known with time.

This “Patent Update” was written by Frank C. Eymard, P.E., a chemical engineer and patent attorney with Albemarle Corp., Baton Rouge, LA; Phone: (225) 388-7750; E-mail: frank_eymard@albemarle.com.