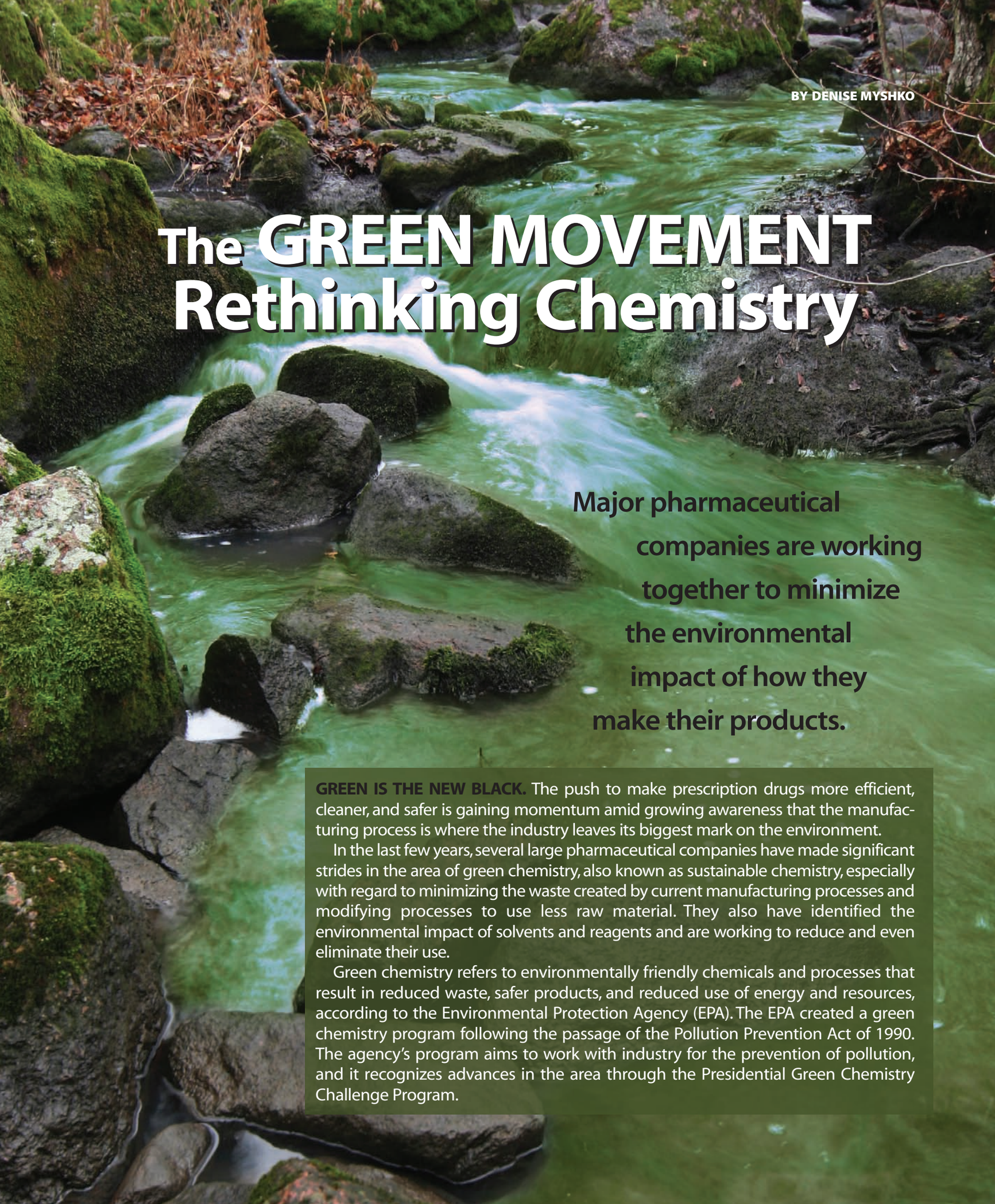


BY DENISE MYSHKO

The GREEN MOVEMENT Rethinking Chemistry

Major pharmaceutical companies are working together to minimize the environmental impact of how they make their products.

GREEN IS THE NEW BLACK. The push to make prescription drugs more efficient, cleaner, and safer is gaining momentum amid growing awareness that the manufacturing process is where the industry leaves its biggest mark on the environment.

In the last few years, several large pharmaceutical companies have made significant strides in the area of green chemistry, also known as sustainable chemistry, especially with regard to minimizing the waste created by current manufacturing processes and modifying processes to use less raw material. They also have identified the environmental impact of solvents and reagents and are working to reduce and even eliminate their use.

Green chemistry refers to environmentally friendly chemicals and processes that result in reduced waste, safer products, and reduced use of energy and resources, according to the Environmental Protection Agency (EPA). The EPA created a green chemistry program following the passage of the Pollution Prevention Act of 1990. The agency's program aims to work with industry for the prevention of pollution, and it recognizes advances in the area through the Presidential Green Chemistry Challenge Program.

The green chemistry movement is gaining traction in Congress as well. In September 2007, the House passed the Green Chemistry Research and Development Act of 2007. This bill, introduced by Rep. Phil Gingrey of Georgia, directs the president to establish a program to promote and coordinate federal green chemistry research, development, education, and technology transfer activities.

Within the scope of the pharma industry, green chemistry entails a rethink about its manufacturing processes.

David Constable, Ph.D., director of environmental product and process stewardship at GlaxoSmithKline, says there needs to be a change in industry perspective regarding chemical processes.

"When people focus on waste, they focus on recycling and reuse," he says. "That's very important but it isn't the only consideration, and it certainly isn't going to get us to more sustainable processes. We need to address why we are buying and paying for more resources than we need, and then paying to manage, use, and throw it out. Why don't we just use what we need? This slightly different focus gets people to start thinking about different chemistries and different technologies."

Green chemistry is really a mindset and a way of working, says Andrew Wells, Ph.D., senior principal scientist at AstraZeneca.

"There is a perception that green chemistry means more work and more expensive equipment," he says. "But it's really about getting all of the chemists and engineers to understand the cost chemistry has on the environment and the impact of waste."

Good chemistry and good science will lead the way to sustainable and scalable processes as well as the best economic and green results, says R.P. "Skip" Volante, Ph.D., VP and global head of process research at Merck Research Laboratories (MRL), Merck & Co. Inc.

"Being green doesn't necessarily mean increased costs; we think green processes will end up being more economical," he says.

Through the American Chemical Society's Green Chemistry Institute (GCI), eight pharmaceutical companies are working together to implement green chemistry and engineering.

The GCI Pharmaceutical Roundtable was formed in 2005 and aims to address the challenges of the pharmaceutical industry and to develop tools, as well as be a forum for cooperation between the member companies. (For more information, see box on page 34.)

The roundtable has resulted in a number of green environmental chemistry collaborations between pharma companies. For example, last year AstraZeneca and Pfizer entered into an agreement to share green chemistry tools, and in 2008 AstraZeneca and GlaxoSmithKline agreed to work together in the area of solvent life-cycle impact.

"Through our consortium efforts and our individual efforts we are advancing state-of-the-art chemistry that could be useful to other fine-chemical industries," says John Kindervater, environmental consultant for Eli Lilly & Co. "We are also working on organic chemistry advances and on engineering changes. Traditionally, pharmaceutical products have been made by batch process. We're working on continuous processing, which can be more efficient."

ACADEMICALLY, CHEMISTS ARE NOT REWARDED FOR GREEN CHEMISTRY. Until we start putting green chemistry as a science deliverable in academia, there is a perception that it's neither good science nor innovative.

DR. DAVID CONSTABLE
GlaxoSmithKline

THERE CAN BE A PERCEPTION THAT GREEN CHEMISTRY TAKES MORE WORK AND NEEDS MORE EXPENSIVE EQUIPMENT, but it's really a mindset and a way of working.

DR. ANDREW WELLS
AstraZeneca

New Processes

Lilly has set a goal to cut hazardous material purchases by one-third by 2010. To drive progress toward this goal, Lilly has established specific material-use efficiency standards for the critical steps in the product development process. The E-factor (a ratio of material used per unit of active pharmaceutical ingredient) of the proposed manufacturing process is evaluated at key development milestones. If the standard is not met at the checkpoint, management review is triggered. These standards are driving improvements in efficiency. For example, Lilly estimates that the improved process identified for one pharmaceutical product will cut material use by 13 million pounds per year at full-scale production.

"We use a numeric system to rate the solvents," Mr. Kindervater says. "We look at the flammability of a solvent and its carcinogenic toxicity. Then we use empirical data from our own experiences, as well as information and literature from the field. We consider potential alternatives; in some solvent classes there are many alternatives that work."

In just two years, Lilly has exceeded its goal to reduce hazardous material purchases by 37.6% as a result of efficiency increases, solvent recovery, changes in product mix, and supply-chain actions.

Similar to Lilly, the educational push at other companies toward improving green chemistry efforts is directed at scientists.

"Initially, we realized we needed to go outside the box to encourage our people to think about innovative chemistry," says Elizabeth Kang, senior manager, environmental technical services in Schering-Plough's Global Safety and Environmental Affairs Group. "Through education and continuous communications, we've overcome this obstacle."

Ingrid Mergelsberg, Ph.D., director of syn-

12 Principles of Green Chemistry

1. PREVENT WASTE
Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.

2. DESIGN SAFER CHEMICALS AND PRODUCTS
Design chemical products to be fully effective, yet have little or no toxicity.

3. DESIGN LESS HAZARDOUS CHEMICAL SYNTHESES
Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

4. USE RENEWABLE FEEDSTOCKS
Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.

5. USE CATALYSTS, NOT STOICHIOMETRIC REAGENTS
Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.

6. AVOID CHEMICAL DERIVATIVES
Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

7. MAXIMIZE ATOM ECONOMY
Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.

8. USE SAFER SOLVENTS AND REACTION CONDITIONS
Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.

9. INCREASE ENERGY EFFICIENCY
Run chemical reactions at ambient temperature and pressure whenever possible.

10. DESIGN CHEMICALS AND PRODUCTS TO DEGRADE AFTER USE
Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.

11. ANALYZE IN REAL TIME TO PREVENT POLLUTION
Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of by-products.

12. MINIMIZE THE POTENTIAL FOR ACCIDENTS
Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

Source: Originally published by Paul Anastas and John Warner in Green Chemistry: Theory and Practice (Oxford University Press).

LILLY'S GREEN CHEMISTRY EFFORTS include implementing new process technologies, such as these coiled tube reactors being used by members of the Alternative Reactor Technology (ART) team to produce drug candidate material for clinical trials.

thetic chemistry at Schering-Plough, says some in the organization considered the green chemistry effort in the beginning as an extra burden.

"As we do with quality, we developed our vision to build in green chemistry principals right from the beginning of development; this way we didn't add to already heavy workloads," she says. "We started to involve discovery regarding green chemistry principals so that we increase awareness very early on."

Schering-Plough has established a cross-functional team comprised of chemists from chemical and physical sciences in the Schering-Plough Research Institute, as well as the company's safety and environmental affairs group.

"We start with a process notification form that lists all of the materials used in the process, and the chemists cross-reference all of the materials against a chemical selection guide," Ms. Kang says. "The guide classifies each chemical as red, yellow, or green. Green means it's good from an environmental perspective. We have regular meetings to talk about ways we can improve and apply green chemistry."

At AstraZeneca, the green chemistry network links environmental specialists with chemistry and engineering organizations within process development to help promote the principles of green chemistry and engineering. Every two years, all of the scientists in the Global Process Research and Development function in Europe have the opportunity to attend training on how they can minimize the environmental impact of the manufacturing processes they are developing.

Dr. Wells says the green chemistry group at AstraZeneca is a multinational, cross-country function and has representation from process chemistry and engineering, environmental, and SHE (social aspects, health, and environment) specialists in the United States, the United Kingdom, and Sweden. And more medicinal chemistry people are also becoming involved.

"We provide software tools, guides, and advice for our synthetic chemists and chemical engineers so they can make the correct choice of solvents on environmental grounds," he says. "We have a tool called the substance avoidance strategy, and this alerts chemists to reagents and solvents that have environmental issues. We also have an API (active pharmaceutical ingredient) removal tool, which guides engineers to the most appropriate technologies to take API out of the water stream.

"Apart from the positive impact on the environment, it's good for the company," Dr. Wells says. "The cost of goods is lower, there is better throughput for pilot plants, we buy fewer solvents, and we dispose of fewer solvents."

GSK's Dr. Constable says typically 80% to 90% of the total mass that goes into the process is composed of solvents. Of that, only about 30% to 40% gets recycled.

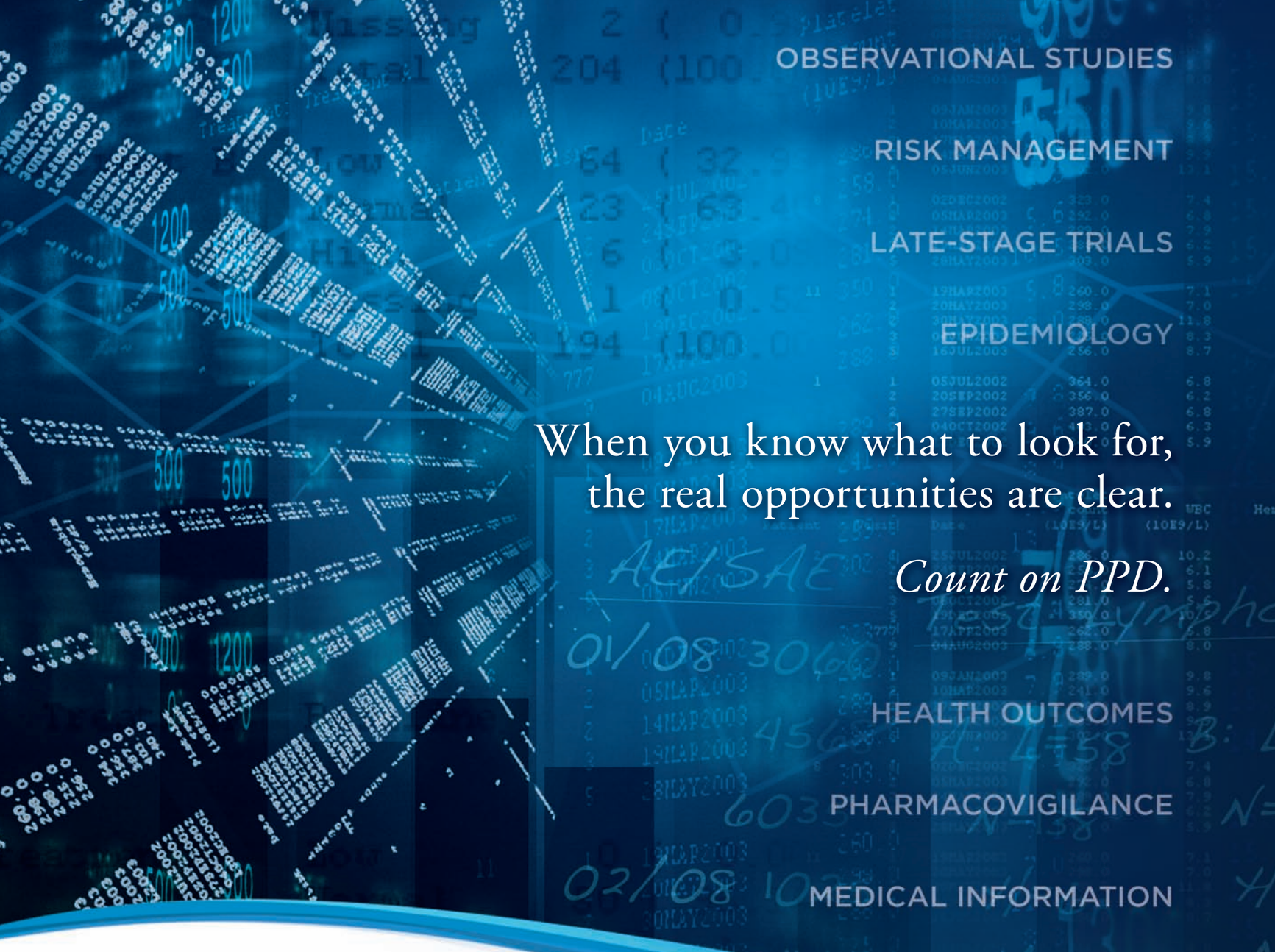
GSK has a set of tools that provides information that can guide chemists in making decisions. It includes: a summary of the most-used chemistries; a review of issues encountered during process design and development; a summary of common technology alternatives for chemical processing; and guidance on materials, process alternatives, synthetic route strategies, and metrics for evaluating chemistries, technologies, and processes.

The company has also developed a materials guide for solvent selection, which compares and ranks 45 solvents according to an environmental waste profile, environmental impact, a safety profile, and a health impact.

"Our desire is to reduce the life-cycle environmental impact associated with using solvents; burning a solvent as fuel in an incinerator comes with a much larger life-cycle impact than burning kerosene," Dr. Constable says. "Our long-term goal is to get people to use different chemistries that aren't as solvent-dependent."

New Technologies

Green chemistry at Merck focuses on the development and application of technology for



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DR. SKIP VOLANTE
Merck Research Laboratories

synthetic processes that reduce or eliminate the use or generation of hazardous substances.

Merck scientists are developing technologies in such areas as separation sciences and catalysis, and they recently demonstrated improved energy efficiency and process throughputs by using supercritical fluid chromatography for the preparation of pure compounds. In addition, MRL scientists are applying state-of-the-art catalysis technology for the industrial-scale manufacture of Merck drugs.

"We want a more efficient process to minimize waste," Dr. Volante says. "The pharmaceutical industry has been known for many years for producing high volumes of waste relative to the amount of product. Green chemistry is all about reducing waste relative to the product that is being produced so that what goes into the process goes into the product and not into the waste."

Merck uses a process called asymmetric catalysis.

"Certain types of molecules have an asymmetric center, which means they have a left-handedness and right-handedness," Dr. Volante says. "Making both images when only the left-handed image is needed means producing 50% of waste in that reaction, in addition to any chemicals or reagents put into the reaction."

The company uses this process for the manufacture of Januvia for type 2 diabetes.

Dr. Volante says roughly 50% of the molecules in Merck's pipeline have asymmetric centers in them, and the technique is applicable to about half of those molecules.

While asymmetric catalysis has been in use in laboratories for some time, Dr. Volante says it's only been in the last four or five years that it has been significantly used in the manufacturing arena. The challenge facing this and other technologies is the ability to use these techniques at the scale required for pharmaceutical manufacturing.

Measuring Impact

The industry experts interviewed for this article say they have in place metrics to evaluate progress with their green chemistry efforts.

Dr. Constable says a GSK initiative begun in 2002 is critical for measuring the impact of its programs. FLASC (Fast Lifecycle Assessment for Synthetic Chemistry) is a Web-based application that allows bench chemists to perform a life-cycle evaluation of the environmental consequences of new or existing processes based upon the input materials used. It quantifies the energy and materials used in product manufacture, as well as emissions released and potential environmental impacts.

The company's tools are applied throughout its pharmaceuticals business. Dr. Constable says it is a bit difficult to apply these tools to GSK's biopharmaceuticals because it is such a different approach.

"We're doing quite a few comparisons between chemical routes and bioprocesses and we've got some case studies," he says. "We know what the areas of concern are, and we have a good handle on them but we aren't as regimented in our approach in biopharma yet."

At Lilly, Mr. Kindervater says the company looks at specific milestones as it develops its chemical manufacturing processes.

"During the systematic approach, we look at the environmental, health, and safety aspects of a process right along with the more tradi-

The Pharmaceutical Roundtable

In 2005, the ACS Green Chemistry Institute (GCI) and global pharmaceutical corporations developed the GCI Pharmaceutical Roundtable to encourage innovation and integration of green chemistry and green engineering.

The global, collaborative organization is currently comprised of eight international pharmaceutical companies: Lilly, GSK, Pfizer, Schering-Plough, Merck, AstraZeneca, Johnson & Johnson, and Wyeth. Membership is open to all pharmaceutical research, development, and manufacturing companies.

The strategic aims of the roundtable are to inform and influence the green chemistry research agenda to help meet the challenges of the pharmaceutical industry; to develop common tools for use across the pharmaceutical industry; to provide resources for education about green chemistry focused on the pharmaceutical industry; and to be a forum for cooperation and collaboration between the member companies to embed green chemistry and science into everyday operations and processes.

One of the major green chemistry challenges for the pharmaceutical industry is to decrease the process mass intensity (the amount of material used to make a drug per kg of drug) of the manufacturing processes used to produce active pharmaceutical ingredients (API). To begin addressing this challenge, roundtable members have developed a common process mass intensity metric that allows data from each company to be compared on a transparent and equitable basis. Data from member companies have been collected as part of a benchmarking exercise and have yielded a representative snapshot of the process mass intensities observed for those compounds under development at each company.

Source: American Chemical Society Green Chemistry Institute, Washington, D.C. For more information, visit acs.org.

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WE DEVELOPED OUR VISION TO BUILD IN GREEN CHEMISTRY PRINCIPLES RIGHT FROM THE BEGINNING OF DEVELOPMENT. We started to involve discovery so that we increase awareness early on.

DR. INGRID MERGELSBERG
Schering-Plough

GREEN CHEMISTRY EFFORTS ARE MULTIFUNCTIONAL. We have a cross-functional team made up of individuals from SPRI chemical and physical sciences and the company's global safety and environmental affairs group.

ELIZABETH KANG
Schering-Plough

tionally reviewed quality of our resulting process and whether the cost of the product is suitable," he says. "We have a formal check on the quantity of materials used to produce a unit of product through the synthesis and a screen for chemicals that may cause environmental concern in bulk production."

AstraZeneca uses process mass intensity, or PMI, to measure resource utilization. This metric was developed in collaboration with the ACS Green Chemistry Institute.

Dr. Wells says the company has used this metric for a component from AstraZeneca's oncology portfolio.

"The molecule had a seven-step sequence to get from start to final product," Dr. Wells says. "We changed it to a three-step process. This reduced the PMI from 400 to around 80."

For another early-stage project, AstraZeneca was able to redesign a synthetic and reduce it to 90 kilos per API from almost 5,000 kilos per API. Dr. Wells says the green chemistry effort for this particular project saved the company about $25,000 per kilogram of API.

"At key trigger points throughout the process, issues that have environmental concerns or impact are picked up and rectified," Dr. Wells says. "We would look at constant environment improvements throughout the project life cycle and make sure there are no environmental issues to impact the launch of the product."

Schering-Plough also uses process mass intensity to measure the impact of its efforts.

"Internally we call it the Process Sustainability Index, PSI for short, which is defined as the kilograms of raw materials to make one kilogram of product," Ms. Kang says. "We have a customized Web-based tool to calculate the PSI for all of our processes, from the pilot plant development to commercial manufacturing."

Schering-Plough's Dr. Mergelsberg says the benefits of companies' green chemistry can be enormous.

"We've started using different technologies that are more environmentally friendly," she says. "For example, instead of doing conventional preparative high-performance liquid chromatography (HPLC) for the separations of racemic mixture of a compound, sometimes we can use a process that uses supercritical CO_2 with small amounts of an organic solvent such as methanol. This is an enormous reduction in solvent use, run time, and costs. Run time was reduced from about 2,000 hours to 90 hours, and costs have gone from about $7,000 per kilo to about $200 per kilo of intermediate." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

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