GREEN SEPARATION Novasep's Varicol industrial-scale system combines continuous chromatography with solvent recycling.

NOVASEP

SUSTAINABLE SYNTHESES

Developing **GREENER PROCESSES** brings many benefits for pharmaceutical and fine chemicals manufacturers

ANN M. THAYER, C&EN HOUSTON

IN 2005, chemists at Boehringer Ingelheim (BI) faced a dilemma. They had developed a synthetic process that would have been difficult to manipulate and too costly at large scale because of the energy it consumed and the waste it produced. The drug they were making was important, though, and they wanted to make changes rather than more investments.

"Our estimation to run this reaction was that we would have to make a multimillion-dollar capital investment," recalls Chris H. Senanayake, BI vice president for chemical development. Clearly, minimizing waste for the sake of being "green" wasn't the only issue at stake. For a drug that would be made by the tens of tons, production economics were paramount.

The chemists' chosen route to synthesize the drug, a macrocyclic hepatitis C protease inhibitor, included ring-closing metathesis (RCM) as a key reaction. They had used the process to make more than 100 kg of the compound, but even then they knew it suffered, as many macrocyclizations do, from highly dilute conditions, high catalyst levels, and long reaction times.

Yet because RCM had already shortened the synthesis, it still seemed a good option, Senanayake says, "if we could only figure out how to run the reaction at a good concentration." Following some subtle clues, the BI chemists found that adding a functional group changed both the molecule's conformation and how it interacted with the catalyst (*Org. Lett.* **2008,** *10,* 1303).

As a result, their new RCM process now runs at a more than 20-fold higher concentration, with 50 times less catalyst, to give 93% yield in about one-fiftieth the reaction time (*Org. Process Res. Dev.* **2009,** *13,* 250). It also can be run in existing standard reactors without added capital outlays.

At the start, the RCM process had an E factor—a measure of process efficiency—of 370 kg of waste per kg of product. Using less solvent dropped the E factor to 28. The team also switched from dichloromethane, which had been used at small scale, to more environmentally acceptable toluene. Further process improvements may be possible through solvent recycling, Senanayake says.

In doing their jobs to develop robust, cost-efficient processes, pharmaceutical

GOING GREEN For more C&EN coverage of green chemistry, go to www.cen-online.org/greenchemistry.html.

"Benchmarking really confirmed that solvent use was the major source of waste in our industry."

process chemists often simultaneously create greener ones. Process chemistry and green chemistry have common goals: generating less waste and emissions, minimizing material and energy use, and operating more safely under more benign conditions. Greater attention to reagent, solvent, and reaction choices by these chemists is making process development even greener.

The need is there because pharmaceutical production can be a dirty business. Although the annual tonnage of drugs produced is maybe one-thousandth that of bulk chemicals, the comparative E factor is at least an order of magnitude higher, at 25–100 kg of waste per kg of product.

Along with E factors, process chemists may track other measures, such as the process mass intensity—the ratio of material quantities going in to the amount of product coming out. They also have developed deeper analyses that take into account not just the amount but also the nature and fate of materials used and of the wastes generated.

BI process chemists, like those at other major drug firms, are being encouraged to incorporate this thinking and even see it among their performance objectives. "Once a compound is transferred from discovery to development, we start to measure E factors as well as do a safety analysis of any reaction that we run on a reasonable scale," Senanayake says. This strategy has helped cut process development costs substantially, he adds.

PHARMACEUTICAL INDUSTRY interest in green chemistry grew in the late 1990s, soon after the principles became widely espoused and success stories started to emerge, says Berkeley W. Cue, president of BWC Pharma Consulting and former vice president for developmental research at Pfizer. Over the past decade, for example, U.S. Presidential Green Chemistry Challenge Awards have gone to Merck & Co., Boots Healthcare, Bristol-Myers Squibb, Pfizer, Roche, and Eli Lilly & Co.

"Activity picked up as companies started to think about the triple bottom line of environmental sustainability, economic performance, and social responsibility," Cue says. "Green chemistry was something that they could do that would tick the boxes for all three bottom-line considerations."

Despite today's economic crisis and the ongoing pressures for high productivity under short timelines, Cue says he's not aware of any drug companies backing away from green chemistry programs already in place. "If the thesis is correct that it is more cost-effective to practice green chemistry in the design and manufacture of drugs, then that should be an even more compelling reason to do it now than it was five or 10 years ago," he says.

In 2005, Pfizer, Merck, Lilly, and the American Chemical Society's Green Chemistry Institute formed the Pharmaceutical Roundtable. Its goal is to foster the integration of green chemistry and engineering into the pharmaceutical industry. Membership has grown to 10 major drug firms, along with services supplier DSM and biocatalyst developer Codexis, both of which joined in 2008.

Member firms have developed their own programs to different degrees and can benefit by sharing experiences and practices, says Peter J. Dunn, Pfizer's green chemistry lead and cochair of the Roundtable with Ingrid Mergelsberg, a director in chemical development at Schering-Plough.

Most companies send representatives from their environment, health, and safety (EHS) and process R&D areas. As a group, the Roundtable has four priorities: informing and influencing research agendas, defining and delivering tools, acting as an educational resource, and supporting global collaboration.

In 2007, the Roundtable published the outcome of a brainstorming session that identified key research needs for the industry, including many highly desired synthetic approaches (*Green Chem.* **2007**, *9*, 411). "We came up with those 12 areas

by a straight voting process, and there was a surprising amount of overlap between what the companies felt were the key problems," Dunn says.

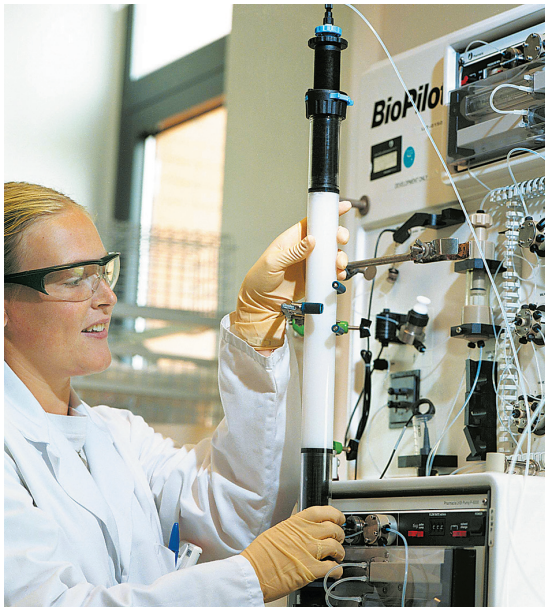
To find solutions, the Roundtable has awarded grants totaling more than $650,000 to academic scientists. To leverage its investment, it looks for other sources to support green chemistry. For example, it worked with the National Institute of General Medical Sciences to identify green pharmaceutical chemistry as a topic area in the 2009 National Institutes of Health Challenge Grants in Health & Science Research, a new program under the American Recovery & Reinvestment Act.

On the academic front, the Roundtable has set up a European student workshop on green chemistry and new pharmaceutically active molecules. The third such workshop, which is also supported by the U.K.'s Royal Society of Chemistry, will be hosted in September by the University of Leeds's Institute of Process Research & Development (see page 23). Past workshops have attracted about 50 undergraduates, Dunn says.

FOR THEIR OWN scientists, the companies have been creating tools they can use to apply green chemistry principles. In 2006, the Roundtable conducted a comparative study using a member-defined process mass-intensity index. "That benchmarking really confirmed that solvent use was the major source of waste in our industry," Dunn says, contributing more than half the mass intensity in making an active pharmaceutical ingredient (API).

Solvent use became a priority topic, and the group will soon complete a solvent selection guide. Solvents are scored on their EHS effects in order to direct users toward more desirable ones. "We also have been planning an initiative to try to influence solvent manufacturers to introduce greener solvents," Dunn explains.

As another resource, the group has created a reagent selection guide that addresses hazard, scalability, and general utility. Since finding alternative or improved reactions is critical, members share the task of sorting through the scientific literature and publishing a biannual compendium of green chemistry article highlights in the ACS journal *Organic Process Research & Development*. The group has also worked with Chemical Abstracts Service to incorporate green chemistry search criteria.



PROCESS CHEMISTRY DSM Pharmaceutical Products conducts research at its Geleen site in the Netherlands.

Highlighting greener and more efficient reactions and providing the guides help chemists address not only the quantity of waste but also the quality of the materials they handle and the nature of what is generated. Many companies have set goals around their E factors or process mass productivities for new late-stage compounds, Dunn explains.

GlaxoSmithKline, for example, has its own eco-design tool kit that encompasses base and solvent selection, chemical legislation, green chemistry and technology guides, and a Web-based Fast Lifecycle Assessment of Synthetic Chemistry tool. FLASC allows users to screen a synthetic method for its environmental life-cycle impact in about 15 minutes, says Concepción Jiménez-González, director for operational sustainability in corporate EHS and sustainability at GSK.

GSK researchers and collaborators used FLASC and other EHS metrics to compare a chemical route with an enzyme-catalyzed process for producing 7-aminocephalosporic acid (*Ind. Biotech.* **2008,** *4,* 180). Cradle-to-grave estimates found that the chemical route had a higher yield but that the biocatalytic route performed better in energy consumption, mass usage, and greenhouse gas emissions.

"Greenness tends to track with the cost."


DSM

Likewise, a new process for manufacturing a diabetes drug in Phase II trials has replaced one that was too resource intensive to use at large scale, Jiménez-González says. Not only is the yield increased by 37%, but the process uses less than half the energy and 81% less solvent, with about 30% less wastewater. "It will save over $175 million each year in raw materials and waste disposal costs," she says.

AS PROJECTS PROGRESS, managers look for opportunities to recover or recycle waste streams. "Early on, with tools like FLASC, we get a very good understanding of what a process will generate," says Philip C. Dell'Orco, director of process engineering in chemical development at GSK. "Some wastes can be used by other industries, such as paint manufacturers, so we seek third parties who can find a beneficial use."

Similarly, Bristol-Myers Squibb (BMS) has developed a Process Greenness Scorecard, which consists of a workbook of spreadsheets for users to track about 15 parameters for each step in a process. Mapping to green chemistry and engineering principles, the parameters are assigned values and weighted to come up with an overall score.

"We tried to come up with something that wasn't overly cumbersome," says Stephan P. B. Taylor, a process R&D director at BMS. The idea is also to direct efforts at fixing the right problems. "The purpose is to help people identify things that are not so green and make decisions about changes in the process," he adds.

Although the BMS scorecard focuses largely on the process to make a material, the choice of commercial reagents affects the score, as do solvent ratings that take into account the energy required to produce solvents and their environmental aspects, Taylor explains. Process changes can positively impact the score. Short of changing the route, he says, the score can be improved by avoiding isolation of a harmful intermediate to limit exposure.

Eventually, Taylor hopes, the tools will become even more effective by being less retrospective. "After using these tools for a while, people understand what makes a process green and what doesn't, but you still need to go through the exercise of using the tool," he explains.

Instead, Taylor would like to see the tools integrated into electronic notebooks and structured recipe applications that chemists and engineers use in their daily activities. "They'd get some feedback instantly, and the score would be in sync with the process, as opposed to them going through an extra activity at some milestone," he says.

But not everything being done is just by the numbers. "Even though we have green metrics that are calculated every time we have a pilot-plant campaign, we focus on making sure we raise awareness and embed sustainability principles into the business," Jiménez-González points out.

Like most companies, GSK has a corporation-wide EHS strategy. But the green chemistry part of chemical development is a grassroots effort, according to Tom D. Roper, director of synthetic chemistry at GSK in Upper Merion, Pa. A sustainable processing team—drawn from discovery, development, and manufacturing—aligns

efforts and enables others within GSK to use the tools and techniques.

Ultimately, however, decisions to move ahead with a given process will depend on financial, technical, and EHS considerations that involve others beyond the team. "Our job is to make sure that what is going forward is the greenest process we can put in place," Roper says. Fortunately, Dell'Orco adds, "greenness tends to track with the cost."

Business needs feed back to the bench, Dell'Orco says. "Our manufacturing sites are constantly asking us to get the highest throughput with the lowest waste and lowest impact that we can get because that really affects their productivity and the bottom line," he explains. But having chemists already thinking about incorporating green chemistry means that "you see a lot of ideas bubble up from the ground level," he adds.

The approach has been similar at BMS, according to senior research investigator David Leahy. With the support of process R&D management, "our green chemistry team was conceived by and is made up of bench chemists," he says. Meanwhile, a corporation-wide green chemistry program involves R&D, technical operations, and EHS areas.

Leahy says the green chemistry team helps educate and advise project teams and tries to heighten awareness of green chemistry. "The team gets together periodically with project teams to review the scorecard as part of the development life cycle," he says. "These reviews try to identify which aspects of a process are the least green so we can then place research effort into these areas."

As in many companies, the team also provides resources, including seminars and training, and is looking at incentives, such as an annual awards program. At BMS, online resources include a Wiki site of green chemistry information and a reaction database. Its team also tries to look across disciplines, collaborating, for example, with engineers on software modeling methods to minimize solvent usage.

"Most people who have been doing this for a while recognize that a good process is going to be fairly green, so to some extent it just happens along the way," Taylor says. "One of the things that we are trying to do is help people know what they don't know so that they don't develop a green process without knowing what made it green. That is what these tools help do."

SIMILARLY, getting easy-to-use tools in the chemists' hands has been critical for delivering results at Pfizer. "In medicinal chemistry, we reduced our chloroform usage last year by 98%, and since 2005, we have reduced diisopropyl ether usage by 100% and dichloromethane usage by 60% on a per chemist basis," Dunn says. Process chemists capture metrics across all the company's development compounds, and there are agreed-upon reduction targets for new chemical entities across all the company's scientific lines.

The drivers for Pfizer include both reducing manufacturing costs, in particular for waste disposal, and producing medicines with a minimum impact on the environment, Dunn says. In its award-winning enzymatic process for Lyrica, its second-highest-selling product, every step is performed in water. Pfizer calculates that between 2007 and 2020 more than 200,000 metric tons of organic chemical waste will be avoided by the process.

From their start in 2001, Pfizer's green chemistry initiatives have involved EHS professionals and process and medicinal chemists, according to Dunn. "By 2003, we had a global network, and in 2005, Pfizer became the first pharmaceutical company to appoint a full-time green chemistry leader," he says. "Progress became much more rapid when we had dedicated resources."

The network involves about 60 volunteers and two steering committees—one for technical matters and one for policy and communications. Although the tools are consistent across Pfizer's global operations, each company site has its own team to implement the tools, set objectives, and organize activities.

Dunn believes a core strength of Pfizer's program has been the ability to influence and change behavior by making green chemistry a part of everyday work. In turn, API development and manufacturing teams have delivered major cost and environmental savings, particularly for second-generation processes developed after the original had been approved by regulators.

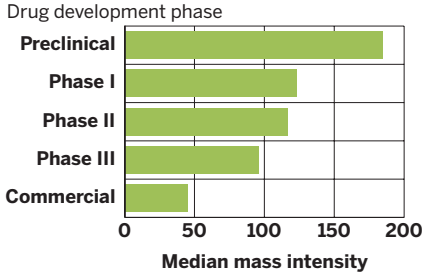
"We are willing to keep working on products during their patent life and make substantial changes," Dunn says. "Over that time, new technologies and methodologies become available, and it just makes sense to apply them and get the environmental and cost savings."

Through benchmarking 46 processes, Roundtable members found that the mass intensities—ranging from a low of 23 kg of material used per kg of API to a high of 887 kg for a complex multistep synthesis—improve as drugs progress through development and routes are refined.

Views are mixed, however, about when to invest effort in exploring alternatives. Some producers wait until later in develop-

BENCHMARKING REACTIONS

Process development improves the mass intensity of pharmaceutical production



NOTE: Based on data for a total of 46 processes across the phases. Mass intensity = kilograms of raw material input/kilogram of bulk active pharmaceutical ingredient.
SOURCE: ACS Green Chemistry Institute Pharmaceutical Roundtable

ment, when a compound looks more promising. Others say they think about it earlier and even try to engage medicinal chemists in the process, realizing that problematic wastes and costs will only accumulate.

Most drug manufacturers are willing to change processes through Phase II clinical development, after which time the chemistry gets locked in for regulatory approval. After a drug is approved, some firms may consider a second-generation method if the benefits outweigh the time and cost of filing again.

"OF COMPANIES we know are practicing green chemistry, the vast majority of their drugs that are going through the R&D process now are being developed with green principles in mind," Cue says. "I've been told some companies actually evaluate the greenness of their manufacturing process at the various decision-making stage gates that happen during the drug development process, and others have specific product stewardship champions who are assigned to figure out how green chemistry can be applied in a postapproval scenario."

Working in the companies' favor, the Food & Drug Administration appears to be moving more rapidly to approve changes that bring EHS benefits. "What FDA wants from us is a process that is well understood and well controlled, and that means having a very high level of understanding about the chemistry we are doing," GSK's Roper says. "And the greener and simpler we can make our processes, then the better understood we can make them, so I can see very clear alignment between what I want to do with green chemistry and what FDA expects."

It's unclear what will happen when mature drugs move into the large and fast-growing generics market. "Generic producers by and large are manufacturing drugs by the same processes that the ethical pharmaceutical companies use," Cue says. "But we can't yet determine whether they are making them with green chemistry considerations in mind and whether the processes are being reworked."

The generic drug sector is catching on, particularly when greener approaches offer improved economics, says Codexis Chief Scientific Officer John Grate, based on the company's experience making generic APIs and working with other generics suppliers. "It's of keen interest because they compete with each other on the same products by price and quality," he adds.

Also unclear is the extent to which things are happening in India and China, the home of many low-cost API producers. The ACS Green Chemistry Institute's Indian affiliate has established a Green Chemistry Network Centre in Delhi to promote green chemistry. In 2008, GCNC gave its Indo-U.S. Green Chemistry Award to Newreka Green Synth Technologies, based in Mumbai.

Newreka's customers include about two dozen Indian firms that have used its process technologies and recycle solutions, says Nitesh H. Mehta, a founder and director. Work has involved converting individual reaction steps, revamping entire routes, and cleaning up effluents to allow solvent recycling. With recent appearances at industry trade shows, Newreka is trying to launch itself in the U.S. and Europe.

CONSIDER THIS

Process chemistry and green chemistry have similar goals

GOAL	PROCESS CONSIDERATION	ENVIRONMENTAL CONSIDERATION
Minimize number of synthetic steps	Efficiency	Less energy and waste
Develop easy isolations	Scalability, throughput	Less waste
Avoid cryogenic conditions	Scalability, robustness, cost	Less energy
Achieve high selectivity	Efficiency, easy purification	Less waste
Avoid hazardous reagents/reactions	Safety, scalability	Safety, less pollution
Use inexpensive, available raw materials	Cost, lead time	Better waste management
Minimize oxidation state adjustments	Efficiency	Less waste (metal pollution)
Minimize use of protecting groups	Efficiency, atom economy	Less waste

SOURCES: Boehringer Ingelheim, *Green Chem. Lett. Rev.* **2008,** *1,* 141

The firm's recycle solutions can involve a range of chemical or physical interactions and transformations to clean effluent streams. After looking at a customer's chemistry, Newreka scientists test 50–60 performance chemicals or additives. "Our strength comes in doing a lot of experiments quickly to find the right formulations and conditions," Mehta explains. A customized result, he says, "should be something simple that is added to the effluent, selectively removes impurities, and allows recycling back into the process."

Newreka's process technologies center on using iron catalysts under mild conditions to replace more toxic or hard-to-use catalysts for reduction, nitration, and acetylation. "With a high level of conversion and selectivity, you automatically create less waste," Mehta says. "And any effluent stream is therefore easier to treat." In one large-scale reduction, he says, the customer has been able to recycle the water reaction medium 25 times.

In another project, a major Indian drug company has hired Newreka to rework a seven-step synthesis. "The initial four steps were pretty dirty," Mehta says, and after more than two years of work, new versions will soon be scaled up. "Making any changes in the last three steps is going to be very difficult," he notes, because they are part of the regulatory filing.

Newreka and other suppliers are trying to fill a need for new technologies by moving them out of the lab and into commercial use for pharmaceutical production. Most large drug firms have been focused on adopting green chemistry in their own manufacturing. Although they outsource work and routinely conduct EHS audits when selecting suppliers, they haven't necessarily looked at the green chemistry performance measures of these firms. Cost, quality, and timing remain the top considerations.

One reason is that large drug firms tend to transfer their own processes to third parties to make materials under contract. Most major drug companies now include outsourced intermediates and the processes to make them in their scorecards for manufacturing an API. In contrast, small drug firms without process development or manufacturing capabilities will likely rely on outside suppliers not only to produce materials but also to meet any environmental goals.

MOVES BY the Roundtable suggest that changes are coming. "Our core membership is still large multinational pharmaceutical companies, but DSM and Codexis have joined and they bring a fresh and different perspective," Dunn says. "I think it is going to be important to expand the membership beyond the multinational pharmaceutical firms, especially to small pharmaceutical and biopharmaceutical companies."

Codexis, itself a Presidential Green Chemistry Challenge Award winner for its biocatalytic route to an intermediate of Pfizer's cholesterol-lowering drug Lipitor, anticipates working with the Roundtable reagent guide team. "Biocatalysis is inherently green," Grate says, "and we saw a way to dovetail into the mission and objectives of the Roundtable."

As far as suggesting greener reactions goes, "we saw that biocatalytic solutions to some of these transformations were leanly represented, so we will help map those kinds of opportunities into the reagent selection guide," Grate says. "There are alternatives out there that with modern biotechnology can be made much more practical."

Likewise, Dunn says the Roundtable has started a team, in which DSM will play an important role, to look at supply issues and how to get standardized green chemistry metrics from suppliers. As a corporation,

DSM has a strong position in sustainability, says Ronald Gebhard, R&D director for DSM Pharmaceutical Products, and the technology development strategy of its pharmaceutical unit closely mirrors the needs defined by the drug industry.

"I am convinced that five years from now sustainability will be part of the checklists of the pharmaceutical company procurement departments," Gebhard says. "It has to be if we take this seriously, and I think the fact that pharmaceutical companies initiated the Roundtable is a sign that they do.

"Together with pharmaceutical partners, we'll try to come up with guidelines that suppliers will need to adhere to," Gebhard continues. Possible ideas include providing E factors or process mass indexes, along with estimates for how these measures might improve over time. "Of course, it is in our interest as a sustainable Western supplier in a highly regulated environment to set the bar quite high," he admits.

Greener technologies may initially be more expensive because of the up-front costs to develop and scale them. "But I have never seen a mature green process that is more expensive than a mature chemical process," Gebhard says. "I would welcome it if there was a premium for suppliers who can show that they have bona fide sustainable processes as compared with low-cost players who most likely do not."

For example, he points to the increased use of chemo- and biocatalysis for large-scale API production, as well as to the emergence of continuous and microreactor processes at DSM.

Another practitioner of continuous production, the French fine chemicals firm Novasep, can provide several alternative technologies, says Jean Blehaut, director of marketing and business development. The company has been developing microreactor and flow technologies as an outgrowth of its expertise in energetic and hazardous chemistries. Reactions can be safer or easier to handle at small scale, and better selectivity and impurity profiles can lead to fewer downstream purification steps.

Novasep also has developed large-scale chromatographic methods used today to manufacture several blockbuster drugs. "Turning batch chemistry or chromatography into continuous processes generally will lead to process improvements," Blehaut explains. "Continuous chromatography allows us to reduce the amount of solvent necessary to purify the material," he says, and, when coupled with efficient

solvent concentration methods, to recycle almost all the solvent.

A dramatic example is the process UCB uses to separate enantiomers of etiracetam for its antiepileptic drug Keppra. While making hundreds of tons of API per year, UCB has been able to recycle 99.97% of the solvent. When the undesired enantiomer can be racemized and reprocessed, chiral separations become even more cost-efficient and less wasteful.

For smaller scale separations, Novasep supplies supercritical fluid chromatography systems. SFC typically uses a mixture of carbon dioxide, which is recycled, and 2–20% organic solvent. "This technology is becoming very popular in the small preparative labs to support medicinal chemistry with milligram to gram amounts and up to kilograms for chemical development needs," Blehaut says.

When reviewing their operations, many pharmaceutical companies are looking for green chemistry opportunities in existing products and are trying to ensure work is under way on those in development. Process chemists say it only makes sense to try to improve process efficiency for a product their companies will likely sell for a long time in large volumes.

Process development managers say it's hard to predict, however, what kinds of medicines will be launched in the future. They expect less reliance on blockbuster drugs and more diversification into biologics and small-volume niche products. Major cost savings, they say, will therefore be harder to come up with through environmentally friendly processes.

AT THE SAME TIME, DSM's Gebhard notes, medicinal chemistry is pumping out more complex molecules that often require challenging multistep syntheses. "The bar is being set higher, which means that process development and custom manufacturing need to come up with more creative solutions to meet sustainability targets," he says.

Although the industry has made progress, it still has opportunities for innovation and areas that need work. "The low-hanging fruit was addressing both qualitatively and quantitatively the solvents that are used," Cue says. Much of the improvement, company managers say, was achieved simply by making people more aware and changing old habits.

Cue also believes that coming up with the right metrics to get baseline data and set improvement goals has begun to help reduce the process mass intensity of pharmaceutical development and production. Meanwhile, money invested in academic research is starting to yield new alternatives for many reactions and reagents.

"From the pharmaceutically unique building block to the active drug, that part of the life cycle is well in hand," he says. But the pharmaceutical industry still relies almost exclusively on fossil-fuel-based raw materials, he adds, "and at some point has got to look at renewable ones as well."

Likewise, the industry faces pressure to address all aspects of a drug compound's life cycle, including formulation, delivery, and persistence in the environment. These areas, Cue says "are a whole work in progress and include huge challenges." ■