Seize the Moment: Opportunities for Green Chemistry and Green Engineering in the Pharmaceutical Industry

U.S. Environmental Protection Agency
Region 2

Summary of Workshop
September 27, 2007

The U.S. Environmental Protection Agency (EPA) Region 2 would like to thank those individuals who agreed to be speakers or moderators for the workshop (Appendix D). In addition, EPA Region 2 would like to acknowledge those individuals who provided suggestions for the agenda for this event (Appendix E). For specific questions regarding the overall workshop, or information in this summary, please contact Walter H. Schoepf, Pollution Prevention Team, EPA Region 2 at (212) 637-3729. Special thanks to Eastern Research Group, Inc. for their assistance in organizing the workshop.

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Introduction

On September 27, 2007, representatives from federal and state government agencies, the pharmaceutical industry, academia, and other interested parties gathered to learn more about opportunities to encourage environmental stewardship (e.g., green chemistry and green engineering) in the pharmaceutical industry. The intensive one-day workshop both educated and offered a dialogue on how to promote green chemistry and green engineering practices to achieve more sustainable outcomes. The participants examined the nature and magnitude of the pharmaceutical manufacturing industry's environmental footprint; discussed opportunities and barriers to improvement throughout the manufacturing process; explored ideas on how to better promote green chemistry and green engineering in manufacturing processes within the pharmaceutical industry; presented the values embodied in green chemistry and green engineering principles and overall thinking, as well as how these values can be integrated into the pharmaceutical industry; demonstrated some exemplary industry-based practices of green chemistry and green engineering; and highlighted some exemplary technical approaches, options, and tools to improve chemical design and process efficiency. Sixty-five participants attended the one-day workshop hosted by the U.S. Environmental Protection Agency (EPA) Region 2. The workshop consisted of five sessions led by green chemistry and engineering champions in the pharmaceutical industry, as well as members from EPA and the U.S. Food and Drug Administration (FDA). The workshop included welcoming remarks by EPA and FDA, eight presentations, one facilitated dialogue, and closing comments by EPA. Presentations are available at the Workshop Web site at www.epa.gov/region2/p2/agenda.html and are available only with permission of the speaker.

Summary

Welcome/Introduction

Walter Schoepf, EPA Region 2, opened the Seize the Moment: Opportunities for Green Chemistry and Green Engineering in the Pharmaceutical Industry workshop by welcoming the participants and reviewing the handouts available. The handouts included the workshop agenda (Appendix B), an evaluation form (Appendix C), American Chemical Society (ACS) Green Chemistry Institute Pharmaceutical Roundtable handouts (including brochures and CDs), information on the Presidential Green Chemistry Challenge, a call for papers for the 2008 American Institute of Chemical Engineers (AIChE) Annual Meeting, and the questions for facilitated dialogue in Session 5. Mr. Schoepf then introduced Kathleen Callahan, Deputy Regional Administrator, EPA Region 2, and D. Christopher Watts, Standards & Technology, U.S. Food and Drug Administration Center for Drug Evaluation and Research/Office of Pharmaceutical Science.

Ms. Callahan emphasized the relationship between an effective economy and a healthy environment. She also discussed the importance of government and industry collaboration to address the complex interactions involved in creating sustainability and cited examples of numerous EPA partnership programs, including a grant with Rowan University.

Dr. Watts thanked EPA Region 2 for hosting the workshop and expressed that he was eager to participate in the upcoming sessions and discussions. He stated that opportunities increase significantly when there is collaboration between agencies and industry, and stressed the importance of innovation.

Session 1: The Pharmaceutical Industry—Environmental Footprint

Sharon Austin

U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics,

Green Engineering Program

Presentation: Environmental Footprint and Opportunities in Pharmaceutical Processes

Ms. Austin emphasized the importance of implementing greener chemical and engineering practices throughout every level of the pharmaceutical industry. She also introduced the concept of "green quality," the notion that as long as product quality is maintained, pharmaceutical manufacturing should have flexibility to make process changes to implement green chemistry and engineering changes. Significant impacts and progress have been made in green chemistry and green engineering, including energy recovery, solvent substitution and reduction, and water efficiency initiatives. Ms. Austin indicated

that the largest contributor to the pharmaceutical industry's environmental footprint comes from solvent use. She said expanding educational efforts, integration of risk assessments, and life-cycle analyses could further reduce the footprint of pharmaceutical production processes. Finally, current congressional activities are stimulating innovation in green chemistry and engineering by allowing opportunities for interagency collaboration and partnership with industry.

David J. C. Constable

GlaxoSmithKline

Presentation: The Pharmaceutical Footprint – Opportunities for Green Chemistry and Engineering

Mr. Constable stated that the complexity of the pharmaceutical industry necessitates a holistic approach to greening its processes, starting with a paradigm shift from focusing only on waste management to an approach that encompasses manufacturing process efficiency, yield, and economic gains for pharmaceutical companies. A barrier to greening the pharmaceutical industry is the misperception that making changes is difficult and costly. He said that the industry has historically focused on waste, but to incorporate green chemistry and green engineering into standard procedures, it is necessary to move away from dialogue about waste and toward dialogue about efficiency.

D. Christopher Watts

Standards & Technology, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science

Presentation: Opportunities for "Green Quality" and Control

FDA's regulatory processes are evolving away from extensive product testing and toward a more flexible and efficient manufacturing approach, said Dr. Watts. If a process is well controlled, product sampling and inspection are redundant and unnecessary, and might hinder innovation. He mentioned the Process and Analytical Technology (PAT) Initiative is a system for designing, analyzing, and controlling manufacturing through timely measurements. Additionally, he said direct measurements gathered during the manufacturing process can serve as the basis for real-time release of the final product, demonstrating that each batch conforms to established regulatory quality attributes and enabling more efficient processes.

Dr. Watts indicated that FDA will continue to provide guidance and regulate the quality of end products, but FDA is shifting supply and process decisions to the manufacturer through increased focus on product quality rather than the entire process. Collaboration between FDA, EPA, and the pharmaceutical industry will create opportunities for innovation and improved processes.

Session 2: Green Chemistry and Green Engineering in the Pharmaceutical Industry

Richard Engler

U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Green Chemistry Program

Presentation: Principles of Green Chemistry & Green Engineering

Dr. Engler gave an overview of the basic principles of green chemistry and green engineering. He explained the overlap between the two disciplines and expounded on the notion that green engineering has a broader focus than green chemistry, which focuses on a smaller scale of reactions. He discussed pollution prevention and the risk management hierarchy, which prioritizes source reduction over recycling, waste treatment, and disposal. The economic benefits of source reduction and green processes should be promoted as incentives for the industry to change. Green chemistry and engineering proponents can highlight the benefits of green processes and conduct outreach to engage stakeholders to earn their support for green initiatives.

The Presidential Green Chemistry Challenge Awards Program provides national recognition of outstanding chemical technologies that incorporate the principles of green chemistry into chemical design, manufacture, and use, and that have been or can be utilized by industry in achieving their pollution prevention goals. Dr. Engler encouraged participants to nominate new technologies for the award to publicize their achievements. More information on the Presidential Green Chemistry Challenge Awards Program can be found on EPA's Green Chemistry Web site, located at www.epa.gov/greenchemistry.

Session 3: Green Chemistry/Green Engineering Technical Approaches

John Leazer

Merck & Co., Inc.

Presentation: Preparative SFC at the Kilogram Scale to Support Pharmaceutical Development

Dr. Leazer explained that Merck's emphasis on innovation in pharmaceutical technologies and practices has contributed to the company's development of several innovative and efficient processes. One such practice is supercritical fluid chromatography (SFC). A supercritical fluid is a substance that is above its critical temperature (Tc) and critical pressure (Pc), and exists as a single phase. SFC facilitates faster analysis, reuses carbon dioxide that would otherwise be released to the atmosphere, and uses significantly less solvents than classical chromatography. New SFC instruments have been developed for both small

and large scale separations. He said SFC has translated into increased productivity and cost savings from energy use and manpower hours for Merck.

John Tucker

BioVerdant, Inc.

Presentation: Green Enzymatic Synthetic Organic Chemistry

Mr. Tucker discussed green chemistry and green engineering as long-term philosophies and behaviors rather than one-time approaches to specific processes. He stated green chemistry evolves through awareness and application of the 12 Principles of Green Chemistry (John Warner and Paul Anastas in their publication Green Chemistry Theory and Practice, Oxford Univ. Press, 1998). Green chemistry also emphasizes changing technical approaches in a broad and general sense, as well as through targeted technologies to achieve goals that are unobtainable using current methodology. The energy and solvent reductions intrinsic to green chemistry, as well as atom economy, increased worker safety, reagent optimization, and convergency reduce manufacturing costs, making green chemistry both cost efficient and environmentally friendly. Mr. Tucker said focused green chemistry considering strengths and weaknesses of biotransformation concomitant with retrosynthetic analysis makes possible the general use of enzyme technology for improved synthetic efficiency and reduced environmental waste with a higher probability of success. He also stressed that any green technology should ultimately be destined for general use by the community of green chemists.

Session 4: Exemplary Practices of Green Chemistry and Green Engineering

Berkeley W. Cue, Jr.

American Chemical Society Green Chemistry Institute, Pharmaceutical Roundtable Association

Presentation: Green Chemistry in the Pharmaceutical Industry: A Model for Industrial Sustainability

Dr. Cue stated that green chemistry is redesigning the future of the pharmaceutical industry by adopting a life-cycle philosophy considering all materials and methods involved in manufacturing pharmaceutical products. The pharmaceutical industry's commitment to improving health should also include a commitment to maintaining a healthy environment. In today's marketplace, sustainability is a benchmark for a company's success. The ACS Green Chemistry Institute Pharmaceutical Roundtable was formed in 2005 and conducts research on issues identified as priorities by its members. Many of the top Fortune 500 companies are members of the Roundtable. The pharmaceutical industry is already using many principles and practices of the 12 Principles of Green Chemistry, including atom economy and less hazardous chemical syntheses, but opportunities to expand the implementation of green chemistry and engineering techniques still exist. Reducing waste in production processes, one option for greening manufacturing

practices, can save money throughout the pharmaceutical industry. Dr. Cue indicated that the Roundtable is a good way to use the collective knowledge of peers in the pharmaceutical industry.

Stephan P. Taylor

Bristol-Myers Squibb Company

Presentation: Integrating Process Greenness into the Business

Dr. Taylor began by saying that there is a clear connection between the popular industrial concept of lean and green chemistry and green engineering. He said that corporate support and commitment is essential to implementing environmentally preferable product design within a company. Bristol-Myers Squibb began using the Process Greenness Scorecard in 2000 to rate the environmental impacts and risks at each step of a compound's development through the pipeline and through manufacturing. The Process Greenness Scorecard has since been integrated into the company's daily activities. A benefit of voluntarily implementing green initiatives is spending less time addressing regulatory requirements, because they have already been met or exceeded. The Process Greenness Scorecard uses a weighted scale to rate 16 parameters that affect production including solvent recovery percentage, amount of liquid and solid process waste, number of listed reagents, and potential to emit. The Scorecard facilitates taking a holistic approach to reviewing the company's impact on the environment. Dr. Taylor explained that one option for creating a corporate atmosphere that encourages the use of green chemistry and engineering is to provide incentives and reward employees that have incorporated green techniques into their chemistry and engineering practices.

Session 5: Facilitated Dialogue—How to Better Promote Green Chemistry and Green Engineering in the Pharmaceutical Industry

In this session, participants were asked to work together to answer the following two questions:

1. What are you doing to promote and/or implement green chemistry and green engineering principles and practices?
2. What suggestions do you have to overcome barriers and/or further promote and implement green chemistry and green engineering principles and practices both within your own organization and in the pharmaceutical manufacturing industry?

A summary of the participants' answers to the questions and ensuing discussions follows:[1]

[1] Participants' contributions are organized and edited only to allow for better ease of presentation for the purposes of this summary.

Question 1: What are you doing to promote and/or implement green chemistry and green engineering principles and practices?

1. Efforts to Promote Green Chemistry/Green Engineering Innovation

Raising Awareness

- Increasing the priority of pollution prevention for upper management. Upper management focuses on social agenda issues. At local, factory, and research and development levels there is significant interest in green chemistry and engineering. Risk aversion is a barrier to green practices.
- Constantly publicizing successes throughout organization, from division heads to vice presidents. If green practices have management's support, there are fewer barriers to implementation. As part of the Environmental Health and Safety (EHS) department, it is daunting for employees to think in terms of green chemistry and engineering. However, EHS employees can act as ambassadors for green chemistry and engineering. EHS can take concrete steps to enact change and be a change agent. One way to promote green chemistry and engineering is to shift the language surrounding green practices from waste to cost savings.
- Organizing minions in the corporation.

Providing Recognition

- *Individual Level*: Using the electronic notebook initiative as an example, publicizing when a "superuser" gets promoted through an announcement that recognizes him as a champion. Companies could use the same principle with green chemistry and engineering by recognizing champions.
- *Corporate Level*: As technical advisors, showcasing companies that have implemented efforts to reduce carbon dioxide, solvent use, and their overall environmental footprint. When Pfizer won the Green Chemistry Presidential Challenge, the company's status in the pharmaceutical industry provided an impetus for other pharmaceutical companies' to begin green chemistry initiatives.
- *All Levels:* Recognizing and rewarding green chemistry efforts.

Encouraging Organizational Networks and Effectively Managing Change

- Johnson & Johnson is involved in green chemistry. The company has an award process recognizing green chemistry initiatives and is looking at the possibility of creating a council for green chemistry. Right now, green chemistry is a part-time effort by many different employees. Having the structure of a council allows for a more systematic approach. The council will bring

information together and disseminate it throughout the company. Johnson & Johnson joined the ACS Green Chemistry Institute Pharmaceutical Roundtable and is using it as a resource.

2. Efforts That Create an External Demand for Green Chemistry/Green Engineering Innovation

- Setting limits on less-green options.

3. Efforts to Encourage Collaborations and Partnerships Related to Green Chemistry/Green Engineering Innovation

- *Individual Level*: Chemists and engineers are working together with the hope of carrying green processes forward into manufacturing. Implementing green practices as early as possible. Thinking green while in development of product, before seeking approval.
- *Individual Level*: Microbiologists and enzymologists are beginning to work with chemical engineers.
- *Corporate Level*: Corporations are joining ACS Green Chemistry Institute Pharmaceutical Roundtable.

4. Efforts to Encourage Education, Training, and Information Exchanges Related to Green Chemistry/Green Engineering Innovation

- Developing workshops about green chemistry and green engineering.
- Improving research and education in green engineering and sustainability.
- Infusing green chemistry and engineering into higher education (e.g., publishing a green engineering and/or green chemistry textbook).
- Sharing information from Seize the Moment workshop with company.

5. Efforts to Provide Information, Measures, Tools, and Technology that Advance Green Chemistry/Green Engineering Innovation

- Developing companywide metrics.
- Promoting new technologies. Proving that the new technologies work and reduce solvent use.
- Developing solvent selection tools.
- The Biomimicry Guild is putting biological literature in the database in chemical language so that chemists can understand it and it can be used in sustainability challenges.
- Using pollution prevention hierarchy to guide new process designs. If a material is not recyclable, selling the material as a feedstock to a company who can use it.

- BioVerdant is using green chemistry tools similar to those used by larger companies, such as solvent selection tools, but in a holistic fashion examining overall effect upon process efficiency in addition to individual solvent safety and toxicology concerns. A process development paradigm is used during discovery-level synthetic design. This incorporates early application of scaleable reagents and methods and minimization of solvent use at an earlier-than-traditional development stage. To measure progress, percent E-factor is used in goal setting, feedback, and improvement. Examining percentage improvement of E-factor from beginning to end of processes as opposed to the raw E-factor number serves to mitigate implicit differences in synthetic chemical difficulty. This can enable direct comparisons across different projects and processes. Bringing in speakers to highlight papers serves to educate and can be done relatively easily in a small company.
- Encouraging people to use class three solvents—solvents with low toxic potential. Chlorohydrocarbons, such as methylene chloride, are used as solvents for many chemical processes. Although methylene chloride is the least toxic of the simple chlorohydrocarbons, it still carries several health risks. To decrease toxic potential in chemical reactions, some chemists have attempted to remove methylene chloride from reactions, although it is a necessary compound for unique reactions. If chemists used less methylene chloride in chemical reactions, they would have to substitute another type of solvent, which might have other environmental impacts. By comparison with other solvents, in some cases methylene chloride might be considered green. The use of methylene chloride should be considered on a case by case basis.
- Using preventative measures as part of green process (e.g., finding fugitive leaks and spills and fixing them).
- Researching the utilization of solid phase micro extraction for identifying volatile to semi-volatile contaminants in the environment.
- Providing consulting on water and wastewater management.
- Implementing energy management programs at corporations.

6. Encourage Ways of Thinking Based on Green Chemistry/Green Engineering Principles, P2, Industrial Ecology, Stewardship, and Sustainability

- Lifecycle thinking.
- Beginning with process design and manufacturing design.
- Promoting green awareness.
- Thinking at system level.

Question 2: What suggestions do you have to overcome barriers and/or further promote and implement green chemistry and green engineering principles and practices both within your own organization and in the pharmaceutical manufacturing industry?

1. Efforts to Promote Green Chemistry/Green Engineering Innovation

Raising Awareness

- Risk adversity awareness needs to be increased. There is a need for management to connect with lower level employees. Those least likely to invest in processes deemed as risks are mid-level employees.
- There is a need for better communication between chemists and upper management. Green chemistry principles are inherently efficient and will help get products to market quickly.

2. Efforts That Create an External Demand for Green Chemistry/Green Engineering Innovation

Pursuing Further Federal, State, and Other Stakeholders' Actions

- Pollution prevention would be taken more seriously if it were implemented by regulatory agencies. Pollution prevention would receive top-down buy-in if bench chemists were being told to stop using a certain chemical.
- Five years ago FDA was not involved in promoting green chemistry. Companies have noticed that FDA is now championing green chemistry.
- There are currently regulatory hurdles to implementing green chemistry and engineering, but if FDA continues to evolve away from regulations, it will make it easier for companies to experiment with green processes.
- Stakeholders and regulators need to be engaged and educated about green chemistry because they do not fully understand the processes involved.
- Media, permitting programs, and enforcement programs need to be engaged as stakeholders in the green chemistry and engineering discussion.
- A state consensus document needs to be developed.

Transforming Larger Incentive Systems

- Larger incentive systems and relationships are in place that keep promoting problematic paradigms that act as barriers to green chemistry. The green chemistry bill in the future may provide additional funds and incentives for green chemistry.

3. Efforts to Encourage Collaborations and Partnerships Related to Green Chemistry/Green Engineering Innovation

- Including a volunteer group, for example, the Interstate Technology & Regulatory Council (ITRC), to work with industry, academia, stakeholders, and regulators to produce materials applicable for all sectors nationwide.
- Developing partnerships between industry, regulatory agencies, and academia.

4. Efforts to Encourage Education, Training, and Information Exchanges Related to Green Chemistry/Green Engineering Innovation

Encouraging Industry—University Information Exchanges

- Remember that green chemistry has only been a topic of conversation for the past 10 years. Over the past 10 years there has been a significant increase in representation at green chemistry meetings from academia and industry.
- Hold more interdisciplinary/inter-sector meetings, but with a larger academic component.

Integrating Concepts Into Classroom Settings

- Bring a greater awareness about green chemistry and engineering to college campuses.
- Realize students understand that green chemistry is important.
- Have industry mentors in the classroom or involved in education.

Creating Other Information Exchange Opportunities

- At the upcoming GC3 meeting in Chicago, the National Pollution Prevention Roundtable will gather to discuss green chemistry.

5. Efforts to Provide Information, Measures, Tools, Technology That Advances Green Chemistry/Green Engineering Innovation

Improving Case Studies on Costs/Benefits

- Case studies to explain the economic benefits of green chemistry are few and many of them were written several years ago. EPA should use current literature to develop new case studies that clearly explain pay back times and cost savings from using green chemistry and engineering.
- Education on green engineering benefits is needed.
- Because of propriety information, the pharmaceutical industry is reluctant to share economic information.

Providing Case Studies to New Audiences

- We need to identify the right target audience and develop case studies that speak to upper management. To reinvent case studies, we should use an objective researcher, involve a multi-disciplinary team, and link case studies into an actual change management process with incentives.

Improving Case Studies on Successes

- Harvard is working on creating new case studies on the use of green chemistry and engineering in the pharmaceutical industry. Harvard business school hosted a conference to brainstorm barriers to green practices in the pharmaceutical industry and will present its findings in the next few months. Once case studies on the barriers to implementing green practices have been published, the next step is to produce case studies on companies or champions who were successful in surmounting those barriers.

Improving Information and Analysis

- Researchers need tools to communicate with each other. Now that companies have facilities located around the world, they need the right mechanisms to communicate and ask questions among themselves.
- Education on the ways, methods, and costs of implementing these ideas or giving more consultation services is lacking.
- Most energy used in the pharmaceutical industry is used in the research process. Production uses energy to make steam, but the largest sink of energy is in research labs.

6. Encourage Ways of Thinking Based on Green Chemistry/Green Engineering Principles, P2, Industrial Ecology, Stewardship, and Sustainability

Promoting Holistic Organizational P2 Planning

- There is a lack of pollution prevention policies and goals. It is necessary to use a holistic approach when reviewing processes. This may include developing a time frame, gaining upper management support, developing pollution prevention policy, and being more aggressive with setting goals.

Changing Perspectives of Chemists

- There is a perception that green chemistry is more difficult, but it is only more difficult if chemists are not trained and if there are not replacement solvents to use green chemistry. Second

and third generation processes are more green and produce higher quality products because at that point in the process the chemists understand the chemistry and use this understanding to improve the process and product.

- Chemists might have a hard time buying into green chemistry for the following reasons:
  - They lack education on the subject.
  - Traditional organic chemists and elite academic scientists don't consider green chemistry a rigorous science. These chemistry leaders' power and influence stops the rest of the chemistry community from actively participating in green chemistry.
  - They lack time to develop green chemistry processes. Academics want to publish research as quickly as possible.
  - The longer it takes to get a product into manufacturing, the less money a company makes.

Overcoming Sector and Marketplace Norms

- Energy use often has the largest environmental footprint. The industry's mindset also acts as a barrier—the industry needs to start thinking outside of the box. In the pharmaceutical context, there are many processes that make it difficult to predict where waste will occur. When addressing waste issues, an important area to keep in mind is energy use. An additional barrier is the mindset that processes cannot occur continuously in chemistry.
- The perception that chemists need to speed up the process of getting a product on the market is a barrier. Green chemistry is not slower, but stakeholders are not aware that green chemistry can be done at the same speed.
- Currently, pharmaceutical companies compete to be the first to put a product on the market. Attempting to get a product on the market as fast as possible might be in conflict with getting the best medicine to society.

Overcoming Ways of Thinking by Other Stakeholders

- Single-issue environmentalism and focusing only on immediate steps in production processes are nonholistic approaches and barriers to green chemistry and engineering.

Overcoming Disciplinary-Based Stove-Pipes

- Eliminate the distinction between green chemistry and green engineering. Change the focus to process and quality design.

Overcoming the Dominant Ways of Thinking

- Complacency and acceptance.
- In some cases, the cradle-to-grave philosophy perpetuates wasteful processes.

Priority Issues to Address

The workshop participants and facilitators identified the following list of priorities to address barriers to promoting and implementing green chemistry and engineering:

1. Communication
    a. Between disciplines (chemistry/biology/engineers/public)
        i. Lack of understanding when communicating with chemists because of jargon.
        ii. More cross-disciplinary meetings are needed.
    b. Between management and those doing work.

2. Education
    a. Recognize that green chemistry and engineering require a hybrid of organic chemistry, chemical engineering, and toxicology education.
    b. Train pharmaceutical chemists to be able to converse about environmental science, regulations, and organic chemistry.
    c. Collaborate.
    d. Question how best to disseminate information.
    e. Create a tool kit—find the green reaction, determine how can it be used, and develop the process.

3. Cultural—Multi-Disciplinary Interaction
    a. Cultural belief that green chemistry is not rigorous, that it is not real science, and not elite.
    b. Lack of understanding from general public.
    c. Lack of support.
    d. Lack of funding opportunities.

4. Data—Information
    a. Sharing and disseminating results.
    b. Data.
    c. Publicizing that green chemistry works.

5. Inertia—Regulatory Barriers

a. Green chemistry/engineering is not widely implemented in the pharmaceutical industry yet.
b. In order to take a holistic approach to greening the pharmaceutical industry, pollution prevention needs to incorporate into green chemistry and engineering.
c. Paperwork required by FDA when a pharmaceutical manufacturer changes chemical processes acts as a barrier to green chemistry.

Appendix A: Questions, Answers, and Comments

Session 1: The Pharmaceutical Industry—Environmental Footprint

Q: David, how well have you done integrating green engineering into GlaxoSmithKline's (GSK's) culture? Has everyone at GSK bought into green engineering?
A: *(Constable)* GSK has a sustainable processing team that works with groups at local facilities to integrate green chemistry and green engineering. The sustainable processing team reports back to management routinely. GSK set corporate targets, identified measures to encourage green chemistry and green engineering, and established sustainable processing teams. There are champions of green chemistry and green engineering at GSK, but not everyone is practicing it or has bought into the idea.

Q: Would developing patents for green pharmaceutical products be an incentive to practice green chemistry and green engineering?
A: *(Watts)* It could be, but developing patents could also be a hurdle for FDA and the U.S. Patent Office to determine what should be considered green. This concept has been discussed for a number of years, and may be worth exploring further.

Q: If FDA steps back from regulating the pharmaceutical industry's intermediate processes, who is responsible for the safety of the process and products?
A: *(Watts)* The manufacturer bears the responsibility for the safety of its products. As long as the material attributes and quality of the end product meet set standards, FDA may not need to be involved in the process. Quality is always considered, but a process change that has no effect on product quality, safety, or efficacy should not require prior approval from FDA.

Q: A trend at API Industries is that the processing of products is outsourced to foreign countries, such as India and China. A main concern of outsourcing is safety and environmental issues. How should we address outsourcing?
A: *(Watts)* As a manufacturer, you are not outsourcing the responsibility, you are still responsible for product quality.

A: *(Constable)* Green processes have to occur throughout the lifetime of the product. Pfizer, for example, is good at focusing on the lifetime of product; GSK is not. Outsourcing might be a short-lived phenomenon, and eventually green chemistry will create less expensive processes.

A: *(Austin)* A manufacturer is responsible for meeting U.S. safety requirements if its product is coming into the U.S. market.

A: *(Constable)* When manufacturers consider international businesses to outsource to, they audit the businesses' practices. GSK recognizes the need to consider health, safety, environmental, and quality issues.

Comment: *(Anonymous)* It is helpful to consider all parts of processes in the pharmaceutical industry when attempting to green the industry. One component to consider when discussing greening the pharmaceutical industry is using environmentally friendly materials and verifying that the supply chain for materials used in the industry are green.

Comment: *(Anonymous)* It would be helpful to include water quality and air quality standards as components of green chemistry and green engineering.

Q: The use of reagents is typically not a main focus when discussing green chemistry. How do reagents fit into green chemistry and green engineering?
A: *(Constable)* Both solvents and reagents are involved in chemical reactions, so both should be considered when attempting to green chemical and engineering techniques. Use a cradle-to-grave analysis to consider the environmental impact of the solvents and reagents needed to create pharmaceutical products.

Q: How long will it take to move FDA's mentality toward the new approach of not becoming involved in the intermediate phases of pharmaceutical processes?
A: *(Watts)* FDA is ready, although it will require training and education to stay on top of what's happening in the pharmaceutical industry. It is up to the industry to say it is ready to move in this direction. FDA is already moving away from sampling and testing. It is also working with sister agencies, such as EPA, and agencies in Europe. By moving away from regulating each step in the production process, it will reduce the chances that FDA is acting as a barrier to innovation. Senior management at FDA has signed on to the new approach. FDA wants to be a catalyst to innovation in the pharmaceutical industry rather than a hindrance.

Session 2: Green Chemistry and Green Engineering in the Pharmaceutical Industry

Q: You mentioned the financial and business case for greening the pharmaceutical industry, but are you aware of any available financial data or case studies?
A: *(Engler)* ACS's Green Chemistry Institute has developed case studies, but they might not be publicly available. It is important to have hard data to use as justification for greening processes.

Most existing case studies do not provide hard numbers. It is difficult to obtain numbers from the pharmaceutical industry, although this would provide good anecdotal evidence for upper management that green techniques are possible and beneficial.

Q: Has EPA considered developing a rating system or labeling program for materials used in the pharmaceutical industry to identify environmentally friendly products, similar to the EnergySTAR program?
A: *(Engler)* EPA has not developed a rating system for materials used in pharmaceutical manufacturing processes, but other organizations have developed greenness rating systems for internal use. For example, SC Johnson developed a "Greenlist" system to rate all of the ingredients that go into its products. Management uses these greenness scores to set goals for improvement. Other companies have developed similar green rating systems for products. It is complicated for EPA to set overarching criteria for rating green products for the entire pharmaceutical industry, but through individual requests EPA can provide guidance on purchasing green products and examples of various green product rating systems developed by pharmaceutical companies.

Q: Would it be helpful to create a guidance tool on developing standards for green suppliers?
A: *(Cue)* Creating tools will be part of the focus of the ACS Green Chemistry Institute Pharmaceutical Roundtable meeting in Washington, D.C., in 2008. Many companies have created internal tools, but the roundtable will discuss developing tools to provide to new companies. There are many tools to choose from, and it is often confusing for chemists to determine which tool will best fit their needs. There is a need for consistency in green procurement tools for the pharmaceutical industry.

Q: If you knew the ratio of money saved from using green chemistry and engineering techniques per kilogram of pharmaceutical product, could you develop a calculation to determine the economic benefits of greening the pharmaceutical industry?
A: *(Constable)* Implementing green chemistry and engineering could potentially significantly reduce costs for a pharmaceutical company, but there are larger cost components that management focuses on,

such as the withdrawal of a product from the market. At a local level, there are many opportunities for cost savings from greening pharmaceutical processes, but at a companywide level, safety takes precedence.

At the organizational level, incorporating green chemistry and engineering into corporate sustainability models and implementing green activities at the grassroots level is important to changing company mentality to support these practices.

At the larger societal level, as green chemistry is incorporated into high school and college chemistry curricula, green chemistry will be synonymous with good chemistry and will be a fundamental part of practiced chemistry.

Q: Do any companies specify "knowledge of green chemistry" in job descriptions?
A: *(Engler)* If companies begin including green chemistry as a desired skill, applicants will request that academic departments teach green chemistry. It would help encourage universities to focus on green chemistry if pharmaceutical companies requested this skill. A long term goal is to publish a green chemistry textbook.

Q: Is there a roundtable for green chemistry education?
A: *(Austin)* There are already many tools for teaching green chemistry, and many lab experiments, but the amount of green chemistry included in chemistry curriculum varies professor by professor.

Q: It is discouraging that there is a lack of impetus to encourage green chemistry in pharmaceutical companies at the highest levels. Also, although cost savings is the main driver for company initiatives, there are many benefits to introducing green activities, including a reduction in outsourcing.
A: *(Schoepf)* Implementing green chemistry and engineering in the pharmaceutical industry is an evolutionary process. The title of the workshop is critical—there is a need to seize the moment and move forward in a steady manner. Additional tools for implementing green chemistry and engineering will be developed as these concepts gain priority and a culture of green chemistry/green engineering gains ascendancy.

Session 3: Green Chemistry/Green Engineering Technical Approaches

Q: One thing that has always concerned me about SFC is the possibility that aerosols might be created during separation processes. Also, carbon dioxide releases from industrial manufacturing and fermentation processes could cause health problems for individuals in the vicinity of the facility.
A: *(Leazer)* Aerosols are created in a pressurized tank, and the process is performed in a safe manner. There is a protocol to handle potential carbon dioxide releases, including carbon dioxide detectors throughout Merck's facilities that alert emergency response teams in the event of a carbon dioxide release. Merck has been using SFC since the early to mid-1990s, and has never had an incident involving a carbon dioxide release.

Q: When I'm discussing green chemistry and using enzymes, chemists often say the process is great if it crystallizes out and can be filtered, but otherwise it has to be extracted out using organic salt.
A: *(Tucker)* Using organic solvents to extract product from an enzyme reaction can be particularly challenging because the textures can be gelatinous. Often, this has translated to copious amounts of organic solvent being used in a non-green fashion to overcome the difficulty in separating the desired product from the gelatinous, aqueous enzyme mixture. It is often advantageous to instead attempt isolation of the enzyme from the water layer rather than extracting the organic product. This can be accomplished by adding small amounts of cosolvents which crystallize the enzymes for filtration and removal, leaving the product in the liquor for easy extraction with very small amounts of organic solvent. It is then possible to increase the over-all efficiency of the process. Used in the correct manner, the advantages of enzyme selectivity and activity outweigh the disadvantages in processing that require significant chemistry skill to overcome.

Q: Looking at the complete life-cycle for SFC, the energy to run the process creates carbon dioxide from burning fuels. Was the carbon dioxide created as a byproduct of industrial manufacturing and fermentation processes accounted for in life-cycle and cost analyses?
A: *(Leazer)* Carbon dioxide is recycled, and not released, when using SFC. Using SFC shortens development work by months or years, reducing energy and labor costs. Merck has not done any specific calculations comparing the energy use of SFC versus classical chromatography, but a comparison between the two types of chromatography would most likely show that SFC uses less energy overall and that with SFC, Merck has developed a greener chromatography technique than any that have existed before.

Session 4: Exemplary Practices of Green Chemistry and Green Engineering

Q: What incentives does Bristol-Myers Squibb offer to scientists for greening processes?
A: *(Taylor)* One of the requirements for promotion is to publish and present a paper. Greening processes is an interesting and popular topic. Employees receive recognition in the industry and at their company for being green.

Q: How do you encourage employees in the research and development department to embrace greening processes?
A: *(Taylor)* The company holds project review meetings where bench chemists and project leaders present products to management that they want manufactured. Management takes greenness scores into consideration, and if the scores are not high enough, the product will not be manufactured.

Q: Does the Process Greenness Scorecard apply to parts of the production process performed in-house, or only to outsourced processes?
A: *(Taylor)* The Process Greenness Scorecard applies to processes that are performed in-house and those that are outsourced. Any process performed in-house, even trial processes, receive a Process Greenness Scorecard. If production processes are outsourced, Bristol-Myers Squibb develops guidelines for the chemistry techniques that the contractor will use in order to standardize the final product's quality.

Q: Do all manufacturing processes receive a greenness score?
A: *(Taylor)* All processes throughout the company receive a Process Greenness Scorecard to identify the environmental, health, and safety implications of new and existing products and practices.

Q: After a project team receives a Process Greenness Scorecard, does the project team receive suggestions for improving their techniques?
A: *(Taylor)* After a project team receives a Process Greenness Scorecard with ratings on 16 parameters, a chemist or chemical engineer can use the scorecard to determine the effect a new or changed process will have.

Q: The ACS Green Chemistry Institute Pharmaceutical Roundtable reviews literature to find potential opportunities for green chemistry. Do you also look for opportunities for biochemistry and enzymes?
A: *(Cue)* Since biochemistry and enzymes can be used to alter chemical transformations in the synthesis of pharmaceutical products, they are important areas to consider when looking at opportunities to green pharmaceutical manufacturing processes. Analyses have found that pharmaceutical companies use large

amounts of water and energy to develop first-stage products into market-quality products. Another reason that biochemistry is an important topic to research further is because it is an area of growing importance in the prescription pharmaceutical industry.

Appendix B: Agenda

United States
Environmental Protection Agency

Seize the Moment: Opportunities for Green Chemistry and Green Engineering in the Pharmaceutical Industry

EPA Region 2
New York City Office, 30th Floor
290 Broadway, New York, NY

September 27, 2007

Agenda

7:30AM	REGISTRATION
8:00AM	**Welcome/Introduction** *Kathleen Callahan, Deputy Regional Administrator, EPA Region 2* *D. Christopher Watts, Standards & Technology, FDA Center for Drug Evaluation and Research/Office of Pharmaceutical Science*
8:30AM	**Session 1: The Pharmaceutical Industry—Environmental Footprint** This session examines the environmental footprint of manufacturing processes associated with the pharmaceutical industry. EPA, FDA, and industry provide perspectives on opportunities and challenges to achieving sustainability in the industry. *Sharon Austin, EPA Office of Pollution Prevention and Toxics* *David J. C. Constable, GlaxoSmithKline* *D. Christopher Watts, Standards & Technology, FDA Center for Drug Evaluation and Research/Office of Pharmaceutical Science*
10:00AM	BREAK (Networking)
10:30AM	**Session 2: Green Chemistry and Green Engineering in the Pharmaceutical Industry** This session provides knowledge on green chemistry and green engineering principles that leads to best design chemistry and process efficiencies *Richard Engler, EPA Office of Pollution Prevention and Toxics*

11:00AM **Session 3: Green Chemistry/Green Engineering Technical Approaches**
This session showcases some synthesis pathways, process routes, technologies and other technical approaches that improve chemical design and process efficiency.
John Leazer, Merck & Co., Inc.
John Tucker, BioVerdant, Inc.

12Noon LUNCH
Lunch will include an opportunity for networking with your colleagues.

1:30PM **Session 4: Exemplary Practices of Green Chemistry and Green Engineering**
This session features inspirational change agents from the pharmaceutical industry that will share their experiences, collaborative efforts, accomplishments to date, and relevance to diverse audiences.
Berkeley W. Cue, Jr., ACS Green Chemistry Institute, Pharmaceutical Roundtable Association
Stephan P. Taylor, Bristol-Myers Squibb Company

2:30PM BREAK (Networking)

3:00PM **Session 5: Facilitated Dialogue—How to Better Promote Green Chemistry and Green Engineering in the Pharmaceutical Industry**
This session explores ideas on how to better promote green chemistry and green engineering in manufacturing processes associated with the pharmaceutical industry.
Introduction by Walter Schoepf, EPA Region 2 and Ann Lee-Jeffs, Johnson and Johnson Worldwide
Facilitators TBD

5:00PM **Closing Remarks**
Nhan T. Nguyen, EPA Office of Pollution Prevention and Toxics

5:30PM ADJOURN

Appendix C: Evaluation Form

United States
Environmental Protection Agency

Seize the Moment: Opportunities for Green Chemistry and Green Engineering in the Pharmaceutical Industry

Evaluation

WE ARE INTERESTED IN YOUR FEEDBACK ON OUR WORKSHOP.
If possible, evaluate each session at its conclusion. Please rate each session and answer the questions below. Please provide specific feedback on individual presenters when possible.

Please return your completed evaluation form to the registration table before departing the event. If you are unable to complete this evaluation onsite, please fax the completed form to (703) 841-1440.

Rate the sessions using the following rating system:
1= Poor 2 = Fair 3 = Good 4 = Very Good 5 = Excellent

	RATE THE SESSION	RELEVANCE OF INFORMATION
Session 1: The Pharmaceutical Industry— Environmental Footprint	1 2 3 4 5	1 2 3 4 5

*What was the most beneficial aspect of the session? Least beneficial?*_____
_____
_____
_____

Session 2: Green Chemistry and Green Engineering in the Pharmaceutical Industry	1 2 3 4 5	1 2 3 4 5

*What was the most beneficial aspect of the session? Least beneficial?*_____
_____
_____
_____

Session 3: Green Chemistry/Green Engineering Technical Approaches	1 2 3 4 5	1 2 3 4 5

*What was the most beneficial aspect of the session? Least beneficial?*_____
_____
_____
_____

Session 4: Exemplary Practices of Green Chemistry and Green Engineering	1 2 3 4 5	1 2 3 4 5

*What was the most beneficial aspect of the session? Least beneficial?*_____
_____
_____
_____

Session 5: Facilitated Dialogue—How to Better Promote Green Chemistry and Green Engineering in the Pharmaceutical Industry 1 2 3 4 5 1 2 3 4 5

*What was the most beneficial aspect of the session? Least beneficial?*_____
_____
_____
_____

Networking Opportunities (Breaks and Lunch) 1 2 3 4 5 1 2 3 4 5

*What were the most useful information exchanges you had in this session?*_____
_____
_____
_____

GENERAL QUESTIONS

1. Are there topics that you would like more information on at future meetings or conferences?
_____
_____
_____
_____

2. What are you doing to promote and/or implement green chemistry and green engineering principles and practices?
_____
_____
_____
_____

3. What suggestions do you have to overcome barriers and/or further promote and implement green chemistry and green engineering principles and practices both within your own organization and in the pharmaceutical manufacturing industry?
_____
_____
_____
_____

4. How will the insights and experiences gained from the workshop motivate you to promote and/or pursue green chemistry and green engineering opportunities?
_____
_____
_____
_____

5. Additional Comments (e.g. major or surprise personal insights gained; new or different personal approaches considered; additional collaborative actions)
_____
_____
_____
_____

Appendix D: Speakers, Moderators, and Participants

James Abulencia
Manhattan College

Nada Anid
Manhattan College

***Sharon Austin**
U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics,
Green Engineering Program

Prabir Basu
National Institute for Pharmaceutical Technology and Education

Gregg Belardo
Wyeth

Raanan Bloom
Standards & Technology, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science

Lampros Bourodimos
U.S. Environmental Protection Agency, Region 2, Division of Environmental Science and Assessment

Andy Bray
Northeast Waste Management Officials' Association

Mary Buzby
Merck & Co., Inc.

***Kathleen Callahan**
U.S. Environmental Protection Agency, Region 2

Joe Cleary
HydroQual Inc.

***David Constable**
GlaxoSmithKline

***Berkeley Cue, Jr.**
American Chemical Society Green Chemistry Institute, Pharmaceutical Roundtable Association

Michael DiGiore
New Jersey Department of Environmental Protection

Mark Dorfman
Biomimicry Guild

Robert Ellis
EXP Pharmaceutical Services Corp.

Edward Elsesser
JohnsonDiversey Inc.

***Richard Engler**
U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics,
Green Chemistry Program

John Filippelli
U.S. Environmental Protection Agency, Region 2, Division of Environmental Planning and Protection

Kevin Fowler
Schering Plough Corporation

Kristin Giacalone
U.S. Environmental Protection Agency, Region 2

Mark Harvey
EXP Pharmaceutical Services Corp.

Roland Hemmett
U.S. Environmental Protection Agency, Region 2, Division of Environmental Science and Assessment

Mary Hendrickson
Capital Returns, Inc.

Al Iannuzzi
Johnson & Johnson Worldwide

Vincenza Imperiale
Manhattan College

* Speaker
** Moderator

Lee Josey
Nalco Company

Cigdem Karayigitoglu
GlaxoSmithKline

Mary Ann Kowalski
U.S. Environmental Protection Agency, Region 2,
Division of Enforcement and Compliance
Assistance

***John Leazer**
Merck & Co., Inc.

****Ann Lee-Jeffs**
Johnson & Johnson Worldwide

Robert Lippincott
New Jersey Department of
Environmental Protection

Weiguo Liu
Wyeth

Nora Lopez
U.S. Environmental Protection Agency, Region 2,
Division of Enforcement and Compliance
Assistance

Ron MacGillivray
Delaware River
Basin Commission

Joseph Malki
U.S. Environmental Protection Agency, Region 2,
Division of Environmental Planning
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Jason Masi
Boehringer Ingelheim Pharmaceuticals Inc.

Viviane Massonneau
Merck & Co., Inc.

Michael Minerva
Schering-Plough Corporation

Judy-Ann Mitchell
U.S. Environmental Protection Agency, Region 2,
Division of Environmental Planning
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Shayne Mitchell
New York State Department of
Environmental Conservation

Carlos Montes
New York State Department of
Environmental Conservation

Siegfried Mueller
Analytical Science and Technologies LLC

Sophie Naftalovich
Perrigo Company

***Nhan Nguyen**
U.S. Environmental Protection Agency,
Office of Pollution Prevention and Toxics,
Chemical Engineering Branch

Tamra Nobles
Capital Returns, Inc.

Ed Nowak
Johnson & Johnson Pharmaceutical
Research and Development

Yemi Odutola
New Jersey Institute of Technology

Maureen O'Neill
U.S. Environmental Protection Agency, Region 2,

David Ono
Amgen

Siddika Pasi
Rutgers University, Center for Advanced
Energy Systems

Dan Pilipauskas
Pfizer Inc

David Plutto
Bristol-Myers Squibb Company

Carols R. Ramos
U.S. Environmental Protection Agency, Region 2,
Division of Environmental Planning and
Protection

* Speaker
** Moderator

Jacqueline Rios
U.S. Environmental Protection Agency, Region 2, Division of Environmental Planning and Protection

Michael Rottas
Pfizer Global Research and Development

Sara Salahi
Rutgers University, Center for Advanced Energy Systems

****Walter H. Schoepf**
U.S. Environmental Protection Agency, Region 2, Division of Environmental Planning and Protection

Nachimuthu Soundararajan
Celgene Corporation

John Sweeney
Analytical Science and Technologies LLC

***Stephan P. Taylor**
Bristol-Myers Squibb Company

Thomas Thornton
Abbott Laboratories

Hugh Tole
Roche

***John Tucker**
BioVerdant, Inc.

***D. Christopher Watts**
Standards & Technology, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science

* Speaker
** Moderator

Appendix E: Planning Assistance Group

Kim Albizati
BioVerdant, Inc.

Piero M. Armenante
New Jersey Institute of Technology, Pharmaceutical Engineering Program, York Center for Environmental Engineering and Science

Raanan A. Bloom
Standards & Technology, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science

David J.C. Constable
GlaxoSmithKline

San Kiang
Bristol Myers Squibb Company

Toni Krasnic
U.S. Environmental Protection Agency, Chemical Control Division

Ann Lee-Jeffs
Johnson & Johnson Worldwide

Nhan Nguyen
U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Chemical Engineering Branch

Mariano J. Savelski
Rowan University, Department of Chemical Engineering,

Walter H. Schoepf
U.S. Environmental Protection Agency, Region 2, Division of Environmental Planning and Protection

C. Stewart Slater
Rowan University, Department of Chemical Engineering

D. Christopher Watts
Standards & Technology, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science