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Concept Article

Green Chemistry, a Pharmaceutical Perspective

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Abstract:

As the Green Chemistry[1,2] movement has gained momentum, definitions of Green Chemistry have been dominated predominantly by academic viewpoints. Green Chemistry concepts, however, apply to an incredible diversity of scientific endeavor, which has invariably led to differences between and amongst both academia and industry regarding what constitutes Green Chemistry. Speaking primarily of the pharmaceutical industry and considering the advances achieved toward promoting Green Chemistry globally,[3] it is surprising how diverse the answers can be when executives, engineers, biologists, and chemists are asked the seemingly simple question "What is Green Chemistry?" Perhaps this should be expected considering that individual priorities change based upon a specific endeavor, altering the focus of Green Chemistry and consequently the message, making general definitions difficult. A common impression obtained appears to be that many do not accurately know or fully understand the true motivations, drivers, and deciding factors that serve to inspire and define Green Chemistry, and in particular Pharmaceutical Green Chemistry. This commentary seeks to shed light upon key aspects with regard to the philosophy of Pharmaceutical Green Chemistry.

What Is Green Chemistry?

Green Chemistry definitions change based upon focus. To answer this elusive question it may in fact be best to first consider what Green Chemistry is not.

Green Chemistry is often described within the context of new technologies. But Green Chemistry is not beholden to ionic liquids,[4] microwave chemistry,[5] supercritical fluids,[6] biotransformation,[7] fluorous phase chemistry,[8] or any other new technology. *Green chemistry is outside of techniques used but rather resides within the intent and the result of technical application.*

Some view Green Chemistry as something process chemists do already...good process chemistry. While often enabling "greener" synthesis, good process chemistry is not equivalent to Green Chemistry. A robust, efficient, and cost-effective chemical process is likely accepted as good process chemistry. The same process examined more rigorously with regard to the twelve principles of Green Chemistry[1] invariably brings to light potential improvements relative to environmental performance. Processes evolve and become "greener" relative to earlier iterations, but only an ideal process embodies Green Chemistry itself. *Green Chemistry is not simply good process chemistry; it is the highest efficiency potential that exists for each chemical process, serving as both an inspiration for and a measure of the best process chemistry.*

Others feel Green Chemistry is a purely environmental agenda, and a condemnation of industrial chemistry or of scientists. This picture neglects the direct relationship between Green Chemistry principles and highly efficient and environmentally benign chemistry. *Green Chemistry is a concept for scientists envisioned by scientists for higher*

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(1) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: 1998.

(2) Clark, J. H. Green Chemistry: Challenges and Opportunities. *Green Chem.* **1999**, *1*, G1. Matlack, A. S. *Introduction to Green Chemistry*; Marcel Dekker Inc.: New York, 2001. Lancaster, M. *Green Chemistry: an Introductory Text*; The Royal Society of Chemistry, Cambridge, 2002. Clark, J. H.; Macquarrie, D. *Handbook of Green Chemistry & Technology*; Blackwell Science Ltd.: Oxford, 2002. Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, *297*, 807. Noyori, R. *Chem. Commun.* **2005**, 1807.

(3) International exposure of these concepts has been enhanced through recognition programs such as the EPA's Presidential Green Chemistry Challenge Award and the Crystal Faraday Award, through initiation of the *Green Chemistry* journal, Green Chemistry conferences, publications, and Green Chemistry curriculum at universities.

(4) Seddon, K. *Green Chem.* **2002**, *4*, G35. Rogers, R. D.; Seddon, K. *Ionic Liquids: Industrial Applications for Green Chemistry*; ACS Ser. 818; Oxford University Press: Oxford, UK, 2002. Wasserscheid, P.; Welton, T. *Ionic liquids in Synthesis*; Wiley-VCH: Weinheim, 2003. Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459. Chauhan, S. M. S.; Chauhan, S.; Kumar, A.; Jain, N. *Tetrahedron* **2005**, *61*, 1015.

(5) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213. Wathey, B.; Tierney, J.; Lidstrom, P.; Westman, J. *Drug Discovery Today* **2002**, *7*, 373. Loupy, A. *Microwaves in Organic Synthesis*, Wiley-VCH: Weinheim, 2002. Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128. Hayes, B. *Aldrichimica Acta* **2004**, *37*, 66. Stadler, A.; Kappe, O. C. *Microwave-Assisted Solid-Phase Synthesis*; Blackwell Ltd.: Oxford, 2005. Tierney, J.; Lidstrom, P. *Microwave Assisted Organic Synthesis*; Blackwell Ltd.: Oxford, 2005.

(6) Jessop, P. G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH: Weinheim, Germany, 1999. Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746. Poliakoff, M.; Ross, S. K.; Sokolova, M.; Ke, J.; Licence, P. *Green Chemistry* **2003**, *5*, 99. Beckman, E. J. *J. Supercrit. Fluids* **2004**, *28*, 121.

(7) Tao, J.; Yazbeck, D.; Martinez, C. A.; Hu, S. *Tetrahedron: Assymetry* **2004**, *15*, 2757.

(8) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174. Curran, D. P.; Lee, Z. *Green Chem.* **2001**, G3. Gladysz, J. A.; Curran, D. P.; Horvath, I. T. *Handbook of Fluorous Chemistry*; Wiley-VHS: 2004.

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efficiency, not a mandate or a condemnation from outside of the scientific community.

In short, Green Chemistry is neither a new type of chemistry nor an environmental movement, a condemnation of industry, new technology, or "what we do already". Green Chemistry is simply *a new environmental priority* when accomplishing the science already being performed...regardless of the scientific discipline or the techniques applied. Green Chemistry is a concept driven by efficiency coupled to environmental responsibility.

Green Chemistry insists that our synthetic objectives are achieved while assuming additional considerations related to the unnecessary environmental burden created during operations. If using a toxic reagent, one should inquire if a less toxic reagent might accomplish similar ends. A literature search may provide no current alternative with similar efficiency and reduced toxicity, but many do not realize that the simple act of inquiry toward reduced toxicity already indicates a new priority and intent, a higher level of awareness and environmental stewardship, and is Green Chemistry! In some cases a safer reagent will exist. Application will improve the process environmental profile and reduce risk related to working with a toxic reagent while maintaining or improving synthetic efficiency. Some believe an environmental priority will add time and cost. Just the opposite, time and cost are reduced by incorporating higher synthetic efficiency the first time, and new methods can be applied toward parallel and future endeavors to enhance overall productivity.

Understanding Pharmaceutical Green Chemistry.

The definition of Pharmaceutical Green Chemistry should include "*The quest for benign synthetic processes that reduce the environmental burden*"...but it must also include..."*within the context of enabling the delivery of our current standard of living*." Pharmaceutical Green Chemistry seeks to eliminate unnecessary environmental impact, but we must enable delivery of life saving medicines and also show value for our stakeholders. Green Chemistry principles do not condemn this but rather encourage that these goals be met through our absolute best performance.

Application of the twelve principles of Green Chemistry[9] can deliver higher efficiency and reduced environmental burden during chemical synthesis. Most of these principles apply directly to pharmaceutical chemistry, but some do not. For instance, designing for degradation can be inappropriate for an active pharmaceutical ingredient (API) that relies upon its precise chemical structure for the desired biological activity and that also must demonstrate adequate stability and acceptable shelf life. Renewable feedstocks are certainly preferred for long-term chemical manufacture but are difficult to achieve with a rapidly changing family of products. Green Chemistry as portrayed by the twelve principles acts as a guide but does not wholly apply to Pharmaceutical Green Chemistry.

Roger Sheldon's E-factor[10] is frequently used to highlight the relative inefficiency of pharmaceutical manufacture as opposed to that of petroleum manufacture. This comparison has flaws, however, due to varying product complexity depending upon the particular industry. For example, petroleum scientists collaborate to design unique facilities providing specific engineering solutions to address the physical properties of relatively simple molecules for large-scale manufacture. In contrast, pharmaceutical scientists must generate a diverse array of exceptionally complex targets with little or no specialized engineering adaptation. This high molecular complexity accompanied by limited engineering flexibility translates to a significant responsibility for efficiency placed directly upon the pharmaceutical chemist.[11] Therefore, *the primary driver of Pharmaceutical Green Chemistry becomes the synthetic and analytical chemist.*

Pharmaceutical green chemists must strive for the correct choice of starting material, ideal number and order of chemical steps, the appropriate use of solvents and reagents, and efficient strategies for isolation and purification. They must achieve a balance for highest efficiency, safety, and robustness, within the existing industry engineering constraints and with concern for the environment. Methodology should be state of the art, and the techniques should be synergistic, accounting for combined synthetic performance as well as individual compound toxicity. Replacing a toxic solvent with a benign solvent that ultimately decreases process throughput is not Green Chemistry! *Processes must be examined holistically to ensure maximum efficiency*. Particular attention should be paid to solvents, however, as 80% of waste generated during manufacture of a typical API is related to solvent use.[12]

Patent life determines the relative success or failure for a new drug, thus time to market must be minimized. Moreover, industry regulation to ensure quality and safety of pharmaceuticals results in significant effort and expense to incorporate and justify process improvements late in the product timeline. Therefore, repeated use of established methodology that minimizes timeline and regulatory risk can become attractive.[13] This perceived risk management might be the greatest inhibitor of Pharmaceutical Green Chemistry. Complacency must be shed, and green chemists must be willing to challenge tried and true techniques in favor of improved techniques for greater synthetic efficiency. The seemingly higher risk implicit in this quest must be embraced, because Pharmaceutical Green Chemistry will translate to higher synthetic efficiency and better chemical processes, which will in turn reduce impact upon the environment (Table 1).

Currently, pharmaceutical scientists are rewarded based upon milestones of achievement such as API delivery or

(9) The twelve principles are as follows: Prevention, Atom Economy, Less Hazardous Chemical Synthesis, Design Safer Chemicals, Safety Solvents and Auxiliaries, Design for Energy Efficiency, Use Renewable Feedstocks, Reduce Derivatives, Catalysis, Design for Degradation, Real Time Analysis, Inherently Safer Chemistry.

(10) Sheldon, R. A. *Chemtech* **1994**, 38. Sheldon, R. A. *J. Chem. Technol. Biotechnol*. **1997**, 381. Sheldon, R. A. *Chem. Ind*. **1992**, 903.

(11) Tucker, J. L. *Chemistry, The Color of Money*; 223rd ACS National Meeting of the American Chemical Society, Orlando, FL, 2002.

(12) Jimenez-Gonzales, C.; Curzons, A. D.; Constable, D. J. C.; Cunningham, V. L. *Int J. LCA* **2004**, 114. Eissen, M.; Hungerbuhler, K.; Dirks, S.; Metzger, J. *Green Chem.* **2003**, G25.

(13) Blaser, H. U.; Studer, M. *Green Chem.* **2003**, *5*, 112.

Table 1. **Green Chemistry principles deliver economic and environmental benefit**

	thinking environmental	thinking economic
atom economy	minimal byproduct formation. **reduced environmental burden**	more from less. incorporate total value of materials. **reduced cost**
solvent reduction	less solvent required, less solvent waste. **reduced environmental burden**	reduced capacity requirements, less energy required. **reduced cost**
reagent optimization	catalytic, low stoichiometry, recyclable. **reduced environmental burden**	higher efficiency, higher selectivity. **reduced cost**
convergency	**reduced environmental burden** related to improved process efficiency.	higher efficiency, fewer operations. **reduced cost**
energy reduction	**reduced environmental burden** related to power generation, transport, and use.	increased efficiency, shorter processes, milder conditions. **reduced cost**
in situ analysis	reduced potential for exposure or release to the environment.	real time data increases throughput and efficiency, fewer reworks. **reduced cost**
safety	nonhazardous materials and processes reduce risk of exposure, release, explosions and fires.	worker safety and reduced downtime. reduced special control measures. **reduced cost**

quantity, as opposed to relative quality or efficiency. Acceptable cost of API manufacture is often based upon a percentage of the potential product profit, rather than the true potential efficiency of the process. While process environmental performance is partially captured in the form of raw material and disposal costs, this is not an adequate measure of process efficiency. It is critical that industry leaders begin to apply a higher level of expectation directed by the understanding that Green Chemistry principles applied equate to higher synthetic efficiency, hence, *offer enhanced chemical process economics* concomitant with a reduced environmental burden.

The potential of Pharmaceutical Green Chemistry will only be realized if scientists are empowered and rewarded based upon higher expectations of efficiency. It is a competitive advantage to reduce the cost of manufacture beyond mere acceptability, and greener chemistry reduces cost. It is encouraging that metrics[14] have been developed which may help business leadership to better understand and reward greener chemistry. It should be clear though that while Pharmaceutical Green Chemistry can be measured by metrics of environmental health and safety, *the real driver of Pharmaceutical Green Chemistry is synthetic efficiency*.[15]

There has been significant investment toward metrics that can help to educate scientists and communicate with nonscientists. There has been less commitment thus far toward developing new, greener, synthetic chemistry methods. Green Chemistry priorities open up a fresh landscape of research opportunities that can improve chemical processes, and these opportunities are not being fully exploited. The education of scientists regarding Green Chemistry principles has been an excellent beginning to the quest for higher synthetic efficiency, but it is now time for the full application of these new priorities and significant investment toward better science. This will deliver reduced cost and sustained success and should be the focus. *Green Chemistry begins with intent*.

A challenge to intent can arise when the pharmaceutical industry relies heavily upon outsourcing for research or pharmaceutical intermediate or API manufacture. Of concern is the potential lack of ownership and responsibility on the part of a vendor company. The deliverables are usually well defined, and it may be in a vendor's best short-term interest to simply deliver the minimum required by the customer, eliminating the potential for improved synthetic efficiency. In fact, intellectual property concerns can frequently preclude innovation. There also exists a serious concern regarding variable application or existence of environmental protection as a result of the country in which a vendor may be operating. A lack of appropriate environmental enforcement or direction may deliver a cost advantage to a vendor, which will ultimately be paid by the global community. Addressing the challenges implicit in outsourcing is the responsibility of pharmaceutical companies selecting the vendors. Environmental stewardship must be a consideration when selecting and negotiating agreements with vendors.

There exists a prevalent misunderstanding regarding Pharmaceutical Green Chemistry as described by nonpharmaceutical scientists. Some suggest that there is sufficient understanding of toxicology to conclude that chemists warrant responsibility for, or choose to generate, toxic substances.[1,16] Others feel that toxicology represents a core incompetence of chemists.[17] These conclusions neglect to consider, or fail to understand, the current state of the art in medicinal and synthetic organic chemistry and overestimate the understanding implicit in structural toxicology. If pharmaceutical chemists could discover new compounds that accomplish medicinal ends free from side effects by applying

(14) Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259. Hudlicky, T.; Frey, D. A.; Koroniak, L.; Claeboe, C. D.; Brammer, L. E. *Green Chem.* **1999**, *1*, 57. Sheldon, R. A. *Chemtech* **1994**, 38. Sheldon, R. A. *Chem. Ind.* **1997**, 12. Sheldon, R. A. *Chem. Ind.* **1992**, 903. Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chem.* **2001**, *3*, 1. Constable, D. J. C.; Curzons, A. D.; Frietas dos Santos, L. M.; Geen, G. R.; Hannah, R. E.; Hayler, J. D.; Kitteringham, J.; McGuire, M. A.; Richardson, J. E.; Smith, P.; Webb, R. L.; Yu, M. *Green Chem.* **2001**, *3*, 7. Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521. Andraos, J. *Org. Process Res. Dev.* **2005**, *9*, 404, and **2005**, *9*, 149.

(15) Tucker, J. L. *Innovating for Sustainability*; Rohm and Hass Symposium; Springhouse, PA, 2002.

(16) Warner, J. C. *Innovating for Sustainability*; Rohm and Hass Symposium; Springhouse, PA, 2002.

(17) Collins, T. *Green Chem.* **2003**, *5*, G-51.

basic hazard data, new drug candidate attrition would approach zero. In fact, a perfect and predictive understanding of structure related toxicology could theoretically eliminate the need for medicinal chemists entirely. Realistically,pharmaceuticals are intrinsically novel and complex; even stereoisomers can have significantly different toxicity and potency.[18] It should be understood that these challenges preclude a reliable prediction of the toxicity of pharmaceuticals without specific, empirical study.

Where Does Pharmaceutical Green Chemistry Application Begin and End?

Pharmaceutical Green Chemistry begins with medicinal (discovery) chemistry. The prevalent argument against this asserts that process optimization techniques applied in discovery consume resources upon projects that fall to attrition, concluding that Green Chemistry proves inappropriate. This is valid *only* if a discovery scientist interprets priorities of process chemistry as representing Medicinal Green Chemistry. *The principles of Green Chemistry do not require that discovery scientist accept a process paradigm but instead insist that all scientists develop their own unique application to improve performance in line with their own priorities.*

There are many examples of Green Chemistry principles successfully applied in discovery, such as using microwave chemistry,[19] supercritical separations,[20] and high-throughput screening[21] to provide drug candidates using less material, with less waste, and in less time. And yet, authoritative overviews describing the future of medicinal chemistry[22] do little more than mention the term Green Chemistry. *The challenge for each scientist in discovery is to apply Green Chemistry principles to address their own list of immediate priorities for higher efficiency*. Pharmaceutical Green Chemistry begins in discovery, and the medicinal scientists who successfully incorporate Green Chemistry principles are the innovators leading the way to more productive medicinal chemistry.

Application of Green Chemistry principles continues during process research and development with an increased focus upon route selection and optimization.[23] Routine process R&D can deliver significant improvement relative to economy and the environment and is frequently characterized as Green Chemistry; but it is important to understand that good process chemistry and Green Chemistry are not interchangeable terms (*vide supra*). *Pharmaceutical Green Chemistry is the ideal that one strives for, and the pursuit of this ideal will lead to ever better process chemistry*.

All scientists, regardless of their role, should embrace Green Chemistry principles to impact all facets of pharmaceutical science throughout the life of a pharmaceutical product.

Why Should Greener Pharmaceutical Chemistry Be Sought?

The chemical industry delivers a higher standard of living and life saving medicines, but the practice of industrial chemistry is nevertheless viewed with hostility and suspicion.[24] Among young adults, the chemical industry suffers a 26% approval rating,[25] suggesting that a majority disapprove of our industry. This approval rating is on a par with that of the nuclear energy and tobacco industries. What impact will this have upon our future talent pool? What regulatory impact upon our industry does this low public trust foreshadow? Claims by the chemical industry for the general good are not taken seriously, but individuals do and will respond to concrete examples.[26] By exemplifying Green Chemistry principles, we can demonstrate positive contributions to society concomitant with a genuine commitment to efficiency and to environmental stewardship. This may offer a timely lever to reverse the prevalent misconception that scientists lack concern for the environment and could in turn lead to improved student interest in scientific study, a critical component of future success of the industry. *Pharmaceutical Green Chemistry offers an opportunity to educate the public with regard to our good environmental stewardship through operational transparency, while also detailing industrial motivations leading to greater public awareness, understanding, and trust*.

Green Chemistry principles applied to a pharmaceutical model clearly deliver *improved economic and environmental performance*. This is accompanied by personal development and success for those willing to assume the additional priorities of Green Chemistry. Increased scientific excellence will inevitably emerge from continual re-examination and questioning, and *the achievement of superior efficiency will ultimately deliver a competitive advantage*.

Embracing concepts of Green Chemistry will be an effort worth pursuing, not only for the sake of economic efficiency and environmental impact but also toward a sustainable future. As pharmaceutical chemists, we have many choices with regard to how we synthesize molecules. These choices

(18) Such as in the well-documented cases of thalidomide and ibuprofen: Eriksson, T.; Bjorkman, S.; Roth, B.; Hoglund, P. *J. Pharm. Pharmacol.* **2000**, *52*, 807. Cheng, H.; Rogers, J. D.; Demetriades, J. L.; Holland, S. D.; Seibold, J. R.; Depuy, E. *Pharm. Res.* **1994**, *11*, 824.

(19) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406. Santagada, V.; Frecentese, F.; Perissutti, E.; Favretto, L.; Claiendo, G. *QSAR Comb. Sci.* **2004**, *23*, 919. Mavandadi, F.; Lidstroem, P. *Curr. Top. Med. Chem.* **2004**, *4*, 773. Stadler, A.; Kappe, O. C. *Microwave-Assisted Solid-Phase Synthesis*; Blackwell Ltd.: Oxford, 2005.

(20) Perrut, M. *STP Pharma Sci.* **2003**, *13*, 83. Bolanos, B.; Greig, M.; Ventura, M.; Farrell, W.; Aurigemma, C.; Li, H.; Quenzer, T. L.; Tivel, K.; Bylund, J. M. R.; Tran, P.; Pham, C.; Phillipson, D. *Int. J. Mass Spectrom.* **2004**, *238*, 85. Alfonso, C. A. M.; Crespo, J. G. *Green Separation Processes*; Wiley-VCH: 2005.

(21) Hunter, D. *J. Cell. Biochem.*, Supplement **2001**, *37*, 22. Aherne, W. G.; McDonald, E.; Workman, P. *Breast Cancer Res.* **2002**, *4*, 148. Crossley, R. *Drug Discovery* **2002**, *5*, 18.

(22) Erhardt, P. W. *Pure Appl. Chem.* **2002**, *74*, 703.

(23) Repic, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; John Wiley & Sons: New York, 1998. Anderson, N. *Practical Process Research and Development*; Academic Press: 2000. Scientific Update, *Chemical Development and Scale Up in the Fine Chemical Industries*.

(24) Bektesevic, S.; Beier, J. C.; Chen, L.; Eghbali, N.; King, S.; Levitin, G.; Mehta, G.; Mullins, R. J.; Reiner, J. L.; Weikel, R.; Xie, S.; Gunn, E. *Green Chem.* **2005**, *7*, 403.

(25) Attitude and Perception Studies, Arlington, Virginia: CMA in Kappas **1997**. Clark, J.; Macquarrie, D. *Handbook of Green Chemistry & Technology*; Blackwell Science Ltd.: Oxford, 2002. Clark, J. *Environmentally Benign Chemistry*; Rochester section of the ACS, 1999.

(26) *Chemical Sciences in the 20th Century: Bridging Boundaries* (foreword by Roald Hoffmann); Reinhardt, C., Ed.; Wiley-VCH: Weinheim, 2001.

must deliver economic viability, but a responsibility also exists that we incorporate environmental consideration toward this ultimate goal of sustainability. Our responsibility should be viewed as a privileged opportunity, an extension of our heritage as chemists, and represents an emerging new frontier of exploration. Chemistry is the "ultimate cult of the new",[26]and chemical literature captures a history of innovation and an inclination toward elegance. There could be no more elegant an endeavor than to better address issues of pharmaceutical science within the higher context of environmental stewardship.

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