

# Green Chemistry in the Pharmaceutical Industry: A Model for Sustainability

The Rachel Carson Legacy Conference  
Green Chemistry: Solutions for a Healthy  
Economy

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# Disclaimer

- The content of this talk solely represents my personal view of green chemistry in the pharmaceutical industry
  - It does not represent the position of the ACS, the ACS GCI, ACS GCIPR or any pharmaceutical industry company, NGO or governmental agency

# PhRMA Companies Mission

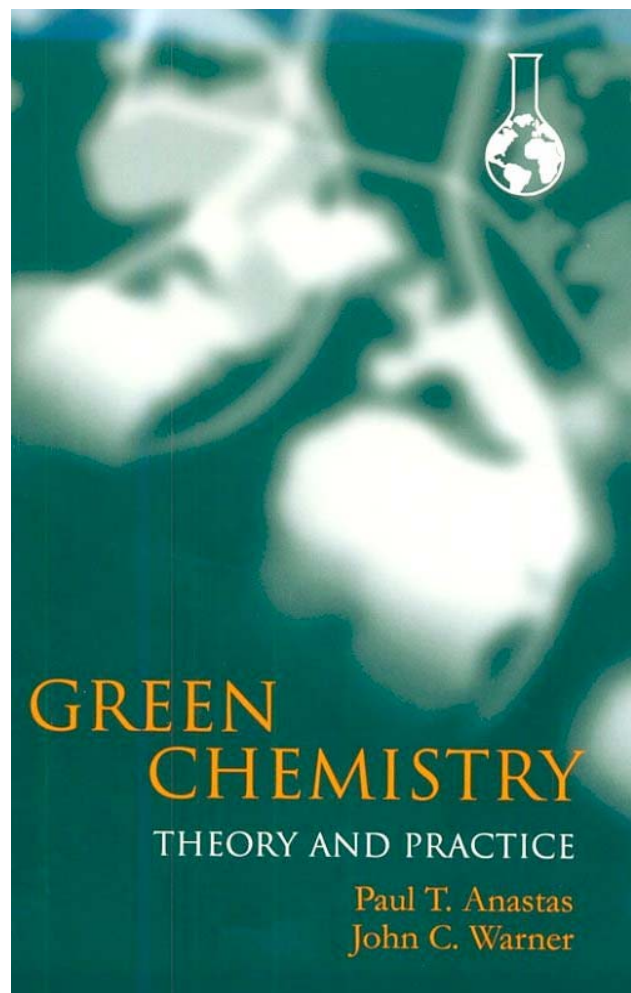
The PhRMA represents the leading research-based pharmaceutical and biotechnology companies in the United States. **PhRMA companies are devoted to discovering and developing new medicines that will enable patients to live longer, healthier and more productive lives.**

In 2007 the global pharmaceutical companies invested over \$58.8 billion in discovering and developing new medicines, marking the 37<sup>th</sup> straight year the industry has increased its investment in R&D

Source: PhRMA Website ([www.phrma.org](http://www.phrma.org))

**BUT- Pharma Industry's commitment to improving health is not complete without a commitment to a healthy environment.**

# Green Chemistry



“...the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products.”

\*Source: Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998). **ISBN 0 19 850698 8**

# 12 Principles of Green Chemistry

1. Prevention
2. Atom Economy
3. Less Hazardous Chemical Syntheses
4. Designing Safer Chemicals
5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis
10. Design for Degradation
11. Real-time Analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998). ISBN 0 19 850698 8 as found on [www.epa.gov/greenchemistry](http://www.epa.gov/greenchemistry)

# The Lay of the Green Pharmaceutical Landscape, circa 2000

- Two years after Anastas and Warner published their seminal work....
  - Some isolated examples of greening pharmaceutical processes
    - Merck (1996), BHC (1997), Roche (2000)
  - No comprehensive strategy to adopt the green chemistry paradigm evident in any pharmaceutical company
  - Belief that pharmaceutical industry waste footprint was very small compared to other sectors and the cost of doing business
    - Meeting EPA-mandated discharge permit levels was all that was needed
  - Belief that the design and manufacture of pharmaceuticals was so beneficial to mankind that its waste should be tolerated.
  - Any improvement was driven by manufacturing divisions and EH&S
    - R&D was largely AWOL
  - Glaxo was developing an very strong lifecycle analysis mindset
  - If the 12 principles were used as a RYG scorecard, most companies would have scored yellow to red in all fields

# Green Chemistry Performance

## Metrics: E-Factor

Roger Sheldon, *Chem Tech*, 1994, **24**, 38

Table 1. Sectors of the chemical industry by quantity of byproduct per kg of product

<b><i>Industry Sector</i></b>	<b><i>Product tonnage</i></b>	<b><i>kg byproducts/ kg of product</i></b>
<b>Oil refining</b>	<b><math>10^6 - 10^8</math></b>	<b>ca 0.1</b>
<b>Bulk Chemicals</b>	<b><math>10^4 - 10^6</math></b>	<b>&lt;15</b>
<b>Fine Chemicals</b>	<b><math>10^2 - 10^4</math></b>	<b>5-50</b>
<b>Pharmaceuticals</b>	<b><math>10^1 - 10^3</math></b>	<b>25-100+</b>
<b>Pharmaceuticals (MW&lt;1000) (source: ACS GCIPR Benchmarking 2006)</b>		<b>200 (10-1000)</b>
<b>Pharmaceuticals (MW&gt;1000)</b>		<b>5000-30000+</b>

(Source: S.V.Ho presentation, 11<sup>th</sup> Green Chemistry and Engineering Conference, Washington, DC, June 2007)

# By 2005 the Landscape Was Changing Rapidly

- Pharmaceutical companies were discussing sustainability and the triple bottom line in their annual reports
- Pfizer won the US EPA Presidential Green Chemistry Challenge in 2002
- Pfizer's green chemistry model, established in 2001, began to be copied by other major players
- A pharmaceutical spokesman (BWC) testified before the House Science Committee in support of the Federal Green Chemistry R&D Act in March 2004
- In 2005, Anastas and Cue formed the ACS Green Chemistry Institute Pharmaceutical Roundtable with seed money from Pfizer and an ACS matching grant
  - R&D, EH&S and manufacturing all participated
- ACS GCI, Lilly, Merck and Pfizer were the first members
  - Met quarterly, developed a mission statement and goals
- Julie Manley (ex Abbott EH&S) was hired as a contractor to support the Roundtable.
- Roche, BMS and Merck won US EPA PGCC awards
- The recruitment of other companies to the GCIPR began

# Now (Mid 2008)

- The success of the ACS GCIPR has created copies (GC3 and a Cleaning/cleansing Products RT within the ACSGCI)
- Nine companies have joined the ACS GCI in the Pharmaceutical Roundtable
  - Astra Zeneca, Boehringer-Ingelheim, GSK, J&J, Lilly, Merck, Pfizer, Schering-Plough and Wyeth
  - Other major pharma companies (Abbott, BMS, Dr, Reddys, Novartis, Sanofi-Aventis) track GCIPR and have active programs with some common components
  - ACS GCI Director Dr. Robert Peoples calls the Roundtable “one of the ACS GCI’s crown jewels” (C&E News, 2008)
  - Companies comprising more than 85% of the sales of the Fortune 500 sector are known to be practicing GC
  - Major initiatives for finding greener reactions, benchmarking mass intensity, solvent selection tools, internal and external education, frequent publications and presentations
- Six companies have won US EPA PGCC Awards
  - BHC(1997), Lilly (1999), Roche (2000), Pfizer(2002), BMS (2004), Merck (2005), Merck (2006)
  - Dozens of applications describing greener API processes have been received by the EPA’s OPPT
  - EU awards: Pfizer (2003), Merck (2005), Pfizer (2006)

# Membership

as of June 23, 2008

AstraZeneca 

*Lilly*

 **gsk**  
GlaxoSmithKline

*Johnson & Johnson*

 Schering-Plough



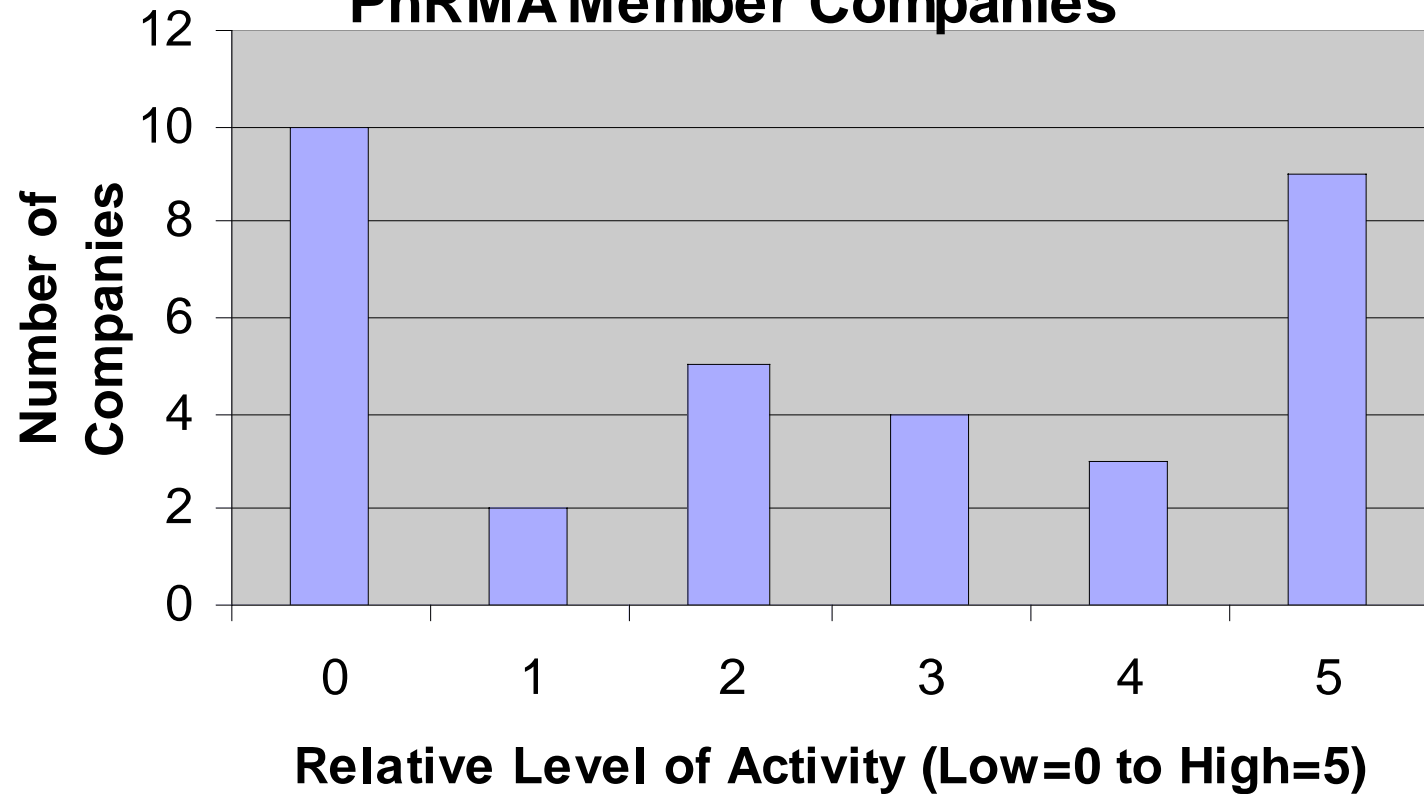
 **MERCK**

 **Boehringer  
Ingelheim**

**Wyeth**

Membership is open to all pharmaceutical research, development, and manufacturing companies. The Roundtable will be strongest when all global pharmaceutical corporations are members.

## Perceived Green Chemistry Activity of PhRMA Member Companies



# But.....

- The analysis in the last slide represents only the PhRMA member companies
  - Worldwide there are many hundreds of companies designing, developing and commercializing drugs
- There are over 10,000 different drugs sold worldwide today
  - Perhaps as few as 1% are made by processes that could be considered green

# My Score Card Legend

Pharma companies' practices are seen as best in class. Practiced extensively within this industrial sector

Pharma companies have begun to adopt this principle. Approaches are being developed to address any shortfalls in technology or process

Pharma companies are not addressing this principle through their green chemistry activities, either due to a lack of a technical solution, or the belief that green chemistry does not play a role here, or the belief that current practices and approaches to address it are sufficient

# The Twelve Principles of Green Chemistry: Buzz's 2008 Assessment for the Pharmaceutical Industry

- 1. Prevent waste:** Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.
- 2. Design safer chemicals and products:** Design chemical products to be fully effective, yet have little or no toxicity.
- 3. Design less hazardous chemical syntheses:** Design syntheses to use and generate substances with little or no toxicity to humans and the environment.
- 4. Use renewable feedstocks:** Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.
- 5. Use catalysts, not stoichiometric reagents:** Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.

Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998). ISBN 0 19 850698 8 as found on [www.epa.gov/greenchemistry](http://www.epa.gov/greenchemistry)

# BWC's Assessment of The Twelve Principles of Green Chemistry (continued)

- 6. Avoid chemical derivatives:** Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.
- 7. Maximize atom economy:** Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.
- 8. Use safer solvents and reaction conditions:** Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.
- 9. Increase energy efficiency:** Run chemical reactions at ambient temperature and pressure whenever possible.
- 10. Design chemicals and products to degrade after use:** Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.
- 11. Analyze in real time to prevent pollution:** Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.
- 12. Minimize the potential for accidents:** Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment

10. Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.

- The most challenging green chemistry principle for the pharmaceutical industry
- Pharmaceutical API's are designed to not be degraded by heat, light, acid, base or oxygen-the very degradation processes active in the environment
  - Product stability is a global regulatory expectation
- Drug delivery technology may be able to reduce the amount of API entering the environment
  - Bioavailability enhancers, Targeted delivery, nano technology
- Practice of medicine may be able to reduce API's footprint
  - Especially “just for you” medicines in the future
  - Better management of “expired” and unused drugs issues
- Need to manage trace API's in WWTF's (ozone, activated carbon, UV light, chemical oxidants)
- No near term solution on the horizon for designing API's to be stable until they enter the environment
- Need better computational toxicology tools to ID and weed out problem compounds

# PhRMA PhATE™ and PhACT™

- PhRMA and its members are committed to furthering the scientific research in order to achieve a better understanding of this topic.
  - For this reason, the industry has developed the PhATE model, a scientific tool that can be used to more realistically estimate the concentration and distribution of active pharmaceutical ingredients discharged into US surface waters as a result of the use of medicines.
  - The industry has also developed the PhACT database, which contains comprehensive aquatic life data on pharmaceutical compounds from the peer reviewed scientific literature.

# Some Pharma Related PIE References

**Human Pharmaceuticals In the Aquatic Environment: A Challenge to Green Chemistry**

Sudil K. Khelil\* and Terence J. Collins\*


Department of Chemistry, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213

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**Pharmaceuticals in the Environment:  
PhRMA Initiatives**

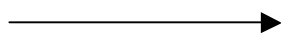
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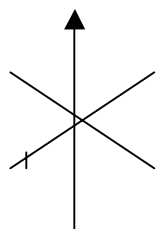
Human Pharmaceuticals: Assessing the Impact on Aqueous Ecosystems,  
 Richard T. Williams (Ed), SETAC Press, 2005

# A Green Chemist's Perspective on the Pharmaceutical Lifecycle

- Petroleum based chemicals to
- Bulk Chemicals to
- Fine Chemicals



- Regulatory starting materials to
- API



- Dosage form to patient
- Patient to the environment



- API to dosage form
- Dosage form to packaged product

# Barriers to More Rapid Implementation: Perceived and Real

- Belief that the pharmaceutical industry practices green chemistry already
- Belief that the environmental footprint is small/inconsequential
- Belief that bringing new medicines to patients is so important that environmental consequences should be minimized
- Belief that co production of waste is a cost of doing business
- I am meeting my regulatory permitting commitments
- Belief that green chemistry costs too much and slows down R&D programs
- Focus on replenishing the pipeline at the expense of initiatives like green chemistry
- Belief that regulators, especially the FDA/EMA, are a barrier to implementing green chemistry

# Barriers Continued

- Relationships: Chemists and EH&S professionals, chemists and chemical engineers, chemists and toxicologists
- Lack of adequate training: in academia, within companies, etc.
- Lack of green chemistry tools in the chemist's toolbox
- Poor to no understanding of life cycle analysis or environmental toxicity
- Little to no interest from CEO's, CFO's or CSO/CTO's
- At companies green chemistry needs to be more inclusive-more than just green process chemistry
- Little cross-talk between academia, industry, government agencies and NGO's

# A Three Horizon View of a PIE Strategy

- Near term (Now to + 5 years)
  - Education on proper disposal
  - Evaluate capture/ destruction technologies for use in WWTP's
  - Focus on SLEP opportunities
  - Determine if over prescribing is an issue
  - Get it right in the emerging markets (Africa, China, India, Latin America, etc)
  - Begin to address environmental fate & effects in the drug discovery phase
- Intermediate term (+ 5 years to + 20 years)
  - Wider use of bioavailability enhancing technologies
  - Explore nano technology to understand the possibilities for PIE
  - Targeted delivery
  - Design formulations for more unstable drugs
  - Simplify/remove regulatory hurdles to reformulation
  - “Just for you” medicines
- Long term (> + 20 years)
  - Targeted drug delivery common place
  - Design of drugs containing molecular switches

# Prospects for Continuing Progress Towards a Greener Pharmaceutical Industry

- Depends on the continued existence of an ACS GCIPR-like forum
- Depends on creating a demand from CEO's, CFO's and CSO's/CTO's
  - A need for more business case studies
- Depends on maintaining focus on green chemistry initiatives in the face of pressure to replenish the pipeline
  - \$140 billion drugs go off patent between now and 2015
  - Minimalist (or biotech investment) paradigm
- Depends on continuing to recruit “green chemistry advocates across the broad industry sector
  - Big Pharma, Biotech Pharma, Generics
- Depends on academia training sufficient quantities of chemists and chemical engineers schooled in the principles of green chemistry and engineering
  - Especially at the research intensive universities
- Depends on solving the significant technical challenges in the pharmaceutical product lifecycle
  - Renewable raw materials to drug delivery to designing drugs to degrade in the environment

# Acknowledgements

To Paul Anastas and John Warner for starting the green chemistry movement more than a decade ago and recruiting me to it

To the members of the ACS GCIPR who have set the standard for greener performance in the pharmaceutical industry

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