Greening the Pharmaceutical Industry

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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

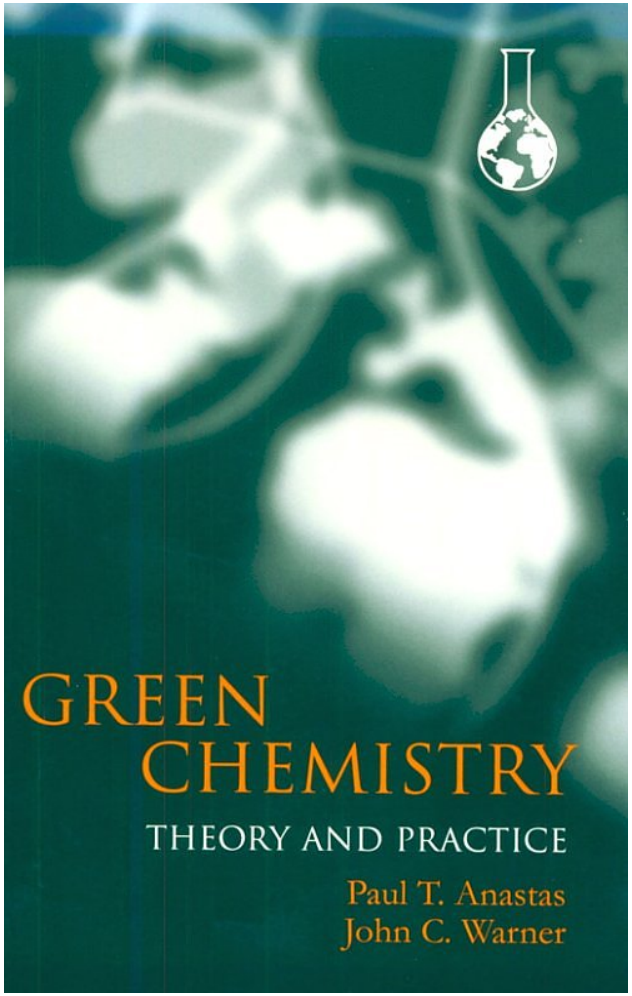
The PhRMA represents the leading research-based pharmaceutical and biotechnology companies in the United States. **PhRMA companies are devoted to discovering and developing new medicines that will enable patients to live longer, healthier and more productive lives.**

In 2008 the global pharmaceutical companies invested over $60 billion in discovering and developing new medicines, marking the 38^{th} straight year the industry has increased its investment in R&D

Source: PhRMA Website (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**

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

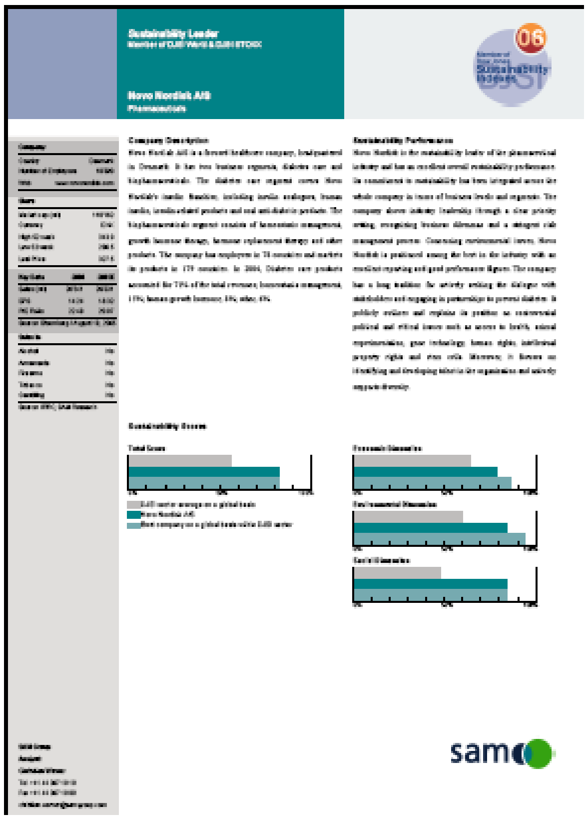
By 2005 the Landscape Was Changing Rapidly

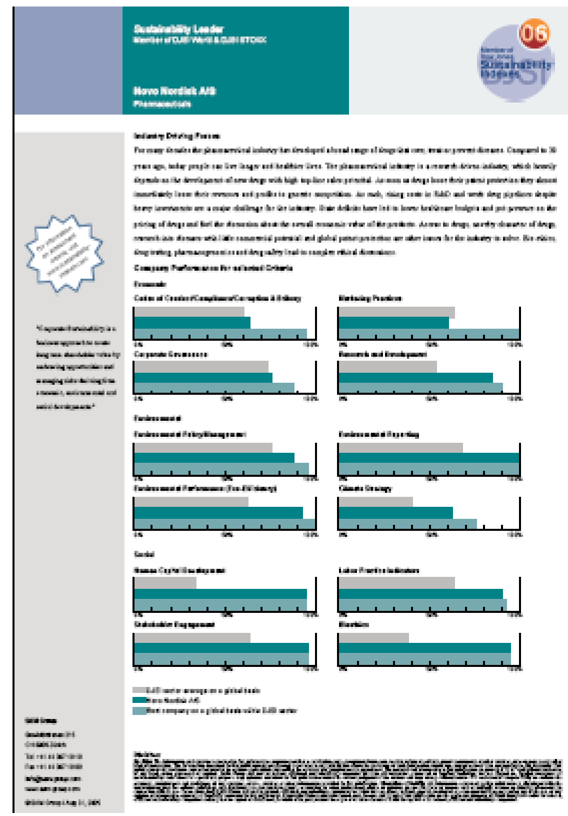
- Pharmaceutical companies were discussing sustainability and the triple bottom line in their annual reports
- Pfizer won the US EPA Presidential Green Chemistry Challenge in 2002
- Pfizer's green chemistry model, established in 2001, began to be copied by other major players
- A pharmaceutical spokesman (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 2009)

- The success of the ACS GCIPR has created copies (GC3 and Formulated Products and Suppliers RT within the ACS GCI)
- Twelve companies have joined the ACS GCI in the Pharmaceutical Roundtable
  - Astra Zeneca, Boerhinger-Ingelheim, Codexis, DSM, GSK, J&J, Lilly, Merck, Novartis, Pfizer, Schering-Plough and Wyeth
  - Other major pharma companies (Abbott, BMS, Dr, Reddys, 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)

The Dow Jones Sustainability Index Measures the Performance of the Pharma Peer Group. In 2008 Novartis Was Recognized for Their Leadership





Source:SAM Group® August 31, 2008

Pharma Peer Group Performance Against Sustainability Performance Criteria Used by SAM

- Over 50% (out of a possible 100%) peer average, best
  - Marketing practices (55%, 95%)
  - Corporate governance (65%, 90%)
  - Environmental policy/management (62%, 100%)
  - Codes of conduct/compliance/bribery (62%, 100%)
  - Environmental reporting (65%, 100%)
  - Labor practice indicators (62%, 92%)
- Under 50% (out of a possible 100%) peer average, best
  - Climate strategy (30%, 80%)
  - Standards for suppliers (43%, 92%)
  - Access to drugs (20%, 100%)
  - Environmental performance/ecoefficiency (47%, 100%)
  - Risk and crisis management (43%, 93%)
  - Talent attraction and retention (37%, 76%)

Current Membership as of July 20, 2009

AstraZeneca

Pfizer

ACS Green Chemistry Institute®

gsk GlaxoSmithKline

Wyeth

MERCK

DSM

Boehringer Ingelheim

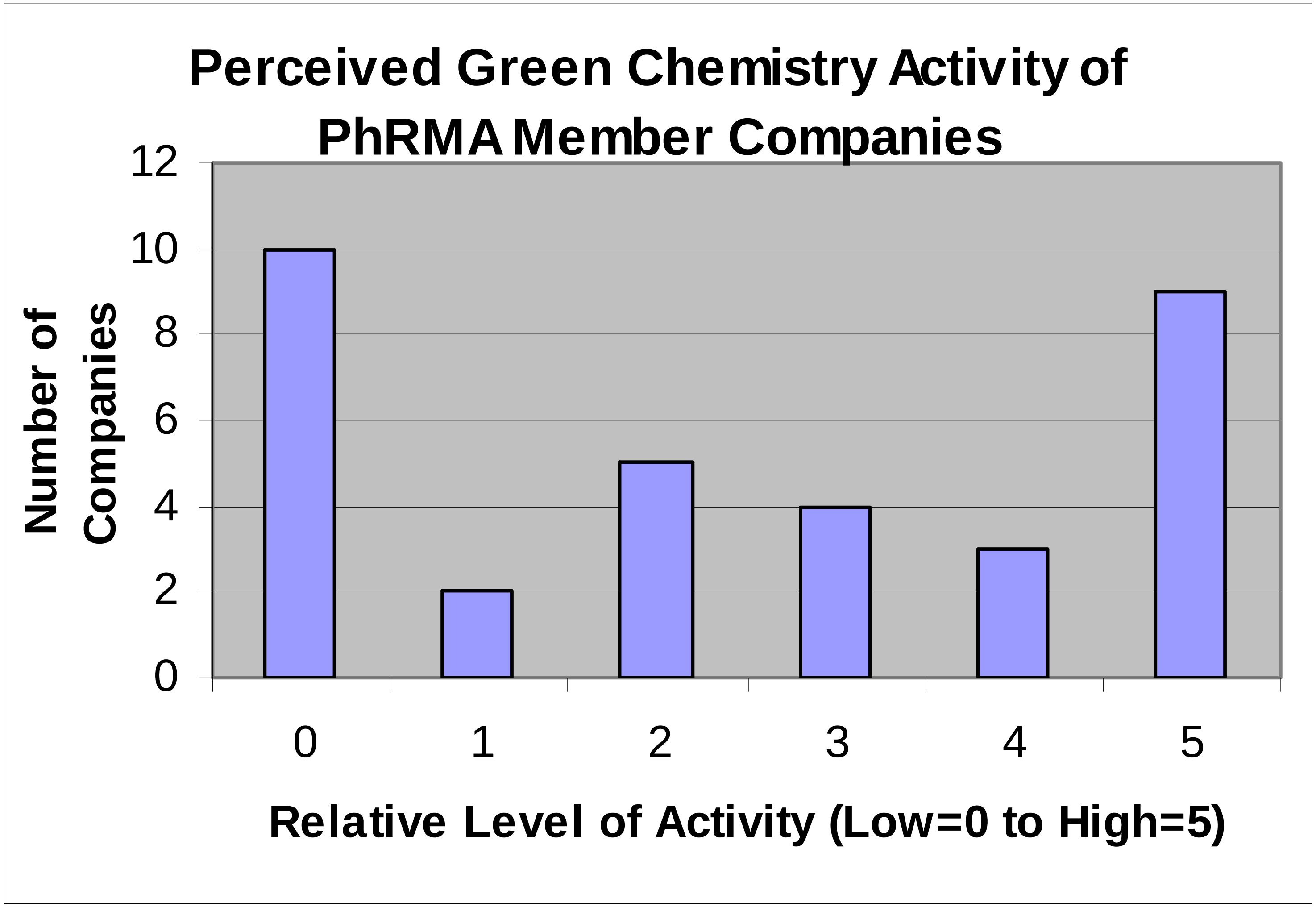
NOVARTIS

CODEXIS®

Schering-Plough

Lilly

Johnson & Johnson



Perceived Green Chemistry Activity of PhRMA Member Companies
Number of Companies
12
10
8
6
4
2
0
0
1
2
3
4
5
Relative Level of Activity (Low=0 to High=5)

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

Pharma companies are not using green chemistry to address this principle, 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 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**

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

1.Prevent waste: Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.

- E-factors (weight of waste/weight of product) have improved, but not dramatically during the last 15-years
  - Sheldon (1992) E = 25-100+. ACS GCIPR (2006) E=200
- Measuring baseline values and setting goals has begun among the top tier pharmaceutical companies.
  - All ACS GCIPR member companies measure and goal-set
- Some companies still see waste as an unavoidable “cost of doing business”
- When green chemistry principles are included in API process design from the beginning, up to 10-fold lower E-factors have been achieved

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

Industry Sector	***Product tonnage***	***kg byproducts/ kg of product***
Oil refining	**10^6 - 10^8**	**ca 0.1**
Bulk Chemicals	**10^4 – 10^6**	**<15**
Fine Chemicals	**10^2 – 10^4**	**5-50**
Pharmaceuticals	**10^1 – 10^3**	**25-100+**

Pharmaceuticals (MW<1000) — **200 (10-1000)**
(source: ACS GCIPR Benchmarking 2006)

Pharmaceuticals (MW>1000) — **5000-30000+**

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

2. Design safer chemicals and products: Design chemical products to be fully effective, yet have little or no toxicity

- Among all the sectors of the chemical enterprise, no sector studies the toxicity of their products, including environmental fate and effects studies, more than the pharmaceutical industry
- Mechanistic-based environmental toxicology is common practice
- Yet, the tools to predict which molecules will be endocrine disruptors/PBT's are not available in a validated HTS protocol suitable for incorporation in the drug discovery process
  - Computational toxicology needs to be adopted
- Toxicity studies are conducted on single agents while drugs in the environment exist in complex "cocktails"

3. Design less hazardous chemical syntheses: Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

- This is becoming more common, but in many cases greener alternatives to the most common chemical reactions used to synthesize drugs do not exist
- The ACS Green Chemistry Institute Pharmaceutical Roundtable has published a list of their "top ten" reactions needing a greener alternative and has awarded three research grants to academic researchers, so far totaling $650,000
  - Several authors, *Green Chem*, **9**, 411, May 2007
- The pharmaceutical industry is well along in addressing solvent use in their processes-both quantitatively and qualitatively
  - www.acs.org/gcipharmaroundtable

Key Pharmaceutical Chemistry Challenges

- Current Reactions
  - Amide Formation, OH activation, Amide Reduction, Green Mitsunobu reactions, Oxidation/Epoxidations
- More Aspirational Reactions
  - C-H activation or aromatics, chiral amine synthesis, Asymmetric Hydrogenation, Green Fluorination Methods, *N*-Centered Chemistry
- Key Ideas outside the Reaction theme
  - Solvent less Reactor Cleaning
  - Green alternatives to polar aprotic solvents

http://www.chemistry.org/portal/a/c/s/1/acsdisplay.html?DOC=greenchemistryinstitute\industry\gcipr.html

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

- Today drugs are manufactured from chemicals derived from fossil fuel byproducts
- No significant discussion about new sources of API building blocks, i.e., cellulose and lignin
- Some interest in using renewable solvents
  - Bio sourced ethanol
  - 2-Methyl THF from biomass waste
  - Regulatory consequences: impurity profiles at < 0.1%
- Finding sources of aromatic building blocks represents a huge R&D opportunity
- FDA and EMEA allow for significant change upstream from RSM, provided quality of API is not compromised

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 .

- API's are synthesized, for the most part, using stoichiometric chemistry
  - Largely the chemistry taught at the universities
  - The "limiting reagent" paradigm and stoichiometry
- Moving from a batch-based manufacturing (scale up) paradigm to the use of flow reactors (number up) represents a large opportunity to use catalysis
  - Could contribute to better process understanding and align with FDA's Quality-by-Design (QbD) initiative
- Increasing use of biocatalysts and biotransformations to make API's
  - Pregabalin

6. Avoid chemical derivatives: Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste

- Using derivatives and blocking groups to protect sensitive parts of the molecule is a common synthetic strategy-<u>except in nature</u>
- Some of the reactions targeted by the ACS GCIPR were selected to reduce or eliminate this need
  - E.g. Making amides from acids and amines
- Biotransformations offer a possibility for direct transformations, i.e., mimicking nature

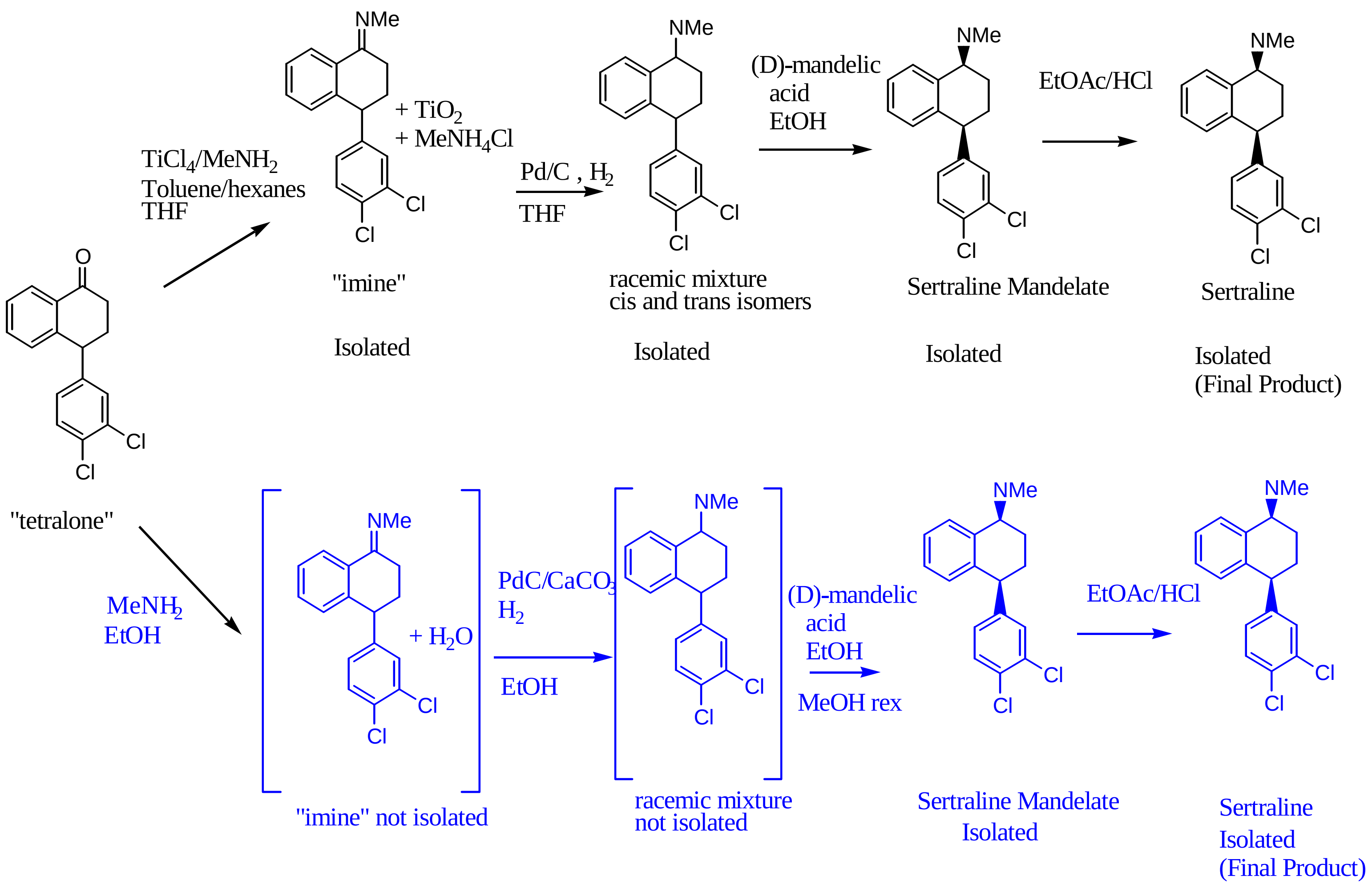
7. Maximize atom economy: Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms

- Atom economy in the synthesis of a pharmaceutical API is usually high.
  - Atom economy = MW product/MW sum of all reactants (excludes solvents)
- Note, atom economy by itself is not necessarily a good predictor of a green process. Yield, reaction concentration and product purity must be taken into account too.
- Beware of the limiting reagent trap.

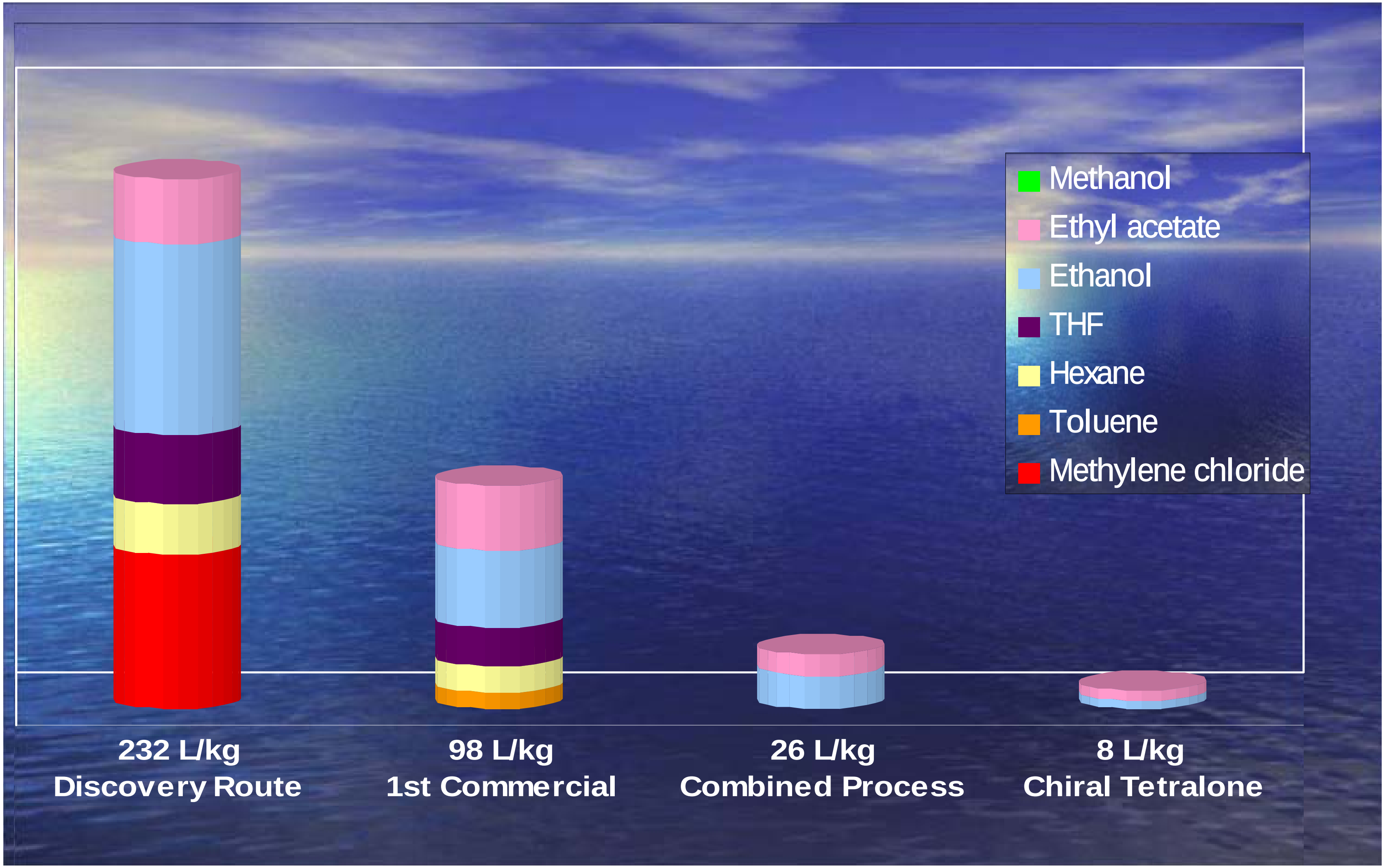
8. Use safer solvents and reaction conditions: Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.

- Solvents comprise the majority of API process waste
  - 80% according to a GSK lifecycle analysis
  - Confirmed by ACS GCIPR member company benchmarking
- Solvents are largely from fossil fuel-based sources
  - Beginning to see switch to bio renewable-based sources
- Use of separations, auxiliary chemicals is common
- Solvents for equipment cleaning are a hidden waste
- Education of R&D chemists on solvent selection and greener reaction options is starting.
- ACS GCIPR member companies have solvent selection guides and the PR is working on a common template
- ACS GCIPR companies have identified top ten reactions for greening and are funding academic R&D to this end

Re-designed Sertraline Process



Sertraline Process – Reduction in Solvent Usage vs. Synthetic Route



"Green" vs. "Non-Green" Solvents

- HAP solvents*

- Methanol
- Methylene Chloride
- Acetonitrile
- Hexane
- Toluene
- Chloroform
- Dichloroethane
- Methyl tert-butyl ether

- Non- HAP solvents
- Ethyl Acetate
- Ethyl Alcohol
- Heptane
- Tetrahydrofuran
- Isopropanol
- Isopropyl ether
- Diethyl ether
- Acetic Acid
- Dimethylacetamide
- Petroleum Ether
- WATER!!
- ACETONE

9. **Increase energy efficiency:** Run chemical reactions at ambient temperature and pressure whenever possible.

- Reaction temperature ranges typically between -78 deg C and +100 deg C (often at reflux temperature of rxn solvent)
  - These are the kinds of conditions developed by the research intensive academic R&D groups
- Almost always batch chemistry; seldom flow chemistry
- Sub optimal use of chemical engineering in the design of API processes
- Solvent recovery is an energy-intensive, usually distillation
  - recovery tends to be low
- Energy sparing (re batch) chemistry beginning to be used
  - Biotransformations
  - Microwave chemistry
  - Catalysis
  - Ultrasonic chemistry
  - Etc.

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

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.

- The pharmaceutical industry is moving rapidly to adopt Process Analytical Technology (PAT) through and FDA/PhRMA collaboration (**Q**uality **b**y **D**esign)
  - Driven by FDA regulatory actions around drug product quality issues
  - cGMP's of the 21^{st} Century
  - Six sigma (pharma is at 3-sigma = 7% product failure = waste)
- The recognition that PAT has a waste elimination/reduction outcome is just beginning
  - Tie in of QbD with Benign by Design (BbD) has started with some FDA buy-in
  - So far it is an API focus area for green chemistry while the FDA/PhRMA collaboration is focused on dosage form

Important reference: Cue, Berridge and Manley, Pharmaceutical Engineering,29,2,8-20 (2009)

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

- Traditional process safety identifies a potential hazard and manages it to eliminate or minimize adverse consequences: Meeting OHSA and EPA regulations drive the approach
  - Process Safety Management 29 CFR 1910.119
  - Risk Management Planning 40 CFR Part 68
- With green chemistry safer alternatives are sought as a first principle
  - Inherently safer design considerations
  - Active involvement of ChE's in process design
  - Control Banding/OEL's
  - Use of full battery of process safety tests
    - DSC, ARC, HAZOPS, etc in the R&D Phase
  - Adopting new technologies
    - Flow chemistry/microreactors
    - Impinging jet crystallization
    - Non isolation of API using separation: SMB, SCF HPLC, etc
  - Persuading academia to consider safety of chemistry they design
    - Science of scale
      - Realization that successful chemistry will be used to make tens to hundred of thousands of kilos of chemicals a year

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

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Barriers (continued)

- Belief that regulators, especially the FDA/EMEA, are a barrier to implementing green chemistry
- 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

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

A Final Word from Someone Who Knows

It's hard to be Green

Kermit the Frog

http://images.google.com/imgres?imgurl=http://i.a.cnn.net/cnn/2005/SHOWBIZ/TV/10/05/kermit.frog/story.kermit.jpg&imgrefurl=http://www.cnn.com/2005/SHOWBIZ/TV/10/05/kermit.frog/index.html&h=220&w=220&sz=12&tbnid=8IM1wAxwCFHCYM:&tbnh=107&tbnw=107&prev=/images%3Fq%3Dkermit%2Bthe%2Bfrog&start=1&sa=X&oi=images&ct=image&cd=1

Acknowledgements

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

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

To all pharmaceutical green chemistry advocates, who have demonstrated leadership, recognized or unrecognized, in their companies

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