Environmental Footprint and Opportunities in Pharmaceutical Processes

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Green Engineering

1

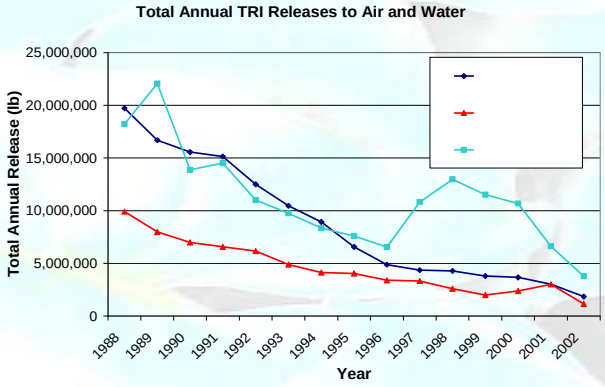
Outline

- Environmental Impacts
  - Successes & Progress to Date
  - Solvents
- Opportunities
  - Green Chemistry (e.g. Atom Economy, chemical substitution)
  - Green Engineering Opportunities (e.g., Mass Efficiency, Fugitive Emissions, Heat & Power)
- FDA Product Spec vs Process Spec: **"Green Quality"**
- Others (GC bill, SMART)

2

Environmental Footprint and Progress

- Success 1998 to 2002
  - 91% decrease in stack air releases
  - 88% decrease in fugitive air releases
  - 79% decrease in water releases



3

Progress – Solvent Substitution (shaded chemicals are not TRI)

	2005 Rank	1999-2000 Rank
2-Propanol	1	5
Ethyl Acetate	2	4
Methanol	3	6
Denatured Ethanol	4	8
n-Heptane	5	12
Tetrahydrofuran	6	2
Toluene	7	1
Dichloromethane	8	3
Acetic Acid	9	11
Acetonitrile	10	14

4

Environmental Footprint of the Pharmaceutical Industry

- The above analyses provide insight and shows the industry is moving in the right direction.
- The challenge is to further minimize the environmental footprint by:
  - Greener Processes to minimize releases and production of waste (green engineering)
  - Use safer chemicals, reduce reaction stages (green chemistry)
- Focus efforts on:
  - Solvents (Largest contribution to environmental footprint)
  - Mass Efficiency (1 kg API/99 kg waste)
  - "Green Quality" Going from process spec to product spec (FDA)

5

Atom Efficiency Example

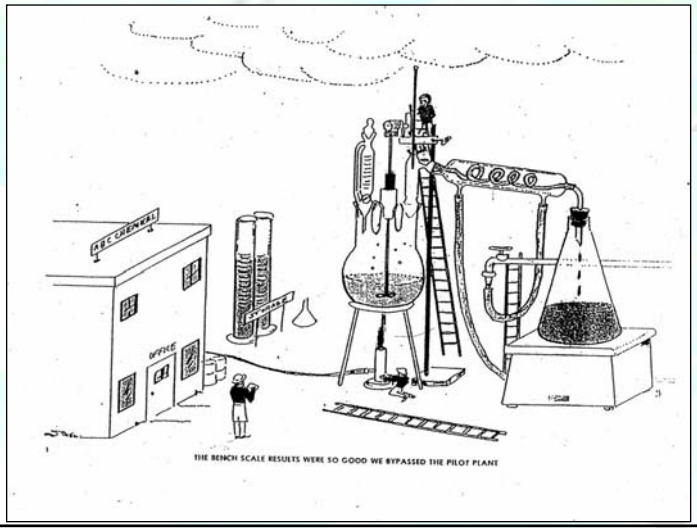
- U.S. Presidents 2006 Green Chemistry Award Winner Merck
- Novel chemistry to alter atom efficiency
  - 270 kg waste/kg API → 50 kg waste/kg API
- 80% decrease in waste
- 85-90% of waste is solvent

Reduction of Reaction Steps Provide Significant Waste Reduction not Obtainable by other Approaches

6

Moving Forward

- Moving from bench scale to the plant



7

New Opportunities

- Mass Efficiency vs Atom Efficiency

	Overall Process	Average per Stage
Atom Economy	43%	87%
Mass Efficiency	1.5%	7.6%
Average Number of Process Stages	7	

99 kg of waste to yield 1 kg of API!!!

8

Green Engineering

3 Tiers of GE Assessments in Design

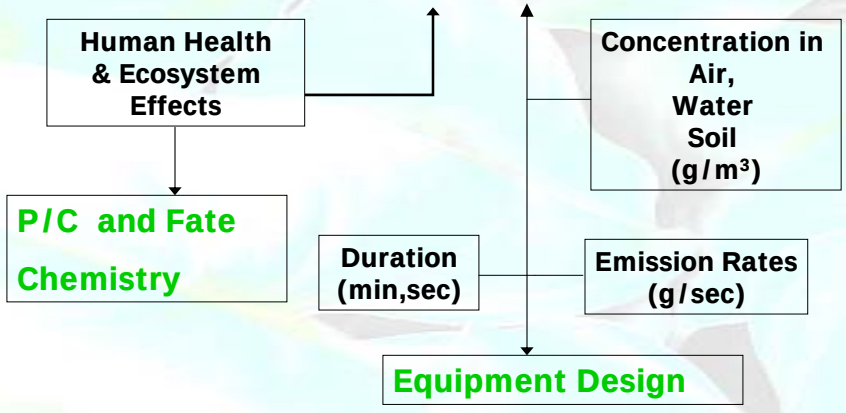
Simple Tier 1	Process Research/Development Material Selection Reaction Pathways	Toxicity Potential Costs, P/C, Fate Potential Exposure
Tier 2	Conceptual/Preliminary Design Unit Operations Specs.	Material/Energy Emissions Costs Exposures
Tier 3	Detailed Design Energy Integration Detailed Evaluation Controls	Detailed Emissions Exposure Env. Fate/Risk

9

Green Engineering

- Minimizing Risk Involves Reducing Both the Hazard and the Exposure

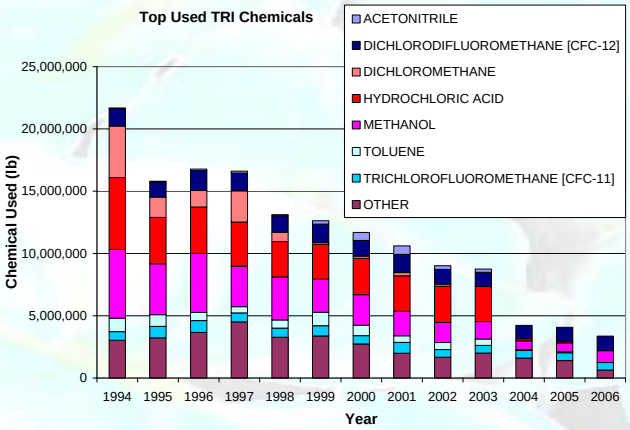
Risk = f (hazard, exposure)



10

Reduction in Mass of TRI Chemicals in New Jersey

- 85% reduction in mass of TRI chemicals used



Michael DiGiore, New Jersey Release and Pollution Prevention Report, Office of Pollution Prevention and Right to Know, New Jersey Department of Environmental Protection

11

Green Engineering Opportunities: Solvents

- Solvent Selection, Recovery and Reuse
  - Solvent selection guides already developed by industry and academia
  - 99 kg waste/1 kg API - recovery has diminishing returns
- Double the reaction concentration
  - Decrease material costs 10-15%
  - Reduce capital and operations time

"We pay for the solvent, we pay for the capital to manage it, and we pay to burn it."

Constable, David J.C. et. al., Perspective on Solvent Use in the Pharmaceutical Industry. *Organic Process Research & Development* **2007**, 11, 133-137

12

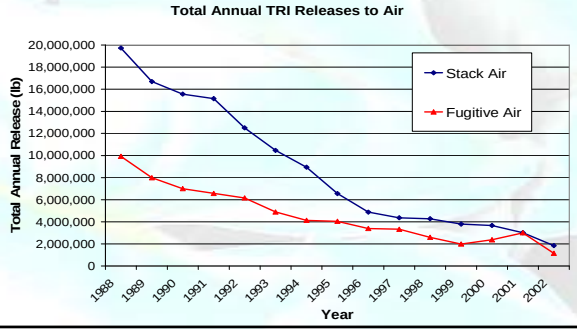
Green Engineering Opportunities: Solvents

- Process optimization at the molecular level
  - Mixing
  - Heat transfer / Mass Transfer
- Perceived Need for homogeneity of reaction mixture
  - Solvent choice focused on solubility with better use of technology → less solvent required

13

Green Engineering Opportunities: Fugitive Emissions

- Reducing Fugitive Emissions
  - Thermal imaging/infrared camera to identify leaks
  - Enhances LDAR Program
  - Once leak is identified, it is fixed
  - Documentation and image of emissions



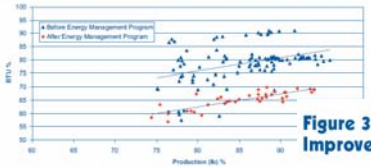
14

Green Engineering Opportunities: Texas Industries of the Future

70% of Base Load Energy Use is for steam and cooling

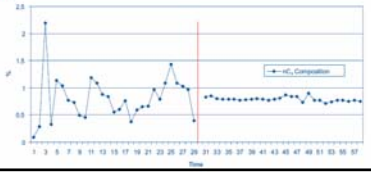
- Distillation Optimization Case Study
- Changes performed in the *power plant*

Figure 2. Distillation Project Energy Efficiency Improvement (Btu/lb)



Pharmaceutical Challenge: SEPARATION

Figure 3. Distillation Project Overhead Composition Control Improvement



Pharmaceutical Largest Expenditure of Energy: STEAM

Green Engineering Opportunities: Utilities

- Cooling Water Example
  - Heat transfer very important
  - Cooling water in coils/jackets leaves deposits and corrosion byproducts
  - Reduces heat transfer and raises electricity costs (increased pumping)
  - Water treatment to prevent deposition and corrosion byproducts
  - Changes performed in the *utility plant*

16

New Opportunities with FDA

"Green Quality"

- Movement away from process spec to product spec
- Changes to manufacturing/purity profile that do not change product quality should not need to involve FDA

Dr. Watts with FDA will expand

17

Relevant Congressional Activities

- Proposed GC Bill
  - National Academy of Sciences will investigate the barriers to GC R&D
  - Report findings and recommendations to the House and Senate Science Committees
- SMART
  - Collaborative Science and Technology Organization of Delaware, Maryland, New Jersey, and Pennsylvania
  - Promotes active partnerships between industry, academia, technical and government institutions

18

Imagine the potential environmental benefits IF . . ..

- Chemists and Engineers trained and apply GC/GE concepts
- Chemical plants modified or built using GC/GE concepts and approaches
- Engineers and Chemists worked together more

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19