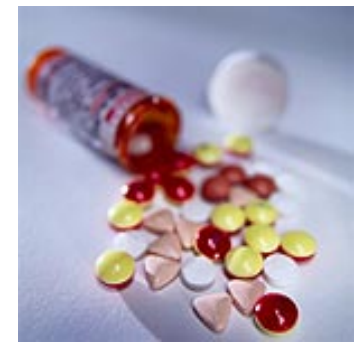


Green Engineering Opportunities in the Pharmaceutical Industry

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Pharmaceutical Industry

- Major commercial sector in Region 2
 - NJ is known as medicine chest to the Nation
- Biotechnology and biochemical synthesis
 - Genetic engineering
 - Fermentation
- Organic synthesis
 - Chemical reaction/purification



- The pharmaceutical industry's main goal is to extend and enhance human life while complying with various pollution prevention and safety regulations*
- API (Active Pharmaceutical Ingredient)
 - The compound within the pill or solution that treats the disease
- 2003, \$216 Billion sales prescription drugs**
 - \$29 Billion sales for top 10 drugs alone
- Energy usage is between 50-300 MJ/kg API***
- Solvent usage is around 300 kg/kg API****

* Bristol Myers Squibb Corporate Responsibility Statement

** Herper, M., "Best Selling Drugs in America," Forbes.com, 2/18/2004

*** Jimenez-Gonzalez, Concepcion, Doctoral thesis, 2000

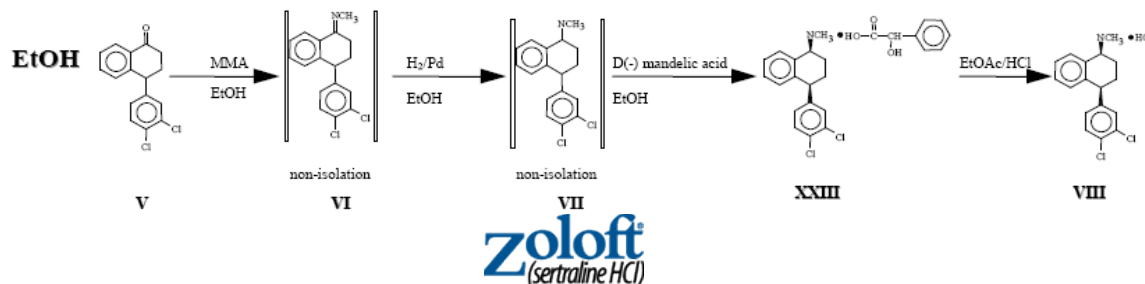
**** Mai, Jing-Chen, et al. US patent 6790984, September 14th 2004



Manufacturing Issues



- Batch-based processes
- Multi-step synthesis, transformations – intermediates
- Isolations (purification)
- Extensive use of multiple organic solvents and reagents – varying degrees of toxicity
- Limited health data on intermediates



Manufacturing Issues

- Processes – solid/liquid – filtration, drying, etc
- Purity and yield
- 7-11 years between development and manufacture – Regulatory steps (Phase I-III)
- 10% success rate for new drug development
- Outsourcing process steps
- Once process is approved by FDA, any changes are hard to implement



What is Green Engineering?

Design, commercialization and use of processes and products that are feasible and economical while minimizing:

- Risk to human health and the environment
- Generation of pollution at the source

Transforms existing practices to promote sustainable development



The SanDestin Declaration of Green Engineering Principles (2003)



- Transforms existing practices to promote sustainability
- Economically viable products, processes, and systems that
 - promote human welfare
 - while protecting human health
 - and elevating the protection of the biosphere
- New criterion for engineering solutions



To fully implement green engineering solutions, engineers use the following principles:

1. Engineer processes and products holistically, use systems analysis, and integrate environmental impact assessment tools
2. Conserve and improve natural ecosystems while protecting human health and well-being
3. Use life cycle thinking in all engineering activities
4. Ensure that all material and energy inputs and outputs are as inherently safe and benign as possible
5. Minimize depletion of natural resources





To fully implement green engineering solutions, engineers use the following principles:

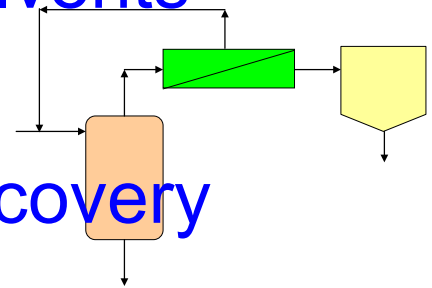
6. Strive to prevent waste
7. Develop and apply engineering solutions, while being cognizant of local geography, aspirations and cultures
8. Create engineering solutions beyond current or dominant technologies; improve, innovate and invent (technologies) to achieve sustainability
9. Actively engage communities and stakeholders in development of engineering solutions

There is a duty to inform society of the practice of green engineering



Green Engineering Opportunities

- Investigate process early in development
- Solvent substitution – more benign solvents
- Solvent reduction
- Novel processes for material reuse/recovery
- Reduction in process steps
 - “Telescoping” to eliminate intermediate isolations



- **Challenge - maintain drug purity and yield**



Green Chemistry Example – Bristol-Myers Squibb Taxol®



2004 Presidential Green Chemistry Challenge
Alternative Synthetic Pathways Award



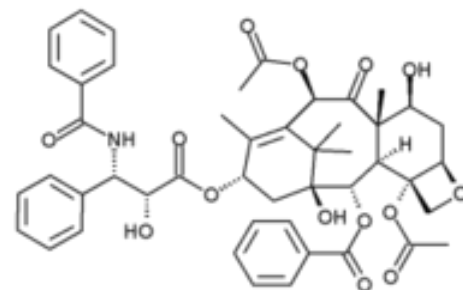
- Development of a green synthesis for Taxol® manufacture via plant cell fermentation and extraction
- Paclitaxel, the active ingredient in the anticancer drug Taxol® originally isolated from yew tree bark



Bristol-Myers Squibb Company

www.epa.gov/greenchemistry/aspa04.html

- Natural purification from yew tree bark
 - 0.0004% paclitaxel
 - Stripping bark and extraction process kills tree – not sustainable
 - Yews take 200 yrs to mature – ecosystem impact
- Chemical synthesis of paclitaxel
 - 40 steps, 2% yield
- Semisynthetic route from naturally occurring yew-based 10-deacetylbaccatin III
 - 11 chemical transformations, 7 isolations
 - 13 solvents
 - 13 reagents, catalysts, etc



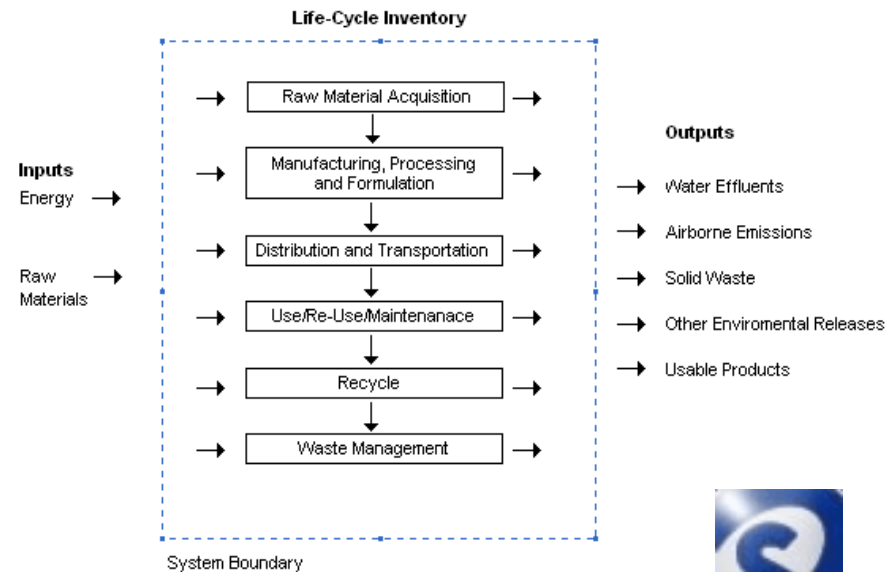
- Plant cell culture fermentation (PCF)
 - Renewable nutrients – sugars, amino acids, vitamins, etc
 - Plant cell culture – consistent quality
 - Paclitaxel obtained directly from plant cell cultures
 - Extraction, chromatography, crystallization
 - Sustainability of paclitaxel supply improved
 - No chemical transformations – no intermediates
 - Elimination of 10 solvents – solvent usage and waste reduction
 - Elimination of 6 drying steps – energy reduction
 - 32 metric tons hazardous waste reduced in 5 yrs production
- Overall sustainable production of complex biochemical with less waste, less solvent use, less energy, less hazardous chemicals required



Green Engineering Future Needs

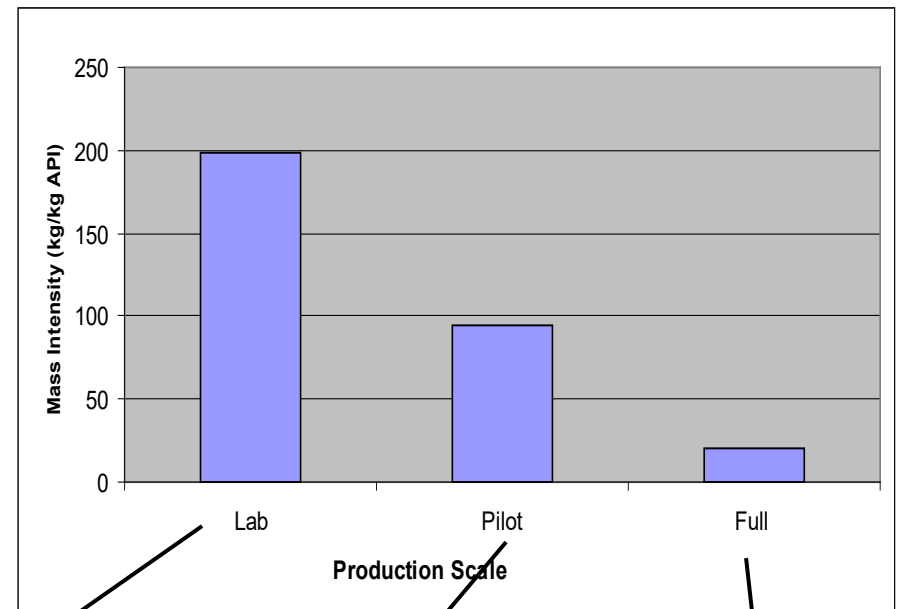
(Role of academia in translating GE throughout pharma industry)

- Institutionalize the “green engineering way”
 - Development of heuristic
- Education & training of scientists and engineers
 - Existing workforce – partnerships with industry, EPA initiatives
 - Next generation – curriculum integration and workshops
(www.rowan.edu/greenengineering)
- Analysis of products and processes
 - Tier 1 analysis
 - Life cycle analysis



Green Engineering Needs (con't)

- Metrics to measure and quantify improvements
 - What to measure, how to quantify – *more than just amount reduced*
- Materials
 - Mass intensity – amount of raw material needed to produce 1 kg of API
 - Solvent intensity
 - Waste intensity
 - Water intensity
- Emissions
- Efficiency
- Energy



Green Engineering Needs (con't)

- Quantify broader environmental impact
 - Global warming, ozone depletion, acidification, etc
- Novel process design, process improvements
 - Solvent reduction, substitution, purification and recovery
 - Membrane separations, novel reactors, hybrid processes, etc
- Goal → The greener process is the better process

