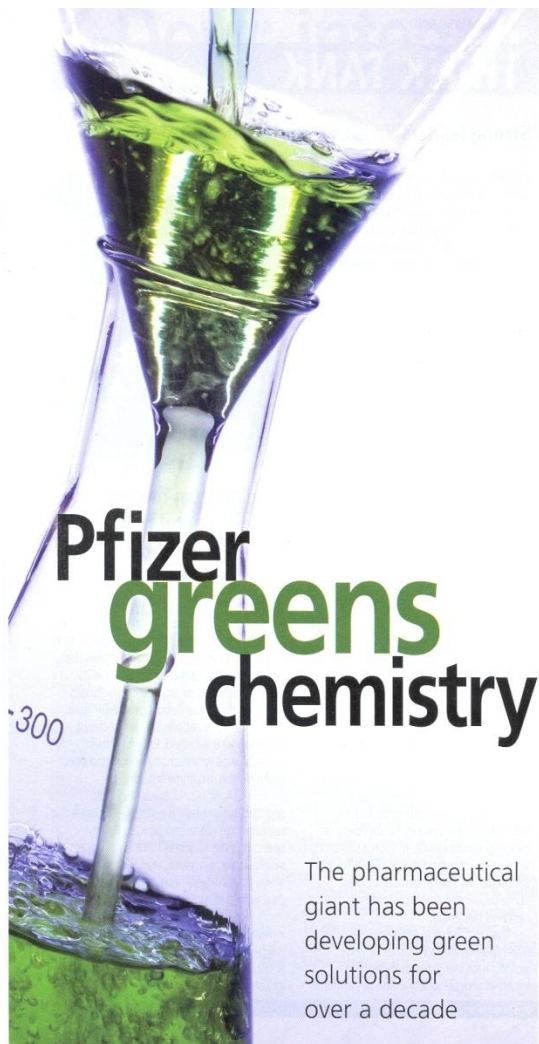




GREEN CHEMISTRY

Green Chemistry at Pfizer



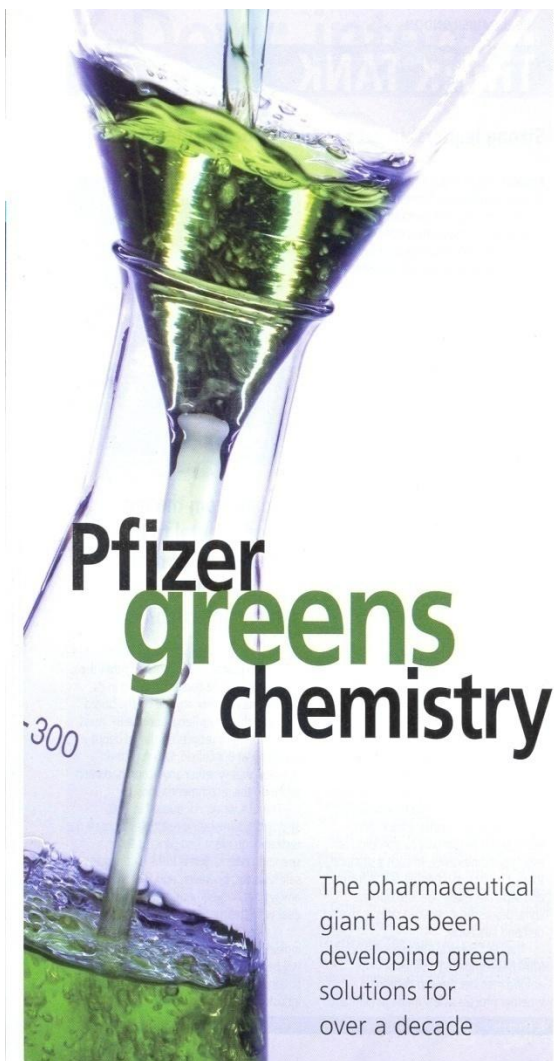
Peter Dunn
Pfizer Green Chemistry Lead





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Presentation Outline

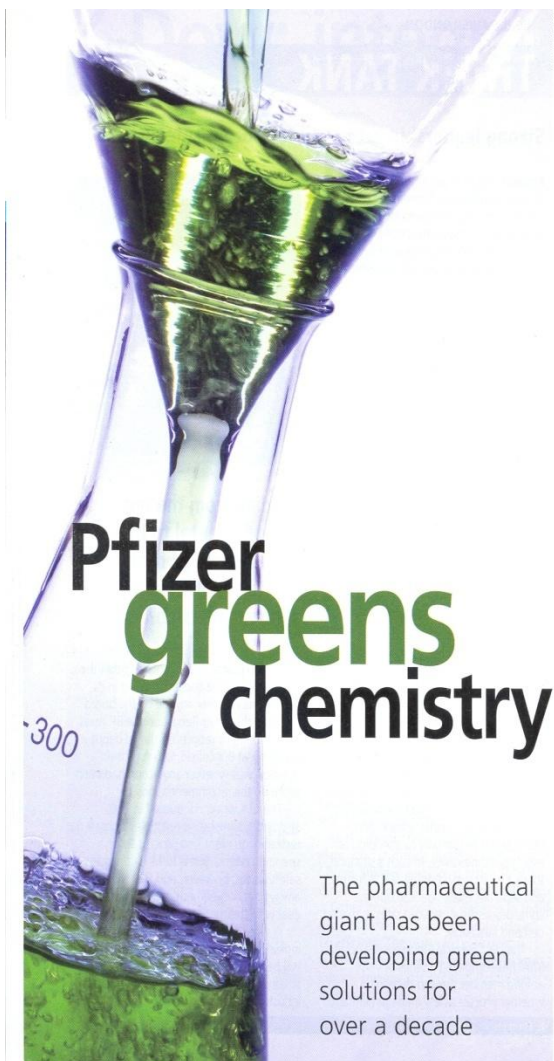


- u **Brief Introduction to the Pfizer Green Chemistry Program**
- u **Green Chemistry Tools with a focus on the Pfizer Reagent Guide**
- u **Pregabalin case history focussing on some very recent results from a detailed life cycle assessment**



GREEN CHEMISTRY

Pfizer Green Chemistry Mission



- u To introduce, educate and promote the application of Green Chemistry across Pfizer and in our key research partners.
- u Key Philosophy: Voluntary restraint is better than enforced constraint.
- u Green Chemistry includes protection of the environment and worker safety.
- u Informing and influencing the Green Chemistry research agenda.

The pharmaceutical giant has been developing green solutions for over a decade



Pfizer Green Chemistry – Engagement & Alignment

.Success required attention to Green Chemistry across all our locations: research, scale-up, and manufacturing facilities.

.We have:

- ✓A full-time GC leader with a company-wide responsibility
- ✓A company GC Policy and Steering Committee (*responsible for the strategic plan, communications plans, key policy decisions, and monitoring of performance*).
- ✓Developed practical tools to help chemists go green.
- ✓GC teams at all chemistry research Sites— Medicinal Chemists, Process Chemists and EHS colleagues, set annual objectives, manage site-based awards programs, hold annual green chemistry seminars, raise awareness, and drive behavior change.
- ✓Integrated GC into our co-development process with manufacturing and initiated Manufacturing GC Awards.



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Pfizer Green Chemistry Tools

Solvent Guides

Simple, More detailed

Biocatalysis Guide

Acid/Base Guide

Metrics Tool

Predictive Distillation Tool

Simple Life Cycle Tool for basic carbon footprint determination



GREEN CHEMISTRY

Pfizer Green Chemistry Tools

Solvent Guides

Simple, More detailed

Biocatalysis Guide

Acid/Base Guide

Metrics Tool

Predictive Distillation Tool

Simple Life Cycle Tool for basic carbon footprint determination

Reagent Guide



Chloroform Usage, Pfizer Research Division



Reagent Selection Guide



Reagent Selection Guide





Example: Oxidation of Primary Alcohol to Aldehyde

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PCC
PDC

CrO₃

DMSO/oxalyl chloride
(Swern)

DMSO/TFAA

DMSO/SO₃-
py
TEMPO/tcca

NiO₂
BaMnO₄
MnO₂

Dess-Martin
periodinane

Me₂S/Cl₂
(Corey-
Kim)

TPAP/NMO

PIPO/NaOCl

Cl₂/py

DMSO/DCC
(Pfitzner-Moffatt)

TEMPO/NaOCl

NaOCl/RuO₂

Air/TEMPO/water

Air/metal(cat)

Air/TEMPO/metal(cat)

References for Reagents without links

.An excellent review covering the Green aspects of alcohol oxidations can be found in [2006 Ang Chem Int 3206](#)

.For a review of Large Scale Oxidations [2006 Chem Rev 2943](#)

.Sustainability in catalytic oxidation [2009 Chem Sus Chem 508](#)

**Green Criteria for
this Transformation**



Example: Oxidation of Primary Alcohol to Aldehyde

GREEN CHEMISTRY

PCC
PDC

CrO3

DMSO/oxalyl chloride
(Swern)

DMSO/TFAA

DMSO/SO3-
py
TEMPO/tcca

NiO2
BaMnO4
MnO2

Dess-Martin
periodinane

Me2S/Cl2
(Corey-
Kim)

TPAP/NMO

PIPO/NaOCl

Cl2/py

DMSO/DCC
(Pfitzner-Moffatt)

TEMPO/NaOCl

NaOCl/RuO2

Air/TEMPO/water

Air/metal(cat)

Air/TEMPO/metal(cat)

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**Green Criteria for
this Transformation**

**Published
P.J. Dunn et al.
Green Chem., 2008, 10, 31.**



Pregabalin the active ingredient in Lyrica



- .Pregabalin is a Drug for the treatment of Neuropathic Pain
- .Launched in the US in September 2005
- .Sales \$1.16 billion (2006), \$3.06 billion (2010)



Process 1 – Launch Process

- Reasonable synthesis of racemic Pregabalin
- Final Step Classical Resolution
- Wrong enantiomer difficult to recycle
- E factor 86 (ie 86 kilos waste per kilo of product)
- Two reactions performed at reflux (High energy use)



Process 2

Incinerated

H₂O

H₂O

H₂O

- Biocatalytic with low levels of protein loading
- All 4 reactions are conducted in water
- Resolution at first step
- Wrong enantiomer is incinerated
- Significant waste reduction (see later)
- Biocatalysis reaction is very concentrated





Process 3

Recycled

H₂O

H₂O

H₂O

- Wrong enantiomer is no longer incinerated but is now recycled and converted to high quality product
- All 4 reactions are still performed in water
- E-Factor improved from 86 to 11





Comparison of Pregabalin Processes

Energy (in house)

118.8 MJ/Kg

21.4 MJ/Kg

42.4 MJ/Kg



Comparison of Pregabalin Processes

Energy (in house)	118.8 MJ/Kg	21.4 MJ/Kg	42.4 MJ/Kg
Energy (total)	155.0 MJ/Kg	49.3 MJ/Kg	58.7 MJ/Kg



Summary of Three Processes

- Easy to see that process 1 is the worst
- To determine whether process 2 or process 3 is the best from an environmental standpoint requires a more detailed Life Cycle Assessment



Life Cycle Assessment Concepts



□ SimaPro® is a detailed environmental analysis tool

- Used for a product or process
- Quantification of the raw material, energy use, and emissions to the air, water, and soil
- Characterization of environmental impacts

□ Ecosolvent® is used to compare waste treatment processes by determining the environmental impact

- Used for solvents or other chemicals that are incinerated, distilled, or sent to waste water treatment
 - Quantification of emissions due to disposal and recovery of solvents
- $$\sum R_i * LCI_i + \sum E_i * LCI_i + \sum W_i * LCI_i = LCA$$
- R_i = Raw Materials, E_i = API Manufacture Energy, W_i = Wastes

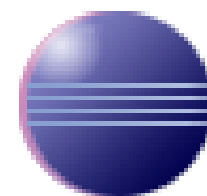
□ ASPEN Batch Process Developer

- Used to model the energy for all three processes
- All logos Pfizer used SimaPro, Ecosolvent and Aspen software for this evaluation, this does not mean Pfizer endorses these products.



Life Cycle Inventory Generation

- .LCIs for each of the compounds from the racemic-CNDE process and the three process routes for pregabalin production
 - .20 different compounds total
 - .12 compounds included in SimaPro® database
 - .LCI for enzyme provided by manufacturer
- .Utilities based on fuel mix at plant site
- .Waste disposal determined by EcoSolvent based on disposal method
 - .Incineration
 - .Waste Water Treatment Plant
 - .Recovery process, e.g., distillation





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Sample Life Cycle Inventory

Life Cycle Inventory Summary for 1 kg THF

◦ This database entry includes the process for materials, infrastructure of the plant, all energy uses, and all emissions



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LCI Generation Options

7 compounds not included in SimaPro® database

Can model as a compound that is included in database

- Isovalderaldehyde
- 3-methyl-1-butanol

Model from a similar compound and substitute emissions for actual functional group assuming similar energy for production and conversion

- Potassium cyanide
- sodium cyanide



Process 1

Raw Material Life Cycle Inventories

24.8 kg



Total emissions of raw materials from Process 1 on 1 kg basis of each chemical manufactured



Process 1

Life Cycle Emissions from Raw Materials

547 kg Total Raw Material Manufacturing Emissions/kg API



On a per kg of API produced basis for API synthesis



Process 1 LCA

954 kg Total Life Cycle Emissions/kg API

On a per kg of API produced basis for API synthesis



Process 2 and 3

Raw Material Life Cycle Inventories

24.8 kg



Total emissions of compounds from Processes 2 and 3 on 1 kg basis of each compound

Process 3 is the same as Process 2 with the exception of a recycle stream



Process 2

Life Cycle Emissions from Raw Materials

148 kg Total Raw Material Manufacturing Emissions/kg API

On a per kg of API produced basis for API synthesis



Process 2 LCA

242 kg Total Life Cycle Emissions/kg API

On a per kg of API produced basis for API synthesis



Process 3

Life Cycle Emissions from Raw Materials

87.4 kg Total Raw Material Manufacturing Life Cycle Emissions/kg
API

On a per kg of API produced basis for API synthesis



Process 3 LCA

183 kg Total Life Cycle Emissions/kg API

On a per kg of API produced basis for API synthesis



Comparison of Selected Raw Material Life Cycle Emissions



LCA of Process 1, 2 and 3



Summary

- .Biocatalytic route significantly reduces emissions and energy use
- .Cradle to gate life cycle analysis shows 81.8% reduction in life cycle emissions (80.8 % CO₂)
- .Majority of life cycle emissions generated from raw materials manufacture
- .Evolution of green process improvements
 - .Raw material decreases
 - .Organic solvent use decreases
 - .Water use small increase
 - .Recycle operations integrated
 - .Waste disposal reduced





Pregabalin enzymatic process – environmental benefits

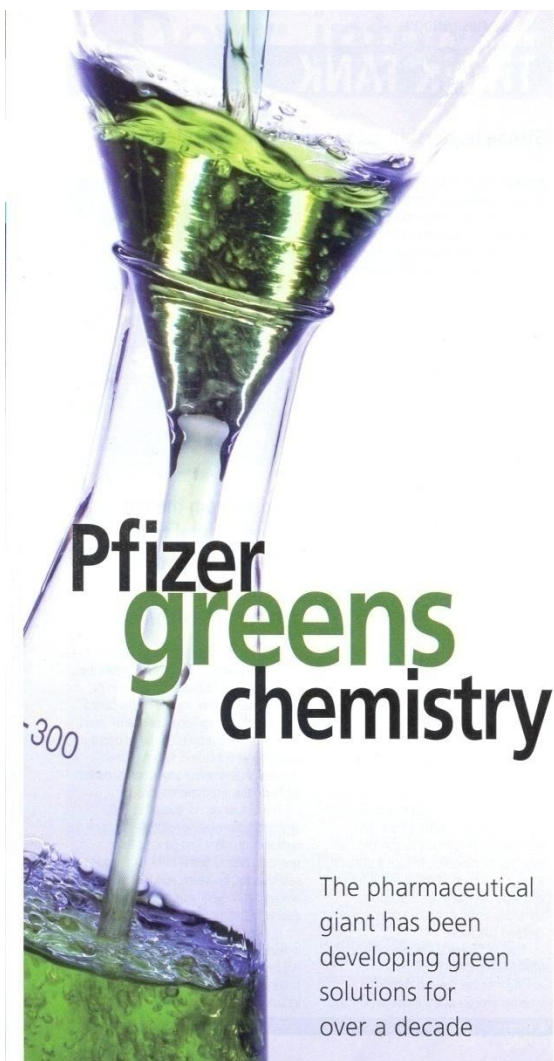
Solvent and Energy savings are the equivalent to saving
3 million tonnes of CO₂ emissions

Equivalent to taking 1 million Indian cars off the road for a year!





Thanks and Acknowledgments



- LCA –Leadership – Professor Stewart Slater, Professor Mariano Savelski (Rowan University)
- LCA - Rowan Univ Engineering Student Team
 - David Hitchcock, Christopher Mazurek, James Peterson, Michael Raymond
- Energy Calculations
 - Kevin Hettenbach, David Place, Michael St Pierre, Jay McCauley, Christine Visnic
- Waste data
 - Chong-Seng Teng, Ramalingam Anbuchelian, RK Ramachandran
- Pregabalin
 - C. Martinez, S. Hu, J. Tao, P. Kelleher, D. Knoechel
- To YOU – today's audience

Back Up Slides



GREEN CHEMISTRY

LCA of the 3 Processes

Energy LCIs

In units kg Emissions
per MJ of Energy

4

0