GREEN CHEMISTRY

Green Chemistry at Pfizer

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Pfizer Green Chemistry Tea

Agenda

- **Introduction to Green Chemistry at Pfizer**
  - ✓ Engagement and alignment across the company
  - ✓ Supporting and influencing external environment
- **Making a Difference through Green Chemistry**
  - ✓ Internal tools – helping chemists “go green”
    - ✓ Solvent Selection Guide
    - ✓ Reagent Selection Guide
  - ✓ Case Study – Pregabalin Process Development Program

Engagement and alignment across Pfize

- Spans whole company from Medicinal Chemistry to Manufacturing
  - ✓ Green Chemistry Team covers Med Chem, Process Development, Pilot Plant Manufacture, EHS and Full Scale Manufacturing
  - ✓ Early engagement of medicinal chemists ensures green concepts are installed early in the development life cycle
  - ✓ Engineering solutions are employed (e.g. PAT, Continuous Processing, Biocatalysis etc)
- Hold **Green Chemistry seminars** at all our research sites - by chemists for chemists with prominent chemistry speakers

Engagement and alignment across Pfize

- Hold annual Green Chemistry Awards
  - Focused on core topics from the 12 Principles of Green Chemistry
    - Prevention and reduction of waste products including energy.
    - Maximisation of atom economy.
    - Develop less hazardous chemical synthesis with safer reagents and solvents.
    - Use of catalysts including enzymes
    - Use of renewable feedstocks with the potential for solvent recycling.
  - Winners nominated a University (which ideally supports and champions GC research) for a £3,000 donation

Supporting and influencing external environment

- Membership in the ACS GCI Pharmaceutical Roundtable
  - Let Academics and Govt agencies know the key challenges in Pharmaceutical Manufacturing so they can be addressed
- Academia – Aim to positively shape today's research to solve industry *(and society's)* needs. Much of our chemistry is based on reactions established 50-100 years ago!
  - Amide Formation with high economy
  - Amide Reduction (through the Roundtable)
  - Oxidations without chlorinated solvents
  - Suzuki Reactions without halogenation (through the roundtable)
  - Solvent Recovery using membrane technology
- Work with other pharmaceutical companies to deliver **Green Chemistry workshops** for university students in the UK and Ireland

Internal Tools

- **Solvent Selection Guide**
  - Solvent Reduction Program
- **Reagent Selection Guide**

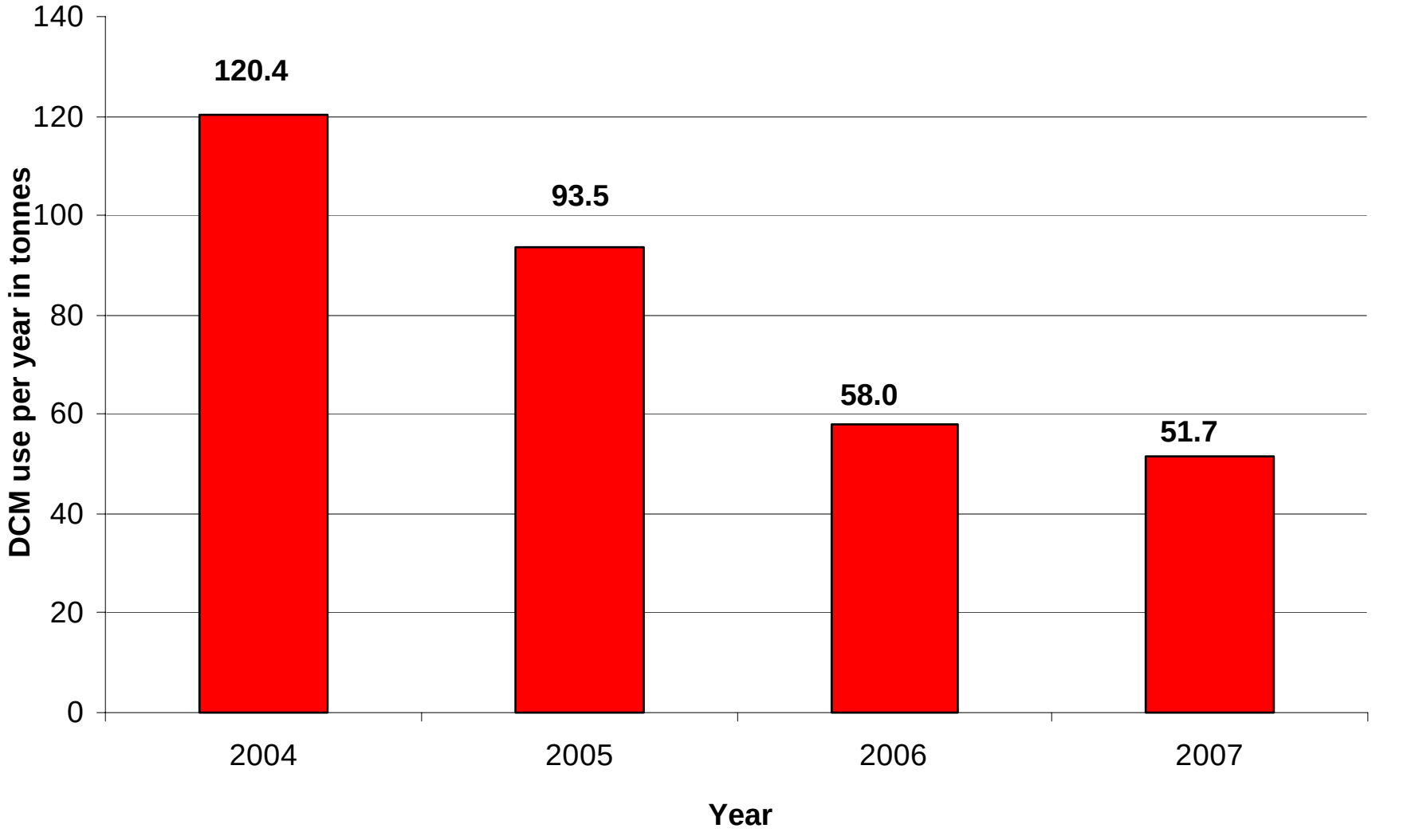
Use of Internal Tools – Pfizer Solvent Selection Guide

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Diisopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	t-Butylmethyl Ether	Dichloromethane
Ethyl Acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-Me Tetrahydrofuran	N-Methylpyrrolidinone
Methyl Ethyl Ketone	Tetrahydrofuran	Dimethyl Formamide
1-Butanol	Xylenes	Pyridine
t-Butanol	Dimethyl Sulfoxide	Dimethyl Acetamide
	Acetic Acid	Dioxane
	Ethylene Glycol	Dimethoxyethane

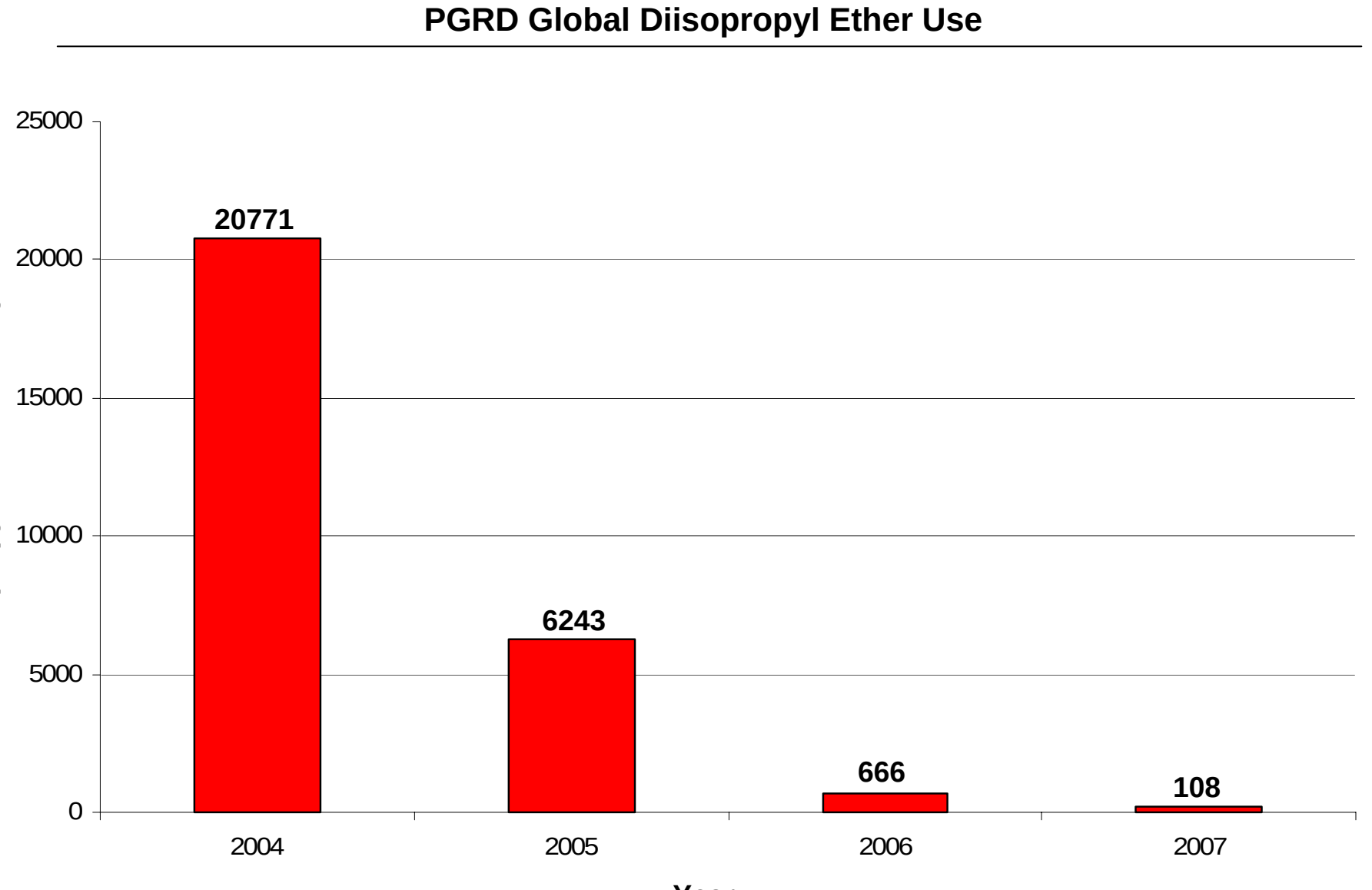
Pfizer Solvent Replacement Table

Red Solvents	Alternative
Pentane	Heptane
Hexane(s)	Heptane
Diisopropyl ether or ether	2-MeTetrahydrofuran (2-MeTHF) or t-Butyl methyl ether (TBME)
DCM (extractions)	EtOAc, TBME, Toluene, 2-MeTHF
DCM (chromatography)	EtOAc, Heptane
Dioxane or dimethoxyethane	2-MeTHF or TBME
Chloroform, dichloroethane or carbon tetrachloride	Dichloromethane
DMF, NMP or DMAc	Acetonitrile
Pyridine	Et_3N (if pyridine used as base)
Benzene	Toluene

Pfizer Green Chemistry Results – Some Examples



Pfizer Solvent Switching Program



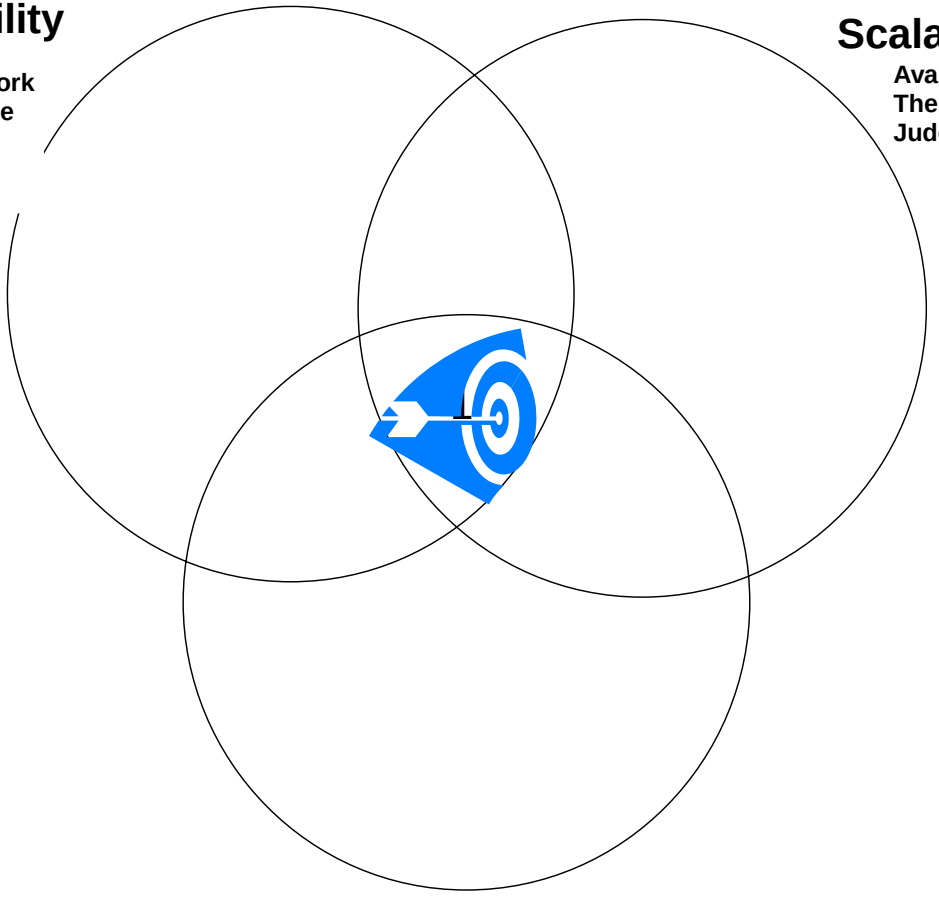
Pfizer Green Chemistry – Reagent Selection Guide

Wide Utility

The ability of a reagent to work On a wide variety of drug like Molecules. As judged by experienced Discovery Scientists

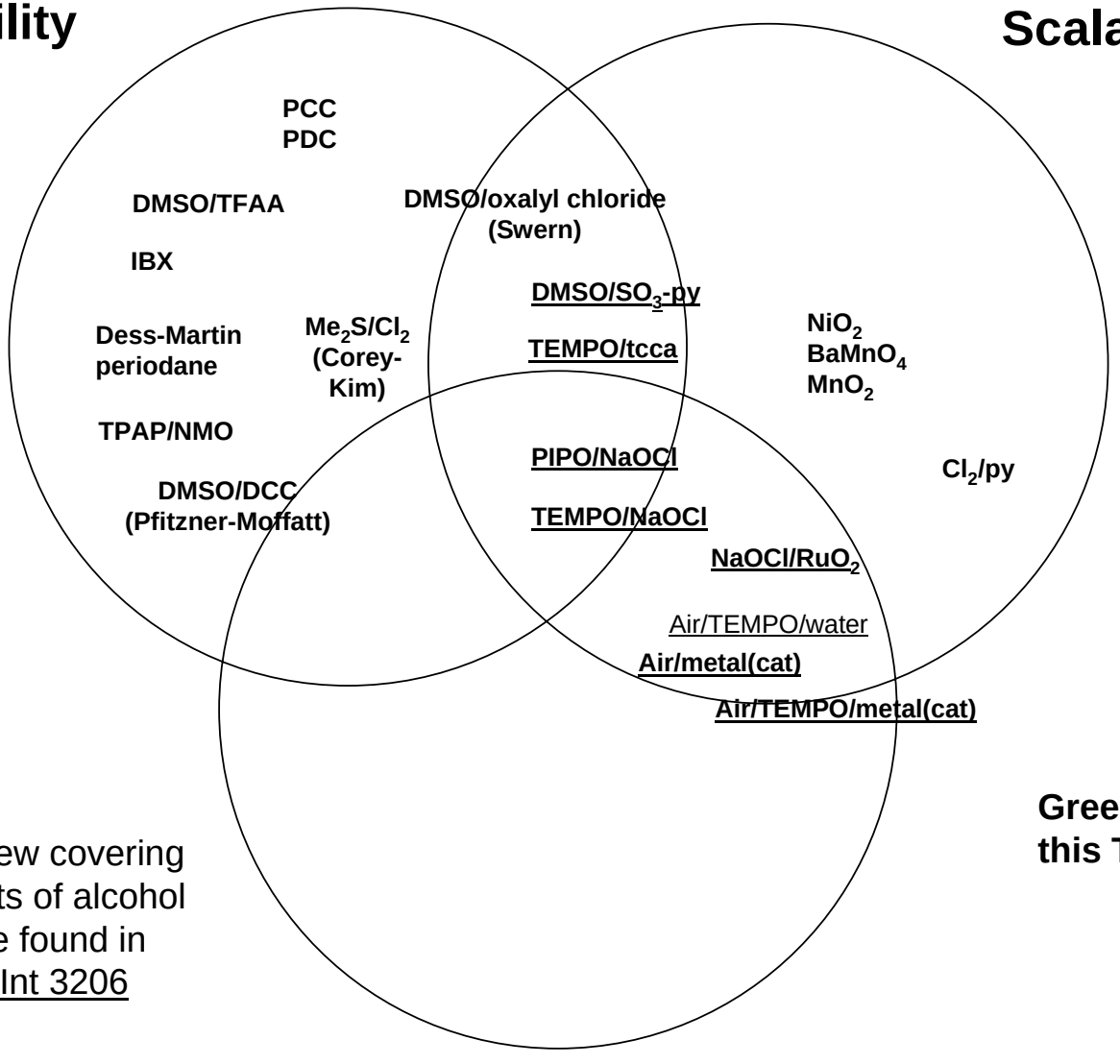
Scalability

Availability, Lack of Major Thermal or Tox Hazards. As Judged by API-Supply Chain



"Greenness **Criteria clearly laid out For each transformation**

Example: Oxidation of Primary Alcohol to Aldehyde



An excellent review covering the Green aspects of alcohol oxidations can be found in 2006 Ang Chem Int 3206

Green Criteria for this Transformation

Microsoft Word Document

List of Transformations

- Alcohol to Aldehyde
- Alcohol to Ketone
- Ester to aldehyde
- Reductive Amination
- Amide coupling (achiral)
- Amide coupling (chiral)
- Redn of primary amide
- Redn of secondary amide
- Redn of tertiary amide
- Alkyl-OH to Alkyl-N
- Het.Aryl-OH to Het.Aryl-N
- Aryl-OH to Aryl-N
- Suzuki
- Heck
- Aldol
- Grignard Formation and Rxn
- Sonogashira Reaction
- Ketones to Chiral Alcohols

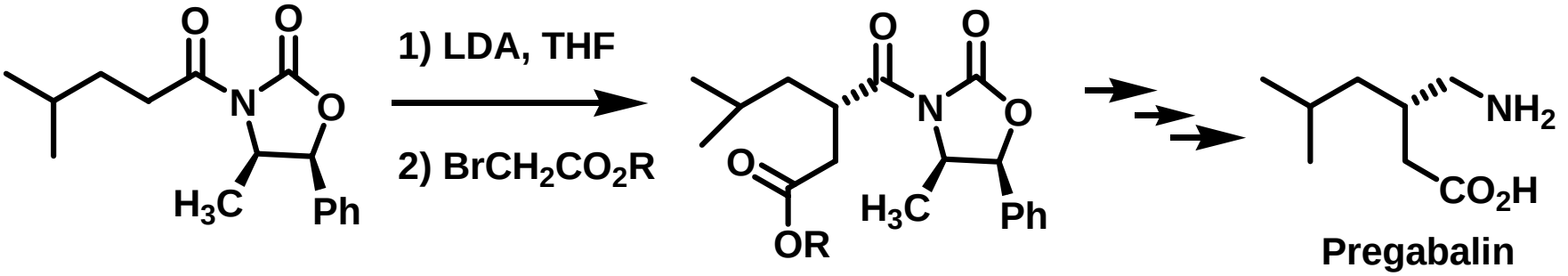
Green Chemistry Results

- **Case Study - Pregabalin**

Green Chemistry in Process Dev.

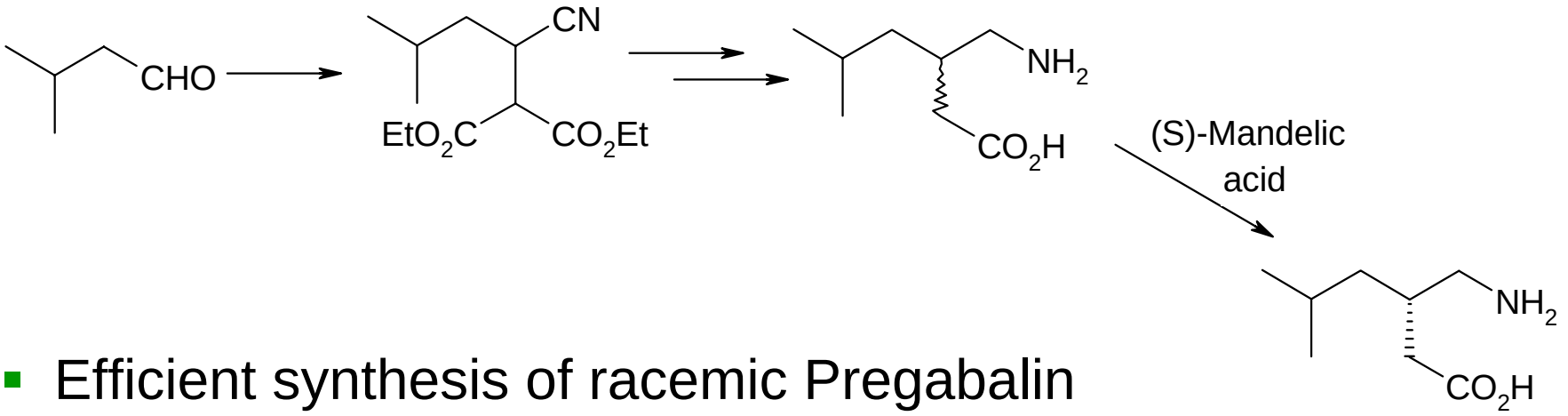
- Exemplified by the Pregabalin Process Dev. Program
- Pregabalin (Lyrica®) is a Drug for the treatment of Neuropathic Pain
- Launched in the US in September 2005
- Sales $1.16 billion (2006), $1.8 billion (2007)

Medicinal Chem. Pregabalin Synthesis



- 10 steps, 33% overall yield
- Cost was 6x target

Pregabalin (Lyrica™) Launch Process

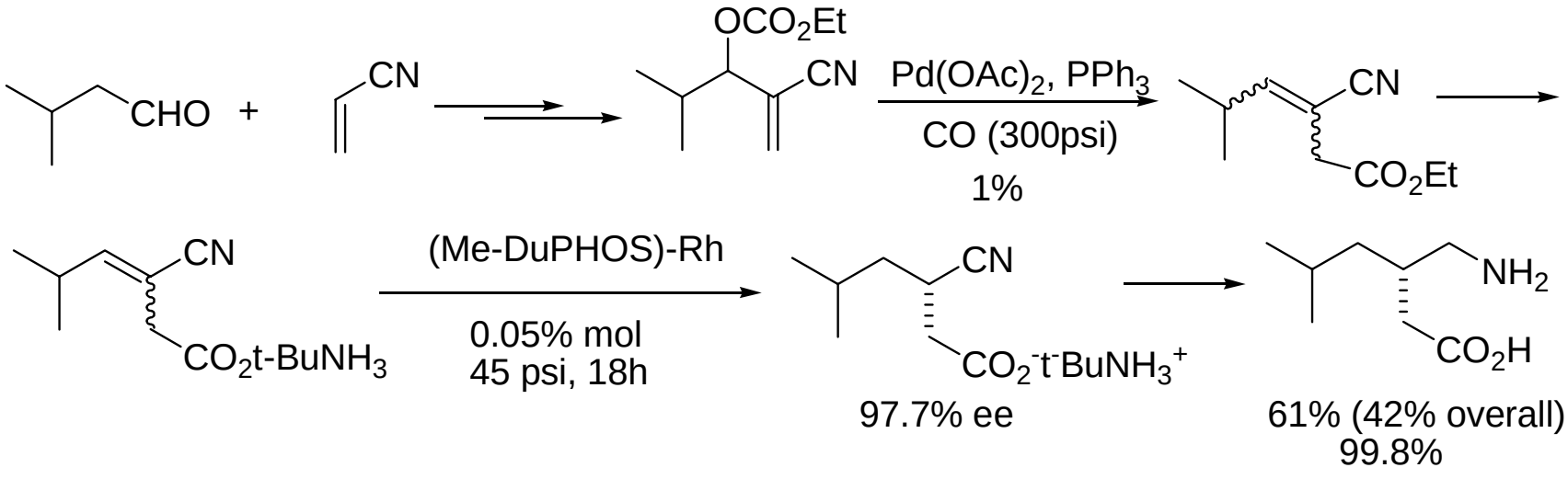


- Efficient synthesis of racemic Pregabalin
- Final Step Classical Resolution
- Wrong enantiomer difficult to recycle
- E-Factor 86
- Significantly cheaper than the Medicinal Chemistry route

25-29 % overall

> 99.5 % ee

Asymmetric Hydrogenation Route



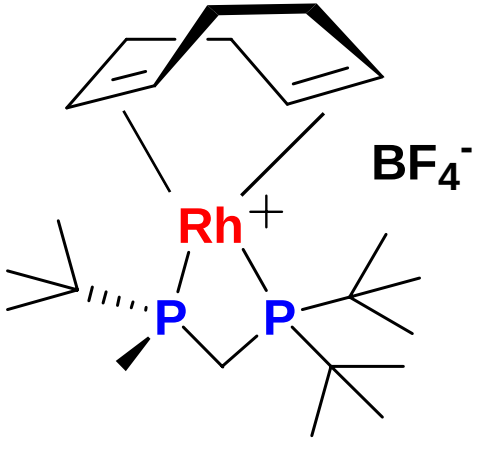
Higher yield (42% overall)

Original Catalyst (1% Pd, 0.05% DuPHOS-Rh)

Licensed chiral ligand expensive

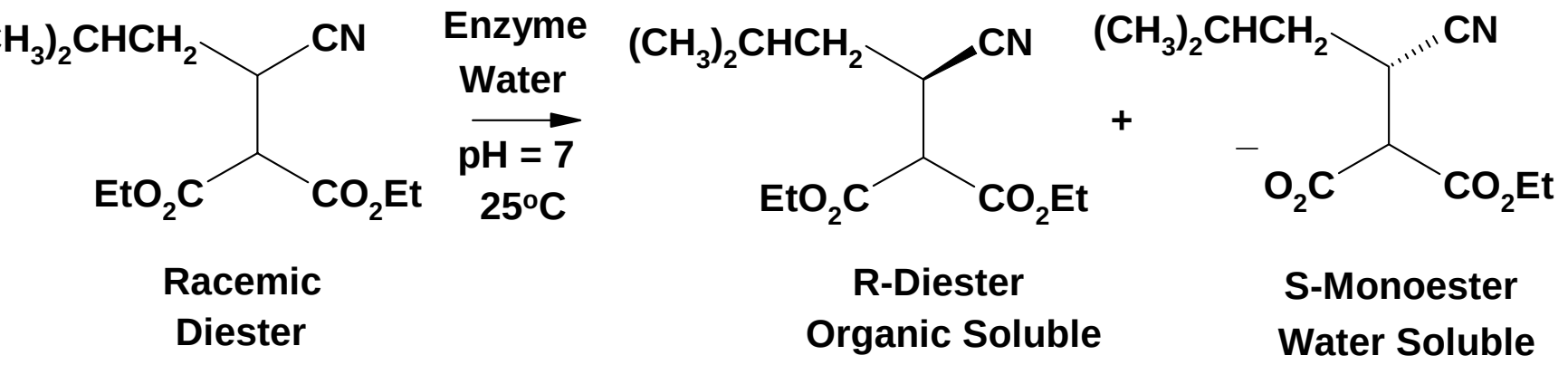
In-house chiral ligand developed – even lower costs

Much improved environmental profile but similar cost to resolution route.



(S)-[Rh-Trichickenfootphos

Enzymatic Resolution of CNDE



Racemic Diester

R-Diester Organic Soluble

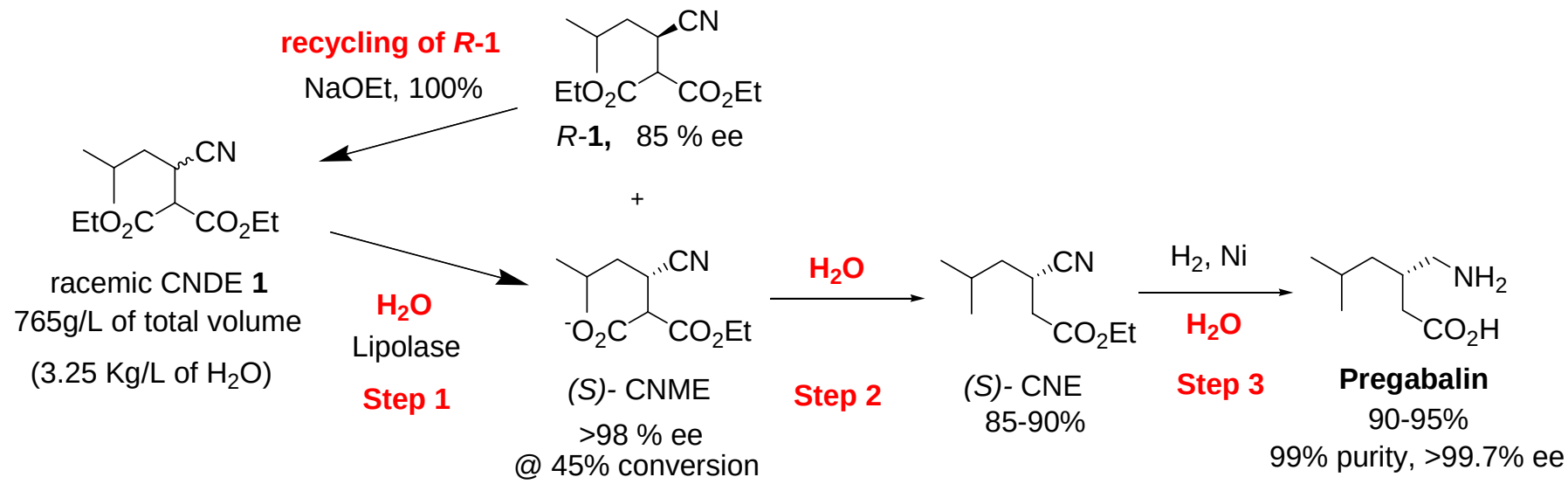
S-Monoester Water Soluble

Enzymatic hydrolysis of Cyano diester enabled early resolution of chiral center

Hydrolase screen revealed 2 (*S*)-selective hits with E>200:

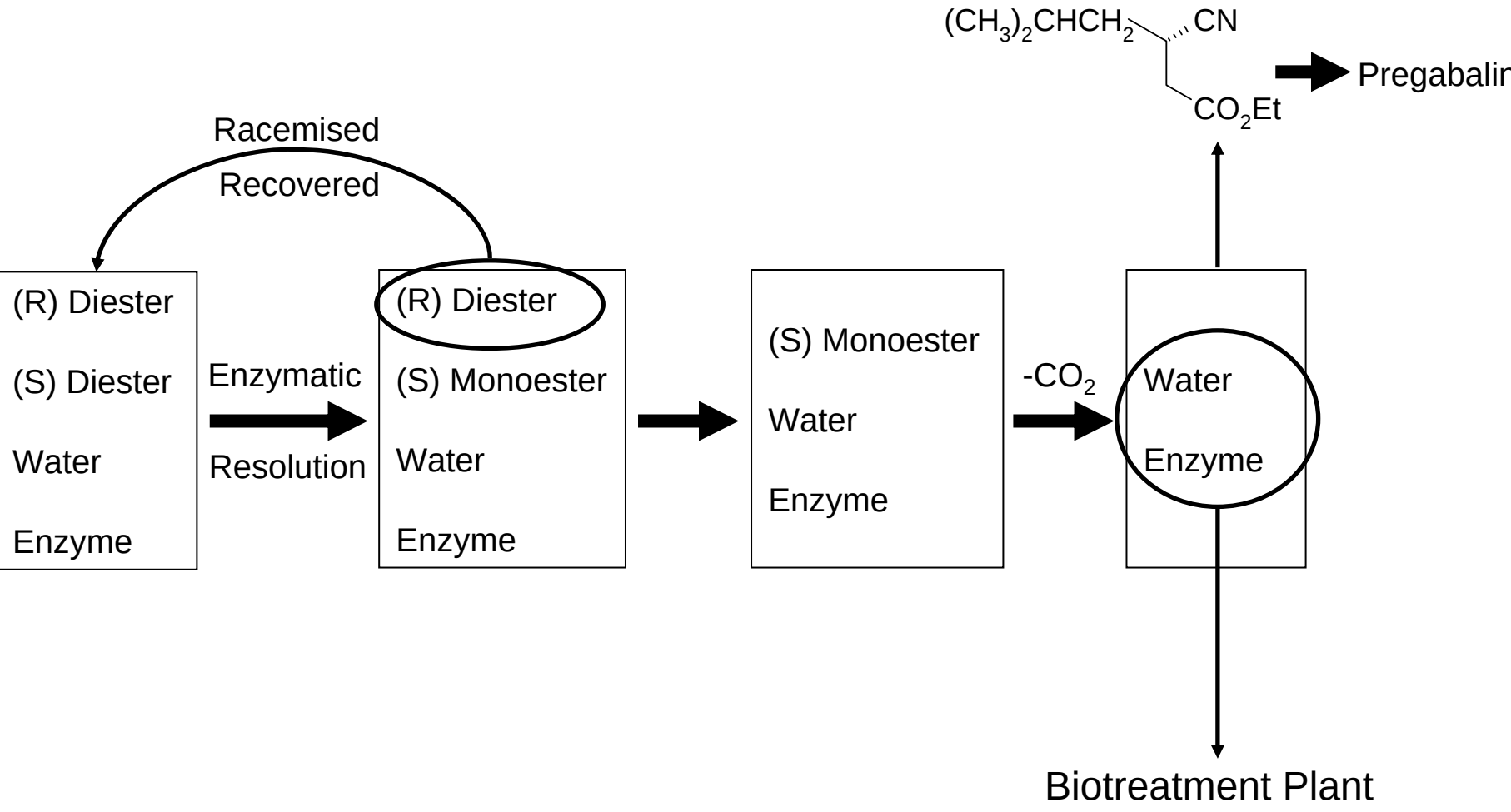
- ***Thermomyces lanuginosus* lipase (Novozymes)**
- ***Rhizopus delemar* lipase (Amano)**

Biocatalytic Kinetic Resolution Route



- Biocatalytic with low (~0.8%) protein loading
- Resolution at first step (wrong enantiomer recycled)
- High throughput; simple operations
- All three reactions conducted in water
- Yield increased to 40% to 45% (after 1 recycle)
- Enzymatic Step scaled up to 10 MT scale
- E-Factor improved from 86 to 17

The Pregabalin Process



Pregabalin Process Comparison

Table 1. Inputs for 1000 kg Pregabalin via 1st Generation and New Routes

	Kilograms	
Inputs	**1st Generation Route**	**New Route**
CNDE	**6212**	**4798**
Enzyme	**0**	**574**
(S)-Mandelic acid	**1135**	**0**
Raney nickel	**531**	**79.5**
Solvents	**50042**	**6230**
Total	**57920**	**11681.5**

- Chemoenzymatic route uses >5x less inputs than 1st generation route

Pregabalin Synthetic Improvements

- By replacing all reaction solvents with water, bringing the Resolution to the beginning, and the Raney nickel reduction to the end, the proposed improvements will yield **annual** improvements of:
  - Starting material usage reduction of 800 tons
  - Solvent reductions:
    - Methanol - 1 million gallons
    - Ethanol - 0.4 million gallons
    - Tetrahydrofuran - 2.2 million gallons
    - Isopropanol - 2 million gallons
  - Mandelic Acid usage eliminated – 500 tons
  - Energy Use reduced by 83 %

Pregabalin Summary

- New Enzymatic Chemistry successfully manufactured on 10MT scale.
- Process was switched in 3Q2006

- By making the switch to optimal route very early in the product lifetime, Pfizer ensures close to maximum benefits to the environment.
- In 2006 Pfizer received the AstraZeneca Award for Excellence in Green Chemistry and Engineering for its work on Pregabalin
- Chemistry published Martinez et al (OPRD 2008, 11, 392)

Take Away Messages

- Green Chemistry starts in Medicinal Chemistry with early engagement of laboratory chemists
- Integrating Green Chemistry as part of the core of our business ensures successes are recognised and rewarded
- Green Chemistry initiatives have resulted in significant environmental benefits
  - 60% reduction in Dichloromethane usage
  - Elimination of Diisopropyl Ether as a solvent in Med Chem
- Provides cost effective solutions
  - Even at lab scale cost savings can be realized
  - Manufacturing scale process changes save $MMs

Thanks and Acknowledgment

Thank You!

- Pregabalin Team
- Members of the Pfizer Green Chemistry teams
- Pete Dunn – Pfizer's "Green Guru"
- Partners in education and research
- To YOU – today's audience!