



GlaxoSmithKline

# Lessons learned through measuring **Green Chemistry** performance: The Pharmaceutical Experience

**Richard Henderson<sup>1</sup>, David Constable<sup>2</sup>, Clare Ruddick<sup>3</sup>, Concepción Jiménez-González<sup>4</sup>, Tom Roper<sup>5</sup>, Graham Geen<sup>3</sup>**

1 GlaxoSmithKline, CEHS, Park Road, Ware, Hertfordshire SG12 0DP, UK

2 GlaxoSmithKline, CEHS, 1 Franklin Plaza, Philadelphia, PA, 19101, USA

3 GlaxoSmithKline, R&D, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

4 GlaxoSmithKline, CEHS, CS.1152, 5 Moore Dr, Research Triangle Park, NC, 27709-3398, USA

5 GlaxoSmithKline, R&D, 709 Swedeland Road, King of Prussia, PA, 19406, USA

\*Corresponding author ([richard.k.henderson@gsk.com](mailto:richard.k.henderson@gsk.com))

# Synopsis

- Introduction to GSK
- Green Chemistry and the Pharmaceutical Industry Challenges
- Measuring Greenness and lessons learned
- Summary and Conclusions

# The World of GSK

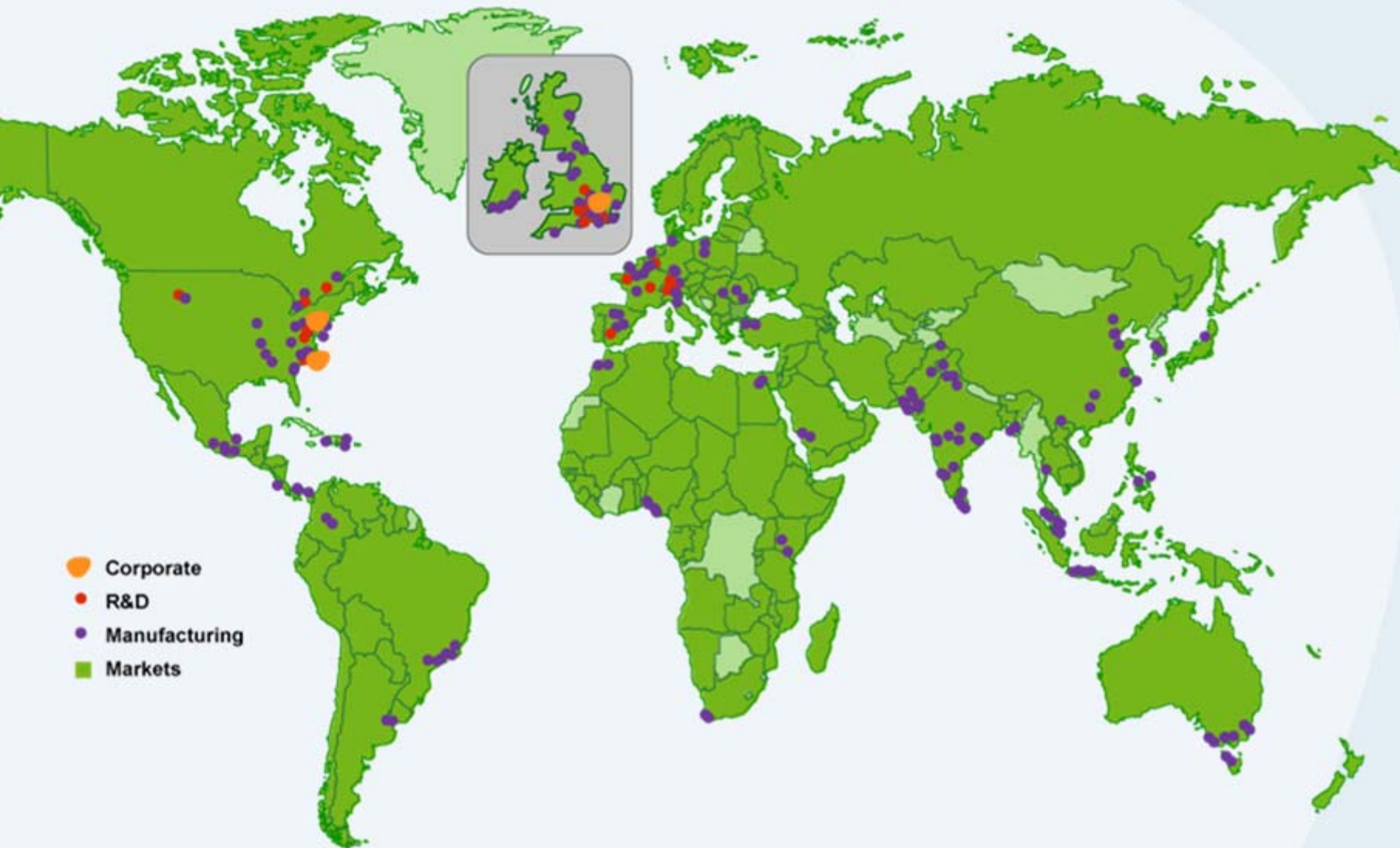


# Who are we?

- We are one of the world's leading producers of prescription medicines, vaccines and consumer healthcare products
- 6.3% of global pharmaceutical sales
- Total company sales: £23.2 billion/ \$43 billion
- We lead the way in respiratory and anti-viral medications and vaccines
- Over 100,000 GSK people in 117 countries



# Where are we?



Our International region covers 80% of the world's population

# What do we do?

- **Every second...**

We distribute more than 35 doses of vaccine

- **Every minute...**

More than 1,100 prescriptions are written for GSK products

- **Every hour...**

We spend more than £300,000 (\$562,000) to find new medicines

- **Every day...**

More than 200 million people around the world use a GSK brand toothbrush or toothpaste

- **Every year...**

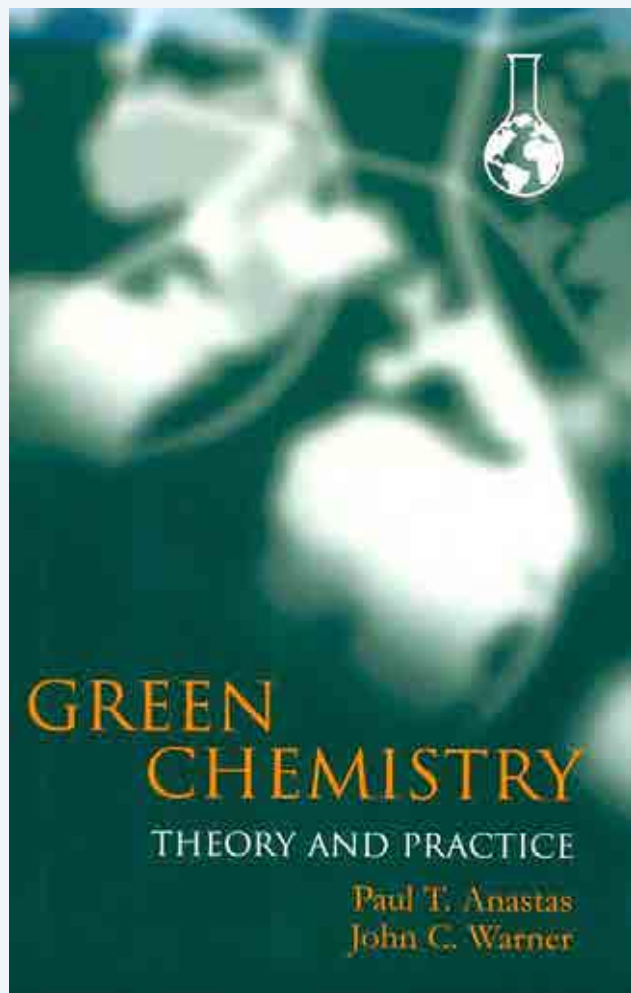
Our factories produce 9 billion *Tums* tablets, 6 billion *Panadol* tablets and 600 million tubes of toothpaste



**Do more,  
feel better,  
live longer**



# What is Green Chemistry?



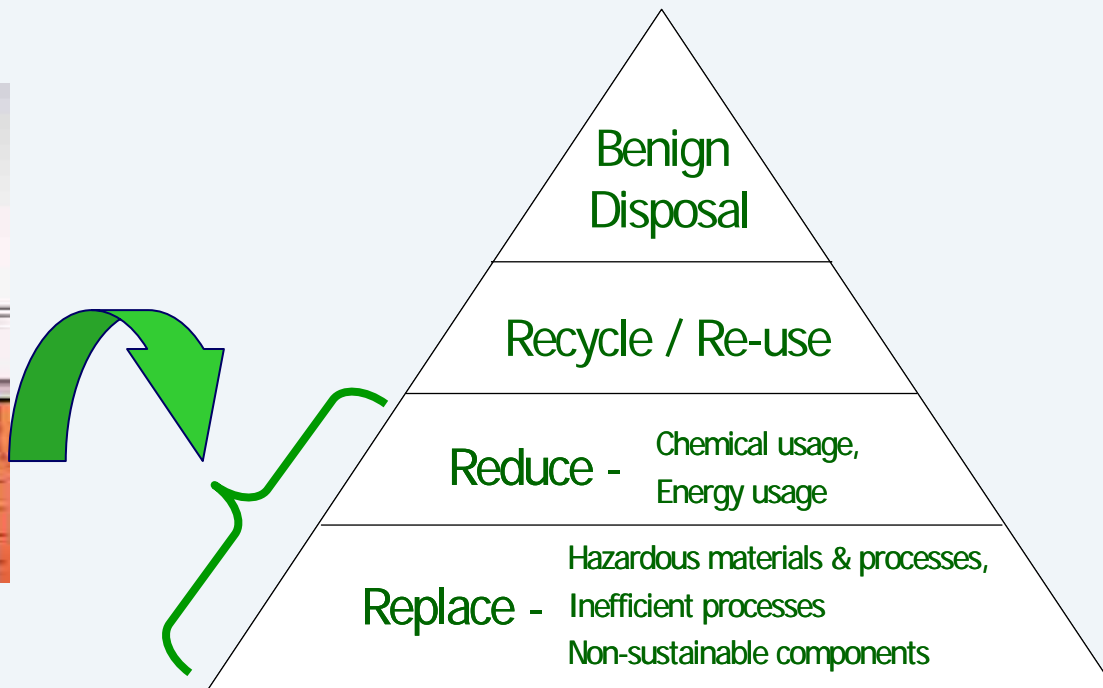
“...the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products.”

Anastas and Warner developed the “12 principles of Green Chemistry”

P.T. Anastas and J.C. Warner, *Green Chemistry: Theory and Practice*, New York, NY: Oxford University Press Inc., 1998.  
ISBN 0 19 850698 8



# What is Green Chemistry?

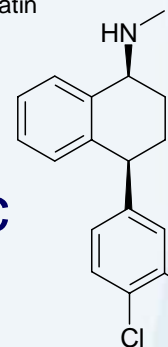
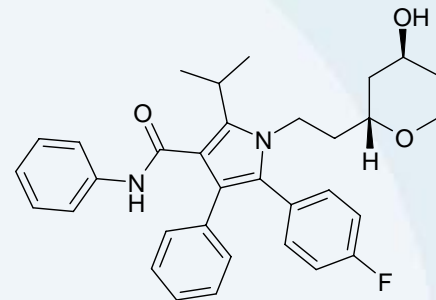
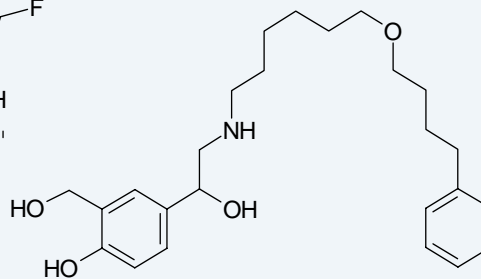
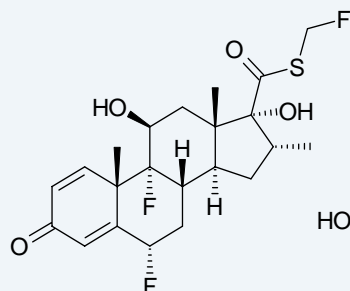
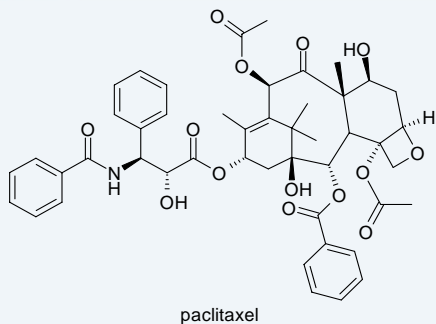


**By design** develop efficient syntheses and processes which:

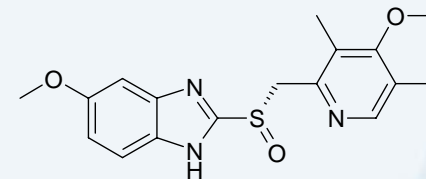
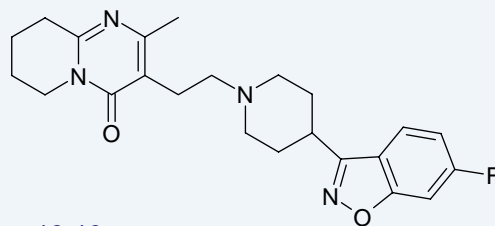
- **Optimize material** and **energy** use.
- **Prevent** and minimize waste.
- **Eliminate or minimize** hazardous chemicals.
- Increase use of **renewable materials and energy**.
- Have **inherently safe** process conditions.

# Special Challenges Presented by Pharmaceuticals

## Challenge



- They are complex:
  - target molecules, reagents and reactants
  - synthetic routes: **6+ stages**
  - processes and wastes: mixed aqueous and organic streams
- Need for early and rapid definition of the synthetic route
- But there is a **high failure** rate for target molecules



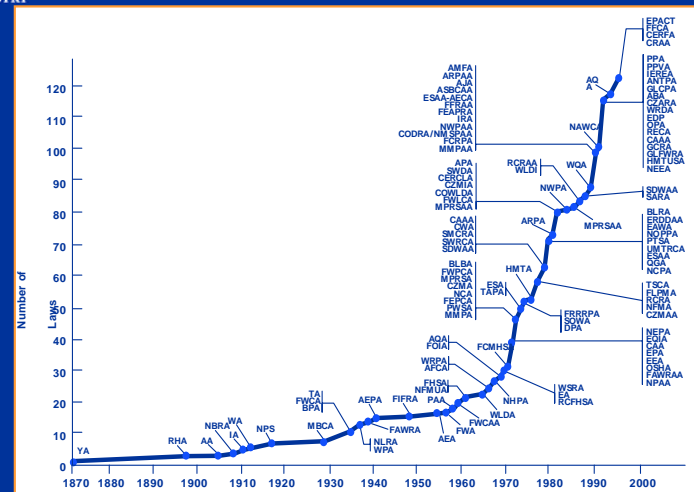
# Special Challenges for the Pharmaceutical Industry

## Challenge

- **Highly regulated** by government agencies
  - process changes
  - use of recovered/recycled solvent
- Route and Process changes post-approval give the **appearance of being costly**
- **Regulatory / Legislative restrictions** on solvent and materials selection
  - EU Solvent Directive,
  - REACH,
  - IPPC,
  - ICH etc



## Growth in Environmental Regulation



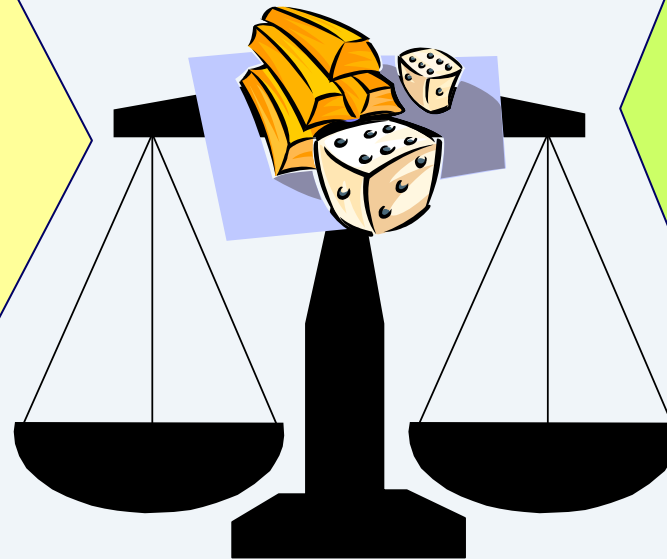
# Finding the Right Balance

Challenge

Commercial  
Focus on  
Speed to  
Market

Green process  
design early  
when costs are lower

Attrition



# GSK's Approach: Sustainability by Design

## Challenge

- If we want to make the **biggest impacts** to products, services and costs, we have to start from the ground up.
- If we want to **build sustainability** into the design of products and services we have to think differently about R&D.
- Increasing demands and decreasing budgets are likely to mean greater reliance on **easily accessible** company wide **tools** that provide **early assessments** and **highlight sustainability issues**.

# Better Products by Design!

Strategy

**Eco-Design Toolkit**

Welcome to the Eco-Design Toolkit

Eco-Design Toolkit is a component of myEHS Community and supports GSK's Plan for Excellence.

**Available Solvents:** - Priority Review: 21, 2003

- Solvent Selection Guide launched in July 2003.
- FLASC (Fast Life Cycle Assessment for Synthetic Chemistry) launched in August 2003.
- WRAP (Wizard for the Rapid Assessment of Packaging) launched in October 2003.
- Base Selection Guide launched in August 2003.

**Green Chemistry Guide**

This site seeks to:

- Reduce environmental, health and safety impacts;
- Promote more efficient use of resources, including energy;
- Minimise costs.

This GSK Green Chemistry Website is designed to help scientists and engineers to better understand and apply Green Chemistry concepts to their work.

Please navigate through the website using the links on the left which take you through a series of guidance and advice.

**Fast Lifecycle Assessment for Synthetic Chemistry (FLASC)**

A new component of the Eco-Design Toolkit, FLASC is located at [greenroute.ask.com](http://greenroute.ask.com)

FLASC uses a 'life cycle' approach to evaluate the environmental consequences of one or more processes based around the input materials used. It generates the energy and water to used in their manufacture, as well as emissions released, and potential environmental impacts.

FLASC will:

- Calculate the life-cycle environmental impact and identify the greatest impact
- Provide guidance and identify the materials that have the biggest impact

For information on how the site was developed, and should be used and at the benefits it will deliver, see the Background section.

Your assessments will be tracked via your LAN ID - [cosah000](mailto:cosah000)

Enter FLASC | Administration | Focus

**...Others make it happen!**

**Solvent Selection Guide**

This guide provides information and guidance to help scientists choose the best solvents for their processes, ensure that key associated issues are understood and help minimise EHS impact associated with their use.

**Key Benefits**

- Features in this guide
- Solvent Selection Guide
- Data for Solvents

**Emerging Issues**

**Solvent Update:** - Revised: September 20, 2004

Solvents are facing increasing regulatory scrutiny especially in the EU under the (Solvent Emissions Directive) including:

- Dimethyl acetamide
- Dimethyl formamide

**Chemical Legislation Guide**

THIS PAGE IS UPDATED 2003 July 2007

This web site was created to support the Chemical Legislation work. It is designed to help scientists and engineers identify those chemicals that are under legislative scrutiny. The guide is delivered through the EDCS...  
LATEST REGULATIONS UNDER REACH, CLP, and other EU Directives, which should be addressed first...  
to ensure that you are referring to the latest version. EHS records must be updated for the EDCS to function correctly.

This guide was compiled based on existing or proposed regulatory systems of different legislative bodies, and mostly... those in the EU (see Scope and Limitations). These substances have been identified as having specific properties... will focus on specific aspects to the environment or human health, and therefore present unacceptable risk to... substances EHS records.

**Green Packaging Guide**

**WRAP up all you need to know to make Green Packaging.**  
[GreenPackaging.ask.com](http://GreenPackaging.ask.com)

The site contains Modules for all aspects of the packaging supply chain and devices.

**Key Features** (accessible via links below or left hand menu):

- Guidance wheel considers all aspects of the packaging lifecycle
- Guidance for packaging material selection
- Device design module
- An environmental assessment process
- Advice on artwork symbols and material identification protocols
- Site waste management guidance
- Key packaging legislation

**Standards and Guidance** (last revised: October 08, 2007)

The site aligns with:

- GSK Global EHS Standard Packaging of Products and Environmental Claims 503
- New Product Development and Supply 201.

**WRAP up all you need to know to make Green Packaging.**  
[GreenPackaging.ask.com](http://GreenPackaging.ask.com)

**WRAP** (Wizard for the Rapid Assessment of Packaging) is an interactive tool to help you determine whether your packaging is green and why.

**...Others make it happen!**

# Why not just focus on yield?

## Green Chemistry Metrics

- A “typical” GSK process has
  - yields from a single stage ranging between 35 and 95% with an **average of 86%**
  - 6 stages, with an overall yield of **30 - 40%**
- Yield does not capture use of **reagents, solvents, or catalysts** .
  - If these are included the average **Mass Intensity** (total materials use) per stage is typically **16 kg/kg of stage product**
    - A stage product is an isolated intermediate in the synthesis of an Active Pharmaceutical Ingredient.

*Green Chemistry* ≠ Yield

# Green Chemistry: Measuring Efficiency

## Chemistry

- Yield
- Selectivity
- Atom Economy
- Reaction Mass Efficiency

Traditional chemistry  
measure of efficiency

## Green Chemistry Metrics

Combines yield, atom economy  
and the actual stoichiometry of  
the reactants used

Mass of everything used to  
make 1 kg of product

$100 \div \text{Mass Intensity \%}$

From GSK's FLASC tool

## Process

- Mass Intensity
  - Process water mass
  - Solvent mass
- Mass Productivity
- Life cycle score
- Solvent score

• Identify '**Materials of Concern**' from an EHS regulatory perspective

• GSK collect metrics for every pilot plant campaign (> 170 to date) and benchmark them against all processes by **Phase of Development**



# What is a Material of Concern?

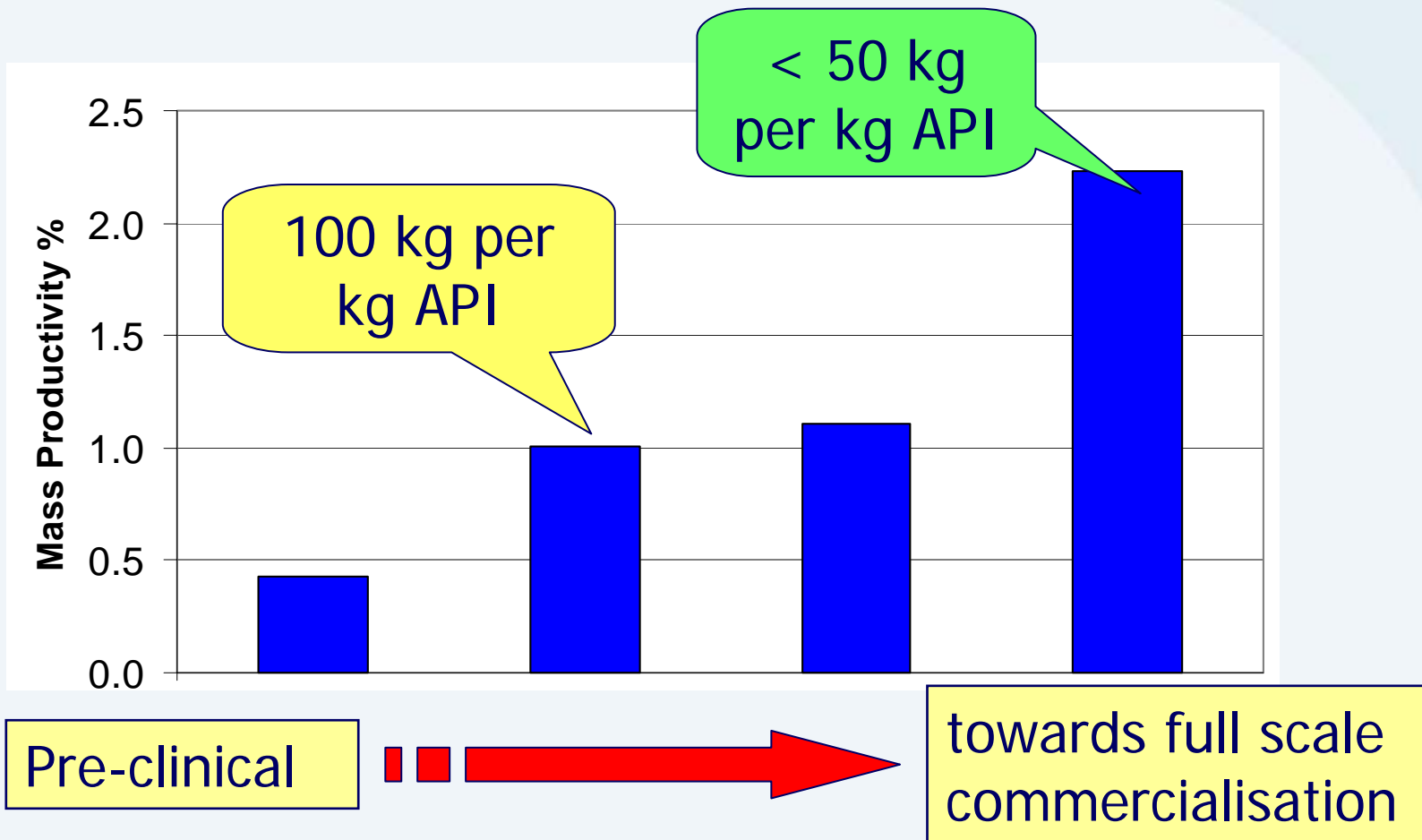
- Chemicals for which there is evidence for probable serious effects to humans or the environment
- The primary criteria for assignment of a **Material of Concern** are those described to identify Priority Chemicals in the GSK public position statement on hazardous chemical management; i.e.
  - those known to be carcinogens, mutagens or reproductive hazards (CMR's),
  - those known to be toxic and bioaccumulate or persist in the environment (PBT's),
  - those known to be very persistent or very bioaccumulative in the environment (vPvB),
  - ozone depleting chemicals,
  - endocrine disruptors
  - those known to cause asthma
- **Materials of Concern** are identified in **GSK's Green Chemistry Metrics** assessments to help project teams to develop strategies to eliminate or substitute the use of these materials where technically and economically feasible.

GSK Public Position Paper – Hazardous Chemicals Management,  
[www.gsk.com/responsibility/Downloads/GSK-hazardous-chemicals-2006.pdf](http://www.gsk.com/responsibility/Downloads/GSK-hazardous-chemicals-2006.pdf)

# Mass Productivity

- Improvements in mass productivity have a beneficial impact on **capacity, throughput, and downstream processing costs**
- Data from GSK's Chemical Development shows that Mass Productivity **improves significantly** as a product is developed from a medicinal chemistry process towards full commercialisation
- But there are still opportunities for improvement

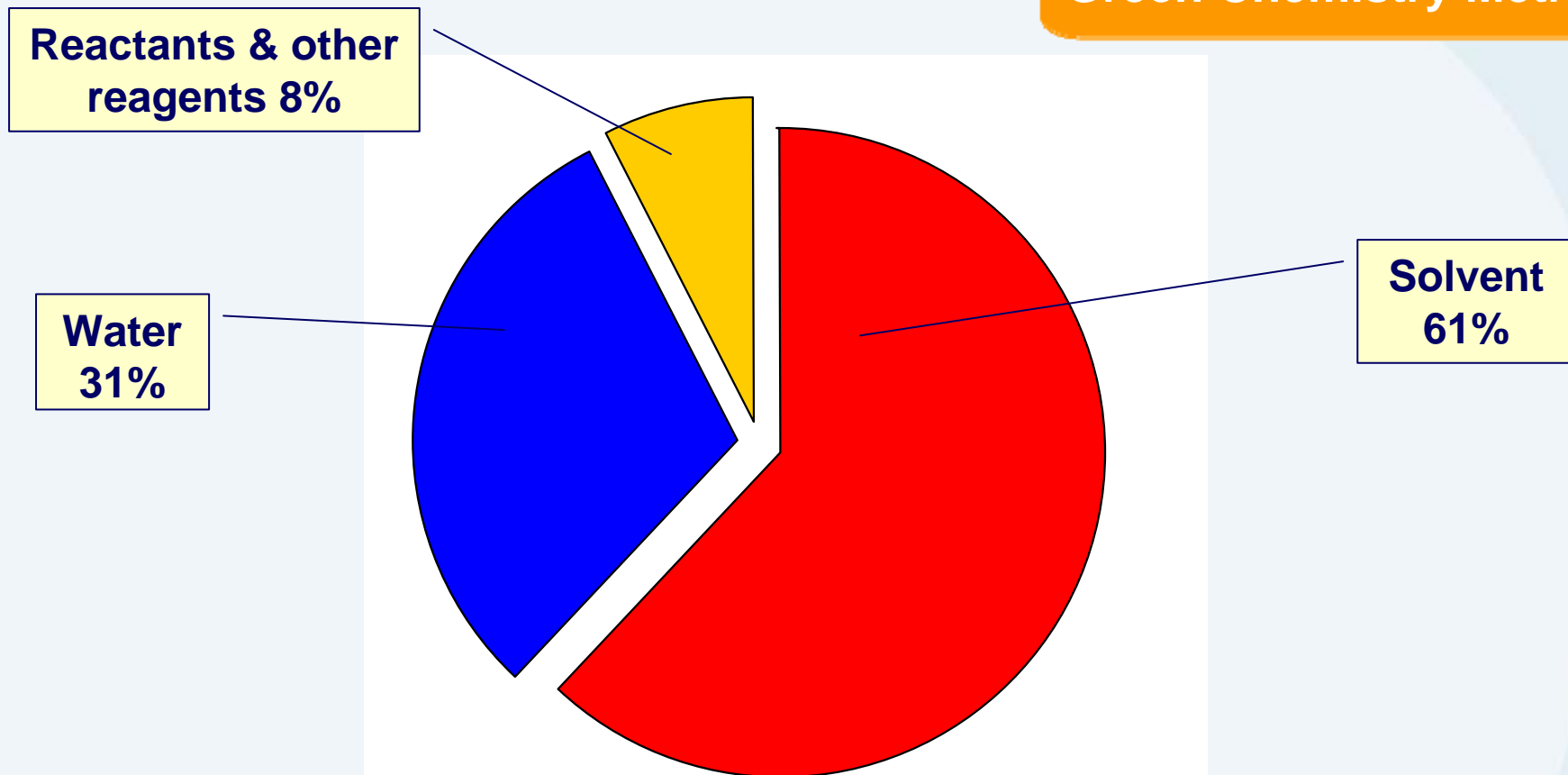
# Measuring Progress: Mass Productivity



PI = Active Pharmaceutical Ingredient

# What's the average reaction mass composition?

Green Chemistry Metrics

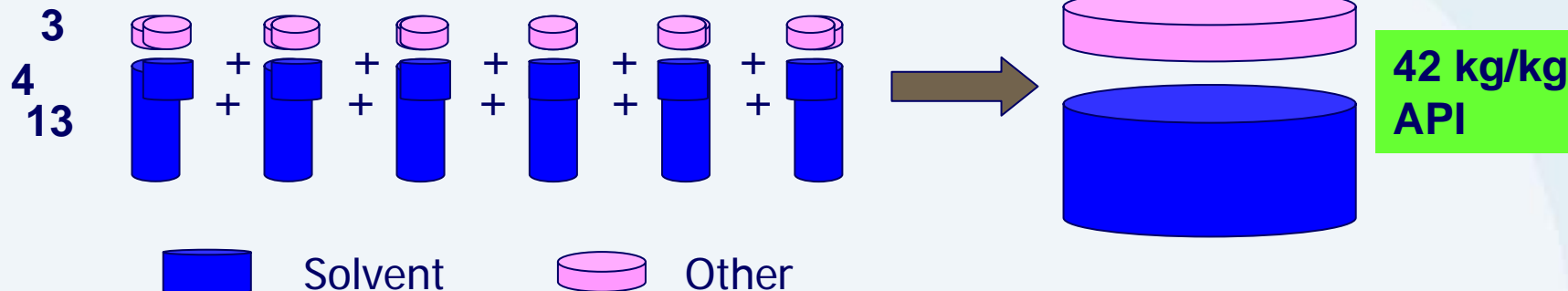


Solvent and water contribute to > 90 % of the reaction mass

Source data: ACS GCI Pharmaceutical Roundtable benchmarking exercise 2007

# Solvents and Mass

## Green Chemistry Metrics



Even with a 100% yield for each stage, using 16 kg/kg materials per stage corresponds to a **mass intensity** of 96 kg/kg API

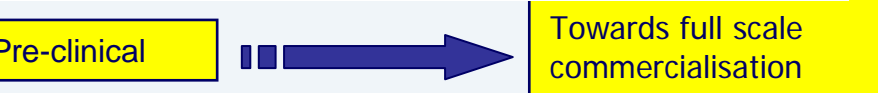
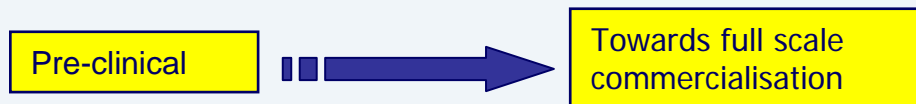
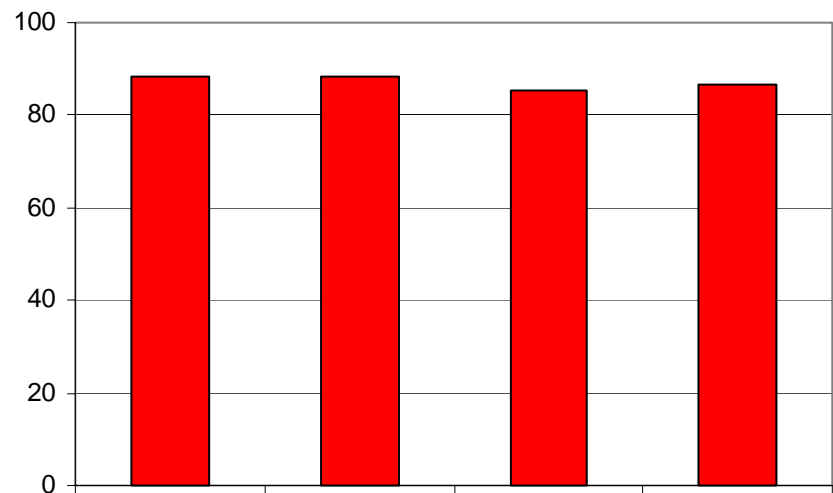
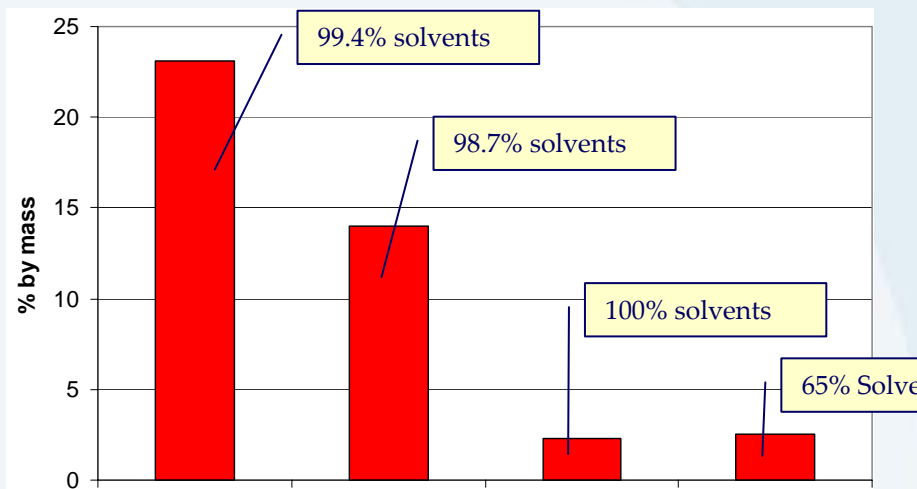
But if there is an average **75% recovery** of solvents and a **100% overall yield**, then...

The **mass intensity** would roughly **halve** reducing the overall mass of solvent needed

But the chemistry is not more efficient

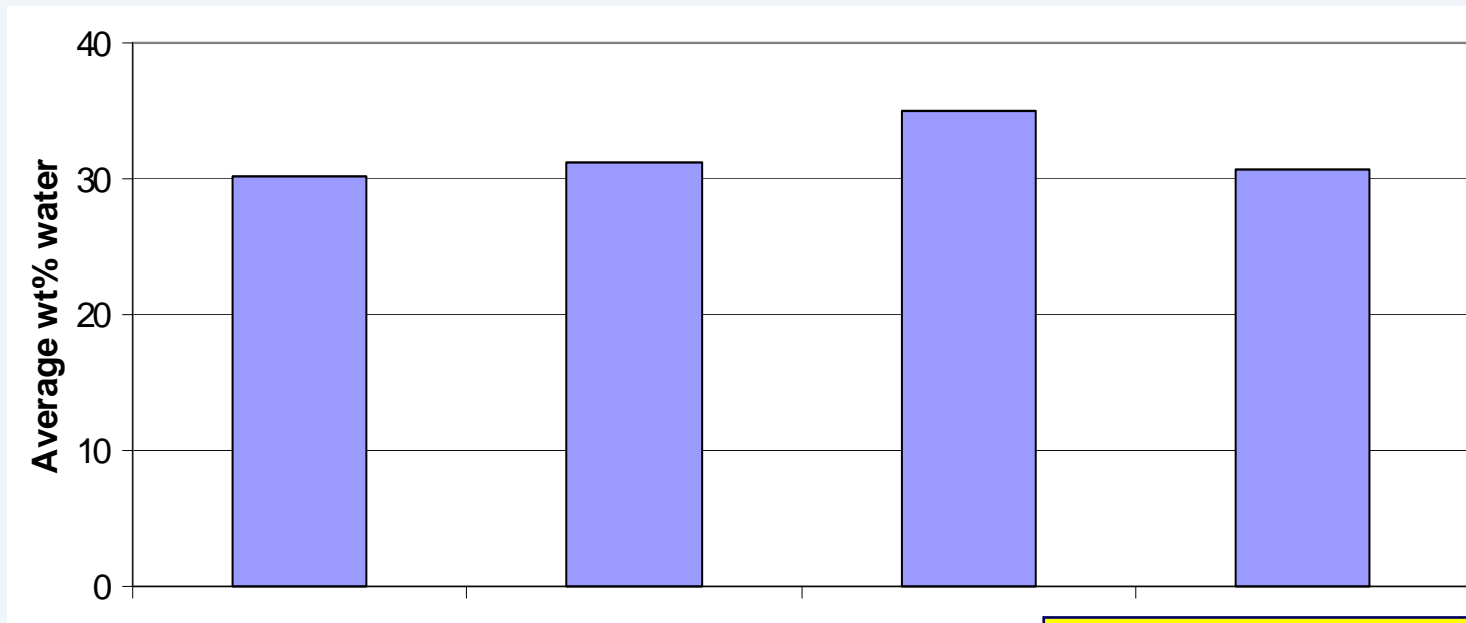
# Solvents and Materials of Concern

Average Mass % of materials of concern in compounds



- Solvent mass is ~90 wt% of reaction mass excluding water
- Dilution of reactions is consistent across all phases of development
- The nature of the solvents used does change  
eg the majority of dichloromethane is removed by Proof of Concept

# Process Water



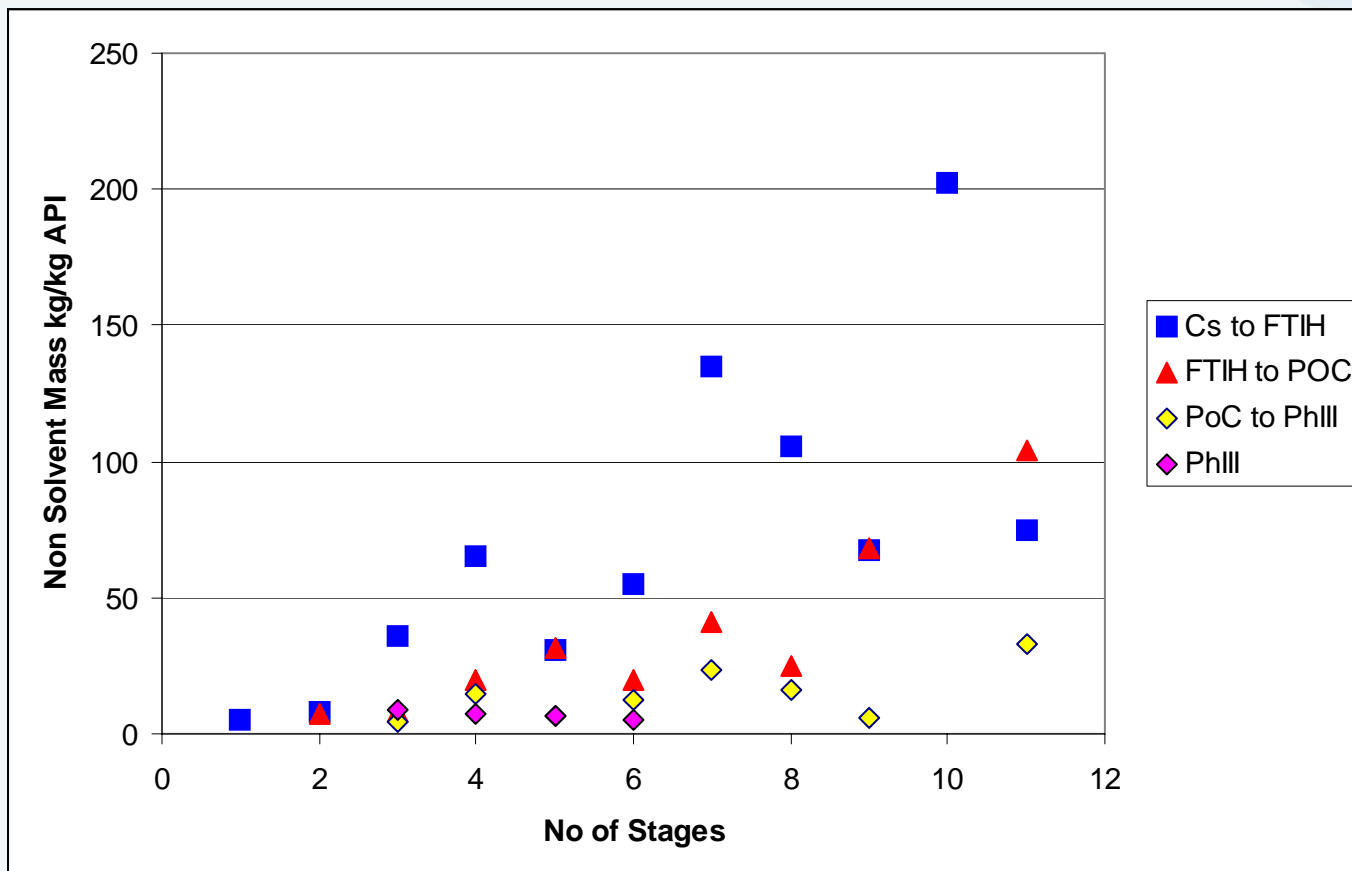
Pre-clinical



towards full scale commercialisation

Data shows that the amount of process water used in washings and extractions per kg API could be optimised further

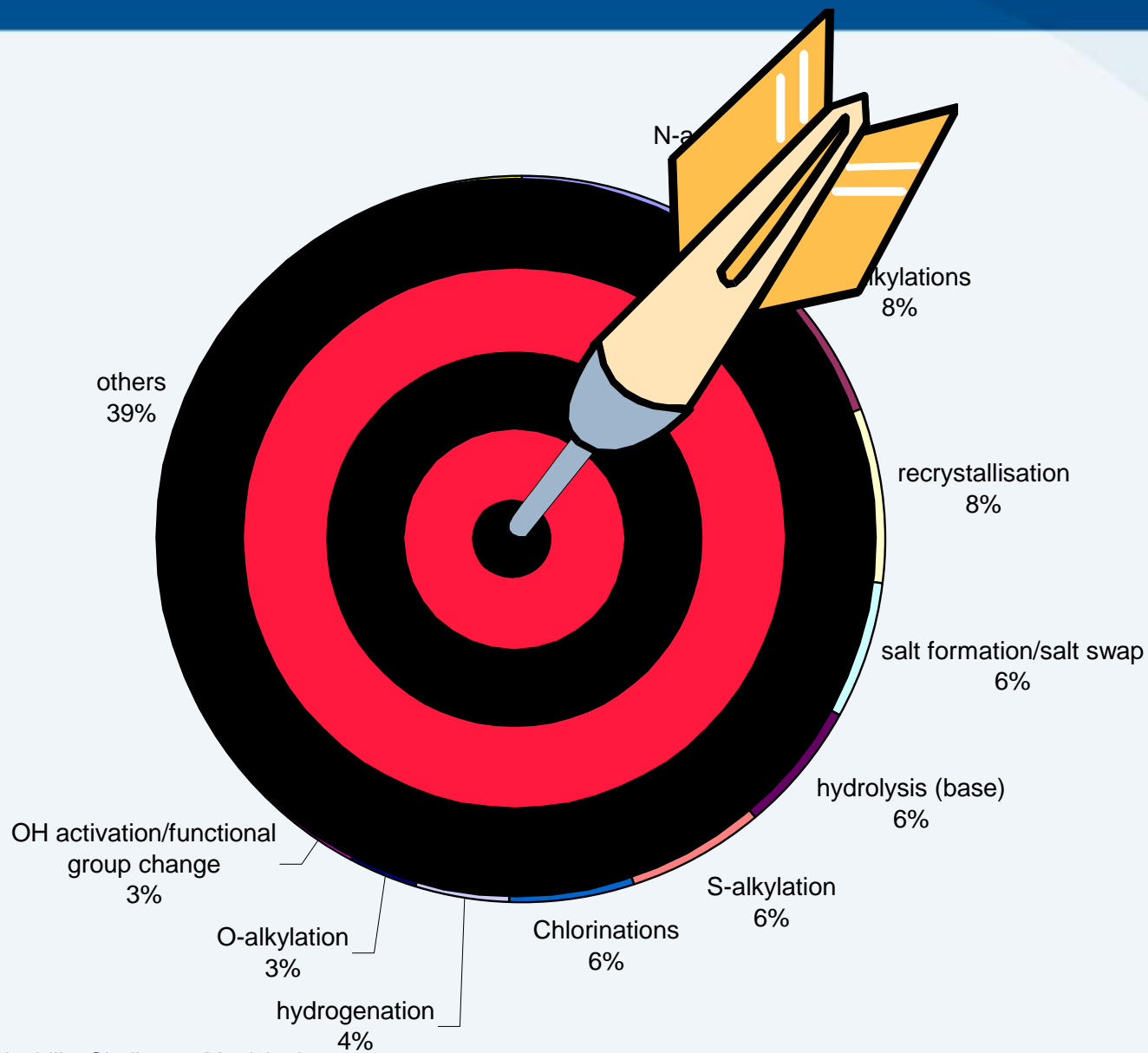
# Average Non-Solvent Mass



- As well as solvent optimisation, there is optimisation of the masses of reagents and reactants during development
- This has the biggest impact in long and complex syntheses



# GSK Portfolio Analysis: Top 10 Chemistries Used 2004 - 2005





# ACS Green Chemistry Institute Pharmaceutical Roundtable



## □ Key Green 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*-Centred Chemistry

### ■ Key Ideas outside the Reaction theme

- Solvent-less (Solvent Free) Reactor Cleaning
- Green alternatives to polar aprotic solvents

# Life Cycle Assessment – The very big picture

Raw material and energy consumption



Life Cycle Assessment (LCA) is a tool for evaluating the **environmental burdens** associated with a product, process or activity over its entire life cycle

Final Consumer Use

Store



Emissions to air, water and land

### Fast Lifecycle Assessment for Synthetic Chemistry (FLASC)

© Copyright 2003 GlaxoSmith

Enter FLASC

Getting Started

Background

Guidance for  
Route  
Improvement

Quick Reference  
Guide

Help



FLASC uses a "life cycle" approach to evaluate the environmental consequences of new or existing processes based around the input materials used. It quantifies the energy and materials used in their manufacture, as well as emissions released, and potential environmental impacts.

FLASC will:

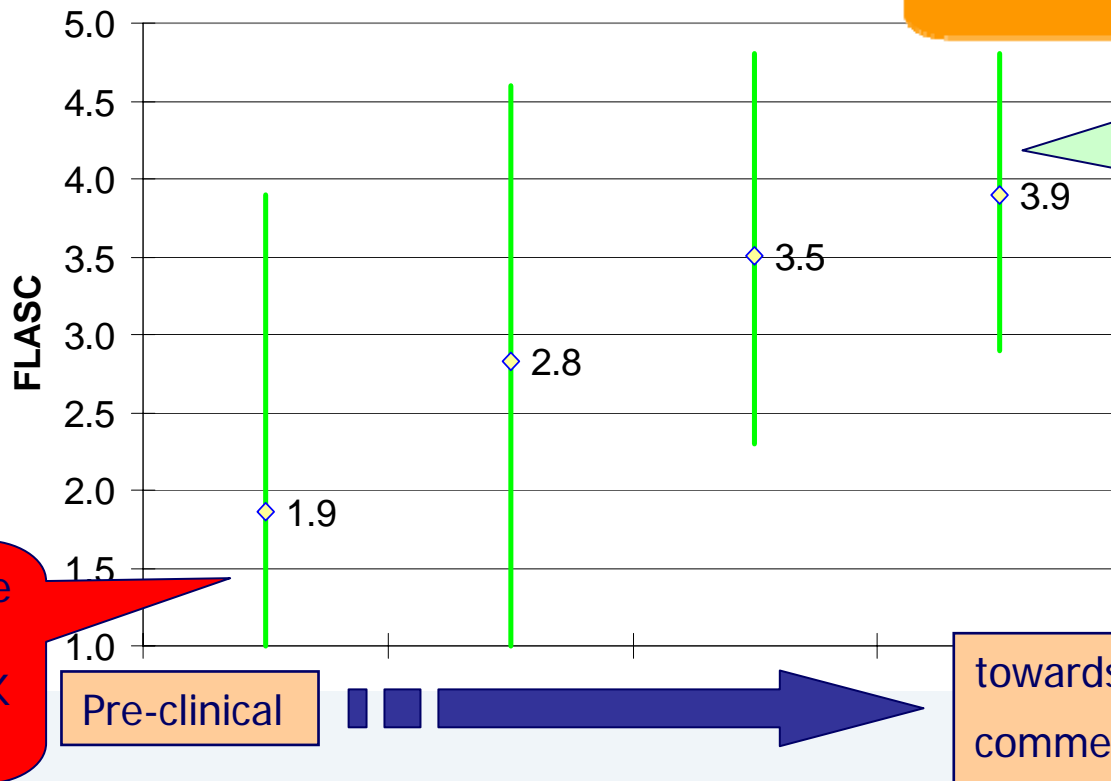
- Compare or benchmark processes/routes and identify the greenest option

GSK's tool to estimate the *Life Cycle environmental impacts* of materials

- The FLASC score allows for *'Greenness' / 'Footprint' Comparisons* of different routes to the same API or routes to different APIs.
- *Avoids hidden impacts* e.g., with outsourcing
- *Normalises* for differences in the complexity of the API
- *Shows percent improvement* between different options
- Enables *"What-if" comparisons*

# Measuring Progress: Life Cycle impacts of the development portfolio

## Green Chemistry Metrics



30% of the Life Cycle impact of the average GSK process\*

27% of the Life Cycle impact of the average GSK process\*

The environmental life cycle impact of all new processes **post-PoC** is potentially **much lower** than for current processes in manufacturing

\* The average performance of the benchmark routes (1990-2000) was assigned a FLASC score of 2.3

# GSK use Green Chemistry Metrics to

## Green Chemistry Metrics

- Enable benchmarking and as a basis for objective comparison
- Drive change through highlighting opportunities for improvement
- Meet the increasing expectations from internal and external audiences to describe progress and demonstrate improvement
- Be transparent
  - ACS Green Chemistry Institute Pharmaceutical Roundtable benchmarking exercise from 7 companies (GSK, Pfizer, AstraZeneca, Eli Lilly, Johnson and Johnson, Merck, Schering Plough) presented at Green Chemistry Conferences in EU and USA in 2007
- BUT Mass Metrics take **no account** of the **type of materials** used.
- GSK have developed the Process Related Materials Review
  - A more **holistic in-depth EHS assessment** of chemical processes
  - Used to identify and **communicate** issues and **opportunities** for introducing more sustainable chemistry and technology
  - Targeted at primary manufacturing route and process developments
- Assessment of “**greenness**” and being “**sustainable**” is a **multivariate exercise** and is inherently complex!

# Summary

- The Strategy is to influence the development of next generation of drugs in development so they are greener
- Green Metrics information helps Project Teams understand their processes, highlight opportunities and monitor improvements
- GSK Green Metrics data include a life cycle assessment
- Metrics are collected for every pilot plant campaign for compounds in development
- Metrics alone do not tell the whole story – more detailed analyses and guidance are also needed



GlaxoSmithKline

# Any Questions?

...Others make it happen!







# ACS GCI Pharmaceutical Roundtable Membership



as of February 1, 2008



Membership is open to all pharmaceutical research, development, and manufacturing companies.  
The Roundtable will be strongest when all global pharmaceutical corporations are members.