Lessons learned through measuring Green Chemistry performance: The Pharmaceutical Experience

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Synopsis

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

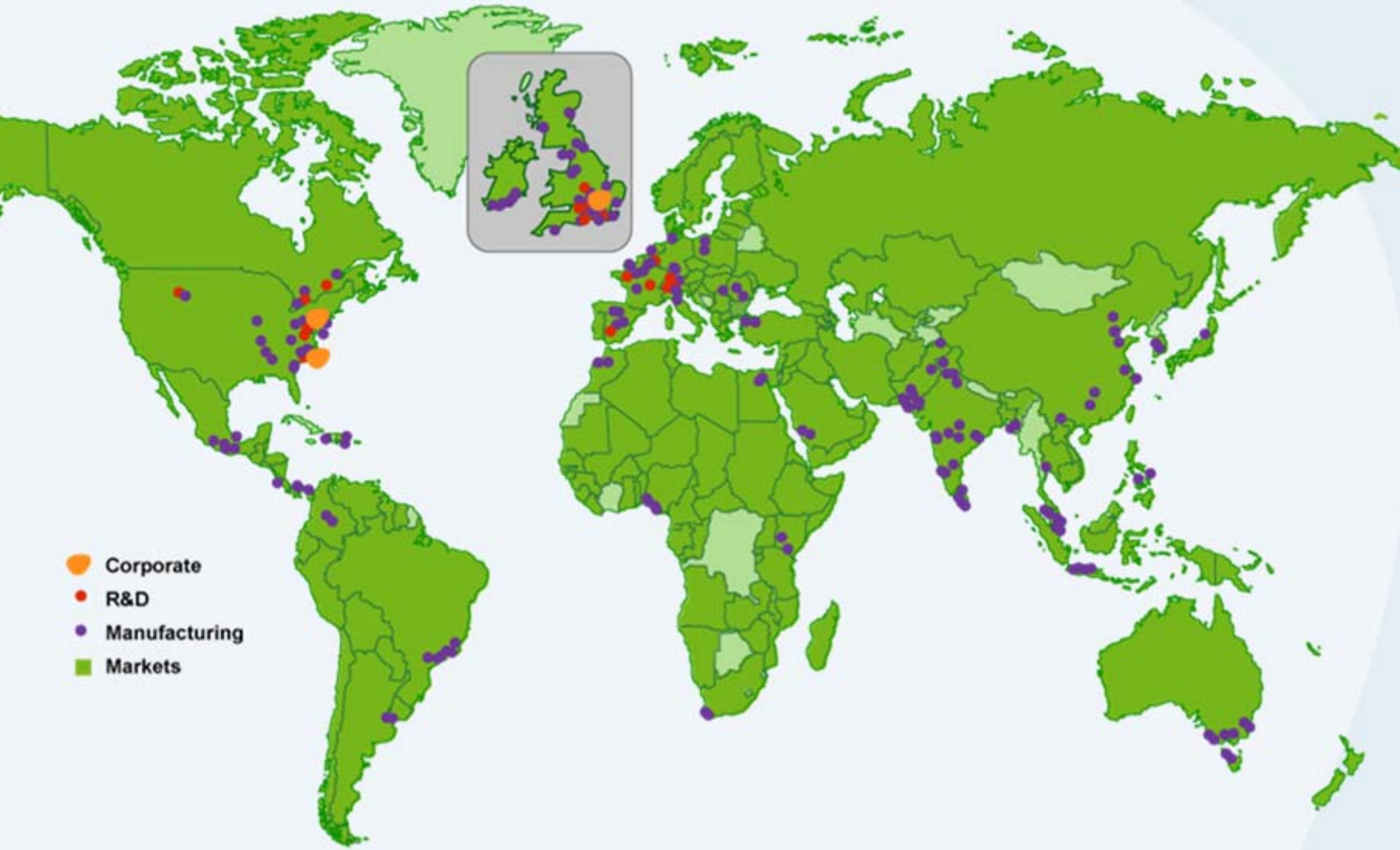
The World of GSK

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

Each year GMS produces over 4 billion packs

Where are we?



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

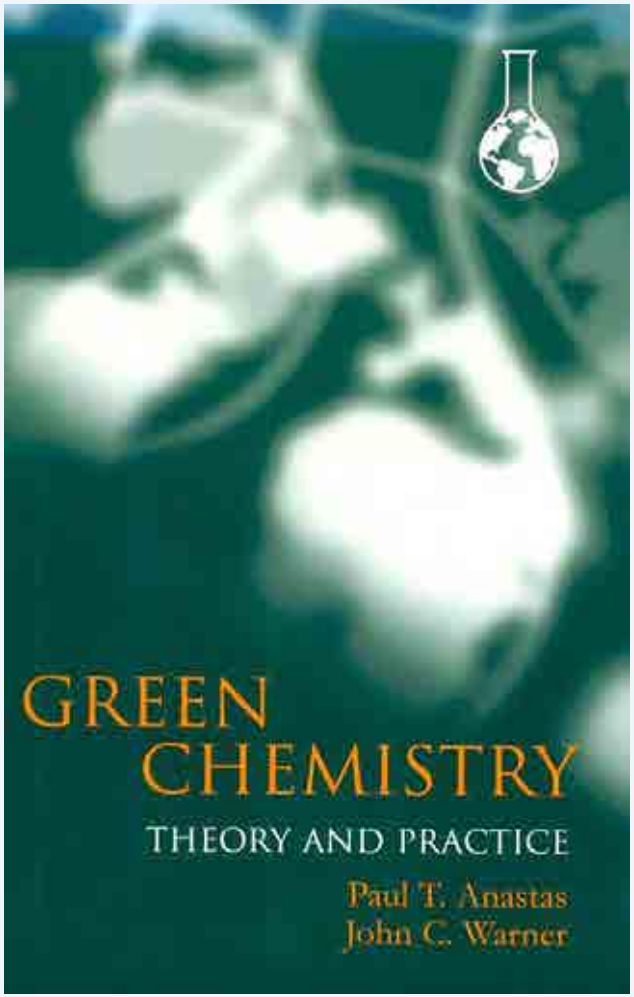
What do we do?

- **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

GlaxoSmithKline

Do more, feel better, live longer

What is Green Chemistry?

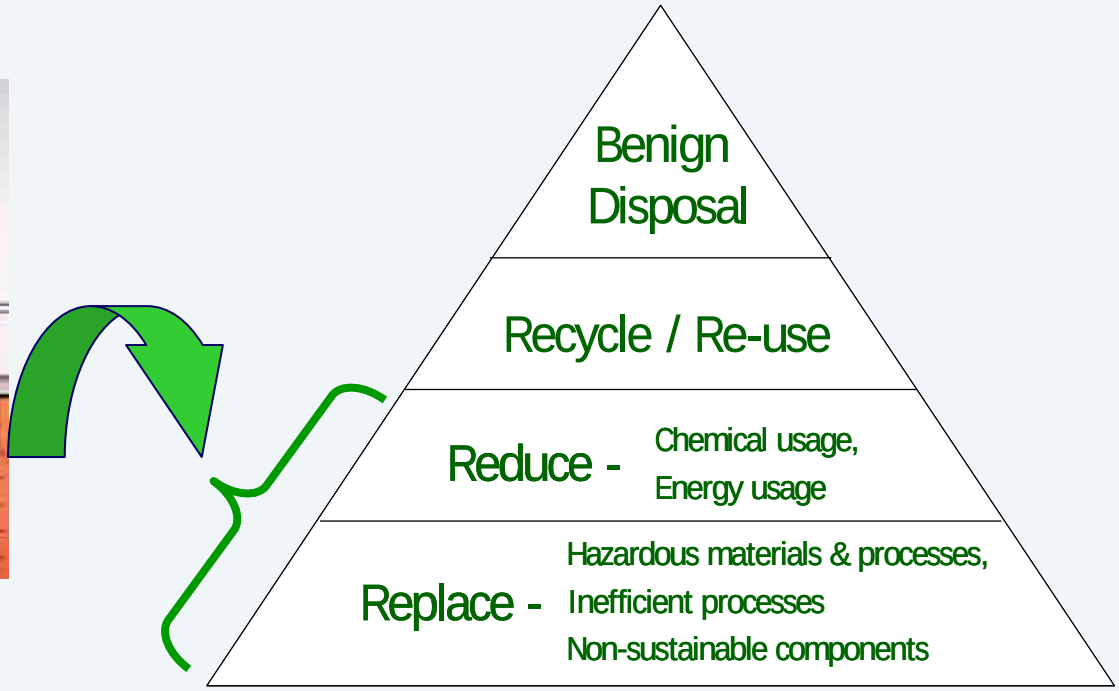


"…the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products."

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?

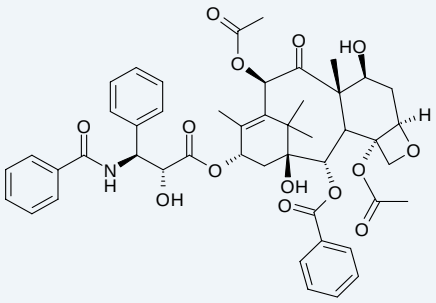


By design develop efficient syntheses and processes which:

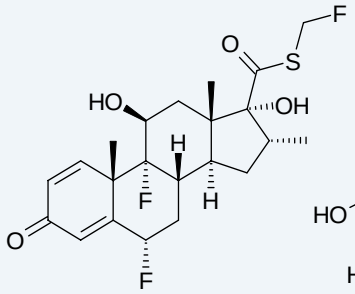
- ***Optimize material*** and ***energy*** use.
- ***Prevent*** and minimize waste.
- ***Eliminate or minimize*** hazardous chemicals.
- Increase use of ***renewable materials and energy***.
- Have ***inherently safe*** process conditions.

Special Challenges Presented by Pharmaceuticals

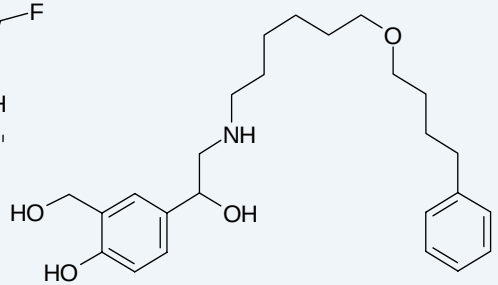
Challenge



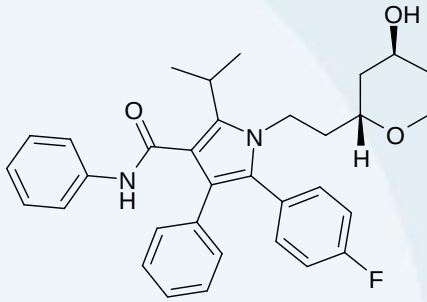
paclitaxel



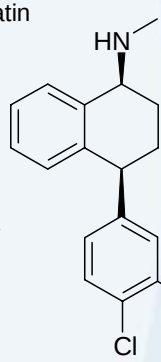
fluticasone



salmeterol

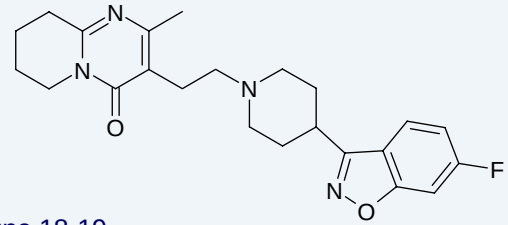


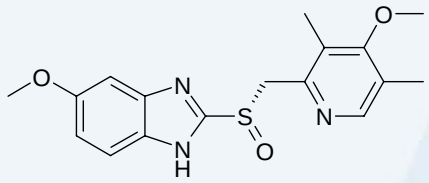
atorvastatin



sertraline

- 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





esomeprazole

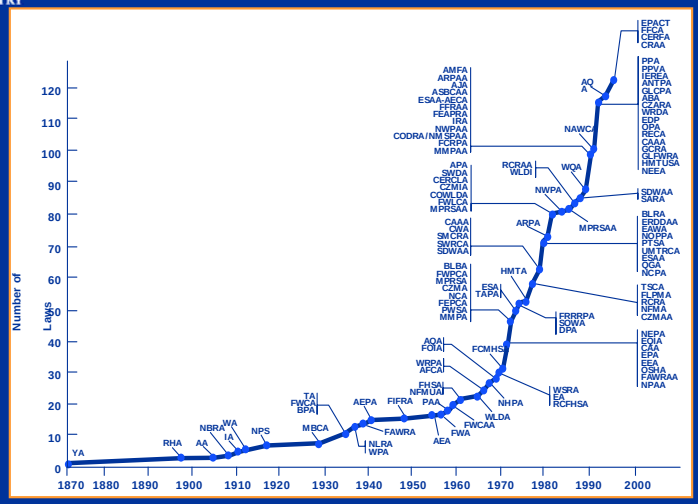
Special Challenges for the Pharmaceutical Industry

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

GREEN CHEMISTRY

Growth in Environmental Regulation

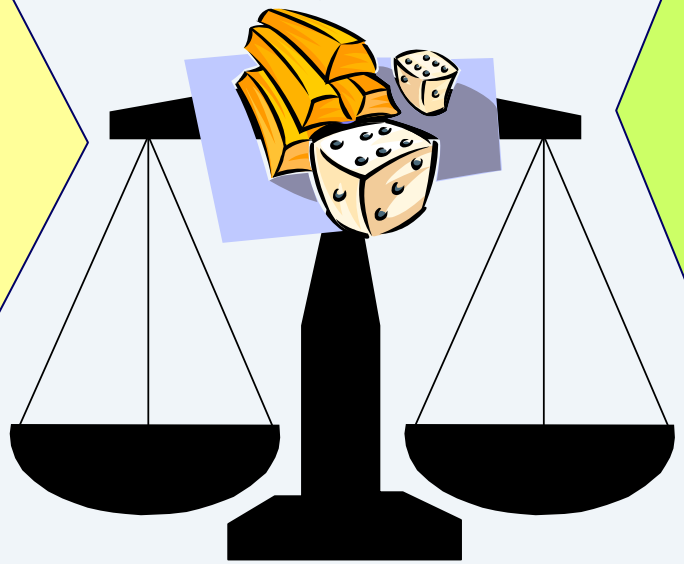


Finding the Right Balance

Challenge

Commercial Focus on Speed to Market

Green process design early when costs are lower



Attrition

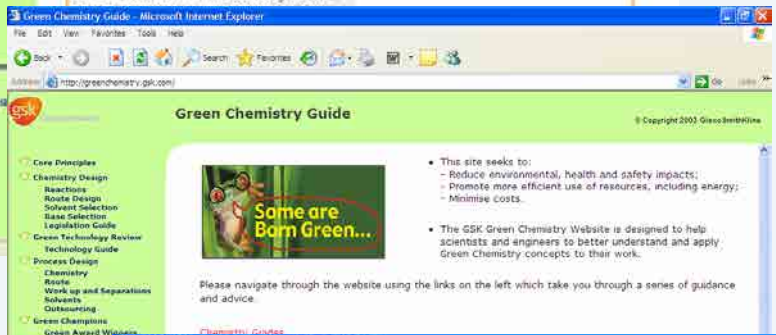
GSK's Approach: Sustainability by Design

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



Why not just focus on yield?

- 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

Traditional chemistry measure of efficiency

- Chemistry
  - Yield
  - Selectivity
  - Atom Economy
  - Reaction Mass Efficiency

Green Chemistry Metric

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

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

Mass of everything used to make 1 kg of product

100 ÷ Mass Intensity %

From GSK's FLASC tool

- 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?

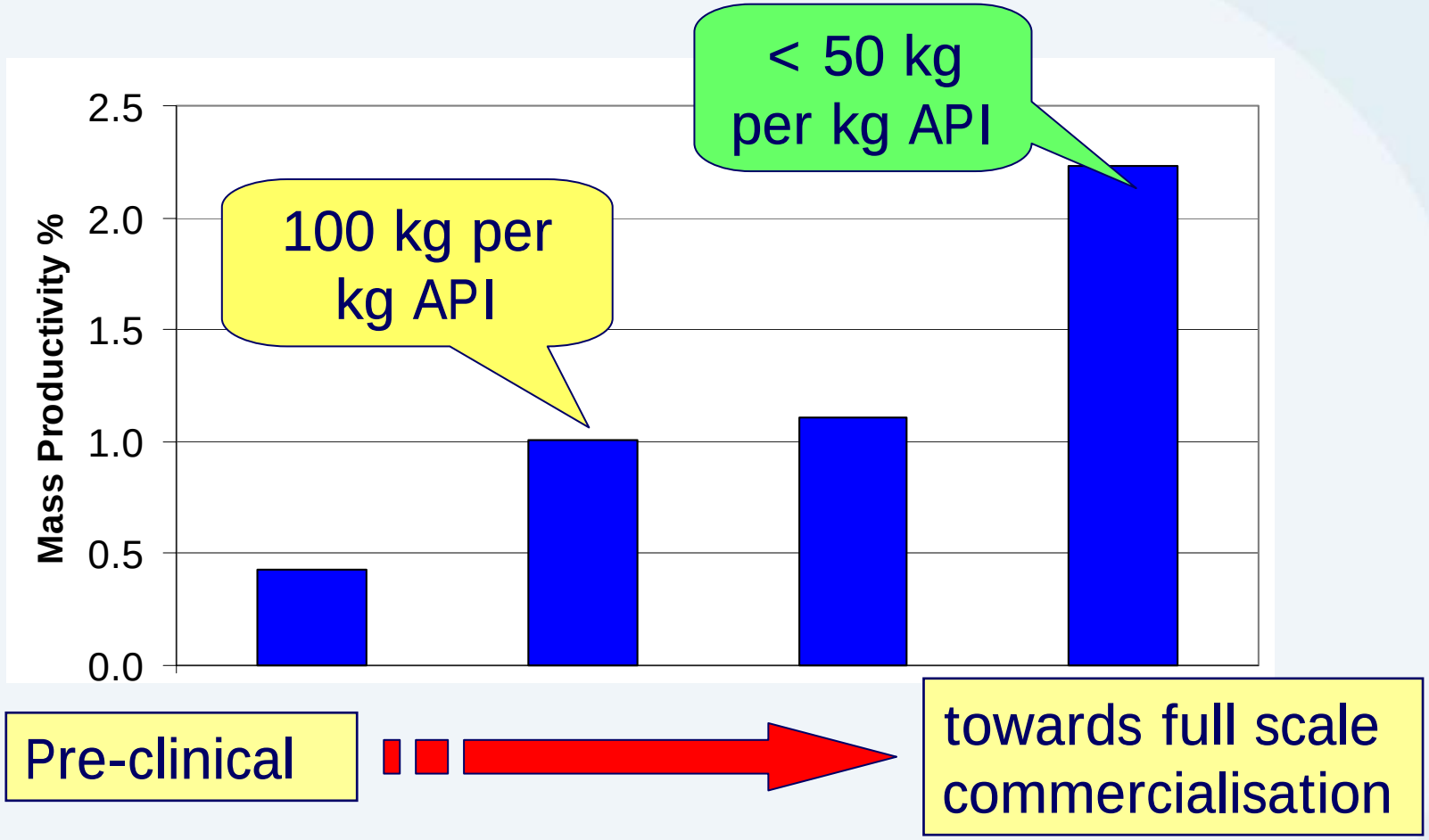
- Chemicals for which there is evidence for probable serious effects to humans or the environment
- The primary criteria for assignment of a **Material of Concern** are those described to identify Priority Chemicals in the GSK public position statement on hazardous chemical management; i.e.
  - those 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

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

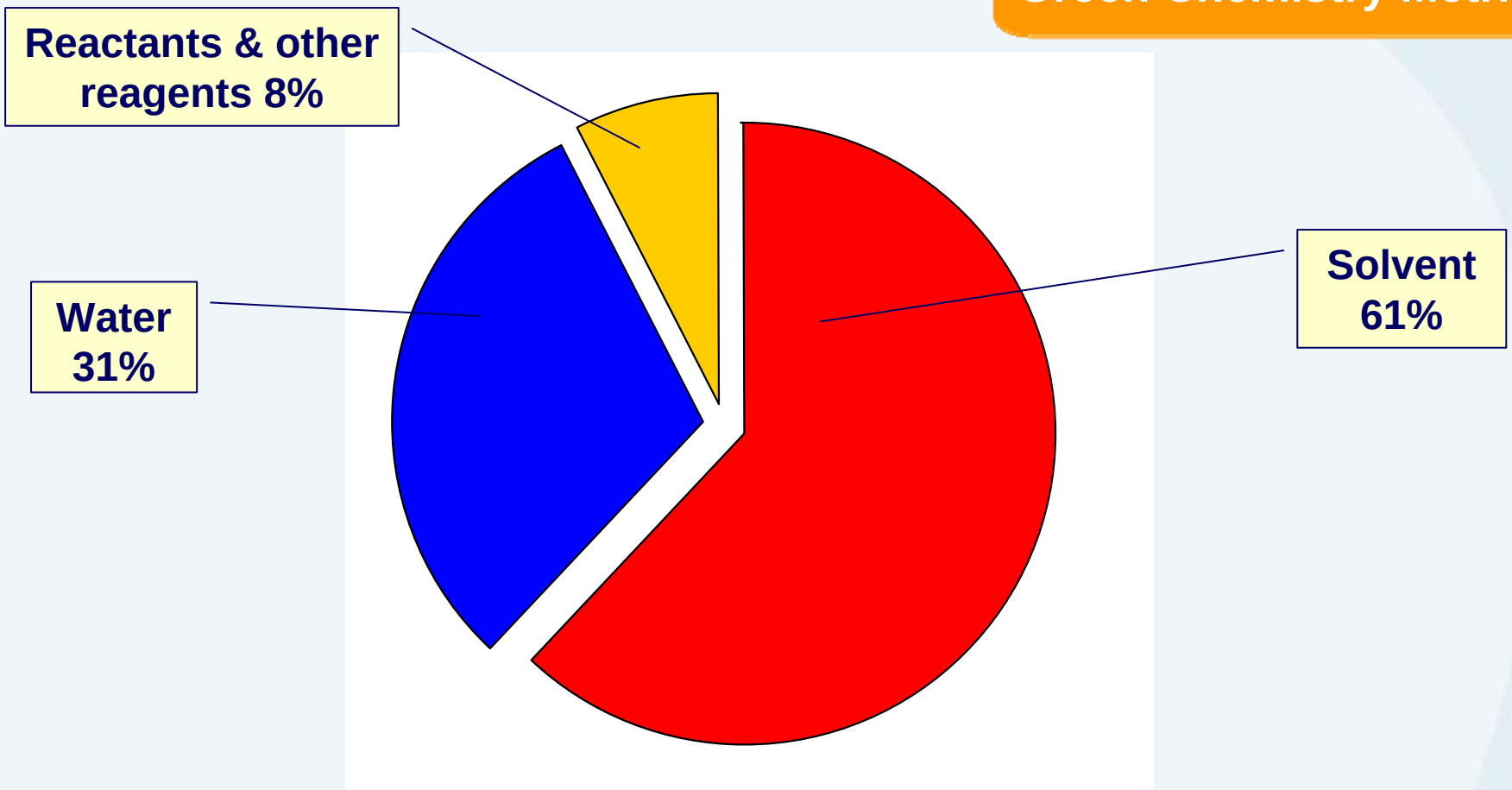
Measuring Progress: Mass Productivity



API = Active Pharmaceutical Ingredient

What's the average reaction mass composition?

Green Chemistry Metric

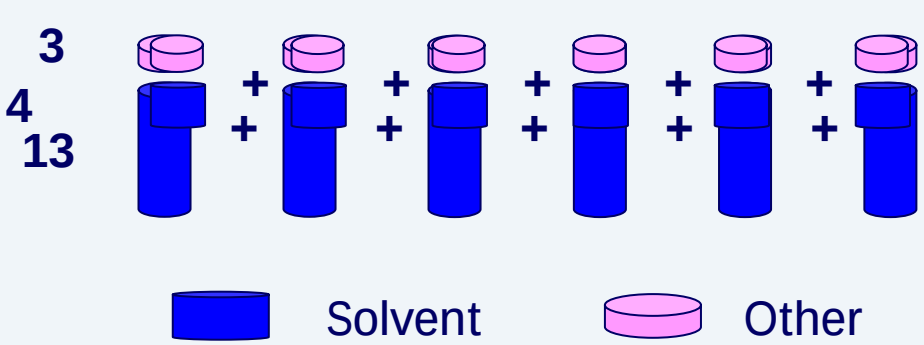


Solvent and water contribute to > 90 % of the reaction mass

Source data: ACS GCI Pharmaceutical Roundtable benchmarking exercise 2007

Solvents and Mass

Green Chemistry Metric



42 kg/kg API

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

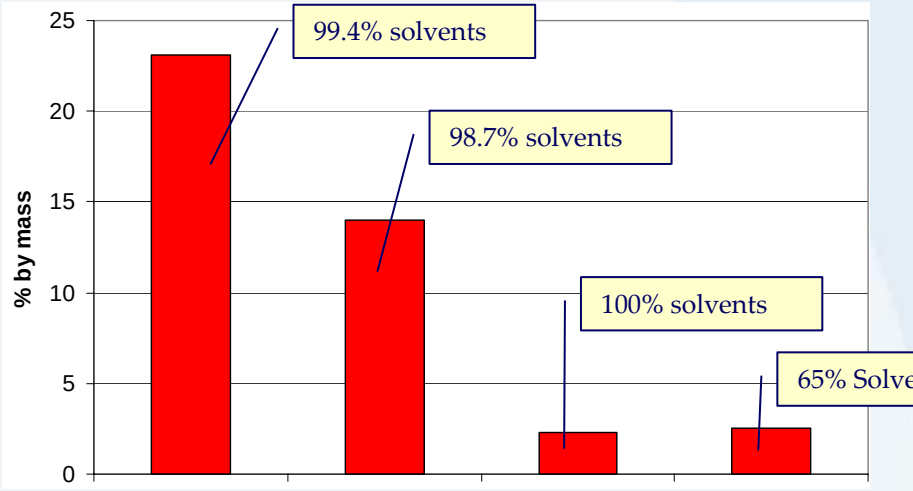
But if there is an average **75% recovery** of solvents and a **100% overall yield**, then…

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

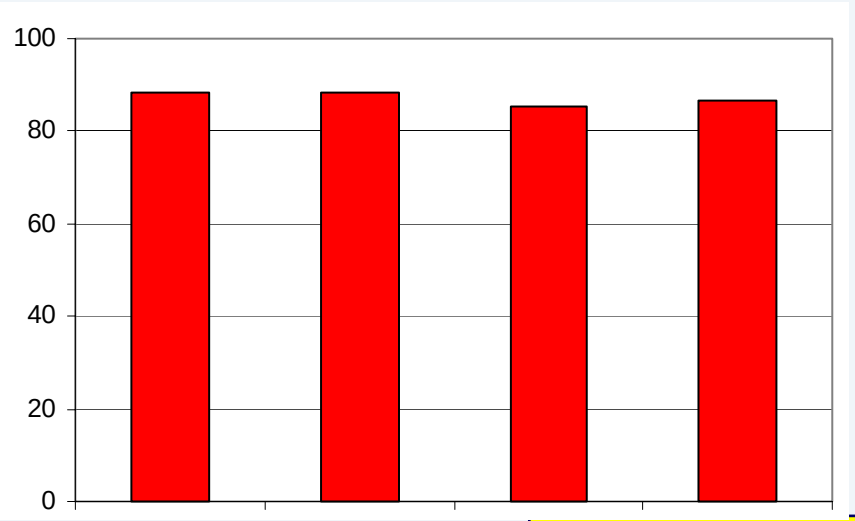
But the chemistry is not more efficient

Solvents and Materials of Concern

Average Mass % of materials of concern in compounds



Pre-clinical → Towards full scale commercialisation

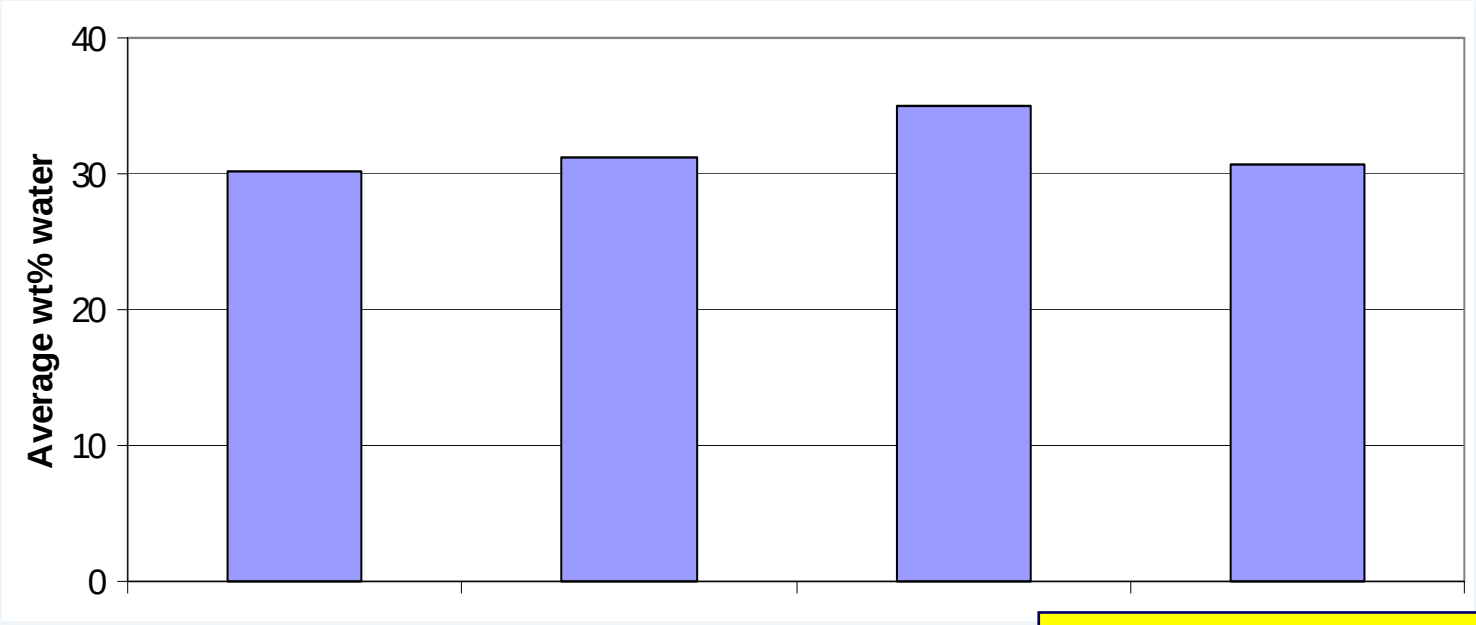


Pre-clinical → Towards full scale commercialisation

- 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

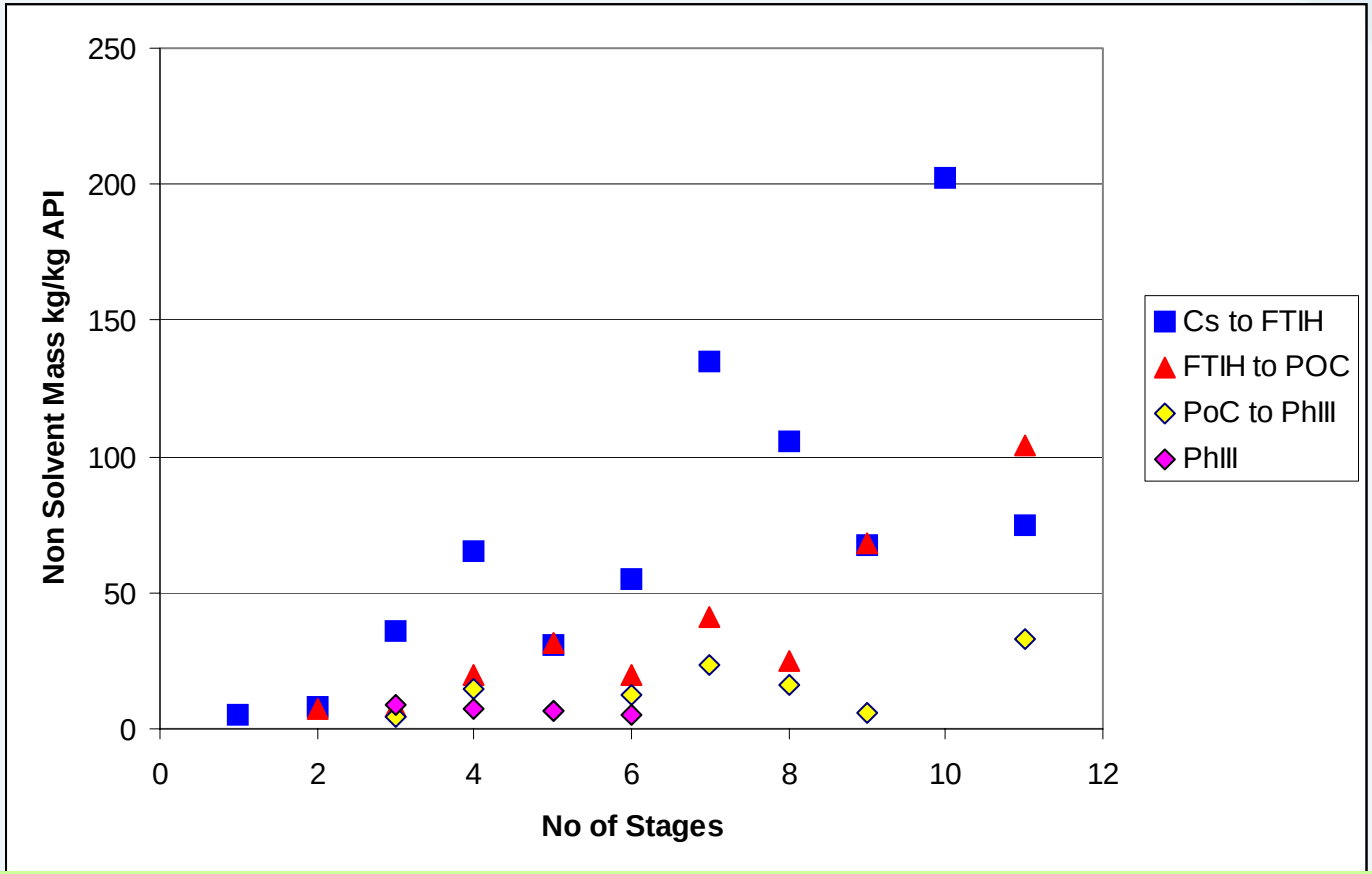


Pre-clinical

towards full scale commercialisation

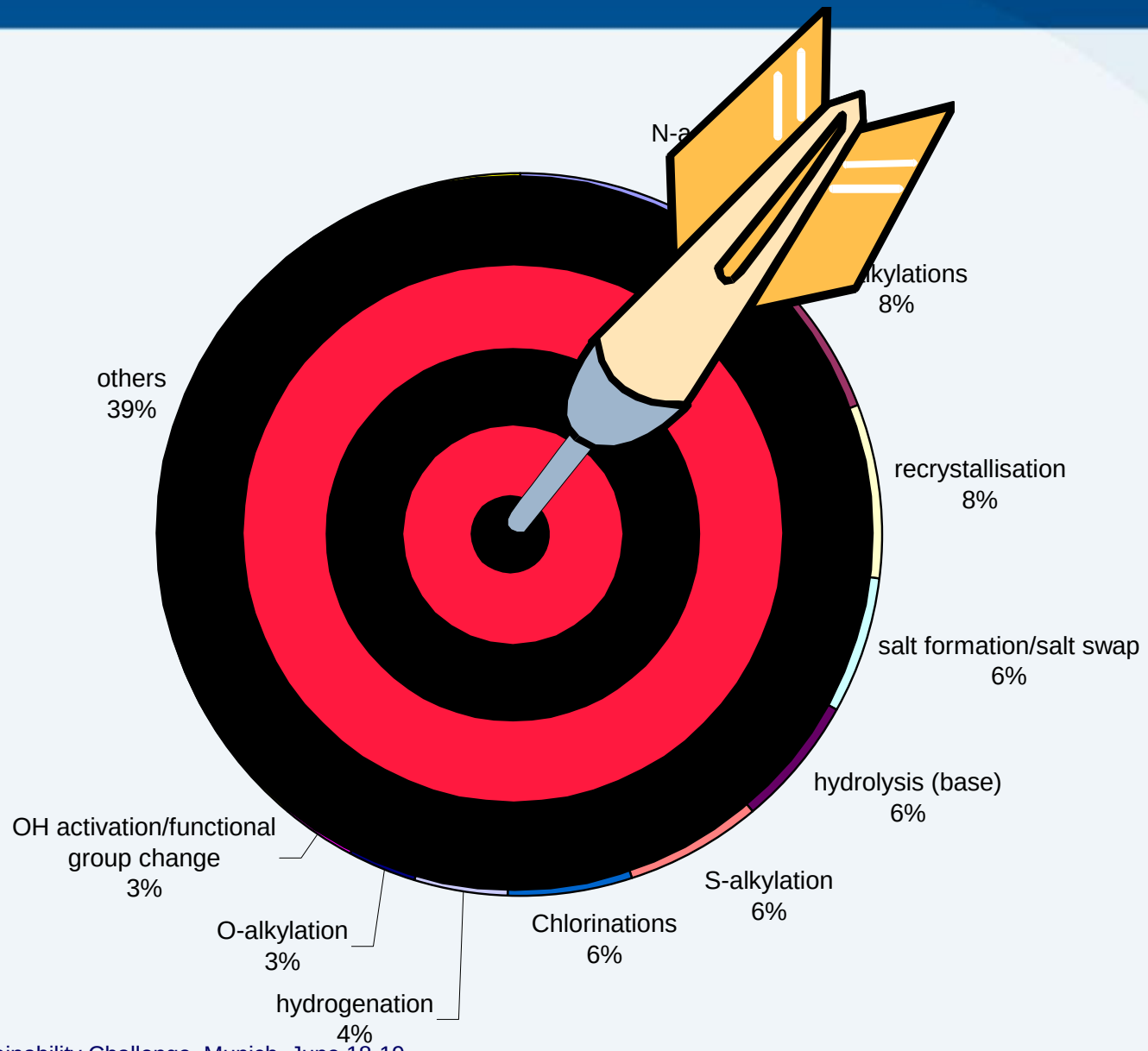
Data shows that the amount of process water used in washings and extractions per kg API could be optimised further

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



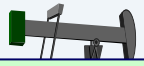
ACS Green Chemistry Institute Pharmaceutical Roundtable

- 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

ACS Green Chemistry Institute Pharmaceutical Roundtable website on the ACS portal
http://portal.acs.org/portal/acs/corg/content?_nfpb=true&_pageLabel=PP_TRANSITIONMAIN&node_id=1422&use_sec=false&sec_url_var=region1

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

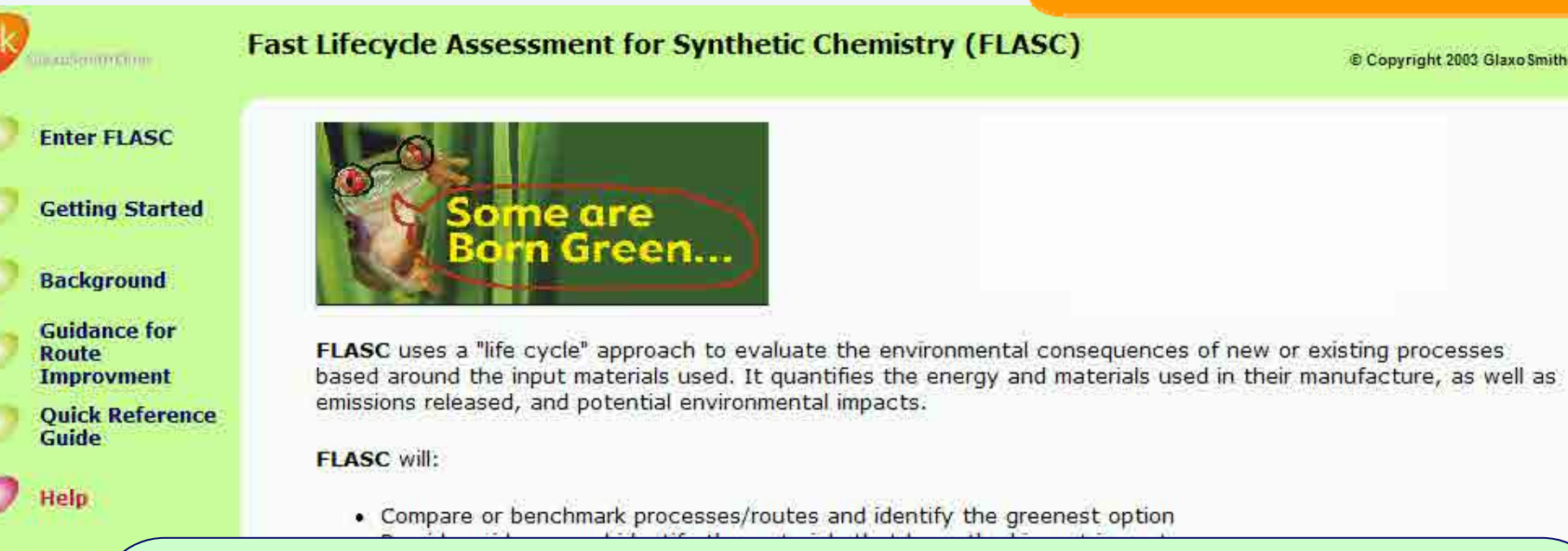
Store

Final Consumer Use

Emissions to air, water and land

FLASC™

Green Chemistry Metric

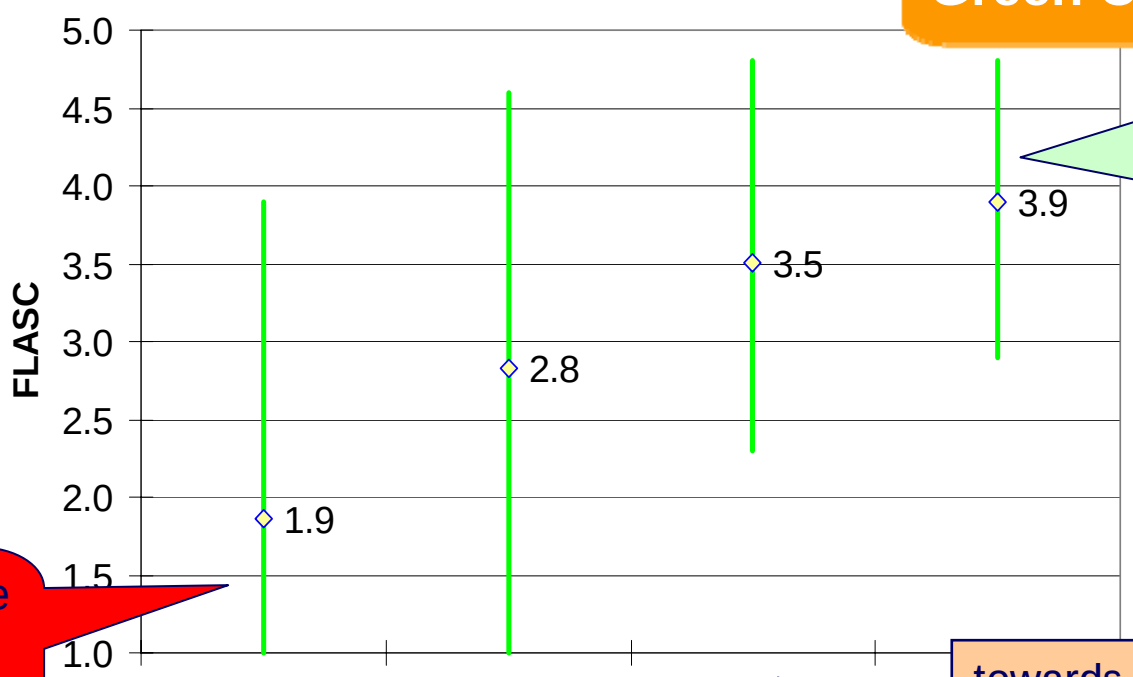


GSK's tool to estimate the ***Life Cycle environmental impacts*** of materials

- 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 Metric



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

130% 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 Metric

- 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 Lilley, 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?

ACS GCI Pharmaceutical Roundtable Membership

as of February 1, 2008

AstraZeneca

Pfizer

Lilly

gsk GlaxoSmithKline

Wyeth

MERCK

Schering-Plough

Johnson & Johnson

Boehringer Ingelheim

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