The Pharmaceutical Footprint – Opportunities for Green Chemistry and Engineering

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Synopsis

- Introduction to GSK
- Pharmaceutical Industry Challenges
- Some thoughts about our footprint
- Summary and Conclusions
- Future Challenges.

Where are we?

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

Who are we?

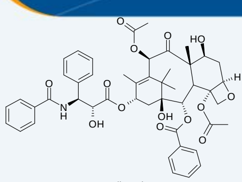
- We are one of the world's leading producers of prescription medicines, vaccines and consumer healthcare products
- 6.3% of global pharmaceutical sales
- Total company sales: £23.2 billion/ $43 billion
- We lead the way in respiratory and anti-viral medications and vaccines
- Over 100,000 GSK people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

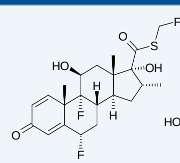
Each year GMS produces over 4 billion packs

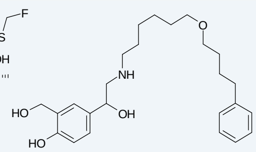
What do we do?

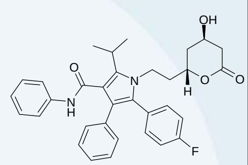
- **Every second...**
  We distribute more than 35 doses of vaccine
- **Every minute...**
  More than 1,100 prescriptions are written for GSK products
- **Every hour...**
  We spend more than £300,000 ($562,000) to find new medicines
- **Every day...**
  More than 200 million people around the world 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

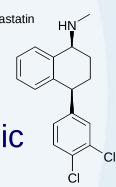
Special Challenges Presented by Pharmaceuticals


paclitaxel

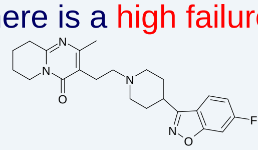

fluticasone


salmeterol


atorvastatin


sertraline

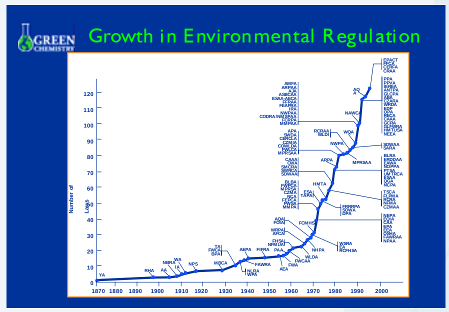
- They are complex:
  - target molecules, reagents and reactants
  - synthetic routes: 6+ stages
  - processes and wastes: mixed aqueous and organic streams
- Need for early and rapid definition of the synthetic route
- But there is a high failure rate for target molecules


risperidone

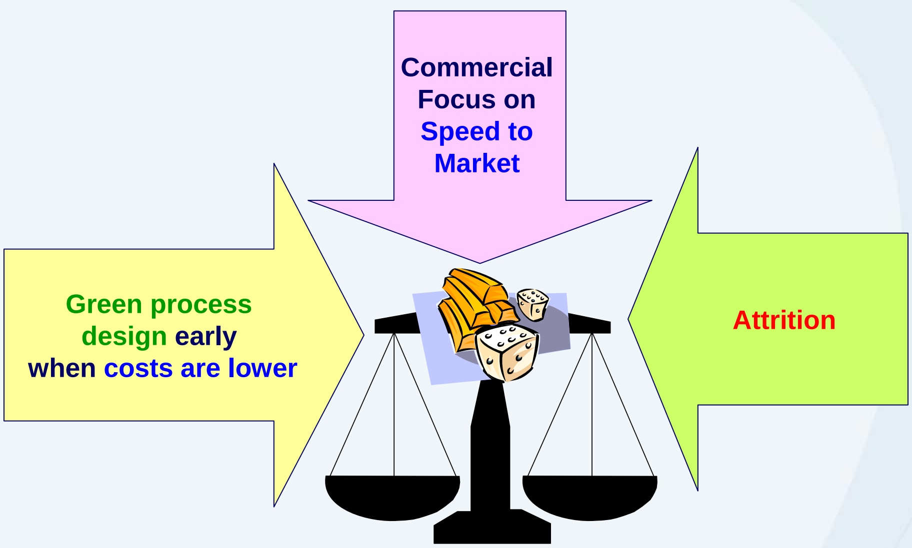

esomeprazole

Special Challenges for the Pharmaceutical Industry

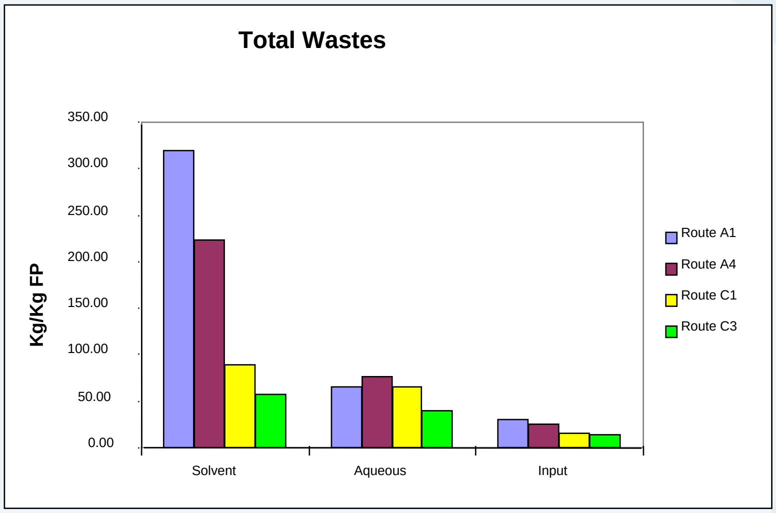
- Highly regulated by government agencies (not just US)
  - process changes
  - use of recovered/recycled solvent
- Route and Process changes post-approval give the appearance of being costly
- Regulatory / Legislative restrictions on solvent and materials selection
  - EU Solvent Directive,
  - REACH,
  - IPPC,
  - ICH,
  - etc.



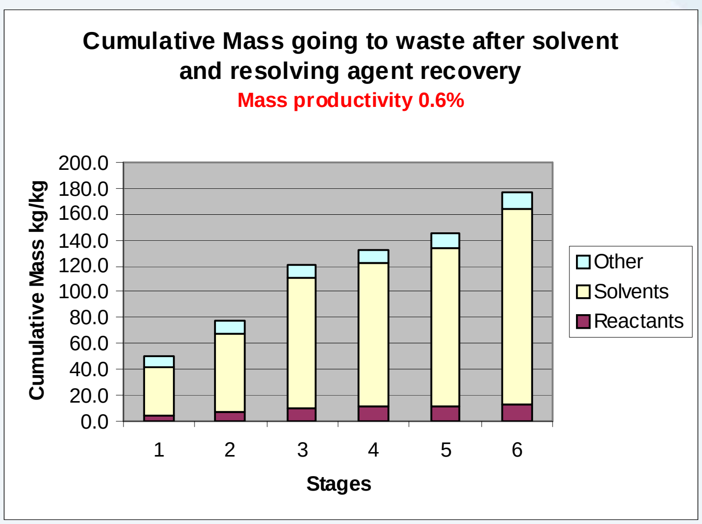
Finding the Right Balance



A Focus on waste....

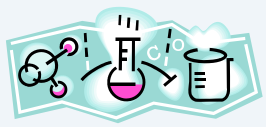


Cumulative Waste Loads for a "Typical" Pharmaceutical



Is it Waste (E-factor) or Mass Intensity?

Relationship between E-Factor and MI:



$$E_{factor} = MI - 1$$

$$\frac{\text{kg waste}}{\text{kg API}} = \frac{\text{kg input}}{\text{kg API}} - \frac{\text{kg API}}{\text{kg API}}$$

So why worry about what side of the equation we focus on???

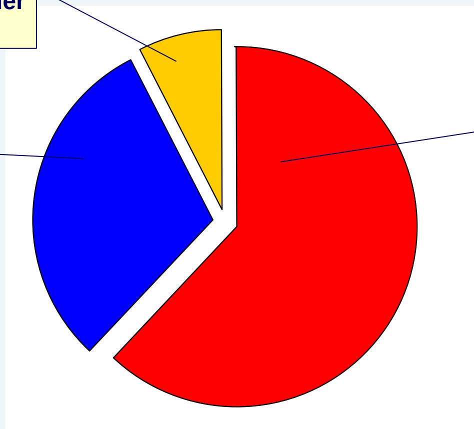
Why not just increase our yields?

For API manufacture, (not finished product):

- “Typical” GSK manufacturing yield from a single stage ranges between 35 and 95% with an average of 86%
- A “typical” GSK primary manufacturing process is on the order of 6 stages with an overall yield of 30 - 40%
- Overall yield does not capture use of reagent, solvent, catalyst. If these are included the average total materials use is 16 kg/kg of stage product (intermediate).
- Even with a 100% yield at each stage, a 16 kg/kg materials use would result in an overall Mass Productivity of about 1%.

Green Chemistry $\neq$ Yield

What's our average reaction mass composition?



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

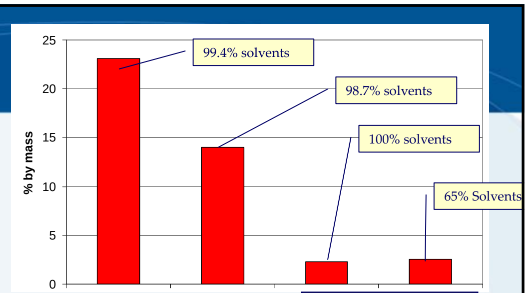
Do we have Materials of Concern?

- 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 **Green Chemistry Metrics** to help project teams to develop strategies to eliminate or substitute the use of these materials where technically and economically feasible.

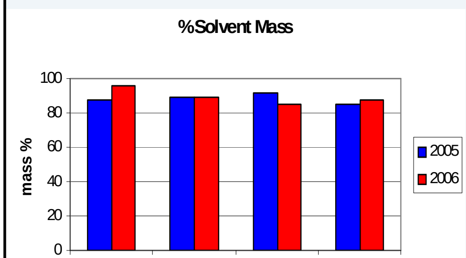
GSK Public Position Paper – Hazardous Chemicals Management
www.gsk.com/responsibility/Downloads/GSK-hazardous-chemicals-2006.pdf
Chemicals Legislation Guidance Available from internal website

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; **e.g., the majority of dichloromethane is removed by Proof of Concept**

Key Learnings of LCI/A

- **Solvent use (excluding incineration) is the major contributor to:**
  - **Energy (ca. 75%)**
  - **Resource utilisation (about 80%)**
  - **Photochemical Ozone Creation Potential (ca. 70%)**
  - **Green House Gases (about 50%)**
  - **associated impacts when compared to GSK processes, transport and manufacture of other raw materials.**
- **Energy use contributes approximately**
  - **30% of the materials**
  - **70% of resource depletion**
  - **90% of the Green House Gas emissions.**

Key Learnings of LCI/A

- **The contribution to overall environmental impacts from transport is low, with the maximum impact on the order of 8% for greenhouse gases**
- **The energy required to incinerate solvent wastes not recovered is approximately equivalent to a total of:**
  - **60% of the energy used to produce the API**
  - **50% of the post-treatment Green House Gas emissions**
- **Waste water treatment does not significantly increase the overall life cycle profile.**
- **The majority of pre-treatment TOC arises from GSK operations**

What would it take for replacement solvents to be routinely used by the pharma industry?

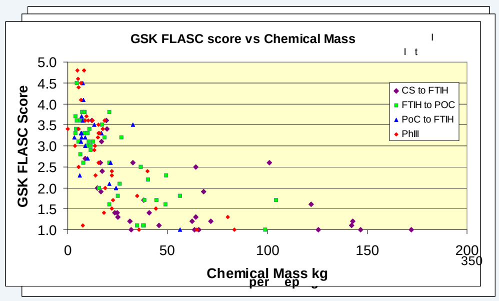
- Stop focusing solely on the chemistry of reactants
- Focus on the interaction of chemistries, synthetic route designs, and materials with technologies
- Start with a superior replacement(s) for MDC, ethers, some dipolar aprotic solvents and perhaps alkanes
  - Demonstrated comparability with conventional solvents from a:
    - life cycle and
    - economic basis
- Limited number of solvents with broad applicability to a significant number of different processes with EHS and operational data established

Ideally, replacements should show significant benefits across the entire process leading to an active pharmaceutical substance!

Are pharmaceutical processes becoming greener?

- If solvent mass is ~ 90% of the reaction mass and ~ 75% of the life cycle energy and mass, what about the other 10% of the reaction mass?
- Are there correlations with current measures of greenness?

GSK FLASC Score vs. Chemical Mass



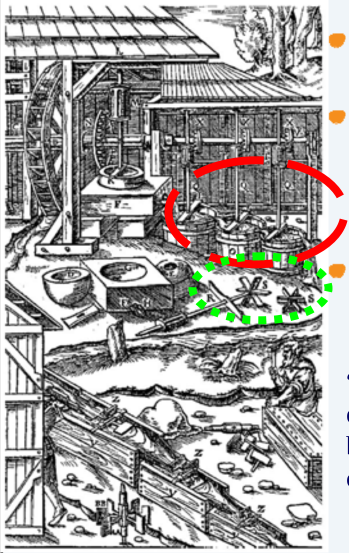
Mass-based factoids

- Data for 110 pharmaceutical manufacturing processes has been assessed since mid-2005
- The impact of non-solvent mass on the greenness of a process has been investigated
- There appears to be no correlation between the amount of non-solvent mass used in a process with *several different measures* of determining the greenness of a process.
- Non-solvent mass metrics alone do not appear to correlate with or account for the complexity of the chemistry being performed.
- Mass based metrics do not give and indication of the nature and/or impact of the chemicals used in a process.

SO……..

- What more should we be doing to influence the selection of reactants and reagents to reduce the impact of solvents in a pharmaceutical manufacturing process?

Do we need to do something with Technology?



- Batch reactor (Bronze age)
- Distillations (e.g., Dutch gin was imported before the English industry for distilled spirits took over in the 18th century)
- Crystallisation (Salt crystallisation during bronze age)

"The difficulty lies, not in the new ideas, but in escaping the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds."

- Keynes, John Maynard

Conclusions

- Solvents have the biggest impact - solvent mass is ~90 wt% of reaction mass and represent 75 – 80% of the total Life Cycle impacts of a typical process
- Not sure what effect replacement and substitution of hazardous with non-hazardous chemicals will have on mass efficiency / intensity
- GSK's life cycle assessment metrics suggest that processes in development are potentially greener than the previous generation of API's in development
- There are still many challenges to overcome

A few (of many) Pharmaceutical Sustainable Chemistry Opportunities

- A general need for the Industry to:
  - Develop:
    - sustainable feedstocks; i.e., break reliance on oil;
    - substitutes
      - high-hazard materials;
      - high risk process chemistries (EHS etc.);
    - a complete set of data on materials, streams, emissions;
  - Integration of chemistry and technology
    - improve process efficiencies;
      - new, cleaner, reactions and methodology
      - continuous processing, novel reactors, solvent systems
  - Bioprocessing
    - Further development of tools to objectively compare bioprocesses with chemical processes
    - Greater attention to downstream processing issues
    - Integration of life cycle considerations
  - Continue to ensure compliance with local, national, EU etc. legislation/regulations and company standards.
    - address Chemical Exposure, O/H monitoring, materials handling;
    - build in Safety (materials, process).

Summary

- The Strategy is to influence the development of next generation of drugs in development so they are greener
- Use of 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
- Assessment of "greenness" is, and should be, a multivariate exercise – "green" as is the case for "sustainable" is inherently complex!

GlaxoSmithKline

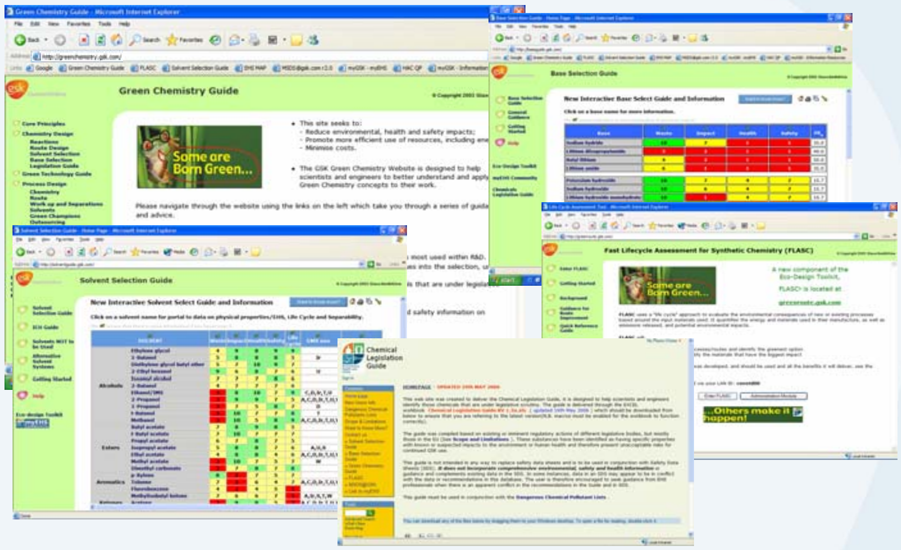
Any Questions?

...Others make it happen!

Conclusions - Solvents

- 10 solvents represent approximately 80% of all solvents used
- Solvent profile is improving compared to 5 years ago:
  - Overall reduction of chlorinated solvents
  - Dichloromethane use in final process down by 50% (kg/kg API)
  - Toluene use is down by 65% (kg/kg API)
  - DMF use has declined by 95% (kg/kg API)
  - THF use has increased by 60% (kg/kg API)
  - Alcohol (MeOH, IPA, IMS/Ethanol) use has increased by 80% (kg/kg API)
  - MIBK and EtOAc have been used as DCM replacements
  - MeOH has been used as DMF replacement

The Green Chemistry Website links to the other Design Tools



Why is life cycle important?

- Evaluates the true greenness of a process
- Provides a common set of accepted metrics to measure specific impacts.
- Identifies trade-offs and hot spots
- Identifies opportunities for resource optimisation
- Highlights hidden costs and impacts
- Provides a better understanding of the environmental impacts of processes for a better decision-making for production systems
- Identifies key impacts at the life cycle stages of system
- Identifies information gaps