Solvent Considerations in Green Chemistry

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Outline

Solvent Selection
Traditional vs. New

Metrics Are Essential
Chemical characteristics to consider

Solvent Selection Guides
Tools for change

How do we know what is “green”?
The importance of metrics
From the 12 Principles of Green Chemistry

• It is better to prevent waste than to treat it or clean it up after it is formed – *in many cases, solvent input equals solvent to be treated and managed*

• Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product – *generally in most batch processes solvent is not incorporated into the product*

• The use of auxiliary substances should be made *unnecessary* whenever possible and *innocuous* when used – *if solvents cannot be avoided, need carefully select appropriate solvents*
Why Solvents? Part 1
The mass challenge

Mass Allocation of a Typical Primary Pharma Process

- Process: 46.0%
- Product: 1%
- Unreacted reagents: 2.0%
- Solvents: 51.0%
From ACS GCI PR

- Solvent and water contribute ~80% of the process mass intensity.
- Emphasizes need for research to reduce the use & hazard of the solvent.
Mass productivity Example with significant Solvent Recovery

- If there is an average 75% recovery of solvents (average is around 50%) and a 100% overall yield, mass productivity would approximately double. For example:

  \[
  \frac{3}{4} \text{ kg total materials /kg API}
  \]

  This corresponds to a mass productivity of approximately 2.4%
Why Solvents? Part 2: LCI/A of a Pharmaceutical

- Basis: 1 kg of API
- GSK process studied has 7 stages
- 26 materials directly used in GSK process
- To make these 26 materials requires the manufacture of a total of 119 materials (125 including GSK’s intermediates)
- Cradle-to-Gate Analysis involves:
  - Process:
    - Materials
    - Energy
    - Transportation
  - Treatment:
    - wastewater treatment,
    - incineration, and
    - landfill.
LCA of API pre-treatment results

Cradle-to-gate pre-treatment contributions:
Solvents, Chemicals, Internal

- Eutrophication (PO4-3-eq)
- Acidification (SO2-eq)
- GHG (CO2-eq)
- POCP (kg-et)
- TOC (kg)
- Energy (MJ)
- Total cradle materials (kg)

0% 20% 40% 60% 80% 100%

Chemicals Solvents Internal
Key Learnings of LCI/A of API

• **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.

• 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
Process Metrics

• **Solvent acceptability**
  – total solvent mass
  – complexity (number and nature of different solvents used)
  – solvent guide scores

• **Energy**
  – solvent switches
  – recovery

• **Green chemistry metrics**
  – FLASC score (based on LCI/A: greenhouse gas, acidification, POCP, eutrophication, Total Organic Carbon (TOC), oil equivalents, mass and energy)
  – Reaction Mass Efficiency

• **Mass productivity**
• **Quality etc**
Solvent Selection Method

Iterative Method of Solution:

- Define problem (problem formulation & method constraint selection)
- Generate & test candidates - check also existing databases (Solvent selection)
- Final selection (analysis)

- Feasible solvents are those that match the specific reaction properties
# GSK’s ‘Materials of Concern’ Pilot Plant Campaigns

<table>
<thead>
<tr>
<th>Top 6 by Mass - 2006</th>
<th>Top 6 by Mass – 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dichloromethane</td>
<td>1. Dichloromethane</td>
</tr>
<tr>
<td>2. 1,4-dioxane</td>
<td>2. NMP</td>
</tr>
<tr>
<td>3. N,N-Dimethylformamide</td>
<td>3. N,N-Dimethylformamide</td>
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<tr>
<td>4. NMP</td>
<td>4. 1,2-Dichloroethane</td>
</tr>
<tr>
<td>5. 1,2-Dimethoxyethane</td>
<td>5. Pyridine</td>
</tr>
</tbody>
</table>

- **2006**
  - 63 campaigns
  - 334 stages

- **2005**
  - 45 campaigns
  - 236 stages

Finding alternative solvents to replace DCM remains a key green chemistry challenge.
Greener Solvents?

Chemical structures and formulas are shown, including molecules with various functional groups and atoms.
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 problems (chemistries, synthetic schemes, separations, flowsheet schemes, etc.) that need a solution
- Start with a superior replacement(s) for DCM, ethers, some dipolar aprotic solvents and perhaps alkanes
- Demonstrated comparability
  - 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!
Some Important Work to do…

• Inclusion of *solvent selection* as an important design consideration in route selection.

• Greater collaboration between synthetic *Chemists and Chemical Engineers*

• *Literature and databases* on solvent selection with respect to specific chemistries

• Synthesis strategies that optimize solvent use, reuse, and end-of-life considerations (*life cycle approach*)

• Development of *solvent options* that provide the desired function without the undesirable EHS issues

• Technology options that facilitate *process intensification*

• Development of *solvent-less and biotechnology options*
Final Thoughts

• **Solvents are a key component** in designing more sustainable synthesis
• **GSK’s Solvent Selection Guide** continues to be updated to meet changing business demands:
  • Inclusion of Life Cycle Assessment
  • Evaluation of new solvents
  • Part of GSK’s efforts towards more Sustainable Practices
• **Key challenges** (materials and processes) remain unsolved in the area of solvents
• Moving towards more sustainable chemical synthesis will require a considerable amount of **creativity, systems thinking and collaboration**
Special Challenges Presented by Pharmaceuticals

• **Complex:**
  – target molecules
  – reagents and reactants
  – synthetic routes - 7+ stages
  – processes and wastes - mixed aq + org

• Need for early and rapid route definition but there is a *high failure rate* for target molecules
Solvent Selection Risks and Challenges for the Pharmaceutical Industry

• 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 selection (solvent directive, REACH, IPPC, ICH etc.)
# Most used Solvents in Manufacturing at GSK

<table>
<thead>
<tr>
<th>Solvent</th>
<th>2005 Rank</th>
<th>1990 - 2000 Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPA</td>
<td>1</td>
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<tr>
<td>Ethyl acetate</td>
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<tr>
<td>Methanol</td>
<td>3</td>
<td>6</td>
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<tr>
<td>IMS/Ethanol</td>
<td>4</td>
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<tr>
<td>Heptane</td>
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<td>12</td>
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<td>THF</td>
<td>6</td>
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<td>Toluene</td>
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<td>Acetic acid</td>
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<td>11</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>10</td>
<td>14</td>
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</table>
Solvents

- “Traditional” organic solvents
  - Supercritical CO$_2$
  - Ionic liquids
  - Switchable solvents
  - Water

- “Newer” organic solvents
  - Renewable, low VOC, biodegradable

- Non-organic solvents
  - Supercritical CO$_2$, ionic liquids, water

“Newer” Organic Solvents

• Renewable solvents
  – Methanol
  – Ethanol
  – Ethyl lactate
  – Glycerol
  – 2-methyl THF

• Lower peroxide formation
  – Cyclopentyl methyl ether (CPME)
Solvent Research Survey Results

a) Responses to the survey question “…what class of solvents will be responsible for the greatest reduction in environmental damage?”

b) Proportion of papers describing each class of solvent published in the journal *Green Chemistry* in 2010.

Traditional organic solvents compared by EHS and LCA

- EHS-preferred solvents were methanol, ethanol, and methyl acetate.
- Life cycle-preferred solvents were hexane, heptane, and diethyl ether.

Traditional organic solvents compared by EHS and LCA

- 47 solvents in life cycle assessment compared to EHS
- Higher scoring (greener) solvents for life cycle:
  - ethylene glycol
  - ethanol
  - t-butanol
  - methanol
  - dimethyl carbonate
- However, except for ethylene glycol, all other of these solvents had at least one poor score in another category (environmental waste, environmental impact, health, or safety).

Materials of Concern

• Chemicals for which there is evidence of probable serious effects to humans or the environment
  – carcinogens, mutagens or reproductive hazards (CMR’s),
  – toxic and bioaccumulate or persist in the environment (PBT’s),
  – very persistent or very bioaccumulative in the environment (vPvB),
  – ozone depleting chemicals (ODC’s),
  – endocrine disruptors (ED’s)
  – those known to cause asthma (asthmagens)

• Materials of Concern should be identified early to develop strategies to eliminate or substitute.
**Human Health**
- Acute and Chronic Inhalation
- Acute and Chronic Dermal
  - Skin/Respiratory Sensitization
  - Eye Irritation & Corrosion
- Acute and Chronic Oral
- Sub-chronic and chronic toxicity
  - Reproductive effects
  - Developmental effects
  - Neurotoxicity
  - Mutagenicity (genotoxicity)
  - Carcinogenicity

**Ecological Effects**
- Persistence
  - Biodegradation
  - Photolysis
  - Hydrolysis
- Partitioning factors
  - Air
  - Soil
  - Water
- Bioaccumulation
- Acute aquatic toxicity
  - Fish
  - Daphnia
  - Algae
- Chronic Ecological Toxicity
- Long Term Impacts
- Eutrophication Potential
- Acidification Potential ThOD/COD
- Groundwater mobility
- Photochemical Smog Potential
- Ozone Depleting Potential

**Physical Properties**
- Flammability
  - Physical state
  - Flashpoint
  - Boiling Point
  - Burning time/rate
- Reactivity
  - Explosivity
- Corrosive to metal
- Oxidizer
- Water reactive
- Radioactive
- Threshold Odor Concentration
- Odor index
Example: Greening of Medicinal Chemistry

What can medicinal chemists do?

- Solvent use is widely scrutinised in the literature, with the majority of chemical waste in the pharmaceutical industry attributed to solvents.

- Therefore the application of environmentally benign solvents (rather than their traditional predecessors) is the most productive mode of action when attempting to reduce our environmental impact.

What is being done in the industry concerning solvent use?

- Whereas examples of ‘greening’ within process development are prevalent, medicinal chemistry is only slowly beginning to catch up.

- Recent initiatives at Pfizer have resulted in significant reductions in hazardous solvent use within medicinal chemistry.

- The introduction of a solvent selection guide was used to raise awareness in this instance.
### Pfizer Medicinal Chemistry Solvent Selection Guide

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Usable</th>
<th>Undesirable</th>
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<tbody>
<tr>
<td>Water</td>
<td>Cyclohexane</td>
<td>Pentane</td>
</tr>
<tr>
<td>Acetone</td>
<td>Heptane</td>
<td>Hexane(s)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Toluene</td>
<td>Di-isopropyl ether</td>
</tr>
<tr>
<td>2-Propanol</td>
<td>Methylcyclohexane</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>1-Propanol</td>
<td>TBME</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>Isooctane</td>
<td>Dichloroethane</td>
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<tr>
<td>Isopropyl acetate</td>
<td>Acetonitrile</td>
<td>Chloroform</td>
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<tr>
<td>Methanol</td>
<td>2-MeTHF</td>
<td>NMP</td>
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<tr>
<td>MEK</td>
<td>THF</td>
<td>DMF</td>
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<tr>
<td>1-Butanol</td>
<td>Xylenes</td>
<td>Pyridine</td>
</tr>
<tr>
<td>t-Butanol</td>
<td>DMSO</td>
<td>DMAc</td>
</tr>
<tr>
<td></td>
<td>Acetic Acid</td>
<td>Dioxane</td>
</tr>
<tr>
<td></td>
<td>Ethylene Glycol</td>
<td>Dimethoxyethane</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbon tetrachloride</td>
</tr>
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</table>

### Pfizer Solvent Replacement Table

<table>
<thead>
<tr>
<th>Red Solvents</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentane</td>
<td>Heptane</td>
</tr>
<tr>
<td>Hexane(s)</td>
<td>Heptane</td>
</tr>
<tr>
<td>Di-isopropyl ether or ether</td>
<td>2-MeTHF or t-Butyl methyl ether</td>
</tr>
<tr>
<td>Dioxane or dimethoxyethane</td>
<td>2-MeTHF or t-Butyl methyl ether</td>
</tr>
<tr>
<td>Chloroform, dichloroethane or carbon tetrachloride</td>
<td>DCM</td>
</tr>
<tr>
<td>DMF NMP or DMAc</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>Pyridine</td>
<td>Et$_3$N (if pyridine used as base)</td>
</tr>
<tr>
<td>DCM (extractions)</td>
<td>EtOAc, MTBE, toluene, 2-MeTHF</td>
</tr>
<tr>
<td>DCM (chromatography)</td>
<td>EtOAc/Heptanes</td>
</tr>
<tr>
<td>Benzene</td>
<td>Toluene</td>
</tr>
</tbody>
</table>

ACS GCI Pharmaceutical Roundtable Solvent Selection Guide

• Delivery of a resource to all member companies enabling scientists to integrate green chemistry and engineering principles
• Validation of existing member company tools
• Potential resource saving if company specific tools do not need to be created or maintained
• Existence of a common tool will provide basis for influencing solvent manufacturers to develop greener alternatives and ensure holistic approach
• Initially limited to ~50 solvents

Solvent Guide Now Freely Available: www.acs.org/gcipharmaroundtable
Criteria considered in ACS GCIPR solvent guide

- **Safety**
  - NFPA rating
  - Flammability
  - Auto Ignition temperature
  - Boiling point
  - Flash point
  - Conductivity (static risk)
  - Peroxide formation

- **Health**
  - Reprotoxic, carcinogenic and mutagenic effects
  - Toxicity
  - Skin effects
  - Sensitisation
  - Occupational Exposure Limit values
  - Vapour pressure

- **Environment (Air impact)**
  - Volatility
  - Odour
  - Photochemical Ozone Creation (POCP) potential
  - Photolysis
  - Ozone Depletion Potential (ODP)
  - Global Warming Potential (GWP)

- **Environment (Water impact)**
  - Persistence (Biodegradation)
  - Bioaccumulation (LogPow)
  - Ecotoxicity
  - Water solubility

- **Environment (Waste)**
  - Potential for incineration (degree of halogenation, heat of combustion)
  - Potential for recycle (boiling point, miscibility with water, number of close boiling solvents, ease of drying, azeotrope formation)
Roll out of the guide

- The summary guide has been made publicly available on ACS GCIPR website – see Solvent Selection Guide link under “Tools and Presentations”
- Details
  - Summary table assigns a score from 1 (least concern) to 10 (most concern) for each solvent under each of the 5 categories
  - Simplified color coding assigned to facilitate quick comparisons as follows
    - Score 1 - 3: Green
    - Score 4 - 7: Yellow
    - Score 8 – 10: Red
  - Guide suggests candidate solvents and flags potential concerns, but there is “no substitute for detailed evaluation in connection with specific uses”
# ACS GCIPR Solvent Selection Guide

<table>
<thead>
<tr>
<th>Solvent Class</th>
<th>Solvent Name</th>
<th>CAS Number</th>
<th>Safety</th>
<th>Health</th>
<th>Env (Air)</th>
<th>Env (Water)</th>
<th>Env (Waste)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halogenated</td>
<td>1,2-DICHLOROETHANE (DCE)</td>
<td>107-06-2</td>
<td>4</td>
<td>9</td>
<td>6</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Halogenated</td>
<td>CHLOROBENZENE</td>
<td>106-90-7</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>6</td>
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<tr>
<td>Halogenated</td>
<td>CHLOROFORM</td>
<td>67-80-3</td>
<td>2</td>
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<tr>
<td>Halogenated</td>
<td>CARBON TETRACHLORIDE</td>
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<td>Hydrocarbon</td>
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<td>Hydrocarbon</td>
<td>METHYL CYCLOHEXANE</td>
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<td>Hydrocarbon</td>
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<td>ACETONE</td>
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<td>AMYL ACETATE</td>
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Note: A blank cell indicates that there is data missing so a score could not be calculated.

### Substance Information

<table>
<thead>
<tr>
<th>Solvent Class</th>
<th>Solvent Name</th>
<th>CAS Number</th>
<th>EC Risk phrases</th>
<th>Score</th>
<th>Lowest Occupational Exposure Limit Value, OEL (ppm)</th>
<th>Vapour pressure at 20°C (mmHg)</th>
<th>Vapour hazard rating (Saturated Concentration / OEL)</th>
<th>Score</th>
<th>TOTAL SCORE</th>
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<tr>
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<td>79</td>
<td>20789</td>
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<td>Hydrocarbon</td>
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<td>11, 38, 50/53, 65, 67</td>
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<td>400</td>
<td>40</td>
<td>132</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
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<td>N-HEXANE</td>
<td>110-54-3</td>
<td>11, 38, 49, 62/223</td>
<td>4</td>
<td>20</td>
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<td>3884</td>
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<td>XYLENE (MIXED ISOMERS)</td>
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<td>10, 20, 21, 38</td>
<td>2</td>
<td>50</td>
<td>62</td>
<td>164</td>
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<td>300</td>
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<td>175</td>
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Data gap
Summary

- Broaden focus beyond the chemistry of reactants
- Focus on the interaction of chemistries, synthetic route designs, and materials with technologies
- Start with replacements 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
Questions?

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Comparison of UV spectra of acetonitrile (neat), methanol (1/2 dilution with purified water), ethanol (1/2 dilution) and acetone (1/500 dilution).

Comparative separation of six test analytes

A Few Key Metrics are Essential

- Reaction Mass Efficiency (RME)
- No. of stages and no. of chemistry steps
- Total no. of solvents and solvents per stage
  - solvent is the biggest influence on mass
- Mass Intensity (PMI) and Mass Productivity (Efficiency)
- Materials of Concern
- Process life cycle environmental impact

Can we change the chemistry?
Telescope, maximize convergency, pay attention to order of side chain coupling
Recycle/reuse 80 – 90% of the mass!
Focus on optimizing use of a few key materials
Starting materials matter!