Green Chemistry Innovation and Opportunity in the Pharmaceutical and Specialty Chemical Industries

IGCW: Pharmaceutical Conference
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Outline

Pharma Supply Chain and Sustainability Risks
There are very real risks

Current Situation
It isn’t pretty

Design
You have to build it in

Innovation
Change is good

Opportunities
There are a lot of options

Industrial Roundtables
Implementing positive change
Outsourcing is typically driven by cost, need for flexibility, increasing capabilities of CMOs. For companies producing chemical APIs, 46% outsource more than half of their needs.
A few (of many) Sustainability Risks

- New products
- Price controls
- Pandemics
- Access to medicines
- Animal testing
- Clinical trial results transparency
- Product Safety
- Counterfeiting
- Generics
- Bioprospecting
- Diseases of the developing world
- Preferential pricing
- Informed Consent
- Sales practices
- Energy
- Genetic testing
- Climate Change
- Pharmaceuticals in the Environment
- Etc.
Current Batch Chemical Process Development Situation

- Generally large portfolio of products to manufacture
- Discovery synthesis routes require significant modifications or complete substitution to deliver multi-kilo supplies.
- Early route defined, followed by standard, routine optimisation of chemical processes.
- Historical focus on meeting quality specifications with related problems managed by external controls.
- Current focus on yield, CoG and number of steps.
- Mass productivities of 8 – 10 % are generally obtained for individual stages with an overall process mass productivity of 2 – 3%.
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 2%.

\[
\text{Green Chemistry} = \frac{\text{Yield}}{Yield}
\]
Is it Waste (E-factor) or Mass Intensity?

Relationship between E-Factor and MI:

\[ E_{\text{factor}} = \text{MI} - 1 \]

\[ \text{kg waste} = \text{kg input} - \text{kg API} \]

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

“Design is a signal of intention”

“Cradle to Cradle”
William McDonough
2002
A model for change – Supporting Innovation

Things could be better

I can see what might be done

I need a convincing demo

My best people can deliver

I know when to do this

I have the skill base to do regularly

The budgetary hurdle

This is the way I do things

Innovation progress

Effort
Sustainability Needs to be Designed into Products and Processes

• 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 the what and how of 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*. 
Pay Attention to the Whole Process

• Recognize and evaluate the trade-offs (e.g., reaction yield vs. isolated recovery vs. mass productivity)

• Operability and real-time control go hand-in-hand

• Evaluate the overall cost of running the process over time, not only reactor cost

• Integrate active ingredient production with formulation or delivery device process
Life Cycle Assessment – The very big picture

Raw material and energy consumption

R&D: Process Development
- Material Selection
- Hazard & Risk assessment

Resource Extraction
Raw Material Manufacture
Intermediate Products
Final Product

Emissions to air, water and land

Final Consumer Use
Store
Distribution

Sales and Marketing

Ultimate Ecological Fate

American Chemical Society
ACS Green Chemistry Institute®
**Key Learnings - LCI/A for an 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

- *WW treatment* does not significantly increase the overall life cycle profile.

- *Transport* contribution to overall impacts is low
Innovations are Needed Everywhere

The laboratory

- Development laboratories are full of batch equipment. They need to contain:
  - Plug-and-play continuous equipment
  - Infrastructure to feed, monitor, control, acquire data from continuous devices
  - Ubiquitous property and kinetic measurement capability

The chemist and the engineer

- Whole process thinking is needed
- New skill sets need to emerge with new ways of processing:
  - Existing “batch” skill sets are effective but restricted
  - Early and effective communication between chemist and engineer is essential to identify process options
  - Increased pressure on quantitative skills – newer process equipment designs are less forgiving
- New ways of developing and optimising processes are needed

Business processes

- Valuing process robustness and quality
- Valuing EHS benefits in DfM
- Planning development activities to allow for working faster
- Taking a portfolio vs. product perspective
- Innovation implies more technical decisions to be taken earlier

Other Resources

- Money/Investment to change!
- Equipment, Time and Information availability
- Software / modelling tools
- Complexity
Extend the envelope of available process conditions

Mass Transfer Performance
- Rotating Packed Bed
- Static Mixer
- Pulse Column
- Educter
- Jacketed Stirred Tank

Heat Transfer Performance
- Static Mixer/Plate Exchanger
- Loop Reactor
- Plate Exchanger
- Spinning Disc Reactor
- Microreactor
Key Message

Asking the right questions!

Avoid “the perfect uselessness of knowing the answer to the wrong question”

The Left Hand of Darkness

Ursula K. LeGuin

1969
Proposal – Shorter Term

• Education and Staff training to overcome ‘technique gap’

• Publicise case for financial benefits
  – Look at total cost (waste treatment, regulatory cost)
  – Develop different financial models that enable technology implementation

• Embedding best practice in development processes
  – Link to Design for Manufacture
  – Knowledge sharing
  – Process Analytical Technology

• A few key metrics

• Updating existing tools and guidance

• Identify and evaluate barriers to new chemistry/technology
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
• 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!
Proposal – Medium Term

• Routine design of more efficient processes;
• Incremental substitution of ‘good’ (greener) materials rather than avoiding ‘bad’ materials;
• Simpler (and easier) sustainable technology changes
• Easier technology transfer into manufacturing
• Routine process mass efficiencies for chemical processes on the order of 5 - 10%
• Protective of people and property;
• Life cycle impacts routinely considered
Target – Longer Term

• More efficient chemistries and processes that:
  – are lower cost,
  – consume less resource (mass productivities ~ 15 - 25% and less energy intensity) / unit of use,
  – utilise inherently less hazardous process chemicals,
  – create less waste that is minimally hazardous and with fewer life cycle environmental impacts.

• Improved profitability, and lower prices, to ensure greater access to products to meet the world’s needs;

• Use of renewable resources and biological systems.
Helping Business Become More Sustainable
ACS GCI Industrial Roundtables
ACS GCI Industrial Roundtables

Catalyzing and enabling the implementation of green chemistry and engineering in the global chemical enterprise

- Collaborate non-competitively
- Address technical challenges
- Develop decision-making tools
- Inform the research agenda
- Drive the use of good science in policy setting
- Influence through the supply chain
ACS GCI Pharmaceutical Roundtable

“…pharmaceutical corporations united by a shared commitment to integrate the principles of green chemistry and engineering into the business of drug discovery and production…”

**Strategic Priorities:**
Influencing Research Agenda ● Tools for Innovation ● Educating Leaders ● Global Collaboration

- Ex: Non-Pt Group Metal Catalysis
Creating New Science - Improving the Toolbox

• Communicating important process chemistry needs
  • Information on process chemistry articles of interest to industry
  • Key green engineering research areas for sustainable manufacturing
• Academic grants to achieve greener reaction mechanisms
  • Chiral amine synthesis
  • C-H activation of aromatics
  • OH Activation
  • Amide Reduction
  • Oxidations without chlorinated solvents
  • Grignard Reaction Research

$1.2 Million Since 2007
# Key Green Engineering Research Areas – from a Pharma Perspective

<table>
<thead>
<tr>
<th>Rank</th>
<th>Main Key Areas</th>
<th>Sub-areas/aspects</th>
<th>Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continuous Processing</td>
<td>Primary, Secondary, Semi-continuous, etc.</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Bioprocesses</td>
<td>Biotechnology, Fermentations, Biocatalysis, etc.</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Separation and Reaction Technologies</td>
<td>Membranes, crystallizations, etc.</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Solvent Selection, Recycle and Optimization</td>
<td>Property modeling, vaporization, recycling technologies, in-process control, regulatory aspects etc.</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Process Intensification</td>
<td>Technology, hybrid systems, etc</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Integration of Life Cycle Assessment (LCA)</td>
<td>Life cycle assessment, Total Cost Assessment, carbon footprint, etc.</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>Integration of Chemistry and Engineering</td>
<td>Business strategy, links with education, etc.</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Scale</td>
<td>Mass and energy transfer, Kinetics, and others</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Energy Intensity</td>
<td>Baseline for pharmaceuticals, estimation, energy optimization</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>Mass and Energy Integration</td>
<td>Process integration, Process Synthesis, Combined Heat and Power, etc</td>
<td>0</td>
</tr>
</tbody>
</table>
Tools & Resources

• Solvent Selection Guide
• Reagent Guide
• PMI Tool
• PMI-LCA Tool
• Electronic Laboratory Notebook
• Workshops
• Publications (Key Research Areas, Articles of Interest, etc.)
• Symposia
• Lecture tours
Decision-Making tools: Process Mass Intensity (PMI) Metric

Chemical Process

PMI = \frac{\text{quantity of raw materials input (kg)}}{\text{quantity of bulk API (product) out (kg)}}

- Reactants
- Reagents
- Solvents
- Catalysts
- Water
Why a Process Mass Intensity (PMI) Metric?

- **Performance** – Quantify the impact of innovations
  - Drive insights for future advances
  - Can’t improve if you don’t measure!

- **Transparency** - Increasing expectations on companies to characterize advances and demonstrate improvement

- **Benchmark** – Objective comparisons and communications
## PMI Calculator Tool

- Embedded calculations
- Only need to fill in amounts of reagents, solvents, and water
- Spreadsheet calculates step and overall PMI for linear sequences
- Calculates separate PMI for solvents, water, and reagents

Publicly available spreadsheet

www.acs.org/gci

Click on Industrial Innovation then ACS GCI Pharmaceutical Roundtable

### Process Step Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mass Substrate (kg)</td>
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<tr>
<td>Mass Reagents (kg)</td>
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</tr>
<tr>
<td>Mass Solvents (kg)</td>
<td>0</td>
</tr>
<tr>
<td>Mass Aqueous (kg)</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PMI</th>
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<tbody>
<tr>
<td>Step PMI</td>
<td></td>
</tr>
<tr>
<td>Step PMI Excluding H2O</td>
<td>#DIV/0!</td>
</tr>
<tr>
<td>Cumulative PMI</td>
<td>#DIV/0!</td>
</tr>
<tr>
<td>Cumulative PMI Excluding H2O</td>
<td>#DIV/0!</td>
</tr>
</tbody>
</table>
Process Mass Intensity

Median = 120 kg Material Use/kg API

- Total Solvents (excludes water)
- Total Reactants
- Total Other Process Materials
- Total Water
- Total Material Use
Composition of PMI: Pharma Benchmarking

2008 Data

- **Water**: 28%
- **Other**: 6%
- **Reactants**: 8%
- **Solvents**: 58%

**INSIGHTS:**
Demonstrated the importance of reducing the use and hazard of solvents.
Solvent Selection is a Key Metric for the Batch Chemical Industry

<table>
<thead>
<tr>
<th>Substance Information</th>
<th>Scoring Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety</td>
</tr>
<tr>
<td>Solvent Class</td>
<td>Solvent Name</td>
</tr>
<tr>
<td>Acid</td>
<td>ACETIC ACID</td>
</tr>
<tr>
<td>Acid</td>
<td>ACETIC ANHYDRIDE</td>
</tr>
<tr>
<td>Acid</td>
<td>FORMIC ACID</td>
</tr>
<tr>
<td>Acid</td>
<td>METHANE SULPHONIC ACID</td>
</tr>
<tr>
<td>Acid</td>
<td>PROPIONIC ACID</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1-BUTANOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1-PROPAHOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2-BUTANOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2-METHOXYETHANOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>BENZYL ALCOHOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>ETHANOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>ETHYLENE GLYCOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>ISOAMYL ALCOHOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>ISOBUTANOL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>ISOPROPYL ALCOHOL (IPA)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>METHANOL</td>
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<tr>
<td>Alcohol</td>
<td>T-BUTANOL</td>
</tr>
<tr>
<td>Aromatic</td>
<td>BENZENE</td>
</tr>
<tr>
<td>Aromatic</td>
<td>TOLUENE</td>
</tr>
</tbody>
</table>

Solvent Guide available for download at www.acs.org/gcipharmaaroundtable.
Venn Diagram for Reagent Selection

Wide Utility
Scalability
Greenness

Zone 1
Zone 2
Zone 3
Zone 4

Ideal – all 3 Desired characteristics
Informed choice
Less favored

Oxidation of Primary Alcohol to Aldehyde

Wide Utility
- PCC
- PDC
- IBX
- Dess-Martin periodidane
- TPAP/NMO
- DMSO/DCC (Pfitzner-Moffatt)

Scalability
- DMSO/TFAA
- DMSO/oxalyl chloride (Swern)
- Me₂S/Cl₂
- TEMPO/tcca
- PIPO/NaOCl
- TEMPO/NaOCl
- NiO₂
- BaMnO₄
- MnO₂
- Cl₂/py
- Air/TEMPO/water
- Air/metal(cat)
- Air/TEMPO/metal(cat)

Greenness
- Air/TEMPO/water
- Air/metal(cat)
- Air/TEMPO/metal(cat)

Conclusions

- The obstacles are large, but not insurmountable
- The Pharma and Specialties industries are uniquely suited to address a range of Sustainability risks and opportunities
- The economics favor the transition even if Sr. managers don’t know it yet
- To proactively promote sustainable chemical technologies the people promoting them may need a different set of skills than in the past, e.g., chemical synthesis, LCI/A, etc.
- Leadership is required
- Envisioning and communicating key Sustainability issues must be part of the business case
Questions?

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What does it take to achieve MP > 1?*

- RME must be > 25% for MP > 1%
- RME 15 – 25% gives a 40% chance of MP > 1%
- Having < 4 stages increases probability of achieving a MP > 1%

<table>
<thead>
<tr>
<th>stages</th>
<th>% probability of MP &gt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>&gt;6</td>
<td>15</td>
</tr>
</tbody>
</table>

*Based on about 40 mature R&D processes
Solvent Use is Significant

In 2008, 10 solvents represented approximately 80% of all solvents used and the solvent profile improved over the previous 5 years:

- Overall reduction of chlorinated solvents
- Dichloromethane use in final process down by 50% (kg/kg API)
- Toluene use down by 65% (kg/kg API)
- DMF use declined by 95% (kg/kg API)
- THF use increased by 60% (kg/kg API)
- Alcohol (MeOH, IPA, IMS/EtOH) use increased by 80% (kg/kg API)
- MIBK and EtOAc used as DCM replacements
- MeOH used as DMF replacement

Solvent use is the largest contributor to:

- Primary process mass intensity
- Primary manufacturing life cycle environment (~80% mass, ~75% energy)