Lessons learned through measuring green chemistry performance – The pharmaceutical experience

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http://chemistry.org/greenchemistryinstitute/pharma_roundtable.html

ACS Green Chemistry Institute Pharmaceutical Roundtable

Current Membership as of June 1, 2007

Lilly

gsk GlaxoSmithKline

Pfizer

Schering-Plough

MERCK

AstraZeneca
life inspiring ideas

Johnson & Johnson

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

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ACS Green Chemistry Institute Pharmaceutical Roundtable

- Mission:

  To catalyze the implementation of green chemistry and engineering in the pharmaceutical industry globally.

- Strategic Priorities
  - Informing and Influencing the Research Agenda
  - Tools for Innovation
  - Education Resource
  - Global Collaboration

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The Challenge

- Decreasing the amount of material used to make a drug is one of the major green chemistry challenges for the pharmaceutical industry

- ACS GCI Pharmaceutical Roundtable members have developed a common process mass intensity metric that allows data from each company to be compared on a transparent and equitable basis

Process Mass Intensity Metric

- Why have a common green chemistry metric definition?
  - Enable benchmarking
  - To be more transparent; basis for objective comparison
  - Define what's possible; drive change
  - Increasing expectations from internal and external audiences to describe progress, demonstrate improvement
  - Proactively establish metric

Process Mass Intensity Metric

Process mass intensity = $\frac{\text{quantity of raw materials input (kg)}}{\text{quantity of bulk API out (kg)}}$

Where:

Process is all steps of a synthetic path from commonly available materials to the final bulk active pharmaceutical

Raw Materials are all materials including water that are used directly in the process of synthesizing, isolating, and purifying the API salt

Bulk API out is the final salt form of the active ingredient that was produced in the synthesis, dried to the expected specification

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It is not the perfect metric; however,
•it is simple and easy to understand
•agreed by all members
-they will all work to it
-pretty good surrogate for measuring greenness

API is active pharmaceutical ingredient:

It is the final dried form of the active pharmaceutical ingredient.

Some products are salts or free base or free acid.

Commonly available starting material:

Example/Clarifications:

•A material that is not made specifically for this process

•Procurement can purchase this material without transfer of intellectual property.

•Commonly commercially available materials

Process Mass Intensity Metric

- Data from all 7 member companies has been collected as part of a benchmarking exercise
- Process mass intensities collected for compounds in the *development pipelines* at each company
  - Still time to influence the manufacturing of the next generation of drugs
- The result is a representative snapshot

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Data compiled here for small molecule pharmaceuticals (rather than biopharma fermentation type processes).

Process Mass Intensity Metric (PMI) in Context

Industry	E-factor	Annual Production tonnage
Oil Refining	*ca*. 0.1	10^6 - 10^8
Bulk Chemicals	<1 to 5	10^4 - 10^6
Fine Chemicals	5 to >50	10^2 - 10^4
Pharmaceuticals	25 to >100	10 – 10^3

R. A. Sheldon, *Chem. Ind*., **1997**, 12 – 15.
E-Factor = Total mass of materials required to produce 1kg product (mass intensity) – 1.

Process Mass Intensity Metric (PMI) in Context

Industry	E-factor	Annual Production tonnes	Total Waste tpa	No of transform-ations	Years of develop-ment
Oil Refining	*ca.* 0.1	10^6 - 10^8	10 million	Separations	100+
Bulk Chemicals	<1 to 5	10^4 - 10^6	5 million	1-2	10 – 50
Fine Chemicals	5 to >50	10^2 - 10^4	0.5 million	3-4	4 - 7
Pharmaceuticals	25 to >100	10 – 10^3	0.1 million	6+	3 - 5

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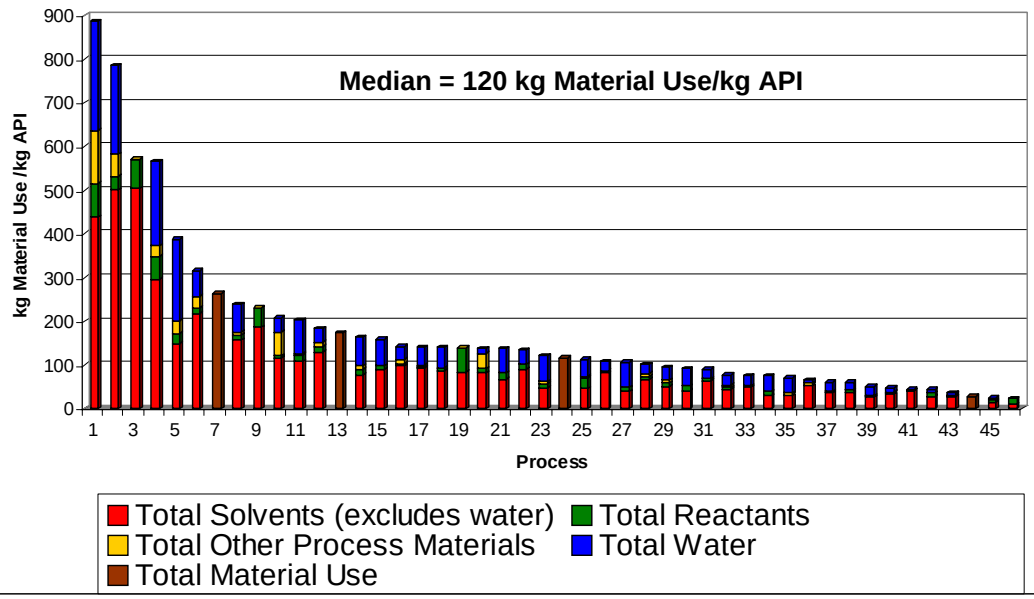
Total Waste tpa = Highest E-Factor x Largest Annual Production Volume

The last two columns were estimated for illustrative and discussion purposes only. These were not taken from a peer-reviewed publication.

Years of development is meant to illustrate the amount of time a process has been able to be optimized.

Process Mass Intensity



Maximum = 887 kg Material Use/kg API

Minimum = 23 kg Material Use/kg API

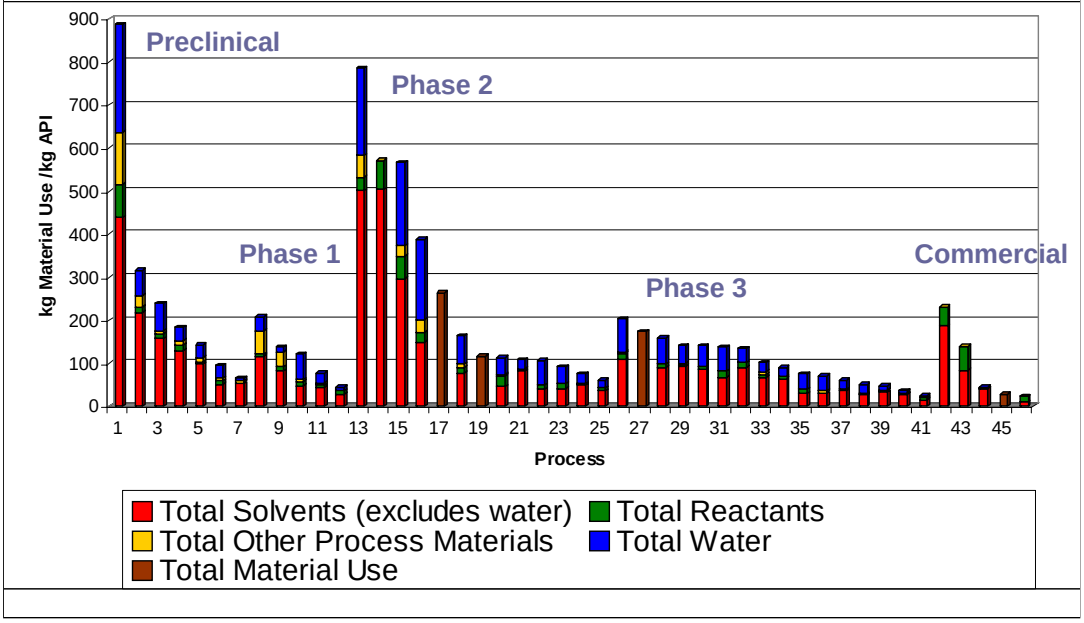
Median = 120 kg Material Use/kg API

Complexity data (# of steps/isolations) was not requested initially from the member companies. This is something we hope to include in the future.

For example, the process with the highest PMI illustrated is a complex 8+ step process.

The processes with the 4 highest PMI values are from 3 separate companies.

Process Mass Intensity



Maximum = 887 kg Material Use/kg API

Minimum = 23 kg Material Use/kg API

Median = 120 kg Material Use/kg API

Preclinical Median = 185 kg Material Use/kg API

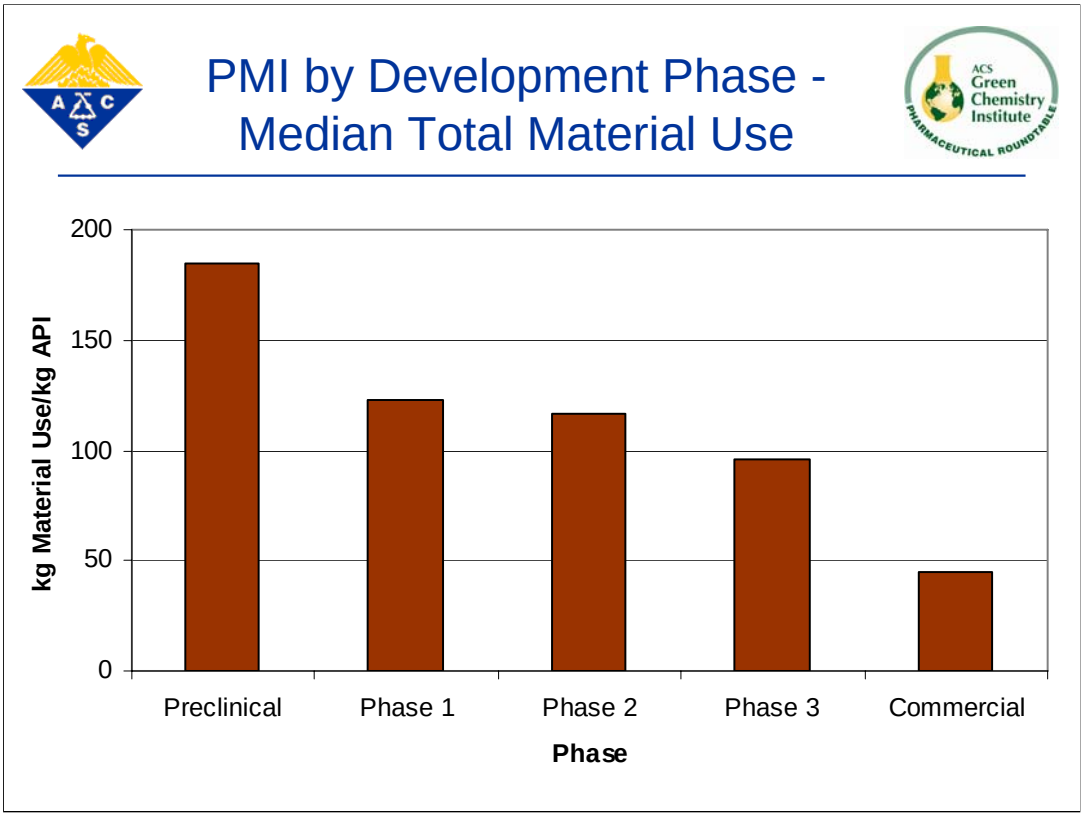
Phase 1 Median = 123 kg Material Use/kg API

Phase 2 Median = 117 kg Material Use/kg API

Phase 3 Median = 96 kg Material Use/kg API

Commercial Median = 45 kg Material Use/kg API

Acknowledge that Phase 1 data is a limited data set. All companies submitted a data set with no requirement for data from all phases.



Processes included in each phase:

Preclinical: 7

Phase 1: 5

Phase 2: 13

Phase 3: 16

Commercial: 5

Calculated median of the total material use (kg Material Use/ kg API) for each phase

Preclinical Median = 185 kg Material Use/kg API

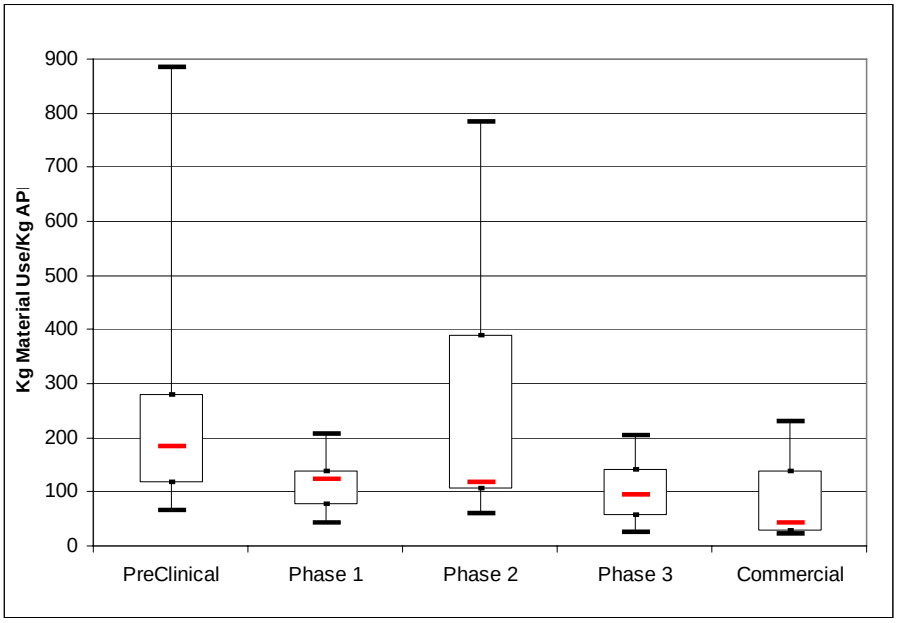
Phase 1 Median = 123 kg Material Use/kg API

Phase 2 Median = 117 kg Material Use/kg API

Phase 3 Median = 96 kg Material Use/kg API

Commercial Median = 45 kg Material Use/kg API

PMI by Development Phase



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Processes included in each phase:

Preclinical: 7

Phase 1: 5

Phase 2: 13

Phase 3: 16

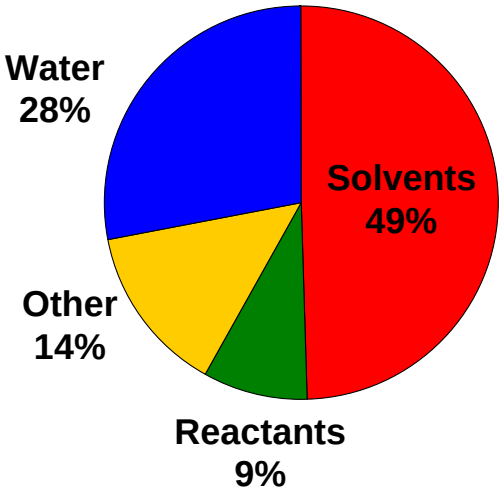
Commercial: 5

Red line = median

Box = 2nd and 3rd quartile

Whiskers are the 1st and fourth quartiles (the total range)

Composition of PMI



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

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Contributing factors:

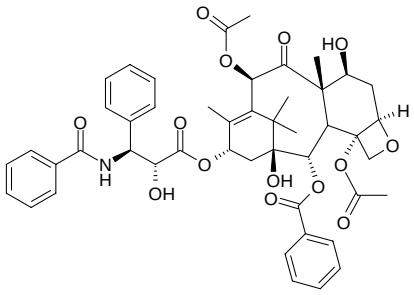
Stringent quality requirements

Stringent cleaning requirements

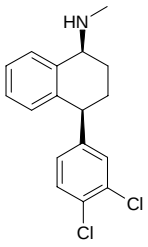
Lab scale technology is simpler and perhaps less efficient than manufacturing scale.

Total component contribution of the total PMI expressed in percent

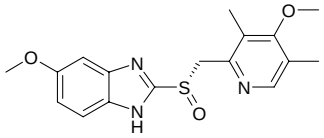
Molecular Complexity of Some Common Drugs



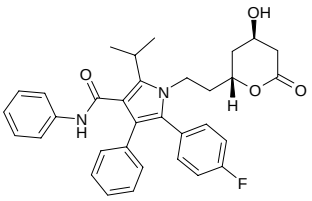
paclitaxel



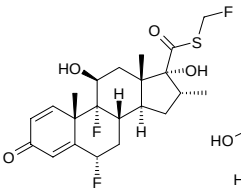
sertraline



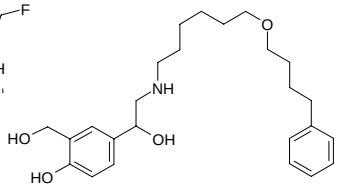
esomeprazole



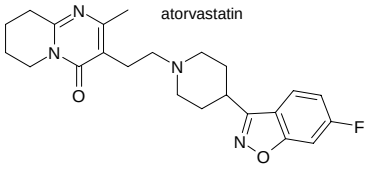
atorvastatin



fluticasone



salmeterol



risperidone

Conclusions

- Successful benchmarking exercise
- Data submitted from 7 companies useful for internal and external purposes
- The results of process development efforts can be seen in the PMI improvements
- Solvents and water are the largest contributions to mass intensity

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Individual companies use their own metrics. PMI is used for comparison across the companies.

Next Steps

- *Repeat* the benchmarking exercise periodically
- *Continually improve* the data set
  - Working towards improving consistency of data
  - Encouraging member companies to submit more data
- *Track improvements* in process mass intensity across the industry
- Use the *PMI data* to drive the industry to be greener
- *Work collaboratively* to set research challenges and to develop tools for continuous improvement

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Consistency of data will improve through inclusion of data back to commercially available starting materials, outsourced early steps, fuller data set from all phases, etc.

For additional information:

- Email gcipr@acs.org
- Call 202-872-6102
- Website: http://chemistry.org/greenchemistryinstitute/pharma_roundtable.html