American Chemical Society

ACS Green Chemistry Institute®

ACS GCI Pharmaceutical Roundtable's Convergent PMI* Calculator

*Process Mass Intensity

ACS GCI Pharmaceutical Roundtable

Mission:

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

ACS Chemistry for Life™

ACS Green Chemistry Institute®

Pharmaceutical Roundtable

ACS GCI Pharmaceutical Roundtable

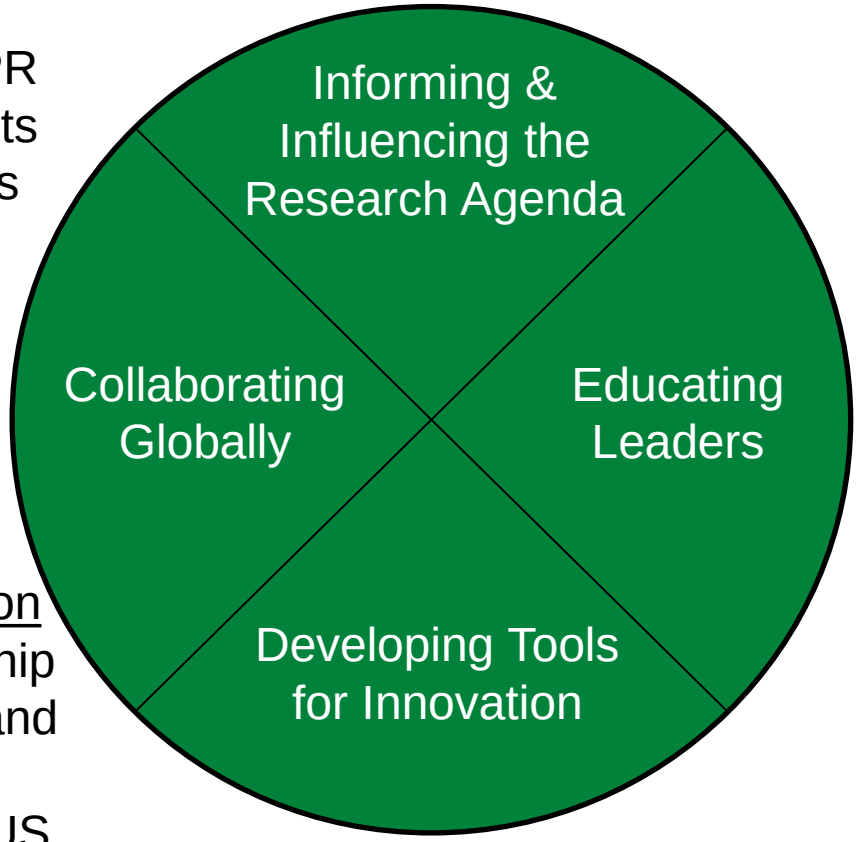
Membership as of Jan 1, 2014

No endorsement or approval by the ACS GCI Pharmaceutical Roundtable has been received or is in any way implied.

Strategic Priorities

Research

- $1.3 M in GCIPR Research Grants
- $1.2 M in grants leveraging government funding



Publications

- Green Chem Articles of Interest
- Key Research Areas
- Key Engineering Challenges

Global Collaboration

- Global membership
- Meetings in EU and US
- Lecture tours in US, EU, India

Tools/Resources

- Solvent Selection Guide
- PMI Tool
- GC in Electronic Lab Notebooks
- Organometallics in greener solvents

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

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

Where:

Process is all steps of a synthetic path from **commonly available materials** to the final bulk active pharmaceutical ingredient (API)

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

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

Why measure PMI?

- Drive change towards more sustainable/green manufacturing processes
  - Track environmental manufacturing footprint
  - Measurement of process efficiency

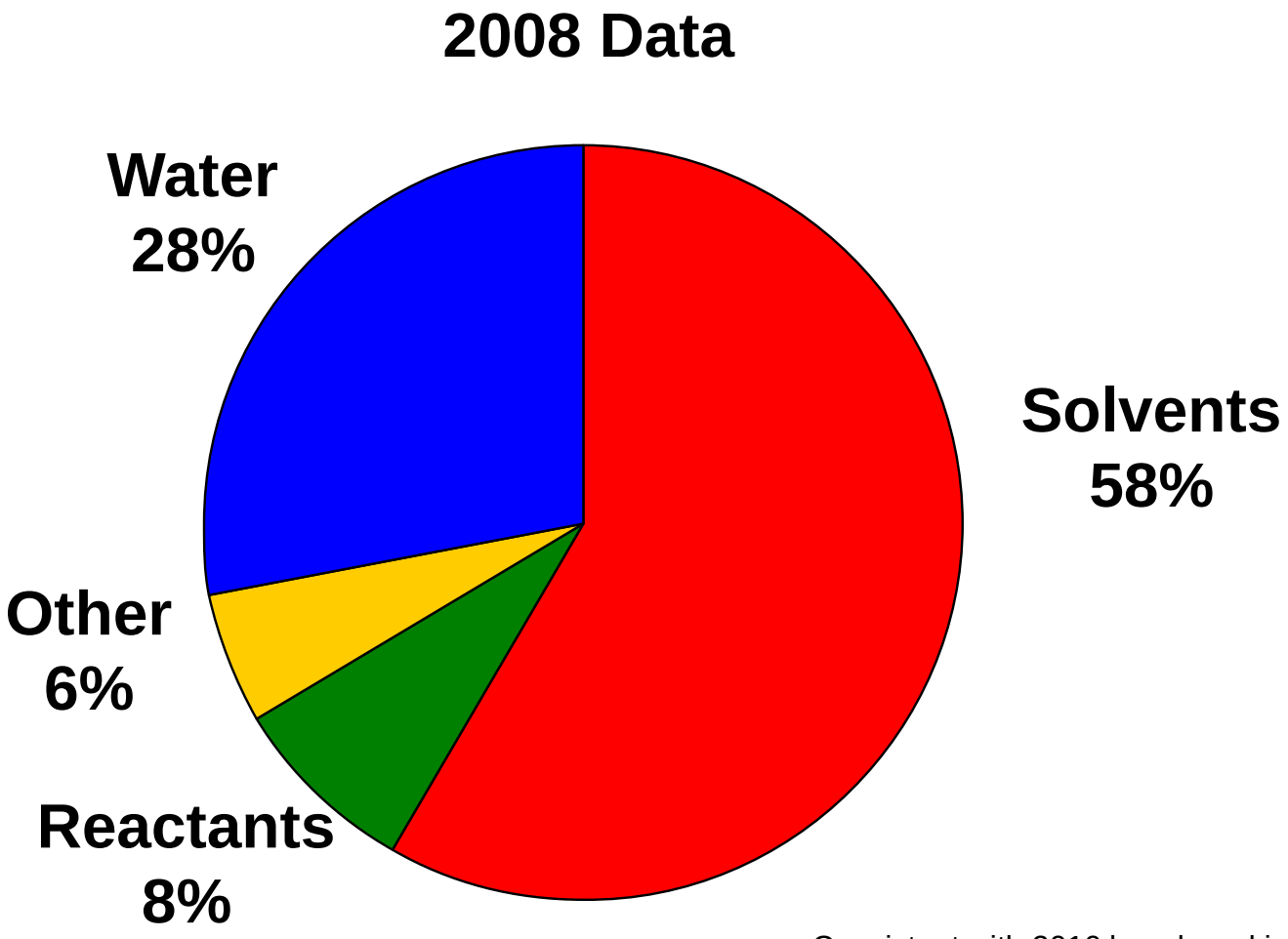
- Quantify improvements throughout process development life cycle

- To be more transparent; basis for objective comparison
  - Increasing expectations from internal and external audiences to describe progress, demonstrate improvement

- Benchmark
  - Allows a simple comparison to the on-going green efforts throughout the industry in the pursuit of mass efficient pharmaceutical processes.

- Insight in sustainability of overall manufacturing process, **from bulk chemicals to API**, is required.

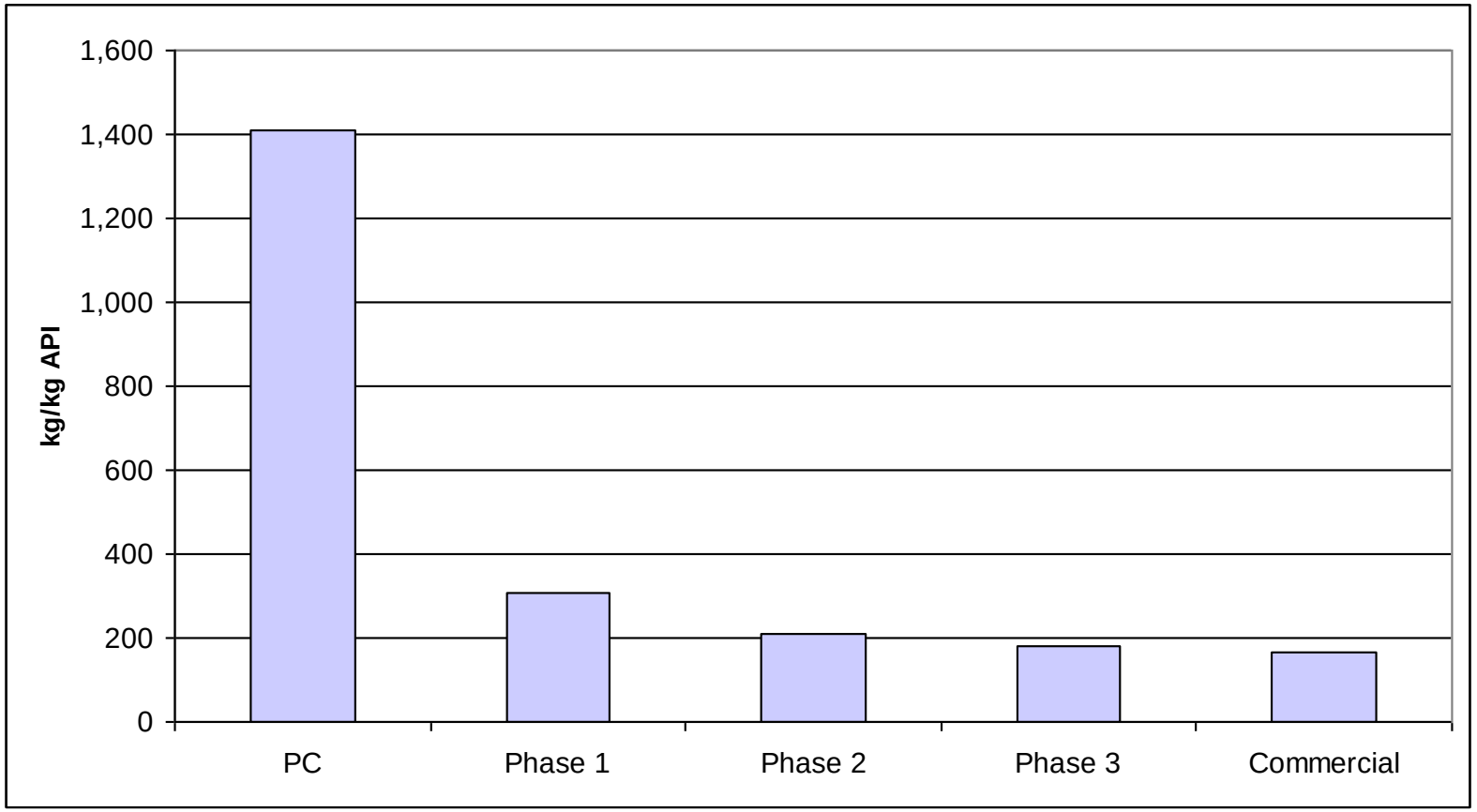
Composition of PMI—Pharma Benchmarking



Consistent with 2010 benchmarking data

PMI by Development Phase

Median Values - 2008



The Next Logical Step…
Involve Suppliers

- Measure PMI for all steps from commodity raw materials
- Use one tool for consistency across the industry

In 2011, the ACS GCI Pharmaceutical Roundtable released a free, publicly available linear PMI calculator.

In 2014, the ACS GCI Pharmaceutical Roundtable is releasing this free, publicly available convergent PMI calculator.

New Convergent PMI Calculator

Goals

- Enhance previous linear PMI calculator to accommodate convergent synthesis
- Maintain current design and methodology (calculations)

  -Thanks to Bill Pyrz and Merck
- Maximize simplicity
- Include instructions

Linear vs. Convergent

Linear PMI Calculations

$$\text{Step PMI} = \frac{\text{Substrate + Reagents + Solvent + Aqueous}}{\text{Assay Product}}$$

$$\text{Cumulative PMI} = \frac{\text{(Substrate * Cumulative PMI Substrate) + Reagents + Solvent + Aqueous}}{\text{Assay Product}}$$

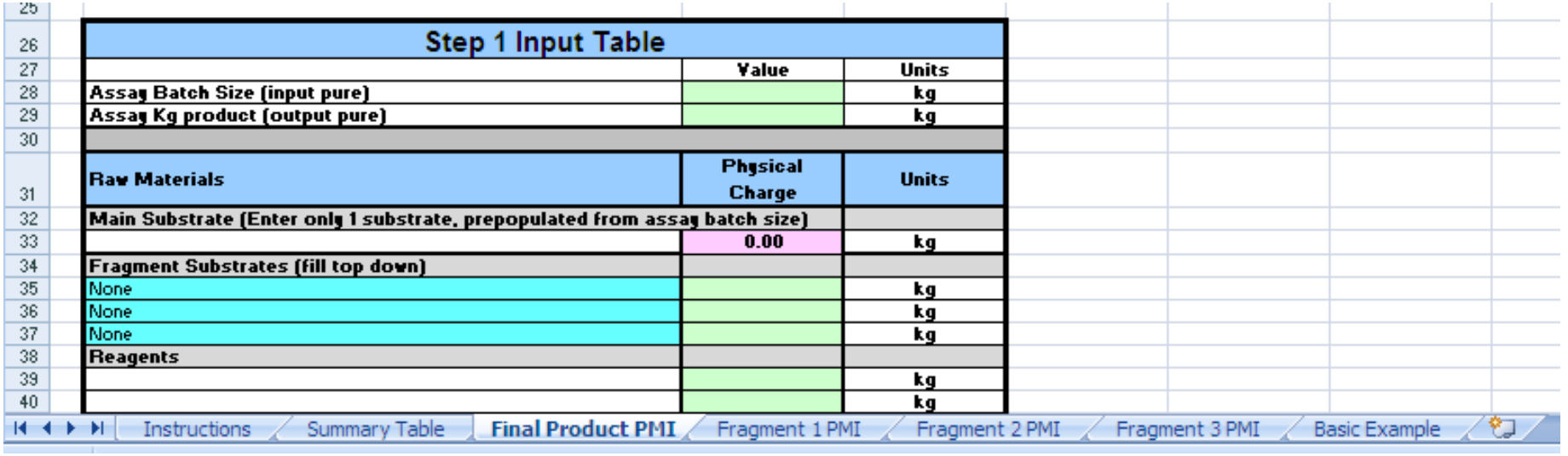
Convergent PMI Calculations

$$\text{Step PMI} = \frac{\text{Substrate + Fragment + Reagents + Solvent + Aqueous}}{\text{Assay Product}}$$

$$\text{Cumulative PMI} = \frac{\text{(Substrate * Cumulative PMI Substrate) + (Fragment * Fragment PMI) + Reagents + Solvent + Aqueous}}{\text{Assay Product}}$$

Convergent PMI Calculator—Layout

- Workbook consists of 7 worksheets
  - Instructions
  - Summary Table
  - Final Product PMI
  - Fragment 1 PMI
  - Fragment 2 PMI
  - Fragment 3 PMI
  - Basic Example



Step 1 Input Table		
	Value	Units
Assay Batch Size (input pure)		kg
Assay Kg product (output pure)		kg
Raw Materials	Physical Charge	Units
Main Substrate (Enter only 1 substrate, prepopulated from assay batch size)		
	0.00	kg
Fragment Substrates (fill top down)		
None		kg
None		kg
None		kg
Reagents		
		kg
		kg

Instructions | Summary Table | Final Product PMI | Fragment 1 PMI | Fragment 2 PMI | Fragment 3 PMI | Basic Example

Convergent PMI Calculator—Final Product

- Simplified input table
- Single cell for main substrate
- Dropdown for fragment substrates
  - Enables convergences
- Color coded cells
  - Only green require values
- Solutions of substrates and products
  - Now manual (instructions included)

Step 1 Input Table		
	Value	Units
Assay Batch Size (input pure)		kg
Assay Kg product (output pure)		kg
Raw Materials	Physical Charge	Units
Main Substrate (Enter only 1 substrate, prepopulated from assay batch size)		
	0.00	kg
Fragment Substrates (fill top down)		
None		kg
None		kg
None		kg
Reagents		
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
Solvents		
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
Aqueous		
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg

Convergent PMI Calculator—Step Metrics Table

Color coded cells

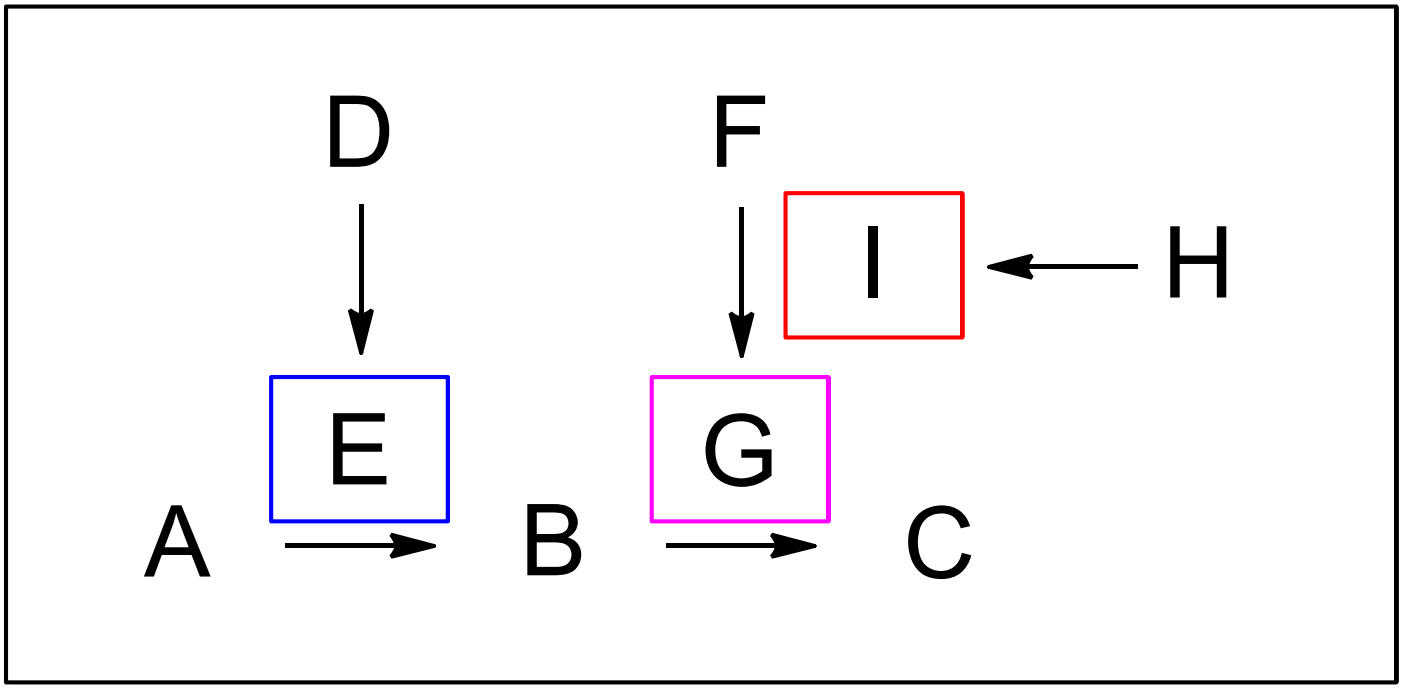
- Calculations unchanged from linear calculator
  -Except to allow for convergence

Step 1 Metrics Table	
Mass Substrate (kg)	1
Mass Reagents (kg)	1
Mass Solvents (kg)	13
Mass Aqueous (kg)	5
Step PMI	10.0
Step PMI Substrate, Reagents, Solvents	7.5
Step PMI Substrates and Reagents	1.0
Step PMI Solvents	6.5
Step PMI Water	2.5
Cumulative PMI	10.0
Cumulative PMI Substrate, Reagents, Solvents	7.5
Cumulative PMI Substrates and Reagents	1.0
Cumulative PMI Solvents	6.5
Cumulative PMI Water	2.5

Convergent PMI Calculator—Capabilities

- Up to 11 step linear sequence
- Up to 3 branches for convergent synthesis
    - 11 steps per branch
- Multiple branch points possible in a single step
- Branches can be further branched
- Up to 44 step linear sequence if treating additional steps as branches
    - Explained in instructions

Convergent PMI Calculator—Example



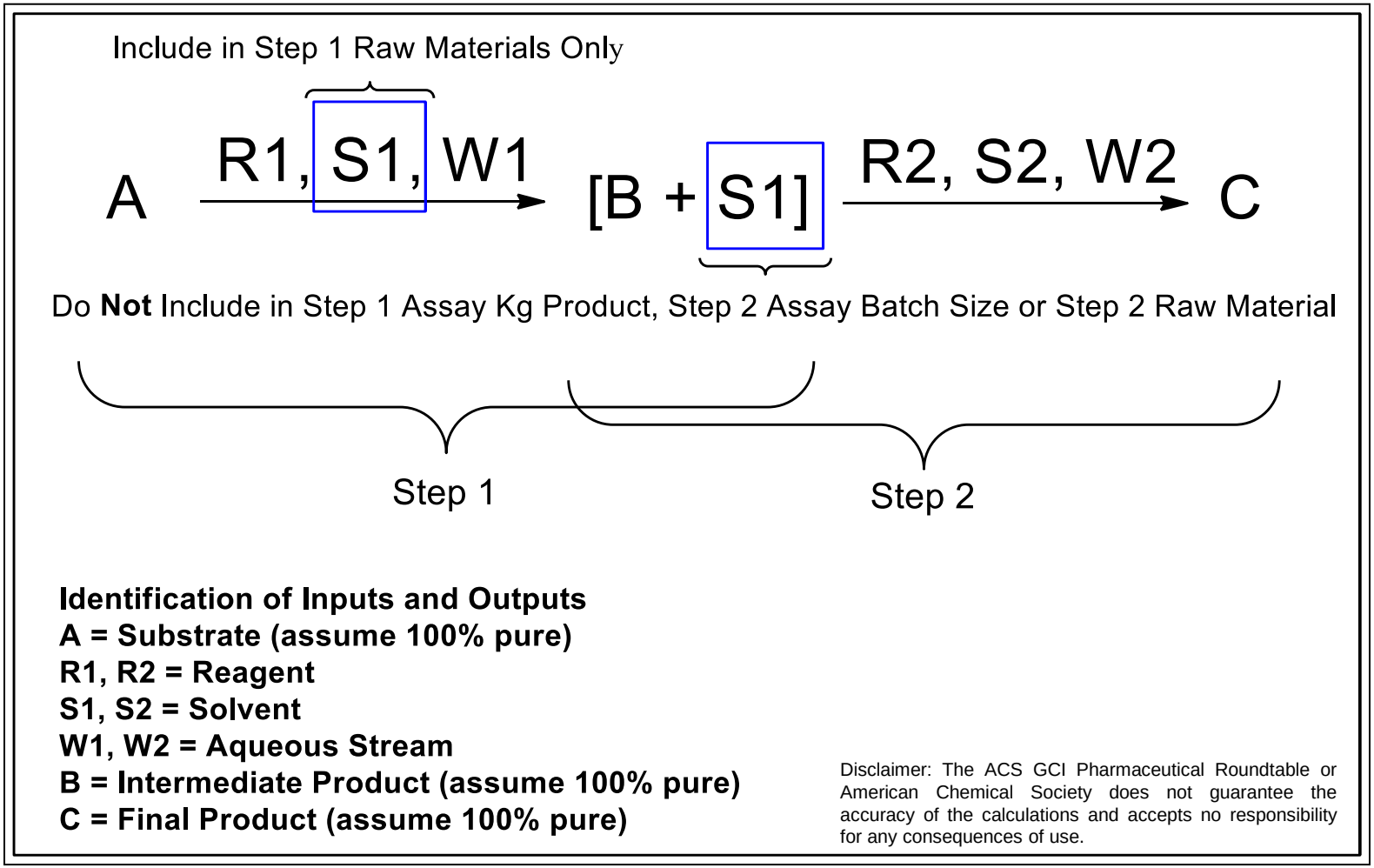
View spreadsheet for calculated example →

Microsoft Excel Worksheet

Disclaimer: The ACS GCI Pharmaceutical Roundtable or American Chemical Society does not guarantee the accuracy of the calculations and accepts no responsibility for any consequences of use.

Convergent PMI Calculator

Use of Solutions of Products and Substrates



Identification of Inputs and Outputs
A = Substrate (assume 100% pure)
R1, R2 = Reagent
S1, S2 = Solvent
W1, W2 = Aqueous Stream
B = Intermediate Product (assume 100% pure)
C = Final Product (assume 100% pure)

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Going Forward

- Encouraging suppliers to calculate and provide PMI data

  - For all APIs and API intermediates
  - At all stages of development
  - Include breakdown of solvent, reagents, and water PMI

Find the Convergent PMI Calculator Tool at
www.acs.org/gcipharmaroundtable

Questions or comments, email: gcipr@acs.org

Any comments, suggestions, or questions are great appreciated.

Thank you!

gcipr@acs.org

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