Useful Green Chemistry Metrics

- *Scientific Update webinar*
- *September 4th, 2019*
- *Speakers: Stefan G. Koenig, Ph.D.*
  Erin M. O'Brien, Ph.D.

https://iqconsortium.org/

https://acsgcipr.org/

Outline

Intro to Green Chemistry

Discussion of current metrics: PMI, cEF

How Green is your process? *Check iGAL!*

Conclusions

Why should we care about Green Chemistry?

The global emphasis on sustainability is expected to continue to intensify and the pharmaceutical industry should find ways to meet patient needs via sustainable manufacturing technology to minimize its environmental footprint

Why Apply Green Chemistry?

In terms of waste……

PHARMACEUTICAL & GENERICS INDUSTRIES MAY PRODUCE ≥ 100 MILLION KG APIS PER YEAR *1

EF ≥ 150 KG WASTE PER KG API (> 99.3%) →

≥ **15 BILLION KG** OF CO-PRODUCED **WASTE**

ANNUAL WASTE DISPOSAL COST OF ~ **$30 BILLION**

OPPORTUNITY FOR INDUSTRY TO UTILIZE **GREEN CHEMISTRY** TO TRIM BOTH PROCESS INPUTS AND WASTE, AND **CREATE $ BILLIONS IN ECONOMIC, ENVIRONMENTAL, AND SOCIAL VALUE**

*1 B. W. Cue, (2012) Green Chemistry Strategies for Medicinal Chemists, in Green Techniques for Organic Synthesis and Medicinal Chemistry (eds. Zhang, W., and Cue, B. W.). John Wiley & Sons, Chichester, UK.

API – active pharmaceutical ingredient, KG – kilogram, EF – environmental impact factor, $ - dollars

What is Green Chemistry?

Innovation aimed at design, development, and implementation of …

chemical products, reactions, and processes that …

minimize hazardous substances and are inherently safe …

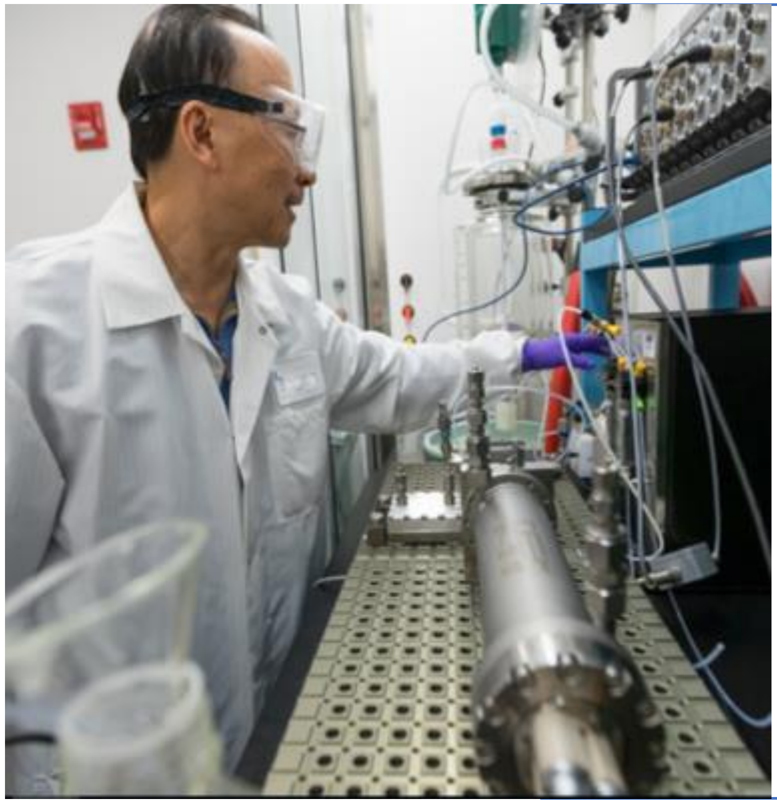
reduce waste and environmental footprint, while …

improving efficiency and economics

Noyori - "…green chemistry is not just a catchphrase. It is an indispensable principle of chemical research that will sustain our civilized society in the twenty-first century and further into the future."

R. Noyori, Synthesizing our future, *Nature Chemistry*, 2009, **1**, 5-6.

Green Chemistry = Efficient Process



- innovative chemical methodologies and new manufacturing platforms;
- consolidation of high-yielding reactions into a minimal number of unit operations with common solvents and limited intermediate isolations;
- vertical integration of advanced starting materials prepared from commodity chemicals (use of feedstock chemicals).

B. Frank Gupton and D. Tyler McQuade *Organic Process Research & Development* **2019** *23* (5), 711-715

Evolution of Green Chemistry

1956
Woodward: Synthetic Design *1

1970
United States Environmental Protection Agency founded
- EPA

1992
Sheldon: E factor *2

1997
Green Chemistry Institute (GCI)
- launched, integrated into ACS in 2001

1998
Anastas & Warner
- "Green Chemistry: Theory & Practice" *3

2011
ACS GCI PR established Process Mass Intensity (PMI)

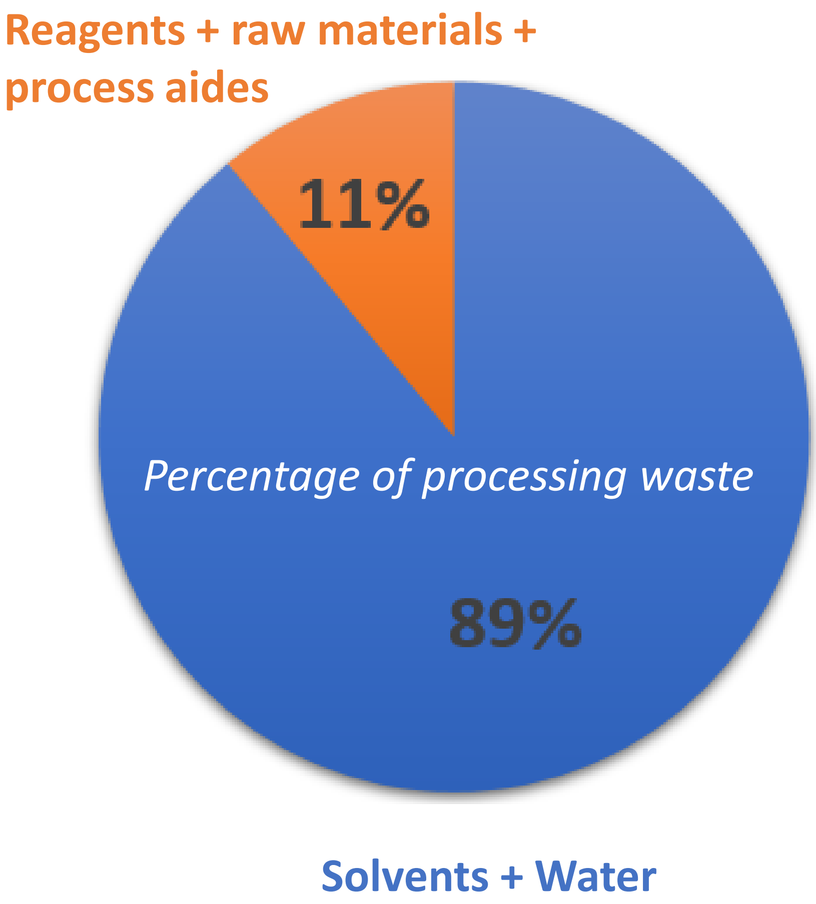
2017
Firms in IQ, ACS GCI PR & Sheldon, launched first green manufacturing goal
- Green Aspiration Level (GAL) supplemented by the Green Scorecard*4

*1 R. B. Woodward, *Perspectives in Organic Chemistry*, Interscience, 1956, pp. 155–184.
*2 R. A. Sheldon, Organic synthesis; past, present and future. *Chem. Ind. (London)*, 1992, 903-906.
*3 P. T. Anastas & J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, 1998.
*4 F. Roschangar et al. *Green Chemistry*, 2017, **19**, 281.

Selection Guides

- Multiple selection guides available
- Solvent selection guides
  - ACS GCI Pharmaceutical Roundtable (free of charge)
    - Safety, health and environmental impact of solvents
    - Other solvents guides from major pharmaceutical companies are also available online
- Reagents guide
  - Green conditions for common transformations (e.g. amide formation, oxidation, etc.)
  - GSK (*Green Chem*. **2013**, *15*, 1542-1549)
  - ACS GCI Pharmaceutical Roundtable (free of charge)

  - www.acs.org/gcipharmaroundtable



Green Chem. **2017**, **19**, 281–285

Table 1: CHEM21 solvent guide: ethers, hydrocarbons, halogenated

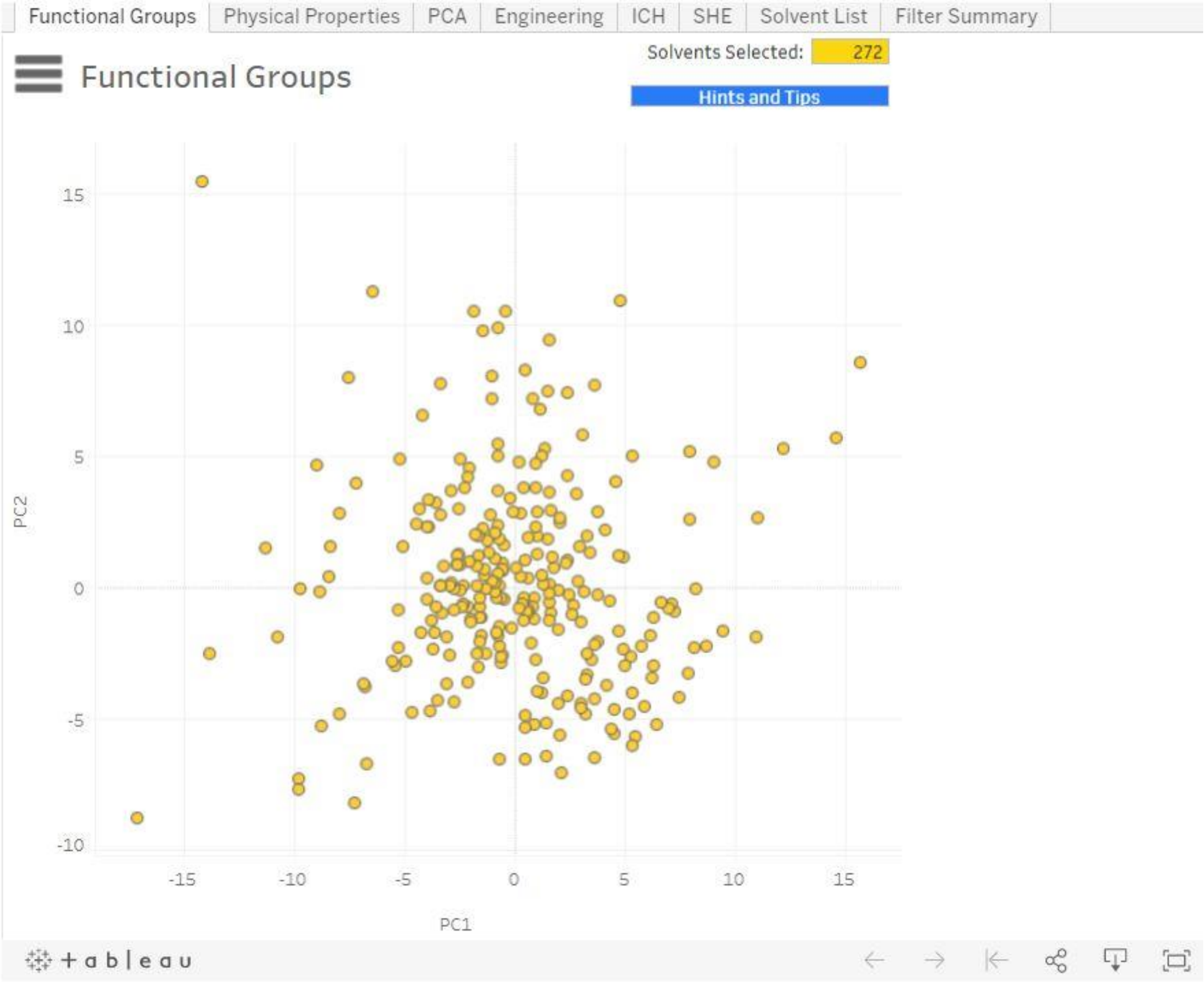
Family	Solvent	CAS	BP (°C)	FP (°C)	Worst H3xx*	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion #
Ethers	Diethyl ether	60-29-7	34	-45	H302	none	10	3	7	Hazardous	Highly hazardous
	Diisopropyl ether	108-20-3	69	-28	H336	none	9	3	5	Hazardous	Hazardous
	MTBE	1634-04-4	55	-28	H315	none	8	3	5	Hazardous	Hazardous
	ETBE	637-92-3	72	-19	H336	none	7	3	3	Problematic	Problematic
	TAME	994-05-8	86	-7	H302	none	6	2	3	Recommended	Recommended
	CPME	5614-37-9	106	-1	H302	H412	7	2	5	Problematic	Problematic
	THF	109-99-9	66	-14	H351	none	6	7	5	Problematic	Problematic
	Me-THF	96-47-9	80	-11	H318	none	6	5	3	Problematic	Problematic
	1,4-Dioxane	123-91-1	101	12	H351	none	7	6	3	Problematic	Hazardous
	Anisole	100-66-3	154	52	none	none	4	1	5	Problematic	Recommended
	DME	110-71-4	85	-6	H360	none	7	9	3	Hazardous	Hazardous
	Pentane	109-66-0	36	-40	H304	H411	8	3	7	Hazardous	Hazardous
	Hexane	110-54-3	69	-22	H361	H411	8	7	7	Hazardous	Hazardous
	Heptane	142-82-5	98	-4	H304	H410	6	2	7	Problematic	Problematic
	Cyclohexane	110-82-7	81	-17	H304	H410	6	3	7	Problematic	Problematic
	Me-Cyclohexane	108-87-2	101	-4	H304	H411	6	2	7	Problematic	Problematic

Solvent Guides

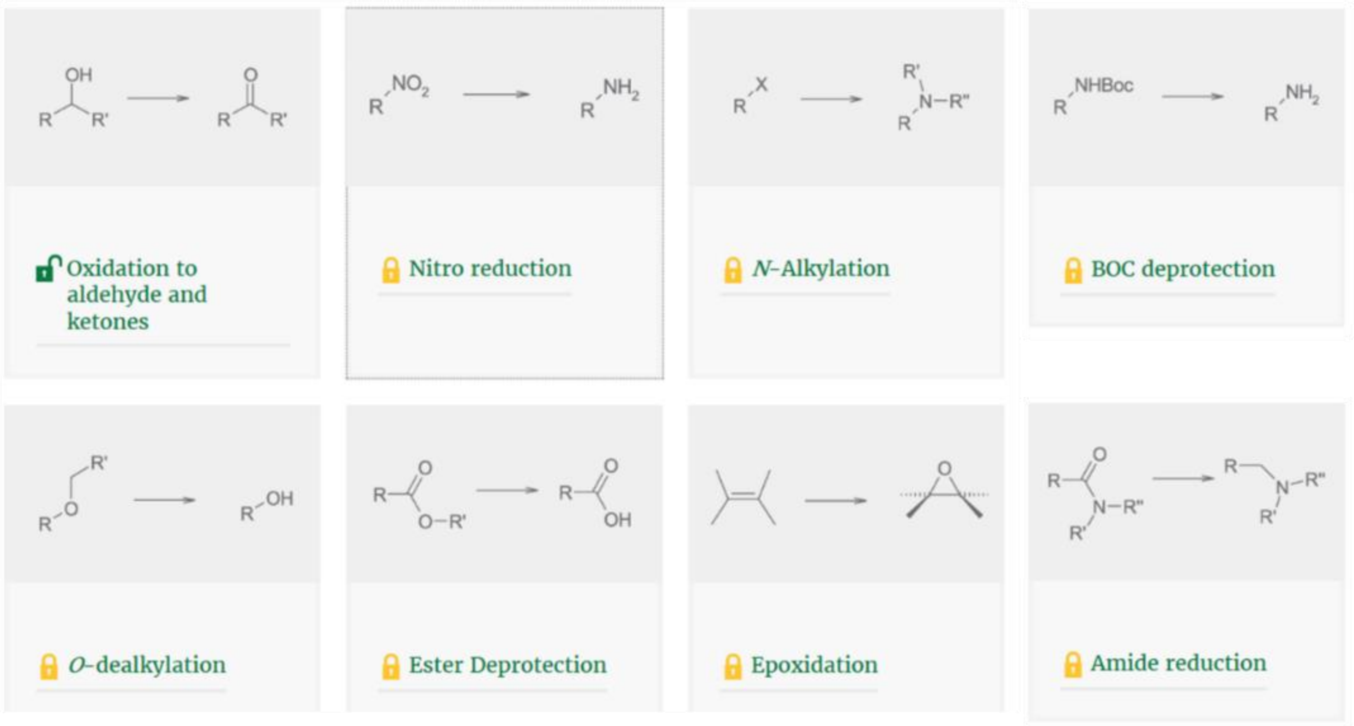
- Solvent & water contribute >85% to the process mass intensity PMI
- Great need to reduce use and hazard of solvents

Solvent Selection Tool

- **acsgcipr.org/tools-for-innovation-in-chemistry**
- Select solvents based on molecular and physical properties, EH&S characteristics, ICH guidelines and more.
- 272 Solvents in data set
- Interactive visualizations



Reagent Guides



Bromination
Fluorination
Chlorination
Iodination
Metals Removal
Chiral Hydrogenation
Oxidation to Acids
Suzuki Rxn
Buchwald-Hartwig Rxn

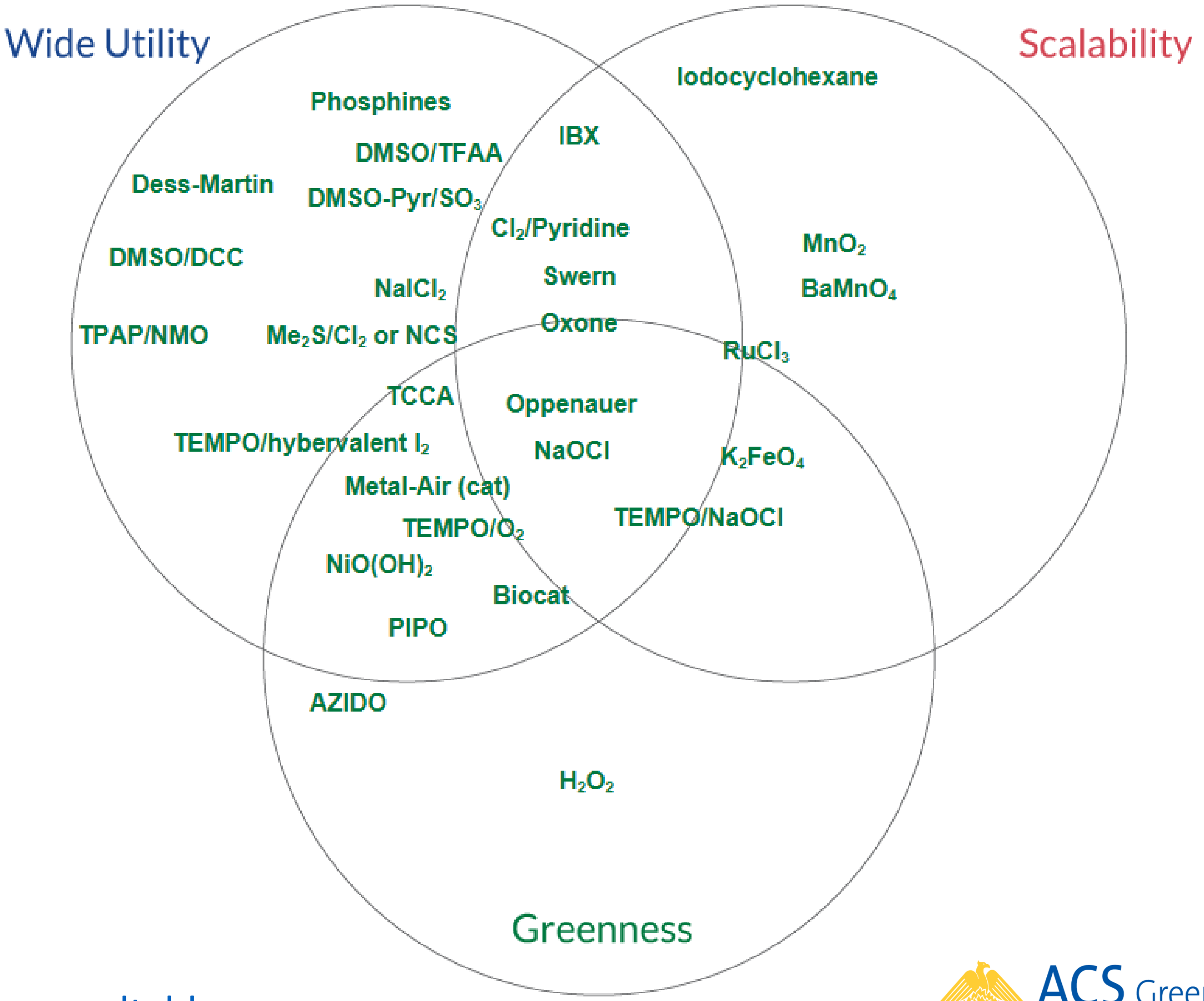
www.acs.org/gcipharmaroundtable

ACS Green Chemistry Institute
Pharmaceutical Roundtable

Oxidation to aldehydes and ketones

Reagent Guides

Venn Diagram



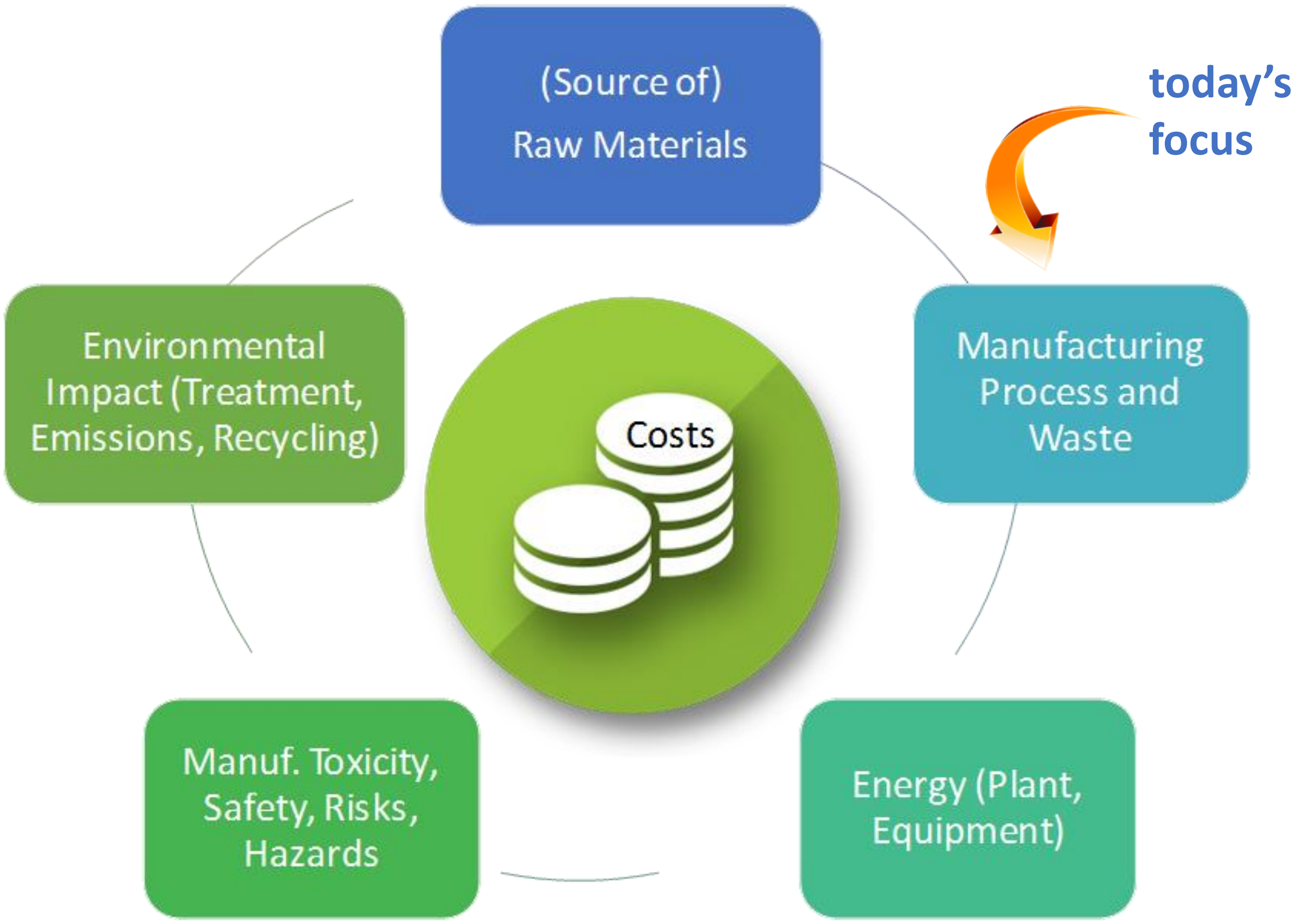
www.acs.org/gcipharmaroundtable

ACS Green Chemistry Institute
Pharmaceutical Roundtable

Manufacturing Components

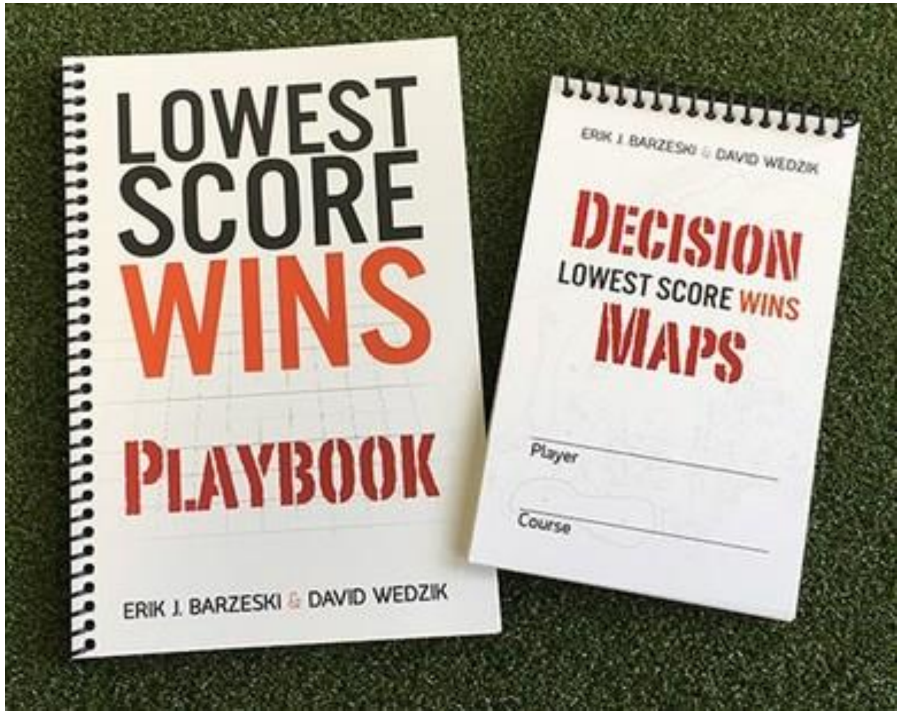
Life Cycle Assessment *[1]

- Solvent selection
- Reagent selection
- Sustainable metals
- Carbon footprint
- Waste treatment



*1 C. Jiménez-González and M. R. Overcash, The Evolution of Life Cycle Assessment in Pharmaceutical and Chemical Applications – a Perspective, *Green Chem.*, 2014, **16**, 3392–3400.

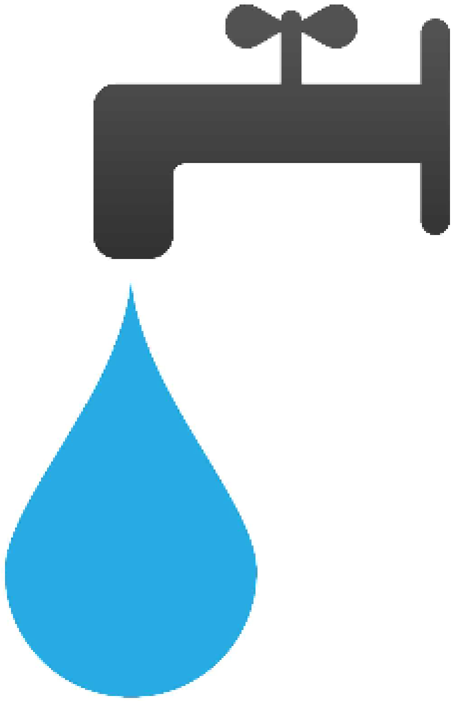
Metrics: You can't improve what you don't measure!



Google images: https://www.google.com/search?as_st=y&tbm=isch&as_q=lowest+score+wins; flickr.com

Green Metrics

Metric	Abbreviation	Formula	Optimum Value
Resource Efficiency			
Chemical Yield	CY	$\frac{m(Product) \times MW(Raw\ Material) \times 100}{m(Raw\ Material) \times MW(Product)}$	100%
Atom Economy	AE	$\frac{MW(Product) \times 100}{\sum MW(Raw\ Materials) + \sum MW(Reagents)}$	100%
Environmental Impact Factor	E factor	$\frac{\sum m(Input\ Materials\ excl.Water) - m(Product)}{m(Product)}$	$0\ \frac{kg}{kg}$
Effective Mass Yield	EMY	$\frac{m(Product) \times 100}{\sum m(Raw\ Materials) + \sum m(Reagents)}$	100%
Mass Intensity	MI	$\frac{\sum m(Input\ Materials\ excl.Water)}{m(Product)}$	$1\ \frac{kg}{kg}$
Reaction Mass Efficiency	RME	$\frac{m(Product) \times 100}{\sum m(Raw\ Materials)}$	100%
Carbon Efficiency	CE	$\frac{m(Carbon\ in\ Product) \times 100}{\sum m(Carbon\ in\ Raw\ Materials)}$	100%
Mass Productivity	MP	$\frac{m(Product) \times 100}{\sum m(Input\ Materials\ excl.Water)} = \frac{100}{MI}$	100%
Process Mass Efficiency	PME	$\frac{m(Product) \times 100}{\sum m(Input\ Materials\ incl.Water)} = \frac{100}{PMI}$	100%
Process Mass Intensity	PMI	$\frac{\sum m(Input\ Materials\ incl.Water)}{m(Product)}$	$1\ \frac{kg}{kg}$
Reaction Mass Intensity	RMI	$\frac{\sum m(Raw\ Materials) + \sum m(Reagents)}{m(Product)} = \frac{1}{EMY}$	$1\ \frac{kg}{kg}$
Optimum Efficiency	OE	$\frac{RME \times 100}{AE}$	100%
simple E factor	sEF	$\frac{\sum m(Raw\ Materials) + \sum m(Reagents) - m(Product)}{m(Product)} = RMI - 1$	$0\ \frac{kg}{kg}$
complete E factor	cEF	$\frac{\sum m(Input\ Materials\ incl.Water) - m(Product)}{m(Product)} = PMI - 1$	$0\ \frac{kg}{kg}$



FREE PMI CALCULATOR *[1]

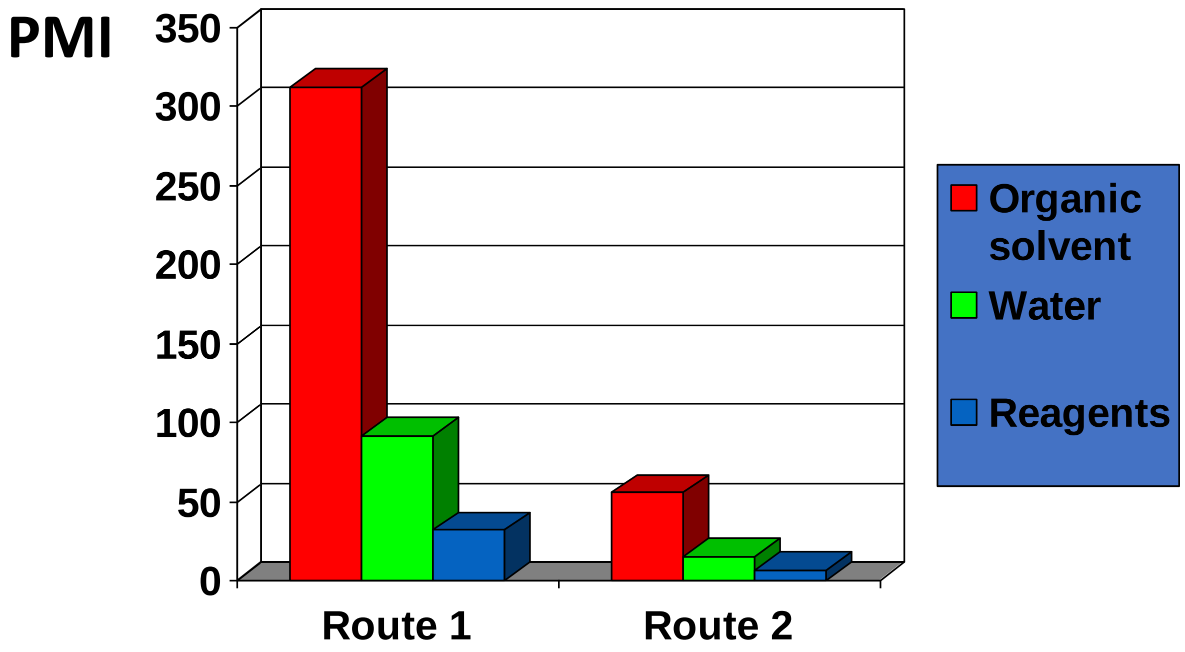
Process Mass Intensity

Considers all process materials including water and workup chemicals

$$PMI = \frac{\sum m(Input\ Materials\ incl.Water)}{m(Product)}$$

*1 Available from: https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html.

Example of route change between Phase 1 and Phase 2



7 steps 3 steps

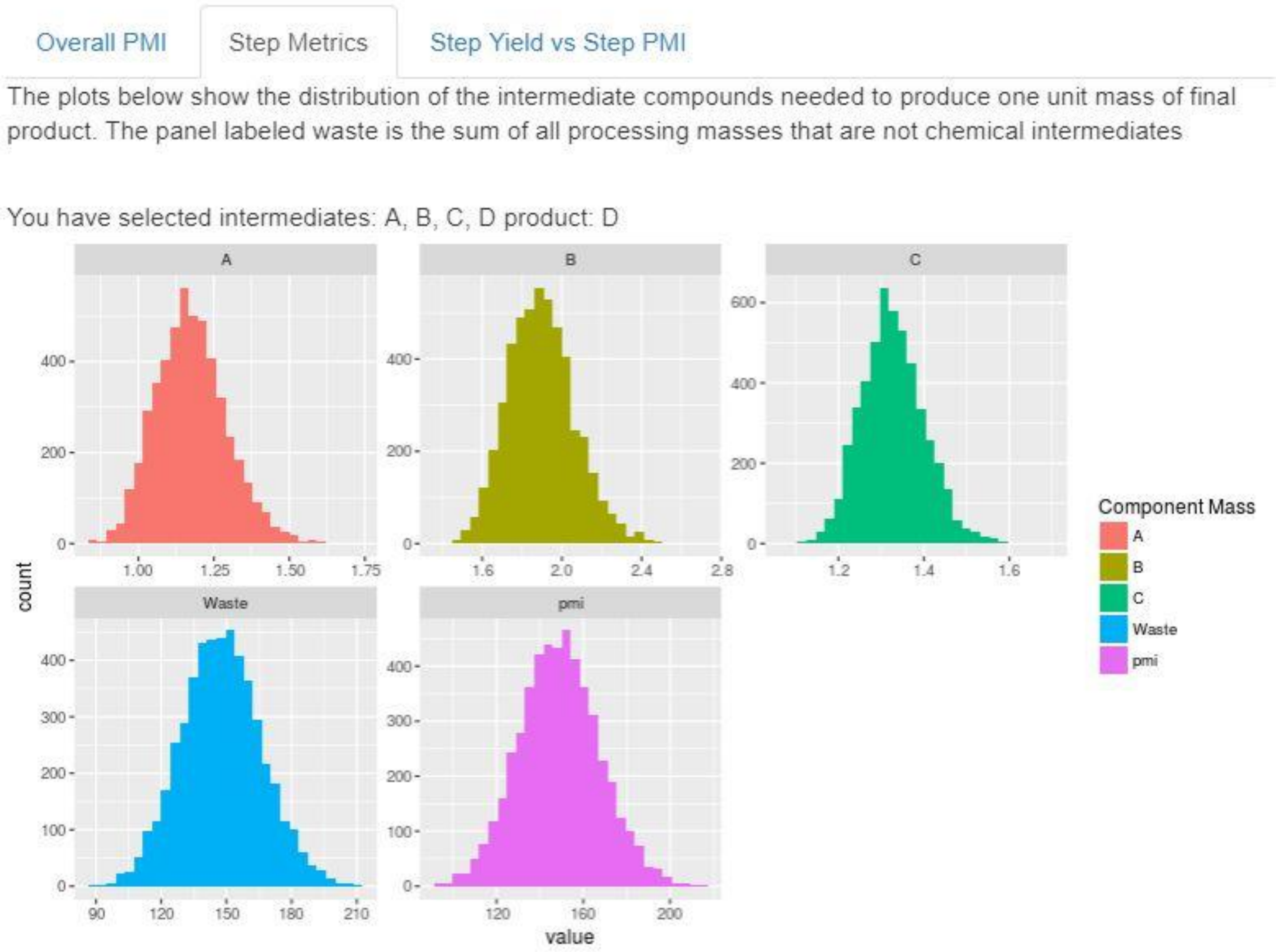
Reduce steps, reduce solvent, reduce # of isolations

= Cost of molecule drops by 80%

PMI Prediction Tool

- **acsgcipr.org/tools-for-innovation-in-chemistry**

- Predicts a range of probable process efficiencies of proposed synthetic routes
- Uses historical PMI data from pharma companies and predictive analytics (Monte Carlo simulations) to estimate the probable PMI ranges
- Assess and compare potential route changes



*1 Available from: https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html.

cE factor

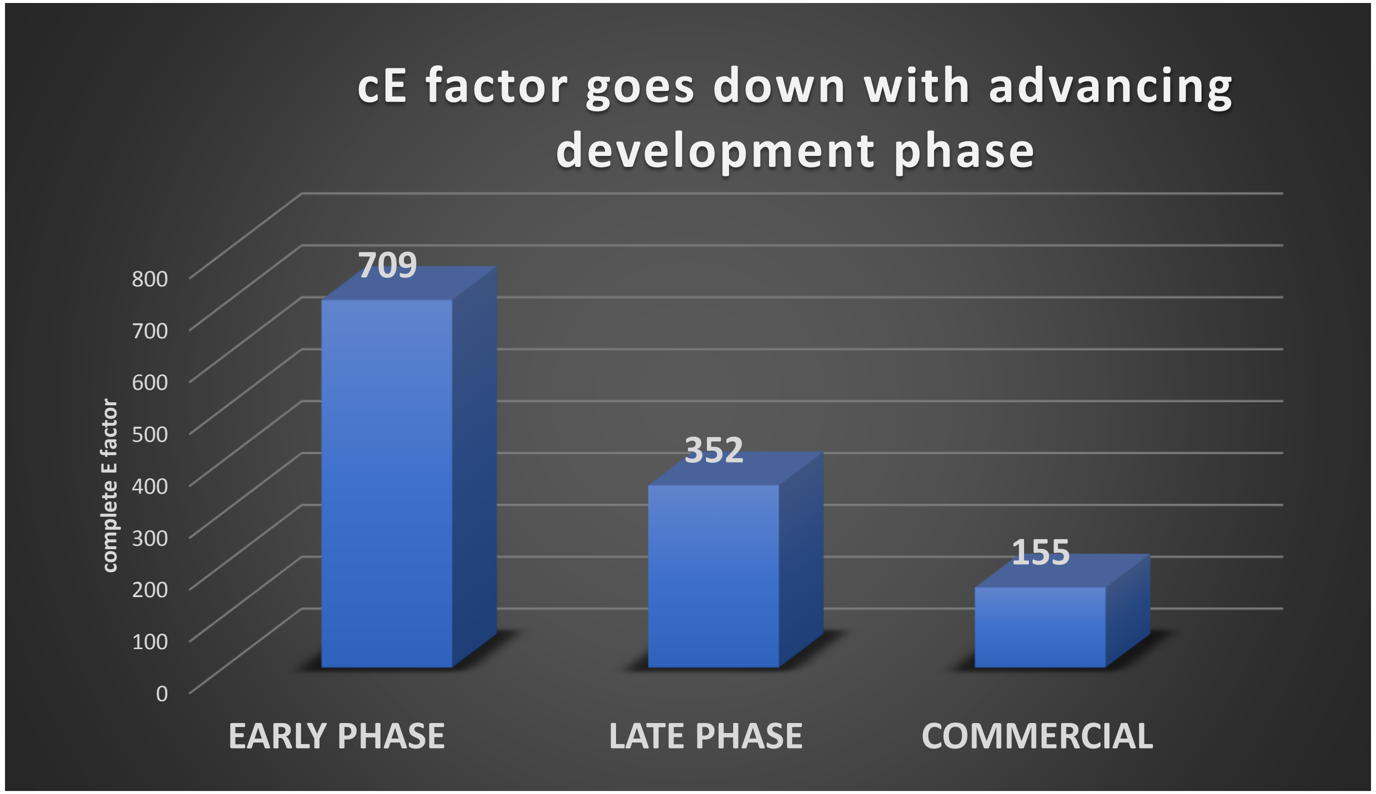
$$cEF = \frac{\sum m(Input\ Materials\ incl. Water) - m(Product)}{m(Product)}$$

Environmental Impact factor (EF) measures total waste relative to product

- High E factor indicates more waste generation and negative environmental impact
- Ideal E factor is 0

Complete E factor or **cEF** analyzes total waste stream and accommodates current trend in pharmaceutical industry to ***include water***

cE factor



Green Chem., 2018, **20**, 2206–2211

Financial Value of Green Chemistry

51% E-Factor Reduction → **>65% Overall Cost Reduction**

Process 1

Step	Yield	E-Factor
1	73%	93
2	81%	66
3	92%	11
4	82%	61
Total	45%	*231*

Process 2

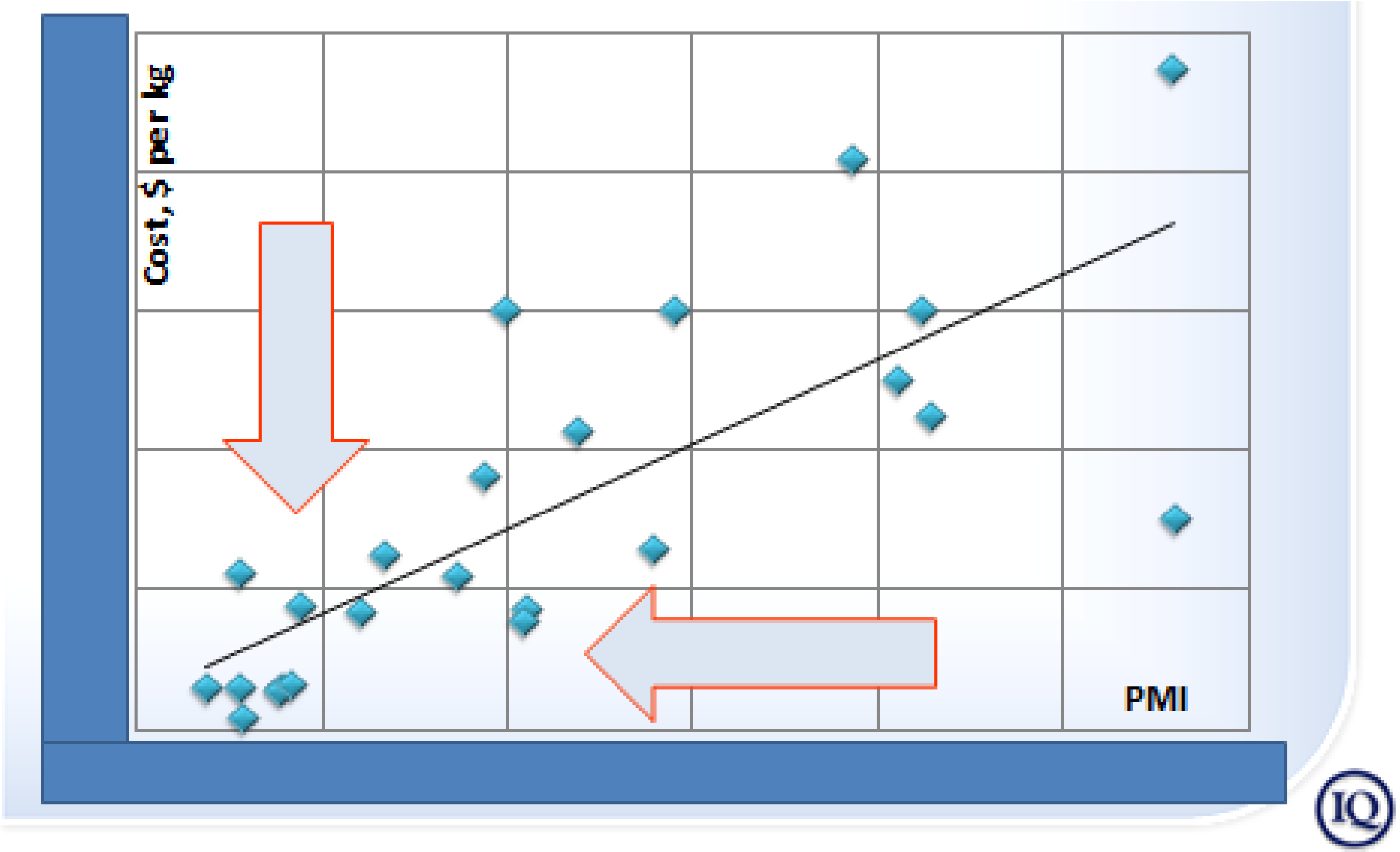
Step	Yield	E-Factor
1	68%	30
2	92%	22
3	86%	23
4	87%	33
5	96%	24
Total	45%	*132*

Process 3

Step	Yield	E-Factor
1	98%	17
2	89%	21
3	86%	23
4	87%	30
5	95%	23
Total	62%	*114*

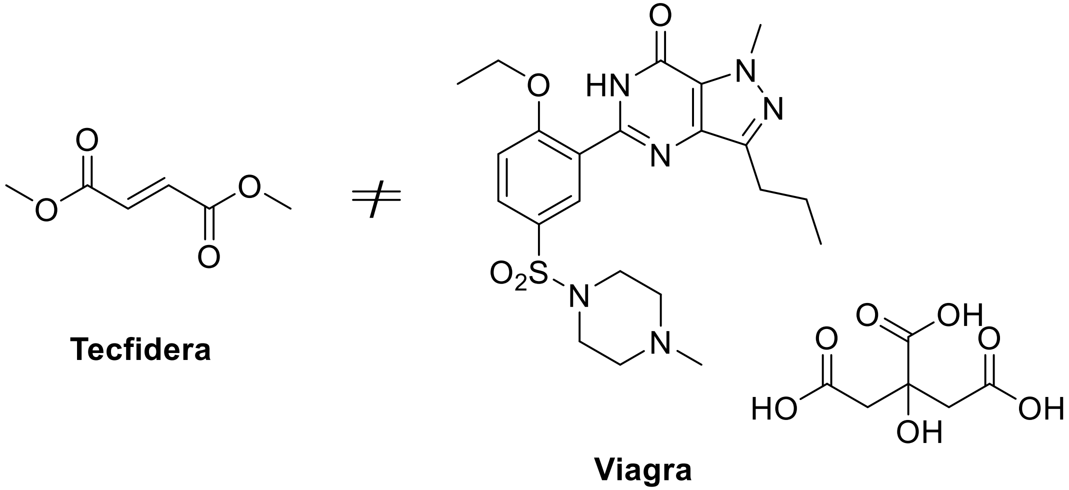
E-Factor represents kg waste produced during manufacture of 1 kg of drug substance

Cost and Metrics

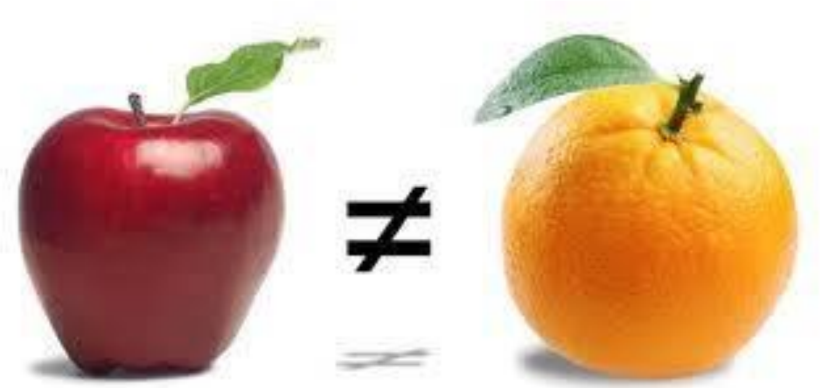


Late stage development compounds and marketed products

innovation Green Aspiration Level (iGAL)



How can you determine if your process is green when not every target molecule is the same?

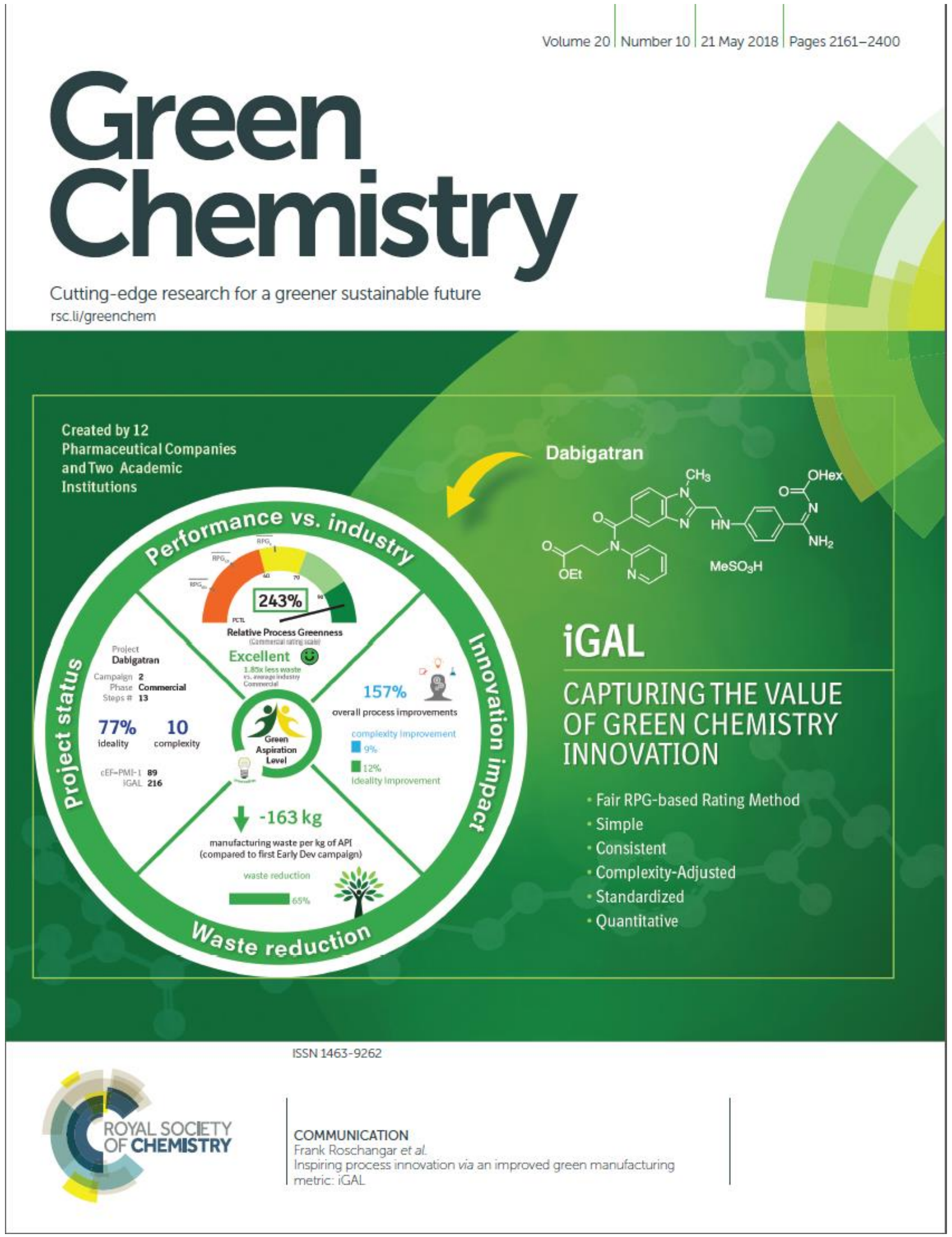


How can you determine if your process is green when not every target molecule is the same?

Hole	1	2	3	4	5	6	7
Par	4	3	5	3	4	4	5

How can you determine if your process is green when not every target molecule is the same?

innovation Green Aspiration Level (iGAL)



iGAL is a unifying green chemistry metric that takes into account molecular complexity with a fixed goal to target the most innovative, mass-efficient process.

iGAL is based on (salt-)Free Molecular Weight (FMW) and rewards process complexity reduction as measured in Relative Process Greenness (RPG).

$$iGAL = 0.344 \times FMW \left[\frac{kg\ waste}{kg\ API}\right]$$

$$\text{RPG} = \frac{iGAL}{cEF} \times 100\% \text{ with cEF = PMI - 1}$$

innovation Green Aspiration Level (iGAL)

- **Process Complexity** = sum of process **construction steps**,*[1] (stereoselective) skeletal API C–C, C–X, C-H, and X-H bond forming steps:

- functional group interconversions
- reductions / oxidations directly establishing correct functionality, stereochemistry, and oxidation state in final product
- chiral chromatography or chemical resolution steps

$$Complexity = \sum Construction\ Steps$$

asymmetric hydrogenation

*1 Similar to definition used by T. Gaich, and P. S. Baran, Aiming for the Ideal Synthesis, *J. Org. Chem.*, 2010, **75**, 4657–4673.

innovation Green Aspiration Level (iGAL)

$$Complexity = \sum Construction\ Steps$$

- **Concession steps** = "non-constructive" reactions forming skeletal but racemic API bonds or non-skeletal API bonds:

- protecting group manipulations
- functional group interconversions not leading to final API functionality
- racemic reductions and oxidations where chirality is needed
- recrystallization steps

*1 Similar to definition used by T. Gaich, and P. S. Baran, Aiming for the Ideal Synthesis, *J. Org. Chem.*, 2010, **75**, 4657–4673.

innovation Green Aspiration Level (iGAL)

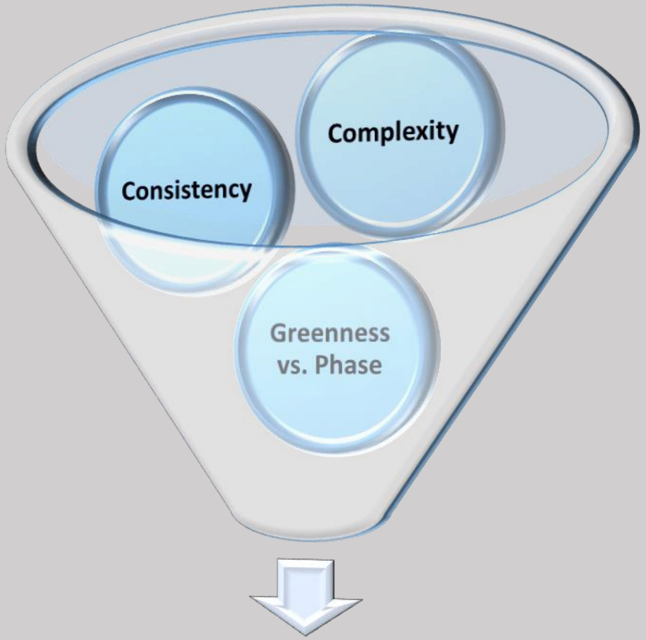
$$Complexity = \sum Construction\ Steps$$

- Only the sum of construction steps are included in complexity

One significant rule for calculation: track back to non-custom materials with ≤ $100 per mole from chemical vendor catalog

*1 Similar to definition used by T. Gaich, and P. S. Baran, Aiming for the Ideal Synthesis, *J. Org. Chem.*, 2010, **75**, 4657–4673.

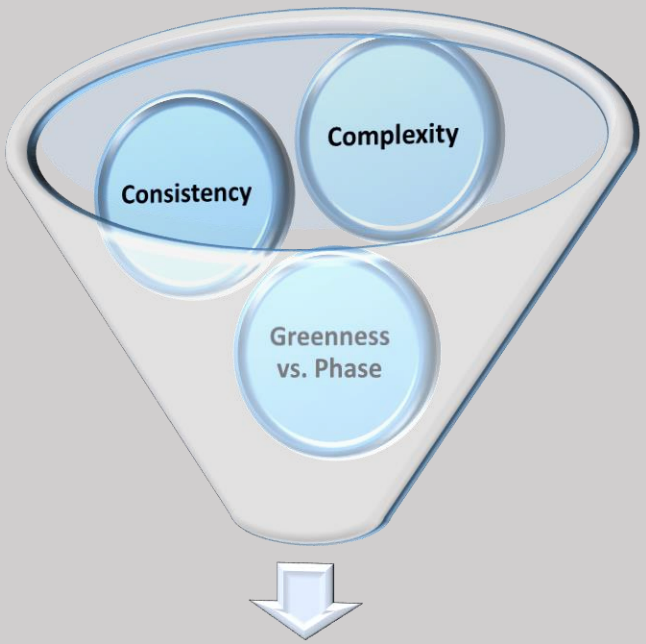
Greenness via an innovation Green Aspiration Level (iGAL)



- **FMW** (“salt-free” MW of API) is
  - an improved proxy for molecular complexity *
  - a **fixed** measure of complexity
- FMW enables us to derive **iGAL** as a **commercial goal** for co-produced waste:

* statistical analysis of best fit of selected complexity parameters (no. of chiral centers, fluorine functional groups, and rings)

Greenness via an innovation Green Aspiration Level (iGAL)



- **FMW** (“salt-free” MW of API) is
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- FMW enables us to derive **iGAL** as a **commercial goal** for co-produced waste:

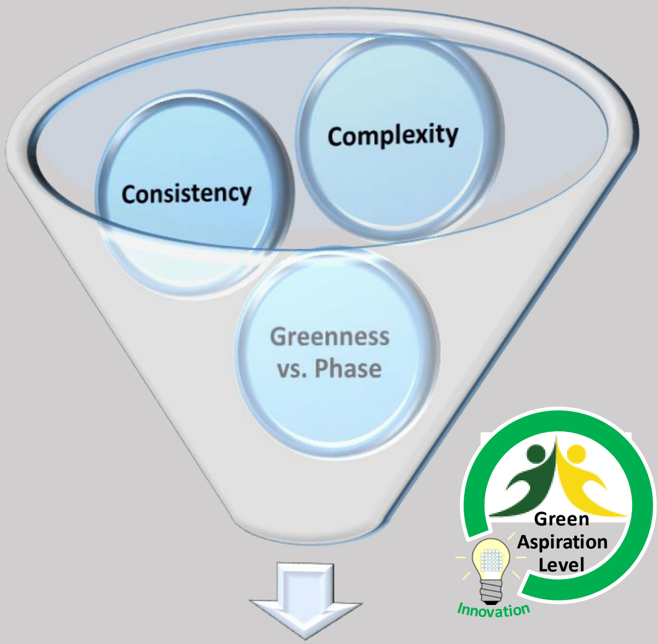
- Statistical analysis of 64 drug manufacturing processes encompassing 703 steps across 12 companies

$$iGAL = 0.344 \times \boldsymbol{FMW} \left[\frac{kg\ waste}{kg\ API}\right]$$

  - 0.344 = data-derived average waste complete E-Factor (cEF) per unit of average commercial drug FMW

* statistical analysis of best fit of selected complexity parameters (no. of chiral centers, fluorine functional groups, and rings)

Greenness via an innovation Green Aspiration Level (iGAL)



$$RPG = \frac{iGAL}{\boldsymbol{cEF}} \times 100\%$$

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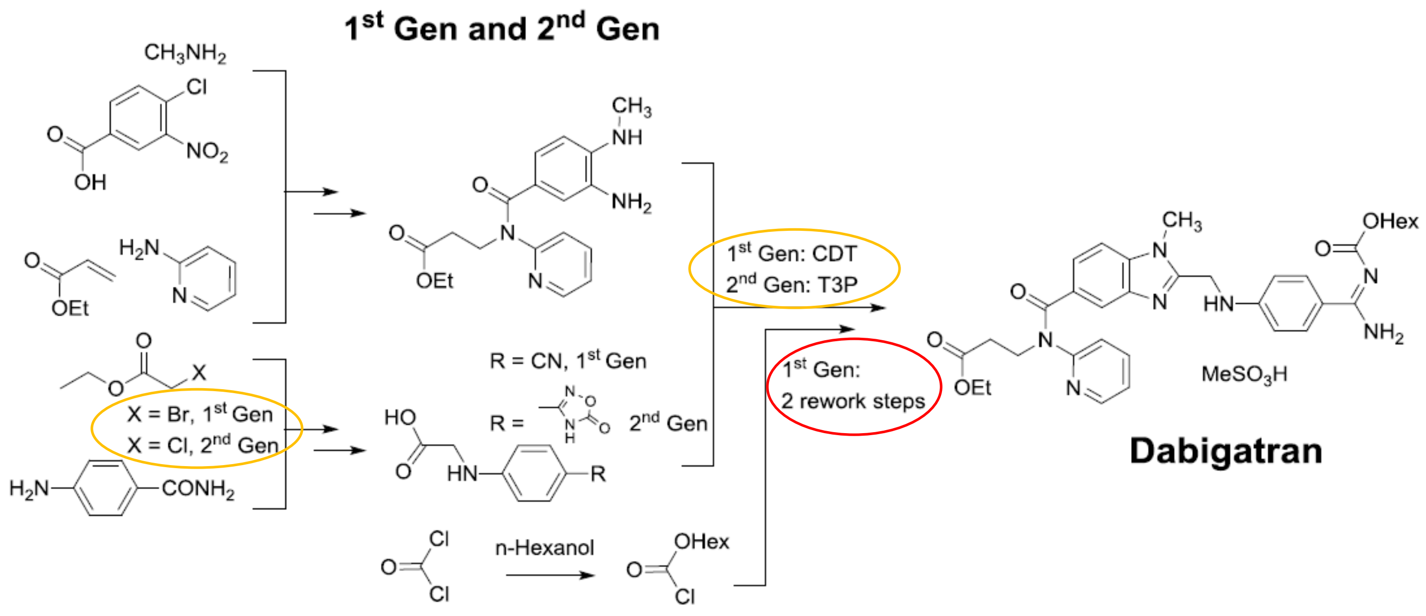
iGAL defines greenness of a process relative to industry averages across phases via Relative Process Greenness (RPG)

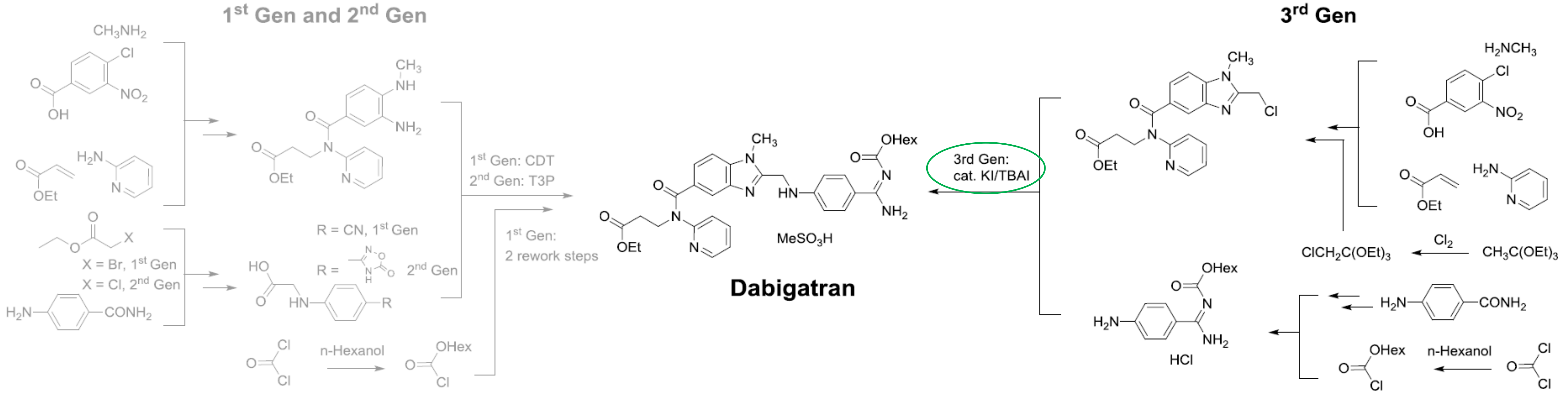
* statistical analysis of best fit of selected complexity parameters (no. of chiral centers, fluorine functional groups, and rings)

Case Study: Dabigatran process evolution



- First generation synthesis: Few desirable reagents and conditions, many rework steps
- Second generation route: Streamlining, including considerations to waste co-production

Case Study: Dabigatran process evolution



- First generation synthesis: Few desirable reagents and conditions, many rework steps
- Second generation route: Streamlining, including considerations to waste co-production
- Final (third) generation process: Omission of protecting groups, inclusion of catalytic reagents and improved volumes, selectivities, and yields

How to inspire green process innovation via iGAL?

Use **iGAL** to capture value and innovation impact

Communicate value

Motivate innovation via a new **Green Chemistry Innovation Scorecard**

RPG rating matrix for process evaluation:

based on average commercial waste

Percentile (PCTL)	Code	Rating	Minimum RPG for Early dev.	Minimum RPG for Late dev.	Minimum RPG for Commercial
90%	(dark green)	Excellent	66%	146%	222%
70%	(light green)	Good	48%	103%	168%
40%	(yellow)	Average	29%	59%	113%
	(orange)	Below average			

Green chemistry innovation scorecard

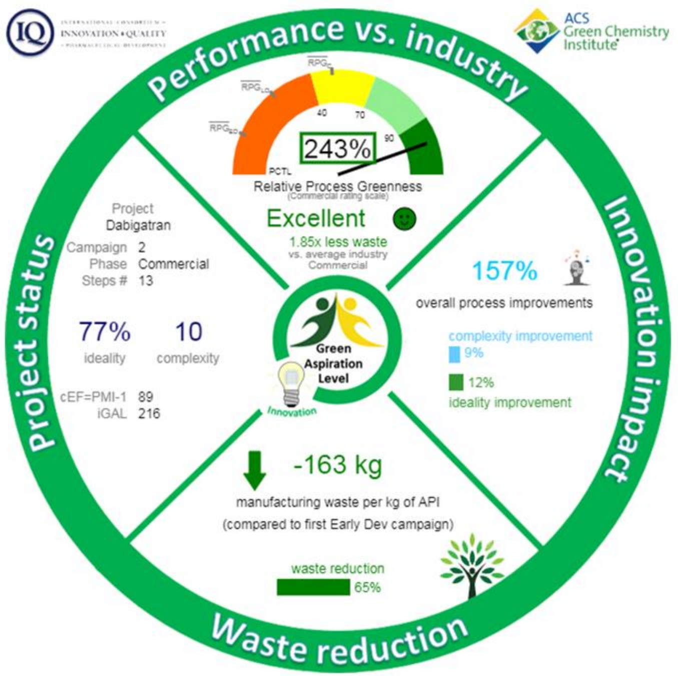
Dabigatran (FMW = 628 g / mol)

Phase of drug mfg	cEF [kg/kg]	Steps	Complexity	RPG	Scorecard rating	Innovation Impact = % RPG upgrade
Early dev (1st gen)	252	16	11	86%	---	---
Late dev (2nd gen)	167	13	11	129%	Good	44%
Commercial (3rd gen)	**89**	**13**	**10**	**243%**	**Excellent**	**157%**

- **process improvement/innovation** is quantified via RPG upgrade & correlates to improvements to the three KPIs Complexity, Ideality and Convergence

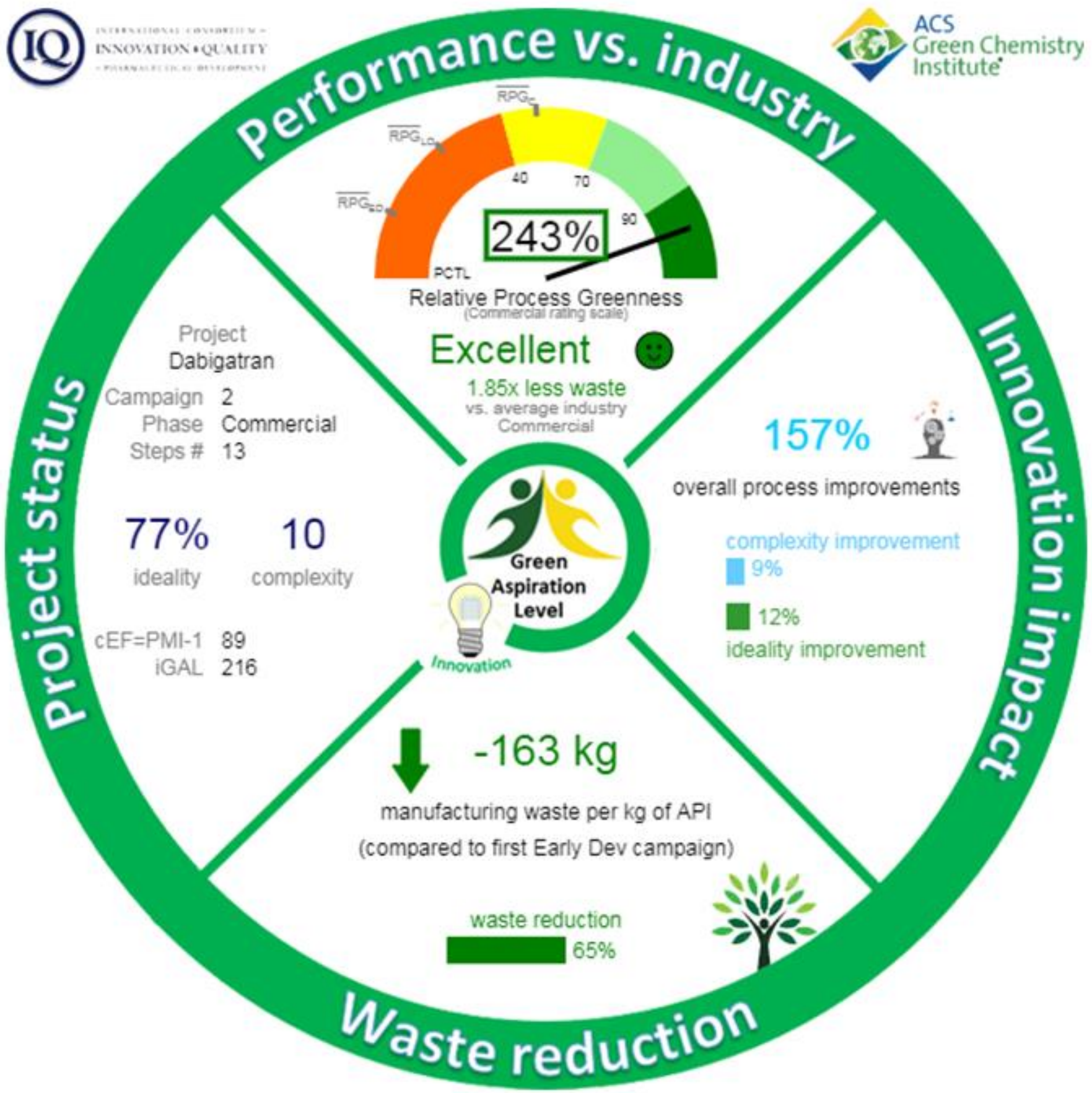
- **process performance** vs phase equivalent industry averages is quantified via RPG

use scorecard to effectively communicate the scientists' added value during process research & development



https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry/green-chemistry-innovation-scorecard-calculator.html

Green chemistry innovation scorecard



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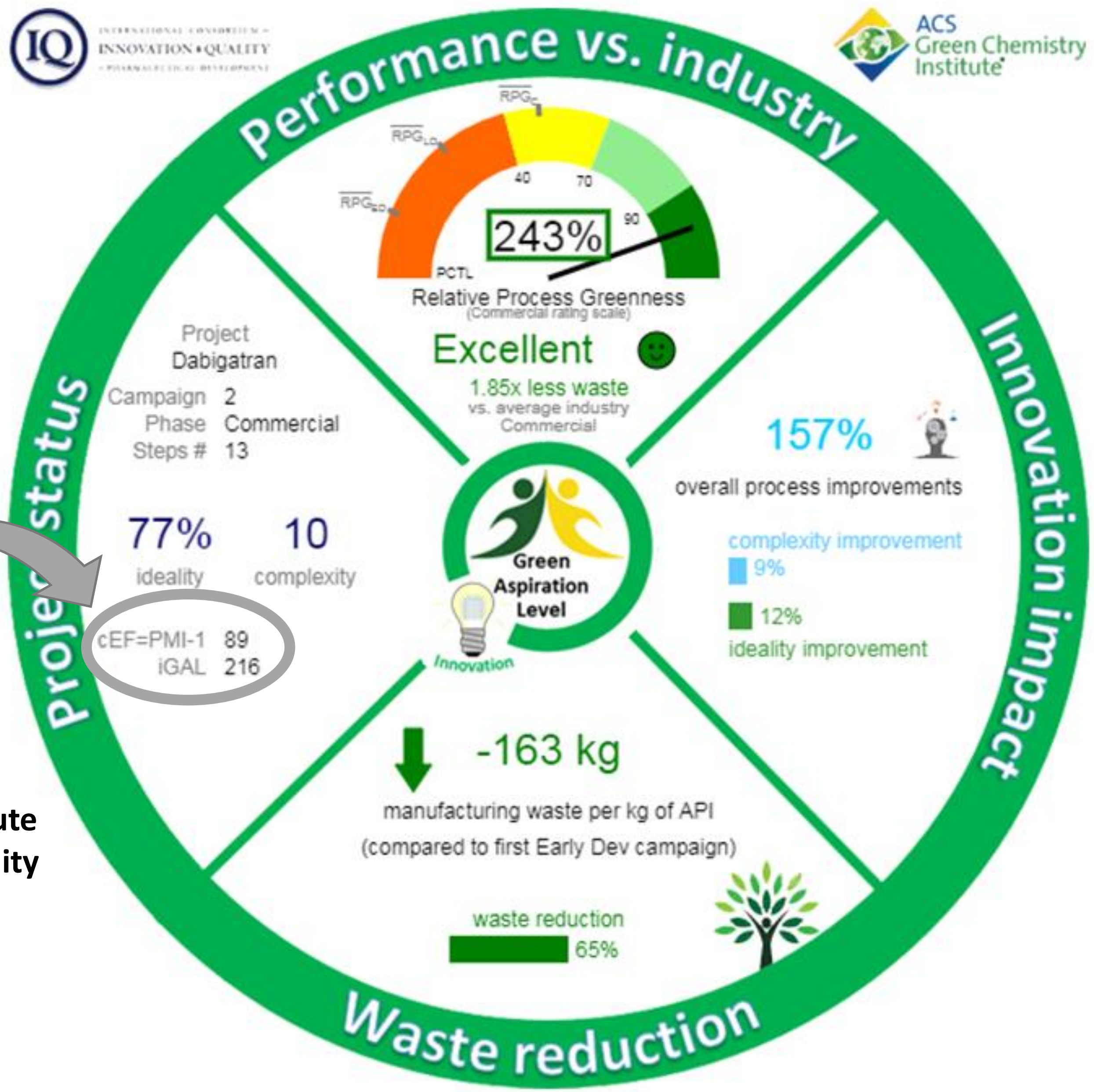
Green chemistry innovation scorecard

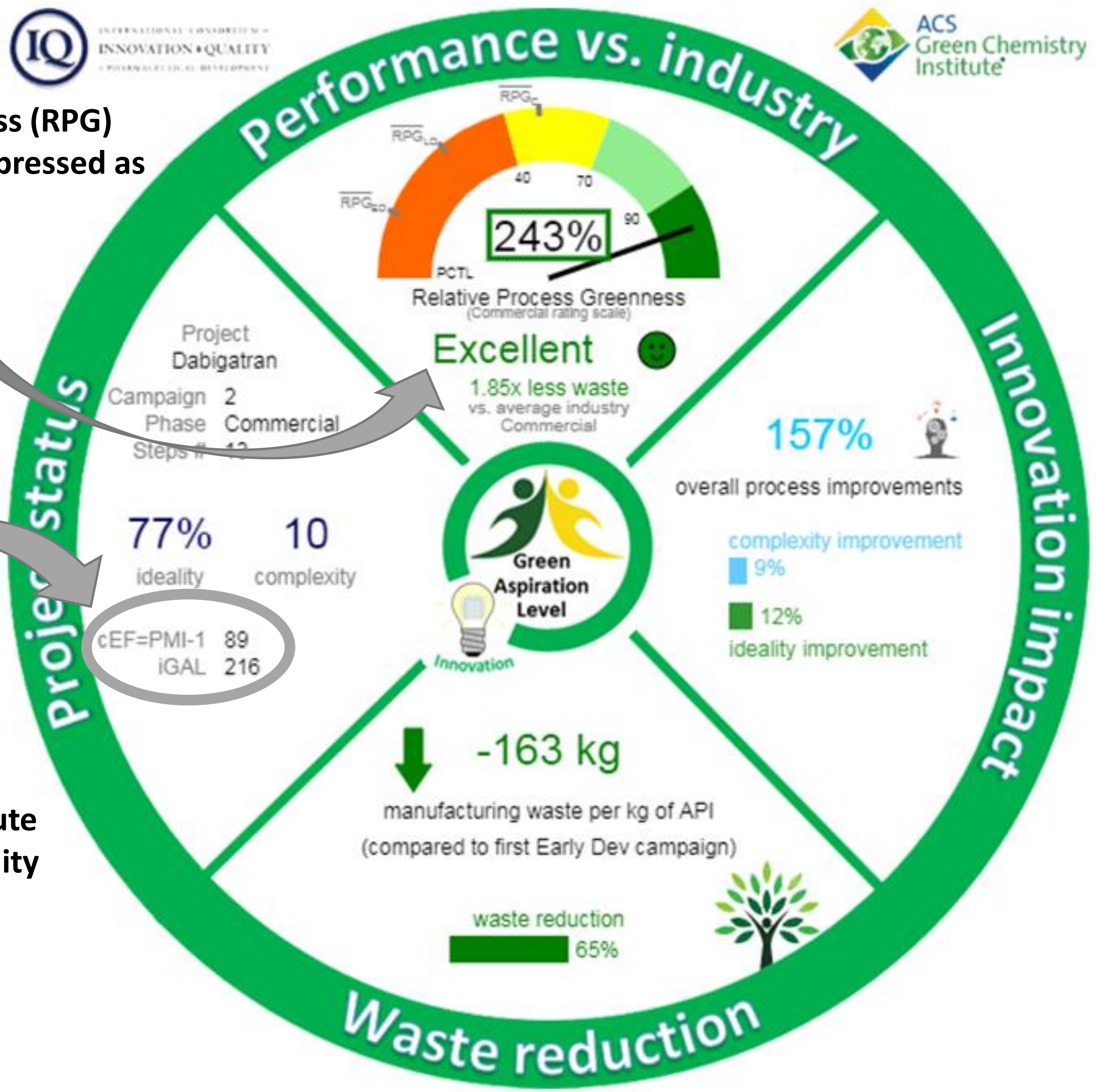


Captures cEF and iGAL absolute numbers, reports out % ideality

https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry/green-chemistry-innovation-scorecard-calculator.html

Green chemistry innovation scorecard

Relative Process Greenness (RPG) comparison to database, expressed as % and category



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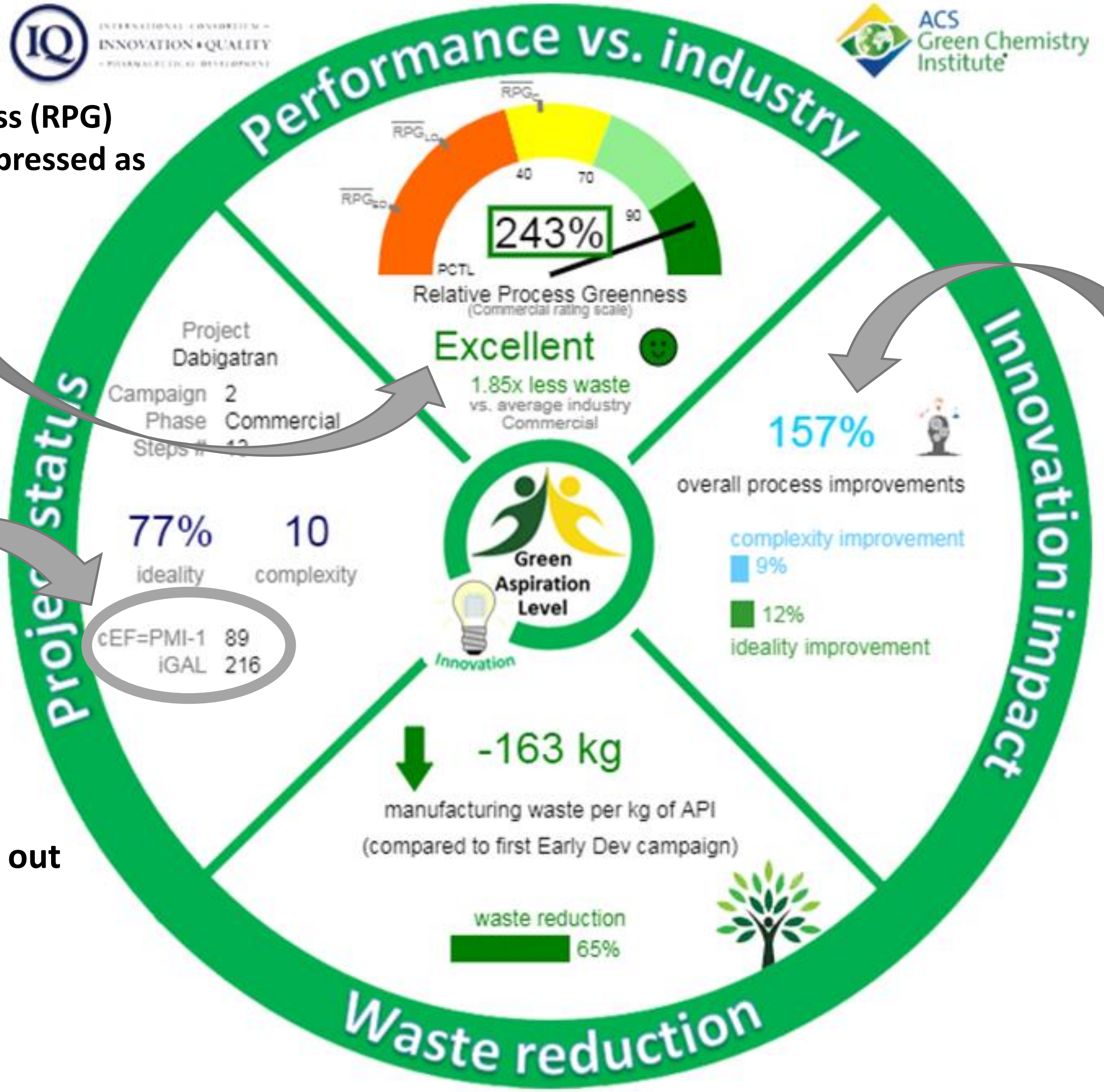

Process improvement & innovation demonstrated by RPG upgrade

Captures cEF and iGAL absolute numbers, reports out % ideality

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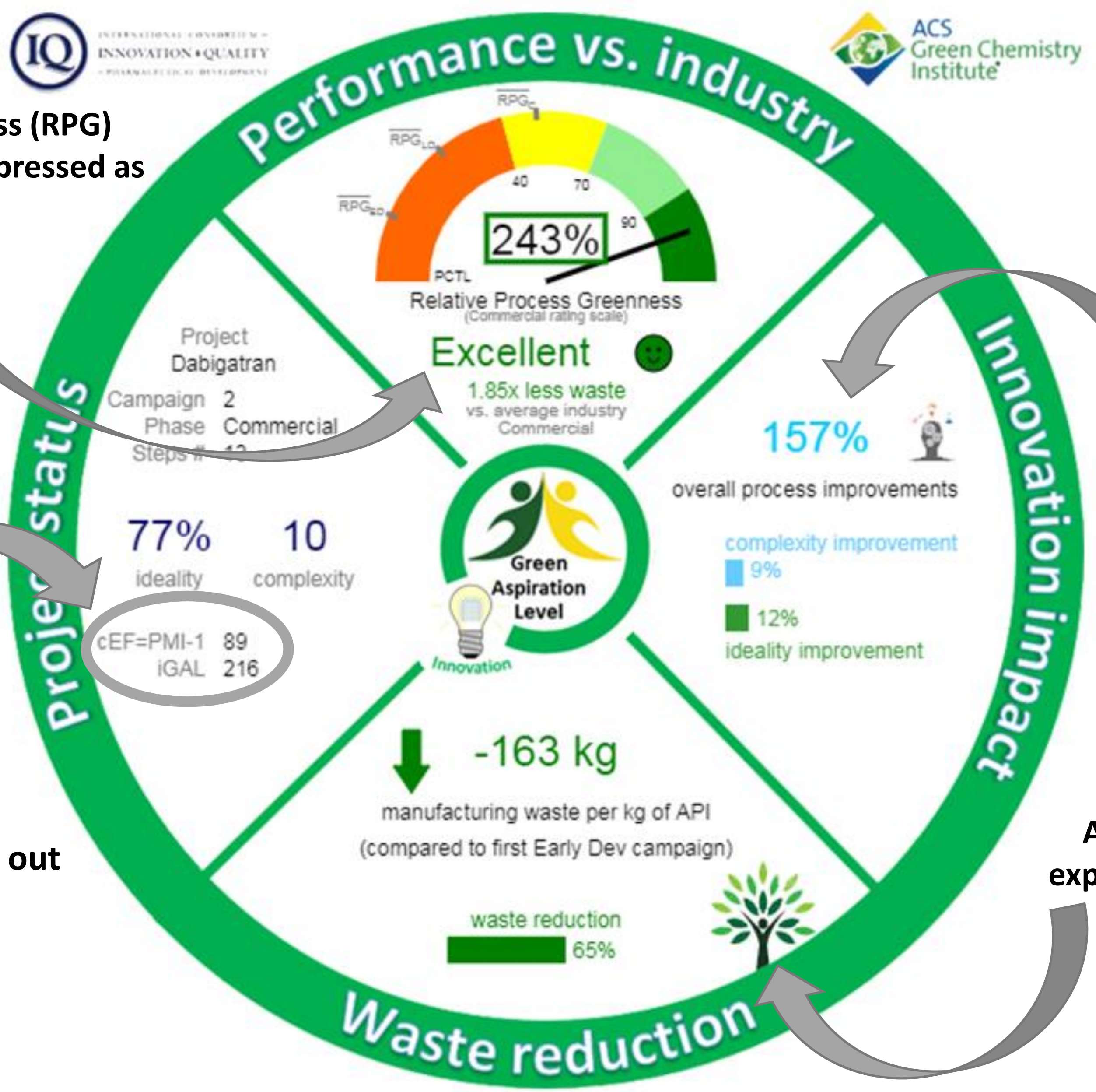
Green chemistry innovation scorecard



Relative Process Greenness (RPG) comparison to database, expressed as % and category

Process improvement & innovation demonstrated by RPG upgrade

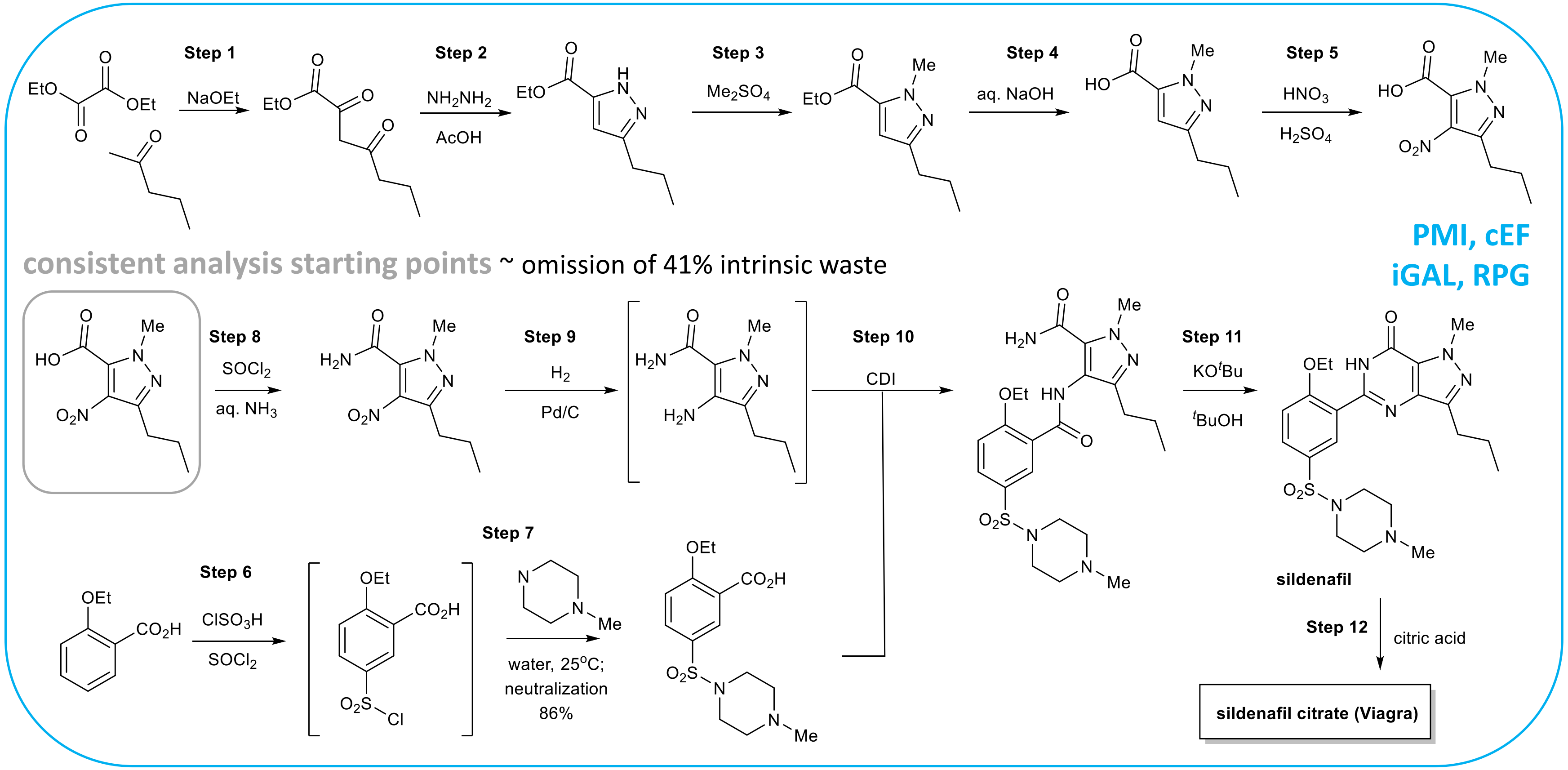
Captures cEF and iGAL absolute numbers, reports out % ideality

Amount waste saved expressed kg/kg and as %

https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry/green-chemistry-innovation-scorecard-calculator.html

Commercial Viagra process

2003 UK Institute of Chemical Engineers (IChemE) Crystal Faraday Award for Green Chemical Technology

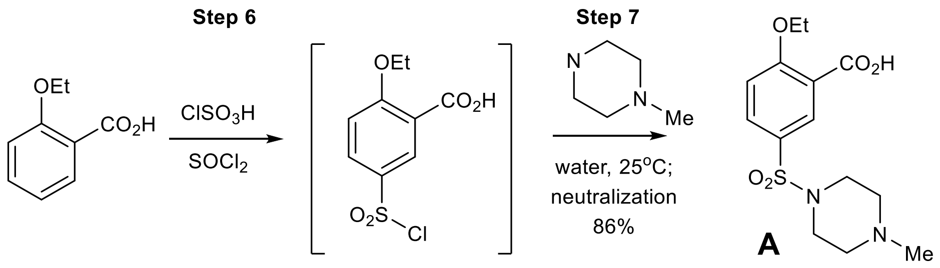


F. Roschangar, R. A. Sheldon and C. H. Senanayake *Green Chem.*, 2015, **17**, 752–768.

Guidance for **uniform** iGAL-cEF green chemistry analysis: F. Roschangar *et al.* *Green Chem.*, 2018, **20**, 2206–2211, ESI Discussion 2.

Exercise 1 - cEF

Q1: Determine cEF (= PMI – 1) for the following two-step sequence of the Viagra manufacturing process. How much waste do we generate for each kg of compound A? (*Note*: workup is included in analysis, but not reactor cleaning)



Step No.	Material	Input Weight	Output Weight
6	2-Ethoxybenzoic acid	0.43 kg	
	Thionyl Chloride	0.31 kg	
	Chlorosulfonic acid	1.26 kg	
	Water	7.47 kg	
	5-Chlorosulfonyl-2-ethoxy-benzoic acid (I1)		**0.63 kg**
7	5-Chlorosulfonyl-2-ethoxy-benzoic acid	0.63 kg	
	1-Methylpiperazine	0.55 kg	
	Water	4.77 kg	
	2-Ethoxy-5-(4-methyl-piperazine-1-sulfonyl)-benzoic acid (A)		**0.67 kg**

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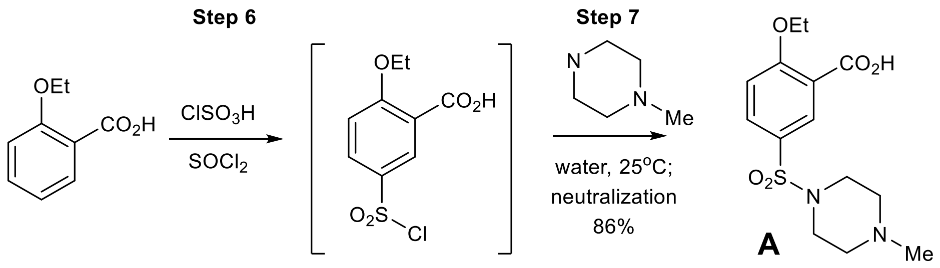

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	Water	4.77 kg	
	2-Ethoxy-5-(4-methyl-piperazine-1-sulfonyl)-benzoic acid (A)		**0.67 kg**

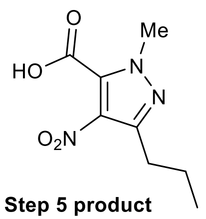
A1: m(all Inputs excl. intermediate **I1**) = 14.80 kg

$cEF(A) = \frac{14.80-0.67}{0.67} = 21.1\ kg$ of waste is generated per kg of **A**

Exercise 2 – cEF and $100 / mol rule

Q2: Determine cEF for the **entire** Viagra manufacturing process. How much waste do we generate for each kg of Viagra?

Step Number	Step cEF [kg waste / kg API]	Step Prodcut needed to make 1 kg API [kg]	cEF Contribution to API Process Waste [kg waste / kg API]
1	12.1 kg/kg	0.72 kg	8.6 kg/kg
2	2.6 kg/kg	0.67 kg	1.8 kg/kg
3	16.9 kg/kg	0.57 kg	9.7 kg/kg
4	12.5 kg/kg	0.35 kg	4.4 kg/kg
5	25.2 kg/kg	0.42 kg	10.7 kg/kg
Subtotal for Step 5 Product (**B**)			**35.1 kg/kg**
6 + 7	21.1 kg/kg	0.67 kg	14.1 kg/kg
8	11.9 kg/kg	0.39 kg	4.6 kg/kg
9 + 10	13.9 kg/kg	0.81 kg	11.3 kg/kg
11	16.1 kg/kg	0.72 kg	11.6 kg/kg
12	8.7 kg/kg	1.00 kg	8.7 kg/kg
TOTAL			**85.5 kg/kg**



Step 5 product
(compound **B**)

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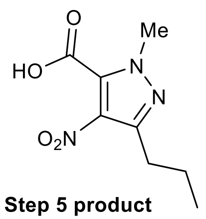

Step 5 product
(compound **B**)

A2: $cEF(Viagra) = \sum_{Step\ 1}^{Step\ 12} cEF\ Contribution\ (Step\ n) = 85.5\ kg$ of waste per kg Viagra

Exercise 2 – cEF and $100 / mol rule

Q2: Determine cEF for the **entire** Viagra manufacturing process. How much waste do we generate for each kg of Viagra?

Q3: How much waste production would have been discounted if not using the $100/mol starting material rule, and if the starting material was the Step 5 product?

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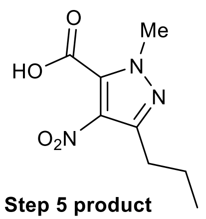

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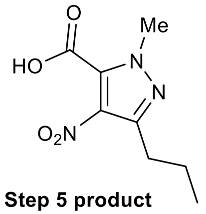

Step 5 product
(compound **B**)

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A3: We would have neglected cEF(**B**) = $[\sum_{Step\ 1}^{Step\ 5} cEF\ Contribution\ (Step\ n)] \ = 35.1\ kg$ of waste per kg Viagra, or **41%** of overall waste! → **importance of standardization**

Exercise 3 – iGAL and RPG

Q4: Determine the commercial green manufacturing waste target for the Viagra process based on the drug's complexity as reflected *via* its FMW. What is its Green Aspiration Level (GAL)? (*Note:* FMW(Viagra) = 474.6 g/mol)

Table 3 iGAL-based RPG Rating Matrix for green drug manufacturing

Percentile (PCTL)	Code	Rating	Minimum RPG for Early Dev	Minimum RPG for Late Dev	Minimum RPG for Commercial
90%	(dark green)	Excellent	66%	146%	222%
70%	(light green)	Good	48%	103%	168%
40%	(yellow)	Average	29%	59%	113%
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1 F. Roschangar *et al.* *Green Chem.*, 2018, **20**, 2206–2211.

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A4: $iGAL = 0.344 \times FMW = \mathbf{163.3\ kg}$ waste target per kg Viagra. This reflects the complexity-adjusted waste produced by the *average* commercial drug mfg. process.

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(*Note:* commercial RPG avg. = 131%)

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A5: $RPG = \frac{iGAL}{cEF} \times 100\% = \frac{163.3}{85.5} \times 100\% = \mathbf{191}\%.$

The Viagra process produces 191%/131% = 1.45 times less waste than the commercial average industry process.

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Q6: Use RPG rating matrix[1] to rate the commercial Viagra process.

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A6: With RPG = 191% the commercial Viagra process falls into the top 30% and is rated **GOOD**.

1 F. Roschangar *et al.* *Green Chem.*, 2018, **20**, 2206–2211.

How to inspire green process innovation via iGAL?

Use **iGAL** to capture value and innovation impact

Communicate value

Motivate innovation via a new **Green Chemistry Innovation Scorecard**

RPG rating matrix for process evaluation:

based on average commercial waste

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		Below average			

Example: Dabigatran (3rd gen process)

RPG = 243%

Example: Viagra process

RPG = 191%

iGAL summary

Green Aspiration Level

Innovation

Standardized: apply $100/mol rule for starting materials (lab catalog pricing)

Consistent: include all process and workup materials, but exclude reactor cleaning

Fair: compare your process to industry averages from same development phase.

Consider molecular complexity via FMW

Simple: determine FMW and process waste (cEF = PMI – 1) for an API campaign

Quantitative: assess your process vs. industry & determine your process improvements

$$RPG = \frac{iGAL}{cEF} \times 100\% = \frac{0.344 \times FMW}{cEF} \times 100\%$$

use web-based Green Chemistry Innovation Scorecard Calculator

Outlook

Green Chemistry

Drug Discovery → Preclinical → Phase 1 Clinical → Phase 2 Clinical → Phase 3 Clinical → FDA Review → Manufacture → Ongoing Research

Throughout Development	Early Development	Late Development
Leverage iGAL goal in conjunction with Green Chemistry Innovation Scorecard to motivate internal and external waste & cost reduction	Establish the "ideal synthesis route" to enable maximum future process greenness with respect to co-produced waste	Optimize the "ideal synthesis route" with respect to Life Cycle Assessment

Overall Summary

- Chemists and engineers have enormous control over manufacturing processes by selection of synthetic routes
- The 12 green chemistry principles are terrific guiding rules
- Solvent and reagent selection guides, coupled with metrics and life cycle analysis can help make routes more sustainable
- Metrics are vital – *you can't manage what you don't measure*
- Green chemistry triple win: cost-effective, better for environment, safer for stakeholders (employees, community)

iGAL team

Amgen
Bayer
Boehringer Ingelheim
Bristol-Myers Squibb
Genentech / Roche
GSK
Lilly
Merck
Novartis
Pfizer
Takeda
Teva

12 pharmaceutical firms

3 universities

California State University East Bay 1957
TU Delft
Yale

2 industry consortia

IQ International Consortium for Innovation & Quality in Pharmaceutical Development

ACS Green Chemistry Institute Pharmaceutical Roundtable

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