Inspiring process innovation

Via an improved green manufacturing metric: IGAL

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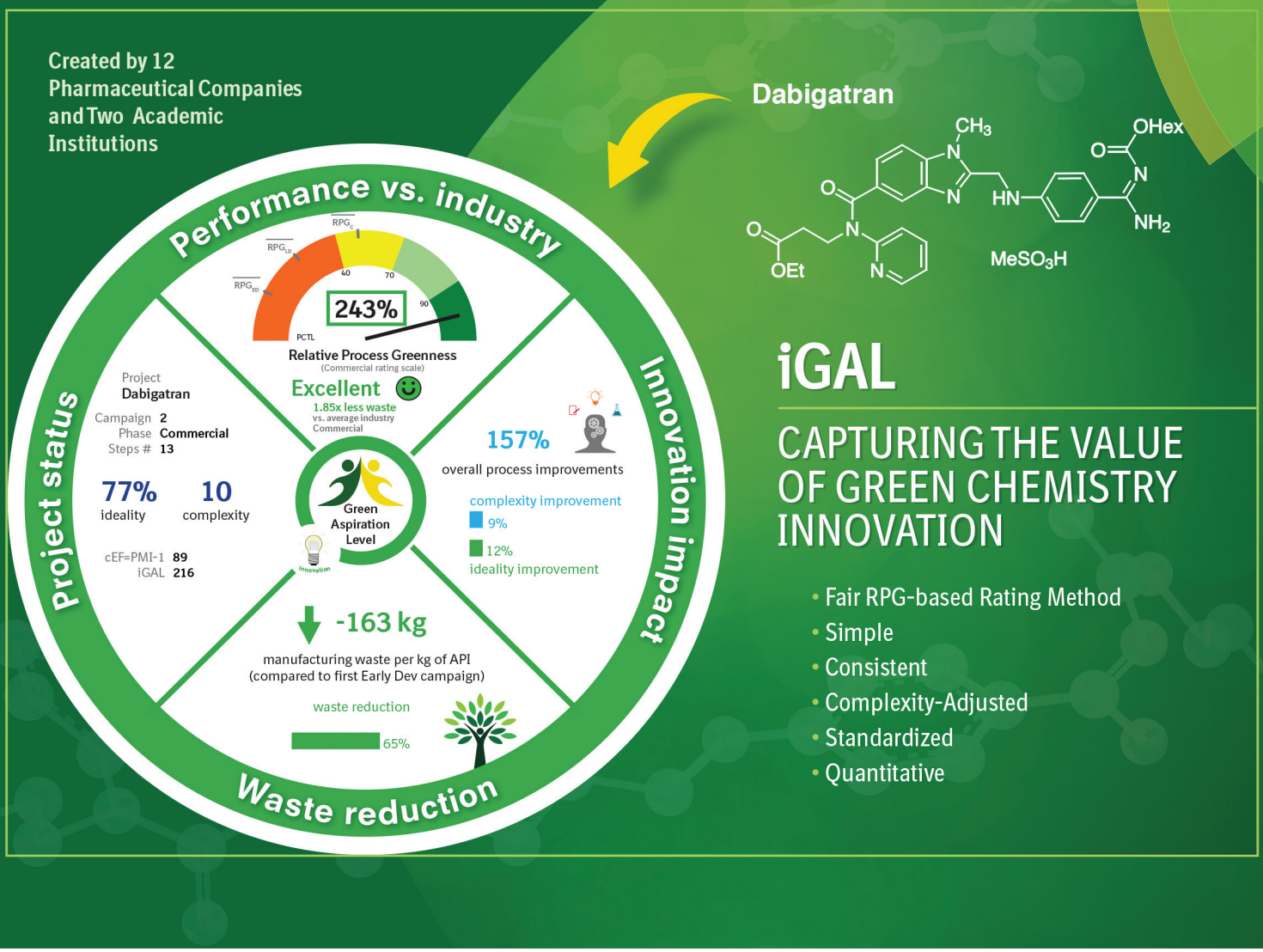

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Inspiring process innovation *via* an improved green manufacturing metric: iGAL†

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Following our goal to devise a unified green chemistry metric that inspires innovation in sustainable drug manufacturing across the pharmaceutical industry, we herein disclose joint efforts by IQ, the ACS GCI PR and academia, leading to the significantly improved 'innovation Green Aspiration Level' (iGAL) methodology. Backed by the statistical analysis of 64 drug manufacturing processes encompassing 703 steps across 12 companies, we find that iGAL affords an excellent proxy for molecular complexity and presents a valuable molecular weight-based 'fixed' goal. iGAL thereby accurately captures the impact of green process inventiveness and improvements, making it a useful innovation-driven green metric. We conclude by introducing the comprehensive, yet easy-to-use and readily adaptable Green Chemistry Innovation Scorecard web calculator, whose graphical output clearly and effectively illustrates the impact of innovation on waste reduction during drug manufacture.

With the advent of the Green Aspiration Level (GAL), the greenness of pharmaceutical drug manufacturing, in terms of quantity of co-produced process waste, can finally be calibrated and quantified across industry.[1–5] Our cohort from IQ,[6] ACS GCI PR[7] and academia created this metric to motivate efforts to reduce the projected 15 billion kg of annual drug manufacturing waste associated with an estimated disposal cost of $30 billion[8] (Fig. 1).

The term "process greenness" has been discussed for many years without broad agreement as to its meaning, so adding GAL represents a major step forward. However one limitation of this approach is that process chemists may develop a

Fig. 1 The new innovation green aspiration level (iGAL) is central to metrics unification and goal-inspired innovation and waste reduction.

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shorter synthesis to a particular drug and thereby reduce process complexity, which could lead to a scenario where the Relative Process Greenness (RPG) score gets worse even though the process is generating less overall waste. Consequently, the original GAL metric does not adequately reflect the impact of synthetic route and process design innovations, which are foundational to achieving more sustainable and state-of-the-art pharmaceutical manufacturing processes, while minimizing environmental impacts and delivering optimal process economics. Herein we explain how we refined the original metric to resolve the aforementioned shortcomings, while keeping the methodology simple. We conclude by illustrating the new iGAL with the evaluation of two drug manufacturing processes.

iGAL – an improved measure for green process performance

Consideration for drug complexity must be a key component of any effective green goal or metric, so that fair and achievable targets can be derived that inspire, engage, and model what 'great' looks like. We originally defined process complexity as such an indicator.[1–4] Process complexity is based on construction step count (ESI Discussion 2†) and delivered a variable manufacturing goal (GAL) that allowed RPG scores to be calculated.

However, we became increasingly aware that a variable goal may not adequately reflect molecular complexity and thus not reward green chemistry-inspired innovation. This is because process improvements that achieve high levels of molecular complexity with fewer process steps (*e.g.* cycloadditions, C–H insertions) reduce overall process complexity. Since GAL = 26 × Complexity,[3] improvements to process complexity lead to a lower GAL that in turn may deliver an unfavorable RPG score, in spite of an overall better and lower waste-generating process. To catalyze greater process innovation, we wanted to identify a goal that remains constant and comprehensively captures process improvements. Herein, we select three complexity parameters (no. of fluorine functional groups, rings, and chiral centers)[9] to evaluate molecular weight of the drug (MW) and its salt-free form (FMW)[10] as alternative complexity indicators.

To determine the best proxy for a complexity-based goal, we collected data from 64 small molecule drug manufacturing processes at the 12 contributing companies (ESI Discussion 1†). We refined our guidance to ensure consistency between the company datasets (ESI Discussion 2†), and then statistically determined the best fit of our complexity parameters with the waste goals derived from process complexity (CP), MW, and FMW. Based on this analysis, the *FMW derived goal proves to be the best descriptor for drug complexity*, as 34% of its variation is being accounted for by variation in the complexity parameters (Table 1, ESI Table 2†). In comparison, the original GAL(CP) is the least accurate indicator with a figure of just 6%. We term the new FMW-derived goal "innovation GAL" or iGAL.

Table 1 Assessing fit of iGAL, GAL(MW), and GAL(CP) as complexity indicator *via* regression[a]

Type of GAL	*R*-Square[b]	Coeff. var.	RMSE[c]	Mean
iGAL(FMW)	33.5%	26.1	34.1	156
GAL(MW)	26.7%	28.2	37.3	150
GAL(CP)	6.3%	45.8	87.1	192

[a] N = 64 = number of manufacturing process data sets. [b] *R*-Squared: ranges from 0 to 1; larger values indicate better fit. [c] RMSE = root mean square error – absolute fit of the model to the data; lower values indicate better fit.

After we define mGAL as the average co-produced waste (complete E factor, cEF)[11] per unit of average commercial drug FMW and determine it per eqn (1), iGAL is simply calculated according to eqn (2) and enables determination of RPG, *i.e.* process greenness relative to FMW-based industry averages per eqn (3) (see also ESI Discussion 1†).

Definition of mGAL

$$\mathrm{mGAL} = \frac{\text{avg. cEF} \times 1000}{\text{avg. FMW}} = 344\left[\frac{\text{kg waste} \times \text{mol drug}}{(\text{kg drug})^2}\right] \quad (1)$$

Determination of iGAL

$$\mathrm{iGAL} = \frac{\mathrm{mGAL} \times \mathrm{FMW}}{1000} = 0.344 \times \mathrm{FMW}\left[\frac{\text{kg waste}}{\text{kg drug}}\right] \quad (2)$$

Determination of RPG

$$\mathrm{RPG} = \frac{\mathrm{iGAL}}{\mathrm{cEF}} \times 100\%, \quad \text{with cEF} = \mathrm{PMI} - 1. \quad (3)$$

Introduction of iGAL is a major improvement in methodology, because it is takes into account molecular complexity while remaining a fixed aspiration target during drug development. iGaL also captures the positive impact chemists and engineers have through process innovations that lead to significant waste reduction. The iGAL-derived RPG averages for the 64 manufacturing processes used in this analysis are shown in Table 2.

The RPG for the average commercial process is 100% since it is based on average cEF, but the average commercial RPG is 131%, as explained in ESI Discussion 4.† We note that the reason for low RPG scores of the less optimized early and late

Table 2 Average RPG results from 64 drug manufacturing processes[a]

Phase of drug manufacturing	N[b]	FMW[c] [g mol^{-1}]	cEF [kg kg^{-1}]	iGAL [kg kg^{-1}]	RPG
Early development[d]	23	451	709	155	35%
Late development[e]	21	464	352	160	73%
Commercial[f]	20	449	155	155	131%

[a] All figures represent the means. kg kg^{-1} reflects kg co-produced waste per kg drug. [b] N = number of manufacturing process data sets. [c] FMW = molecular weight of free acid or free base component of the drug. [d] Campaigns making drug supplies for up to Phase IIa/Proof of Concept clinical trials. [e] Campaigns supporting phase IIb clinical trials up to registration. [f] Campaigns providing market-scale supplies.

Table 3 Revised iGAL-based RPG rating matrix for green drug manufacturing

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

development processes is that they are compared against commercial averages. However, we take this into account with our RPG rating matrix (Table 3, ESI Discussion 5†) and thus render ratings equitable across phases.

Highlighting green process innovation

A key reason for establishing iGAL as a green chemistry metric of choice is to offer scientists an inspirational yardstick to design the most innovative and mass-efficient drug manufacturing process. We believe that iGAL will be most impactful if we can quantify and effectively communicate the scientists' added value by correlating their improvements to Key Process Performance Indicators (KPPI) with waste (cEF) reduction during process evolution. We chose the KPPI process Complexity (CP) and Ideality (I)[12] as explanatory variables, and fit our 64 observations with a multivariate linear regression using cEF as the response variable. It turns out that we require a logarithmic model to describe the effect of the KPPI on waste co-generation (eqn (4), ESI Discussion 6†).

Impact of KPPI on cEF

$$\ln(\text{cEF}) = 5.789 + 0.1437 \times \text{Complexity} - 1.725 \times \text{Ideality}. \quad (4)$$

Accordingly, cEF is positively correlated to Complexity and negatively to Ideality. Thus, a process design that minimizes Complexity and maximizes Ideality will help deliver the greenest possible route. From eqn (4) we infer that (1) every one unit decrease in process complexity leads to a 13% average decrease in cEF, and (2) every 10% increase in ideality leads to a 16% average decrease in cEF. Therefore, we can highlight the degree of the scientist's achieved green process innovation by capturing improvements to both Complexity and Ideality.

Since, unlike its predecessor, iGAL is constant and rewards process Complexity reduction, we can also define green Innovation Impact as quantifiable improvements to RPG (eqn (5)).

Determination of Innovation Impact

$$\text{Innovation Impact(Campaign X)} = \text{RPG(Campaign X)} - \text{RPG(Campaign1)}. \quad (5)$$

We are now in a position to accurately measure the value-added impact of process scientists *via* (1) *RPG improvements* (Innovation Impact) *versus* earlier process variants of the same project, and (2) *RPG performance versus* project phase-equivalent industry averages, respectively. This represents another major step forward in the field of green chemistry metrics.

Green chemistry innovation scorecard

The ideal vehicle to effectively highlight Innovation Impact and attain broad adoption of iGAL is an improved version of our previously reported green scorecard.[3,4] We illustrate it using data from manufacturing processes of the drugs Dabigatran[13–15] and Rivastigmine across three project phases (Fig. 2),[16–18] inputting cEF, FMW, complexity, steps, and outputting ideality, RPG, rating, Innovation Impact, and overall waste reduction (Table 4, ESI Discussion 7†).

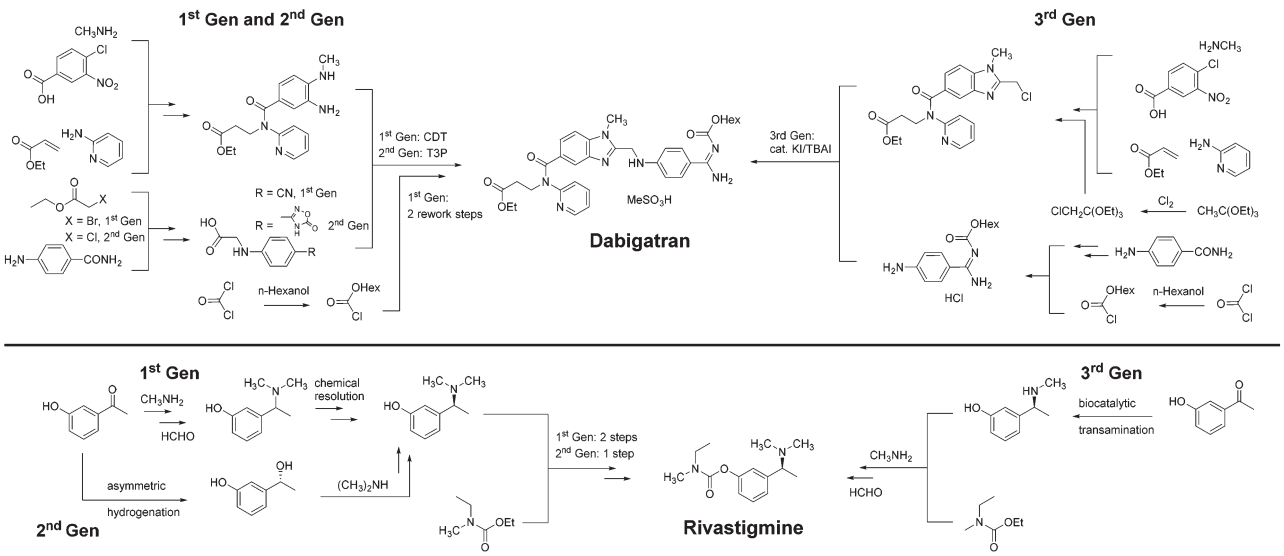

Fig. 2 1st, 2nd and 3rd generation routes to Dabigatran and Rivastigmine.

Table 4 KPPI rating and innovation impact of Dabigatran and Rivastigmine manufacturing process improvements

Phase of drug manufacturing	cEF [kg kg^{-1}]	Complexity	Ideality	RPG	Green innovation scorecard rating	Innovation impact = % RPG upgrade	Waste reduction/kg API
Dabigatran (FMW = 628 g mol^{-1})							
Early development (1st gen)	252	11	69%	86%	Excellent	—	—
Late development (2nd gen)	167	11	85%	129%	Good	44%	85 kg
Commercial (1st gen)	234	10	71%	92%	Below Average	7%	18 kg
Commercial (2nd gen)	141	11	79%	154%	Average	67%	111 kg
Commercial (3rd gen)	89	10	77%	243%	Excellent	157%	163 kg
Rivastigmine (FMW = 250 g mol^{-1})							
Early development (1st gen)	110	3	50%	78%	Excellent	—	—
Late development (2nd gen)	65	3	60%	132%	Good	54%	45 kg
Commercial (3rd gen)	42	3	100%	205%	Good	127%	68 kg

Dabigatran

Green improvements from Dabigatran's 1st to 2nd generation processes entail avoiding two late-stage rework steps, using the environmentally more favorable coupling agent T3P, and reducing the steps required for the amidine installation. From the 2nd to 3rd generation process, protecting groups were avoided, coupling agents KI and TBAI were used catalytically, and reaction volumes, selectivities and yields were improved. Overall, the scientists upgraded RPG by 157% to 243% and reduced co-generated waste by 163 kg per kg drug.

Rivastigmine

The 1st generation process was racemic utilizing the inherently low-yielding chemical resolution, thus requiring 3 concession steps and delivering low 50% ideality. The 2nd generation process relied on transition-metal catalyzed asymmetric hydrogenation, which increased the yield, but required alcohol activation that translated to still modest 60% ideality. Significant improvements were made with the 3rd generation process that implemented direct introduction of the amine *via* biocatalytic transamination and delivered perfect 100% ideality alongside improved overall efficiency.

The redesigned scorecards for the 3rd generation Dabigatran and Rivastigmine processes are shown in Fig. 3. They emphasize the scientists' Innovation Impact on the process and show how they compare to our calculated industry standard. We obtain a RPG performance rating of "excellent" and "good" from the rating matrix in Table 3 for Dabigatran and Rivastigmine, respectively, indicating that the processes generate 1.9 and 1.6 times less waste than the industry average. The online calculator that generates this scorecard output can be freely accessed by all from the ACS GCI PR website.[19]

While the Green Innovation Scorecard has been applied retrospectively, one can readily imagine how the new tool will motivate scientists to reduce waste even further.

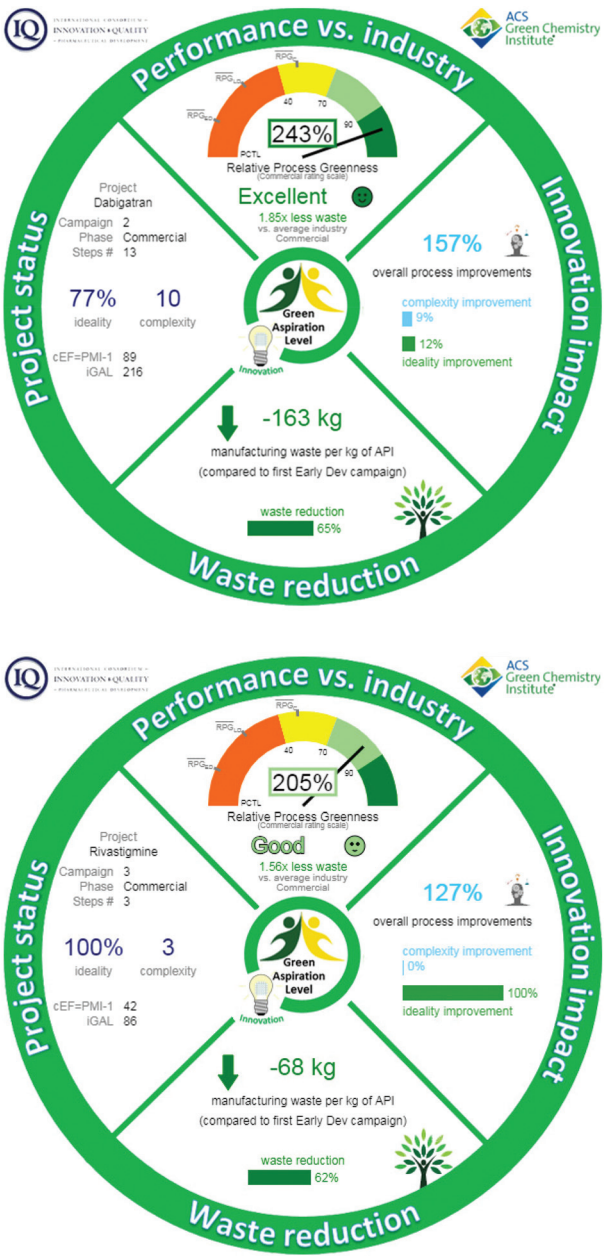

Fig. 3 Green chemistry innovation scorecard for 3rd gen Dabigatran and Rivastigmine processes.

Summary and outlook

The new methodology improves upon the earlier metric by establishing a statistically more significant complexity indi-

1. Determine FMW, process waste (cEF = PMI–1), complexity and steps, using the $100/mol starting material rule
2. Calculate iGAL = 0.344 *x* FMW
3. Calculate RPG = iGAL/cEF
4. Obtain rating from RPG matrix (Table 3)
5. Determine Innovation Impact = ΔRPG

Chart 1 The five easy steps of iGAL.

cator, FMW, that provides the basis for establishing the iGAL goal. It is highly correlated to GAL, so we measure the same content as before, but we now have a better yardstick. By being a fixed goal, iGAL enables full recognition of process innovation *via* RPG improvements and thus establishes itself as a key link between green chemistry innovation and inspired environmental waste reduction efforts. We believe this relationship, coupled with the graphically appealing Green Chemistry Innovation Scorecard as an effective communication tool, will achieve our goal to encourage broad adoption within the pharmaceutical and allied industries. In lieu of access to the online calculator,[19] iGAL remains easy to use as shown in Chart 1.

Future work aims to expand evaluation and utilization of iGAL in industry *via* consortia collaboration, lectures and webinars by ACS GCI PR and IQ, including application to alternate modalities beyond traditional small molecules. We are also evaluating integration of iGAL with Life Cycle Analysis (LCA)[20] and PMI prediction[21] tools, and plan to study the correlation of manufacturing waste with economics to strengthen the strategic business case for iGAL. Finally, the new methodology might allow us to collaborate with government agencies on standards to recognize improvements, identify greener pharmaceutical processes, and enable rewards such as pharmaceutical "Ecolabels".[22]

Abbreviations

ACS GCI PR	American chemical society green chemistry institute pharmaceutical roundtable
API	Active pharmaceutical ingredient, drug substance
cEF	Complete E factor
FMW	Salt free MW of API; MW of API excluding salt, co-crystal, or solvate components
GAL	Green aspiration level
iGAL	Innovation GAL
IQ	International consortium for innovation & quality in pharmaceutical development
LCA	Life cycle analysis
mGAL	cEF normalization factor for iGAL: average co-produced waste per unit of average commercial drug FMW
MW	Molecular weight
PMI	Process mass intensity
RPG	Relative process greenness

Conflicts of interest

There are no conflicts to declare.

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11 The complete E factor (cEF) is a comprehensive measures for co-produced waste and accounts for all process materials, including raw materials, reagents, solvents and water. The cEF and its relationship to and Process Mass Intensity (PMI) has been defined in ref. 1 and 3: .

$$\mathrm{cEF} = \mathrm{PMI} - 1 = \frac{\sum m(\text{Raw Materials}) + \sum m(\text{Reagents}) + \sum m(\text{Solvents}) + \sum m(\text{Water}) - m(\text{Product})}{m(\text{Product})}$$

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