Green Chemistry

SUPPLEMENTARY INFORMATION

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

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List of 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

ESI Discussion 1 Manufacturing process data

ESI Table 1 summarizes our collected data for co-produced drug waste (*cEF* = complete E factor = *PMI–1*) from 64 small molecule drug manufacturing processes across 12 large pharmaceutical companies. In each case the molecular weight of the drug (MW), molecular weight of the parent drug excluding salt, co-crystal, or solvate component (FMW), development phase (early and late development, as well as commercial), step number (Steps), and the Key Process Performance Indicators (KPPI) Complexity (CP) and Ideality (I) (see ESI Discussion 6).

Process complexity and ideality are determined according to ESI Eqn. 1–2.

ESI Eqn. 1 Determination of process complexity

$$Complexity = \sum Construction\ Steps$$

ESI Eqn. 2 Determination of process ideality

$$Ideality = \frac{Complexity}{Steps} \times 100\%$$

GAL and RPG outputs are calculated as follows. Our preceding version of GAL, which has been normalized based on process complexity[1] and herein labeled GAL(CP), is calculated per ESI Eqn. 3, with 26 kg/kg reflecting the commercial waste goal for the average constructive manufacturing step in industry.

ESI Eqn. 3 Determination of GAL(CP)

$$GAL(CP) = Complexity \times 26\frac{kg\ waste}{kg\ API}$$

The new iGAL, which has been normalized based on FMW, is calculated per Eqn. 2, with mGAL reflecting the commercial waste goal for the average commercial drug FMW unit of 1 g/mol according to Eqn. 1.

[Main Article] Eqn. 1 Determination of mGAL (FMW)

$$mGAL = \frac{avg.\ cEF \times 1000}{avg.\ FMW} = \frac{154.6 \times 1000}{449.4} = 344\left[\frac{kg\ waste \times mol\ drug}{(kg\ drug)^2}\right]$$

[Main Article] Eqn. 2 Determination of iGAL (FMW)

$$iGAL = \frac{mGAL \times FMW}{1000} = 0.344 \times FMW\left[\frac{kg\ waste}{kg\ drug}\right]$$

GAL(MW) is determined similarly to iGAL according to ESI Eqn. 4 and 5.

ESI Eqn. 4 Determination of mGAL (MW)

$$mGAL(MW) = \frac{avg.\ cEF \times 1000}{avg.\ MW} = \frac{154.6 \times 1000}{498.4} = 310\left[\frac{kg\ waste \times mol\ drug}{(kg\ drug)^2}\right]$$

ESI Eqn. 5 Determination of GAL (MW)

$$GAL(MW) = 0.310 \times MW \frac{kg\ waste}{kg\ API}$$

ESI Eqn. 6 Determination of Relative Process Greenness

$$RPG = \frac{'GAL'}{cEF} \times 100\%$$

All variants of RPG are determined according to ESI Eqn. 6, with 'GAL'=GAL(CP), GAL(MW), and iGAL=GAL(FMW).

ESI Table 1 Data for 64 small molecule drug manufacturing processes

Early development phase

Project	MW [g/mol]	FMW [a] [g/mol]	# Chiral	# Fluorine	# Rings	Steps	Complexity	Ideality	cEF = PMI –1	GAL (CP) [b]	RPG (CP)	GAL (MW)	RPG (MW)	**iGAL** (FMW)	**RPG** (FMW)
1	340	340	2	0	2	8	2	25%	208	52	25%	105	51%	117	56%
2	295	295	1	0	3	19	7	37%	1781	182	10%	91	5%	101	6%
3	311	311	0	0	4	11	9	82%	383	234	61%	96	25%	107	28%
4	533	533	1	0	6	34	15	44%	829	390	47%	165	20%	183	22%
5	537	537	0	0	5	21	13	62%	426	338	79%	166	39%	185	43%
6	382	382	2	0	4	21	10	48%	746	260	35%	118	16%	131	18%
7	317	280	0	1	1	13	7	54%	535	182	34%	98	18%	96	18%
8	318	318	1	0	3	11	7	64%	2746	182	7%	99	4%	109	4%
9	583	583	0	0	6	22	10	45%	879	260	30%	181	21%	201	23%
10	512	396	2	0	4	23	12	52%	746	312	42%	159	21%	136	18%
11	401	401	1	0	3	14	10	71%	430	260	61%	124	29%	138	32%
12	484	484	2	1	5	10	7	70%	244	182	74%	150	61%	166	68%
13	588	588	0	2	5	9	9	100%	973	234	24%	182	19%	202	21%
14	525	525	0	1	4	11	8	73%	204	208	102%	163	80%	181	89%
15	591	591	2	0	4	17	11	65%	1361	286	21%	183	13%	203	15%
16	675	675	1	0	7	13	9	69%	781	234	30%	209	27%	232	30%
17	200	200	2	0	1	5	3	60%	128	78	61%	62	48%	69	54%
18	724	628	0	0	4	16	11	69%	252	286	113%	224	89%	216	86%
19	472	393	2	0	5	10	4	40%	825	104	13%	146	18%	135	16%
20	363	363	0	0	5	9	5	56%	328	130	40%	113	34%	125	38%
21	506	506	1	1	3	21	12	57%	740	312	42%	157	21%	174	24%
22	704	586	0	0	4	9	5	56%	316	130	41%	218	69%	202	64%
23	456	456	0	0	4	10	6	60%	452	156	35%	141	31%	157	35%
Mean	470	451	0.9	0.3	4.0	14.7	8.3	59%	709	217	45%	146	33%	155	35%
Median	484	456	1	0	4	13	9	60%	535	234	40%	150	25%	157	28%
Min	200	200	0	0	1	5	2	25%	128	52	7%	62	4%	69	4%
Max	724	675	2	2	7	34	15	100%	2746	390	113%	224	89%	232	89%
SD [c]	140	129	0.9	0.5	1.5	6.7	3.3	16%	595	86	28%	44	23%	44	24%

Late development phase

Project	MW [g/mol]	FMW [g/mol]	# Chiral	# Fluorine	# Rings	Steps	Complexity	Ideality	cEF = PMI –1	GAL (CP[a])	RPG (CP)	GAL (MW)	RPG (MW)	**iGAL** (FMW)	**RPG** (FMW)
24	582	463	0	1	3	14	10	71%	387	260	67%	180	47%	159	41%
25	461	461	0	0	5	22	17	77%	572	442	77%	143	25%	159	28%
26	484	484	2	1	5	9	7	78%	165	182	110%	150	91%	166	101%
27	486	388	2	3	4	4	4	100%	115	104	90%	151	131%	133	116%
28	547	547	9	1	5	5	3	60%	91	78	86%	170	187%	188	207%
29	390	390	1	0	3	5	4	80%	266	104	39%	121	45%	134	50%
30	282	282	3	0	4	9	7	78%	479	182	38%	87	18%	97	20%
31	462	462	4	0	4	14	13	93%	387	338	87%	143	37%	159	41%
32	439	439	1	0	2	7	7	100%	325	182	56%	136	42%	151	46%
33	588	588	0	2	5	8	8	100%	486	208	43%	182	38%	202	42%
34	492	401	0	1	3	10	9	90%	247	234	95%	153	62%	138	56%
35	569	569	4	0	3	16	10	63%	743	260	35%	176	24%	196	26%
36	573	573	1	2	5	10	10	100%	159	260	164%	178	112%	197	124%
37	426	426	0	1	3	10	10	100%	137	260	190%	132	96%	147	107%
38	611	535	3	1	6	11	8	73%	652	208	32%	189	29%	184	28%
39	523	483	1	0	5	7	5	71%	349	130	37%	162	46%	166	48%
40	393	393	0	0	3	7	5	71%	66	130	197%	122	185%	135	205%
41	254	254	0	0	2	9	4	44%	317	104	33%	79	25%	87	28%
42	429	429	1	1	6	8	4	50%	186	104	56%	133	72%	148	79%
43	545	545	5	2	5	12	9	75%	1095	234	21%	169	15%	187	17%
44	724	628	0	0	4	13	11	85%	167	286	171%	224	134%	216	129%
Mean	489	464	1.8	0.8	4.0	10.0	7.9	79%	352	204	82%	151	70%	160	73%
Median	486	462	1	1	4	9	8	78%	317	208	67%	151	46%	159	48%
Min	254	254	0	0	2	4	3	44%	66	78	21%	79	15%	87	17%
Max	724	628	9	3	6	22	17	100%	1095	442	197%	224	187%	216	207%
SD[b]	109	96	2.3	0.9	1.2	4.2	3.5	17%	254	91	55%	34	53%	33	57%

Commercial phase

Project	MW [g/mol]	FMW [g/mol]	# Chiral	# Fluorine	# Rings	Steps	Complexity	Ideality	cEF = PMI –1	GAL (CP[a])	RPG (CP)	GAL (MW)	RPG (MW)	**iGAL** (FMW)	**RPG** (FMW)
45	724	628	0	0	4	14	11	79%	141	286	203%	224	160%	216	154%
46	667	475	0	0	4	12	11	92%	86	286	335%	207	242%	163	191%

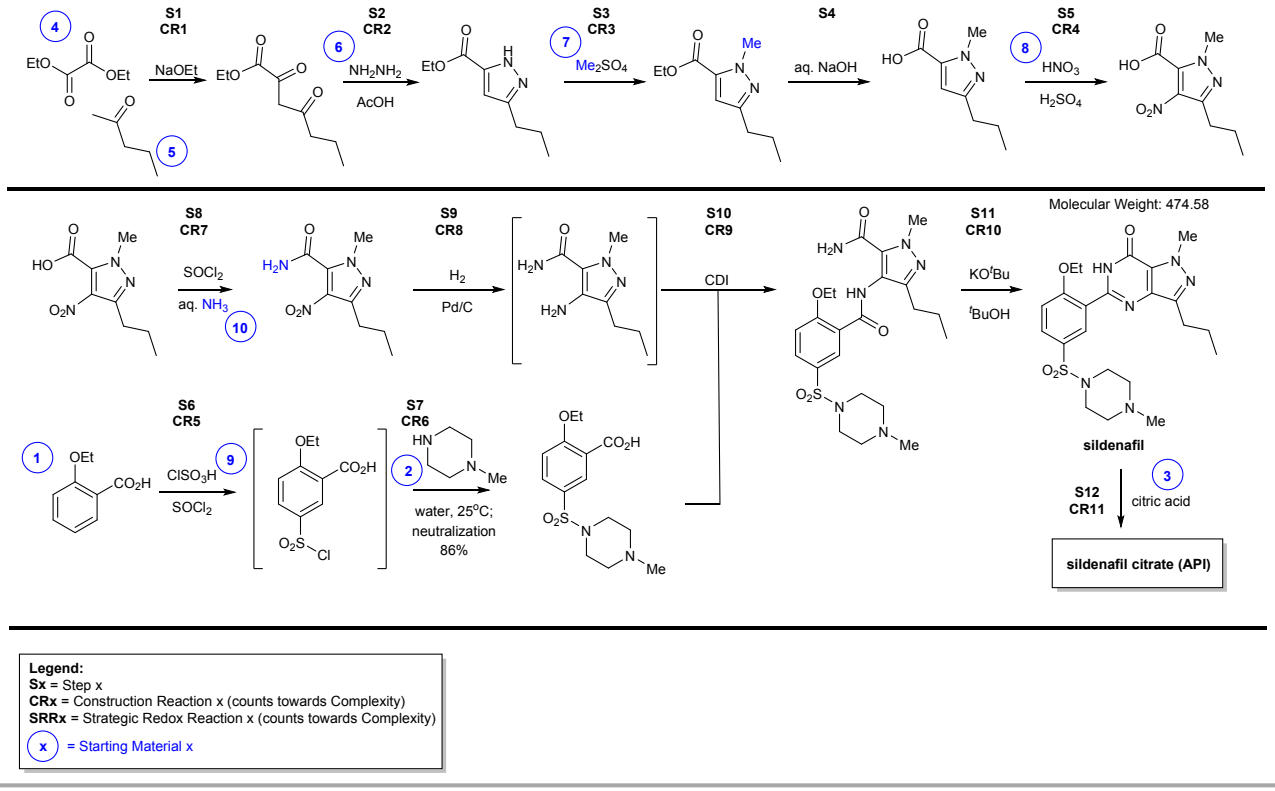
Project	MW [g/mol]	FMW [g/mol]	# Chiral	# Fluorine	# Rings	Steps	Complexity	Ideality	cEF = PMI −1	GAL (CP[a])	RPG (CP)	GAL (MW)	RPG (MW)	**iGAL** (FMW)	**RPG** (FMW)
47	313	313	2	0	3	7	6	86%	153	156	102%	97	63%	108	70%
48	304	304	1	0	5	3	2	67%	65	52	81%	94	146%	105	162%
49	304	304	1	0	5	3	2	67%	37	52	140%	94	253%	105	281%
50	486	388	2	3	4	5	4	80%	54	104	194%	151	282%	133	249%
51	390	390	1	0	3	5	4	80%	222	104	47%	121	55%	134	61%
52	541	516	0	0	7	6	6	100%	152	156	103%	168	110%	178	117%
53	361	361	3	0	2	8	7	88%	252	182	72%	112	44%	124	49%
54	588	588	0	2	5	6	5	83%	144	130	90%	182	126%	202	140%
55	460	460	0	0	5	6	6	100%	197	156	79%	143	72%	158	80%
56	812	739	4	0	6	5	4	80%	323	104	32%	252	78%	254	79%
57	724	628	0	0	4	14	10	71%	234	260	111%	224	96%	216	92%
58	724	628	0	0	4	13	10	77%	89	260	292%	224	252%	216	243%
59	436	436	1	0	4	6	5	83%	90	130	144%	135	150%	150	167%
60	534	461	0	0	5	9	8	89%	257	208	81%	165	64%	159	62%
61	395	358	0	0	2	13	4	31%	258	104	40%	122	47%	123	48%
62	273	273	1	0	2	5	3	60%	50	78	156%	85	169%	94	188%
63	472	393	2	0	5	9	3	33%	182	78	43%	146	80%	135	74%
64	461	345	0	1	3	7	4	57%	108	104	96%	143	132%	119	110%
Mean	498	**449**	0.9	0.3	4.1	7.8	5.8	75%	**155**	150	122%	155	131%	155	131%
Median	467	415	1	0	4	6.5	5	80%	148	130	99%	145	118%	143	113%
Min	273	273	0	0	2	3	2	31%	37	52	32%	85	44%	94	48%
Max	812	739	4	3	7	14	11	100%	323	286	335%	252	282%	254	281%
SD[b]	162	133	1.2	0.8	1.3	3.6	2.9	19%	83	75	81%	50	75%	46	71%
OVERALL AVERAGE		455	1.2	0.4	4.0	11.0	7.4	71%	419	192	81%	150	76%	156	78%

[a] FMW = molecular weight of the drug without salt component. [b] Derived from process complexity. GAL(CP) = original GAL. [b] SD = Standard Deviation.

ESI Discussion 2 Guidance for uniform analysis

In this section, we describe the updated iGAL methodology we used to collect *consistent* data using the published Viagra manufacturing process (ESI Fig. 1).[2] We encourage all to review this brief section prior to running an iGAL analysis.

ESI Fig. 1 Viagra manufacturing process



Active Pharmaceutical Ingredient (API) / Drug. The drug is defined as the final synthesis product before milling and formulation; but including the salt forming step. Salt and solvate components are excluded to determine the salt-free

molecular weight (FMW). This also applies for drugs that are quaternary ammonium salts.

Starting Material is a compound that contributes to the final API structure (C, N, O, S, P, etc., but not H). The starting material is a commodity that we define per our **$100/mol rule** which includes the following stipulations:

a) commercially available from a major reputable chemical laboratory catalog company, and its price listed in the (online) catalog. Materials requiring bulk or custom quotes do not qualify as process starting materials

AND

b) laboratory catalog cost at its largest offered quantity does not exceed US $100/mol

In ESI Fig. 1 a process starting materials is indicated as (x), with x = starting material number. The Viagra process has 10 structure-forming starting materials. They include:

- simple starting materials such as ammonia (10), hydrazine (6), chlorosulfonic acid (9), dimethyl sulfate (7), and nitric acid (8)
- API salt formers such as citric acid (3). If the API is a sodium salt and NaOH is used to make it, NaOH is counted as a starting material. The same goes for HCl to make a HCl salt.
- oxidants if the introduced oxygen is incorporated in the final API structure

Excluded as starting materials are reductants (H-delivery reagents).

Step is a key parameter of ideality. In ESI Fig. 1 each arrow reflects one step, independent of whether it is constructive or not. We define a step as a either a technical operation (e.g. chromatography, recrystallization) or a chemical operation involving one or more chemical transformations that form and/or break covalent or ionic bonds and lead to a stable and isolable intermediate, but not necessarily include its isolation. Examples:

- simultaneous removal of two or more protection groups involves multiple transformations, yet it is carried out in one chemical operation → counted as one step
- sequential transformations via an isolable intermediate that are carried out in two operations and with intermediate workup (incl. quench, in-line filtration to a second reactor, distillation) → counted as two steps
- sequential addition of reagents (or sequential transformations) without workup between additions (transformations) → counted as one step
- separate operation of salt formation from an isolated intermediate → counted as one step (in-process salt formation during workup does not count as a step)
- isolation of a compound, following work-up, as a solution that can be stored → counted as one step
- SMB / column chromatography → counted a one step
- recrystallization of API or intermediate → counted as one step

Solid state operations such as milling or spray-drying are considered part of formulation and not counted as a step.

The Viagra process has 12 steps beginning with ≤ $100/mol commodity starting materials.

Complexity. We closely align our definition with that of Baran,[3] but simplify methodology by including Strategic Redox Steps within the Construction Steps category that counts towards Complexity (ESI Eqn 1).

Construction Steps are chemical transformations that form skeletal API C–C, C–X, C-H, and X-H bonds (X = hetero atom), directly with the correct stereochemistry, if applicable. They include:

- functional group interconversions
- reductions and oxidations that establish the correct functionality with the correct stereochemistry and the correct oxidation state of the drug
- asymmetric reductions and oxidations

Concession Steps are all "non-constructive" reactions and do not form skeletal API bonds, or they do form skeletal but racemic API bonds. They include:

- protecting group manipulations (protections, deprotections)
- functional group interconversions not leading to final API functionality
- racemic reductions and oxidations that do not establish the correct functionality with the correct stereochemistry and the correct oxidation state of the drug
- recrystallization steps
- chromatography
- dynamic kinetic resolution and chemical resolution

In the Viagra example the ester hydrolysis in Step S4 is a Concession Step and therefore not counted towards Complexity.

The Viagra process has a Complexity of 11 beginning with ≤ $100/mol commodity starting materials.

ESI Discussion 3 Which GAL goal is best indicator for molecular complexity?

This section covers the statistical analysis of our data from ESI Table 1, using SAS 9.4, with respect to best fit of selected complexity parameters (no. of fluorine functional groups, rings, and chiral centers) with the waste goals derived from process complexity [GAL(CP), the "old" GAL], molecular weight [GAL(MW)], and molecular weight of the drug excluding salt component [GAL(FMW) = iGAL].

GAL(FMW) – the "new" iGAL. 34% of the variation in iGAL is accounted for by the variation in # (the number of) Chiral Centers, # Fluorine functional groups, and # Rings (ESI Table 2), which renders it the best molecular complexity indicator. # Rings was found to be a significant contributor ($Pr < 0.0001$).

ESI Table 2 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)	26.6%	28.2	37.3	150
GAL(CP)	6.3%	45.8	87.1	192

iGAL Complexity Predictor	DF	Type III SS	Mean Square	F-Value	P-Value [d]
# Chiral	1	53.8	53.8	0.05	0.831
# Fluorine	1	516.1	516.1	0.44	0.508
# Rings	1	33281.0	33281.0	28.57	0.000

[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. [d] F-test: if significant (Pr < 0.05), it indicates that the explanatory variable (# Chiral, # Fluorine, # Rings) contributes significantly to the difference of the response variable iGAL.

GAL(MW) turned out to be the 2nd best complexity indicator with R^2 = 27%.

GAL(CP) – the "old" GAL turned out to be the least accurate indicator for the chosen complexity parameters. Just 6% of the difference in GAL is explained by variation in # Chiral Centers, # Fluorine functional groups, and # Rings.

In summary, the new iGAL reflects complexity better than the old GAL – if molecular complexity is measured by # Chiral centers, # Fluorine functional groups, and # Rings. The GAL(CP) and iGAL goals are also highly correlated with a P-value of 0.000 (ESI Table 3). This means that we measure the same information with iGAL as with GAL(CP) (reliability), but we now have a better measure, i.e. a goal that more accurately reflects molecular complexity.

ESI Table 3 Correlation of iGAL with GAL(CP)

Pearson Correlation Coefficients, N = 64 Prob > |r| under H0: Rho=0	iGAL	GAL(CP)
iGAL	1.00	0.448 0.000
GAL	0.448 0.000	1.00

ESI Discussion 4 Why is the commercial RPG average > 100%?

It may be puzzling to our readers why the commercial RPG average of our dataset is not 100%, but rather 131%. By definition, the RPG for the average commercial process is 100%, because it is based on average commercial cEF (ESI Eqn. 7, ESI Table 4):

ESI Eqn. 7 Determination of RPG for the average commercial process

$$RPG(avg\ commercial\ process) = \frac{iGAL}{avg.\ cEF} \times 100\% = \frac{155}{155} \times 100\% = 100\%$$

ESI Table 4 Understanding average commercial RPG

	cEF [kg/kg]	FMW [g/mol]	iGAL [a] [kg/kg]	RPG [b]
Average commercial process [c]	155	449	155	100% [d]
Fictive Process 1	217	449	155	71%
Fictive Process 2	93	449	155	167%
Average (Process 1&2)	155	449	155	120%

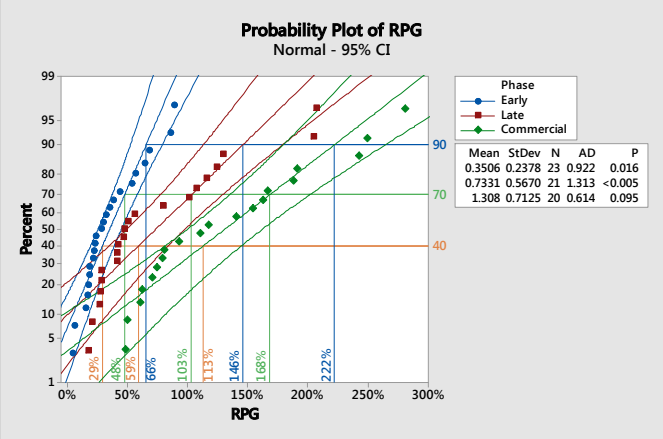
[a] iGAL = 0.344 *x* FMW. [b] RPG = iGAL / cEF *x* 100%. [c] data from commercial phase means of ESI Table 1. [b] derived from ESI Eqn. 7.

As an example for why the average commercial RPG is always greater than 100%, consider two fictive processes of drugs with an average commercial FMW of 449 g/mol as derived from ESI Table 1: process 1 has a cEF that is 40% worse than the average commercial cEF, and process 2 is 40% improved. So, cEF (process 1) = 155 *x* 1.4 = 217 kg/kg, and cEF (process 2) = 155 *x* 0.6 = 93 kg/kg. One would intuitively assume that the RPG average for those two processes is 100%, since the cEF average remains 155 kg/kg. However, the RPG average turns out 119%, which is the result of cEF being in the denominator of the RPG equation (RPG = iGAL/cEF). Thus, cEF reductions (improvements) have a much larger positive effect on cEF than worsening cEF do negatively impact RPG. The lower the variation in cEF values, the closer is the RPG average to 100%.

ESI Discussion 5 iGAL-based RPG rating matrix

RPG scores are derived by comparison of waste of a given process with the average commercial process waste, independent of its development phase. Therefore RPG scores for early and late development phases tend to be low because limited process R&D could be invested into their optimization. Since we consider it critical to encourage green chemistry across the entire spectrum of drug development, we created an equitable rating scale that evaluates the process RPG score against the RPG industry average for the same phase. Thus, the RPG rating matrix is based on three 90, 70, and 40 percentiles for early and late development as well as the commercial phases (ESI Fig. 2, generated from Minitab 17).

ESI Fig. 2 Probability plot of RPG vs. project phase



The top 10% of phase-dependent industry RPG scores receive a rating of "excellent", the 70 percentile "good", the 40 percentile "average", and the bottom 40% get "below average".

ESI Discussion 6 Estimating the impact of selected KPPI on co-generated API waste

In this section we explore and assess the impact of our chosen Key Process Performance Indicators (KPPI) process Complexity (CP, ESI Eqn. 1) and Ideality (I, ESI Eqn. 2) on co-generated drug waste (cEF = PMI – 1) through multiple regression analysis.

We first confirm that cEF and KPPI are not linearly linked and model assumption on normality of the error was checked and failed. Thus a non-linear log transformation to the response variable cEF was applied prior to model fitting. The results of our regression analysis are shown in ESI Table 5 and expressed with Eqn. 4 of the main article.

ESI Table 5 Regression model: effect of Complexity and Ideality on process waste [ln(cEF)]

Parameter	Estimate	Standard Error	T-Value	P-Value
Intercept	5.789	0.390	14.86	0.000
Complexity	0.1437	0.029	5.04	0.000
Ideality	−1.725	0.509	−3.39	0.001

[Main Article] Eqn. 4 Impact of KPPI on cEF

$$\ln(cEF) = 5.789 + 0.1437 \times CP - 1.725 \times I$$

From this model we can infer the following effects of the KPPI on drug manufacturing waste:

1. *Effect of Complexity on cEF*: for every one unit decrease in process complexity there is an 13% average decrease in cEF. For instance, a process with complexity=5 and ideality=80% is expected to deliver cEF=169 (=exp{5.789+0.1437*x*5–1.725*x*0.80}). Holding ideality constant and decreasing complexity from 5 to 4, the expected cEF will decrease by 13% to 146.
2. *Effect of Ideality on cEF*: for every 10% increase in ideality there is an average 16% decrease in cEF. For instance, a process with complexity=5 and ideality=80% is expected to deliver cEF=169. Holding complexity constant and increasing ideality from 80% to 90%, the expected cEF will decrease by 16% to 142.

The appropriateness of our multiple regression model was checked and the normality assumption satisfied (ESI Table 6: goodness-of-fit tests >> 0.05).

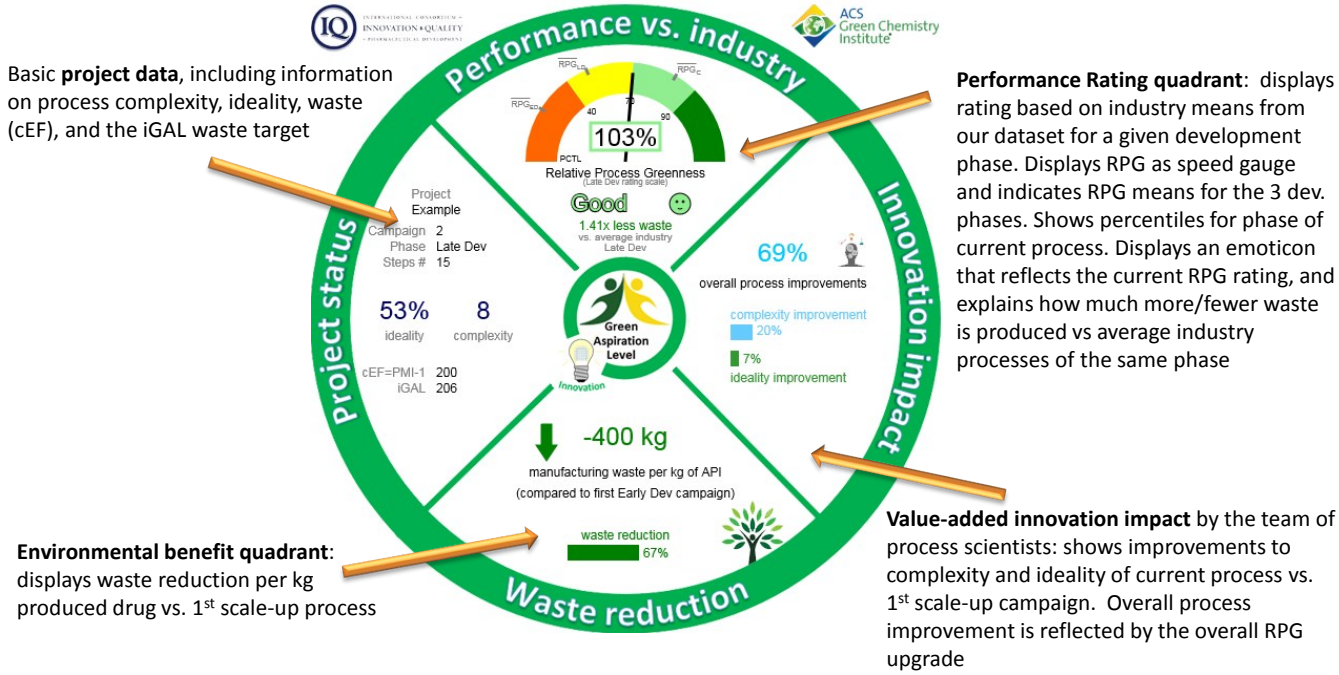
ESI Table 6 Appropriateness check of our multiple regression model

Test for Normality				
Test	Statistic		P-Value	
Shapiro-Wilk	W	0.986	Pr < W	0.697
Kolmogorov-Smirnov	D	0.052	Pr > D	>0.150
Cramer-von Mises	W-Sq	0.019	Pr > W-Sq	>0.250
Anderson-Darling	A-Sq	0.154	Pr > A-Sq	>0.250

ESI Discussion 7 Green Chemistry Innovation Scorecard

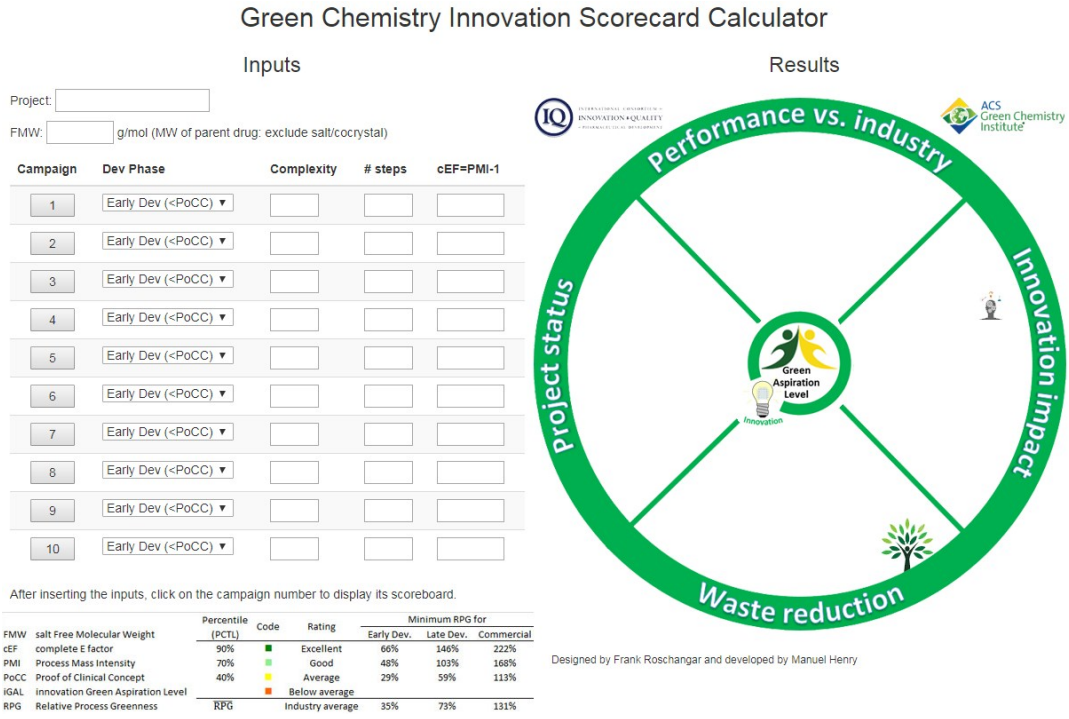
The new Innovation Scorecard keys in on both improvements of the current process *vs.* earlier versions and comparing the greenness of the current process *vs.* industry averages. We herein redesigned the Scorecard to place much greater emphasis on the scientists' value added impact via process innovation, as defined by their improvements to ideality and complexity, and via environmental benefits through overall waste reduction. We furthermore enhanced the rating section 'Performance vs. industry', with a visually appealing performance speed gage, and added in-graph explanatory statements to render the output clear and intelligible to a broad target audience. All of the improvements are reflected in the new and intuitive web-based Scorecard app that represents a greater ease of use from the prior Excel-based version.

ESI Fig. 3 The new Green Chemistry Innovation Scorecard explained



How do we generate the Scorecard shown in ESI Fig. 3? When you navigate to the Green Innovation Scorecard website, you land on a page that requires data from your process for the input section that will be analyzed and the results displayed pictorially in the results section as shown in ESI Fig. 4. At the bottom of the page, you'll find the legend for abbreviations used, as well as the RPG ratings matrix, and RPG industry averages for early development, late development, and commercial phase projects.

ESI Fig. 4 Green Chemistry Innovation Website



Green Chemistry

SUPPLEMENTARY INFORMATION

The inputs are to be filled in with your project name and the free molecular weight (FMW, drug minus any salt component). You can enter data for up to 10 campaigns for the same drug. Campaign 1 should be the first scale-up campaign and *not* reflect data from a small-scale Medicinal Chemistry synthesis. For each campaign, you will need to determine its Complexity, step number, and cEF (= PMI – 1). Obviously, if you have data for only one campaign, you can only measure your performance vs. industry; there can be no output for innovation impact and waste reduction as these reflect improvements over the 1st campaign.

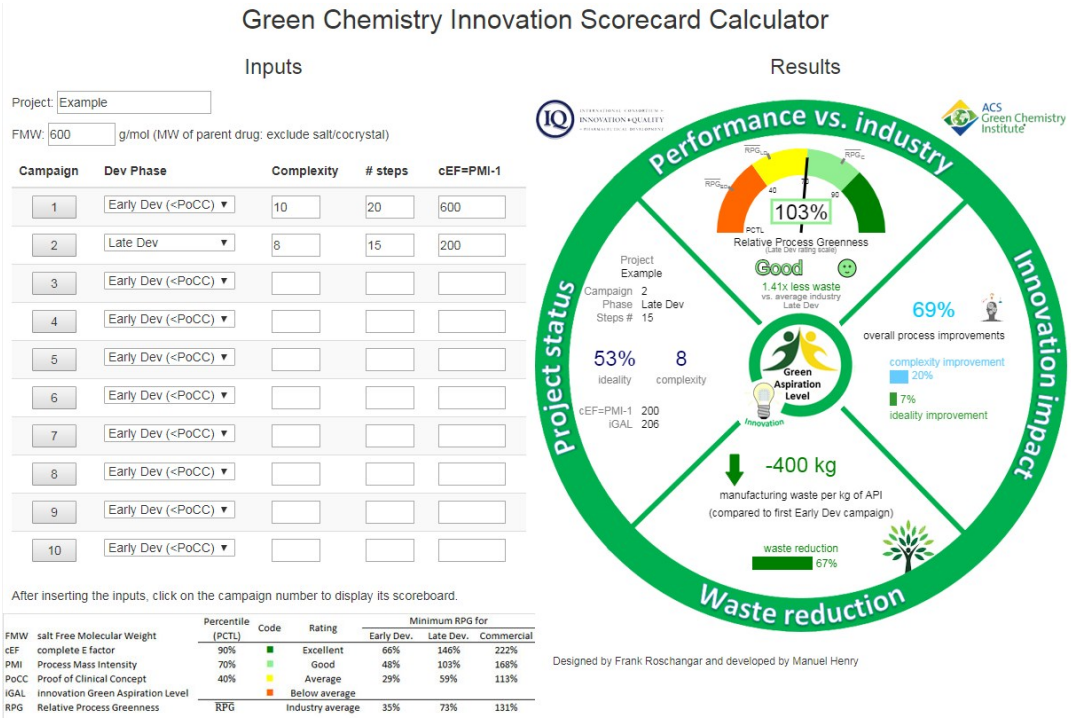
After entering data for two hypothetical campaigns and clicking on the "2" campaign box, we obtain the output shown in ESI Fig. 5. Our current process #2 has a complexity of 8, which is the number of construction reactions necessary to synthesize the API, with an ideality of 53%, which is the ratio of construction steps to overall steps. Thus, almost half of our steps can be considered non-constructive and likely "wasteful." The iGAL for this process is 206 kg waste per kg of produced drug.

Performance vs. industry is rated "good" with an RPG of 103% for this Late Dev project. The average industry RPG for Late stage Development processes is 73%, so ours is better producing 1.41 times less waste, and achieving a rank in the top 30% (= 70th percentile) of same-phase industry processes in terms of amount of co-generated waste.

The innovation impact quadrant displays quantitatively the team's value added process improvements. From campaign #1 to #2, complexity is reduced by 20% while ideality improved by 7%, resulting in an overall innovation impact, or process improvement, of 69% which is the difference between the RPG of campaign #2 and #1. All of the team's improvements lead to an overall reduction of 400 kg co-produced waste for every kg produced drug. Thus, if we had to make 1,000 kg drug we would now co-produce 400,000 kg less waste as result of the realized process innovations.

In summary, we quantify both the impact of process improvements as well as performance of the current process versus industry averages. Both of these metrics in combination are valuable in motivating efforts to achieve the most innovative and greenest manufacturing process.

ESI Fig. 5 Green Chemistry Innovation Scorecard – results screen



Supplementary References

1 See main article, ref. 3.
2 See main article, ref. 1.
3 See main article, ref. 12.