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Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept†

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“Green chemistry” refers to the promotion of safe, sustainable, and waste-minimizing chemical processes. The proliferation of green chemistry metrics without any clear consensus on industry standards is a significant barrier to the adoption of green chemistry within the pharmaceutical industry. We propose the Green Aspiration Level™ (GAL) concept as a novel process performance metric that quantifies the environmental impact of producing a specific pharmaceutical agent while taking into account the complexity of the ideal synthetic process for producing the target molecule. Application of the GAL metric will make possible for the first time an assessment of relative greenness of a process, in terms of waste, *versus* industry standards for the production process of any pharmaceutical. Our recommendations also include a simple methodology for defining process starting points, which is an important aspect of standardizing measurement to ensure that Relative Process Greenness (RPG) comparisons are meaningful. We demonstrate our methodology using Pfizer’s Viagra™ process as an example, and outline aspiration level opportunities for industry and government to dismantle green chemistry barriers.

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Introduction

Green chemistry as a concept for chemical research, development, and operations was introduced in the 1990s. Noyori eloquently expressed that “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.”¹ The cultural shift towards green chemistry has accelerated in recent years, as reflected by numerous review articles and books,^{2–10} and more focused research towards sustainable feedstock for pharmaceutical firms.¹¹

Discussion

Barriers

Full green chemistry adoption in the scientific community still faces significant obstacles that include economic, financial, regulatory, technical, organizational, and cultural barriers.^{12–18} Indeed, “the absence of clear definitions and metrics for use by researchers and decision makers” is a significant impediment to realization of green chemistry’s full potential.

In addition, there are barriers specific to the pharmaceutical industry. Any change to the synthesis process for an Active Pharmaceutical Ingredient (API) of a drug becomes increasingly challenging as the drug progresses through development, because there are increasing regulatory requirements at each phase, and process changes closer to the end of the manufacturing process have a larger potential impact on API quality. The US Food and Drug Administration’s (FDA) International Conference on Harmonization (ICH) Q11 document offers guidance for the development and manufacture of APIs, including recommendations for qualifying process changes.¹⁹ In early preclinical development through early Phase 2, one expects changes in the production process, since the process knowledge base is limited and growing. These early process changes have minimal impact to regulatory filings because only limited synthesis and control information is typically included in the initial regulatory filings.²⁰ However, at the end of Phase 2, the initial regulatory filing is updated with more detailed process and control information, and the synthesis is ideally “locked” for use in production of Phase 3 clinical trial API supplies. Any changes post-Phase 2 are higher risk due to the potential impact on the Phase 3 trial supplies, because the API process is considered to be the foundation of the safety and efficacy of the clinical trial medication. Process changes during Phase 3, in a worst-case, could invalidate a Phase 3 clinical trial. Post New Drug Application (NDA) approval, any fundamental change in technology, site, or manufacturing process (including any modification of the API synthesis that

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may affect its impurity profile) requires submission of a supplement and approval by FDA prior to distribution of the drug.²¹ Given all of these regulatory concerns, pharmaceutical companies have an incentive to implement all necessary improvements to the production process for API's prior to late Phase 2 or Phase 3 trials and then lock the final manufacturing process, in order to avoid time-consuming revalidation and regulatory resubmission activities that would be associated with any process changes during late-phase development. Adding to the time pressures associated with green process development for production of pharmaceuticals is the fact that after FDA approval, the average effective patent life of a brand name drug is just 12 years.²² In this context, pharmaceutical firms have little tolerance for delays in bringing a new drug to market, especially when the current costs of drug development are so high. Research and Development (R&D) costs for each FDA-approved drug, considering project attrition rates of failed drug development projects, are estimated at \$1.2–1.8 billion, and must be recouped through sales of marketed drugs.^{23,24} Given all of these concerns, the reality is that the API processes developed by pharmaceutical companies do not always reflect the best possible molecular assembly strategies. This outcome leads to higher environmental and economic costs for the firm, and a less favorable environmental impact than might be achieved under a different set of constraints.

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ consortium)²⁵ has recently recognized some of the barriers to green chemistry that are inherent in the current regulations governing the approval of new drugs and the quality of drugs already on the market. Encouragingly, this recognition has led to an ongoing dialogue with the FDA.²⁶ Our perspective on green chemistry barriers within the pharmaceutical industry is summarized in Fig. 1.

Metrics

An old yet proven management adage is that “you can't manage what you don't measure.” The specific metrics chosen to serve as indicators of the performance of any system are crucial.²⁷ Green chemistry metrics currently in use have demonstrated strong positive correlation to process economics.



Fig. 1 Green chemistry barriers in the pharmaceutical industry.

For example, lower *E* factors have been shown to be indicative of reduced manufacturing costs,^{18,28} reflecting lower process materials inputs and outputs; reduced costs from hazardous and toxic waste disposal, improved manufacturing capacity utilization, and reduced energy demand.²⁹ These findings demonstrate that the pharmaceutical industry has strong economic incentives to integrate green chemistry into the entire process research, development, and manufacturing lifecycle.

The conceptual design of the “ideal” commercial synthetic route is of paramount importance for creating the greenest possible process. In 1990 Corey won the Nobel Prize for his concept of effective synthetic planning *via* “retrosynthesis”, in which the chemist starts with the target molecule, and works backward *via* efficient bond dissection to arrive at simple and readily available raw materials.^{30,31} Trost and Sheldon went beyond synthesis design and recommended assessing efficiency through Atom Economy (AE)^{32,33} and Environmental Impact Factor (*E* factor),^{34–40} with the implied goal of achieving the highest degree of efficiency coupled with lowest possible environmental impact. Trost received the Presidential Green Chemistry Award for his contributions in 1998,⁴¹ which motivated process chemists to explicitly consider waste generation as a factor in molecular design, in addition to the common criteria of synthetic convergence, raw material strategy, chemical yield, and cost of goods. Green chemistry metrics have subsequently proliferated in number (Table 1),^{42–45} but have not yet reached industry-wide standardization and adoption.

Since various metrics may be confusing to the reader (and are not always used consistently in the literature), we summarize them and their relationship to process materials graphically in Fig. 2. For example, the metrics encompassing the API and the raw materials are Reaction Mass Efficiency (RME), Atom Economy (AE), Chemical Yield (CY), and Carbon Efficiency (CE), the metrics including API, raw materials and reagents are Reaction Mass Intensity (RMI) and Effective Mass Yield (EMY), *etc.* The most common mass metrics are *E* factor and Process Mass Intensity (PMI).

The *Environmental Impact Factor*, or *E* factor, assesses the efficiency of a step or process by measuring the total amount of chemical waste generated relative to each kg of isolated product, accounting for yield, spent reagents and solvent losses, except for water. The *E* factor is simply the ratio of kg waste to kg product whereby, in the original publication,³⁴ waste was defined as “anything that is not the desired product.” The rationale for excluding process water was possible skewing of *E* factors (thus rendering meaningful process comparison difficult), and the fact that water use would not constitute a significant environmental impact in most cases. However, the current trend in the pharmaceutical industry is towards including water use in the *E* factor, and in a recent paper *E* factors were calculated for a biocatalytic process to an atorvastatin intermediate with and without water for comparison.⁴⁶ A high *E* factor indicates more waste generation and a more negative environmental impact. The ideal *E* factor is 0.

Table 1 Common process efficiency metrics

Common green chemistry process metrics	Common abbreviation	Formula	Unit of measure	Consideration for				Optimum value	Inventor consideration
				Waste?	Yield?	Stoichiometry?	Solvents? Water?		
Chemical yield	CY	$\frac{m(\text{Product}) \times \text{MW}(\text{Raw material}) \times 100}{m(\text{Raw material}) \times \text{MW}(\text{Product})}$	%	✓	✓	✗	✗	100%	
Atom economy	AE	$\frac{\text{MW}(\text{Product}) \times 100}{\sum \text{MW}(\text{Raw materials}) + \sum \text{MW}(\text{Reagents})}$	%	✓	✗	✗	✗	100%	Trost (1991) ³¹
Environmental impact factor	E-factor	$\frac{\sum m(\text{Input materials}) - m(\text{Product})}{m(\text{Product})}$	kg kg ⁻¹	✓	✓	✓	✗	0	Sheldon (1992) ³⁴
Mass intensity	MI	$\frac{\sum m(\text{Input materials})}{m(\text{Product})}$	kg kg ⁻¹	✓	✓	✓	✗	1	Constable, Curzons (2001) ⁴²
Process mass intensity	PMI	$\frac{\sum m(\text{Input materials incl. process water})}{m(\text{Product})}$	kg kg ⁻¹	✓	✓	✓	✓	1	ACS GCI Pharmaceutical Roundtable (2007)
Process mass efficiency	PME	$\frac{m(\text{Product}) \times 100}{\sum m(\text{Input materials incl. process water})}$	%	✓	✓	✓	✓	100%	EPA & Hanson (2006)
Mass productivity	MP	$\frac{m(\text{Product}) \times 100}{\sum m(\text{Input materials})}$	%	✓	✓	✓	✗	100%	Constable, Curzons (2001) ⁴²
Reaction mass efficiency	RME	$\frac{m(\text{Product}) \times 100}{\sum m(\text{Raw materials})}$	%	✓	✓	✓	✗	100%	Constable, Curzons (2001) ⁴²
Effective mass yield	EMY	$\frac{m(\text{Product}) \times 100}{\sum m(\text{Raw materials}) + \sum m(\text{Reagents})}$	%	✓	✓	✓	✗	100%	Hudlicky (1999)
Reaction mass intensity	RMI	$\frac{\sum m(\text{Raw materials}) + \sum m(\text{Reagents})}{m(\text{Product})}$	kg kg ⁻¹	✓	✓	✓	✗	1	Senanayake (2012)
Carbon efficiency	CE	$\frac{m(\text{Carbon in product}) \times 100}{\sum m(\text{Carbon in raw materials})}$	%	✓	✓	✓	✗	100%	Constable, Curzons (2001) ⁴²
Solvent intensity	SI	$\frac{\sum m(\text{Solvents})}{m(\text{Product})}$	kg kg ⁻¹	✓	✗	✗	✓	0	Constable, Curzons (2001) ⁴²
Wastewater intensity	WWI	$\frac{\sum m(\text{Process water})}{m(\text{Product})}$	kg kg ⁻¹	✓	✗	✗	✓	0	Constable, Curzons (2001) ⁴²

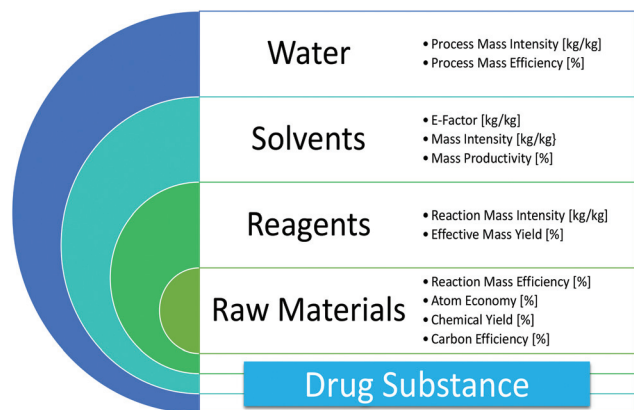


Fig. 2 Process material – green mass metrics relationships.

Typical *E* factors for various segments of the chemical and allied industries, originally estimated by Sheldon in 1992,³⁴ indicated that the pharmaceutical industry faces a substantially elevated waste burden (Table 2).⁴⁰ As noted above, the *E* factor included solvent losses if they were known. If they were not known, it was assumed that 90% of the solvent would be recovered and recycled based on personal experience.³⁶ In hindsight, this was probably too optimistic in the context of pharmaceutical operations where combinations of solvents and reagents are often used, making recycling efforts difficult. The original *E* factor table was expanded by the American Chemical Society (ACS) Green Chemistry Institute (GCI) to include total annual waste tonnage as calculated by multiplying the highest *E* factor with the largest annual production volume, estimated number of steps, and development times used for process optimization.⁴⁷

A primary cause of the high *E* factors within the pharmaceutical industries is the high molecular complexity and the corresponding large number of chemical transformations required to assemble APIs. This stands in contrast to other sectors of the chemical industry, where target molecules are simpler and require a smaller number of steps for their synthesis. As noted earlier, we also need to consider regulatory constraints, high R&D costs, and limited sale exclusivity periods of innovative drugs as constraints in the pharmaceutical industry that specifically curb the penetration of green chemistry. These factors, in the setting of high industry profit margins,⁴⁸ diminish the incentives for pharmaceutical firms to 'green' the chemical processes during development or after commercial launch. In addition, process inefficiencies may

arise from stringent analytical control requirements often necessitating additional isolations (*e.g.* recrystallizations, reworks) of current Good Manufacturing Practice (cGMP) intermediates as quality control points.

Process Mass Intensity (PMI)^{47,49,50} was introduced by the EPA and ACS GCI in 2006 and assesses efficiency by considering all materials as well as water used in a step or process, inclusive of workup chemicals (eqn (1)). Energy consumption, safety and environmental impact are not considered.

Determination of PMI

$$\text{PMI} = \frac{\sum m(\text{Input materials incl. process water})}{m(\text{Product})} \quad (1)$$

The ACS GCI also made a philosophical argument in favor of using the PMI,⁵⁰ and recently compiled industry waste data for pharmaceutical manufacturing processes of projects across various development phases including commercial phase in 2007 and 2008, which allowed for their correlation with PMIs (Fig. 3).^{47,51,52} As expected, we observe that PMI improves over the course of development, trending downward with each advancing development phase. The most pronounced reduction in PMI occurs at the transition from preclinical development to Phase 1.

In an analysis of PMIs, the ACS GCI determined that solvents and water make up 58 and 28 weight% of process waste, respectively, supporting the conclusion that water and solvents are a major waste source in pharmaceutical manufacturing, while raw materials account for 8% of overall process waste (Fig. 4).⁵¹ However, one must keep in mind that the waste problem associated with raw materials and reagents is much larger than is reflected by their waste percentage contributions as they are generally not recyclable.

The PMI analysis also enables us to correlate the ACS GCI results with Sheldon's original *E* factor analysis (see Table 2 above), which discounts process water and assumes 90% solvent recycling.³⁶ Sheldon had postulated that pharmaceutical industry *E* factors range from 25 to greater than 100, and the ACS GCI analysis confirmed this assumption. When excluding values for preclinical projects, the PMI-derived *E* factors are in the range of 47–86 with a commercial median of 47 (Table 3).

Table 2 *E* factors, waste and process complexity across chemical industries

Industry segment (examples)	Annual product tonnage (each)	<i>E</i> -factor (kg waste/kg product)	Total annual waste tonnage	No. of steps	Years of development
Petrochemicals (solvents, detergents)	1 000 000–100 000 000	~0.1	10 000 000	'Separations'	100+
Bulk chemicals (plastics, polymers)	10 000–1 000 000	<1–5	5 000 000	1–2	10–50
Fine chemicals (coatings, electronic parts, pharmaceutical raw materials)	100–10 000	5–>50	500 000	3–4	4–7
Pharmaceuticals (antibiotics, drugs, vaccines)	10–1000	25–>100	100 000	6+	3–5

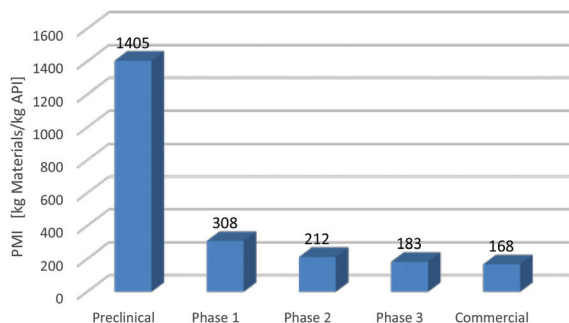


Fig. 3 2008 median PMI by development phase.

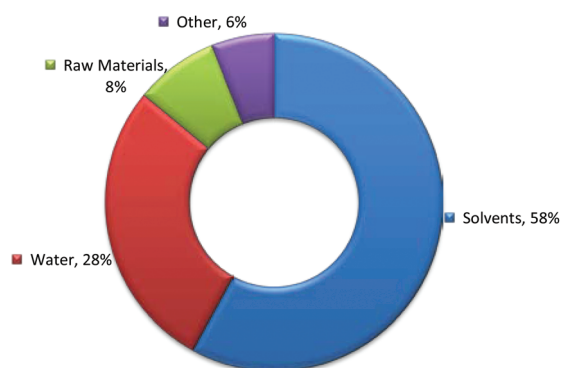


Fig. 4 Pharmaceutical manufacturing PMI composition.

Table 3 PMI to *E* factor conversion

	PMI and <i>E</i> -factor (kg materials per kg API) by development phase				
	Preclinical	Phase 1	Phase 2	Phase 3	Commercial
PMI median	1405	308	212	183	168
– Est. water @ 28% of PMI	393	86	59	51	47
– 90% of solvents @ 49% of PMI	620	136	93	81	74
Sheldon's <i>E</i> -factor	392	86	59	51	47

including raw materials, reagents, solvents, water, and drug substance, and is more appropriate for total process waste stream analysis, while the sEF metric discounts water and solvents and is more appropriate for early development phase process route scouting activities. The cEF does not consider recycling since process developers cannot estimate to what degree solvents and process water will ultimately be recycled across the entire supply chain, due to competitive region-specific waste economics associated with energy recovery burning and treatment options.⁵³ The 'true' commercial *E* factor will therefore fall somewhere between the sEF and cEF, and we recommend calculating a recycling-adjusted *E* factor when reliable commercial solvent loss data are available.

sEF and cEF formulae

$$\begin{aligned}
 \text{cEF} &= \frac{\sum m(\text{Raw materials}) + \sum m(\text{Reagents}) + \sum m(\text{Solvents}) + \sum m(\text{Water}) - m(\text{Product})}{m(\text{Product})} \\
 \text{sEF} &= \frac{\sum m(\text{Raw materials}) + \sum m(\text{Reagents}) - m(\text{Product})}{m(\text{Product})}
 \end{aligned}
 \quad (2)$$

Opportunities

The green chemistry community is currently dealing with a plethora of similar metrics (Table 1) without standardized definitions or agreed upon process starting points. This circumstance inhibits industry-wide green chemistry integration. We herein present our suggestions to standardize nomenclature, definitions, and methodology; and introduce our novel concept of a quantitative green chemistry aspiration level.

(1) *Metrics Standardization with E factor Concepts.* When evaluating PMI for a multi-step process, we find the *E* factor concept more suitable and mathematically simpler since step *E* factor contributions are additive while step PMI contributions are not, because the PMI does not discount the step product from the step mass balance (for details see Appendix 1). Given that the *E* factor is widely accepted within the scientific community, but sometimes prone to inconsistent application for total waste since it is up to the evaluator to estimate solvent recycling levels if they are not known,³⁶ we propose two new *E* factor derivatives for green chemistry analysis: (a) the "complete *E* factor," (cEF), and (b) the "simple *E* factor", (sEF) (eqn (2)). The cEF metric accounts for all process materials,

The appropriate time to switch from using the simple *E* factor (sEF) metric to the complete *E* factor (cEF) metric is post finalization of the API process, *i.e.* after raw materials, intermediates, and synthesis step sequence for the final commercial manufacturing route have been selected. This ideally occurs after the Investigational New Drug (IND) filings and before Phase II, in order to allow sufficient time to develop a robust process prior to the NDA. Early phase drug development activities from preclinical development to the end of Phase I require about 2–3 years, while late-phase development until commercial launch takes about 6–7 years.⁵⁴ Thus, the timeline to identify and select the final manufacturing process is short, and the simple yet valuable sEF green chemistry metric is needed to motivate productive green process R&D under such time constraints.

(2) *Intrinsic Raw Material E factors & Synthesis Starting Points.* Intrinsic raw material *E* factors directly relate to the definition of synthesis starting points. In green process analysis, firms often look solely at insourced process steps. In other words, their analysis encompasses only those processes conducted at the manufacturing site of the pharmaceutical

firm, and considers procured materials as the starting points for synthesis. However, such purchased materials may themselves constitute complex advanced intermediates, prepared over multiple prior synthetic steps from readily available raw materials.

The definitions of starting points for synthesis are almost certainly inconsistent when green chemistry metrics are applied today to production processes in the pharmaceutical industry.^{55,56} For example, one can dramatically reduce the process *E* factor overnight by purchasing an intermediate rather than making it. A good demonstration of the importance of this matter is reflected in our subsequent analysis of the commercial ViagraTM process. Selection of synthesis starting points is based on the individual firm's procedures and departmental perspectives, and typically evolves throughout the development process, *i.e.* the further a project progresses in development, the greater is the proportion of outsourced chemistry steps and the closer the process starting points get to the API as reflected by reduced process step count. From our internal project analysis spanning from 2006 through 2013, we find that about 20–50% of the chemistry steps are outsourced in early development, and about 30–70% in late development and after commercial launch.

For the purposes of our analysis, we can reasonably assume that 50% of the process chemistry steps of commercial innovator drugs are typically outsourced. We infer that at least 50% of the overall process waste is outsourced as part of the procured raw materials, since waste generation during early steps is amplified through yield losses of late synthesis steps as result of higher input requirements. Therefore, it is important to consider the intrinsic *E* factors associated with the procured raw materials. But what should be the synthesis starting point to determine those *E* factors?

Obviously, we could define natural resources as the earliest starting point for any synthesis. However, it is impractical for process chemists to estimate the *E* factors that are associated with the conversion of natural resources to basic commodity chemicals. The ACS GCI started to address the topic of process starting point. Ref. 47, page 6. Its definition of a process starting point is aligned with our proposal in that commonly available starting materials, herein called raw materials, are defined as the starting points of synthesis. In order to qualify as such, these raw materials must be easily commercially available, not include transfer of IP from the innovator to the supplier, and not be made specifically for a particular process or firm. These commodity-type raw materials should serve as the starting point for any *E* factor analysis within the pharmaceutical industry. However, the ACS GCI's definition may not lend itself to ready implementation by process researchers, due to the lack of resources to research raw material availability and their commercial usage.

One longer-term solution to the intrinsic *E* factor dilemma may be to introduce government regulations that mandate *E* factor labelling for all chemical products, which we discuss later. However, it would be expeditious to have a more immediate

solution. So how can we better define commodity chemicals and arrive at a simple and practical solution that any process researcher can readily implement? For the purposes of our *E* factor analysis, we suggest using catalog pricing from Sigma-Aldrich, the world's largest supplier of research compounds, currently offering 147 000 chemicals.⁵⁷ We now propose that a commodity-type raw material be defined as a synthesis starting point if it meets the following criteria: (1) the raw material is commercially available from Sigma-Aldrich's website, and (2) the cost of the raw material at its largest offered quantity does not exceed \$100 mol⁻¹. This pricing requirement does not apply to reagents, catalysts, ligands, and solvents, since they are produced for widespread application and are not specific to the process being evaluated.

(3) *API and Process Complexity*. It can take a significant number of synthesis steps to convert commercial raw materials to the API,⁵⁸ depending on the respective API's intrinsic molecular complexity as well as its manufacturing process complexity. While progress has been made to correlate molecular with process complexity in terms of PMI or *E* factor, we will utilize process complexity in order to derive at an achievable and measurable green process goal.⁵⁹

One could correlate the complexity of an API solely with the number of chemical transformations required to make it from raw materials. However, this definition would oversimplify the analysis, since it does not reflect how efficiently the final product is being prepared. For example, a process chemist could synthesize the same API in 10 or in 20 steps from the same raw materials, and in that case we would assume that the 10-step process more closely reflects the "ideal" synthesis as an indicator for API complexity, rather than its 20-step inferior alternative. In 1975, Hendrickson first defined an ideal synthesis as one that "creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalization, and leading directly to the target, not only its skeleton but also its correctly placed functionality."⁶⁰ In 1993, Wender refined the definition of an ideal process to one that "may be defined as one in which the target molecule is prepared from readily available starting materials in one simple, safe, environmentally-acceptable, and resource effective operation that proceeds quickly and in quantitative yield."⁶¹ Of course, a single step operation from basic raw materials is not achievable in the pharmaceutical industry, as drugs tend to have high molecular complexity. The concept of process ideality by Hendrickson and Wender is in full alignment with the green chemistry principles proclaiming minimal use of protecting groups and functional group inter-conversion (principles #2 and 8 – atom economy and minimization of derivatives), and reflects the underlying consideration for economic process design.⁶² Metrics assessing process ideality were subsequently framed *via* Trost's atom economy in 1991,^{32,33} Wender's *step economy* in 2006,^{63–65} and Baran's redox economy in 2008.^{66,67}

For purpose of assessing relative process greenness, we find it most practical to utilize Baran's process% ideality metric,

introduced in 2010, which elegantly and simply combines the aforementioned definitions of an ideal synthesis, and is mathematically shown in eqn (3).⁶⁸

Baran's process ideality metric (reactions = transformations)

$$\% \text{ideality} = \frac{\text{no. of construction reactions} + \text{no. of strategic redox reactions}}{\text{total no. of reactions}} \quad (3)$$

In this metric, Construction Reactions (CR) are defined as chemical transformations that form skeletal C–C or C–heteroatom bonds. Strategic Redox Reactions (SRR) are a type of construction reaction that directly establish the correct functionality found in the final product, and include asymmetric reductions or oxidations. All other types of “non-strategic” reactions are considered as Concession Steps (CS), and include functional group interconversion, non-strategic redox reactions, and protecting group manipulations. These concession steps are often required in modern synthesis. To define our measure of process complexity, we deploy an extension of Baran's methodology and use the combination of total number of reactions or chemical transformations, multiplied by % ideality. It is apparent that this measure simply corresponds to the number of productive transformations, *i.e.* the number of constructions reactions plus the number of strategic redox reactions (eqn (4)). The higher this number, the greater is the complexity of the process.

Simple definition of process complexity (reactions = transformations)

$$\begin{aligned} \text{Complexity} &= \% \text{ideality} \times \text{total no. of reaction} \\ &= \text{no. of construction reactions} \\ &\quad + \text{no. of strategic redox reactions} \end{aligned} \quad (4)$$

We point out that the process complexity for a given API can be reduced through process re-design and development of a novel, more efficient synthetic route.

(4) *Electronic Laboratory Notebook*. In order for green chemistry initiatives to be successful, green metrics analysis must not only be standardized but also made simple and user-friendly using automation whenever possible. We recommend following the suggestion of Kopach to make the electronic laboratory notebook (ELN) an integral part of every green chemistry program.^{69,70} The ELN has the potential to comprehensively automate calculations of step and process *E*

factors and raise warning flags for chemicals listed on EPA's toxics release inventory (TRI), persistent bioaccumulative and toxic chemicals (PBT), Drug Enforcement Administration (DEA) controlled substances, Occupational Safety and Health Administration (OSHA) carcinogens, reproductive toxins, and REACH⁷¹ substances of very high concern. Use of the ELN can also alert the user to the company's reagent and solvents preferences according to selection guides.¹⁸ At Eli Lilly, the PMI analysis, hazardous chemical designation, and solvent selection have already been integrated into the ELN.¹⁸

The Green Aspiration Level™ concept

Herein we introduce the novel Green Aspiration Level™ (GAL) concept that will allow for an unbiased metric of green process performance relative to industry. Application of the GAL concept will provide an opportunity to standardize the measurement of green chemistry processes across the pharmaceutical industry. We base the concept on modified *E* factors and process complexity, and note that PMI could be used as a substitute for the *E* factors. While process researchers at pharmaceutical companies typically use comparative *E* factors to showcase the positive impact of their chemical waste reduction efforts during evolution of medicinal chemistry routes to commercial manufacturing processes, we see an opportunity to define industry-wide SMART⁷² green chemistry process goals. To date, the green chemistry community lacks such goals and has been defining success as a reflection of the amount of waste reduction relative to earlier process routes, going so far as to compare manufacturing processes with Medicinal Chemistry routes, even though the latter have entirely different aims and focus on producing molecular diversity rather than convergence. To exemplify the shortcomings of defining “greenness” in relative terms, if we were to start out with a non-ideal and high waste-generating process, and we significantly reduced waste relative to the original process without changing the process, even the “optimized” process might still be far from ideal. In other words, we might still have an inefficient synthetic process with unnecessarily adverse environmental impact, and yet we would consider the process to be “green,” if greenness were defined only in relative terms.

In order to measure green chemistry process performance in specific and absolute terms, we first have to define a standardized aspiration level. We call it the process *Green Aspiration Level* measure, or GAL. In order to determine GAL, we first derive average development phase-dependent *E* factors for the pharmaceutical industry as a whole from the PMIs as reported by the ACS GCI. Based on our recommendation to utilize the sEF prior to Phase 2 and the cEF in later phases, we select the median *E* factor for Phase 1 as early phase aspiration baseline input, and the commercial phase values as late phase baseline input, with PMI (Phase 1) = 308 kg kg^{−1} and PMI (Commercial) = 168 kg kg^{−1} (Fig. 3). Knowing that solvents constitute 58% and water 28% of the pharmaceutical waste stream (Fig. 4), we can infer the average early and late development phase industry values for cEF (= PMI − 1) = 307 kg kg^{−1} for Phase 1 and

167 kg kg⁻¹ for commercial projects, and sEF (= $PMI - 1 - SI - WWT$) = 42 kg kg⁻¹ for Phase 1 and 23 kg kg⁻¹ for commercial projects (for definitions see Table 1). We further assume that the average number of steps per drug target that went into ACS GCI's PMI analysis is seven,⁴⁴ and estimate that we have an average of 1.3 transformations per step with no concession transformations,⁷³ so we obtain an average process complexity of about 9 (= $7 \times 1.3 - 0$) per drug target. This allows us to derive aspiration levels for the average chemical transformation (transformation-GAL or tGAL) and process (GAL) per eqn (5).

Definition of transformation-GAL (tGAL) and process-GAL (GAL)

$$\begin{aligned} \text{tGAL} &= \frac{\text{xEF}}{\text{Average complexity}}, \quad \text{with xEF} = \text{sEF or cEF} \\ \text{GAL} &= (\text{tGAL}) \times \text{Complexity} \end{aligned} \quad (5)$$

We can now determine the development phase-dependent tGALs for sEF and cEF (Table 4), which we recommend as basis for harmonized development of phase-dependent pharmaceutical green chemistry process goals.

The GALs permit us to measure the green status of a synthetic process relative to its aspiration level, using a new metric that we refer to as *Relative Process Greenness* (RPG, eqn (6)). An RPG greater than 100% exceeds the process greenness goal (GAL) based on average green chemistry process performance in the industry. In contrast, RPG values less than 100% indicate green chemistry performance that is below the industry average, suggesting the synthetic process in question might benefit from further process optimization.

Determination of relative process greenness (RPG)

$$\text{RPG} = \frac{\text{GAL}(\text{xEF})}{\text{xEF}(\text{actual})}, \quad \text{with xEF} = \text{sEF or cEF} \quad (6)$$

Now we are able to express overall process improvements not only by relative reductions of cEF and sEF, but also by examin-

ing changes in RPG from one phase of development to the next, using a metric that we refer to as *Relative (Green) Process Improvement* (RPI), while accounting for *Relative (Process) Complexity Improvement* (RCI). For example, if we have a process for project X that was improved along development from Phase 1 to Phase 3 from an "original process" to a "new process", we can determine RPG and RPI for the two *E* factors with eqn (6) and (8), and RCI with eqn (8). The results for the hypothetical project are summarized in the Green Scorecard shown in Table 5.

Determination of relative (Green) process improvement (RPI)

$$\text{RPI} = \text{RPG}(\text{Current process}) - \text{RPG}(\text{Earlier process}) \quad (7)$$

Determination of relative (process) complexity improvement (RCI)

$$\text{RCI} = 1 - \frac{\text{Complexity}(\text{Current process})}{\text{Complexity}(\text{Earlier process})} \quad (8)$$

For simplicity, we assume that RPI and RCI contribute equally to overall (Green) Process Improvement (PI, eqn (9)).

Determination of overall green process improvement

$$\text{PI} = \frac{\text{RPI} + \text{RCI}}{2} \quad (9)$$

In our example in Table 5 the original process from Phase 1 is first improved by eliminating two concession steps. Process complexity remains at 8, so RCI is 0%, and the cEF-based RPG increases 86 to 109%. The process chemists and engineers subsequently implement an efficient new process in which process complexity is reduced from 8 to 5, so RCI is 38%. We chose this example to illustrate that RPG can actually decrease (from 109 to 94%) due to higher waste generation per step relative to industry standards, even though overall process waste is reduced (from 140 to 96 kg kg⁻¹). The green goal to arrive at a process that is in line with or better than industry targets (RPG ≥ 100%) does remain, but this example shows that reductions in process complexity must be considered, and hence we introduced the PI as measure for overall green process improvement. In our example, the cEF-based PIs are 11% and 25% when comparing original and new Phase 3 processes against the original Phase 1 process, respectively, so the overall green process improvements for the new process are greater.

Table 4 Suggested pharmaceutical development phase-dependent GALs

E-factor type	Complexity	Aspiration level type	Phase 1 [kg kg ⁻¹]	Commercial [kg kg ⁻¹]
sEF Process	9	GAL	42	23
sEF Step	1	tGAL	5	3
cEF Process	9	GAL	307	167
cEF Step	1	tGAL	34	19

Table 5 The green scorecard: RPG, RPI, RCI, and PI analysis for sample project X

Project X	Transformations/ concession steps	sEF-based analysis				cEF-based analysis				
		Complexity	Actual [kg kg ⁻¹]	tGAL [kg kg ⁻¹]	GAL [kg kg ⁻¹]	RPG	Actual [kg kg ⁻¹]	tGAL [kg kg ⁻¹]	GAL [kg kg ⁻¹]	RPG
Phase 1/original process	10/2	8	45	5	40	89%	315	34	272	86%
Phase 3/original process	8/0	8	20	3	24	120%	140	19	152	109%
Phase 3/new process	5/0	5	16	3	15	94%	96	19	95	99%
Improvements of phase 3 original v. phase 1 process	0		25		Improvement metric	Improvement result	175		Improvement metric	Improvement result
					RPI	31%			RPI	22%
					RCI	0%			RCI	0%
Improvements of phase 3 new v. phase 1 process	3		29		PI	16%	219		PI	11%
					RPI	5%			RPI	13%
					RCI	38%			RCI	38%
					PI	21%			PI	25%

In summary, for full evaluation of green performance, RPG and RPI should be reported conjointly with RCI, PI, as well as sEF and cEF improvements. When multiplying cEF of a commercial product with the product's annual production volume, we obtain the amount of its annual process waste stream.

We are hopeful that the new Green Aspiration LevelTM (GAL) concept, coupled with measures of Relative Process Greenness (RPG), Relative Green Process Improvement (RPI), Relative Process Complexity Improvement (RCI), and Overall Green Process Improvement (PI) will motivate and enable scientific leaders and researchers across pharmaceutical R&D and manufacturing to set SMART internal green process goals, and thereby drive and integrate green chemistry performance into daily workflows. However, in order for the GAL concept to be successful, pharmaceutical firms need to cooperate and publish up-to-date greenness transformational GAL industry targets. Influential green chemistry organizations such as the ACS GCI and IQ Consortium cooperatives could play an important role by facilitating the transparent sharing of such green chemistry performance data across the pharmaceutical industry. Going forward, we aim to implement an API complexity-derived GAL that would reflect a process *E* factor target based on a process complexity goal. Our current methodology does not include an aspiration level for process complexity. The Eli Lilly API complexity concept⁵⁹ may be suitable for our purposes, but will require more industry process analyses for validation and refinement.

In Fig. 5 we graphically summarize integration of the GAL concept into process design, development, and manufacturing, through use of simple and complete *E* factors in combination with considerations for process ideality and complexity that enables the setting of standardized RPG goals in order to arrive at measurably green manufacturing processes.

Pfizer's commercial ViagraTM process

We use Pfizer's ViagraTM (sildenafil citrate) process to exemplify the new concepts of process complexity, GAL, and RPG, and to showcase the critical importance of harmonized process starting points (for analysis details see Appendix 2). The commercial process for ViagraTM won the 2003 UK Institute of Chemical Engineers (IChemE) Crystal Faraday Award for Green Chemical Technology by significantly reducing the amount of generated organic process waste.^{74–77} To start our analysis, we evaluate the process with sEF and cEF metrics in combination with our starting point concept. The overall commercial process scheme for Pfizer's ViagraTM is shown in Scheme 1.

We first determine the amounts of all materials required to make 1 kg of ViagraTM, and identify those materials that do not meet the \$100 mol⁻¹ price criteria to qualify as raw materials. For any materials that do not qualify as raw materials, their respective synthesis is considered in the *E* factor analysis. This allows us to derive the step and process sEFs and cEFs. For comparative purposes, we include the traditional *E* factor which assumes 90% solvent recycling if no data are available³⁶ and fully discounts process water (Table 6).

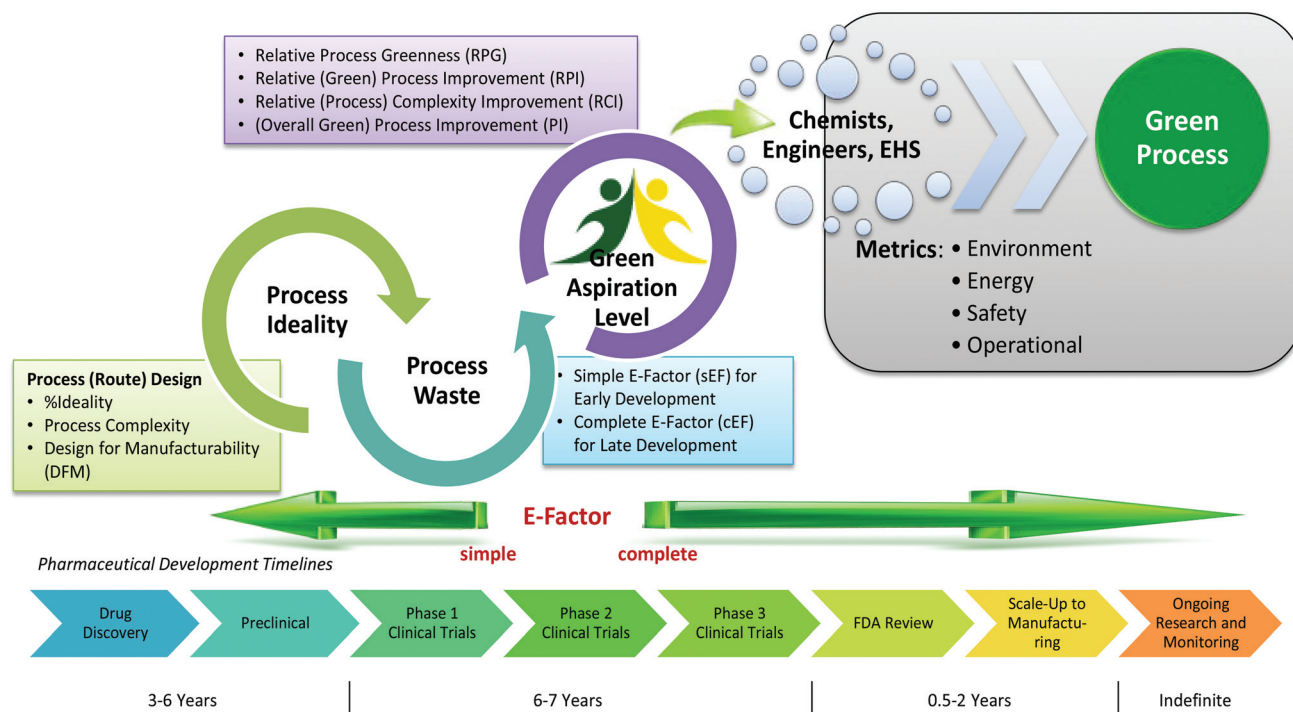
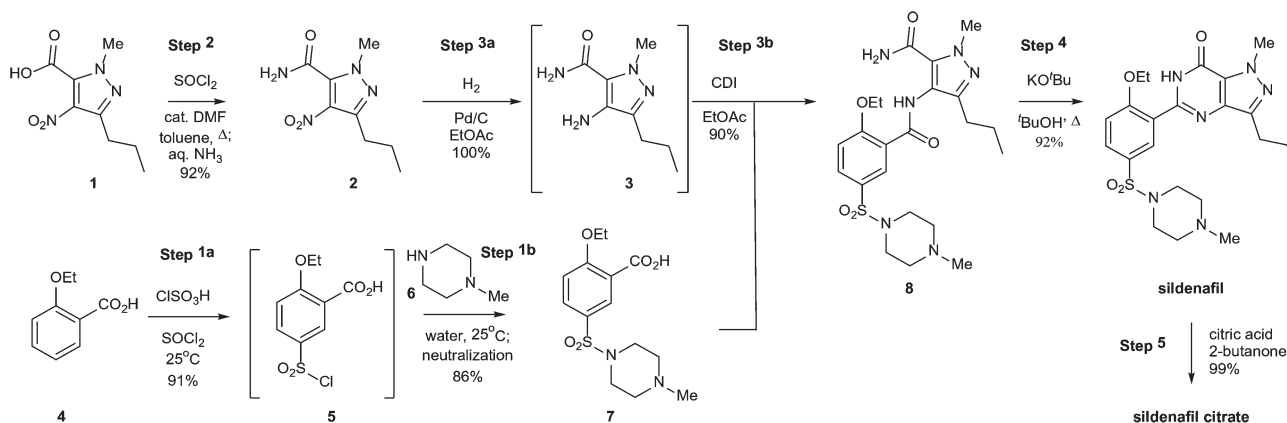


Fig. 5 Development of green pharmaceutical processes utilizing the Green Aspiration Level concept.



Scheme 1 Pfizer's commercial synthesis of sildenafil citrate (ViagraTM).

Our result for Sheldon's traditional E factor is 6.4 kg kg^{-1} and corresponds well with Pfizer's reported 6 kg kg^{-1} of actual waste. The process sEF, which excludes solvents and process water, is calculated as 3.9 kg kg^{-1} , and the all-inclusive cEF is 50.3 kg kg^{-1} .

Next we assess the matter of defining synthesis starting points. One of Pfizer's primary synthesis starting points, 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (**1**, not available from Sigma-Aldrich's website), does not meet our starting point requirements. Some may disagree with our proposed starting point rules, but their application helps to emphasize that this material is significantly more complex than the other process materials. We therefore argue that its

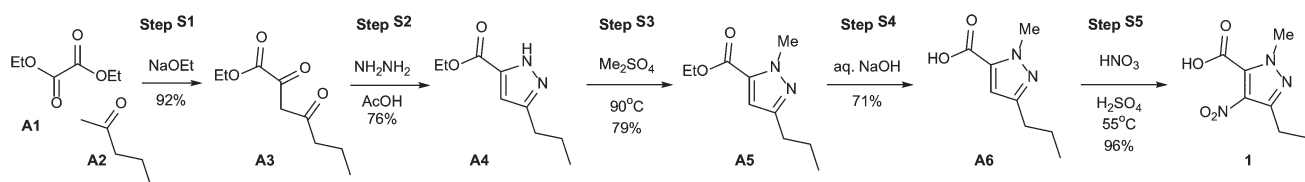
intrinsic E factor ought to be included, and so we begin the process of determining it.

The complex pyrazole starting point **1** is derived in five steps from readily available diethyl oxalate (**A1**; $\$5.53 \text{ mol}^{-1}$) and 2-pentanone (**A2**; $\$1.90 \text{ mol}^{-1}$) as shown in Scheme 2. In analogy to the sildenafil citrate process discussed above, we first derive the material table for the process to produce 1 kg of compound **1** and then perform the E factor analysis (Table 7).⁷⁸

As a result, the *intrinsic* sEF, E factor, and cEF for 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (**1**) are determined as 14.2, 17.6, and 82.8 kg kg^{-1} , respectively, which when multiplied with the quantity of **1** needed to produce 1 kg

Table 6 sEF, cEF, and *E* factor analysis of the commercial ViagraTM process

Step number	Raw materials	Reagents	Solvents (excl. water)	Water	Product	Step sE-factor	sE-factor contribution to process	Step cE-factor	cE-factor contribution to process	<i>E</i> -factor contribution to process
1a + b	2.2 kg	0.3 kg	0.0 kg	12.2 kg	0.7 kg	2.8 kg kg ⁻¹	1.9 kg kg ⁻¹	21.1 kg kg ⁻¹	14.1 kg kg ⁻¹	1.9 kg kg ⁻¹
2	1.1 kg	0.4 kg	1.8 kg	1.7 kg	0.4 kg	2.8 kg kg ⁻¹	1.1 kg kg ⁻¹	11.9 kg kg ⁻¹	4.6 kg kg ⁻¹	1.3 kg kg ⁻¹
3a + b	1.1 kg	0.3 kg	10.7 kg	0.0 kg	0.8 kg	0.7 kg kg ⁻¹	0.6 kg kg ⁻¹	13.9 kg kg ⁻¹	11.3 kg kg ⁻¹	1.7 kg kg ⁻¹
4	0.8 kg	0.2 kg	3.1 kg	8.1 kg	0.7 kg	0.5 kg kg ⁻¹	0.3 kg kg ⁻¹	16.1 kg kg ⁻¹	11.6 kg kg ⁻¹	0.7 kg kg ⁻¹
5	1.0 kg	0.0 kg	8.7 kg	0.0 kg	1.0 kg	0.0 kg kg ⁻¹	0.0 kg kg ⁻¹	8.7 kg kg ⁻¹	8.7 kg kg ⁻¹	0.9 kg kg ⁻¹
Total	3.6 kg	1.3 kg	24.3 kg	22.1 kg	1.0 kg		3.9 kg kg ⁻¹		50.3 kg kg ⁻¹	6.4 kg kg ⁻¹

**Scheme 2** Sub-process for 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (1).**Table 7** sEF, cEF, and *E* factor analysis for the 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (1) sub-process

Step number	Raw materials	Reagents	Solvents (excl. water)	Water	Product	Step sE-factor	sE-factor contribution to sub-process	Step cE-factor	cE-factor contribution to sub-process	<i>E</i> -factor contribution to sub-process
S1	3.0 kg	0.1 kg	18.9 kg	0.0 kg	1.7 kg	0.9 kg kg ⁻¹	1.5 kg kg ⁻¹	12.1 kg kg ⁻¹	20.4 kg kg ⁻¹	3.4 kg kg ⁻¹
S2	2.2 kg	0.0 kg	3.5 kg	0.0 kg	1.6 kg	0.4 kg kg ⁻¹	0.6 kg kg ⁻¹	2.6 kg kg ⁻¹	4.1 kg kg ⁻¹	1.0 kg kg ⁻¹
S3	2.7 kg	1.1 kg	11.6 kg	8.8 kg	1.4 kg	1.8 kg kg ⁻¹	2.4 kg kg ⁻¹	16.9 kg kg ⁻¹	22.8 kg kg ⁻¹	3.6 kg kg ⁻¹
S4	1.4 kg	1.6 kg	0.0 kg	8.2 kg	0.8 kg	2.6 kg kg ⁻¹	2.1 kg kg ⁻¹	12.5 kg kg ⁻¹	10.3 kg kg ⁻¹	2.1 kg kg ⁻¹
S5	1.2 kg	7.3 kg	0.0 kg	17.6 kg	1.0 kg	7.6 kg kg ⁻¹	7.6 kg kg ⁻¹	25.2 kg kg ⁻¹	25.2 kg kg ⁻¹	7.6 kg kg ⁻¹
Total	5.0 kg	10.2 kg	34.1 kg	34.5 kg	1.0 kg		14.2 kg kg ⁻¹		82.8 kg kg ⁻¹	17.6 kg kg ⁻¹

of sildenafil citrate (0.424 kg), provide the sEF, *E* factor, and cEF contributions of **1** to the sildenafil citrate process of 6.0, 7.5, and 35.1 kg kg⁻¹, respectively (Table 8).

By not considering the intrinsic *E* factor, the sildenafil citrate analysis inherently assumed an *E* factor contribution of 0.424 kg kg⁻¹ for compound **1** in the commercial process, which equals the compound's mass needed to produce 1 kg of sildenafil citrate. Thus, we may have discounted between 5.6 kg (= 6.0 – 0.4) in terms of sEF and 34.7 kg for cEF of intrinsic waste associated with the production of 1 kg compound **1**.⁷⁸ If this material, as we assume, is not a commodity

and is specifically made for the ViagraTM process, the intrinsic waste must therefore be considered in an objective process greenness analysis.

Overall, when including the intrinsic *E* factors of the non-commodity-type raw material **1**, the overall sildenafil citrate process analysis changes are shown in Table 9. We observe significant increases of the *E* factors, with the sEF jumping from 3.9 kg kg⁻¹ using Pfizer's synthesis starting points to 9.9 kg kg⁻¹ using our proposed commodity-type starting principles, the *E* factor going from 6.4 to 13.8 kg kg⁻¹, and the cEF changing from 50.3 to 85.5 kg kg⁻¹.

Therefore, depending on the type of *E* factor utilized, the exclusion of waste associated with the production of the two non-commodity-type raw materials in the analysis of the commercial ViagraTM process fails to recognize 40–60% of the process waste. This example shows how widely *E* factors can vary depending on the selected synthesis starting point and stresses the importance of implementing an industry-wide standardized starting point concept to render green process analysis and benchmarking more meaningful.

Before we can evaluate the commercial ViagraTM process against our calculated industrial Green Aspiration Level (GAL), we need to determine the process complexity. By applying process ideality eqn (3) and process complexity eqn (4) to the entire ViagraTM process, including steps S1 through S5 according

Table 8 Conversion of intrinsic *E* factors to *E* factor process contributions for compound **1**

Intrinsic		
sEF	cEF	<i>E</i> -factor
Contribution to compound 1 sub-process		
14.2 kg kg ⁻¹	82.8 kg kg ⁻¹	17.6 kg kg ⁻¹
× <i>Quantity needed to make 1 kg of sildenafil citrate</i>		
× 0.424		
=		
sEF	cEF	<i>E</i> -factor
Contribution to sildenafil citrate process		
6.0 kg kg ⁻¹	35.1 kg kg ⁻¹	7.5 kg kg ⁻¹

Table 9 sEF, cEF, and E factor analysis of the commercial ViagraTM process starting from commodity raw materials

Total	Input material	Raw materials	Reagents	Solvents (excl. water)	Water	Product	Step sE-factor	sE-factor contribution to process	Step cE-factor	cE-factor contribution to process	E-factor contribution to process
		2.1 kg	1.1 kg	0.0 kg	3.0 kg	0.4 kg	2.8 kg kg ⁻¹			5.8 kg kg ⁻¹	2.8 kg kg ⁻¹
Step number											
1a + b	1	2.2 kg	0.3 kg	0.0 kg	12.2 kg	0.7 kg	2.8 kg kg ⁻¹	1.9 kg kg ⁻¹	21.1 kg kg ⁻¹	14.1 kg kg ⁻¹	1.9 kg kg ⁻¹
2		1.1 kg	0.4 kg	1.8 kg	1.7 kg	0.4 kg	2.8 kg kg ⁻¹	6.0 kg kg ⁻¹	11.9 kg kg ⁻¹	35.1 kg kg ⁻¹	7.5 kg kg ⁻¹
3a + b		1.1 kg	0.3 kg	10.7 kg	0.0 kg	0.8 kg	0.7 kg kg ⁻¹	1.1 kg kg ⁻¹	13.9 kg kg ⁻¹	4.6 kg kg ⁻¹	1.3 kg kg ⁻¹
4		0.8 kg	0.2 kg	3.1 kg	8.1 kg	0.7 kg	0.5 kg kg ⁻¹	0.6 kg kg ⁻¹	16.1 kg kg ⁻¹	11.3 kg kg ⁻¹	1.7 kg kg ⁻¹
5		1.0 kg	0.0 kg	8.7 kg	0.0 kg	1.0 kg	0.0 kg kg ⁻¹	0.3 kg kg ⁻¹	8.7 kg kg ⁻¹	11.6 kg kg ⁻¹	0.7 kg kg ⁻¹
Total		5.3 kg	5.6 kg	38.8 kg	36.7 kg	1.0 kg	0.0 kg kg ⁻¹	9.9 kg kg ⁻¹	8.7 kg kg ⁻¹	85.5 kg kg ⁻¹	13.8 kg kg ⁻¹

to our starting point definition, we obtain a process complexity of 11 along with an ideality metric of 92% (Table 10). We also apply ideality analysis to the sub-processes for material 1. The functional intergroup interconversion from the ethyl ester to the corresponding carboxylic acid in step S4 for intermediate 1 leads to reduced % ideality and reflects the only concession step in the entire ViagraTM process.

Given a process complexity of 11, we can determine ViagraTM's process GALs (Table 11). We also determine the GALs for the sub-process leading to external intermediate 1.

Now we are ready to determine Relative Process Greenness using eqn (6) (RPG, Table 12).

The new methodology leads us to conclude that the 'full' commercial ViagraTM process is indeed 'very green', *i.e.* it exceeds its aspiration level by 143% in terms of cEF, based on the current industry average as reported by the ACS GCI. The RPG for synthesis of intermediate 1 as estimated from literature procedures⁷⁸ could perhaps be further optimized [RPG < 100%].

In order to highlight the simplicity of the procedure, we summarize the three steps needed to conduct the standardized green process analysis and establish a green score card: (1) determine process complexity and *E* factors, (2) calculate RPG, (3) calculate RPI, RCI and PI for a new or improved process. The ViagraTM example demonstrates the high utility of GAL and RPG that allows for quantitative measure of green process performance, for the first time, relative to industry averages, and thus enables process researcher and managers to establish practical and specific green chemistry goals.

Perspectives

"The difficulty lies, not in the new ideas, but in escaping the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds." These words from early 20th century British economist Keynes eloquently describe the predicament of today's pharmaceutical manufacturing operations, which have not experienced disruptive innovation for over a century. The lack of innovation in pharmaceutical operations and historic prioritization of launch timelines over process ideality was articulated by the FDA in 2004: "Pharmaceutical manufacturing operations are inefficient and costly. Compared to other industrial sectors, the rate of introduction of modern engineering process design principles, new measurement and control technologies, and knowledge management systems is low. Opportunities for improving efficiency and quality assurance...are not generally well recognized."

Green chemistry principles have the power to refocus pharmaceutical operations on integration of development and production. The cost savings opportunity if optimal process efficiency could be achieved has been estimated at \$50 billion for the pharmaceutical industry worldwide.⁷⁹ In fact, process and technology innovation driven by green chemistry is already underway. Recently published examples include appli-

Table 10 Ideality analyses for ViagraTM process and sub-process

Target	Transformations	Strategic redox reactions	Construction reactions	Concession steps	%Ideality	Complexity
Viagra TM	12	1	10	1	92%	11
1	5	0	4	1	80%	4

Table 11 Green Aspiration Level (GAL) analysis for the commercial ViagraTM process

Commercial process	Complexity	sEF-based analysis		cEF-based analysis	
		tGAL [kg kg ⁻¹]	GAL [kg kg ⁻¹]	tGAL [kg kg ⁻¹]	GAL [kg kg ⁻¹]
Viagra TM	11	3	33	19	209
1	4		12		76

cation of biocatalysis with fully renewable and biodegradable enzymes or microorganisms as the ultimate green catalysts, improved homogeneous and heterogeneous chemical catalysis with non-precious metal catalysts, continuous flow technology benefiting from superior mixing and heat transfer, efficient chromatography, and refocus on recycling of solvents and catalysts in pharmaceutical manufacturing operations. All of these innovative applications of green chemistry principles have been thoroughly reviewed.⁴

Thus far, however, green chemistry and technology have primarily played a role as occasional design elements for second generation processes in advanced development or post-commercialization phases, but they have not been a primary consideration in early development due to barriers such as tight project timelines, high R&D costs, and high project attrition rates. We have argued that green chemistry ought to be a major factor right from the start of process R&D activities, and should play a key role – through close collaboration of chemists, engineers, and Environment, Health and Safety (EHS) staff – on the synthetic route design and process optimization. This approach will drive innovative operational efficiencies by functionally integrating between API design and production in development and operations, and deliver the greenest possible manufacturing process. Furthermore, green chemistry should be transposed to the pharmaceutical supply chain, using the same metrics and standards in close collaboration with suppliers. Based on the above discussions, we now outline our perspectives on how to overcome the barriers to green chemistry and summarize those graphically in Fig. 6.

1. Standardized metrics. When questioning how the pharmaceutical industry and its supply chain can enhance incentives to implement green chemistry practice, we found that a significant barrier is the absence of clear definitions and unified metrics for use by researchers and managers. Until such time as government regulates labeling of commercially available raw materials, reagents, and solvents with complete *E* factors (cEF), the pharmaceutical industry will need a practical, unambiguous definition of *process starting points*. Analyses of process greenness to date have used a variety of green chemistry metrics, without a harmonized and precisely defined starting point concept. Therefore, starting points were inconsistently defined, leading to exclusion of varying amounts of intrinsic raw material waste. We exemplified the green chemistry community-wide starting point problem with the ViagraTM process and proposed use of *E* factor as a simpler concept for process analysis than PMI. A weakness of the original *E* factor was the omission of process water, which we included with the *complete E factor* (cEF) concept. In addition, to better reflect focus on process ideality during early process R&D activities, we introduced the *simple E factor* (sEF) which excludes both solvents and water from consideration. In order to accomplish metrics standardization it is important that legacy attitudes within industry and academia are tackled and *E* factors⁸⁰ gain industry-wide acceptance to facilitate benchmarking and communication using one unified system.

2. Labeling. Currently, intrinsic *E* factors for raw materials, reagents, and solvents from chemical, specialty chemical and fine chemical producers are not publicly available, and would need to be determined by process chemists through literature analysis. In addition to being labor intensive and inefficient, there is no guarantee that the researcher will find accurate references since compounds are often produced under trade secrets. Also, different scientists may determine varying *E* factors for the same chemical when basing their analyses on divergent literature sources and assumptions. Government could therefore critically aid green chemistry standardization efforts by introducing labeling requirements for intrinsic waste associated with the manufacture of any chemical that is imported, manufactured, or sold, using the complete *E* factor

Table 12 RPG analysis for commercial ViagraTM process

Commercial process	sEF-based analysis			cEF-based analysis		
	Actual [kg kg ⁻¹]	GAL [kg kg ⁻¹]	Relative process greenness (RPG)	Actual [kg kg ⁻¹]	GAL [kg kg ⁻¹]	Relative process greenness (RPG)
Viagra TM	10	33	330%	86	209	243%
1	14	12	86%	83	76	92%

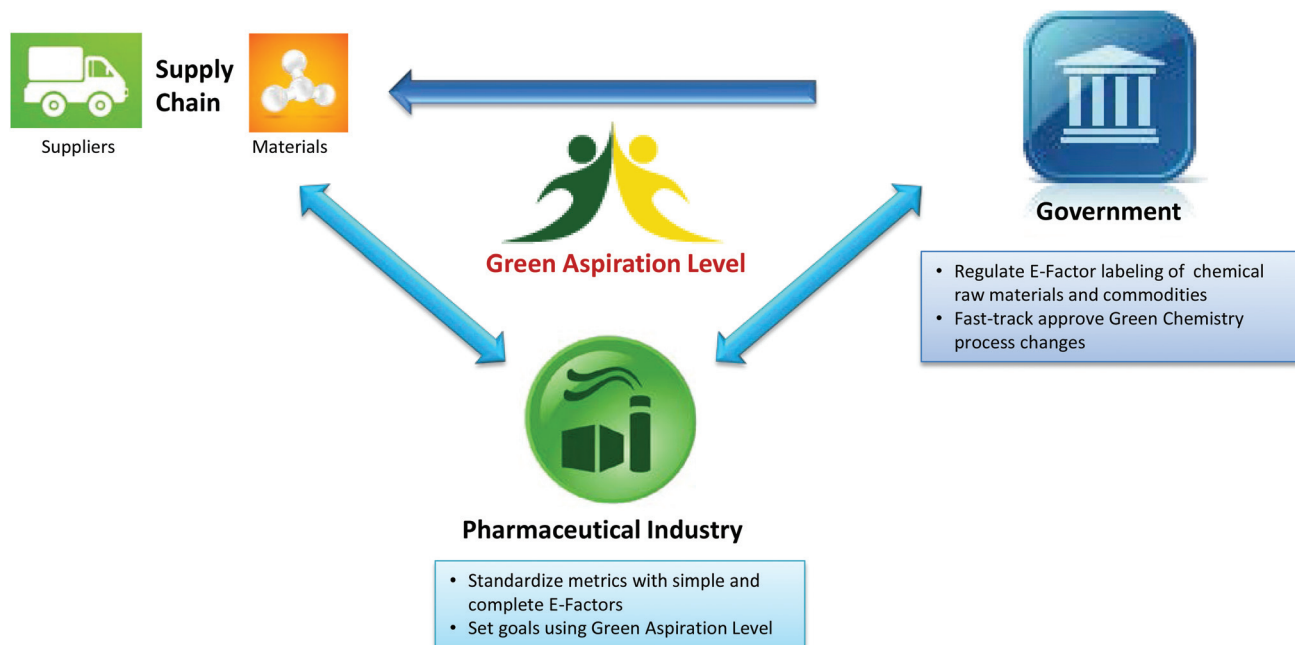


Fig. 6 Breaking the barriers to green chemistry – the Green Aspiration Level is key.

(cEF). The cEF can be readily determined by the manufacturers, plus the labeling disclosure does not pose a risk in terms of IP since no process details are being revealed. With intrinsic waste being displayed on chemical labels and in chemical catalogs, and consequently also in every chemist's ELN, the process chemists will become greatly aware of the environmental impact of their chosen process chemicals. In this way, intrinsic waste would become a new material selection criterion for the green process chemist, in particular when considering chemical alternatives with similar performance that are differentiated only by their intrinsic cEF.

3. *Fast-track regulatory approvals for green process changes.* A recent publication by Dunn analyzed the duration of global regulatory approvals for process changes.⁸¹ The author found wide disparity among countries, with the FDA being the fastest agency having mean approval times of just 4.5 months, the European Medicines Agency (EMA) being slightly slower, but most countries requiring from one to three years. The author proposes that late phase development of second generation green processes could be incentivized if all international regulatory bodies would make harmonized adjustments to refiling procedures by prioritizing and fast-track reviewing green process change applications within 12 months. This is where our new methodology could be helpful. In order for a process change application to be considered green, the RPG should equal at least 100%. Green chemistry process changes are mutually beneficial to industry, regulators and consumers as they drive down the cost of API, reduce chemical hazard, and reduce waste generation.

4. *Green Aspiration Level (GAL) concept and SMART green chemistry goals.* In order to encourage productive green chemistry efforts, we proposed SMART goals and introduced the

Green Aspiration Level (GAL) concept. This consists of a process *E* factor target based on average industry *E* factors and a process complexity measure derived from Baran's % ideality metric, rather than the commonly used simple step count that would not differentiate between poorly designed processes (low % ideality) and well-designed processes (high % ideality). If accepted as new industry standard, the GALs would need to be maintained and periodically updated by influential green chemistry organizations such as the ACS GCI and the IQ Consortium, and made available on their respective websites. Determination of the process GAL allows us to measure process greenness against industry averages, using sEF and cEF, as baseline. We termed the performance measure Relative Process Greenness (RPG), and consider a value greater than 100% desirable as it exceeds the industry average. We recommend implementation of a green chemistry scorecard (Table 5), displaying actual *E* factor, GAL, RPG, RPI, RCI, and PI for both sEF and cEF. We are optimistic that our simple yet useful methodology will facilitate standardization of green chemistry metrics and allow managers and scientists to drive performance of their green chemistry teams by using SMART RPG goals.

In summary, we have informed the reader about the importance of green chemistry to pharmaceutical development and operations, discussed the barriers to implementing green chemistry within the pharmaceutical industry, and developed a novel practical yet simple solution to overcome those barriers through Green Aspiration Level (GAL)-based standardization. The GAL will not only facilitate SMART green chemistry goal-driven process R&D within the industry through incorporation of ideality-adjusted process complexity and allow for better goal alignment of process R&D with operations, but it will also establish a reference standard that can be used by governments

to initiate green-chemistry-based regulations and incentives. Industry-wide collaboration will be the key to standardization, and the IQ Consortium and the ACS GCI can be instrumental in realizing this opportunity. We are hopeful that our analysis will stimulate productive discussions within the green chemistry community, lead to cross-pollination of ideas, help overcome the existing hurdles, and make green chemistry an integral part of the pharmaceutical industry and its supply chain. We conclude our article with a quote from William Ford Jr, great grandson of Henry Ford: "A good company delivers excellent products and services. A great company does all of this and strives to make the world a better place."⁸²

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