Part I

General Topics in Green Chemistry

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Green Chemistry Metrics

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1.1 Business Case

Green chemistry is an integral, strategic component for pharmaceutical firms to inspire development of drug manufacturing processes with optimal environmental impact, process safety, and energy consumption, all of which bring about improved economics. Manufacturing contributes a substantial part of industry expenditures that has been estimated at one-third of total costs to one-third of total sales, or about $200 billion worldwide in 2008 [1, 2]. This figure includes about 10 billion kg of annual drug manufacturing waste treatment with costs of $20 billion [3]. Therefore, if effectively utilized, green chemistry represents a significant opportunity for industry to increase drug development and manufacturing efficiencies that could translate to trillions of dollars in social value for the public health consumer surplus [4]. This is precisely the reason why industry should optimally utilize green chemistry. In this context, metrics become vital as a reflection of corporate priority, in line with the proven management adage "you can't manage what you don't measure." Unless improvements are defined, quantified, and measured, we cannot establish clear objectives that allow us to estimate manufacturing improvements. We must, therefore, measure green chemistry by carefully choosing metrics that matter. Ideally, those selected metrics are standardized and aligned within the industry, and also leveraged within the firms with key stakeholders, namely company leadership, technical staff, and suppliers, thereby promoting a culture of continuous ambition and improvement. It was not until 23 years after introduction of the E factor [5] that the first standardized and unified green manufacturing goal metric became available that will be detailed *vide infra* [6, 7].

1.2 Historical Context

The origins of metrics date back to 1956 when Nobel laureate Woodward questioned how to create the best possible synthesis, and invented the concept of synthetic design [8]: "synthesis must always be carried out by a plan, and the synthetic frontier can be defined only in terms of the degree to which realistic planning is possible, utilizing all of the intellectual and physical tools available." In 1989, Corey leap-frogged the field of synthetic design by introduction of retrosynthesis methodology, in which the chemist starts planning from the product backward via the most efficient bond dissection to arrive at simple and readily available raw materials [9]. For these contributions, he was awarded the 1990 Nobel Prize in Chemistry. The initial considerations for environment in synthetic planning, and thus the first environmental green chemistry metrics, can be traced to Trost and Sheldon who went beyond synthesis design and assessed efficiency through Atom Economy (AE) [10] and Environmental impact factor (E factor) [11] in 1991 and 1992,

Table 1.1 E factors, waste and process complexity across chemical industries.

Industry Segment (Examples)	Annual Product Tonnage	E-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)	10–1,000	25–>100	100,000	6+	3–5

respectively, with the implied goal to consider waste as a criterion for molecular design and thereby minimize it. AE measures what proportion of the reactants becomes part of the product, and as such addresses a shortcoming of chemical yield (CY). For example, we can have a step with 100% CY that produces more waste than product weight, as was the case with the key step of the first commercial process of phenol via pyrolysis of sodium benzenesulfonate that was developed in Germany in the 1890s (Equation 1.1). Trost received the Presidential Green Chemistry Challenge 1998 Academic Award for development of the AE concept [12].

Equation 1.1 Key step of commercial phenol process.

$$PhSO_3Na + 2\,NaOH \rightarrow PhONa + Na_2SO_3 + H_2O$$

MW   180.15   40.00   116.09   126.04   18.02
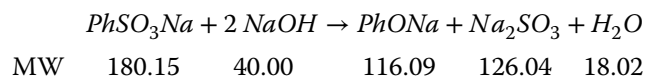
Unlike AE, the E factor considers CY and selectivity of a process by measuring the amount of waste, excluding water, that is co-produced with 1 kg of the target molecule. A high E factor indicates more waste and greater negative environmental impact. The ideal E factor is 0. Typical E factors for various chemical industries were estimated by Sheldon in 1997 and indicate that pharmaceuticals face substantially elevated waste burden compared to the allied chemical industries (Table 1.1) [13].

The primary cause for the high E factors of pharmaceutical manufacturing is the greater molecular complexity of drugs and the resulting larger step number count to produce them. In addition, the industry faces internal and external barriers that may obstruct optimal manufacturing efficiencies as summarized in Table 1.4 *vide infra*.

1.3 Metrics, Awards, and Barriers

1.3.1 Mass-Based Metrics

Efficiency and productivity metrics conceived after AE and E factor focused on the amount of generated waste with respect to the product, and for simplicity, assumed that all waste had the same environmental impact, independent of its nature. The ACS GCI PR compiled drug manufacturing waste data and showed that solvents and water make up the majority, or 86% of waste for the processes studied, and should therefore be included in comprehensive waste analysis (Figure 1.1) [14, 19]. Thus, the Pharmaceutical Roundtable consequently introduced the Process Mass Intensity (PMI) metric that does consider all materials used in the process and workup, including water.

Figure 1.1 Typical pharmaceutical drug manufacturing waste composition.
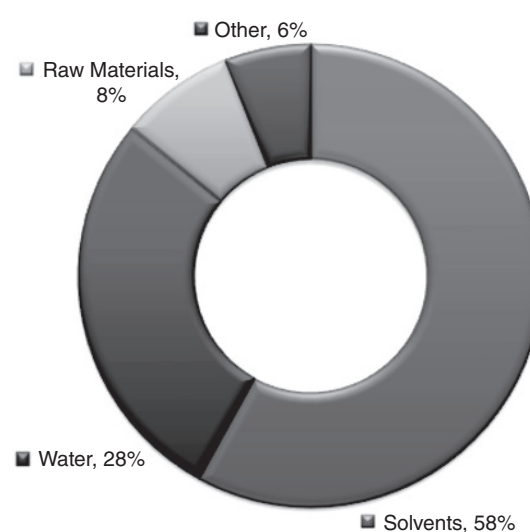
For a comprehensive overview, we summarize the common mass-based metrics and their consideration for resources in Table 1.2.

From the above group of diverse green chemistry mass metrics, both E factor and PMI emerged as the most utilized in industry. Recently, the complete E factor or cEF was introduced, combining the advantages of PMI that is the inclusion of water and solvents in analysis, with E factor that is step mass balance, as a well-suited metric for *multi-step* manufacturing process analysis [6].

However, while mass-based metrics can measure process improvements and thereby aid route design to a specific drug target, they do not allow for comparison of manufacturing processes between different drugs, and thus by themselves cannot deliver a standardized green process goal.

Table 1.2 Mass-based environmental process waste metrics.

| Metric	Abbreviation	Formula	Optimum Value	Inventor (Year)
Resource Efficiency				
Chemical Yield	CY	$\dfrac{m(Product) \times MW(Raw\ Material) \times 100}{m(Raw\ Material) \times MW(Product)}$	100%	–
Atom Economy	AE	$\dfrac{MW(Product) \times 100}{\sum MW(Raw\ Materials) + \sum MW(Reagents)}$	100%	Trost (1991) [10]
Environmental Impact Factor	E factor	$\dfrac{\sum m(Input\ Materials\ excl.\ Water) - m(Product)}{m(Product)}$	$0\ \dfrac{kg}{kg}$	Sheldon (1992) [11]
Effective Mass Yield	EMY	$\dfrac{m(Product) \times 100}{\sum m(Raw\ Materials) + \sum m(Reagents)}$	100%	Hudlicky (1999) [15]
Mass Intensity	MI	$\dfrac{\sum m(Input\ Materials\ excl.\ Water)}{m(Product)}$	$1\ \dfrac{kg}{kg}$	Constable/Curzons (2001) [16]
Reaction Mass Efficiency	RME	$\dfrac{m(Product) \times 100}{\sum m(Raw\ Materials)}$	100%	Constable/Curzons (2001) [16]

(continued)

Table 1.2 (*Continued*)

Metric	Abbreviation	Formula	Optimum Value	Inventor (Year)
Carbon Efficiency	CE	$\dfrac{m(Carbon\ in\ Product) \times 100}{\sum m(Carbon\ in\ Raw\ Materials)}$	100%	Constable/Curzons (2001) [16]
Mass Productivity	MP	$\dfrac{m(Product) \times 100}{\sum m(Input\ Materials\ excl.\ Water)} = \dfrac{100}{MI}$	100%	Constable/Curzons (2002) [17]
Process Mass Efficiency	PME	$\dfrac{m(Product) \times 100}{\sum m(Input\ Materials\ incl.\ Water)} = \dfrac{100}{PMI}$	100%	Hanson (2006) [18]
Process Mass Intensity	PMI	$\dfrac{\sum m(Input\ Materials\ incl.\ Water)}{m(Product)}$	$1\ \dfrac{kg}{kg}$	Constable/Curzons/ ACS GCI PR (2007) [19]
Reaction Mass Intensity	RMI	$\dfrac{\sum m(Raw\ Materials) + \sum m(Reagents)}{m(Product)} = \dfrac{1}{EMY}$	$1\ \dfrac{kg}{kg}$	Song/Senanayake (2012) [20]
Optimum Efficiency	OE	$\dfrac{RME \times 100}{AE}$	100%	Clark (2015) [21]
Simple E factor	sEF	$\dfrac{\sum m(Raw\ Materials) + \sum m(Reagents) - m(Product)}{m(Product)}$ $= RMI - 1$	$0\ \dfrac{kg}{kg}$	Roschangar/ Senanayake/ Sheldon (2015) [6]
Complete E factor	cEF	$\dfrac{\sum m(Input\ Materials\ incl.\ Water) - m(Product)}{m(Product)}$ $= PMI - 1$	$0\ \dfrac{kg}{kg}$	Roschangar/ Senanayake/ Sheldon (2015) [6]
Solvents				
Solvent Intensity	SI	$\dfrac{\sum m(Solvents\ excl.\ Water)}{m(Product)}$	$0\ \dfrac{kg}{kg}$	Constable/Curzons (2001) [16]
Water Intensity	WI	$\dfrac{\sum m(Water)}{m(Product)}$	$0\ \dfrac{kg}{kg}$	Jiménez-González/ Curzons (2001) [22]
Renewables				
Renewables Intensity	RI	$\dfrac{\sum m(Renewably\ Derivable\ Input\ Materials)}{m(Product)}$	$1\ \dfrac{kg}{kg}$	Jiménez-González/ Constable/Ponder (2012) [24]
Renewables Percentage	RP	$\dfrac{RI \times 100}{PMI}$	100%	Clark (2015) [21]
Equipment Utilization				
Space Time Yield	STY	$\dfrac{m(Product)}{Nominal\ Reactor\ Volume \times Reactor\ Time}$	$'max'\ \dfrac{kg}{m^3 h}$	–
Volume Time Output	VTO	$\dfrac{Nominal\ Reactor\ Volume \times Reactor\ Time}{m(Product)} = \dfrac{1}{STY}$	$'min'\ \dfrac{m^3 h}{kg}$	Dach/Roschangar/ Senanayake (2012) [23]

1.3.2 Life-Cycle Assessment

Accurately measuring the greenness of a manufacturing process unquestionably goes beyond quantifying co-produced waste, and includes assessing sustainability of process inputs such as metals, reagents, and solvents, evaluating overall environmental impact including eco-toxicity and carbon footprint, energy consumption,

Figure 1.2 Comprehensive green metrics categories for life cycle assessment.
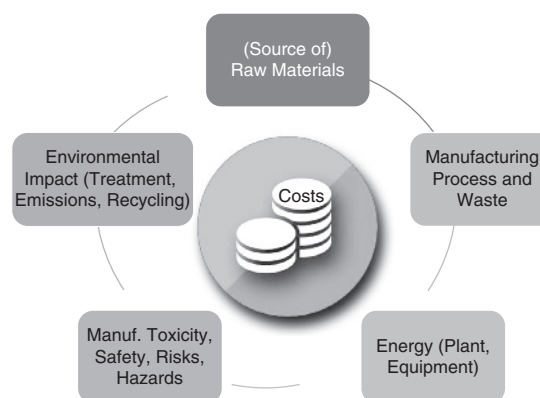
as well as occupational health and risk factors, all of which are integral part of the comprehensive life-cycle assessment (LCA) (Figure 1.2) [24, 25].

LCA methodology encompasses cradle-to-grave impact analysis starting from sources and upstream processes for process inputs, the processes themselves to manufacture intermediates and the drug, including equipment cleaning and waste handling, all the way to pharmaceutical manufacturing, packaging, and eventually drug disposal and recycling over the useful life of the drug. However, there are several hurdles to overcome with LCA [26]. A significant challenge is the lack of life-cycle inventory (LCI) input data and standardization [27], as well as the difficulty to allocate energy consumption to a particular process within pharmaceutical multi-purpose plants. A further barrier is that analysis remains time-consuming, and thereby inhibits widespread use, particular during early phases of drug development where LCA is expected to have the biggest impact during the synthesis design phase, despite efforts to simplify the methodology via fast life-cycle assessment of synthetic chemistry (FLASC) tool [28]. Recently, a more practical model combining PMI methodology with LCA was demonstrated for the Viagra process and used literature and patent data to estimate missing LCI [29].

1.3.3 Green Analytical Chemistry (GAC)

The GAC concept emerged from the field of green chemistry [30, 31] with intent to motivate development of analytical methods that minimize solvents and hazards, and maximize operator safety [32]. This could be achieved by application of techniques such as sample and device miniaturization, solvent-less extractions, and use of greener solvents [33, 34]. Efforts have been made to develop GAC metrics that include NEMI labeling as pictographic indication of hazards and waste [35], analytical method volume intensity (AVMI) as measure of total solvent consumption of HPLC methods [36], and the analytical eco-scale scoring system [37]. The 12 principles of GAC provide guidance for green analytics [38].

1.3.4 Awards

An important element to move toward greener drugs is recognition of scientists by industry and government. Awards within companies create a sense of employee involvement and inspire staff to adapt greener thinking patterns in everyday work routines, and also demonstrate the firm's commitment to green chemistry. Recognition by government is even more visible and impactful. The most prestigious government recognition for industry is the Presidential Green Chemistry Challenge Awards (PGCCA) awards by the U.S. Environmental Agency (EPA) [39]. The PGCCA is the *only* award issued by the president of the United States that honors work in the field of chemistry! PGCCA awardees and winners of the UK Institute of Chemical Engineers (IChemE) from the pharmaceutical industry, along with the applied green chemistry principles [40] and metrics, are summarized in Table 1.3.

Table 1.3 Green Chemistry Challenge Award winners in pharmaceutical drug manufacturing.

Year	Awardee	Category/Summary	Issuer	Green chemistry principles
2012	Codexis Prof. Y. Tang (UCLA)	Greener synthetic pathways/efficient biocatalytic process to manufacture Simvastatin/Zocor	PGCCA	Replaced multistep synthesis with process starting from natural product using an engineered enzyme and low-cost feedstock
2010	Merck Codexis	Greener reaction conditions/greener manufacturing of Sitagliptin/Januvia by an evolved transaminase	PGCCA	Replaced asymmetric catalytic high-pressure hydrogenation with transaminase enzyme, eliminated all metals and chiral purification step
2006	Merck	Greener synthetic pathways/novel green synthesis for β-amino acids to produce Januvia	PGCCA	Increase CY, innovative asymmetric catalytic hydrogenation, reduces waste by 80%
2006	Codexis	Greener reaction conditions/ directed evolution of three biocatalysts to produce the key chiral building block for Atorvastatin/Lipitor	PGCCA	New genetic method for "designer enzymes," waste reduction, less processing equipment and fewer unit operations, increase CY, improve worker safety
2006	Pfizer	Excellence in green chemistry and engineering/revised Lyrica synthesis	IChemE	Waste reduction via an enzymatic process, carrying out all reaction steps in water
2005	Merck	Greener synthetic pathways/ redesigned, efficient synthesis of Aprepitant/Emend	PGCCA	Synthetic convergence, increase AE, feedstock raw material
2004	Bristol-Myers Squibb	Greener synthetic pathways/ development of a green synthesis for Paclitaxel/Taxol manufacture via plant cell fermentation and extraction	PGCCA	Plant cell fermentation instead of plant extraction to reduce biomass waste
2003	Pfizer	Crystal Faraday Award for green chemical technology/process redesign of Viagra/Sildenafil	IChemE	Setting a new benchmarking standard for minimizing solvent use
2002	Pfizer	Greener synthetic pathways/green chemistry in the redesign of the Sertraline/Zoloft process	PGCCA	Increase CY, reduction of raw material, energy, and water use, increase of worker safety by combining three steps into one
2000	Roche Colorado (now Corden Pharma)	Greener synthetic pathways/efficient process for the production of Ganciclovir/Cytovene	PGCCA	Increase CY, doubling production throughput, waste reduction, non-toxic and non-hazardous feedstock
1999	Lilly	Greener synthetic pathways/ practical application of a biocatalyst in pharmaceutical manufacturing for anticonvulsant drug candidate	PGCCA	Waste reduction, use of biocatalytic yeast reduction to replace chemical process, elimination of chromium waste
1997	BHC (now BASF)	Greener synthetic pathways/ Ibuprofen process	PGCCA	Step reduction from six to three, recovery and recycling of a waste by-product, elimination of aqueous salt wastes, increase AE

1.3.5 Barriers

Despite having a strong business case alongside a wide selection of green chemistry metrics, significant hurdles to their broad adoption remain [6, 41–43]. They can be categorized into barriers directly addressable by industry, and into opportunities government could help tackle, as summarized in Table 1.4.

The opportunities can be realized with a standardized, unified, and quantifiable metric to assess the greenness of any drug manufacturing process that now has become available [6, 7].

Table 1.4 Barriers to adoption of green chemistry metrics in industry.

Stakeholder	Barrier	Potential Impact	Opportunity
Industry	Metrics are not harmonized	Difficulty evaluating greenness of processes across industry	Unify metrics and make methodology simple
	Analysis starting points are inconsistent	Lower credibility of analysis results	Define analysis starting points
	Complexities of drug molecule are neglected	Unfair green process targets	Consider manufacturing complexities
	Absence of an objective/smart green manufacturing process goal	Irrelevance of green chemistry measurements to scientists	Establish fair green chemistry manufacturing goal
Government	Regulatory requirements for late-phase and commercial process changes	Firms do not commercialize the greenest process	Ease regulations on green process changes
	Limited patent life and high Research & Development costs (high project attrition)	Firms do not commercialize the greenest process	Fast-track approval for drugs made by green manufacturing processes
	Absence of avenues (metrics) to showcase drugs manufactured via green processes	Firms do not commercialize the greenest process	(i) Allow "green labeling" of drugs. (ii) Enhance visibility and number of green drug manufacturing award programs
	Absence of intrinsic waste data for catalog chemicals	Intrinsic waste of raw materials, reagents, process aids, catalysts, and solvents is excluded from analysis	Regulate labeling requirements to show intrinsic waste of catalog chemicals to help guide green process design

1.4 Metrics Unification Via Green Aspiration Level

Green chemists from Boehringer Ingelheim, Pfizer, Novartis, GlaxoSmithKline, Genentech (Roche), Eli Lilly, Bristol-Myers Squibb, Merck, and Amgen, in collaboration with Prof. Sheldon, who is the inventor of the E factor, recently made a strong push to unify green mass-based metrics in industry [7]. The cohort simplified and improved the original green aspiration level (GAL) methodology [6] to help overcome the aforementioned industry barriers to green chemistry. By working through two of the leading green chemistry industry consortia, the International Consortium for Innovation & Quality in Pharmaceutical Development (IQ, https://iqconsortium.org/initiatives/working-groups/green-chemistry) and the ACS Green Chemistry Institute Pharmaceutical Roundtable (ACS GCI PR, https://www.acs.org/content/acs/en/greenchemistry/industry-business/pharmaceutical.html), they achieved support within those consortia to consider the GAL a valuable tool to make optimal choices in green chemistry process design. We will review how the barriers

have been tackled with the GAL, and exemplify the new methodology with Pfizer's Viagra and Boehringer Ingelheim's Pradaxa manufacturing processes [6, 7].

1.4.1 Standardizing Metrics

The group of inventors selected the complete E factor (cEF) and process mass intensity (PMI) as most suitable proxy metrics for green process analysis [7]. Both metrics can be used interchangeably in GAL methodology, thereby appealing to all pharmaceutical firms that use one or the other metric. We note that determination of cEF and PMI could be greatly simplified and automated via integration to electronic lab notebook (ELN) solutions [44, 45].

1.4.2 Defining Analysis Starting Points

The GAL methodology uses this simple yet useful definition for process starting materials [7]:

1) The material is commercially available from a major reputable chemical laboratory catalog company, and its price is listed in the (online) catalog. Materials requiring bulk or custom quotes do not qualify as process starting material.
   AND
2) The laboratory catalog cost of the material at its largest offered quantity does not exceed U.S. $100/mol.

The impact of standardized $100 per mol catalog pricing requirement can be profound as shown with the commercial Viagra process outlined in Scheme 1.1 [6, 46, 47]. The synthetic sequence considered for the original green metrics analysis is boxed and starts from pyrazole **1**, benzoic acid **3**, and piperazine **6**.

However, pyrazole **1** does not meet the $100 per mol rule, and we need to move upstream by five steps to oxalate **9** and pentanone **10** to fulfill the condition. The intrinsic waste that is associated with the production
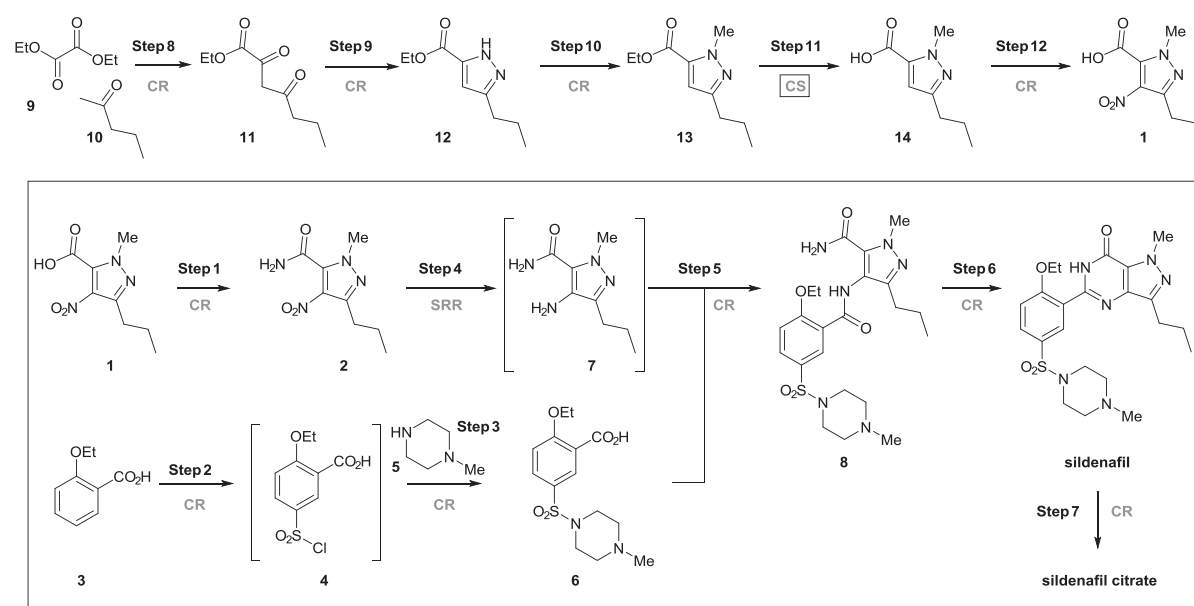
Scheme 1.1 Commercial viagra process [CR = construction reaction, SRR = strategic redox reaction, CS = concession step].

of pyrazole **1** increases the cEF of Viagra by 70% from 50.3 to 85.5 kg/kg. This example demonstrates how E factors can widely vary depending on the selected analysis starting points, and thus stresses the importance of an industry-wide standardized starting point concept to allow for meaningful process comparisons.

1.4.3   Considering Drug Manufacturing Complexity

Fair green chemistry goals can only be established if one considers the diverse molecular and manufacturing complexities of drugs [6, 7]. For the purpose of assessing process complexity, Baran's ideality methodology was selected, since it was considered a good proxy of both molecular complexity and optimal implementation of available synthetic methodology, plus it is fast and easy [48]—one simply adds the number of "productive" steps to determine the complexity of the process (Equation 1.2).

Equation 1.2 Determination of process complexity.

$$Complexity = no.\ of\ construction\ steps + no.\ of\ strategic\ redox\ steps$$

Thus, the complexity of the Viagra process in Scheme 1.1 equals 11. Complexity of a process can be reduced with innovative and effective process research. In fact, it has been shown that average pharmaceutical process complexity significantly decreases over the course of early and late development into commercialization from 9.4 to 8.0 and then to 5.9 [ref. 7, Table 1].

1.4.4   Green Aspiration Level (GAL)

The new GAL methodology has been introduced [6] and improved [7] as the first unified measure for any pharmaceutical manufacturing process against a common and fair green chemistry goal. It is readily calculated as follows [Equation 1.3]:

Equation 1.3 Determination of GAL.

$$GAL = Complexity \times 26\frac{kg}{kg}$$

26 kg/kg is the average expected (productive) process step waste per kg of commercial drug manufacture [7]. Importantly, cEF or PMI can be used interchangeably in GAL-based analysis, thus enabling companies to use either for calculating their green performance scores. Thus, the GAL of the Viagra process equals $11 \times 26\frac{kg}{kg} = 286\frac{kg}{kg}$, which represents the commercial cEF or PMI process goal.

1.4.5   Relative Process Greenness (RPG)

The GAL methodology allowed for unification of metrics via RPG (Equation 1.4) [6, 7]. RPG is a reflection of the green status of a process relative to its commercial aspiration level.

Equation 1.4 Determination of relative process greenness (RPG).

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

An RPG greater than 100% exceeds the commercial GAL based on average green process performance in industry. In contrast, RPG values less than 100% indicate green chemistry performance below industry standard. It was shown that average RPG significantly improves and increases from early to late development into commercialization from 49 to 96 and then to 132% [ref. 7, Table 1]. Thus, the RPG of the Viagra

process equals $\dfrac{286\frac{kg}{kg}}{85.5\frac{kg}{kg}} \times 100\% = 335\%$, which shows that it is 3.35 times greener in terms of manufacturing waste than the average commercial drug manufacturing process, and by this metric, well deserves the 2003 IChemE Crystal Faraday Award for Green Chemical Technology.

1.5 Green Scorecard

The Green Scorecard was introduced by the IQ Green Chemistry working group as a communication tool for green chemists and engineers to visualize their value-added impact of green chemistry improvements simply and effectively [7]. It is based on the following phase-dependent ratings matrix that was derived from analysis of 46 drug manufacturing processes from nine large pharmaceutical firms (Table 1.5).

Table 1.5 Rating matrix for RPG for Green Scorecard [7].

| Percentile | Color Code | Rating | Minimum RPG for | | |
			Early Dev	Late Dev	Commercial
90%	Blue	Excellent	109%	179%	248%
70%	Green	Good	76%	137%	197%
40%	Yellow	Average	40%	67%	93%
	Orange	Below Average	0%	0%	0%

Source: Royal Society of Chemistry.

The rating matrix along with detailed instructions and a free Green Scorecard calculator are available from the IQ website [49].

The Green Scorecard was showcased with the commercial Pradaxa process shown in Scheme 1.2 [50].
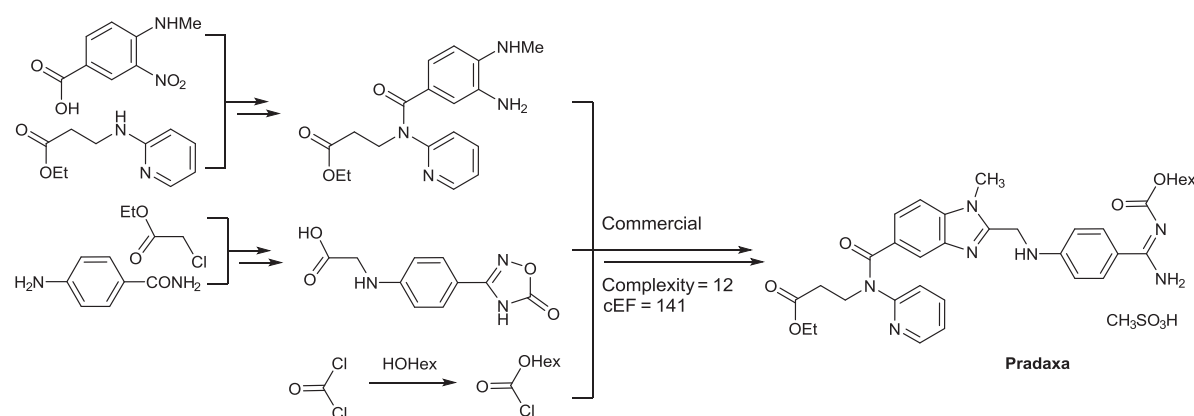
Scheme 1.2 Commercial Pradaxa process.

Table 1.6 The four easy steps of using GAL [7].

Step	Description	Example: Pradaxa (commercial)
1.	Determine waste (cEF or PMI) and complexity of the process [≤$100/mol for process starting materials | exclude reactor cleaning | exclude solvent recycling]	cEF = 141 kg/kg Complexity = 12
2.	Calculate GAL = Complexity × 26 kg/kg	GAL = 312 kg/kg
3.	Calculate RPG = GAL/cEF (or PMI) × 100%	RPG = 222%
4.	Obtain rating from RPG matrix (Table 1.5)	Good (Top 30%)

Source: Royal Society of Chemistry.

The Pradaxa example has been used to summarize the ease and quickness of the GAL methodology [7], as shown in Table 1.6.

This delivered the Green Scorecard output for Pradaxa (Figure 1.3) [7].

The Green Scorecard accounts for process innovation via reduction in process complexity versus earlier manufacturing processes of the same drug via the relative complexity improvement (RCI) metric
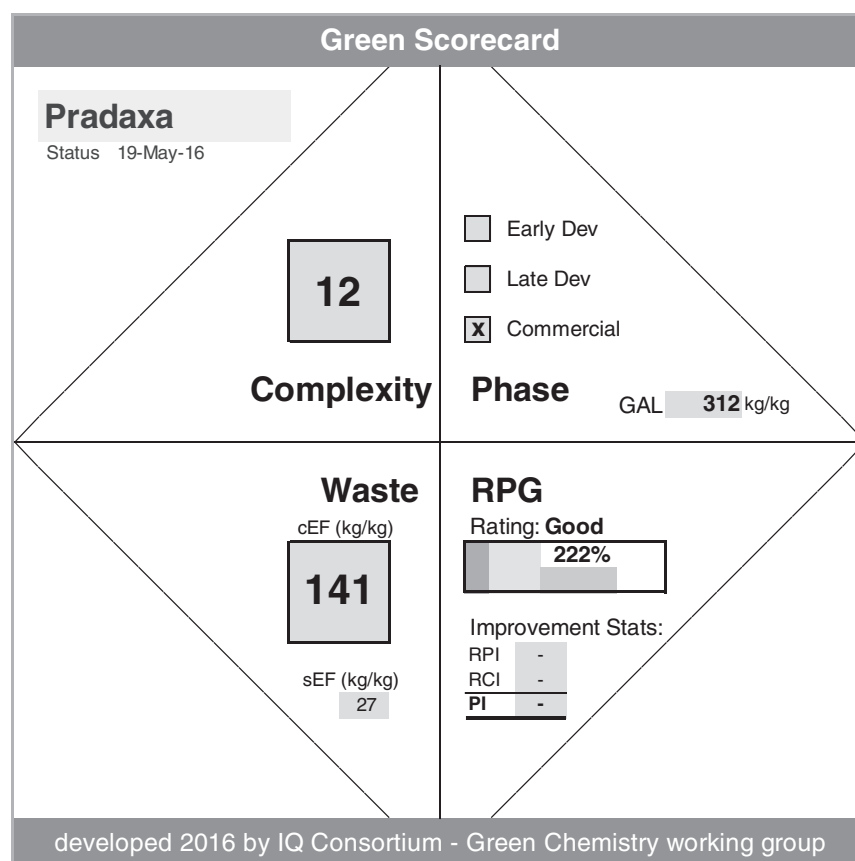

Figure 1.3 Green Scorecard.

(Equation 1.5) [6, 7]. In conjunction with the relative process (waste) improvement (RPI) metric (Equation 1.6), the RCI feeds into an overall process improvement (PI) measure (Equation 1.7).

Equation 1.5 Determination of relative complexity improvement (RCI).

$$RCI = 1 - \frac{Complexity\ (Current\ Process)}{Complexity\ (First\ Development\ Process)} \times 100\%$$

Equation 1.6 Determination of relative process improvement (RPI).

$$RPI = RPG(Current\ Process) - RPG(First\ Development\ Process)$$

Equation 1.7 Determination overall process improvement (PI).

$$PI = \frac{RPI + RCI}{2}$$

If GAL-based Green Scorecard methodology indeed can be widely integrated within pharmaceutical drug manufacturing, it would break down the aforementioned industry-internal barriers to adoption of green chemistry in industry (Table 1.4), by unifying the metrics with intuitive methodology, clearly defining starting points of process greenness analysis, integrating the complexity of the drug manufacturing processes, and consequently establishing industry-standardized phase-dependent green chemistry manufacturing goals, which were not possible in the pre-GAL era.

1.6 Supply Chain

Green chemistry programs in the pharmaceutical industry continue to be one of the most important pillars of delivering their environmental sustainability's commitments [6, 51]. Increasing environmental regulations across the globe and customer demand for greener products continue to put pressure on industry to maintain environmentally sound and responsible practices in supply chain operations. In addition, external stakeholders have recently increased pressure on companies to address the environmental performance of external supply chains. Groups like the UN have been quoted indicating that companies just "don't outsource responsibility and insource economic benefits," with respect to external vendors [52]. A recent publication by members of the IQ Green Chemistry working group and the ACS GCI PR quantified that 41% to 61% or about half of the drug manufacturing process waste was generated externally. As such, tracking green chemistry in the supply chain is pivotal to generate a complete picture of environmental performance of pharmaceutical products [7]. To effectively address this topic, pharmaceutical firms need to simplify the way they collect environmental sustainability performance from their suppliers, products, and services.

Green chemistry metrics have used by industry to track and improve performance in their internal supply chain operations, however, external suppliers have received much less attention [6, 7]. As such, many pharmaceutical companies have recently attempted to balance their environmental, social, and economic objectives with their suppliers, by requiring them to adopt and maintain sustainability programs with meaningful goals on metrics compliance. A challenge with reaching this goal is that suppliers purchase some raw materials from subcontractors, making it more difficult, if not impossible, to track green chemistry metrics of the purchased compounds, and what impact on sustainability occurs in these up-stream segments of the supply chain, which is likely to be highest. The lack of harmonization among available metrics has also inhibited opportunities for industry to provide guidance to their external supply chain partners and improve their green performance.

As described in Section 1.4, the use of GAL together with the Green Scorecard provide a harmonized metrics system that could be used to predict the greenest of chemical processes not only for drugs, but also advanced

intermediates and raw materials. Moreover, the Green Scorecard described earlier could be generated directly by suppliers and included in their final manufacturing reports.

Another benefit of using harmonized green chemistry metrics across industry is the opportunity to influence green branding programs. Some global markets use environmental performance as selection criteria for tenders. An example of these incentives includes the Parisian Hospital Association that often requests environmental and sustainability data during their purchasing evaluation. Another example is the incentive scheme of the Swedish Association of the Pharmaceutical Industry (LIF), which is currently conducting a pilot for over-the-counter (OTC) products [53, 54]. Working together with the Swedish National Pharmaceutical Strategy, LIF is developing a framework for green economic incentives for OTC medicines. Under this model, environmental considerations will be accounted for in the national reimbursement scheme. The ACS GCI PR's PMI-LCA tool is being used for sustainability assessment of this program [25]. We believe that a simpler, harmonized approach like GAL may be an alternative metric system for this and other emerging incentives programs.

1.7   Outlook and Opportunities

1.7.1   Industry-Wide Adaption

With the recent unification of green chemistry metrics in drug manufacturing [7], the next important step for the inventors of the optimized GAL-RPG-Green Scorecard methodology in breaking down barriers to green chemistry is to achieve the envisioned industry-wide adoption of the methodology to measurably reduce waste and cost of global drug manufacturing. This goal can be realized through communicating the GAL methodology via webinars, seminars, and short courses, by consistent inclusion of the applied methodology in forthcoming publications, and achieving buy-in from company management and scientists across industry to set up GAL-based process performance goals. In addition, GAL methodology could be extended to allied chemical manufacturing industries.

1.7.2   Integration with LCA

It was envisioned that GAL could be integrated with LCA [7] in terms of consistent analysis starting points, establishment of fair LCA goals, and Green Scorecard reporting. If such standardized LCA can be further simplified through web-based calculators hosted by the ACS GCI PR, for example, it would become the most valuable method for comprehensive process greenness analysis and rating, and could be applied to drugs in the early development phase during definition of synthesis route.

1.7.3   Application of GAL to Supply Chain

GAL could be used as the first fair and quantifiable metric to manage, reward, and encourage green performance in the pharmaceutical manufacturing supply chain that was shown to contribute about 50% to the overall manufacturing waste [7], as discussed *vide supra*.

1.7.4   Transformation-Type–Based GAL

Recently, a quantitative approach for comparing synthesis routes and designing and selecting the greenest via PMI prediction for drugs was introduced [55]. The Bristol-Myers Squibb authors first determined probable phase-dependent step PMIs for all major chemical transformation types from analysis of historic data, and then applied them to calculate process PMI from the step sequence, type of transformations, and step yields. The probable transformation-based step PMI is essentially a "transformation-type GAL" of a productive step

(CR or SRR, see caption of Scheme 1.1). Thus, this PMI prediction strategy could be integrated with GAL's complexity measure and standardized starting point concepts to potentially deliver more accurate manufacturing process goals and thus improved rating system.

1.7.5 Opportunities for Government

It has already been suggested that government could drive broad adoption of green chemistry by rewarding greener drug manufacturing processes with fast-track regulatory approval [6]. However, what has been critically missing until now was methodology that would allow government to do so by objectively quantifying process greenness of any drug. Government now has the opportunity to embrace and apply GAL by validating its methodology via incorporation as key metric in issuing prestigious awards such as the U.S. PGCCA. Use of GAL could extend beyond awards and expedited regulatory benefits. For example, government could motivate pharmaceutical firms to create greener processes by introducing a "green drug" label based on predefined RPG parameters that would enhance public reputation of the firms.

In summary, industry has made a significant step forward with metrics evolution in an attempt to break down the barriers to broad green chemistry adoption via the improved GAL methodology [7]. Its unifying potential within industry and for industry with government and supply chain is graphically summarized in Figure 1.4.
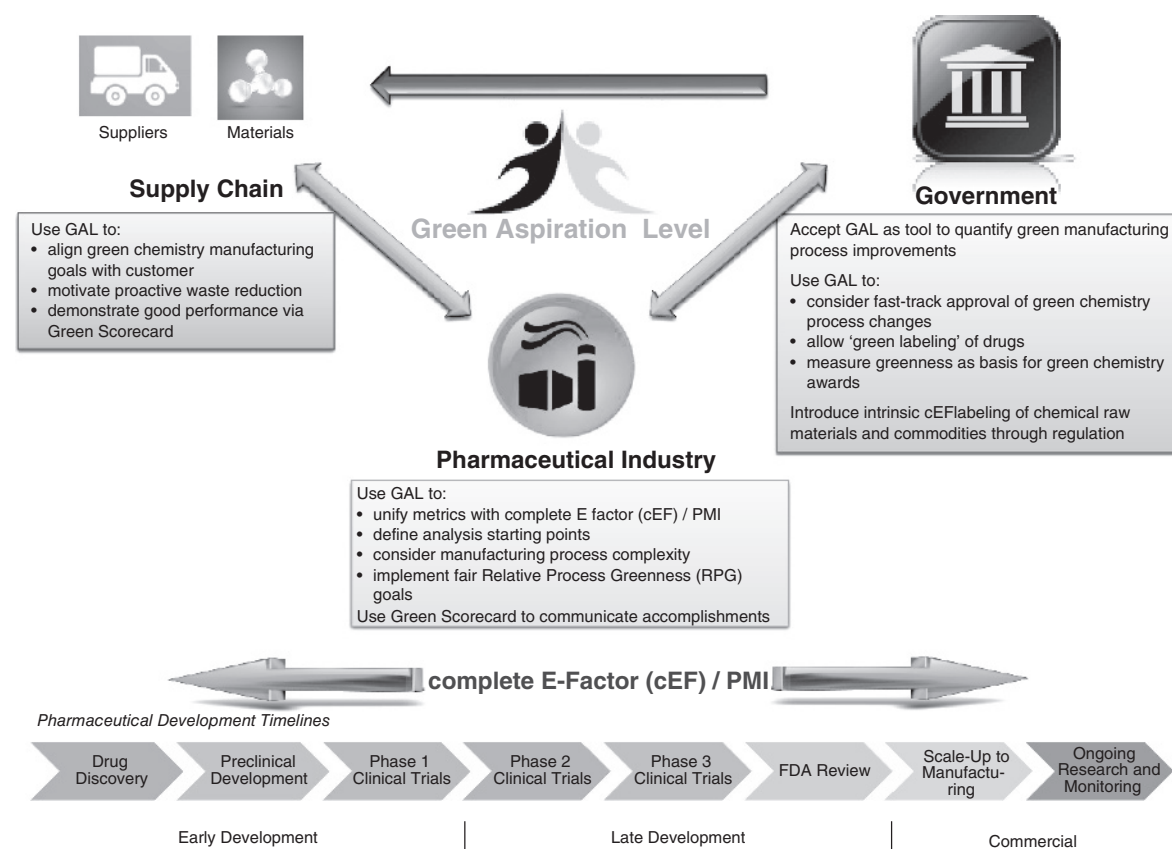

Figure 1.4 Breaking down barriers to green chemistry with GAL methodology.

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