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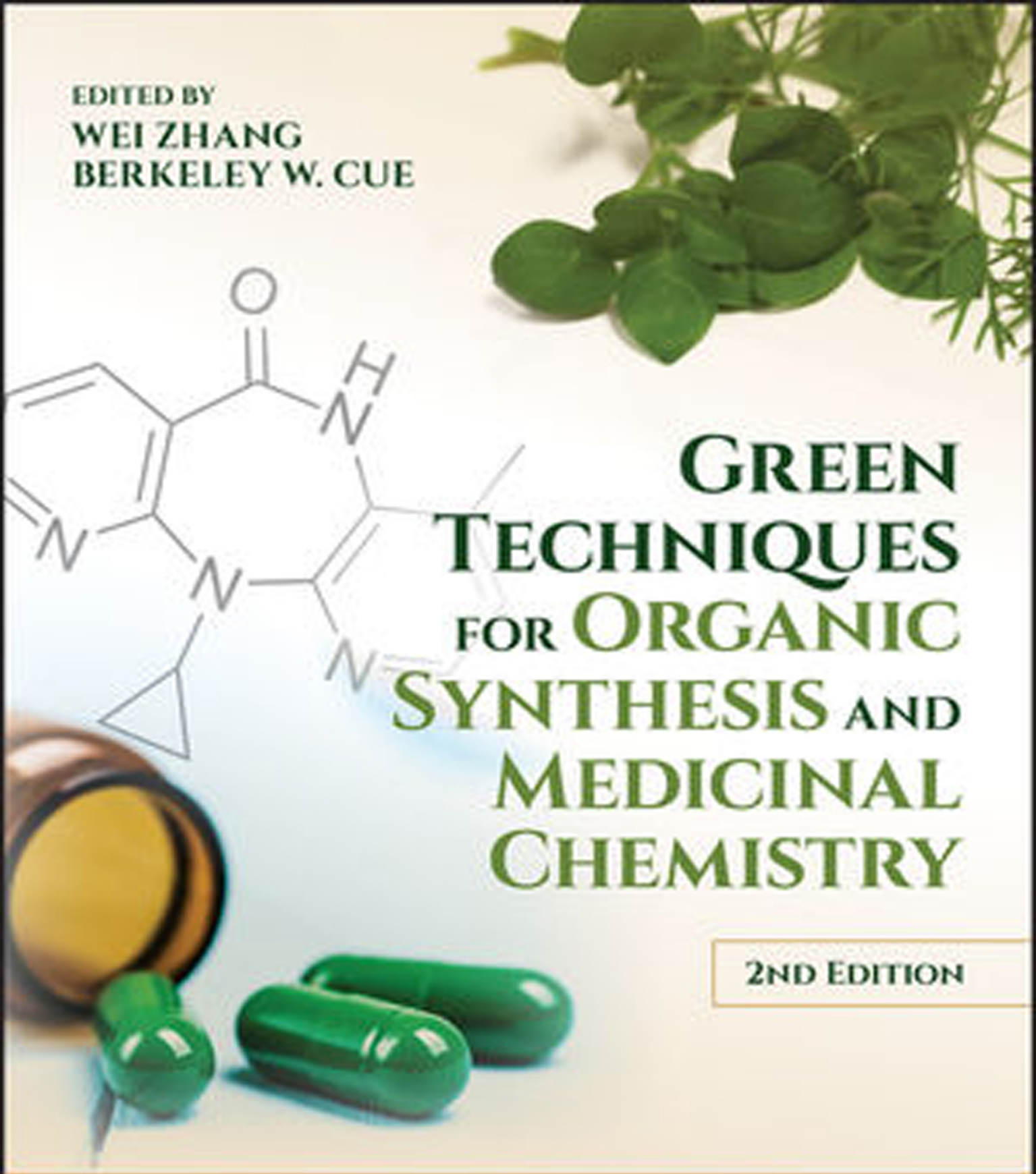

GREEN TECHNIQUES FOR ORGANIC SYNTHESIS AND MEDICINAL CHEMISTRY

2ND EDITION

WILEY

Green Techniques for Organic Synthesis and Medicinal Chemistry

Green Techniques for Organic Synthesis and Medicinal Chemistry

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Foreword

This second edition of *Green Techniques for Organic Synthesis and Medicinal Chemistry* by Cue and Zhang is a collection of the cutting-edge research and intellectual perspectives from the leaders in the field of chemistry in both industry and academia. It reflects the exponential growth that is taking place in the chemical enterprise around the world and the ways that elegance in chemistry is being defined. Within the context of their time, the giants of synthetic chemistry of the past would undertake and accomplish herculean feats of molecular manipulation that were previously thought impossible. While those feats need to be recognized for the historical advances that they were, it is equally true that we have evolved to see their limitations in the current day. Many of the techniques that were developed were harsh, or toxic, or posed physical hazards, or caused inordinate waste generation. In other words, they caused a number of new problems while they were solving the problem that they were focused upon. Two steps forward and one (or more) steps back.

This book more than anything else shows the elevation in thinking that has allowed the field to recognize that a systems perspective is essential to avoid unintended consequences. More importantly, a systems perspective is one of the most powerful drivers to genuine impactful innovation. Each of the topics covered in this book demonstrates not merely an advance in the discovery, demonstration, and development of a molecule or synthetic pathways, but also an advance in the design thinking behind the chemistry.

The topics in the book are as varied and diverse as the field of green chemistry itself, which is a tribute to the vision of the editors. When the area of catalysis is addressed it covers new thinking in terms aqueous catalysis in Chapter 12, "Asymmetric Catalysis in Aqueous Media" by Kartik C. Bhowmick and Tanmoy Chanda that combines the perspective on catalyst development with the insights of how the properties of water can be used to facilitate stereo-selectivity. The founder of fluorous solvents, István T. Horváth (along with co-author László T. Mika), brings his decades long perspectives on catalysis to bear Chapter 10, "Fluorous Catalysis." The advantages of biocatalysis to the goals of industrial green chemistry are addressed in Chapter 8 by James Lalonde from Codexis and Chapter 9 by Luo and Zhang portray the leading edge of asymmetric and C-H bond catalysis respectively.

Just as the chapters on catalysis look at the broader systems that enable and empower green catalysts, the section on synthetic techniques takes a similar approach. Alternative approaches to chemical media and synthetic processes is exemplified through the chapters on solvent-free synthesis, microwave synthesis, ultrasonic synthesis by Mack, Van der Eycken, and Stefani, respectively and demonstrate the need for demonstration and scale up of these innovative approaches to synthesis. Chapters from Yi, Rogers, Shamshina, Kitchens, Soh, and Sun highlight the combining of the thinking of traditional methodologies with solvent systems and engineered systems in the chapters. Too often synthetic methodologies have been tossed over the proverbial transom to the process engineers, which has brought about frustration, delays, cost, and sub-optimal results. These chapters are indicative of the thinking in green chemistry and green engineering that is taking place to displace those old inefficiencies.

The chapters that focus on real-world examples from the pharmaceutical sector provides current perspectives on the critical topics ranging across processes, metrics, regulations, and industrial collaborations in green chemistry. This section has particular value for those wishing to know what the essential elements are for any individual or company wishing to engage or advance green chemistry within the pharmaceutical sector.

Of all of the innovative parts of the book, perhaps the most intellectually challenging is Part I, which combines thinkers from across the spectrum of industry, academia, and not-for-profit institutions to discuss the grand state of affairs in green chemistry, including a chapter by Stohl and Warner who illustrate green chemistry innovation with examples of their research into non-covalent derivatives. The remaining chapters survey the field from regulations to formulations to analysis and provide a definitive overview for the reader.

This book gives the readers a glimpse at the horizons that can be accomplished through green chemistry thinking and innovation. By moving from a focus on efficiency, to effectiveness, toward the ideal, the field of green chemistry has evolved over 25 years and that evolution is reflected in the chapters. The editors of this volume, Cue and Zhang, have combined the broadest perspectives of green chemistry with the most insightful scientists in the field and produced a volume that represents the frontier of the green chemistry enterprise in 2017.

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Preface

We are pleased to present the second edition of *Green Techniques for Organic Synthesis and Medicinal Chemistry*. According to a Web of Science search by the end of 2016, more than 40% of all the papers in the field of green chemistry have appeared since our first edition was published in 2012, documenting the continuing explosive growth of green chemistry. In this new edition we have presented topics in chapters that reflect the breadth and depth of this growing field of chemistry. This 24-chapter book has 55 contributing authors, including 20 who contributed chapters to the first edition and 35 who are new contributors to this edition, and who represent academia and industry from around the world. Of the 24 chapters, 9 introduce subjects that are new to this edition and all of them contain a major focus on the science that has emerged in recent years. We sincerely thank all our authors for their excellent and dedicated work to complete this project. We acknowledge Ms. Sarah Higginbotham from Wiley for inviting us to contribute this new edition and for her help with the preparation and review of our book proposal. We thank Ms. Elsie Merlin, Ms. Rebecca Ralf, Ms. Emma Strickland, Tricia Lawrence, and Shalini Sharma at different stages of this project including communicating with authors, typesetting, proofreading and cover design, and Dr. Paul Anastas for contributing the foreword. Each of them helped to make this book better than it would otherwise have been. Finally, and most importantly, we thank our family members. A project like this always seems to demand more time and a higher priority than we realize and often this time is taken from them. For their patience and understanding we are grateful.

Wei Zhang is a faculty member and Berkeley W. Cue is a 1969 alumnus and adjunct professor in the Chemistry Department of the University of Massachusetts-Boston (UMB). UMB has a strong tradition in green chemistry and many outstanding alumni including Dr. Paul Anastas, Dr. Nicholas Anastas, Dr. Amy Cannon, and Dr. John Warner. UMB established the first PhD program in green chemistry and the Center for Green Chemistry. So far over 20 students have been awarded their PhD degrees in this field. In 2015, UMB hosted the third Global Green Chemistry Centers (G_2C_2) conference in its newly opened Integrated Science Center (ISC). In 2016, the Green Chemistry Centers of Yale University and UMB held a joint symposium celebrating UMB alumni's green chemistry achievements. We sincerely thank the UMB Chemistry department, the College of Science and Mathematics, and the university for providing continuous support to green chemistry-related activities, including the publication of this book.

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Part I

General Topics in Green Chemistry

1

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,

Green Techniques for Organic Synthesis and Medicinal Chemistry, Second Edition. Edited by Wei Zhang and Berkeley W. Cue.

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.

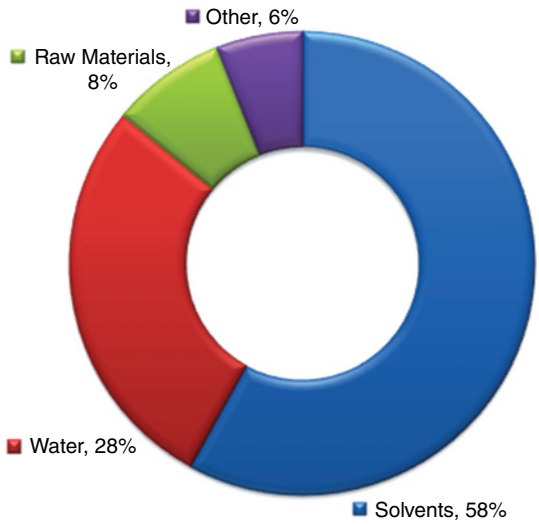

Figure 1.1 Typical pharmaceutical drug manufacturing waste composition.

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

(*continued*)

Table 1.2 (*Continued*)

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

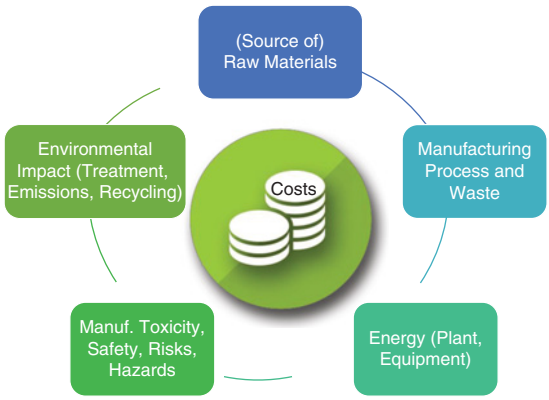

Figure 1.2 Comprehensive green metrics categories for life cycle assessment.

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