

# A method to characterize the greenness of solvents used in pharmaceutical manufacture

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- 5 This paper describes the development of a method to calculate the overall “greenness” of a pharmaceutical process that uses multiple solvents. This calculation is made by taking into account various environmental parameters and determining an overall greenness index. Through this method a scientist or engineer can effectively determine alternative, “greener” solvents or processes based on the use of a solvent database and greenness score. The objective is to develop a means to improve the process of drug development through solvent replacement/reduction. A solvent selection table, using a common spreadsheet software routine, was developed for
- 10 the purpose of allowing a user to compare the greenness between two different process routes. This table includes over 60 solvents and associated chemicals common in the pharmaceutical and chemical industries. The comparison was made possible by the creation of a user-defined, weighted-solvent, greenness index that is an overall weighted factor taking into consideration solvent type, quantity used, and environmental impact. A given process or solvent receives an index ranking based on a variety of environmental and health parameters. The index values, along with the mass of solvents used in the given process, are used to compute the index, which allows
- 15 for a quick and easy quantitative environmental comparison between two potential process routes.

**Keywords:** Green engineering, green chemistry, solvent metrics, pharmaceutical processing.

## Introduction

### *Background*

- 20 The majority of drug products made through organic synthesis routes are made in batch processes, and they require many sequential reaction steps and large quantities and number of organic solvents with varying degrees of toxicity. None of the preceding situations are optimal from a green engineering manufacturing standpoint. Pharmaceutical manufacturing utilizes batch processes and numerous
- 25 solid-liquid separation and purification steps. Liquid waste streams containing these solvents occur from crystallization, extraction and solids washing, and cleaning processes as well as byproducts from inefficient reactions. Solvent
- 30 wastes released in the air as volatile organic compounds (VOCs) are produced from solid drying processes, tabletting and coating operations, and fugitive emissions from the manufacturing process. Besides releases into the air, solvents can be found in the solid and liquid wastes that occur
- 35 in the filtration and centrifugation operations of the

API (active pharmaceutical ingredient) and intermediate production.

Consequently, green engineering and sustainability issues have become a concern for the pharmaceutical and specialty chemical processing industries. Reported incidents concerning toxic release of chemicals into the environment, food supply contamination, and hazardous work conditions led to measures such as the Clean Air Act, the Clean Water Act, and the Occupational Safety and Health Act.<sup>[1]</sup> In addition, federal agencies such as the U.S. Environmental Protection Agency (EPA) have developed a number of programs promoting increased environmental and health awareness.<sup>[2]</sup> One such program, the National Environmental Performance Track, recognizes and rewards industrial facilities that exceed environmental/health standards while working closely with the surrounding community.

Design for Environment (DfE) is another government program that works with specific industries to integrate health and environmental considerations into typical business decisions. This program promotes source reduction or prevention when it comes to human or environmental risks, rather than controls at the end of the process. The Pollution Prevention and Source Reduction Assistance Programs offer opportunities for collaborative pollution prevention and training activities. Other EPA programs such as the Presidential Green Chemistry Awards recognize specific

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achievements in green chemistry. The outcomes measured by many of these programs are typically total lbs/year of waste reduction with little emphasis on the relative nature of the pollutants reduced or their broader environmental consequences.

Based on a review of the 2005 Toxic Release Inventory data,<sup>[3]</sup> the pharmaceutical industry sector (SIC codes 2833 and 2834) reported over 530 million pounds of waste to the EPA's Toxic Release Inventory. These wastes represent organic solvents and associated chemicals (acids, bases, nitrates, etc.) from the various processes used in drug manufacture. Generally, the pharmaceutical industry has the highest waste generation and the highest amount of organic solvents used per mass of product produced for any commercial sector. The solvent use rates can range from 10–800 kg/kg API depending on the type of pharmaceutical and stage of development.<sup>[4]</sup> Typical waste streams from drugs made through organic synthesis contain over 80% organic solvents.<sup>[5]</sup> These include organic solvents classified in the TRI as priority pollutants or hazardous air pollutants and those that fall outside of the TRI classification, but still pose risk to the environment if released. According to Jimenez-Gonzalez et al.<sup>[6]</sup> approximately 60% of the overall energy usage in pharmaceutical production and 50% of the post-treatment greenhouse gas emissions are a result of the solvent usage throughout the process.

The top 20 solvents released by the pharmaceutical sector according to the 2005 Toxic Release Inventory (TRI) are shown in Table 1. Out of over 170 chemicals listed on

**Table 1.** Top 20 chemicals released by the pharmaceutical sector in 2005 according to the EPA Toxic Release Inventory<sup>[3]</sup>

<i>Chemical</i>	<i>Releases (Million lb/year)</i>
Methanol	166.71
Dichloromethane	57.09
Formaldehyde	47.76
Toluene	43.57
Hydrochloric acid	34.85
Ammonia	25.51
Acetonitrile	20.51
<i>n</i> -Hexane	16.27
<i>n</i> -Methyl-2-Pyrrolidone	11.47
Formic acid	11.09
<i>n</i> -Butyl alcohol	10.11
<i>n, n</i> -Dimethylformamide	9.21
Chloroform	7.80
Nitrate compounds	6.32
Methyl tert-butyl ether	5.44
Xylene (mixed isomers)	4.18
Arsenic compounds	3.62
Certain Glycol Ethers	3.39
1,1,2-Trichloroethane	3.30
Bromine	2.89
Total (for the top 20 listed)	491.11
Total (for all TRI chemicals)	532.36

the TRI, the top 20 solvents comprise over 90% of the total listed releases. The TRI listing does not report many commonly used solvents such as acetone and ethyl acetate since they are not classified by EPA as priority pollutants or hazardous air pollutants. Despite this fact, the data is useful in examining the major environmental pollutants released and examining trends in solvent usage. Solvents are the most heavily used and disposed of chemicals in the pharmaceutical industry, and a great deal of improvements can be made to decrease the amount of solvents used and released. The solvents included in the TRI pose significant environmental concerns regarding their release into the environment. These solvents have varying degrees of toxicity to humans and animals, and some are known or possible carcinogens.

Research is underway to examine the reduction and substitution in the use of these solvents through innovative green chemistry/green engineering and environmental design strategies. The positive impacts of these new strategies are the reduction of solvent use and environmental releases as well as the substitution of greener and more benign solvents that can be used in the various processing steps. Effective solvent selection and evaluation tools are necessary so that the pharmaceutical industry can gauge its progress in developing alternate syntheses and manufacturing processes. This paper focuses on the development of a solvent selection measurement tool that will allow the user to compare solvents and processes with relative ease based on multiple environmental and physical properties. It can help scientists and engineers who need to quantify broader environmental implications of solvents used in a process.

### *Review of current solvent selection methodologies*

Solvent selection techniques have been developed that can help a scientist/engineer to make better informed decisions when choosing solvents. According to Gani et al.<sup>[7]</sup> there are basically four areas from which information can be drawn: benchmarking, databases, expertise and experience, and computer-aided technologies. Benchmarking uses existing processes or chemicals with similar properties to draw conclusions on unknown processes and chemicals. As scientists/engineers gain expertise in solvents and processes, they become able to make better informed decisions based on what they have experienced and learned. Computer-aided technologies, along with databases, offer sources and methods to determine and estimate properties of various solvents to provide a basis of comparison. Table 2 shows some of the computer-aided technologies that are available and are used by pharmaceutical and specialty chemical companies.<sup>[8]</sup> Some of these are methods, such as the GlaxoSmithKline (GSK) and Bristol-Myers Squibb (BMS) techniques, were developed “in-house” for their use, while others are publicly available.<sup>[9]</sup>

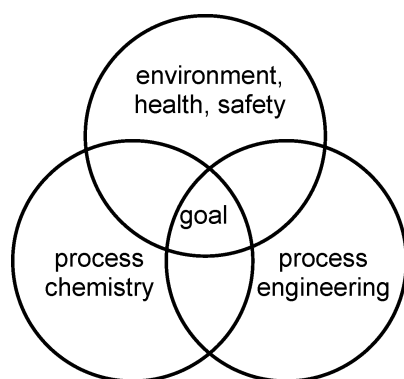
Gani et al.<sup>[7]</sup> have also proposed a four-step method that clearly defines the problem of solvent selection and provides

**Table 2.** Computer-aided solvent selection and property tools

<i>Solvent selection tool</i>	<i>Main features</i>
GSK-Solvent Selection Guide	A proprietary visual, web-based solvent-selection tool for selecting “greener” solvents for various reactions common in pharmaceutical synthesis.
BMS Process Greenness Scorecard	A computer tool to rate the relative greenness of solvents based various green chemistry process parameters. Integrates with AspenTech and IntelliChem.
ProCAMD (ProPred, PDS, Solu-Calc, CAPEC-Database); SMSwin	Hybrid computer-aided technique for solvent selection; applies to wide range of industrial applications.
NRTL-SAC AND eNRTL-SAC	Method uses chemical thermodynamic parameters such as activity coefficient. Applicable for crystallization solvent selection and electrolytes.
ISSDS	Method permits alternative solvent selection from multiple databases though one “Integrated Solvent Substitution Data System.”
SAGE	A logic tree system that evaluates an operating scenario and then identifies possible alternative solvent chemistries. Originally developed for surface treating/cleaning applications.
COSMO-RS, COSMO-SAC	A physical property predictive modelling method for solvent fluid phase thermodynamics.

Adapted from Jimenez-Gonzalez et al.<sup>[8]</sup>

145 a means to find that most appropriate solvent. The first step  
 in addressing the solvent selection issue is to define and  
 identify the problem clearly in terms of process applica-  
 tions, process formulations, and/or cleaning and washing.  
 150 Once the problem or issue is defined, the search criteria can  
 be identified with respect to physical and chemical proper-  
 ties, environment, health and safety (EHS) properties and  
 concerns, operational concerns, and economic issues. To  
 reduce the number of potential solvents and optimize the  
 selection process, computational and experimental studies  
 155 should be conducted to analyze and reduce the number of  
 potential solvents. This method is just a basis to narrow the  
 solvent search. The ultimate goal in choosing the best sol-  
 vent incorporates all the areas of concern (EHS, chemistry  
 and engineering) as seen in Figure 1.  
 160 Quantitative analysis programs have been generated for  
 similar solvent selection purposes and have included not



**Fig. 1.** Environment, health, and safety concerns of the solvent; effect on reaction yield; and processing concerns such as ease of purification all have to be considered in determining the optimal solvent. Adapted from Gani et al.<sup>[7]</sup>

only environmental, chemical, and engineering parameters  
 but also economics. Heinzle et al.<sup>[10]</sup> offer three types  
 of indices that include mass-loss, environmental, and  
 economical parameters. Hoffmann et al.<sup>[11]</sup> propose an  
 165 approach to be used during research and development  
 stages to expand green process optimization on the bases of  
 both economical and environmental concerns. Allen and  
 Shonnard<sup>[1]</sup> propose reaction stoichiometry and toxicity  
 be examined for green chemistry approaches to selecting  
 170 materials in a process.

Multi-step procedural environmental reviews, check lists,  
 and hierarchical decision procedures have been other sug-  
 gested methods.<sup>[12–14]</sup> Another approach highlights envi-  
 175 ronmental concerns and offers methods of waste reduc-  
 tion to incorporate in early process development through  
 use of a material defined database.<sup>[15]</sup> These qualitative ap-  
 proaches are restricted in that they provide limiting process  
 comparisons.

Chen and Shonnard<sup>[16]</sup> suggest some of these methods  
 180 have limited applicability and accuracy because emission-  
 based environmental parameters can be overestimated. This  
 is due to the fact that these proposed methods assume all  
 reagents, whether consumed or not, will have an impact  
 on the environment. They neglect reacting reagents that  
 185 convert raw material to desired product, in which case not  
 every stream output is removed as waste. Other methods  
 exploit toxicity-weighted mass indicators, though neglect  
 effects of environmental fate.

### *Solvent selection table*

190

This paper describes a means of simplifying the green sol-  
 vent selection process and providing a “score” or “index”  
 for process greenness through use of a solvent selection ta-  
 ble database and calculation procedure. This was developed

195 through collaborative efforts with Bristol-Myers Squibb  
 and supported by the U.S. Environmental Protection  
 Agency. The intent is to enable the user to combine more  
 quickly the various chemical and environmental properties  
 of over 60 solvents and associated chemicals that are com-  
 200 monly used in the specialty chemical and pharmaceutical  
 industries and quantitatively compare the “greenness” of  
 these solvents or an overall process using multiple solvents.

This task is achieved by employing the use of a customiz-  
 able overall solvent index that takes into account twelve en-  
 205 vironmental parameters for each solvent programmed into  
 the database that have been derived from various industrial,  
 professional society, and governmental sources.<sup>[17–20]</sup> This  
 method does not intend to incorporate all of the features of  
 the previously reviewed techniques, as it would be too com-  
 210 plex to develop and use. It is also different from commer-  
 cially available life cycle assessment software, as it addresses  
 health, safety and environmental parameters at the solvent  
 use step and not for the full “cradle to grave” analysis of  
 the environmental impact.<sup>[21]</sup> It does allow for expansion in  
 215 terms of new solvents or chemicals and more parameters  
 to include such areas of concern such as economics.

## Results and discussion

### Methodology

220 This solvent selection table program generates a score,  
 which will subsequently be called an index, that allows for

a quick comparison between different solvents and process  
 routes showing what alternative is the greener. A weighted  
 index was established to measure which solvent or process  
 would be “greener” yielding a lower index score. The in-  
 dex is based on 12 environmental parameters representing  
 225 hazards associated with workers’ safety as well as air, water  
 and land contamination. Table 3 shows all the parameters  
 incorporated into the solvent selection table.

Because each environmental metric represents something  
 different, i.e., exposure limit, toxicity, consequence, envi-  
 230 ronmental impact, etc and has different units, a method  
 needed to be developed to bring this disparate information  
 into uniform scales of measurement. Our approach was to  
 take the range of values for each environmental parameter  
 for all of the solvents in the database and develop a scale that  
 235 would essentially convert all information to a 0 to 1 scale  
 that is dimensionless. Each category from Table 3 (i.e., in-  
 gestion toxicity, biodegradation, aquatic toxicity, etc.) was  
 initially weighted on a log scale with a log base equivalent  
 to the maximum value of that particular parameter. These  
 240 values were then scaled in a linear fashion utilizing either  
 Equation 1 or 2.

$$M_i = 1 - \frac{\log_{x_{\max}} x_i - \log_{x_{\max}} x_{\min}}{\log_{x_{\max}} x_{\max} - \log_{x_{\max}} x_{\min}}$$

where  $x_i$  increases as greenness increases (1)

$$M_i = \frac{\log_{x_{\max}} x_i - \log_{x_{\max}} x_{\min}}{\log_{x_{\max}} x_{\max} - \log_{x_{\max}} x_{\min}}$$

where  $x_i$  decreases as greenness increases (2)

**Table 3.** Parameters used in the environmental analysis of the solvent selection table and overall solvent index calculation

Parameter	Abbreviation	Definition
Inhalation Toxicity–TLV (Threshold Limit Value)	TLV	Maximum concentration of a chemical allowable for repeated exposure without producing adverse health effects
Ingestion Toxicity	Inges	Mass of chemical ingested that results in a toxic effect, most commonly represented as mg chemical/kg rat.
Biodegradation	Biodeg	Capacity of being decomposed by biological agents, especially bacteria
Aquatic Toxicity	Aqua	Quantity of chemical compound proven toxic to aquatic fish in mg per liter of water
Carcinogenicity	Carcin	Capacity to cause cancer (0-proven non-carcinogenic; 5-proven carcinogenic)
Half-Life	$1/2$	Time required for chemical to fall to half its initial value
Ozone Depletion	O3	Predicted time- and height integrated change $\delta$ [O3] in stratospheric ozone caused by the release of a specific quantity of the chemical relative to that caused by the same quantity of a benchmark compound, trichlorofluoromethane
GWP (Global Warming Potential)	GWP	Cumulative infrared energy capture from the release of 1 kg of a greenhouse gas relative to that from 1 kg of carbon dioxide
Smog Formation	Smog	Solvent’s capacity to release smog forming agents into atmosphere
Acidification	Acid	Related to the number of moles of $H^+$ created per number of moles of the compound emitted
Soil Adsorption Coefficient	Soil	Equilibrium ratio of the mass of a compound adsorbed per unit weight of organic carbon in a soil to the concentration of the compound in a liquid phase
Bio Concentration Factor	BCF	Ratio of a chemical’s concentration in the tissue of an aquatic organism to its concentration in water

*Solvents used in pharmaceutical manufacture*

where  $M_i$  is the scaled value of metric  $M$  for solvent  $i$  (dimensionless)

- 245  $x_{\min}$  is the minimum value for all of the solvents in the database for metric  $M$
- $x_{\max}$  is the maximum value for all the solvents in the databases for metric  $M$
- 250  $x_i$  represents the value of the environmental parameter for the specific solvent  $i$

Applying just the log to each individual parameter generates values ranging from  $-3.9$  to  $1$  (Table 4), which is difficult to linearize for all the parameters. The linear scale shown above in Eqs. 1 and 2 fit the log scale factors into a normalized 0–1 scale. Both equations enable our scales to invert between 0–1 and 1–0. High values for some parameters would signify a more environmentally benign effect and therefore would employ Eq. 1 to generate low weighted scales. Eq. 2 is used to generate low weighted scales if the parameters have low values signifying relative greenness. This issue becomes extremely important when summing parameters into an overall weighted index factor where those that are greener are lower than those deemed toxic. Table 4 depicts how each factor was scaled in terms of greenness due to relatively high/low parameter values. According to this table, TLV, ingestion, biodegradation, and aquatic toxicity are scaled using Eq. 1. The remaining parameters were scaled using Eq. 2.

For example, to find the scaled value for the ingestion toxicity of acetonitrile, Eq. 1 would be employed. Out of all the solvents and chemicals in the table, the highest value for ingestion toxicity is 25,000 ppm for water and the lowest value is 24 ppm for mesitylene, also known as 1,3,5-trimethylbenzene. The ingestion toxicity of acetonitrile is 3800 ppm. Inserting these values into Eq. 1, as shown next, would lead to a linearized value of 0.27 for acetonitrile. All other chemicals would be linearized in a similar manner for the other parameters. Instead of assigning an absolute greenness to a particular chemical, this method allows

the table of solvents to be expanded with other chemicals. Values for the other parameters for acetonitrile are shown in Table 5.

$$\text{Scaled Ingestion Toxicity}_{\text{Acetonitrile}} = 1 - \frac{\log_{25000} 3800 - \log_{25000} 24}{\log_{25000} 25000 - \log_{25000} 24} = 0.27$$

An overall solvent index was then tabulated as a summation of each of the parameters for a given solvent or chemical with the option to weigh factors more so than others. The tabulation was determined using Eq. 3.

$$\text{Overall solvent index, } OSI_{\text{solvent}} = \sum_{i=1}^n \alpha_i M_i \quad (3)$$

where  $\alpha_i$  is the weighting factor for the environmental/health/safety parameter and  $M_i$  is the weighted metric previously defined in Eqs. 1 and 2.

The overall solvent index can be adjusted by these weighting factors to represent concerns of a particular industry. Based on discussions with the pharmaceutical industry, the index for pharmaceutical manufacture is dependent more on issues concerning worker's safety (i.e., threshold limit value, ingestion, and carcinogenicity) than ecological interests.<sup>[22]</sup> Therefore the overall solvent index modified for the pharmaceutical industry would be represented in the following way:

$$\begin{aligned} \text{Overall Pharmaceutical Solvent Index} &= 2(M_{\text{TLV}} + M_{\text{Ingestion}} + M_{\text{Carcinogenicity}}) + M_{\text{Biodeg}} \\ &+ M_{\text{Aqua}} + M_{\text{half life}} + M_{\text{O}_3} + M_{\text{GWP}} + M_{\text{Smog}} + M_{\text{Acid}} \\ &+ M_{\text{Soil}} + M_{\text{BCF}} \end{aligned} \quad (4)$$

One of the most prominent features of this method is the incorporation of a user-defined weighting factor for each metric. While incorporating all the given environmental parameters, this feature also addresses the issue concerning the ambiguity of green engineering by letting users define which metrics they wish to incorporate into their overall weighted

**Table 4.** Maximum and minimum values of parameters in which solvents are scaled upon based on all 64 solvents in database

Parameter	$x_{\min}$	$x_{\max}$	$\log_{\min}$	$\log_{\max}$	High values (use Eqn 1)	Low values (use Eqn 2)
TLV (ppm)	0.8	1000	0	1	Greener	
Ingestion toxicity (rat mg/kg)	24	25000	0.3	1	Greener	
Biodegradation (log Biodegradation)	1.60	3.90	0.00	1	Greener	
Aquatic Toxicity (mg/L)	3.8	84318	0.1	1	Greener	
Carcinogenicity (Unitless)	0	5	0	1		Greener
Half Life (12 hr days)	0	8333	-0.2	1		Greener
Ozone Depletion (Unitless)	0	1.1	0	0		Greener
GWP (Unitless)	0	1400	0	1		Greener
Smog Formation (Unitless)	0	6.5	-0.2	1		Greener
Acidification (Unitless)	0	0	0	0		Greener
Soil Adsorption (log Koc)	0	3.1	-3.9	1		Greener
Bio Concentration Factor (log BCF)	0.3	2.9	-1.3	1		Greener

Greenness with respect to relative values set in specified parameters.

**Table 5.** Original and scaled values (0–1) of each metric derived for acetonitrile from solvent table database

<i>Metric</i>	<i>Original value</i>	<i>Scaled value, M<sub>i</sub>(unitless)</i>
TLV	40 ppm	0.45
Ingestion	3800 (rat mg/kg)	0.27
Carcinogenicity	0 (unitless)	0
Biodegradation	3.03 (log Biodeg)	0.27
Aquatic Toxicity	4111 (mg/L)	0.3
Half-Life	414 (12 hr days)	0.73
Ozone Depletion	0 (unitless)	0
GWP	11 (unitless)	0.33
Smog Formation	0 (unitless)	0.2
Acidification	0 (unitless)	0
Soil Adsorption	0.653 (Log Koc)	0.72
BioConcentration Factor	0.500 (log BCF)	0.27

305 index. The larger the weighting factor is, the more heavily that parameter is considered in the calculation of the overall index. Any metric omitted or given a weighting factor of zero will not be factored into the final index.

310 The overall solvent index is then further normalized on a 0 (green)–10 (not green) scale using the following equation

$$\text{OSI}_{10, \text{solvent}} = \frac{y - y_{\min}}{y_{\max} - y_{\min}} \times 10 \quad (5)$$

where  $y = \text{OSI}_{\text{solvent}}$

$y_{\max}$  = maximum value of  $\text{OSI}_{\text{solvent}}$  for all solvents in database

315  $y_{\min}$  = minimum value of  $\text{OSI}_{\text{solvent}}$  for all solvents in database

This value is then multiplied by the mass of that solvent used in the process to generate a total weighted solvent greenness index for that particular solvent.

$$\begin{aligned} \text{Weighted Solvent Greenness Index}_{\text{solvent}} \\ = (\text{OSI}_{10, \text{solvent}})(\text{Mass}_{\text{solvent}}) \end{aligned} \quad (6)$$

320 Then the values for all of the solvents used in the process are summed, and a final process score is obtained.

$$\begin{aligned} \text{TotalProcessGreennessIndex} \\ = \sum \text{WeightedSolventGreennessIndex}_{\text{solvent}} \end{aligned} \quad (7)$$

325 If the weighting factors for a particular industry are used such as in Eq. 4, the greenness score can be named for that industry, e.g., pharmaceutical process greenness index. The lower the total score, the greener the process. Therefore, the index can be used as a guide to assess quantitatively the greenness between two or more solvents or processes.

330 The quick and relatively easy greenness comparison between two processes can be accomplished through this method. The technique uses two data sets for two different solvents or processes. The different data sets enable the user to compare differences in the overall solvent indices

and the other environmental metrics for the two processes in the form of a “percent difference.” The values generated for each process are mass-dependent and, therefore, require the user to input the mass quantities from individual process streams or batch quantities. 335

Another feature available within the spreadsheet is a vapor pressure calculation using Antoine’s equation. Although vapor pressure is not directly considered an environmental metric, it is important in determining the ease of separation by distillation in binary systems. If a mixture is difficult to separate, more chemicals (such as entrainers) or energy will need to be utilized in order to carry out the separation and, therefore, will have more of an environmental impact. 340 345

Essentially, the method is designed to compare similar processes that generate the same final product. The method is a valuable tool in aiding the selection of solvents for a particular process, but it has its limitations and should not be used exclusively. For example, solubility of an intermediate or API in a solvent is an important parameter in solvent selection. Therefore, the thermodynamic performance parameters and solvent/API interaction need to be considered in solvent selection. Despite the limitations, the method is useful on many levels. The solvents included in the database are some of the most commonly used solvents within the pharmaceutical industry. The database has the ability to grow continually in terms of the number of solvents and parameters used to calculate the index. 350 355 360

This method is useful to help assess how process greenness improves as a drug goes through various stages of development over its lifespan. In the “discovery” phase of a drug compound, which is also known as the medicinal chemistry route, the goal is to produce the pure API for initial pre-clinical testing. At this stage of development, no efforts have been made to optimize process routes or solvent use, the sole goal being to obtain a pure API. As the drug moves to “kilo” and “pilot scale” production for clinical trials, the process chemistry is more refined, and solvent usage decreases. This is due to both green chemistry in reducing synthesis steps and green engineering using separation processes and sequences that reduce solvent consumption. In the final commercial route for producing the API, further green engineering is employed for solvent recovery. The total pharmaceutical process greenness index score obtained through this method can be used to quantify the green improvements and represent variables that go beyond just quantities of solvent reduced. 365 370 375 380

### Case studies

Several illustrative applications of the solvent selection index tool will be given below. First, a simple comparison of two different solvent systems used in an API filtration step will be shown. Then the techniques will be applied to show quantitatively the improvements made in an 385

**Table 6.** Values of filtration Process 1 and 2 solvent components based on TLV

Calculation	Process 1			Process 2		
	Acetone	Acetonitrile	Methyl isobutyl ketone	n-Butanol	n-Pentane	n-Heptane
Single Index Scale, SIS	0.19	0.9	0.83	0.83	0	0.19
SIS <sub>10</sub>	0.96	4.47	4.16	4.16	0	0.96
Mass of Solvent (kg)	120	100	90	80	80	100
Weighted Solvent Index	116	447	375	333	0	96.3
Process Solvent Index		938			429	

overall pharmaceutical manufacturing process where synthesis steps and solvent quantities and toxicity are reduced.

**Filtration case study**

390 An illustrative example is provided to show one particular  
 process design in which two solid-liquid filtration unit  
 processes generate the same amount of final product. Process  
 1 uses 120 kg acetone, 100 kg acetonitrile, and 90 kg methyl  
 isobutyl ketone. Process 2 uses 80 kg n-butanol, 80 kg n-  
 pentane, and 100 kg n-heptane. For this design, both API  
 395 and solvent reagents undergo filtration to obtain high purity  
 product. Solvents used to make the API soluble vary within  
 both processes, thus emit variable liquid waste or emissions.

400 This example shows how the method determines which  
 process is greener assuming all other parameters such as  
 equipment, energy expenditure, product yield, etc. remain  
 constant. To illustrate the importance of having a method  
 calculate a greenness score based on several factors, a calcu-  
 lation based on only one parameter is first shown. If the two  
 processes are compared using only solvent inhalation expo-  
 405 sure, TLV, then a single index scale based on that parameter  
 would be used. No other health or environmental factors  
 would be used in the solvent index equation and therefore  
 the weighted solvent index would rely solely on the scaled  
 TLV values for each of the solvents in the process multiplied  
 410 by their respective amounts used (Table 6). The final scores  
 comparing the two processes represent only TLV as the en-  
 vironmental metric and show that Process 2 appears to be  
 greener since it has an overall score of 429 compared to 938  
 for Process 1. However, if the total process greenness index,  
 415 which includes all 12 environmental metrics weighted for

the pharmaceutical industry is considered, Process 1 is greener (Table 7). Process 1 has a pharmaceutical process greenness index of 892 vs. Process 2 score of 1091.

This comparison shows the importance of the user's definition of what metrics constitute a green process design. If 420 just one metric is considered in the environmental assessment of a process, then the assessment is limited to one area of impact. For instance, TLV describes the highest concentration at which no adverse health effects will be seen on inhalation, but it does not show the impact to aquatic life 425 or the ability to bioaccumulate in the environment upon release. Comparison of both processes using more than one metric incorporates all the aspects of an environmental assessment and provides a more thorough evaluation of the relative greenness of the process. Process comparisons need 430 to be made using the same group of metrics for each process. The overall index weighs the parameters selected then normalizes the calculated value again to produce a final index that would be different than just performing a calculation of each of the separate index scales and adding 435 them.

**Commercial drug production routes**

Pfizer's sildenafil citrate process was recently recognized for its green chemistry improvements.<sup>[23]</sup> Improvements include a reduction in aqueous waste, organic solvent waste, 440 and the variety and toxicity of solvents used. Their new synthesis route does not require extensive purification operations. Solvent-intensive purification processes such as extraction are eliminated saving organic solvent usage and waste. Multiple chemical steps were combined, using a 445

**Table 7.** Values of filtration Process 1 and 2 solvent components using overall solvent index weighted for the pharmaceutical industry

Calculation	Process 1			Process 2		
	Acetone	Acetonitrile	Methyl isobutyl ketone	n-Butanol	n-Pentane	n-Heptane
Overall Solvent Index, OSI	3.4	4.3	4.5	5.4	5.3	4.6
OSI <sub>10</sub>	2.2	3.2	3.5	4.6	4.5	3.7
Mass of Solvent (kg)	120	100	90	80	80	100
Weighted Solvent Greenness Index	259	321	312	369	356	366
Total Pharmaceutical Process Greenness Index		892			1091	

**Table 8.** Solvent usage at various phases of the sildenafil citrate process development (L/kg API)

<i>Solvent</i>	<i>Medicinal Chemistry Process (1990)</i>	<i>Process Enabled Route (1994)</i>	<i>Commercial Route (1997)</i>	<i>Commercial Route (1998)</i>	<i>Commercial Route (2005)</i>	<i>Future Target</i>
Ethyl ether	20					
Methanol	70					
Pyridine		0.5				
Acetone	130	29.2				
Dichloromethane	970	23.9				
t-Butanol		5.3	3.0	3.0	2.0	
Toluene		14.7	2.1	0.3	0.3	0.3
Ethanol	80					0.5
Ethyl acetate	10	14.3	7.9	1.6	1.5	1.5
2-Butanone	10	11.0	9.3	9.3	2.3	2.3
Total Solvent (L/kg API)	1290	98.9	22.3	14.2*	6.1**	4.6***

\*Following the implementation of solvent recovery for toluene and ethyl acetate.

\*\*Following implementation of 2-butanone recovery and yield improvements on acylation cyclisation steps

\*\*\*Following introduction of ethanol/ethoxide process.

Values courtesy of Peter Dunn, Pfizer, Inc. See also Reference 23.

single solvent, which can be recovered. The overall organic solvents reduced as a result of the green chemistry improvements from the discovery scale to commercial production are shown in Table 8. The organic solvents used are reduced from 1290 to 6.1 L/kg API (1540–5.0 kg/kg API), and although the listing of solvents shows which ones were reduced, another measure is needed to quantify the degree of which more benign solvents were substituted.

Applying our total pharmaceutical process greenness index, we can show how significant and broad-based their improvements were (Fig. 2). In our example, we assume that each route would scale up to produce the same API quantity and convert the volumetric solvent amounts to mass (kilograms) and report our index value per kg API. The greenness index decreases from 7472 in the original 1990 medicinal chemistry process to 16.9 in the latest 2005 commercial route. Our greenness score more thoroughly represents the benign nature of solvents substituted and reduced in terms of health exposure factors and environmental impact. For example, the elimination of highly volatile solvents such as dichloromethane, ethyl ether, acetone, and methanol, which reduces air pollution, is represented in our pharmaceutical greenness index score. Likewise, the elimination in the use of chlorinated solvents, e.g., dichloromethane, that pose serious health concerns are also represented in our pharmaceutical solvent index score. The score shows the level of green chemistry/engineering achieved in each sequential process improvement. The final commercial sildenafil citrate process uses more relatively benign solvents, which are recovered. The future target commercial route would include an ethanol/ethoxide process to reduce solvent use even further to 4.6 L/kg (3.86 kg/kg API) representing a greenness index of 13.15.

### Tracking drugs in development

Our greenness index tool can also be used to show overall green improvements in a process or track environmental improvements without releasing details on specific process chemistry or specific solvents used. Through our partnership with Bristol-Myers Squibb (BMS), the company has given us access to process chemistry and engineering information on the development of new cancer drug, drug “C.” To document how BMS has improved the process and incorporated greener processing strategies, an evaluation of the drug from discovery to pilot scale production (Phase II clinical trial) was performed. Since “drug C” is still in development, specifics can not be disclosed, but our solvent greenness measurement method can be used to show how the process was improved.

Our analysis shows that the magnitude and variety of solvents was reduced in total amounts and toxicity. In the discovery phase where small amounts (<1 g) of API are made, chromatography is typically used on the bench-scale and is quite inefficient in solvent use. There is a reduction in process steps as drug proceeds through development. The scale-up phases consist of the API being made in low kilogram quantities in glass pilot plant equipment, which is typically referred to as “kilo” scale or “glass plant.” Further process development, to make larger quantities of API, occurs at the pilot scale where the batch size is typically in the ~100 kg API range. Solvents are substituted as development proceeds to streamline the process while at the same time maintain API purity and yield. Optimization of crystallization and filtration processes is also accomplished with the number of recrystallizations and washes reduced.

The amount of solvents used in the various stages of development and the pharmaceutical process greenness index (based on kg solvent used/kg API) is shown in Figures 3 and

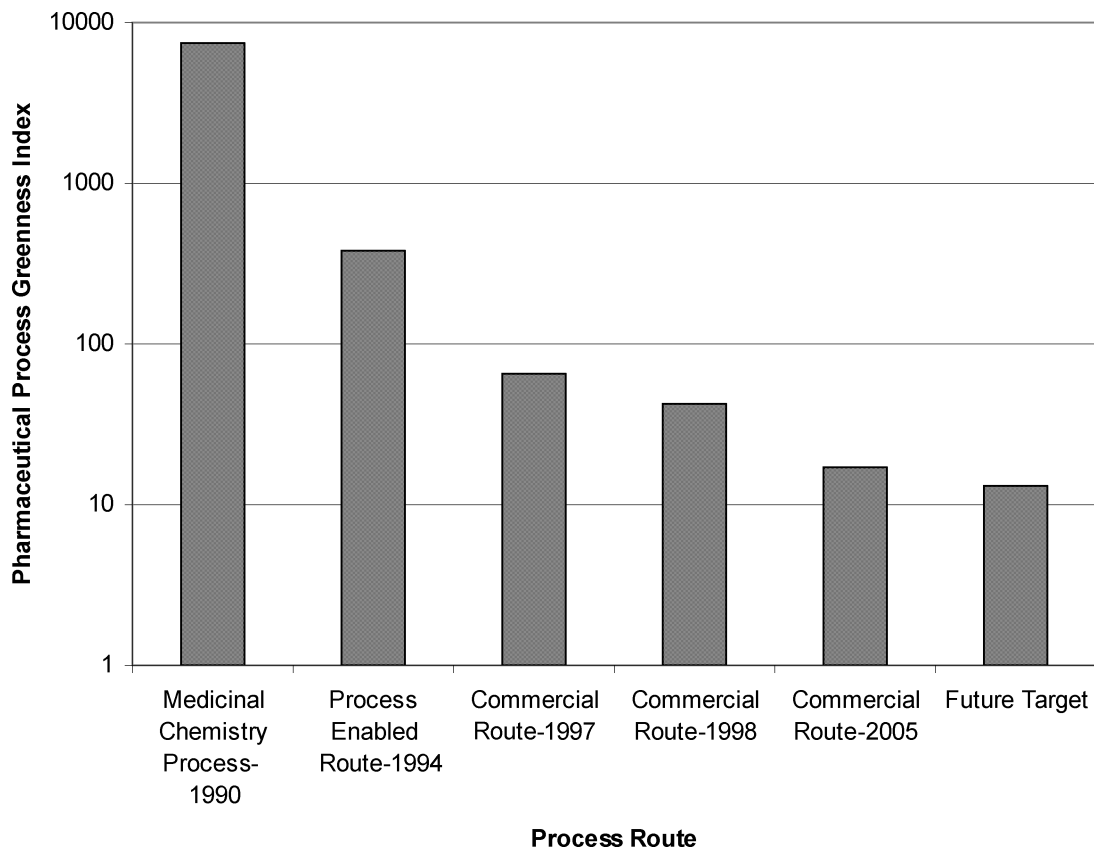


Fig. 2. Total pharmaceutical process greenness index for the sildenafil citrate process as a function of development phase.

515 4, respectively. This shows that most of the improvements occur early in the development cycle with the most significant decreases in solvent use and greenness index for the transition from discovery to initial scale-up. At this stage, the pharmaceutical greenness index is reduced from 11,990 to 788 representing a 93% reduction. Further improvements are made on the pilot scale process where the greenness score is reduced 32% further to 533. 520

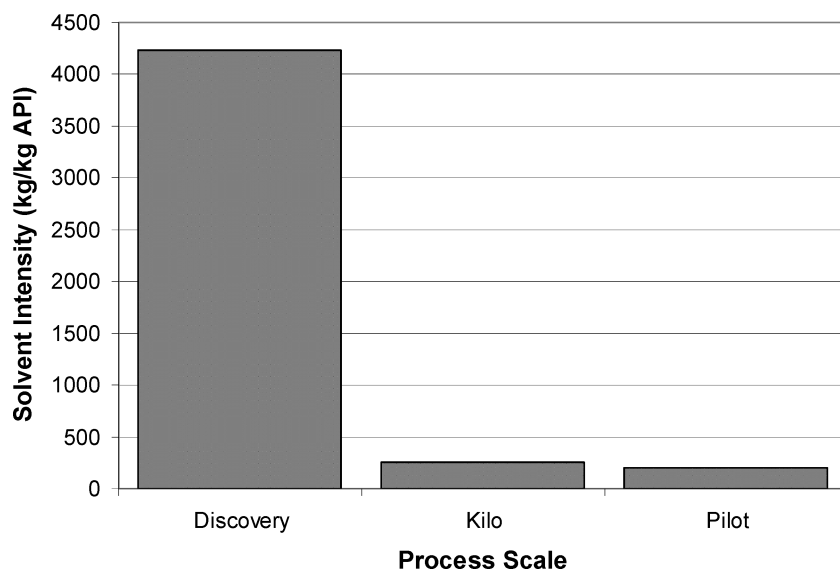
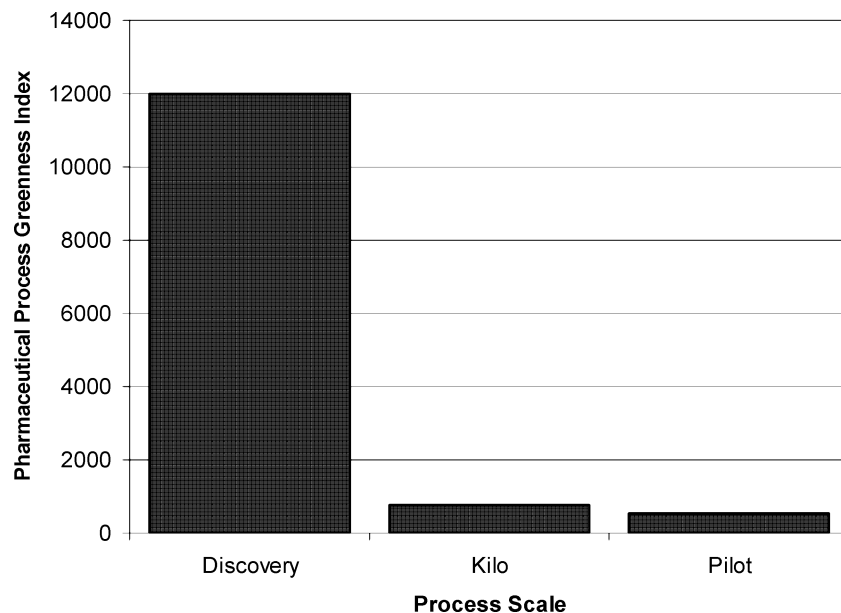


Fig. 3. Solvent mass intensity (usage) for the Bristol-Myers Squibb cancer drug as it goes through various stages in the development process from discovery to kilo to pilot scale.



**Fig. 4.** Total pharmaceutical process greenness index for the Bristol-Myers Squibb cancer drug as it goes through various stages in the development process from discovery to kilo to pilot scale.

The process solvent greenness calculation method is available to use from the Rowan University Green Engineering Education web site ([www.rowan.edu/greenengineering](http://www.rowan.edu/greenengineering)).<sup>[24]</sup> The software and a tutorial can be accessed by logging onto the site as a “guest” (user name = guest; password = guest) and going to the Software section and selecting the Solvent Selection Table software. The software and accompanying tutorial can then be used on-line or downloaded. Users must make sure that their Microsoft Excel program is set with “macros enabled” for the program to run.

### Conclusions

There are many process challenges in the green engineering of pharmaceutical development and manufacture. Effective and efficient use of solvents and other chemicals is an important issue. The solvent selection table and total process greenness index method have many applicable features designed specifically for use in pharmaceutical industries. Its capabilities include the compilation of several metrics, tabulation of solvents’ relative greenness, and computation of ease of separation. The intent of this program is to quantify the relative greenness of possible solvent substitutes that sustain green engineering principles. It can help scientists and engineers early in the life cycle of product development and to those in manufacturing looking at improving a process.

One of the advantages of using the method as opposed to other comparable alternatives is that it is easy to implement. The user has to input only the mass of each chemical

in the process, and the method calculates an overall index based on the environmental parameters. Another advantage is that the database is completely expandable. If the user wants to include more chemicals or more parameters, they could be incorporated into the database with relative ease. One feature that most other tables or databases do not have is the customizable weighted index option. The method presented in this paper allows the user to choose which metrics are most important and allows those to be weighted more than the others.

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