Metrics to 'green' chemistry—which are the best?

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A considerable amount has been written about the use of metrics to drive business, government and communities towards more sustainable practices. A number of metrics have also been proposed over the past 5–10 years to make chemists aware of the need to change the methods used for chemical syntheses and chemical processes. This paper explores several metrics commonly used by chemists and compares and contrasts these metrics with a new metric known as reaction mass efficiency. The paper also uses an economic analysis of four commercial pharmaceutical processes to understand the relationship between metrics and the most important cost drivers in these processes.

Selected metrics used in the past

A considerable number of publications have been written about the use of metrics to drive business, government and communities towards more sustainable practices. The reader is referred elsewhere for a discussion of what metrics have been proposed. There has also been much written about the characteristics of metrics, or what constitutes a good metric.[1–4] It is generally agreed that metrics must be clearly defined, simple, measurable, objective rather than subjective, and must ultimately drive the desired behaviour.[5] Over the past 5–10 years, a number of metrics have been proposed to make chemist's aware of the need to change the practice of chemical syntheses so they are less wasteful. A few of these metrics will be reviewed.

Effective mass yield

Hudlicky *et al.*[6] proposed a metric known as effective mass yield that is defined 'as the percentage of the mass of desired product relative to the mass of all non-benign materials used in its synthesis.' Or, stated mathematically:

$$\text{Effective mass yield (\%)} = \frac{\text{Mass of products} \times 100}{\text{Mass of non-benign reagents}}$$

This metric attempts to define yield in terms of that proportion of the final mass, *i.e.*, the mass of the product, that is made from non-toxic materials. The introduction of reagent and reactant toxicity is an extremely important consideration that is frequently absent from discussions about yield. While Hudlicky's metric makes an attempt to define benign (*i.e.*, 'those by-products, reagents or solvents that have no known environmental risk associated with them for example, water, low-concentration saline, dilute ethanol, autoclaved cell mass, *etc.*'), the explanation suffers from a lack of definitional clarity. Defining 'non-benign' is difficult in practice when working with complex reagents and reactants that have limited environmental or occupational toxicity information.

Unless and until human toxicity and ecotoxicity information is routinely available for all chemicals, it would be difficult to use this metric for most synthetic chemical operations. In addition, depending on the situation, even saline, ethanol and autoclaved cell mass have some environmental impacts of one kind or another that would need to be evaluated and addressed.

E-factor

A second and earlier metric, E-factor, was proposed by Roger Sheldon[7] and is defined as follows:

$$\text{E Factor} = \frac{\text{Total waste (kg)}}{\text{kg product}}$$

This metric is relatively simple and easy to understand, and draws attention to the quantity of waste that is produced for a given mass of product. It also exposes the relative wastefulness of different parts of the chemical processing industries that includes industries as diverse as petrochemicals, specialities and pharmaceuticals. This metric may certainly be used by industry and can, if used properly, spur innovation that results in a reduction of waste.

It may, however, be difficult for an industry such as the Pharmaceutical Industry to routinely use this metric in its operations. This is because there may be a lack of clarity

Green Context

It is now widely accepted that the quantification of sustainable practices such as measuring the "greenness" of different chemical processes is essential if we are to make real progress. How else can we aim to compare the often numerous green chemistry approaches to reducing the environmental impact of an important chemical process? Here one of the worlds leading industrial groups studying process metrics critically compare and analyse some of the quantification methods available to the process chemist. Much interesting data resulting from applying these methods to important chemical transformations is presented.

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depending on how 'total waste' is ultimately defined and accounted for, and where the boundaries of the process are drawn. One may draw a boundary around the immediate process, around the facility or within the broader geographic region of the facility.

Some examples of this lack of clarity in defining waste might include: is waste that passes over the fence line the only waste considered? Is waste that is produced as a result of emissions treatment (*e.g.*, acid gas scrubbing, pH adjustment in waste-water treatment plants, *etc.*) included? Is waste that is produced as a result of energy use (heating or cooling reactions, abatement technology, *etc*) included? Finally, is waste solvent passed on to a waste handler to be burned in a cement kiln included?

From an operational perspective, these kinds of questions complicate the routine use of this metric for individuals whose primary concern is to get new products on to the market in as short a period of time as possible.

It may also be argued that drawing attention to waste does not always drive chemists to think about what might be done to avoid producing wastes. Instead, the tendency may be to ignore waste generated in a chemical reaction or process and let others focus on waste treatment at a later date.

Atom economy

When developing chemical processes, chemists for obvious reasons focus mainly on maximising selectivity and yield. In recent years, another variable some chemists have been considering is atom economy.[8] This term, first introduced by Barry Trost, was an attempt to prompt synthetic organic chemists to pursue 'greener chemistry'. Simply stated, atom economy is a calculation of how much of the reactants remain in the final product. Final product in this context applies to a single chemical transformation, a series of chemical transformations in a single stage of a multistage synthetic route, or to the entire route to a final product.

The method for calculating atom economy is kept deliberately simple by making certain key assumptions, ignoring reaction yield and molar excesses of reactants. It also does not account for solvents and reagents.

Assumptions regarding atom economy

Reactants

A reactant is a substance of which some part is incorporated into a reaction product although not necessarily into the final product. The process of calculating atom economy may be simplified by only considering key reactants. For example, 'catalysts' used in stoichiometric quantities, or the acid or base used for hydrolysis, are considered to be reactants. These examples are in contrast to common inorganic reagents, even when used in stoichiometric quantities (*e.g.*, potassium carbonate in a Williamson ether formation), which have been ignored. Inorganic reagents and/or other materials are not included in the calculations as long as at least two other reacting substances are identified.

Reactants also include those materials incorporated into a reaction *intermediate*. Even if no part of a reactant is present in the final product itself (*e.g.*, in the case of addition and removal of a protecting group) it was part of an intermediate and is therefore included in the calculation. A good example of this would be the *in situ* formation of an acid chloride during an N-acylation reaction as shown in reaction scheme (1). The chlorinating agent, in this case the chemical complex formed

from the reaction between DMF and oxaloyl chloride, would be included in the calculation, even if the chlorination is not a distinct step in the process.

Oxaloyl Chloride   Dimethylformamide

(1)
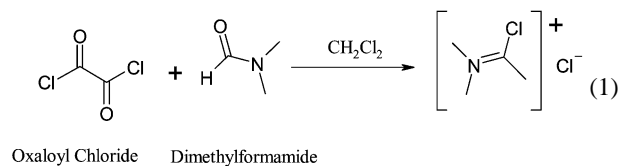
Stoichiometry

An excess of either or both reactants to maximise reaction yield/selectivity is not included in the calculation of atom economy. Reaction stoichiometry, on the other hand, has been taken into account. Thus, when two molecules of one substance combine with a single molecule of another to form a new molecule (either a reaction or process intermediate), the relevant ratio has been used.

Resolution and optical purity

In calculating atom economy for syntheses that employ a resolution step, the reaction stoichiometry needs to be adjusted to account for the fact that some portion of the mass will be discarded as the unwanted enantiomer. This includes those cases where the resolving agent is in a 1:1 or 2:1 ratio with respect to the desired enantiomer, or 1:2 as in the case where the desired enantiomer is difunctional.
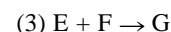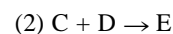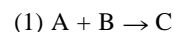
How atom economy is calculated

For a generic reaction:
$$A + B \rightarrow C$$
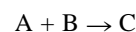
$$\text{Atom economy} = \left(\frac{\text{m.w. of product C}}{\text{m.w. of A + m.w. of B}} \right) \times 100$$

The calculation considers only the reactants used and ignores the intermediates that are made in one stage and consumed in the next. *Because of this it is not possible to multiply the atom economy of each stage to give an overall process atom economy.* Process atom economy must be calculated as follows:

For a generic linear synthetic process:

$$(1)\ A + B \rightarrow C$$

$$(2)\ C + D \rightarrow E$$

$$(3)\ E + F \rightarrow G$$

Atom economy

$$= \left(\frac{\text{m.w. of product G}}{\text{m.w. of A + m.w. of B + m.w. of D + m.w. of F}} \right) \times 100$$

Processes with two or more separate branches are treated in an analogous way by taking into account all of the reactants but none of the intermediates in the calculation. Thus, for the

A + B $\longrightarrow$ C   F + G $\longrightarrow$ H

C + D $\longrightarrow$ E   H + I $\longrightarrow$ J

E + J $\longrightarrow$ **P**
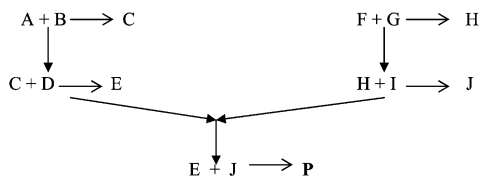
branched synthetic process where C, E, H and J are intermediates and E and J are coupled in the final step, atom economy is calculated as follows:

$$\text{Atom economy (\%)} = \frac{\text{mw P}}{\Sigma \, (\text{mw A, B, D, F, G, I})} \times 100$$

Mass intensity

A fourth metric discussed elsewhere[4] is mass intensity. Mass intensity is defined as follows:

$$\text{Mass intensity (MI)}$$
$$= \frac{\text{Total mass used in a process or process step (kg)}}{\text{Mass of product (kg)}}$$

Mass intensity takes into account the yield, stoichiometry, the solvent, and the reagent used in the reaction mixture, and expresses this on a weight/weight basis rather than a percentage. In the ideal situation, MI would approach 1. Total mass includes everything that is used in a process or process step with the exception of water; *i.e.*, reactants, reagents, solvents, catalysts, *etc*. Total mass also includes all mass used in acid, base, salt and organic solvent washes, and organic solvents used for extractions, crystalisations, or for solvent switching. Water has been excluded from mass calculations since it skews mass data in many processes. Water *per se* also does not, in most instances, constitute a significant environmental impact.

It may also be useful to compare MI with E-Factor where:
$$\text{E Factor} = \text{MI} - 1$$
By expressing mass intensity as its reciprocal and making it a percentage, it is in a form similar to effective mass yield and atom economy. This metric will be called mass productivity.

$$\text{Mass productivity} = \frac{1}{\text{MI}} \times 100$$
$$= \frac{\text{Mass of product}}{\text{Total mass in process or process step}} \times 100$$

Other metrics that have been explored

Several other metrics related to atom economy have been developed and explored at GlaxoSmithKline. These are known as carbon efficiency (CE) and reaction mass efficiency (RME).[4] CE takes into account the yield and the amount of carbon in the reactants that is incorporated into the final product. RME takes into account yield, the actual molar quantities of reactants, and atom economy.

Carbon efficiency

When calculating carbon efficiency, yield and stoichiometry of reactants and products are included. CE is defined as the percentage of carbon in the reactants that remain in the final product.

For a generic reaction A + B $\rightarrow$ C

$$\text{\% Carbon efficiency} = \frac{\text{Amount of carbon in product} \times 100}{\text{Total carbon present in reactants}}$$

Thus, where the reaction is A + B = Product + co-product

Carbon efficiency

$$= \frac{\text{no. of moles of product} \times \text{no. of carbons in product} \times 100}{(\text{moles of A} \times \text{carbons in A}) + (\text{moles of B} \times \text{carbons in B})}$$

Reaction mass efficiency (RME)

When calculating reaction mass efficiency, atom economy (AE), yield and the stoichiometry of reactants are included. RME is the percentage of the mass of the reactants that remain in the product. There are two ways to calculate RME.

For a generic reaction A + B $\rightarrow$ C

Reaction mass efficiency

$$= \left(\frac{\text{m.w. of product C}}{\text{m.w. of A} + (\text{m.w. of B} \times \text{molar ratio B/A})} \right) \times \text{yield}$$

or more simply:

$$\text{Reaction mass efficiency} = \left(\frac{\text{mass of product C}}{\text{mass of A} + \text{mass of B}} \right) \times 100$$

An example of how atom economy, carbon efficiency, reaction mass efficiency, mass intensity and mass productivity are computed follows: benzyl alcohol (10.81g, 0.10 mol, FW 108.1) is reacted with *p*-toluenesulfonyl chloride (21.9 g, 0.115 mol, FW 190.65) in toluene (500 g) and triethylamine (15 g) to give the sulfonate ester (FW 262.29) isolated in 90% yield (0.09 mol, 23.6 g).

$$\text{Atom economy} = \frac{262.29}{(108.1 + 190.65)} \times 100 = 87.8\%$$

Carbon efficiency

$$= \frac{(0.09 \times 14)}{(0.1 \times 7) + (0.115 \times 7)} \times 100 = 83.7\%$$

$$\text{Reaction mass efficiency} = \frac{23.6}{(10.81 + 21.9)} \times 100 = 70.9\%$$

Mass intensity

$$= \frac{(10.81 + 21.9 + 500 + 15)}{23.6} = 23.2 \text{ g/g} = 23.2 \text{ kg/kg}$$

$$\text{Mass productivity} \frac{1}{\text{Mass intensity}} \times 100 = 4.3\%$$

The atom economy is less than 100% due to the formation of HCl as a by-product. The carbon efficiency accounts for the excess stoichiometry and the less than 100% yield of the product in terms of the number of carbons in the final molecule. The reaction mass efficiency also takes into account the 90% yield and the need for a 15% molar excess of *p*-toluenesulfonyl chloride.

To show how these metrics compare, the stoichiometry, yield, atom economy, carbon efficiency, reaction mass efficiency, mass intensity and mass productivity for 28 different chemistries are shown in Table 1. The values in Table 1 are averages of at least three examples for a given type of chemistry.

Detailed analysis of these data has revealed a number of things

1. Carbon efficiency, while an interesting attempt at an alternate metric, exhibits the same trends as RME, and offers

no additional insights on how one might improve chemistry or process conditions.

2. There are several chemistries that appear to be outliers in the data set; *e.g.*, resolutions and N-dealkylation reactions are significantly different in relation to the other chemistries.
3. These data indicate that most reactions are run at significant stoichiometric excesses which is not accounted for in atom economy.
4. Another observation is that reaction yield, a metric used almost universally by synthetic chemists, does not account for poor reaction mass efficiencies and a correspondingly significant waste of resource (mass or energy). While this may be an obvious statement, it should be noted that wasted resource may be expensive from both a direct materials cost and a more comprehensive life cycle costing perspective.
5. Data for mass intensity, yield, atom economy and stoichiometry do not correlate with each other in any meaningful way. These appear to be discretely different types of metrics, and following one metric in isolation of the others may not drive the best behaviour for 'greening' reactions.
6. Because reaction mass efficiency accounts for all reactant mass (*i.e.*, actual stoichiometric quantities used) and includes yield, and atom economy, the combined metric is probably the most helpful metric for chemists to focus attention on how far from 'green' current processes are being operated.
7. Mass productivity may be a useful metric for businesses since it highlights resource utilisation. This is illustrated in Table 2 where the average atom economy is compared with the average mass productivity for 38 drug-manufacturing processes.

As can be seen from Table 2, the average atom economy of 43% for a multi-step synthesis would not appear to be unreasonable to most chemists for a seven stage synthesis of a complex drug. However, the average mass productivity for these synthetic processes is only 1.5%. This means that 98.5% of the total mass used to make a drug is being wasted. Even if

Table 2 Comparing atom economy and mass productivity for 38 processes (average number of stages = 7)

	Overall process average (%)	Range (%)
Atom economy	43	21–86
Mass productivity	1.5	0.1–7.7

the atom economy for individual steps of the process were raised above 95%, this may not necessarily increase the overall average mass intensity of the process to a significant extent. Since a majority of the mass in a given process is not accounted for by atom economy or even reaction mass efficiency, it may be argued that atom economy may not be the most robust measure or the best measure of sustainability for industrial use.

Cost implications

It would be a mistake to leave a discussion of metrics at the point of only considering mass implications. Clearly, wasted resources may have significant cost implications. Using the atom economy metric as an example, it is readily seen that reactions possessing low atom economy will affect the cost of synthesising a new chemical entity because:

(a) not all portions of each reactant molecule are incorporated into the molecule; *i.e.*, materials (and energy) are not used efficiently;
(b) the synthetic strategies will affect the length and complexity of the route;
   (i)   portions of the molecule may be in the wrong oxidation state;
   (ii) protection/deprotection may be required;
   (iii) chiral resolutions may be required;

Table 1 Comparison of metrics for different chemistries

	Stoichiometry of B mol (%)	Yield (%)	Atom economy (%)	Carbon efficiency(%)	Reaction mass efficiency (%)	Mass intensity excluding water (kg/kg)	Mass productivity (%)
Acid salt	135	83	100	83	83	16.0	6.3
Base salt	273	90	100	89	80	20.4	4.9
Hydrogenation	192	89	84	74	74	18.6	5.4
Sulfonation	142	89	89	85	69	16.3	6.1
Decarboxylation	131	85	77	74	68	19.9	5.0
Esterification	247	90	91	68	67	11.4	8.8
Knoevenagel	179	91	89	75	66	6.1	16.4
Cyanation	122	88	77	83	65	13.1	7.6
Bromination	214	90	84	87	63	13.9	7.2
N-Acylation	257	86	86	67	62	18.8	5.3
S-Alkylation	231	85	84	78	61	10.0	10.0
C-Alkylation	151	79	88	68	61	14.0	7.1
N-Alkylation	120	87	73	76	60	19.5	5.1
O-Arylation	223	84	85	69	58	11.5	8.7
Epoxidation	142	78	83	74	58	17.0	5.9
Borohydride	211	88	75	70	58	17.8	5.6
Iodination	223	96	89	96	56	6.5	15.4
Cyclisation	157	79	77	70	56	21.0	4.8
Amination	430	82	87	71	54	11.2	8.9
Lithal	231	79	76	76	52	21.5	4.7
Base hydrolysis	878[a]	88	81	77	52	26.3	3.8
C-Acylation	375	86	81	60	51	15.1	6.6
Acid hydrolysis	478	92	76	76	50	10.7	9.3
Chlorination	314	86	74	83	46	10.5	9.5
Elimination	279	81	72	58	45	33.8	3.0
Grignard	180	71	76	55	42	30.0	3.3
Resolution	139	36	99	32	31	40.1	2.5
N-Dealkylation	2650[a]	92	64	43	27	10.1	9.9

[a] Inflated by use of solvent as reactant.

(c) purifications and separations may be required to remove by-products, reactants, reagents, solvents, *etc.*;

(d) there are environmental, safety and health costs associated with the management of materials and treatment of waste products.

The relationship between atom economy and cost

To illustrate the relationship between atom economy and cost, we employed a traditional costing approach to evaluate the cost of materials used to synthesize four different drugs. Seven different economic models were used and the results are shown in Table 3 and Fig. 1. These cost models are:

Minimum cost for minimum process stoichiometry + standard yield, reactant stoichiometry and solvent

This is the cost when process chemicals are not used in stoichiometric excess; *i.e.*, no more than 1 mol is used. All other costs are based on using standard amounts; *i.e.*, what is actually used and obtained in plant.

Minimum cost at 100% atom economy + standard yield, solvent and process stoichiometry

Reactant costs may be used to assign a cost to the proportion of each material that is incorporated into the product. From this, it is possible to calculate the cost if the AE were 100%. All other costs are based on using standard amounts; *i.e.*, what is actually used and obtained in plant.

Minimum cost at 100% yield + standard solvent and process stoichiometry

This is the cost for using standard quantities of reactants, process chemicals and solvent, but the yield is 100%.

Minimum cost at 100% solvent recovery and standard yield and process stoichiometry

This is the cost if 100% of all solvents are recovered and reused (assumes zero recovery cost). All other costs are based on using standard amounts; *i.e.*, what is actually used and obtained in plant.

Table 3 Comparison of cost models for four different drugs

	% Total cost[a]			
Cost model	Drug 1	Drug 2	Drug 3	Drug 4
Minimum cost for minimum process stoichiometry + standard yield, reactant stoichiometry and solvent	86	99	92	97
Minimum cost at 100% atom economy + standard yield, solvent and process stoichiometry	87	40	84	69
Minimum cost at 100% yield + standard solvent and process stoichiometry	71	32	56	57
Minimum cost at 100% solvent recovery and standard yield and process stoichiometry	63	84	64	55
Minimum cost at 100% atom economy, process stoichiometry and solvent recovery	36	22	40	21
Minimum cost at 100% yield, solvent recovery and standard process stoichiometry	34	16	20	11
Minimum cost at 100% yield, solvent recovery and reactant and process stoichiometry	20	15	12	8

[a] Total cost = cost of all materials actually used in the process. The table was constructed by calculating the theoretical cost associated with each cost model (column 1) and dividing by the total cost.
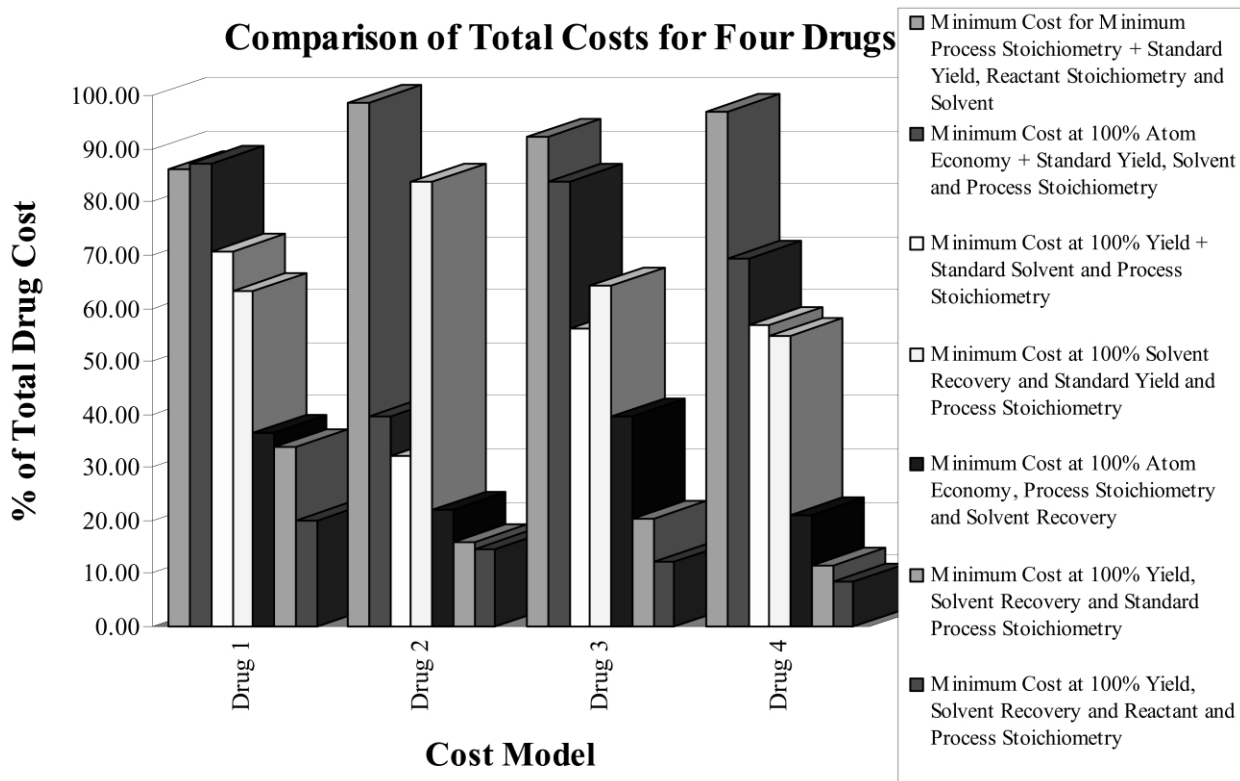
Fig. 1 A comparison of cost models for four different drugs.

Minimum cost at 100% atom economy, process stoichiometry and solvent recovery

Reactant costs may be used to assign a cost to the proportion of each material that is incorporated into the product. From this, it is possible to calculate the cost if the AE were 100%. Additional costs include the cost when process chemicals are not used in stoichiometric excess; *i.e.*, no more than 1 mol is used, and the cost if 100% of all solvents are recovered and reused (assumes zero recovery cost).

Minimum cost at 100% yield, solvent recovery and standard process stoichiometry

This is the cost when the yield is 100%, all solvents are recovered and reused (assumes zero recovery cost), and all other costs are based on using standard amounts; *i.e.*, what is actually used and obtained in plant.

Minimum cost at 100% yield, solvent recovery and reactant and process stoichiometry

A theoretical minimum cost may be derived assuming no stoichiometric excess, 100% solvent recovery, and a 100% overall yield.

As can be seen from Fig. 1 and Table 3, the pursuit of atom economy may be less of an economic driver than may be thought. This analysis suggests that progress towards higher yield reactions, a reduction in stoichiometric excesses of reactants, and elimination or complete solvent recycle and reuse may be more economically effective, at least in the short term.

A more detailed analysis of the costs associated with three of the four drugs evaluated is illustrated in Table 4 for drug 3 and in Figs. 2 and 3 for drug 1 and 2.

Our analysis of the materials costs for these drugs also indicates that more than 75% of the total costs are for either those portions of reactants that do not remain in the final product or reagents (column 4, Table 4) and this high percentage is attributable to about four materials. A review of costs in this fashion will help to identify those portions of the synthetic process that might be changed to afford the greatest economic and environmental benefit (*e.g.*, recovery and reuse). The data in Table 4 also illustrates the typical cost structure that might be expected when a chiral resolution is used. Replacing this

synthesis and resolution by a chiral synthesis would, rather obviously, be a more beneficial economic and atom economical strategy.

A further comparison of the four drugs is shown in Table 5 and reveals that for three of the four compounds, the cost of poor
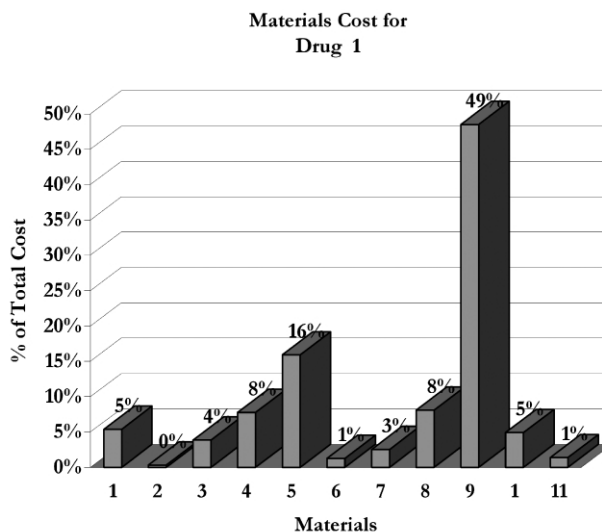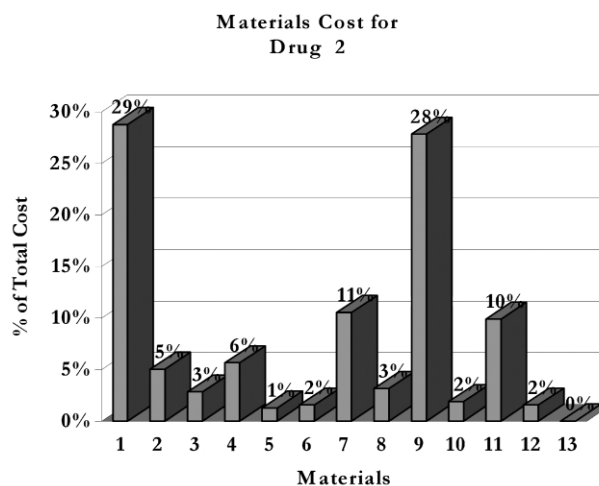
Fig. 2 Materials cost for drug 1.

Fig. 3 Materials cost for drug 2.

Table 4 Comparison of costs for drug substance 3

Reactants	Molar equivalents used	% Of molecule in final drug[a]	% Contribution to overall cost of drug 3	% Of total cost for non-incorporated reactants[b]
Intermediate 1	2	43	12.8	12
Reducing agent	4.6	5	30.4	49
Resolving agent	2.2	0	16.0	26
Intermediate 2	2	27	4.5	6
Intermediate 3	1	0	0.6	1
Intermediate 4	1	0	0.7	1
Material 1	3	0	1.2	2
Material 2	1	0	0.1	
Material 3	1	100	10.4	
Material 4	6	0	0.5	1
Material 5	1.2	0	0.5	1
Material 6	1	100	0.0	
Material 7	10	14.5	0.3	
Material 8	2	0	0.3	
Solvents			21.7	
All other materials			0.1	

[a] This is the proportion of the molecule that remains in the final product molecule and can be calculated by the process chemist. [b] This is the wasted cost (in terms of percentage) for each material due to inefficient incorporation into product

Table 5 Comparison of solvent and poor atom economy costs for drug substances

	Solvent cost as % of total	Cost for non-incorporated reactants as % of total
Drug 1	45	32
Drug 2	36	21
Drug 3	22	61
Drug 4	14	10

atom economy is less than the solvent cost. In addition, yield and stoichiometry are the most significant cost drivers and exert significantly more influence on cost than poor atom economy.

Another point of interest is noted for drug 4 where the opportunity to reduce cost through atom economy does not appear to be significant. In this instance, a catalyst used for the synthesis is relatively costly. In the isolated case of using the catalyst within the gates of the company, a 10% loss of catalyst to effluent represents 16% of the total materials costs paid by the company for this drug. It should be noted that 16% of the total materials cost is not a small number! This cost does not include the life cycle total cost perspective, *i.e.*, the cost of raw materials extraction, catalyst production, use, recovery and loss to effluent, all of which may have significant costs in addition to environmental impacts. While this is not an argument against using catalysts, it is certainly true that the type of catalyst, its potential for re-use, and its recoverability are important features of good process design and environmental and economic performance.

It is recognised that this economic evaluation only considers costs for several existing industrial processes that represent the current state of affairs for drug manufacture. This evaluation also does not consider the total cost of drug synthesis; *i.e.*, those costs beyond simple materials costs. While it has been shown that the EHS costs in a total cost assessment for many industries can be quite significant, our studies have shown that the EHS costs for high value added materials are generally less than traditional materials costs, unless total life cycle costs are included. Until society forces markets to focus greater attention on, and build standardised, accepted economic models for life cycle costs, it will remain difficult to assess these costs and make acceptable business decisions based upon these costs.

This analysis also ignores the potential benefits from alternative more atom economical routes where it may be possible to have only two reactants producing a single easily isolated product in a completely recyclable reaction medium at room temperature and pressure. A second alternative would be a synthesis without solvent, but this may increase the energy or capital requirements. Thus, it must be understood that the point of striving for more atom economic reactions in the future is the hope that they use less resources (materials and energy) and have higher overall process efficiencies.

Effect of technology

While new chemistries will assist in delivering higher atom economies they are likely to require the use of different technologies. In the short to medium term, it is clear that the integration of technology and chemistry may deliver significant benefits when using current less atom economical chemistries.

Questions to be addressed:

Questions and considerations for further research currently being explored include.

(a) Is there a correlation between any of these metrics and the molecular complexity of the drug substance?
(b) Can a model for molecular complexity correlated with reaction mass efficiency be developed?
(c) Can realistic targets be set for reaction mass efficiency based on this complexity model?
(d) How does a pursuit of reaction mass efficient reactions influence energy intensity?

Conclusions

Exploration of a variety of metrics has revealed the following:

● Pursuing a metric such as yield, a ubiquitous metric chemist's utilise to evaluate reaction efficiency, will not by itself drive business towards sustainable practices. However, from an economic standpoint, yield remains a very good metric, especially for high value added materials such as pharmaceuticals;
● Atom economy may be useful as an organising concept or in combination with other metrics, but at this time it is not considered to be useful as a stand-alone metric;
● Reaction mass efficiency combines key elements of chemistry and process and represents a simple, objective, easily derived and understood metric for use by chemists, process chemists or chemical engineers;
● Mass intensity may be usefully expressed as mass productivity, and as such, seems to be more broadly understood by business managers;
● Reaction mass efficiency appears to be a useful metric for focusing attention away from waste towards the use of materials. As such, it is more likely to drive chemical and technology innovations that will lead to more sustainable business practices.

As current chemistries and the processes associated with these chemistries are reviewed, it appears that chemistry, in isolation of process, will not 'green' the chemical process industries, especially as represented by the pharmaceutical industry. It also appears that chemical process technology must change with changes in chemistry if industry is to move towards more sustainable business practices. The importance of this connection between 'green chemistry' and 'green technology' is being highlighted elsewhere.

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