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Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes

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ABSTRACT: There have been a many publications and much discussion about green metrics. While many have been proposed, The American Chemical Society Green Chemistry Institute's Pharmaceutical Roundtable has chosen process mass intensity (PMI) as the key, high-level metric for evaluating and benchmarking progress towards more sustainable manufacturing. This paper provides the philosophical and technical arguments on why PMI was chosen above other related metrics such as E factor or atom economy.

INTRODUCTION

In the past decade or so there have been many publications and much discussion about the use of metrics to drive business, government, and communities towards more sustainable practices. In general, it is widely accepted that a good metric must be simple, easily measurable, clearly defined, objective, and must ultimately drive the right behavior.

Several metrics have been proposed under this premise to encourage chemists and engineers to design greener, safer, and more sustainable chemistries and processes. For instance, some of the mass-based metrics include process mass intensity (PMI), mass efficiency, reaction mass efficiency, E factor, atom economy, space-time yield, amongst others. The reader is referred elsewhere in the literature for a comprehensive view of green metrics.[1−12]

Since sustainability, by definition, is a multivariable optimization exercise, the challenge is to select the few metrics that would drive the right behaviors towards more sustainable, greener practices. In the context of mass-based metrics, the recent years have been full of discussion about whether the best approach for a simple high-level mass metric is to focus on the total mass of materials used (e.g., PMI or Mass Efficiency)[3,5,6] or on the mass of the waste generated from any given process (e.g., E factor).[11,12]

The pharmaceutical industry, through the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (the Roundtable) has selected Process Mass Intensity (PMI, the total mass of materials per mass of product) as the key mass-based green metric. The Roundtable routinely uses PMI to benchmark the greenness of processes and uses it to drive greater efficiency and innovation in the pharmaceutical and fine chemicals industries. The objective of this paper is to present the philosophical rationale and scientific merits behind the selection of PMI as the key mass-based green metric for the pharmaceutical industry, instead of using a waste-focused metric such as E factor. However, we recognize that individual companies will utilize the set of metrics that work most effectively for their respective organizations.

GREEN METRICS IN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry is devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives and is committed to bringing key medicines to the patient with minimal environmental impact. The concepts of green chemistry and green engineering are not new in the pharmaceutical industry. In recent years, significant effort has been invested to improve efficiency, reduce waste, and enhance quality and control in research and development (R&D) and manufacturing. This is driven by the desire not only to reduce costs but also to increase the sustainability of the manufacturing process.

In 2005, the American Chemical Society (ACS), Green Chemistry Institute (GCI), and several global pharmaceutical corporations founded the ACS GCI Pharmaceutical Roundtable (ACS GCIPR).[13] The activities of the Pharmaceutical Roundtable (the Roundtable) reflect the joint belief that the pursuit of green chemistry and engineering is an imperative for making businesses more sustainable and less environmentally impactful. The Roundtable has translated its belief into a mission that seeks to catalyze the implementation of green chemistry and engineering into the business of drug discovery, development, and production

One of the aims of sustainability, green chemistry, and green engineering is the optimization of resource use. This challenge has been recognized by the ACS GCIPR, and has resulted in the adoption of Process Mass Intensity (PMI) as the preferred metric aimed to drive greater efficiencies in pharmaceutical syntheses. Process Mass Intensity is defined as the total mass of materials used to produce a specified mass of product (eq 1). Materials include reactants, reagents, solvents used for reaction and purification, and catalysts. Ideally this equals unity when no waste is produced and all materials are incorporated into the product (eq 1). Another way to express this is in terms of

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efficiency, where Mass Efficiency is the inverse of PMI, in other words, the percentage of the total input mass that is incorporated into the product.

$$\text{process mass intensity} = \frac{\text{total mass in a process or process step (kg)}}{\text{mass of product (kg)}} \quad (1)$$

The Roundtable members have used this common process mass intensity metric to compare data from each company on an equivalent basis. The calculation of the PMI is performed starting from commonly available materials. This therefore accounts for all the steps in a chemical synthesis, whether they are performed in-house or are being outsourced to contract manufacturing organizations, that is an increasing practice in the pharmaceutical industry. Accounting for the mass used across the entire synthesis also intends to start driving more efficient and sustainable practices throughout the supply chain as part of potential outsourcing strategies.

For instance, the results of the 2008 PMI benchmarking are shown in Figure 1. This benchmarking has also provided the means for prioritizing the Roundtable's efforts. As it can be seen (Figure 1), solvents contribute significantly to the PMI,[14] and to environmental life cycle impacts associated with the production of active ingredients.[15] For instance, the Roundtable has an ongoing research grant and has decided to focus its 2010 call for proposals on solvent-related research, such as looking for suitable replacements for dipolar aprotic solvents and solventless reactor cleaning. In addition, the Roundtable has recently produced an industry-wide solvent selection guide.[16]

THE PHILOSOPHICAL ARGUMENT FOR PROCESS MASS INTENSITY

Others have generally argued that using metrics such as E factor would help drive the reduction of waste, and this is certainly a good starting point, although not the best. After all, one can argue that the only difference between E factor and PMI is one (eq 2):

$$\text{E factor} = \frac{\text{total mass of waste (kg)}}{\text{mass of product (kg)}} = \frac{\text{total mass used in process or process step} - \text{mass of product (kg)}}{\text{mass of product (kg)}}$$

$$\text{E factor} = \text{PMI} - 1 \quad (2)$$

However, that difference of "one" is equivalent to the saleable product of a company; in other words, it is the factor that produces revenue for any business in the chemical and allied industries. For instance, the ideal state of PMI is when all the materials going into the process are integrated into the product, thus contributing actively to the generation of revenue (this corresponds to a PMI value of 1 and therefore an E factor of zero). However, the waste from the manufacturing process is only a part of the equation. In a way, the use of E factor can be seen as the legacy of the end-of-pipe view of waste-management philosophy from the 1980s. When talking about truly green and sustainable manufacture, it is not sufficient to target waste; one needs to look at increasing efficiency and perhaps reinventing "business-as-usual", especially in the broader context of the supply chain.

While in a broad sense it can be argued that it does not really matter which of these metrics one uses, historically waste and waste reduction have not come anywhere close to capturing management attention to the extent that the cost of high-value materials does. In the business context, efficiency metrics

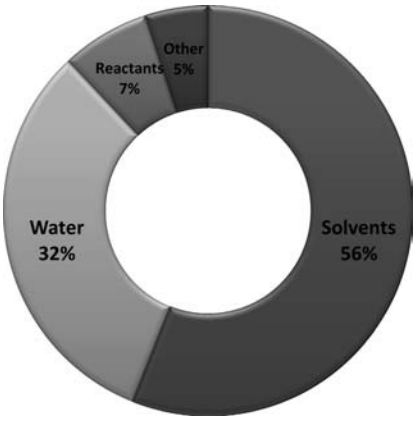

Figure 1. Composition by Mass of the type of materials used to manufacture API. ACS GCI Pharmaceutical Roundtable 2008 PMI Benchmarking.[14]

Figure 2. Comparison of the relative carbon footprint contributions of materials/supply chain vs waste generation and treatment (on-site and off-site) for GlaxoSmithKline. These relative contributions do not include other life cycle phases (e.g., production, transportation, product use, or end of life) but are intended to show a comparison between the relative importance of the impacts.[22,23]

(e.g., mass efficiency) have the advantage over waste metrics (e.g., E factor) of communicating and framing sustainability in terms of adding value (e.g., increasing productivity) instead of managing costs (e.g., reducing waste).

To truly integrate green chemistry and engineering into chemical processes, one has to look at the inputs instead of the outputs—leading metrics that allow us to facilitate changes as the processes and routes are being designed and tested. In this context, mass and energy inputs (how much and what types) are the first line leading metrics for chemists and engineers designing chemical and pharmaceutical routes.

The materials and energy we chemists and engineers use are more closely aligned with the core activities of the company and how the manufacturing processes transform those materials efficiently and effectively into value-added products. Metrics such as PMI or mass efficiency (its counterpart), although not perfect, allow us to focus people's minds on how to make processes more efficient—how to create a better process instead of solve a problem. Focusing on reducing waste helps companies to reduce costs, but focusing on efficiency also enables innovation to create additional value.

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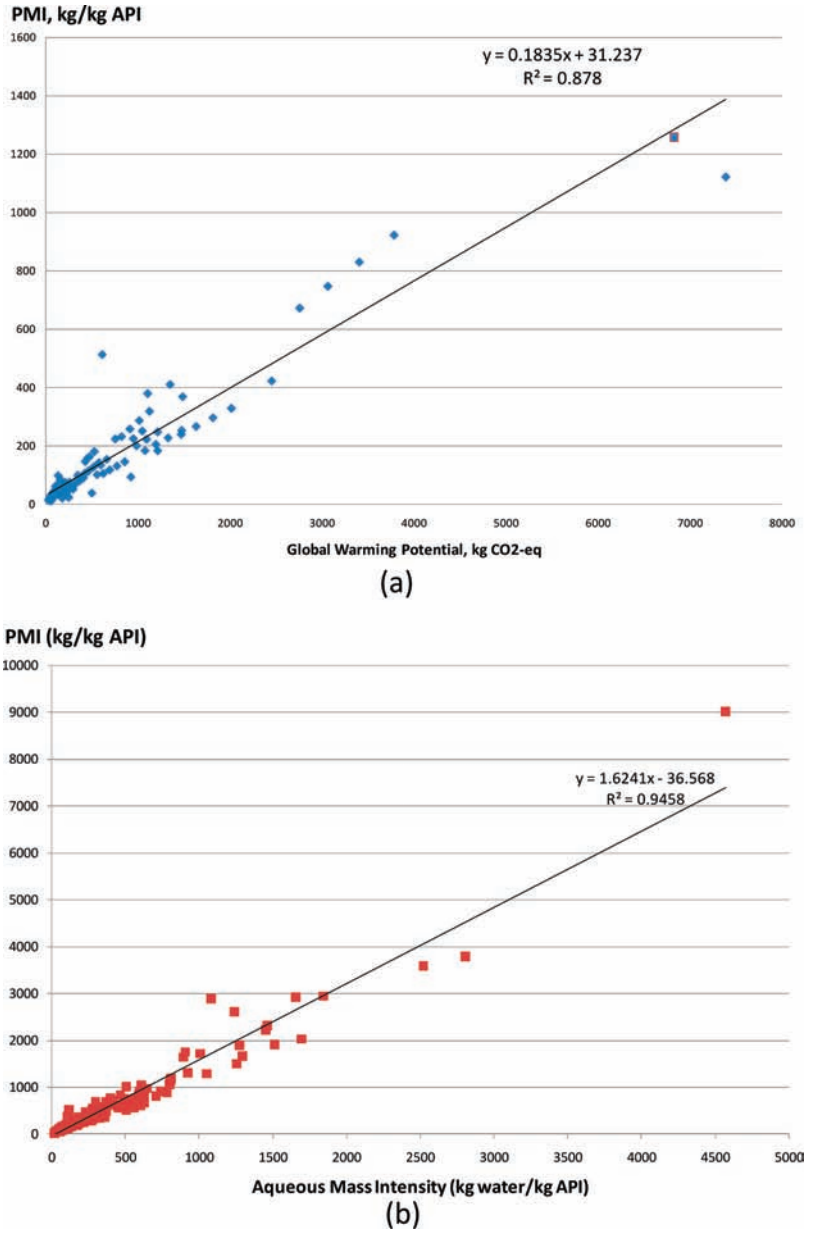

Figure 3. Correlation between PMI and (a) Global Warming Potential/carbon footprint and (b) aqueous mass intensity forAPIs in a development portfolio.

Simply put, the good focus is on minimizing waste. The greater focus is on maximizing value and efficiency. If one maximizes value, waste reduction will be one of the benefits.

THE SCIENTIFIC ARGUMENT FOR PROCESS MASS INTENSITY

In addition to the philosophical stance focusing on value or efficiency instead of waste, there is robust technical and scientific evidence that supports a strong focus on mass intensity (or mass efficiency). For that, one needs to look beyond the factory boundaries to the broader context of sustainability and develop a better understanding of how the impacts of processes and business activities accumulate across their supply chains and life cycles—in other words, one needs to use life cycle thinking and ideally Life Cycle Inventory and Assessment.

Life Cycle Inventory and Assessment (LCI/A) is a methodology that allows one to more precisely estimate the cumulative environmental impacts associated with manufacturing all the chemicals, materials, and equipment used to make a product or deliver a service, thus providing a comprehensive view of the potential trade-offs in environmental impacts associated with a given process or product across the entire life cycle.[17−19] The results of a Life Cycle Assessment (LCA) often include impacts not considered in more traditional analyses and provide a comprehensive view of the environmental impacts of the product or process with a more accurate picture of the true environmental trade-offs in product and process selection.[20]

If one wants to measure the 'greenness' of a process, the ideal is to have at hand a variety of metrics that include LCI/A metrics to best represent the overall sustainability of a process or product. However, performing the LCI/A consumes significantly more

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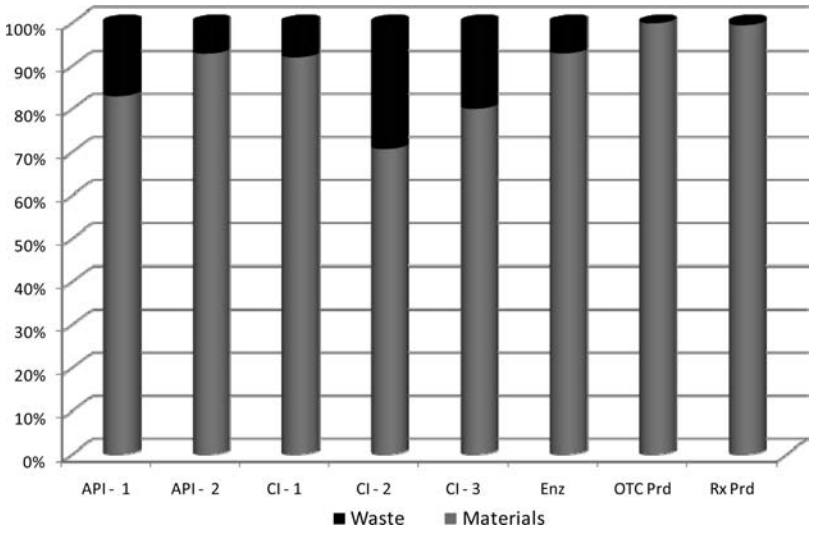

Figure 4. Comparison of the average contribution to life cycle impacts of materials and waste for some reported LCAs of pharmaceutical processes. API = active pharmaceutical ingredient, CI = complex intermediate, enz = supported enzymes used in pharmaceutical synthesis, OTC Prd = over-the-counter product, pharma prd = pharmaceutical product.

time and effort than estimating PMI or even E factor. However, if one does take the time to perform an LCA, it will be readily seen that PMI is a better surrogate for the cumulative environmental impacts than is E-Factor.

There is some work that has been performed since the late 1990s on the LCA of pharmaceutical processes. It has been consistently reported that the environmental life cycle impacts related to the production of raw materials needed to produce an API are significantly larger than the impacts related to operations or waste treatment.[21] For instance, GlaxoSmithKline has recently performed a global cradle-to-grave carbon footprint of the company operations, and it was clear that the supply chain impacts (PMI or mass efficiency related) dwarf the impacts related to waste production and treatment (E factor related). Figure 2 shows a comparison between the relative importance of the impacts due to materials and those impacts due to on- and off-site waste treatment. The results shown in Figure 2 were calculated using global warming potential factors based on mass.[22,23] The waste treatment carbon footprint includes all waste treatment impacts for all media, both on-site and off-site. The carbon footprint of the materials includes the entire external supply chain. These relative contributions shown in Figure 2 do not include other life cycle areas analyzed in the study such as production, distribution, product use, or end of life.

This correlation also seems to hold across several active ingredients. For instance, Figure 3a shows the correlation between PMI and global warming potential across all development compounds in GlaxoSmithKline's portfolio. Figure 3a shows that, although the correlation is not perfect, it is still fairly good. In general one can say that, for each kilogram of mass not used through a more efficient process (or different route), one can avoid the production of about 5.5 kg of CO_2 equivalents. For PMIs of less than 200 kg/kg API, the savings may be on the order of 6.5 kg of CO_2 equivalents per kg. This trend is not only confined to climate change impacts. As expected, a similar correlation has been found between PMI and aqueous process mass intensity (the amount of water expressed as kg per kg of API) as shown in Figure 3b. It is worth noting that, in addition to the correlation to life cycle water, another distinction between the PMI and E factor is that the PMI used by the Roundtable accounts for and tracks process water as part of the metric, while water is generally excluded from the E factor.[12] Although this difference may be easily aligned, it is indeed an important one, as water used in chemical and biosynthetic processes could involve significant capital, energy, and direct environmental impacts.

In addition, the LCAs that have been performed on active pharmaceutical ingredients (APIs), complex intermediates (CIs), enzymes, and formulated products, the contribution of supply-chain impacts related to the production of materials is consistently and significantly larger than the contribution of waste production and treatment. For instance, DSM Pharma Chemicals recently calculated carbon footprint (C-footprint), Eco-footprint, and PMI for a number of process generations of a complex pharmaceutical intermediate. For the first-generation process (a long linear stoichiometric organic chemical process) the relative importance of the total waste treatment as a percentage of the C-footprint was estimated and found to be around 20% (percent of kilograms of CO_2 equivalents attributable to waste treatment compared to overall kilograms of CO_2 equivalents for the full manufacturing process).[24]

Figure 4 shows the average contribution to several life cycle impacts from the production of materials and the production and treatment of waste as reported in several LCAs of pharmaceutical processes and formulated products. **API-1** and **API-2** denote active pharmaceutical ingredients for which LCAs were performed to evaluate and compare the LCIs of different synthetic routes and chemicals.[15,21,25] **CI-1**, **CI-2**, and **CI-3** are complex intermediates for which LCAs have been conducted, including the LCA performed by DSM as explained in the paragraph above,[24] an LCA performed to compare the impacts of chemical and enzymatic routes,[26] or an LCA performed to compare several synthetic routes.[25] **Enz** stands for supported enzymes used in pharmaceutical synthesis for which the life cycle impacts were evaluated.[27] **OTC Prd** is a formulated over-the-counter pharmaceutical product for which an LCA was performed to evaluate the supply-chain steps that contribute the most to the eco-footprint.[28] Finally, **Rx Prd** represents a formulated prescription product for which an LCA was performed to assess the biggest

contributors within the supply chain and identify opportunities to reduce the environmental footprint at the design stage.[29] The impacts included were global warming potential, eutrophication potential, acidification potential, and smog formation potential.

The summary above shows starkly that the impacts of producing the input materials simply dwarf the environmental impacts attributable to the waste produced. Thus, this proves a very compelling argument to focus on mass metrics instead of waste metrics using a life cycle thinking rationale. In addition, mass metrics such as mass efficiency or PMI have many practical advantages: they are leading indicators instead of lagging indicators, are easy to generate and compare, and are easily and directly measured by chemists and engineers in laboratory settings.

Furthermore, as seen in the examples shown in Figure 4, in the long run there is the necessity of companies to measure the true environmental impacts of products and operations. The need to estimate and report footprints (carbon-, water-, eco-, or yet another LCA metric) is becoming increasingly common. The reason that eco-footprinting is not done widely and routinely in pharma at this time is because of the lack of accessible and verifiable life cycle inventory information of complex organic materials. However, a mass indicator is an indispensable intermediate step to estimate the footprint. By definition, the E factor only takes the waste part into account and thus will never be able to serve as the basis for a footprint calculation, which is understandable as the need to perform LCAs was simply not recognized in the development of the E factor. By selection of the PMI, we are now also preparing our industry to make the next quality leap in sustainability assessment, once the necessary information and tools are available.

CONCLUSIONS

In summary, when one looks at the impacts of producing materials used in pharmaceutical production compared to the impacts of treating the waste produced in a pharmaceutical synthesis, it has been shown repeatedly that the cumulative environmental impacts of producing the materials dwarf the environmental impacts attributable to the waste produced. This leads us to conclude that focusing on a metric related to the input materials (PMI) is a far better indicator of the overall greenness of a process than is focusing on a metric for waste produced and the impacts resulting from rendering it harmless.

Therefore, the decision of the ACS GCI Pharmaceutical Roundtable of using PMI as the primary mass-related green chemistry metric instead of alternate metrics (such as E factor or atom economy) appears to be a solid one, supported by scientific data and aligned to a philosophy of efficiency and innovation instead of an end-of-pipe focus on waste.

The Roundtable recognizes that PMI is not perfect, as it does not provide a holistic LCA view, and it does not include specific concerns regarding environment, health, and safety of the materials involved or the waste produced. However, mass metrics such as PMI or its inverse, mass efficiency, are an indispensable intermediate step to estimate LCAs and footprints. In addition, mass metrics such as PMI or mass efficiency seem to be very reliable; high-level metrics are easy to generate and compare, can easily and directly be measured by chemists and engineers in laboratory settings, are easy to communicate and benchmark, and can be used to quickly obtain an estimation of the greenness of a process or route, with minimum investment in time and effort.

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GLOSSARY OF TERMS

E factor Total of waste produced [kg] per units of mass of product [kg]; water is normally excluded from the calculation.

Eutrophication Potential (EP)

Estimation of the potential impacts that emissions containing nitrogen and phosphorus have on the loss of water bodies causing overgrowth of algae and other aquatic species. It is normally expressed in units of mass (e.g., kg) of phosphate equivalents.

Global Warming Potential (GWP)

Estimation of the potential impacts that green house gas emissions have on climate change. It is a simplified index of the radiative properties of a gas relative to carbon dioxide over a period of time. It is expressed in units of mass (e.g., kg) of carbon dioxide equivalents.

Process Mass Efficiency (PME)

It is percent of raw materials integrated into the final product. It is calculated as the inverse of PMI expressed in percentage.

Process Mass Intensity (PMI)

Total mass of materials used to produce a specified mass of product, measured units of mass of input materials (e.g., kg) per units of mass of product (e.g., kg). The calculation of the PMI is performed starting from commonly available materials

Smog Formation Potential

Estimates the potential impacts of volatile organic compounds on smog formation. It is a simplified index of the potential of volatile organic compounds to release smog-forming ozone, compared to that of ethylene. It is expressed in units of mass (e.g., kg) of ethylene equivalents

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