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APPENDIX 1

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Overcoming Barriers to Green Chemistry in the Pharmaceutical Industry - The Green Aspiration Level™ Concept

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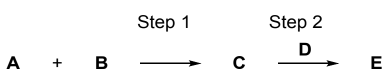
Appendix 1 – E factor preference explained

Here we rationalize why the E factor is more appropriate and mathematically consistent for multi-step process analysis using the generic two-step process example shown in Scheme 1 and detailed in Table 1.



Scheme 1. Generic Two-Step Process.

We first determine the values for the Step and Process PMI and cEF using the formulas of Equation 1 and show the results in Table 2.

Equation 1. Formula for PMI and CEF Determination.

$$PMI = \frac{\sum m(Raw\ Materials) + \sum m(Reagents) + \sum m(Solvents) + \sum m(Water)}{m(Product)}$$

$$cEF = \frac{\sum m(Raw\ Materials) + \sum m(Reagents) + \sum m(Solvents) + \sum m(Water) - m(Product)}{m(Product)}$$

The PMI and cEF *step contributions* to the process are calculated by multiplying the results for step PMI and step cEF with the amount of step 1 intermediate C required to make 1 kg of the process product, which is 1.1 kg. The total product amount is the amount of Step 2 product, and the total raw materials are the sum of the raw materials used in Step 1 and 2 minus the amount of Step 1 product since it has a net mass effect of zero kg on the overall process after considering it as Step 2 raw material.

Table 1. Material Input-Output Table for the Generic Two-Step Process.

Step Number	Input Material	Input Type	Output Material	MW [g/mol]	Equiv	Input Weight	Input Mol	Output Weight	Yield
1	A	Raw Material		100.00	1.0	0.558 kg	5.6		80%
	B	Raw Material		200.00	1.2	1.339 kg	6.7		
		Reagent		120.00	2.0	1.339 kg	11.2		
		Solvent		80.00	10.0	4.464 kg	55.8		
		Water (Workup)		18.02	50.0	5.028 kg	279.0		
		Intermediate	C	240.00				1.071 kg	
2	C	Intermediate		240.00	1.0	1.071 kg	4.5		80%
	D	Raw Material		100.00	1.2	0.536 kg	5.4		
		Reagent		100.00	2.0	0.893 kg	8.9		
		Solvent		80.00	15.0	5.357 kg	67.0		
		Water (Workup)		18.02	70.0	5.631 kg	312.5		
		Product	E	280.00				1.000 kg	

Table 2. PMI and cEF Results for the Generic Two-Step Process.

Step Number	Raw Materials	Reagents	Solvents (excl. Water)	Water	Product	Step PMI	PMI Contribution to Process	Step cE-Factor	cE-Factor Contribution to Process
1	1.9 kg	1.3 kg	4.5 kg	5.0 kg	1.1 kg	11.9 kg/kg	12.7 kg/kg	10.9 kg/kg	11.7 kg/kg
2	1.6 kg	0.9 kg	5.4 kg	5.6 kg	1.0 kg	13.5 kg/kg	13.5 kg/kg	12.5 kg/kg	12.5 kg/kg
TOTAL	2.4 kg	2.2 kg	9.8 kg	10.7 kg	1.0 kg		25.1 kg/kg		24.1 kg/kg

When determining process PMI and process cEF, we sum raw materials, reagents, solvents, and water, and deploy the formulas of Equation 1 that were previously used to determine the corresponding step values. It is important to note that the total amount of process raw materials is determined by adding the step raw materials including step 1 intermediate C (1.9 and 1.6 kg from Table 2), and subtracting the amount of step 1 intermediate C (1.1 kg), because intermediate C is not only the product of Step 1 but also fully consumed as raw material in Step 2, so its net process mass contribution is zero kg. We determine that process PMI is 25.1 kg/kg and process cEF is 24.1 kg/kg.

Now we can relate step to process PMI and cEF as follows for this two-step process, with PMI (step *n*) = PMI contribution of step *n* to overall 2-step process, and m(i,step1) = mass of step 1 intermediate C needed to make 1 kg of the process product E (Equation 2).

Equation 2. Process PMI and cEF for the Sample 2-Step Process.

$$PMI(2-step\ process) = \sum_{1}^{2} PMI(step\ n) - m(i,1) = PMI(Step\ 1) + PMI(Step\ 2) - m(i,step1)$$

$$cEF(2-step\ process) = \sum_{1}^{2} cEF(step\ n) = cEF(Step\ 1) + cEF(Step\ 2)$$

For a three-step process, we subtract the mass of step 1 and step 2 intermediates required to make 1 kg of process product from the sum of the step PMIs, for a four-step process we subtract the mass of step 1-3 intermediates required to make 1 kg of process product, etc., which can be mathematically formulated as follows (Equation 3):

Equation 3. General Process PMI formula.

$$PMI(n-step\ process) = \sum_{1}^{n} PMI(step\ n) - \sum_{1}^{n-1} m(i,step\ n)$$

Unlike with the E factors, we cannot simply add up the step PMI contributions to obtain the process PMI, because the PMI does not discount the step product from the step mass balance. For a two step-process, therefore, in which the step 1 product that in in our example is intermediate C, has no net mass contribution to the process, the mass of intermediate C required to make 1 kg API, which is 1.1 kg, needs to be subtracted out from the sum of the step PMIs to arrive at the process PMI:

$$PMI(process) = PMI(Step\ 1) + PMI(Step\ 2) - m(i,step1) = (12.7 + 13.5 - 1.1)\frac{kg}{kg} = 25.1\frac{kg}{kg}$$

Therefore, the PMI is *inconsistent* in its application to a step versus a process since it largely discounts the step products and intermediates for *process* PMI analysis, but does not discount the step product for *step* PMI analysis. In other words, the PMI always equals cEF+1, independent of the number of process steps, and for infinite number of process steps it will be equal to the cEF. The E factor concept is more coherent in terms of relating step and process values, as the process E factor represents simply the sum of the step E factor contributions as expressed with the general formula for the cEF shown in Equation 4. The same formula would apply to the sEF.

Equation 4. General cEF Formula.

$$cEF(n-step\ process) = \sum_{1}^{n} cEF(step\ n)$$

