How to estimate the cost of manufacturing an organic chemical

Berkeley W. Cue, Jr., Ph.D.

ctcuefamily@aol.com

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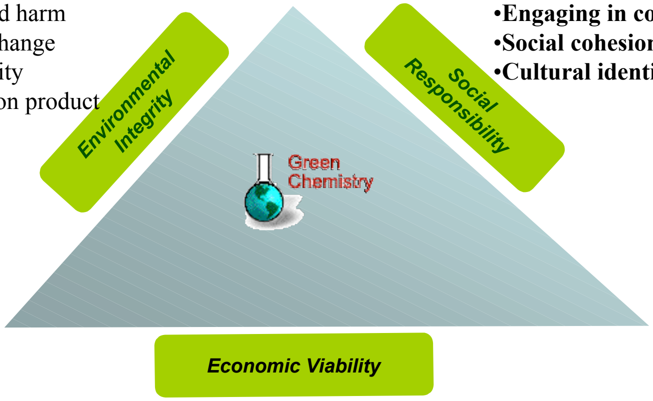
Sustainability



- Efficient use of natural resources
- Minimized harm
- Climate change
- Biodiversity
- Reduce non product output

- **Protect employees**
- **Competitive benefits**
- **Engaging in comms.**
- **Social cohesion**
- **Cultural identity**

Dividend, share price, capital growth, competitiveness, profitability

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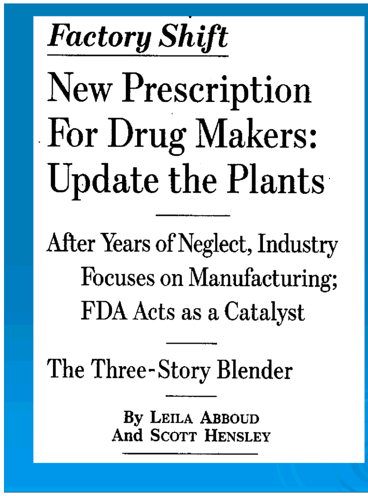


Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst

The Three-Story Blender

By Leila Abboud And Scott Hensley

Main points from this:

- High tech in R & D
- Relatively low tech in Manufacturing
- It matters
  - Big Pharma manufacturing costs are $ 90 Bn
  - Significantly more than R&D

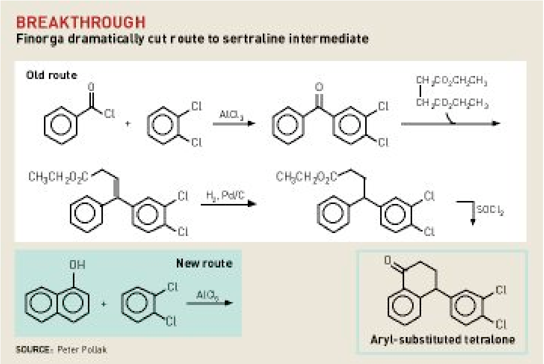
Quality by Design: A Challenge to the Pharma Industry

(CAMP, R. Scherzer. FDA Sci. Board. 4/9/02)

FDA Definition of a Starting Material

- Described in CFR in 1988, revised in 1998
- Several key elements include
  - Must be commercially available
  - Must be well characterized so specifications can be set
  - Its method of synthesis must be precedented and well understood
  - It must be early enough in the synthesis so that significant downstream chemistry remains
- Provides flexibility to change manufacturing route provided changes do not adversely impact quality of API

Tetralone Process Options



Source: C&E News

Stepwise Tool for Estimating Manufacturing Costs

- A simple tool that can predict “commercial scale manufacturing costs” at a 5000 kilogram manufacturing campaign scale. Assume for this exercise yield is 80%.
- Step 1. Establish the chemical formulas and molecular weights for all reagents and the product(s).
  - Alpha-naphthol is $C_{10}H_8O$ = 144 g/mole
  - Ortho-dichlorobenzene is $C_6H_4Cl_2$ = 147 g/mole
  - Aluminum trichloride is $AlCl_3$ = 129.5 g/mole
  - “tetralone” is $C_{16}H_{12}Cl_2O$ = 291 g/mole

Stepwise Tool for Estimating Manufacturing Costs

- Step 2. Calculate the number of moles in 1 kilogram of product (note: this is the unit typically used in the pharmaceutical industry, i.e., $X/kg) and adjust for yield
  - 1 kg = 1000 g, 1000 g/291 g/mole = 3.44 moles but since yield is 80% you need 4.3 moles (3.44/0.80).

Stepwise Tool for Estimating Manufacturing Costs

- Step 3. Calculate the weight of each reagent, expressed in kilograms, needed to produce 1 kg of product tetralone. The ratio of kg raw material per kg product is called the raw material utilization factor (UF).
  - For alpha-naphthol: 144 g/mole X 4.3 mole = 600 g = 0.6 kg
  - For ortho-dichlorobenzene: 147 g/mole X 4.3 mole X 3 = 2200 g (note: o-DCB is used in 3 –fold excess as both a reagent and a solvent) = 2.2 kg
  - For aluminum trichloride : 129.5 X 4.3 X 2 = 1040 g = 1.04 kg

Stepwise Tool for Estimating Manufacturing Costs

- Step 4. Estimate the cost of each reagent
  - using either published values in the “Chemical Market Reporter (a trade magazine that lists costs for bulk commodity chemicals)
  - or by calculating the cost to purchase 1 kilogram of reagent from Sigma-Aldrich and dividing by 7.
  - For the purpose of exemplifying this calculation the following costs were “guesstimated.”
    - Alpha-naphthol is $C_{10}H_8O$ = 144 g/mole $20/kg
    - o-dichlorobenzene is $C_6H_4Cl_2$ = 147 g/mole $10/kg
    - Aluminum trichloride is $AlCl_3$ = 129.5 g/mole $5/kg

Sources: Cost of Chemicals

Log onto www.chemicalmarketreporter.com

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2003-2004 Aldrich Handbook of Fine Chemicals

Stepwise Tool for Estimating Manufacturing Costs

- Step 5. Multiply the calculated weight of each reagent by the per kilogram cost of that reagent to get the cost contribution of that reagent to the overall manufacturing cost.
  - Alpha-naphthol is 0.6 kg X $20/kg = $12
  - o-dichlorobenzene is 2.2 kg X $10/kg = $22
  - Aluminum trichloride is 1.0 kg X $5/kg = $5

Stepwise Tool for Estimating Manufacturing Costs

- Step 6. Estimate the “processing cost” per step (for simplicity a reaction arrow = 1 step) using the following guideline:
  - Simple processing = $25/step
  - Average processing = $50/step
  - Complex processing = $100/step
- Which to select is guided by your knowledge of the step and experience and is somewhat subjective. **Be Consistent**
  - Processing costs include such things as labor costs (salaries), overhead (facilities and equipment depreciation), utilities, waste disposal, analytical testing charges, process aids, etc. **Account For Everything**
  - I would select simple processing cost for this reaction. Also, dilution should be considered-the more dilute the reaction the more complex the processing since dilution increases the number of batches per step for fixed equipment size.
  - Solvent costs can be calculated and added if solvents are expensive or used in large volume.

Stepwise Tool for Estimating Manufacturing Costs

- Step 7. Add reagent costs and processing costs to determine total manufacturing costs.
  - $12 + $22 + $5 + $25 = <u>**$62/kg tetralone**</u>
- The raw material costs are sometimes referred to as <u>variable or cash costs</u> and the processing cost is called a <u>fixed cost</u>

Refinements

- For expensive solvents, ie., dichloromethane, their cost should be added.
  - Cost contributions can be adjusted for solvent recovery (assume 50%).
- For this example we need to account for AlCl3 byproducts from reaction quench:
  - $AlCl_3 + 3 H_20$ -> $Al (OH)_3 + 3 HCl$
  - and HCL must be neutralized
    - $HCl + NaOH$ -> $NaCl + H_20$

Stepwise Tool for Estimating Manufacturing Costs

- For multi-step processes you calculate the total process cost by calculating the overall yield of the n-step process. For example, consider the following hypothetical process:
  - A + B -> C (step 1)
  - C + D -> E (step 2)
  - E + F -> Product (step 3)
  - The linear sequence is $A + B \rightarrow C \xrightarrow{D} E \xrightarrow{F} \text{Product}$
- The yield for each step is 90%, the molecular weight (MW) of the Product is 300 g/ mole, and the molecular weights of A, B, C, D and F are 200 g/mole. The costs of A, B, D and E are $100/kg each.
- Then for the three-step process the yield is 73% (100 X 0.9 X 0.9 X 0.9).

Stepwise Tool for Estimating Manufacturing Costs

- To make 1000 g Product with a MW of 300 g/mole, 1000/300/0.73 = 4.56 moles of A and B are needed, 1000/300/0.81 = 4.10 moles of C and D are needed and 1000/300/0.90 = 3.7 moles of E and F are needed.
- Determine utilization factors (UF's): For A and B UF's are 4.56 mole X 200 g/mole = 912 g = 0.912. For C and D UF's are 4.1 mole X 200 g/mole = 820 g = 0.82, and for E and F UF's are 3.7 mole X 200 g/mole = 740 g = 0.74.
  - E + F → Product: 200 g/mole X 3.7 moles = 740 g @ $100/1000 g = $74 each for raw materials E and F plus $25 processing costs = $173 for step 3.
  - C + D → E: 200 g/mole X 4.1 moles = 820 g @ $100/1000 g = $82 each for raw materials E and F plus $50 processing costs = $214 for step 2.
  - A + B → C: 200 g/mole X 4.56 moles = 912 g @ $100/1000 g = $91 each for raw materials E and F plus $100 processing costs = $282 for step 1.
- Total process costs = $ step 1 + $ step 2 + $ step 3 = $282 + $214 + $173 = $669/kg

Conclusions

- A simple manufacturing cost analysis
  - Suitable for incorporating into a lab course
  - Suitable for calculating E-Factors
    - R.A. Sheldon, *Chem. Tech*, 1994, **24**, 38
  - Suitable for calculating atom economy
    - B.Trost, *Angew. Chem. Int. Ed. Engl.* 1995*,* **34***,* 259
  - Teaches that high yield sometimes comes with high waste
  - Suitable for identifying areas for yield improvement through waste reduction and elimination

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Thank You