

The background of the slide is decorated with several red line-art chemical structures. These include various polycyclic aromatic hydrocarbons (PAHs) and other organic molecules, such as naphthalene, anthracene, and more complex fused ring systems. The structures are drawn in a simple, skeletal style with red lines on a white background.

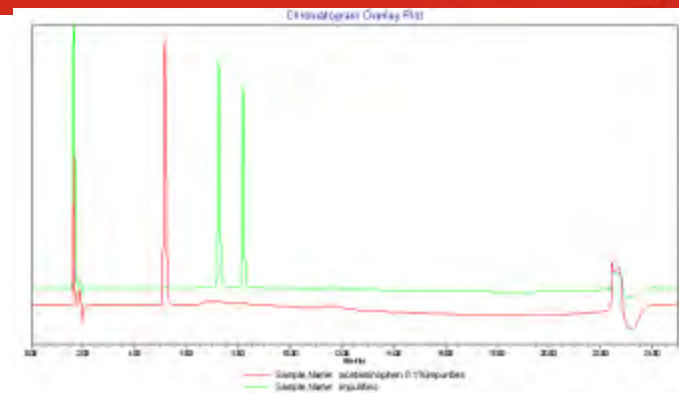
Inspiring Focus on Waste Minimization during Development

Douglas P. Kjell, Ph.D.

Lilly

Route Design Criteria

- ◆ Quality
 - Consistent impurity profiles
- ◆ Minimized Environmental impact
 - Process Mass Intensity (PMI)
- ◆ Cost
 - Must be economically viable
- ◆ Safety
 - Maximize intrinsic safety



Process Mass Intensity

- ◆ Adopted by Pharma as metric for sustainability
- ◆ Process Mass Intensity (PMI) = Total kg waste generated/ kg API produced
- ◆ Start the calculation at true articles of commerce
- ◆ Before this work Lilly set a PMI target of 100 for all small molecules (not biologics) leaving development

So why not a one size fits all PMI target?

- ◆ In general reducing PMI also reduces cost

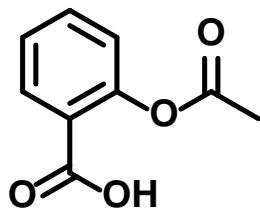


- ◆ In general improving purity raises PMI
 - Purifications are by separation:
 - Filtration leaving waste in the mother liquor
 - Layer separations leaving waste phase
 - Distillation rarely used in pharma
- ◆ In general lowering PMI increases risk
 - Dilute reactions are intrinsically more safe*
- ◆ Therefore reducing PMI while maximizing purity, and process safety is difficult

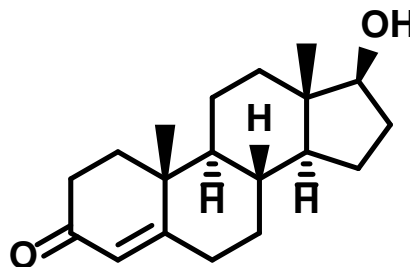
* While not the subject of this presentation, Lilly has a strong focus on process safety. Amongst the initiatives is a redesign of manufacturing from batch to continuous

Target complexity

- ◆ Molecular Complexity of small molecule pharmaceuticals varies wildly



aspirin



testosterone

- ◆ PMI 100 not realistic for all pharmaceuticals
 - One complex API project was at PMI 1250 after substantial development. Research was not focused on waste reduction.

Market Demand

- ◆ Chronic treatment, prevalent disease, high dose can mean 1000s kg/year



- ◆ Shorter treatments, orphan indication, low dose can be 10s kg/year



- ◆ Given fixed resources it makes sense to focus waste reduction efforts on high potential demand projects

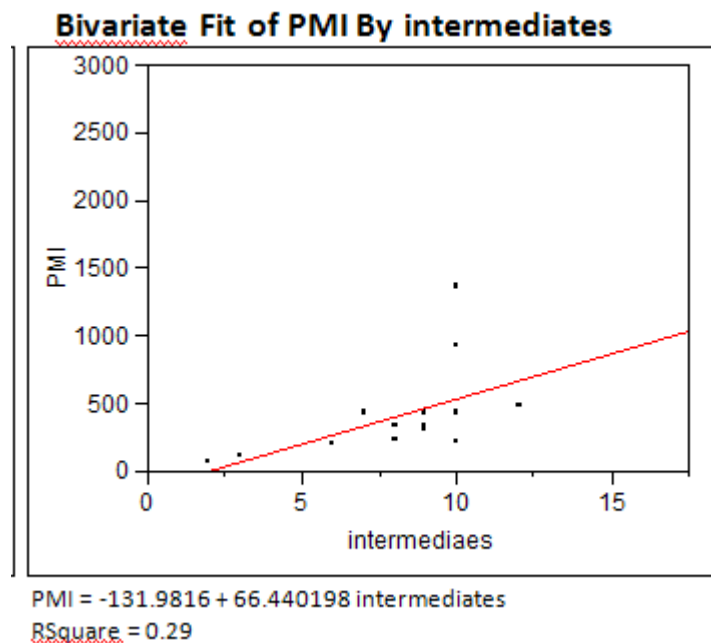
Therefore..

- ◆ Process Safety & product purity must be maintained! Failure is catastrophic. Suboptimal PMI has a less detectable outcome. So of the three PMI was sometimes less of a focus
- ◆ The one-size fits all PMI target failed to inspire as it was unrealistic for some targets and unfocused for demand.
- ◆ Developed a PMI target which inspires and focuses effort by:
 - Adjusting for molecular complexity
 - Correcting for estimated peak market

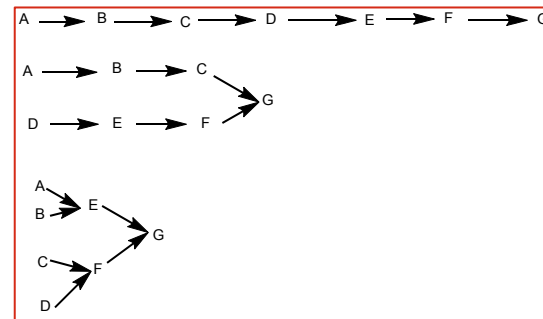
Molecular Complexity

- ◆ Molecular Complexity is not easily defined.
- ◆ We used linear regression of various parameters in Lilly's late phase portfolio to search for correlations

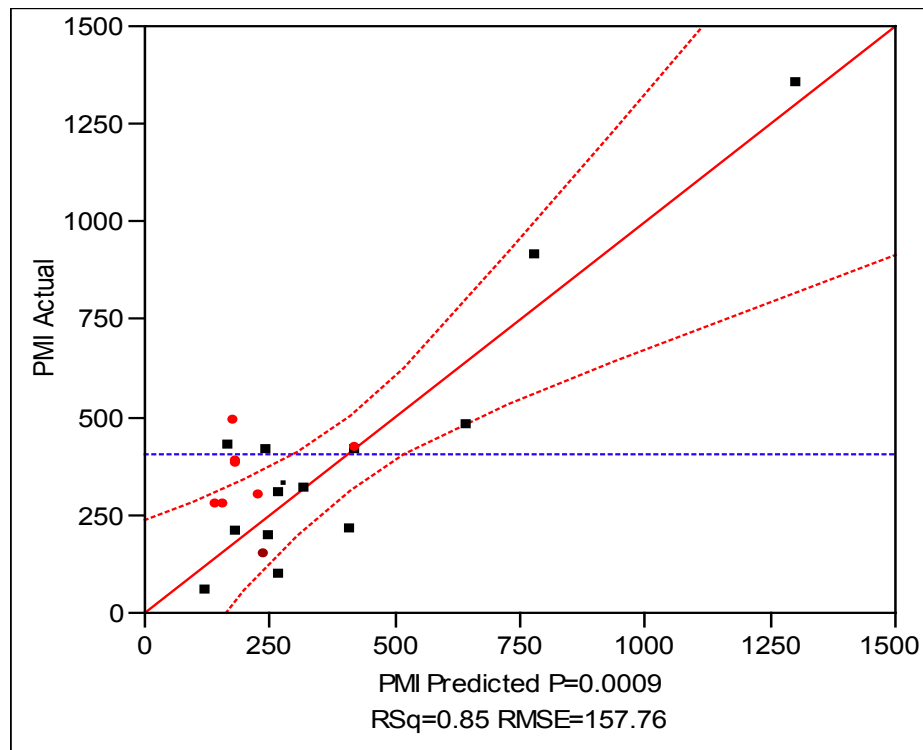
Poor Correlation to “Steps”



- ◆ Defining “Steps” isn’t straight-forward
- ◆ Poor yielding steps early hurt
- ◆ “Linear” vs. “Convergent” matters
- ◆ “Steps” isn’t an intrinsic property



Got a Good Fit to several intrinsic properties



A = # of non-hydrogen atoms C = Chiral centers H = Heteroatoms

$$\text{PMI} = 131 + (26 \cdot C) + (40 \cdot H) + (-515 \cdot A) + 57(C - 1.5)(H - 8)$$

Kjell, Douglas P.; Watson, Ian A.; Wolfe, Chad N.; Spitler, Jeremy T. Organic Process Research & Development (2013), 17(2), 169-174.

Adjustment for expected demand

$$\text{PMI target} = \text{Raw PMI target} * \text{Volume adjustment}$$

- ◆ Regression against intrinsic properties allows estimation of what PMI to expect based on Lilly historical results. For low kg/year that was deemed good enough. Volume adjustment ≥ 1
- ◆ As volume estimate increased multiplier becomes smaller. Volume adjustment < 1

Application to new project

- ◆ The discovery route had a PMI of 1000
- ◆ A rough estimate of experts predicted a PMI of 500 at point of launch
- ◆ PMI target of 50 set!
- ◆ This complex a molecule had never achieved a PMI close to that target

Approach to the New Project

- ◆ Only one route idea had a chance to reach that target. Therefore all effort was focused on that route.
- ◆ New chemistry had to be invented on two steps to make the route functional
- ◆ “Outside the box” thinking required – solvents can be used above their ambient pressure boiling point, hydrazine can be handled safely, mixed solvents can be better than pure solvents...

Results

- ◆ For the new project the PMI target of 50 was achieved in time for campaigns supporting clinical trials.
- ◆ In first development campaign using the new route 450,000 kg of waste were eliminated.
- ◆ After launch yearly savings were estimated to be at least that
- ◆ Remember that difficult project with PMI of 1250? It's target was set at 950. The new target inspired research. The target was met.