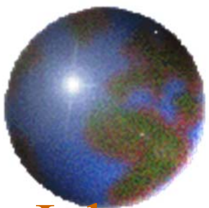
Global Optimization of Portfolio
Therapeutic Area Considerations



Vish Viswanathan, Ph.D.

Johnson & Johnson Pharmaceutical Research and Development

DAAG conference

May 14-16, 2003

Objective

- In the global optimization of a drug development portfolio, some key therapeutic area considerations become important
  - Economies of scale
  - Economies of scope (or synergy)
  - Risk reduction through diversification
- These are non-linearities that impact the overall results of the projects through their impacts on
  - Cost
  - Commercial value
  - Risk
- Omission of these considerations could lead to sub-optimal investment across therapeutic areas
- Our objective is to illustrate this with examples

Pharmaceutical Portfolio Problem

- Multiple therapeutic franchises
- Each with many new chemical entities (NCE) and line extension (LE) opportunities
- NCEs can take as many as 12 to 15 years to go from laboratory to commercialization
- LE's can take 3 to 6 years to get to the market
- There are risks in each stage of the project
- Global optimization approach will typically maximize the value (ENPV) of the portfolio over time with constraints on budget and possibly on yearly addition to revenues

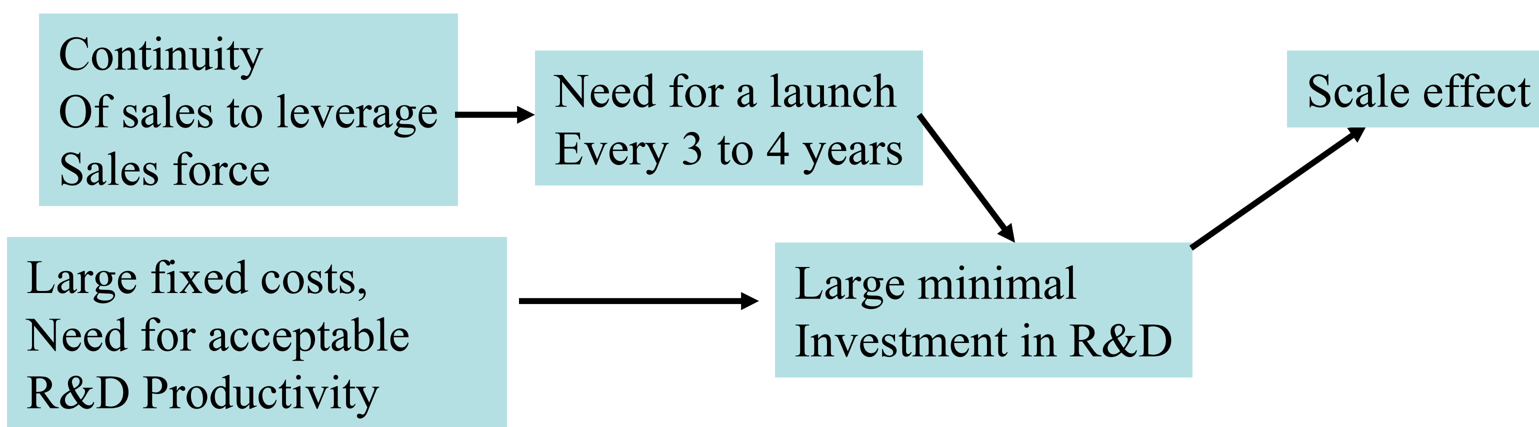
Global Vs Therapeutic Area Considerations

- Global optimization across therapeutic areas, however, typically ignores the three factors mentioned earlier that characterize the economics of the business –
  - scale effect
  - scope effect
  - potential diversification benefits

  and thus could yield solutions that are less than optimal
- Therapeutic area level optimization, on the other hand, would ignore an apple-to-apple comparison of the opportunities across the portfolio, and thus can be a sub-optimal process
- A realistic approach may be to use a global optimization approach with requirements that capture the therapeutic area level considerations
- We inquire into these individual effects and show with examples why it may be important to consider them

Scale Effect
What causes it

- Drug discovery, development, and commercialization are resource intensive processes, and often require a large minimal level of investment.
- Overall acceptable levels of R&D productivity can only be reached by pursuing multiple projects within the same therapeutic area → certain minimum scale of operation within each therapeutic area.
- In order to compete effectively and ensure commercial success in a therapeutic area, a company may need a continuity of presence in the chosen therapeutic market with at least a certain minimum level of presence in the market place.
- This again implies the need for a continuing flow of sales from new and existing products that requires the launch of a new product or indication every few years, which can happen only when a certain minimal scale of R&D is pursued



Scale Effect
How it impacts

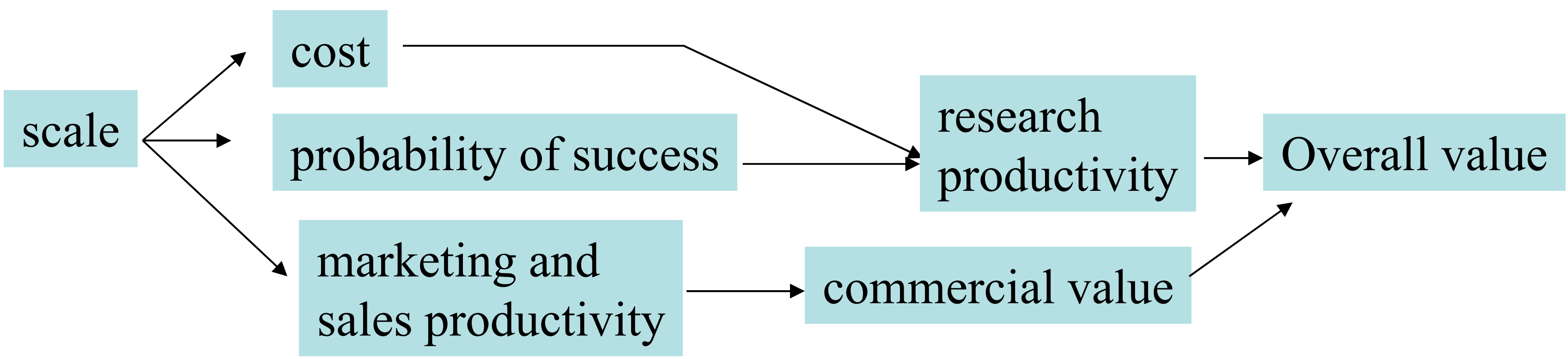
- Mathematically one can represent the scale effect in terms of cost as the following:

  AC(x) > AC(y), if y>x

  Average cost goes down with volume of activity

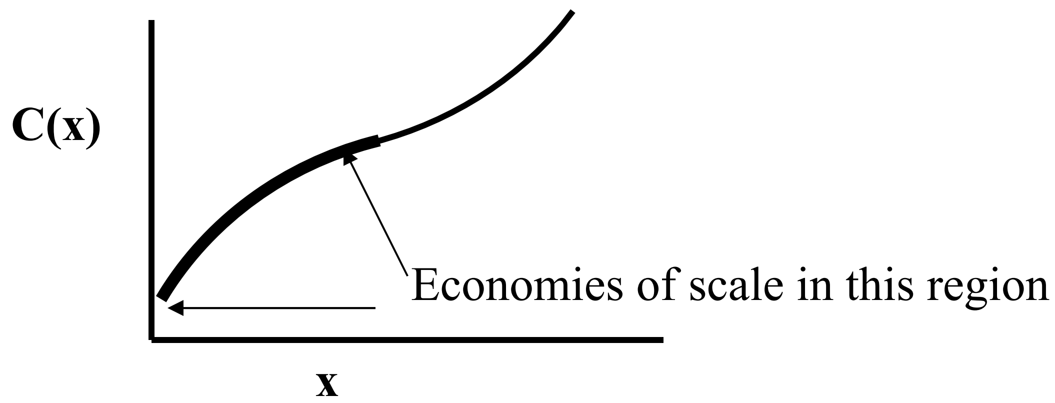
  Using a discrete model, with projects A & B,

  C(A&B) < C(A) + C(B)
- The advantage resulting from scale can be interpreted in terms of (a) the ability to share fixed costs (b) an experience effect from cumulative learning
- These advantages could also extend to (a) improved probabilities of success thereby generalized to improved research productivity (b) increased commercial value from increase in marketing and sales productivity



A Simple Example

- 2 therapeutic areas are considered (example: large primary care franchise like antiinfectives and a smaller specialty franchise like HIV)
- Projects exhibit scale economies within the therapeutic area -- in terms of cost, revenue, and probability of success
  - Cumulative cost reverse S-shaped (we use a cubic polynomial)



- While the real problem is multi-year and dynamic we simplify it and look at it in terms of ENPV metrics
- The projects are assumed probabilistically independent
- The objective is to maximize total ENPV
- The total costs are subject to a budget constraint

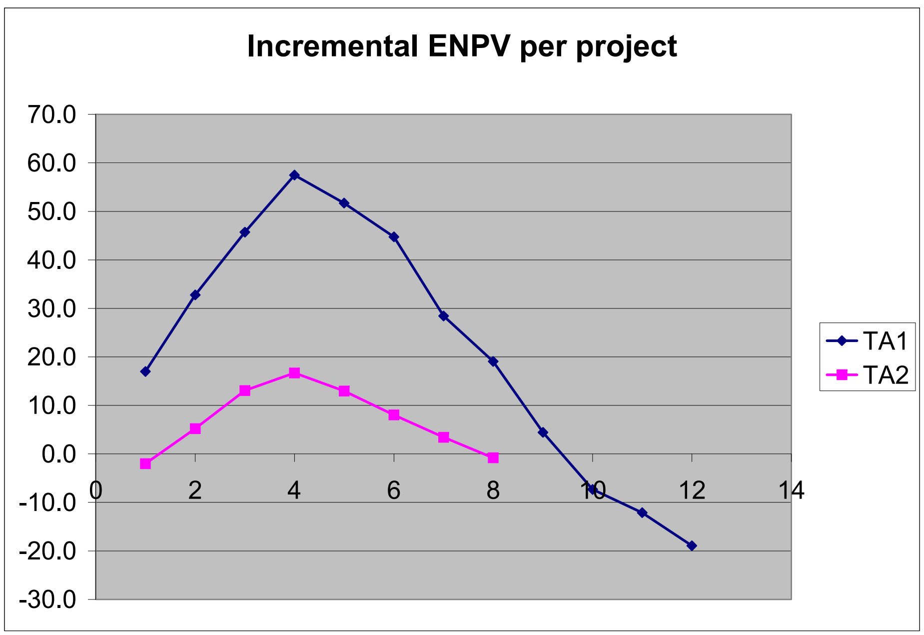
Economies of Scale -- Example

Therapeutic Area 1

Project	PTRS	Incremental ENPV Revenue	cost	profit	Prob. of success 1 or more	2 or more	PI
1	0.4	32.0	15.0	17.0	40%	0%	113%
2	0.6	49.0	16.2	32.8	76%	24%	202%
3	0.7	57.1	11.4	45.7	93%	60%	401%
4	0.8	65.3	7.8	57.5	99%	86%	737%
5	0.7	57.1	5.4	51.7	100%	95%	958%
6	0.6	49.0	4.2	44.8	100%	98%	1066%
7	0.4	32.6	4.2	28.4	100%	99%	677%
8	0.3	24.5	5.4	19.1	100%	99%	353%
9	0.2	12.2	7.8	4.4	100%	99%	57%
10	0.1	4.1	11.4	-7.3	100%	99%	-64%

Therapeutic Area 2

Project	PTRS	Incremental ENPV Revenue	cost	profit	Prob. of success 1 or more	2 or more	PI
1	0.5	15.0	17.0	-2.0	50%	0%	-12%
2	0.7	21.4	16.2	5.2	85%	35%	32%
3	0.8	24.5	11.4	13.1	97%	75%	115%
4	0.8	24.5	7.8	16.7	99%	93%	214%
5	0.6	18.4	5.4	13.0	100%	97%	240%
6	0.4	12.2	4.2	8.0	100%	98%	191%
7	0.3	7.7	4.2	3.5	100%	98%	82%
8	0.2	4.6	5.4	-0.8	100%	99%	-15%



TA1	TA2	cost	profit
9	2	111	305
8	3	114	313
7	4	117	311
6	5	118	295
5	6	118	259
4	7	117	210

True maximum with cost Constraint = 114

Lower ENPV when the higher value Project 9 in TA 1 is preferred to lower value Project 1 in TA 2

Economies of Scale -- Takeaway

- Presence of economies of scale could shift the optimal portfolio allocation so as to ensure a critical mass in each area: From an area which might already be operating in a decreasing return phase to another area which has not reached a critical mass

Economies of Scope

- Economies of scope are realized when multiple businesses are pursued which are related in some sense – yielding “synergy” or “scope effect”
- The traditional model is based on cost saving from multiple activities
- The cost model can be represented mathematically as

$$C(x,y) < C(x,0) + C(0,y)$$

Economies of Scope

- One can expand the “scope effect” to overall productivity increase

$$ENPV(x,y) > ENPV(x,0) + ENPV(0,y)$$

- This could be due to knowledge spillovers across therapeutic areas from an R&D perspective and also a marketing advantage resulting from expanded presence
  - Economies of scope in R&D could come from NCEs targeting different therapeutic areas sharing a common underlying mechanism of action – Example: Anxiety vs. Depression as two sub-areas within CNS.
  - Similarly, economies of scope in marketing could result from the ability to leverage the sales force in reaching a customer audience like Internal Medicine that treats multiple disease areas.

Economies of Scope
Simple Example Continued

- We model the scope impact as incremental value (incremental ENPV) $\Delta = \phi(z)$, with z = xy

  where $\phi(.)$ is an increasing concave function that is maximized for values of x, y such that x = y (synergy effect is highest when therapeutic area investments are relatively balanced)

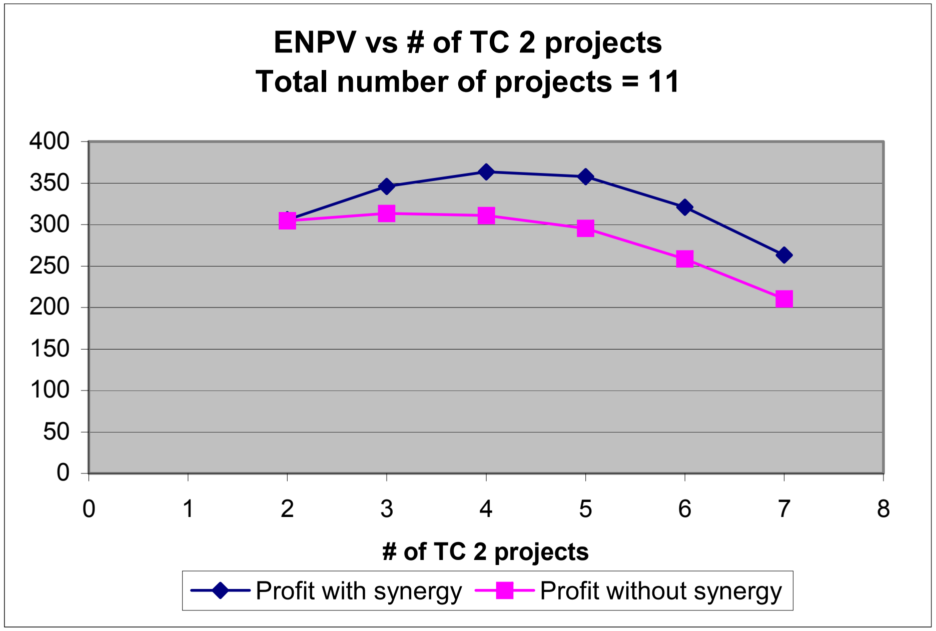
- The incremental value is due to cost synergies, knowledge spillovers that could help improve probability of success, and increased commercial value from marketing synergies

- While it can be analytically demonstrated that the optimal (x,y) shifts in favor of a solution that reduces the difference between x and y, we use a numerical example continuing on the same simple model framework

Economies of Scope

TA1	TA2	profit	synergy effect included	Synergy effect
9	2	305	306	1
8	3	313	346	33
7	4	311	363	53
6	5	295	358	62
5	6	259	321	62
4	7	210	263	53

Synergy effect
Shifts the optimum
To a more
Balanced solution



Economies of Scope -- Takeaway

- Presence of economies of scope could shift the optimal portfolio allocation towards a solution with more balance across therapeutic areas

Risk Diversification

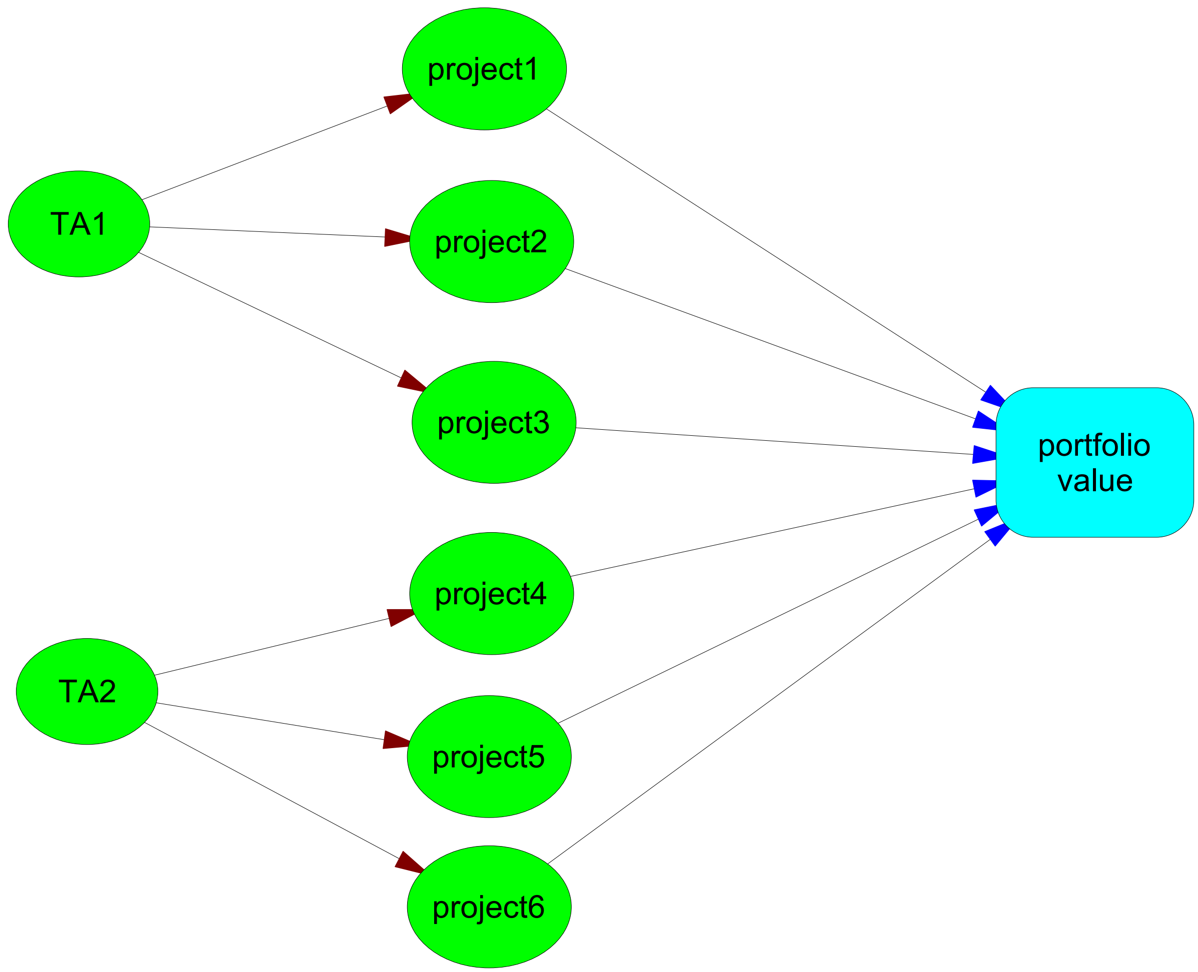
- This is somewhat analogous to the financial portfolios, in which stocks within an industry group are more correlated than across industry groups
- There is greater correlation of project outcomes within a therapeutic area than across the therapeutic areas. This could be due to a common underlying mechanism of action relating to the drugs within a therapeutic area
- Similar correlation on the marketing side -- risks in commercial value that might be correlated (same competitive threats and so forth)
- By having more diversified investments across multiple therapeutic areas, one could achieve a less risky portfolio
- The important thing is to look at the risk profiles of alternatives bearing in mind such correlations

Simple Example Continued

- Each of the projects within a therapeutic area now is strongly positively correlated with an underlying uncertain event for that therapeutic area (based on Keefer's underlying event model).
- We did this using the "correlate" feature of Crystal Ball.
- We use simulations look at the distributions of profits under alternative selections of projects in the two TA's in our example.

Risk Reduction through Diversification

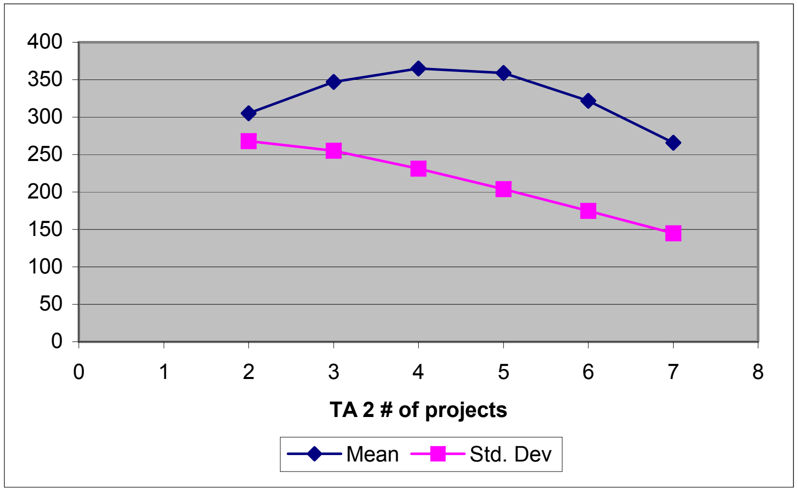
Underlying Event Model Structure

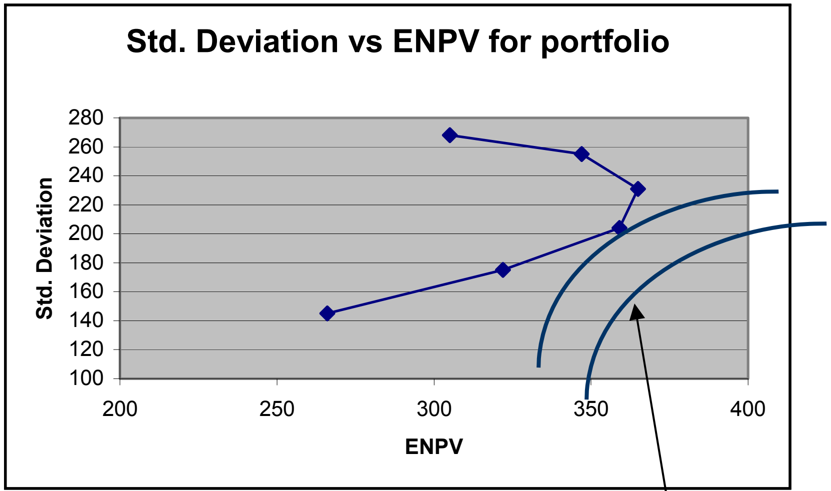


Diversification -- Example

There is a risk Vs return trade-off Between these two alternatives

TA1	TA2	Cost	Mean ENPV	Std. Dev of NPV
9	2	111	305	268
8	3	114	347	255
7	4	117	365	231
6	5	118	359	204
5	6	118	322	175
4	7	117	266	145





Hypothetical indifference curves

Diversification -- Takeaway

- Portfolio diversification presents opportunities for risk-return trade-offs. With less correlation in projects across therapeutic areas, the allocation could shift towards more balance across therapeutic areas.

Conclusions

- The choice of therapeutic area is a major policy decision for a pharmaceutical company.
- Once that decision is made, it would be necessary to ensure that the company has a critical mass of operations in that therapeutic area to ensure successful technical execution of R&D projects and an adequate level of market presence that ensures reasonable degree of commercial success.
- While allocating resources, it would be important to keep in mind the benefits from
  - (a) scope effects or synergies
  - (b) portfolio risk reduction accruing from greater diversification in portfolio