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White Paper 4

Indication Sequencing for a New Molecular Entity with Multiple Potential Indications

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Every pharmaceutical or biotechnology company aims to maximize the value of a new molecule. One common strategy involves securing, early on, the intellectual property (IP) rights for a variety of potential indications in which there is a hint of effectiveness. But once a company has been granted a patent for multiple indications, what is the best development strategy for the molecule?

Whether the decision is about which indication should be a) the focus in assessing efficacy and safety in the first exploratory Phase IIa study, b) the first submitted for regulatory approval, or c) the focus of initial negotiations regarding reimbursement and market access, each pharmaceutical company struggles to optimize the sequence for evaluating and launching into the potential indications. Additionally, the New Product Development Team struggles with questions such as:

- How should we optimize the sequence of developing follow-on indications?
- Should we consider each indication as a separate project, independent of the other indications?
- If we consider inter-dependencies, how can they be accounted for?
- Is the complete value of the molecule simply the sum of the individual indications?

In the following Case Study, we illustrate three different approaches for optimizing the sequence of indications to pursue:

1. **Simple (Indication) Ranking Method**
2. **Decision Tree Method (analysis at the molecule level)**
3. **Multiple Objective Decision Analysis (MODA)**

Case Study Background

A potent new drug candidate has shown tremendous promise in pre-clinical studies and is currently being assessed within a Phase I first-in-human trial. Based on a multidisciplinary team analysis, three indications are judged to be scientifically, medically, and commercially promising.

Management has made a policy decision that only one indication will be developed at a time to mitigate the R&D cost impact in any one year and reduce the risk of the new mechanism of action (i.e. only one Phase II trial will start in any given year).

Simple Ranking Method

The most common method involves selecting the initial indication by ranking each indication on selected key measures which are hopefully aligned with the company's objectives. The New Product Development Team would assess these measures for each of the 3 indications being considered for development.

Table 1 reflects an example of how the Simple Ranking Method was applied to this particular Case Study. There is value in assessing these key measures, but the correct choice is not at all clear. Should the team choose to develop Indication A because it has the best chance of launching, Indication B because it has the highest estimated NPV, or Indication C because of its alignment with the company objective of addressing high unmet medical need? Clearly, the use of a Simple Ranking Method has limitations, (see below).

Indication	Strategic Metric	Technical Metrics		Commercial Metrics		Financial Metrics	
	Degree of Unmet Medical Need *	Risk (PTRS)	R&D Cost ($M)	Market Size ($B)	Peak Sales ($M)	NPV ($M)	Risk Adjusted NPV ($M)
A	4	20%	$130M	$4B	$160M	$50M	$10M
B	3	17%	$220M	$2B	$210M	$70M	$15M
C	8	9%	$75M	$2.5B	$110M	$35M	$5M

Table 1. Simple Ranking Method. List of measures and the assessment / data for the three indications; Green indicates highest scoring, Yellow is 2nd highest, and Red is lowest; * scale of 1 (low) to 10 (high).

Simple Ranking Method: Limitations

- When one indication scores highly on some measures and other indications score highly on other measures, which measure(s) is most appropriate to utilize for making the decision?
- Is the company's objective a) to select the best indication, or b) to maximize the value of the compound through an optimized sequencing of indications?
- If point estimates are used, how valuable are the estimates given the early stage of the molecule?
- Once the "Best" indication is selected, what assumptions should be made regarding the sequencing of follow-on indications?

Decision Tree Method

A second, more holistic approach, addresses some of the questions raised in the Simple Ranking Method; it leverages decision analysis principles to improve decision quality and structure the problem using a **Strategy Table**, and an **Influence Diagram** / **Decision Tree**.

The focus changes from evaluating the development strategy for an initial indication to the three-indication strategy. Such a method generates much greater insights and helps a team develop a coherent strategy. In this example, the assessment and decision are made purely on the basis of expected NPV.

For our Case Study, a Strategy Table was developed (Table 2) to outline 3 coherent indication sequencing strategies (i.e., molecule development strategies).

Strategy	Elements of Strategy			Strategy Level Data		
	First Indication	Second Indication	Third Indication	Year of First Launch	PTRS of First Indication	Pricing ($ / PTD)
Cheapest First (Low Cost)	C	A	B	2018	9%	$10
Easiest First (Best Chance)	A	B	C	2018	20%	$8
Biggest First (Go for the Gusto)	B	A	C	2019	17%	$8

Table 2. Decision Tree Method: Strategy Table. Three strategies are shown (each strategy = indication sequence), along with examples of key data for assessing the strategies.

Using the Strategy Table, the team could include interdependencies and make some molecule level assumptions:

- Pricing of the first indication sets pricing for all subsequent indications
- Development of the other indications would continue regardless of success or failure of the first indication
- Regardless of sequencing, the patent for all indications would expire in 2028

What's important to recognize is that the Decision Tree Method and Strategy Table already helped the team think about their objectives at a molecule level, something that was missing in the Simple Ranking Method. Other strategies could have been developed but must be coherent and be defensible by the team.

Following the creation of an aligned Strategy Table, the team moved to develop an Influence Diagram (Figure 1). The Influence Diagram shows a high-level relationship of the three strategies and the associated values and uncertainties. It also forms a straightforward schematic for the development of a more powerful decision analysis model.

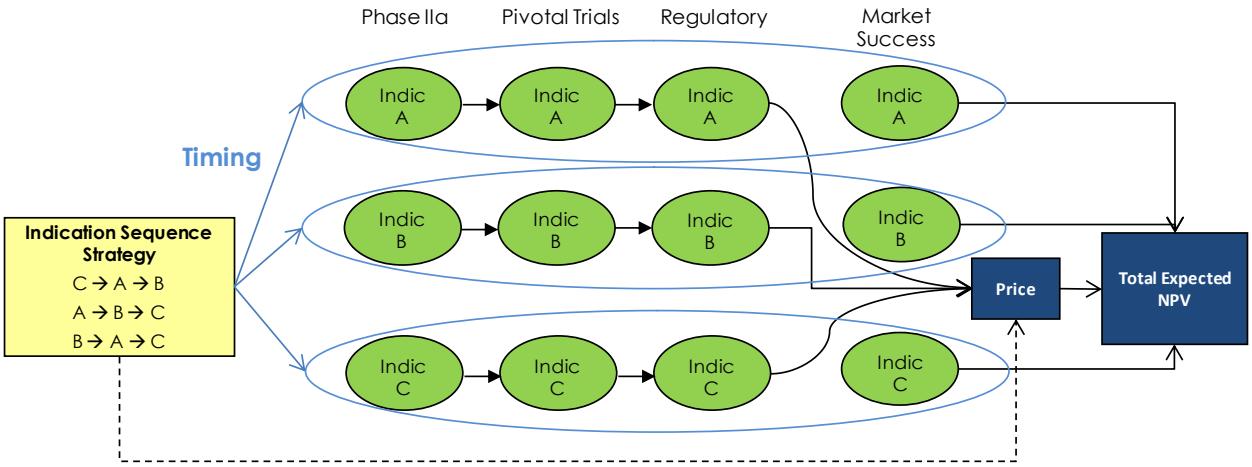

Figure 1.Decision Tree Method: Influence Diagram. The key variables (uncertainties and values) and their relationship to the three strategies to be evaluated; alternatively, what influences Total Expected NPV, what influences those factors, and how selecting one of the three strategies influences Total Expected NPV. Green ovals represent outcomes with an associated uncertainty (e.g., the uncertainty of a positive outcome of a Phase IIa Trial in Indication A), while the blue boxes represent numerical values or calculations. (e.g., Price); DPL 7.0 (Decision Programming Language 7.0, Syncopation Software, Concord, MA) used to model Influence Diagram.

The base values and associated level of uncertainty for each of the key variables were then determined. Uncertainty was incorporated using the 10th (low), 50th (base), and 90th (high) percentile values. For this Case Study, the key variables included the **Probability of Success (POS)** of the Phase IIa trial, the Pivotal Trials, and the Regulatory submission, giving an overall **Probability of Technical & Regulatory Success (PTRS)**. In addition, commercial variables included an overall measure of Market Success (Total Volume) and Peak Annual Volume. Tables 3a and 3b below show examples of data used to assess the variables in this Case Study.

Indication	Probability of Success			Total PTRS
	Phase IIa	Pivotal Trials	Regulatory	
A	45%	50%	90%	20%
B	35%	50%	95%	17%
C	25%	40%	85%	9%

Indication	Market Success (Total Volume) 10th - 50th - 90th Percentiles		
	Launch Now	1 Yr Launch Delay	2 Yr Launch Delay
A	115-230-320	70-140-220	50-100-150
B	190-250-380	20-100-200	10-60-90
C	30-75-115	20-60-90	10-35-50

Tables 3a and 3b. Decision Tree Method: Technical Risk and Commercial Uncertainty. 3a (Left). Probabilities of Success (POS) shown for each stage of the development pathway, for each indication, along with Total PTRS (Probability of Technical and Regulatory Success); 3b (Right). Values at the 10th, 50th, and 90th percentile for each Indication shown for Market Success (Total Volume). Values are shown for Base Case launch timing, one year delay, and two year delay, which depend upon the sequencing. Select variables shown for illustration.

Once all of the values and associated uncertainties have been assessed, we incorporate them into the decision tree model. In this particular Case, the Indication Sequence Strategy with the greatest eNPV would give a value of $260M eNPV (eNPV of $189M for C-A-B (*Cheapest First*), eNPV of $159M for A-B-C (*Easiest First*), and eNPV of $260M for **B-A-C (*Biggest First*)**.

While these figures represent the average expected probability adjusted value (eNPV) of each strategy, the distributions around these averages represent the hundreds or thousands of possible scenarios that may surface from the sequencing decision and the associated uncertainties following that decision.

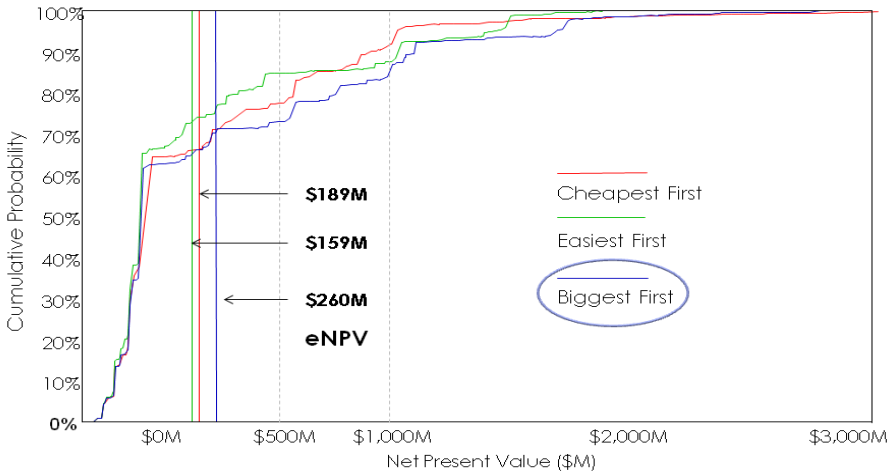

Figure 2. Decision Tree Method: Analysis. Cumulative Distribution of the eNPV values of the three strategies.

For example, Figure 2 shows that, while the *Biggest First* strategy is not completely dominant over the other two strategies, it does have the highest expected NPV and has the best 'behaving' cumulative distribution.

What is meant by best 'behaving'? If we examine the $500M NPV line, we see that the *Biggest First* (blue) strategy has approximately a 70% probability of being below $500M and a 30% probability of being above that point, a probability greater than the other two strategies. Similarly, the *Biggest First* strategy has the largest remaining probability to reach $1,000M or more in NPV and the lowest probability of resulting in a negative NPV.

Decision Tree Method: Limitations

The Decision Tree method addresses many of the shortcomings of the Simple Ranking Method, but still leaves several unresolved issues:

- Commercial value of indications at significantly early developmental stages (prior to proof of concept) and more than 5 years out (2018+) are difficult to estimate.
- Decision is being made based solely on one financial metric (eNPV) ignoring other valuable corporate objectives such as strategic fit or unmet medical need.

Multiple Objective Decision Analysis (MODA) Method

The most comprehensive approach available to pharmaceutical companies today is **Multiple Objective Decision Analysis (MODA)**[1,2]. MODA integrates multiple, often competing objectives, when assessing the value of a compound and different strategies for that compound. These objectives can be financial in nature, as discussed above (e.g., eNPV or topline revenue); they can also be non-financial (e.g., align with corporate strategy, maximize patient centricity, address the greatest unmet medical need).

The MODA Method involves seven key steps, which allow for the multi-objective prioritization of different strategies:

1. Identifying the desired objectives
2. Structuring objectives into a hierarchy
3. Developing a measure and value function for each objective
4. Assigning weights to objectives, i.e. prioritizing objectives vs. one another
5. Developing creative alternatives
6. Assessing each alternative on each objective.
7. Conducting an analysis to identify the best strategy or produce a better alternative.

Often, teams responsible for compound development are multidisciplinary and global in nature, adding to the inherent complexity of decision making. A well-facilitated workshop(s) focused on elicitation of corporate and disease area objectives helps stimulate discussion and align the organization and key stakeholders on achievable and measurable objectives that are relevant to the compound.

In this Case Study, a multidisciplinary team created objectives through facilitated and focused workshops (Step 1). A team of functional experts (e.g., pharmacologists, clinicians, marketing

experts) assisted in developing suitable measures aligned with each overarching objective, using strategy level data (as opposed to indication level data). Measures were organized using an **Objective Hierarchy** (Step 2). In some cases, multiple measures of a particular overarching objective were introduced. Figure 3 shows the final set of objectives.

Next, the Management team considered the relative importance of one objective over the other, assigning both value functions (Step 3; how to measure each objective and the value of achieving different levels of the objective) and weights (Step 4; the relative contribution of each objective to the overall value). Figure 3 also shows the result of a second workshop, focused on Steps 3 and 4 of the MODA Method.

For example, Management determined that the most important objective was Commercial Success (40% weighting), followed by European Presence (25%). By incorporating this functionality, the MODA Method is considerably more sophisticated than the regular Decision Tree Method, which is completely based on Commercial Success.

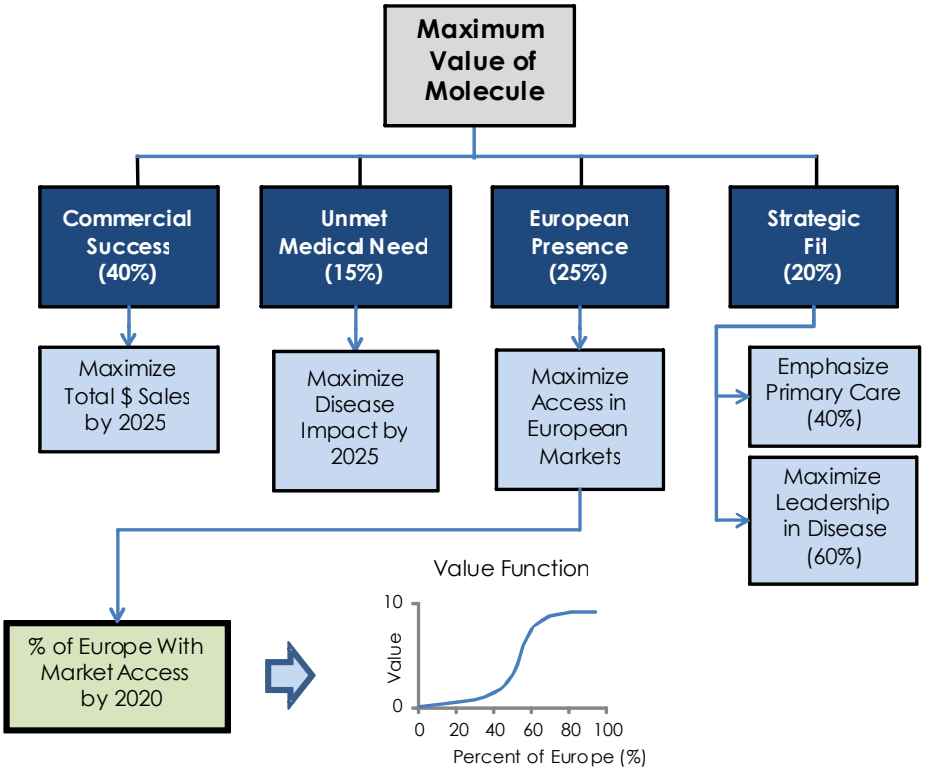

Figure 3. MODA Method: Objective Measurement and Weighting. Management agreed-upon objectives, along with the associated weights for each objective (in parentheses). The breakout shows a Value Function for one of the objectives and measures – Percent of Europe with Market Access by 2020.

A critical and often difficult part of this phase is identifying an adequate measure of a qualitative objective. In addition, a **Value Function** shows the

relative value of achieving one level of a particular objective / measure (here, European Presence). For example, Figure 3 shows how achieving Market Access in 60% of Europe would provide a value of 7.5, while achieving 30% might only provide a value of 2. In this fashion, the value function reflects the objectives of the company.

Once value functions were established for each objective / measure, each strategy was assessed on its ability to achieve each objective (Step 5). Table 4 shows the data for each measure. Appropriate values were determined using value functions like that described in Figure 3.

Objective →	Commercial Success	Unmet Medical Need	European Presence	Strategic Fit	
Measure →	Total $ Sales by 2025	Disease Impact	% Market Access in EU	Primary Care Emphasis	Leadership in Disease Area
Cheapest First	$740M	5000	20%	None	Achieve
Easiest First	$680M	5330	60%	Medium	Maintain
Biggest First	$920M	5980	40%	High	Decline

Table 4. MODA Method: Strategy Assessment. Three strategies are shown (Strategy = Indication Sequence), along with the assessment of each strategy along the 6 objective measures for 4 objectives.

As a last step in MODA, the overall value assigned to each strategy is calculated. This value is a combination of several financial and non-financial measures (as described above). Figure 4 shows the cumulative score / valuation of the three strategies under consideration.

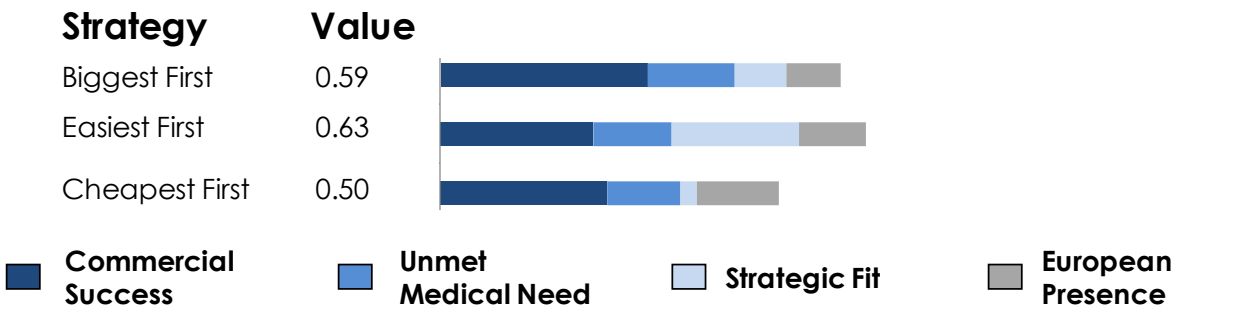

Figure 4. MODA Method: Valuation. Three strategies are shown with the cumulative value according to the sum of the values of each objective (see Table 4 for values of each measure). The length of the bar shows the level of value contribution from each objective (standardized to a value between 0 and 1).

Interestingly, the inclusion of non-financial objectives / measures resulted in the recommendation of a different strategy compared to the Decision Tree Method, as well as a richer and more insightful discussion. The desire to address Strategic Fit and European Presence drove the strategy with a slightly lower financial value to be the recommended alternative. This is in contrast to a recommendation of the *Biggest First* strategy, when using a financial measure alone (i.e., Decision Tree Method).

Value of the MODA Method

In this Case Study, the MODA Method addressed several shortcomings of the Decision Tree Method. The consistency in value assessments and its transparency led to better and more open discussions about tradeoffs between strategies. Management particularly appreciated this facet of MODA, which led to better alignment around objectives and selecting a strategy that addressed a combination of objectives.

Summary

In this Case Study, three different analytical approaches were evaluated for their value in helping to find the best indication sequencing strategy for a new molecule. All of this modeling and interaction with a multidisciplinary team of experts and Management enabled the company to look at this molecule in a new light. Clarity for the decision makers increased significantly and confidence that a particular strategy was the best way to meet multiple objectives was achieved for many stakeholders. Management gained trust in the working team and became confident that the recommended strategy captured the key objectives and main areas of uncertainty / risk.

This Case Study illustrates the particularly strong value of MODA, which addresses several more issues than does either a Simple Ranking Method or a financially driven Decision Tree Method (Table 5). MODA can be leveraged for other issues as well, including decisions regarding which projects to fund and other portfolio level decisions [3, 4, 5].

Issue	Simple Ranking	Decision Tree	MODA
Indication Sequence	X	X	X
Incorporation of Uncertainties	X	X	X
Most Appropriate Measures		X	X
Indication Dependencies		X	X
Molecule Level Analysis		X	X
Uncertainty of Commercial Value (Early Stage)		X	X
Incorporation of Non-Financial Metrics			X

Table 5. Assessment of Three Analytical Approaches. Comparison of the three approaches and the issues that each can successfully deal with as per the case study.

Abbreviations

- DPL: Decision Programming Language by Syncopation
- eNPV: Expected NPV, a probability weighted average of all possible NPV outcomes, including technical risk.
- IP: Intellectual Property
- NPV: Net Present Value, a sum of discounted cash flows over a defined time horizon using an agreed upon discount rate.
- MODA: Multiple Objective Decision Analysis
- POS: Probability of Success (technical success for a phase)
- PTD: Patient Treatment Day
- PTRS: Probability of Technical and Regulatory Success (combined POS for all phases)
- R&D: Research and Development

References

1. Keeney, R. (1992) Value Focused Thinking: A Path to Creative Decision-Making. Harvard University Press.
2. Keeney, R., Raiffa, H. (1993) Decisions with Multiple Objectives. Cambridge Books, Cambridge University Press.
3. Kloeber, J. (2010) Deciding Which Projects to Fund: Using Value Focused Thinking in Pharmaceutical Decision Making. KROMITE, LLC, White Paper.
4. Kloeber, J. (2011) Current and Cutting Edge Methods of Portfolio Decision Analysis in Pharmaceutical R&D. In *Portfolio Decision Analysis*, International Series in Operations Research & Management Science, Volume 162, Part 3, pp 283-331.
5. Kloeber, J., Kim, C. K. (2012) Horses for Courses: Portfolio Management Methods for Different Stages of Drug Development. KORMITE, LLC. White Paper.

About KROMITE

KROMITE is a leading strategic advisory firm that specializes in the application of decision science to help clients make strategic decisions, manage risk, and create value. KROMITE was founded in 2003 to provide independent and unbiased support for tough decisions in the life science industry.

Our team, headquartered in New Jersey and located throughout North America and Europe, possesses unparalleled expertise in scenarios analysis and decision making. From years of working for pharmaceutical, biotech, medical device and agricultural companies, our team commands intimate knowledge of tools, terminologies, organizational roles & responsibilities, R&D processes, common deal term structures, and organizational decision making processes, which allows our clients to rely on us as a partner and external expert.

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