Evaluating Backup Compound Development Strategies Using Simulation

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OBJECTIVES

To illustrate how to evaluate and optimize among strategies for developing backup compounds in conjunction with a lead compound, accounting for probabilistic learning about the product profile both within and across compounds, market value as a function of this profile, and differing development costs. This is important to manage risk and improve productivity in drug development.

INTRODUCTION

Pharmacometricians typically build exposure-response models for efficacy, and sometimes side effects, of *individual* compounds, using Monte Carlo simulation to test and optimize dosing, sample sizes, and other trial design factors. These models can provide input into more strategic Monte Carlo simulation models to support economic go/no-go decisions and development program design [1, 2], and in particular decisions about whether and how to advance backup compounds. Many factors complicate optimal backup compound decisions but can be accounted for in simulations, including the:

- potential to learn from lead compound results throughout development
- risk that a backup is so correlated with the lead that it will perform no better
- differing remaining development costs (ignoring sunk costs from previous phases)
- loss of total market share when a successfully developed backup must share the market with the lead compound
- value of speed to market, which may give the lead compound an insurmountable advantage.

METHODS

An example problem was specified in which a lead compound "L" is entering Phase 2B and its backup "B" is ready for Phase 1 (or multiple backups). L has low positive expected value, e.g., due to disappointing Proof-of-Concept results, raising the question of how B should be advanced. Efficacy and Side Effect outcomes of B have a specified correlation with those of L, which was varied from 0% to 100%. If both L and B reach the market, a specified fraction of B's market share, which was varied from 0% to 100%, is lost to "cannibalization" by the other drug. Dosing decisions were left implicit for simplicity.

A tool to simulate development of L and B by phase and their net expected value (expected market value minus development cost) was created in Microsoft Excel (Fig. 1). Normal Bayesian learning (see box) from simulated results of each phase updated prior distributions for Efficacy (E) and Side Effects (SE). Simulated "true" values of E and SE were used to simulate these phase outcomes and determine the expected market value if successfully developed: a function of E and SE and development costs. Development was stopped if the expected Net Present Value (ENPV) for completing development after a specified phase (2A here) became negative. (Note: while this rule is simple to implement and may be reasonably descriptive, it is suboptimal, because a negative ENPV could turn positive after properly accounting for the option to stop development later.) Sunk costs from completed phases were properly ignored for go/no-go decisions but included in the final ENPV. Averaging ENPV over the 1000 simulations gave the overall ENPV.

Normal Learning Models

(a) From Trial Observations
X = Unknown population mean
X_1 = mean of n observations of X

$X \rightarrow X_1$
$N(\mu_0, \sigma_0^2)$ Uncond.: $N(\mu, \sigma^2/n + \sigma_0^2)$
Given X: $N(X, \sigma^2/n)$

Bayes' Rule

$X \leftarrow X_1$
$N(\mu_0 + (x_1 - \mu)\,\sigma_0^2/(\sigma_0^2 + \sigma^2),\ 1/(1/\sigma_0^2 + n/\sigma^2))$ $N(x_1, 0)$
(take weighted avg. mean, add precisions)

(b) From Lead to Backup
X = Lead compound measure
Y = Backup compound measure

$X_1 \leftarrow X \rightarrow Y$ Correlation ρ, Slope $b = \rho\,\sigma_y/\sigma_x$
$N(\mu_x, \sigma_x^2)$ Uncond.: $N(\mu_Y, \sigma_Y^2)$
Given X: $N(\mu_Y + b(X - \mu_X),\ \sigma_Y^2 - b^2\,\sigma_X^2)$

Bayes' Rule

$X_1 \rightarrow X \leftarrow Y$
Given X_1: $N(\mu_x', \sigma_x'^2)$ (updated as at left)
Given X_1: $N(\mu_Y + b(\mu_x' - \mu_x),\ \sigma_Y^2 - b^2(\sigma_x^2 - \sigma_x'^2))$

Figure 1. Part of simulation spreadsheet for backup compound (lead compound is similar without entries in blue).

Development Simulation with Normal Learning Model

Backup Compound Example with Learning from Lead Compound (via links to its sheet)

		Efficacy	Corr.		Side Effects	Corr.	
# Phases behind Lead Cpd. (1-3)		2					
Prior Mean, Correlation w/Lead		1	0.5		1	0.5	(blank input: same as Efficacy)
Prior SD		2			3		
Mkt Value Weight ($M)		100			50		
Mkt value = $Wt_E\,2^E - Wt_S\,2^S$		100%	cannibalization loss of Backup's market share if both Lead & Backup reach market (0-100%)				

	All Phases					Remainder Starting in Phase 1 (phase being entered: 1 or 2A or 2B				
Phase:	1	2A	2B	3	Total	1	2A	2B	3	Total
PV Development Cost ($M)	10	25	100	300	435	10	25	100	300	435
n in Phase	25	50	100	300	475	25	50	100	300	475

	Efficacy					Side Effects				
	Prior	1	2A	2B	3	Prior	1	2A	2B	3
SD per Subject Studied			3	2	1		4	3	2	1
SD of Mean of Phase Data	2		0.4243	0.2	0.058	3	0.8	0.4243	0.2	0.058
Posterior Standard Deviation	2	2	0.415	0.1802	0.055	3	0.773	0.3719	0.176	0.055
Slope of Mean w/Lead Cpd.	0.5	0.5	1.0427	1.6247	0	1.5	0.3865	0.9482	1.59	0
Posterior SD w/Lead Results	2	1.7349	0.364	0.1802	*0.055*	3	0.6737	0.3264	0.176	*0.055*
P(regulatory success)	0.85	*Note: regulatory success/failure is not simulated; instead its probability derates (multiplies) market value.*								

Random Efficacy and Side Effect Levels Given Lead Compound Results, and Mean Phase Outcomes

	(Unknown)		(w/sunk cost)	Efficacy			Side Effects			
Sim. #	Efficacy	Side Ef.	ENPV	dev.	1	2A	2B	1	2A	2B	3
1	0.2747	2.8507	-638.7		0.1062	0.1654	0.168	3.9651	2.9906	3.168	2.879
2	0.0861	-0.649	-371.9		0.0513	-0.493	0.125	-0.707	-1.026	-0.628	-0.659
3	4.0705	-3.331	988.87		3.8226	3.8844	4.037	-3.603	-3.974	-3.079	-3.38
4	0.3958	0.5001	-383.3		0.7194	0.3986	0.379	0.5117	0.2542	0.549	0.463
5	1.453	2.4914	-441.3		2.2682	1.7709	1.456	2.8059	2.1729	2.081	2.457
6	-2.176	1.0001	-501.2		-2.613	-2.027	-2.158	0.2594	1.3509	0.749	1.03
7	4.8339	3.061	1634.5		4.9446	4.7865	4.877	1.9744	2.2526	2.981	3.037
8	-0.257	8.2641	-13430		0.2451	-0.068	-0.258	8.8692	8.1396	8.206	8.209
9	1.8064	5.251	-1756		1.8303	1.7259	1.787	4.657	5.2071	5.426	5.28
10	2.839	0.8392	499.2		2.595	2.86	2.785	1.5614	0.9658	0.693	0.89
1000	2.9919	-1.218	222.94		2.8684	2.9507	3.088	-0.639	-1.45	-1.039	-1.224
Mean	0.9988	0.9953	-638.6		0.9986	0.9989	0.999	0.9942	0.9936	0.995	0.993

Prior & Posterior Mean if Develop

	Efficacy			
Prior	1	2A	2B	
1	0.8111	0.3248	0.2023	0.1
1	1.2199	0.311	-0.307	0.0
1	2.4584	4.0516	3.9231	4.0
1	0.1788	0.4089	0.401	0.3
1	1.1606	2.5241	1.9455	1.5
1	2.1924	-2.46	-2.128	-2.1
1	2.3323	4.7431	4.7765	4.8
1	1.5523	0.4259	0.0465	-0
1	0.2406	1.7499	1.7315	1.1
1	0.153	2.599	2.799	2.1
1	1.6281	2.4829	2.8422	3.0
1	1.004	0.9992	0.9989	0.9

RESULTS

Fig. 2 illustrates random evolutions of an expected drug profile through development, based on information available through each phase. Fig. 3 shows how uncertainty decreases, helped by learning from L especially in the early phases. Simulation results (Fig. 4) show that in the example problem, higher correlations with L makes B less valuable, even not worth developing if both correlation and cannibalization levels are high, due to likely cannibalization losses if L succeeds, or additional failure of B in the case that L fails.

Simultaneous development of a second backup with identical inputs was evaluated as well. With >~35% cannibalization for each backup, any correlation with the lead compound resulted in negative incremental ENPV for the second backup. However, with 35% cannibalization, low correlations with L resulted in small positive incremental ENPVs.

Figure 2. Five of 1000 simulated changes in expected Efficacy and Side Effects from preclinical (Initial) to Phase 1, 2A, 2B, and 3 (asterisk is simulated true value).

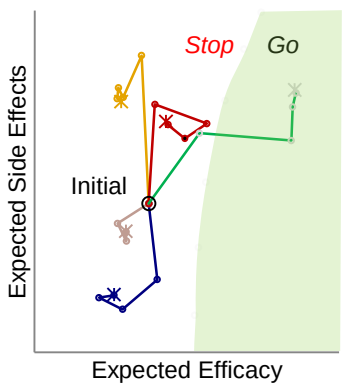


Figure 3. Decrease in standard deviation of Efficacy due to learning in each phase, for B before and after cross-compound learning with L. Note there is no Efficacy learning in Phase 1.

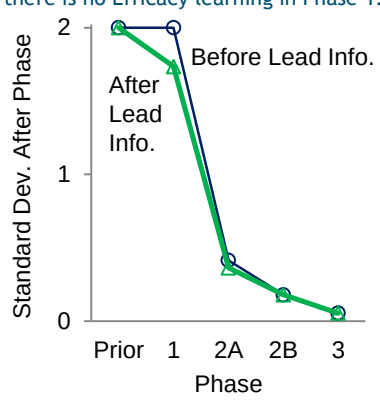
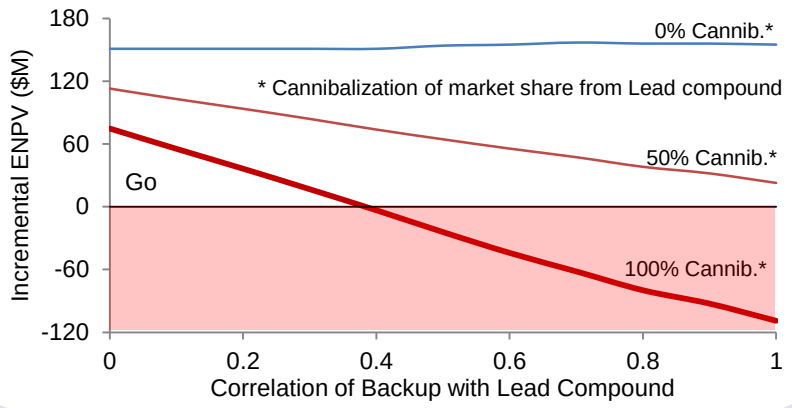


Figure 4. Incremental Expected NPV for B vs. its correlation with L, for 3 levels of market share cannibalization.



CONCLUSIONS AND RESEARCH DIRECTIONS

- Simulations of intra-compound and inter-compound learning can be used to optimize development of a lead compound together with backups, including the risk that a backup is so correlated with the lead compound that it will perform no better.
- Economic factors can and should be incorporated in the simulated decisions, such as differing remaining development costs and the loss of value when the backup must share the market with the lead compound.
- Thus simulations can properly weigh alternative development strategies—and may even be critical to making and justifying difficult backup compound decisions.
- To more rigorously account for downstream decisions and to evaluate many backups simultaneously, optimization techniques [3, 4] can be combined with simulation, though diminishing returns are expected from multiple backups [5].

Potential research directions include:

- Improve the go/no-go decision rule for each compound (with or without backups) to account for the option to stop development in the future, not just complete development vs. stop immediately.
- Consider the dose selection sub-problem explicitly.
- Incorporate more detail within each phase, in correlations, and in Bayesian learning.
- Include more detail in market value, e.g., its decline over time due to competition.

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