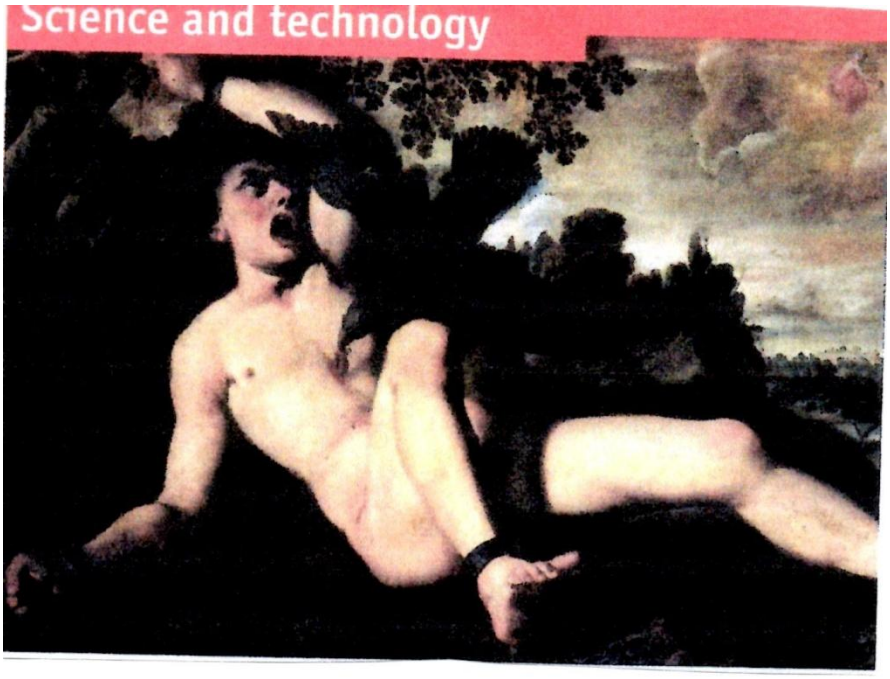
Sequential StemCell R&D[1]



The Titan picture shows Prometheus bound to a rock by Zeus, with an eagle feasting daily on his liver, which is regrown each night (cited in the *Economist*, July 2013, page 74 "Prometheus unbound" article on stem cell science and technology). A stem cell is a cell that can both reproduce itself and generate offspring of different functional cell types[2], so eventually perhaps such a Prometheus self-regenerated organ is possible.[3]

---

[1]© This case was prepared by Dean A. Paxson for purposes of class discussion and student coursework only, and not as an illustration of either good or bad business practices. The model is based on parts of "An Analytical Model for a Sequential Investment Opportunity" presented at the Real Options Conference in Tokyo, July 2013, by Roger Adkins and Dean Paxson, and uses as purely illustrative examples material from Stem Cells Inc. 10K 2012, and LifeTech Capital reports on Stem Cells prepared by Stephen M. Dunn May 20 and July 30, 2013. Since this paper extracts from those documents, and typically simplifies and/or amends the figures, often based on strict assumptions, it should not be used as a representation of those documents or opinions, or as the basis for investment decisions. Manchester Business School, Booth St West, Manchester, M15 6PB, UK. dean.paxson@mbs.ac.uk

[2] See Slack (2012).

[3] See Sklott (2010) for the story of HeLa immortal global cell regeneration.

Stem Cells Inc.

Stem Cells Inc. is engaged in R&D and commercialization of stem cell therapeutics. Their lead product is a CNS (central nervous system) program, developing applications for HuCNS-SC ® cells, their proprietary human neural stem cell product candidate. CNS includes the brain, spinal cord and eye, and Stem Cells is in clinical development for indications in all three organs. Specifically, for the brain, in October 2012, data from their Phase I clinical trial in Pelizeaus-Merzbacher Disease (PMD) showed evidence of progressive and durable donor cell-derived myelination for all four patients transplanted with HuCNS-SC cells. For the spinal cord, Stem Cells is conducting a Phase I/II clinical trial of HuCNS-SC cells in Switzerland for the treatment of chronic spinal cord injury. In February 2013, the data from the first patient cohort showed multi-segment gains in sensory function in 2 out of 3 patients. For the eye, a Phase I/II clinical trial was initiated in June 2012 for dry age-related macular degeneration (AMD). In addition, Stem Cells is engaged in numerous other applications and developments such as Alzheimer's, not considered in Figure 1 because clinical trials have not yet commenced.

Martin McGlynn, CEO, holds a Bachelor of Commerce degree from University College, Dublin. Ann Tsukamoto, EVP R&D, received a Ph.D. from UCLA, and did postdoctoral research with Dr. Harold Varmus (Amherst College graduate, and Nobel Prize winner) at UCSF.

Figure 1 is from reports on May 20 and July 30, 2013, of LifeTechCapital, which reiterated a Strong Speculative Buy with a 12-18 month Price Target of $4.50, (180% over the current stockmarket price of $2.50) based on projections from the "unprecedented results in human patients" for PMD and for Complete Thoracic Spinal Cord injury, because the Dry AMD trial is progressing, and Stem Cells recently received up to $19 million funding from CIRM for application of HuCNS-SC in treating Alzheimer's Disease. The California Institute for Regenerative Medicine (CIRM) was set up in 2001 with public money raised from state bonds precisely to invest in California companies doing stem cell research.

*For the forecast PMD sales for 2017, it is assumed that there will be around 87 applications to newly diagnosed cases per year in the U.S. and the same number for the rest of the world (ROW). The estimated initial selling price is $500,000 per patient for HuCNS-SC times 87 times a risk factor of 78% equals $33.93 million sales. An assumed price earnings ratio (PE) of

35 times the expected earnings per share (EPS) (net income divided by outstanding shares) in 2017 then times 16% (although LifeTechCapital states "discounted 50% for cumulative risks") equals a target price of $4.50, for a target market capitalization of $397 million, or almost double the current market capitalization (assuming the outstanding shares expected in 2017). Net book equity (total assets less liabilities) is $10 million.

Figure 1

StemCells Inc. Consolidated Income Statement ($ 000)										
	2009	2010	2011	2012	2013E	2014E	2015E	2016E	2017E	
Sales										Applications
HuCNS-SC PMD US								11,310	33,930	I*
HuCNS-SC PMD ROW								11,310	33,930	II
HuCNS-SC Spinal Cord ROW								3,750	15,000	III
HuCNS-SC AMD US									18,000	IV
HuCNS-SC AMD ROW									3,000	V
Other	994	1,418	1,221	1,368	1,042	1,216	1,668	3,285	4,413	
Total Sales	994	1,418	1,221	1,368	1,042	1,216	1,668	29,655	108,273	
Cost of Sales	261	168	215	263	258	305	350	4,341	10,810	
Gross Profit	733	1,250	1,006	1,105	784	911	1,318	25,314	97,463	
R&D	19,931	21,020	19,938	15,847	19,671	19,868	20,067	20,267	20,470	
G&A& Other	10,180	9,599	9,144	7,804	8,476	8,569	8,651	8,385	8,468	
Total Expenses	30,111	30,619	29,082	23,651	28,147	28,437	28,718	28,652	28,938	
Operating Income	-29,378	-29,369	-28,076	-22,546	-27,363	-27,526	-27,400	-3,338	68,525	
Other Income	2,352	4,116	6,748	-5,945	-1,627	-1,077	-1,077	2,153	2,153	
Net Income	-27,026	-25,253	-21,328	-28,491	-28,990	-28,603	-28,477	-1,185	70,678	
Shares Outstanding	10,606	12,330	14,188	28,824	46,729	66,291	72,920	80,212	88,233	
EPS	-$2.55	-$2.05	-$1.50	-$0.99	-$0.62	-$0.43	-$0.39	-$0.01	$0.80	
Balance Sheet 3/31/13							Current	Price	$2.50	
Assets			* HuCNS-SC PMD US					EPS	$0.80	
Current	18614		Number	Price				PE	35	
Fixed	1520		87	$500,000				Discount	0.1605	
Intangibles	4630		Risk	0.78			Target	Price	$4.50	
Total Assets	24764		Sales	$33,930		Target	Market	Cap	**$397,034**	
Liabilities	14556					Current	Market	Cap	**$220,583**	
Equity	**$10,208**									
Total Liabilities & Equity	24764						NAV Per Share		$0.12	

Stem Cells Inc. has issued employee stock options and various warrants over millions of shares. For accounting purposes, as of December 31, 2012, the expected volatility of Stem Cells shares is assumed to be 74.1%, presumably reflecting the recent historical volatility of Stem Cell shares.

The LifeTechCapital analysis does not directly consider the probability of failure over the four stages past the first stage Phase I clinical trials (the other three stages are Phase II, III clinical trials, then FDA approval and project launch), or the volatility of possible sales or earnings, or the ability to not proceed with further investments at any of the stages due to an insufficient

number of expected sales, unsatisfactory (from Stem Cells viewpoint) pricing, or actual and perceived future project failures.

Brach and Paxson (2001) incorporated jump processes (of a secretory protein gene discovery) in drug development investment evaluation procedures. Lee and Paxson (2003) provided an approximate solution for two phase sequential exchange (K for V) real options. Paxson (2007) extended this approach to sequential environmental restoration options allowing for a time-to-build for each stage investment. Cassimon et al. (2004) valued up to six stages of a new drug development process using the Geske (1979) compound option model, but assuming a specified time interval for each stage. Cassimon et al. (2011) included a technical jump process in the previous model.

Pennings and Sereno (2011) have provided illustrative numbers for a drug development program past Phase I over five years, with a probability of failure 20% in Stage 4 (furthest from completion), 10% in Stage 3, 5% in Stage 2 and 0% at the launch Stage. The following four-stage opportunity provides an illustration: (i) undertaking Phase II clinical trials, (ii) Phase III clinical trials, (iii) seeking FDA approval, including supplementary widespread clinical trials and (iv) product launch including manufacturing, education and marketing. (Various other illustrative numbers for failure possibilities of drug development programs are available from Tufts University). In valuing the project volatility for a drug development program, these authors used as a proxy the historical volatility of the project developer's share price.

Building on Adkins and Paxson (2011), Adkins and Paxson (2013) conceive a real sequential R&D investment opportunity as a set of distinct, ordered investments that have to be made before the project can be completed. No stage investment, except the initial stage, can be started until the preceding stage has been completed. Success at each stage is not guaranteed because of the possibility of a catastrophic failure that reduces the option value to zero. The project value is realized when all the stages have been successfully completed. Bearing in mind that a project can be composed of any number of distinct stages, multiple sequential investment opportunities are common amongst industries as diverse as oil exploration and mining, aircraft manufacture, pharmaceuticals and consumer electronics. Cortazar, Schwartz and Casassus (2003) describe three natural resource stages of a project (exploration and development) with technical success

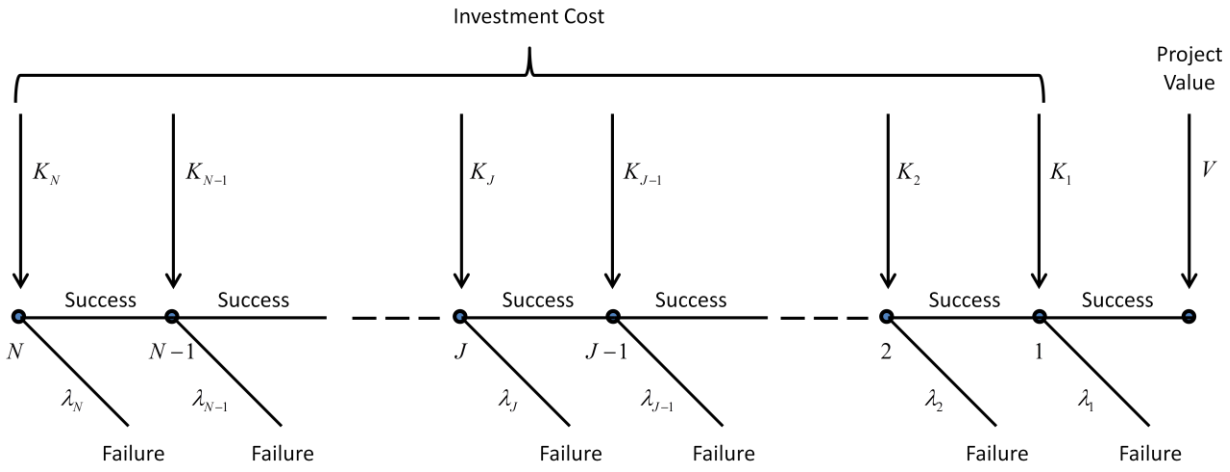
probability increasing over each phase, and then an extraction-production phase which is subject to commodity price uncertainty.

Sequential Investment Model

Suppose a firm is a monopolist in its market (perhaps due to achieving orphan drug status[4]), and is considering an investment project made up of a discrete number of sequential stages, each involving a separate investment cost. The project as an entity is not fully implemented and the project value not realized until all of the sequential stages have been successfully completed. Each successive investment stage relies on the successful completion of the investment made at the preceding stage.

A representation of the sequential investments process for a J=N stage project is illustrated in Figure 2. This figure reveals the ordered sequence of stage investments comprising the project. It also shows that after an investment, the possible outcomes are success and failure. If all the stage outcomes are successful, then the entire project is successfully completed and its value can be realized. However, there is a possibility of failure at each stage. Other forms of optionality, such as terminating a project before completion for any positive abandonment or alternative value, or using the products for other cures, are not considered.

Figure 2



[4] The U.S. FDA (Food and Drug Administration grants a finite time exclusivity right to develop and market certain orphan drugs, which have a very limited (rare) patient base.

The value of the project is defined by V. The investment expenditure made at any stage J is denoted by K_J for all possible values of J. Both the project value and the set of investment expenditures are treated as uncertain. It is assumed that they are individually well described by a process that has a constant drift θ (price escalation over time) and constant volatility σ, and there is a possible correlation between the project value and the investment cost $\rho_{V,K}$, and between the different investment costs $\rho_{K1,K2}$.

Different stages may have different factor volatilities and correlations. The risk-free rate is r, and the investment expenditure at each stage K is assumed to be instantaneous.

One-Stage Model

The stage $J=1$ model represents the investment opportunity for developing a project value V following the investment cost K_1, given that the research effort may fail totally with probability λ_1. The value F_1 of the investment opportunity at stage $J=1$ depends on the project value and the investment cost, so $F_1 = F_1(V, K_1)$. The real option value for the final stage is a two-factor power function:

$$F_1 = A_1 V^{\beta_1} K_1^{\eta_1}, \tag{1}$$

where β_1 and η_1 denote the unknown parameters for the two factors, project value and investment cost, and A_1 denotes an unknown coefficient.

The threshold levels for the project value and the investment cost signaling the optimal exercise for the investment option at stage $J=1$ are denoted by $\hat{V}_1$ and $\hat{K}_1$, respectively. The value matching relationship describes the conservation equality at optimality that the option value $\hat{F}_1 = F_1(\hat{V}_1, \hat{K}_1)$ exactly compensates the net asset value $\hat{V}_1 - \hat{K}_1$. Then:

$$A_1 \hat{V}_1^{\beta_1} \hat{K}_1^{\eta_1} = \hat{V}_1 - \hat{K}_1. \tag{2}$$

As well the first derivatives of equation 2 with respect to each factor can be expressed as:

$$A_1 \beta_1 \hat{V}_1^{\beta_1 - 1} \hat{K}_1^{\eta_1} - 1 = 0. \tag{3A}$$

$$A_1\eta_1\hat{V}_1^{\beta_1}\hat{K}_1^{\eta_1-1}+1=0 \tag{3B}$$

Also under these conditions $\beta_1+\eta_1=1$. So a characteristic additional equation is the quadratic equation:

$$Q_1\left(\beta_1,1-\beta_1\right)=\tfrac{1}{2}\sigma_1^2\beta_1\left(\beta_1-1\right)+\beta_1\left(\theta_V-\theta_{K_1}\right)-\left(r+\lambda_1-\theta_{K_1}\right)=0, \tag{4}$$

where $\sigma_1^2=\sigma_V^2+\sigma_{K_1}^2-2\rho_{V,K_1}\sigma_V\sigma_{K_1}$. Further, the threshold levels are related by:

$$\hat{V}_1=\frac{\beta_1}{\beta_1-1}\hat{K}_1, \tag{5}$$

with $A_1=\beta_1^{-\beta_1}\left(\beta_1-1\right)^{\beta_1-1}$. The solution involves solving four equations (2), (3A), (3B) and (4) for four unknowns, which is easily done with a spreadsheet solver. It is also convenient if $K_1=\hat{K}_1$, that is the V threshold is expressed as a multiple of the current estimated investment cost for that stage. Alternatively, it is easy to solve equation 2 and an equation combining 3A and 3B, since equation 4 has an analytical solution.

Multi-Stage Model

A similar analysis can be made for the Stage 2, 3 and 4 thresholds and real option values, with simplifying parameter values $\phi_1=\beta_1$, $\phi_2=\beta_2/\beta_1$, and so on. Decisions relating to the sequential investment opportunity are affected by three distinct sources of uncertainty, arising from an uncertain project value, uncertain investment costs and a failure probability at each investment stage. For an easy model solution the failure probabilities for the various stages have to obey the constraint $\lambda_1<\lambda_2<\lambda_3<\ldots$, which implies that the project becomes increasingly more likely to succeed as the stage approaches the completion stage-1. A secondary condition for a meaningful solution is that the options are exercised (investment expenditures made) according to their order, so that the stage-1 start is restricted by the stage-2 start, the stage-2 start by stage-3 start, and so on. This is achieved provided that the stage project value thresholds obey the constraint $\hat{V}_1>\hat{V}_2>\ldots>\hat{V}_J>\ldots$. This constraint implies that the ratio of consecutive investment cost thresholds complies with the lower bound LB_J, which tends to be more binding for stages

closest to completion stage-1 because the magnitude of LB_J is inversely related to the stage overall volatility σ_J.

Suppose that current V is in excess of all of the derived V thresholds. Then there is no advantage to deferring an investment cost for any stage, and the investments should be made immediately. Where V is less than the derived V thresholds, which depend on the expected investment cost at each stage, real option value exceeds the then realizable V-K. This occurs provided that the ratio of the investment cost thresholds for stages-one and –two, for example, exceeds the lower bound $LB_2 = \phi_2 (\beta_1 - 1)/(\phi_2 - 1)$ *that is* $\frac{K_1}{K_2} > LB_2$. This lower bound depends on the parameter values for the relevant uncertain factors at the two stages, the probabilities of stage failure, λ_1 and λ_2, and the risk-free rate.

Standard real-option theory tells us that the underlying volatility has a profound effect on the solution, that is the greater the overall volatility, the greater the real option value and the higher the V/K ratio threshold that justifies commencing the investment at any stage. Greater uncertainty implies waiting for that uncertainty being resolved, or alternatively the difference between V and K is sufficiently large so that the option value is equal to the then actual V-K, which is the value matching condition.

Numerical Illustrations

Here is a numerical illustration of a 4-stage sequential investment project using the base case specification in Table 1. The set of probabilities of catastrophic failure at the stages adheres to the requirement $\lambda_1 < \lambda_2 < \lambda_3 < \lambda_4$.

In the Stem Cell Template.xls, the inputs are entered in the red cells, with θ denoting the expected V and K drifts, here assumed to be zero, σ_V the expected volatility of the project value V, σ_K the expected volatility of the investment costs, here assumed to be 5%, the failure probability λ at each stage as indicated, with zero probability of failure at the last stage 1, and 40% at the early stage 4. The correlations between V and K and between all of the Ks are

assumed to be zero, and the risk-free interest rate is 6%. Current estimated V=100 is inputted into cell E18, and the investment cost at the early stage is only 1, while at the last stage K_1=1000 is inputted into cell E19. Thresholds for V are calculated assuming each of these investment costs still prevail when the investment decision is required at the appropriate time for each stage, that is the K threshold levels equal the current expected factor levels.

	A	B	C	D	E	F	G	H	I
1	INPUT	TABLE 1							
2	**Project value**			Input the correlations:					
3	θ_V	0			V	K1	K2	K3	K4
4	σ_V	25%		V	100%				
5				K1	0%	100%			
6	**Stage 1**			K2	0%	0%	100%		
7	θ_K1	0		K3	0%	0%	0%	100%	
8	σ_K1	5%		K4	0%	0%	0%	0%	100%
9	Failure probability: λ	0%							
10	**Stage 2**								
11	θ_K2	0		**Threshold Levels**					
12	σ_K2	5%		K1^	1000				
13	Failure probability: λ	10%		K2^	50				
14	**Stage 3**			K3^	10				
15	θ_K3	0		K4^	1				
16	σ_K3	5%							
17	Failure probability: λ	20%		**Factor Levels**					
18	**Stage 4**			V	100				
19	θ_K4	0		K1	1000				
20	σ_K4	5%		K2	50				
21	Failure probability: λ	40%		K3	10				
22	Risk-free rate	6%		K4	1				

	A	B	C	D	E	F	G	H
1		TABLE 2						
2	OUTPUT							
3	**Stage**	**Overall Volatility**	**ϕ**	**K^**	**V^**	**ROV**	**LB**	**K (J-1)/K(J)**
4	1	0.2550	1.9478	1000	2055.0638	2.9251		
5	2	0.4918	1.4294	50	796.2719	0.3608	3.15	20.00
6	3	0.7015	1.2176	10	612.0198	0.0989	2.40	5.00
7	4	0.8535	1.2760	1	310.8607	0.0268	1.01	10.00

Table 2 is the output automatically calculated, indicating that overall project volatility declines over each stage, with an indicated overall project volatility of only 25.5% at the last stage 1, compared to the 25% volatility for the project value V alone. Even for K_4=1, investment at stage 4 would not currently be justified until V exceeds 310, and there is very little real option value (ROV) at this stage. This no doubt arises due to the very large investment cost required at

the final stage, compared to the current V. Generally at the last stage, V would have to be somewhat more than double K to justify investment at that stage, or some 20 times the current V value. This is about the same ratio of V to K with standard parameter values especially for project value volatility, for a single stage investment opportunity. A rule of thumb is that even though V might exceed K_1, so using the net present value approach investment would be justified, considering the real option value, waiting is indicated if nothing is lost by waiting, and project value is volatile. Of course, these conclusions are based on a strict set of assumptions, which may not be realistic.

Note that $\hat{V}_1 > \hat{V}_2 > \hat{V}_3 > \hat{V}_4$ so that even if V reaches $\hat{V}_4$ justifying the investment at the initial stage 4, it does not imply that all of the other subsequent investments should be made immediately. Note also that $\frac{K_1}{K_2} > LB_2, \frac{K_2}{K_3} > LB_3, \frac{K_3}{K_4} > LB_4$.

Any sensitivity analyses on the solution should examine the impact of parametric changes on the option value and the exercise threshold, particularly for changes in the stage project value. A change in parameter values yields a corresponding variation in the lower bound conditions LB_J, which affects the option value compared to V-K and the ordering by magnitude of the project value threshold for the various stages.

Summary

Here is an easy spreadsheet solution for a multi-factor, multi-phase sequential investment process, where there is the real option at any stage of continuing, or abandoning the project development. This model is particularly appropriate for real sequential R&D investment opportunities, such as geological exploration in natural resources that may be followed by development and then production, or stem cell therapeutics development processes, where after an initial scientific discovery there are subsequent tests and trials required before production and marketing is feasible or allowed. Also, in these cases often there is a decreasing probability of project failure, as more information appears, and the efficacy and robustness of the original discovery are examined.

Increases in volatility for a single-stage investment opportunity are associated with greater option values and greater project value thresholds, ceteris paribus. In the main, this finding remains valid for a numerical illustration on a four-stage sequential investment opportunity. Increases in the project value volatility raise the option value at each stage, but differentially. The absolute effect is greatest for stage-1 when the project value is realized and least for stage-4 when the project is initiated.

The uncertainty due to possible catastrophic failure has the opposite effect. When an increase in the stage-1 failure probability occurs, this change produces an option value fall for each of the four stages. The corresponding impact on the exercise decision is to lower the stage-1 project value threshold, but to raise the stage-2, -3 and -4 thresholds.

Note some analysts prefer the practical real option approach and arrive at the adjusted enterprise value per share by substituting the aggregate ROV of all projects for the book value of intangible assets (a figure provided by accountants which reflects accumulated R&D costs, including acquisition costs, not the value of the R&D), thus deriving a new adjusted net asset value per share.

An alert CEO/CFO of a research driven firm might realize that greater project volatility increases the real firm value, while increases in the probability of catastrophic failure result in a decrease in the real firm value. So her business strategy might be to go for highly risky drug development processes in terms of eventual revenues (uncertainty in the number of patients and product prices) while focusing on programs with a low risk of complete failure.

LifeTechCapital did not provide all of the required inputs for the sequential investment option model. It might seem reasonable to assume base parameter values appropriate for a real option valuation of StemCell's combined five applications (counting U.S. and ROW separately) of HuCNS-CS using the estimates for 2017 in Figure 1, where V=(Net Operating Income + R&D) times (1-cost of sales) times an annuity factor for seven years (orphan drugs), where the cost of sales is the same ratio of sales as in 2017E. (Normally R&D is deducted from operating income, but in this case consider R&D as a discretionary investment.) Assume K_1 is one-fifth the 2013 expected R&D for each of the five applications for the initial stage, increasing by a factor of 5x,

10x and 15x at each subsequent stage. Assume the value volatility is proxied by the stock price volatility, σ_K=5%, and correlations are zero for V and K, and all the Ks, and estimates of the probability of failure at each stage are double the Pennings & Sereno estimates.

References

Adkins, R., and D. Paxson. "Renewing assets with uncertain revenues and operating costs." *Journal of Financial and Quantitative Analysis* 46 (2011), 785-813.

Adkins, R., and D. Paxson. "An analytical model for a sequential investment opportunity." presented at the Real Options Conference, Tokyo July 2013.

Brach, M. A., and D. A. Paxson. "A gene to drug venture: Poisson options analysis." *R&D Management* 31 (2001), 203-214.

Cassimon, D., P. J. Engelen, L. Thomassen, and M. Van Wouwe. "The valuation of a N.D.A. using a 6-fold compound option." *Research Policy* 33 (2004), 41-51.

Cassimon, D., M. De Backer, P. J. Engelen, M. Van Wouwe, and V. Yordanov. "Incorporating technical risk in compound real option models to value a pharmaceutical R&D licensing opportunity." *Research Policy* 40 (2011), 1200-1216.

Cortazar, G., E. S. Schwartz, and J. Casassus. "Optimal exploration investments under price and geological-technical uncertainty: a real options model." In *Real R&D Options*, D. Paxson (ed.), Oxford: Butterworth-Heinemann (2003), 149-165.

Geske, R. "The valuation of compound options." *Journal of Financial Economics* 7 (1979), 63-81.

Lee, J., and D. A. Paxson. "Approximate valuation of real R&D American sequential exchange options." In *Real R&D Options*, D. Paxson (ed.), Oxford: Butterworth-Heinemann (2003), 130-148.

Paxson, D.A. "Sequential American exchange property options." *Journal of Real Estate Finance and Economics* 34 (2007), 135-157.

Pennings, E., and L. Sereno. "Evaluating pharmaceutical R&D under technical and economic uncertainty." *European Journal of Operational Research* 212 (2011), 374-385.

Sklott, R. *The Immortal Life of Henrietta Lacks*, Random House, New York, 2010.

Slack, J. *Stem Cells: A Very Short Introduction*, Oxford University Press, Oxford, 2012.

Case Questions:

1. What is the threshold for V at each stage which would justify making the investment and proceeding to the next stage?
2. What is the real option value at each stage for each application, and what is the initial ROV today for the estimated 2017 overall V?
3. What is the real option value of StemCells, compared to the current market value and the LifeTechCapital target market value?
4. What are the advantages and disadvantages of the PE (net present value equivalent) and real option analysis?