R&D of Biotech Start-ups in Global Financial Uncertainty

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Abstract—As the research background, there is a high possibility of difficulty of research and development (R&D) continuity for biopharmaceutical start-ups due to the deep valley of deficit especially since the financial crisis in 2008. The research question is; how is it possible to promote the continuity of R&D projects of biotech start-ups at the trade-off situations between the passive attitudes of venture capital from financial markets and the continual progress of life science researches as aptamer, siRNA, iP cells, and personal medicine. As the research approach, the effectiveness of real options is promising for applying to overcome the valley of deficit. We will examine the gap between the passive waiting option and the active learning option. Another research objective is to find the evidence of the flexible value of compound chooser option for switching chance between two types of projects, that both have independently each negative NPV, one is the base case and the other is inserting the indication expansion for the drug development. We could confirm the possibility of positive NPV by just creating only selection chance from these both alternatives.

I. INTRODUCTION

As the research background, it is high possible for biopharmaceutical start-ups to continue the Research and Development (R&D) for deep valley of deficit since 2008 financial crisis.

Then the research question is; how can they keep continuing the R&D project under the trade-off between the passive reluctance to invest by venture capital (VC) and capital market investors and the continual progress of basic research of life science as aptamer, iP cells, siRNA, and personal medicine.

As main concepts, the start-ups are defined as the portfolio of real options from the business opportunities based on entrepreneurs’ ideas [7]. On the other hand, the real options are investment decision tools to utilize the asymmetry idea of return and risk of financial options as simultaneous risk hedge against downside risk and upside opportunity, for irreversible investment in real assets as R&D projects under uncertainty [5].

II. PRESENT CONDITION OF BIOTECH FINANCING

A. The Japan’s IPO condition of biotech start-ups

The Japan Biotechnology Council was established by 20 companies of main biotech start-ups and venture capital firms on July 1st in 2009, in addition to existing Japan Bio-industry Association, for the proposal drawing to government to support biotech start-ups, because there are so far very fewer social systems to support the roles of biotech start-ups on commercializing the basic research findings at life science than that of the USA. There are 26 public biotech start-ups in Japan as of September 1st in 2010. There were recent IPOs by 4 companies in 2008, by 4 companies of JCL Bioassay, Tella, CanBas, and D.Western Therapeutics Institute in 2009, and by 1 company, Cell Seed as a regenerative medicine company at JASDAQ, new market on March 16th, 2010. Thus, there is an increasing tendency of IPO number of biotech start-ups along with improving the eco-system supporting the growth and survival of biotech start-ups.

But there are some cases that VC firms are making the biotech start-ups that are poor in R&D money to buy back stocks from the reason of expiration of funds, in the severe condition of IPO markets due to financial crisis. On the other hand, Takara Bio and R-Tech Ueno are making the positive ordinary profits from the contract manufacturing for other companies. OncoTherapy Science is also making the positive ordinary profits from March 2009 by multiple out-license agreements as each anti-cancer peptide vaccine agreement with Otsuka Pharmaceutical in January 2008, and with Shionogi in February 2009, and a pharmaceutical agreement for central nervous system with Otsuka in June 2010. This company has started the phase I/II clinical trial for angiogenesis factor inhibitor, OTS102 based on an anti-cancer drug target VEGFR (vascular endothelial factor receptor) 2 for the milestone improvement.

Thus the number of public companies is only about one twentieth in about 500 domestic biotech start-ups, less than one fifth in the USA, where there are about 300 public in 1500 biotech start-ups. But there are some companies that can make sure enough R&D money by strategic partnerships as license agreements.

B. The situation of biotech finance in the USA

At the end of 2008, US biotech industry made the positive net income $3.7billion (B) for the first time in history since 1976 with the cash and equivalents $75.6B, the sales/revenue $99.5B and the R&D cost $23.7B in terms of statistics of public biotech companies [1]. Afterwards in the end of 2009, it was still at the exit or matured stage over the break-even point with the increased positive net income $4.3B, the cash and equivalents $747B, the sales/revenue $91.6B, and the R&D cost $19.3B [2].

In the end of 2009, the industry market capitalization is $346B, with the decrease of $58B from previous year. But there are each increase of total capital raised $8.8 B to $18.9 B, and total partnership capital $16.9B to $63.9B. For instance, total capital raised change from IPO (Initial Public Offering) is $0.5B increase to $1.1 B, from follow-on is $4B
increase to $5.7B, from PIPE (Private Investment in Public Equity) is $0.6B increase to $1.6B, from debt is $3.5B increase to $6.3B, and from VC is $0.3B decrease to $4.2B.

Within 2009, there were at least 10 cases of partnerships in $B level, as the $1.9B cooperative research on drug discovery between PTC Therapeutics and Roche, the $1.5B license on pain-killer between Nektar Therapeutics and AstraZeneca, and the $1B license agreement on obesity drug between Amylin Pharmaceuticals and Takeda Pharmaceutical. Thus there are the increase trends in risk averting type of financing.

As the ecosystem for biotech start-ups in 2009, there were mega mergers and acquisitions (M&As) as Genentech acquired by Roche with additional $46.8B payment, Wyth bought by Pfizer with $68B, and Schering-Plough merged by Merck with $41B. Behind such movement, big pharmaceutical firms are worried about patent cliff of blockbuster drugs as Lipitor and Singular in their pipelines. Then they are getting biotech R&D ability and biotech drugs on the market as Avastin, Enbrel, and Remicade from such M&As. It seems their policy change from chemical to biotech companies.

Additionally, the stock prices of such big pharmaceutical firms as Pfizer and Merck had significantly declined during December 2007 and early 2009 as main “Lehman Shock” period. Otherwise, the stock prices of Gilead Sciences and Celgene were relatively stable during financial crisis. This means the sustaining of robustness to financial crisis and fluctuation of capital market based on the expectation for innovative technology. And before the acquisition, the whole company value of Genentech was estimated at $100B, bigger than that of Pfizer which had not acquired Wyth yet. Furthermore recently the stock prices of Human Genome Sciences, Dendreon and Targacept have jumped up reflecting the smooth progress of their pipelines.

Thus the biotech start-ups’ ability of technology development can show the robustness to financial crisis. Big pharmaceutical firms are exposed to the pressure of transformation from chemical to biotech firms from regulation reinforcement, patent cliff of their blockbuster drugs, price discount demand, and introduction of generic drugs. Big biotech firms are relatively robust and considering the financial crisis as the chance rather than the crisis. And biotech start-ups have technology development capability but lack the financial robustness. Hereafter the partnership and M&A between biotech start-ups and big pharmaceutical or biotech firms are forecasted for considerable increase. For example, there can recently be found the large scale of such partnerships even in phase I testing or preclinical stage different from past typical types in phase II testing stage.

III. SWITCHING OPTION INTEGRATING WAITING OPTION AND LEARNING OPTION

The existing models by Dixit [4] and Brennan & Schwartz [7] on the waiting option have emphasized the hysteresis effect by the sunk cost as irreversible investment under the uncertainty. That is, the higher the uncertainty and sunk cost, the stronger the effectiveness of maintaining the present pathway.

Assuming $\mu$ business growth rate, $\rho$ CAPM (Capital Asset Pricing Model), $\rho \mu > \rho \sigma$ the relationship of both, $\sigma$ volatility, $c$ variable cost of operation, $e$ sunk cost of the entry time, and $x$ sunk cost of the exit time, each trigger criterion of Marshal’s investment $C_I$ and abandonment $C_A$ is

$$C_I = c + \rho e$$
$$C_A = c - \rho x$$

These criteria mean the optimal behavior is the entry if the market value of asset $P > C_I$ (thus $P_H = entry price$) and is the exit if $P < C_A$ ($P_L = exit price$). And within the range of both criteria, like hysteresis curve the optimal behavior is to continue the business operation even in deficit when the path is $P_H \rightarrow P_L$, but not to enter the business even in positive profits when the path is $P_L \rightarrow P_H$. Thus each path shows the inertia of sustenance influenced by sunk cost (Figure-1).

Additionally, the size of interval depends mainly on interest rate and sunk cost at the steady-state as mean recurrence. Basically, the robustness in investment irreversibility can be kept even without uncertainty. But, the function of the waiting option is passive, and has the disadvantage as the difficulty of preventing the opportunity loss during the interval.

As another idea, including the learning option as the search in whether Do or Stop must be decided through the switching options, it is more highly possible to shorten the wasteful waiting time and to utilize the more valuable
opportunity. However, the search has, in this case, 2 parameters as the investment of sunk cost and the up ratio of the underlying asset value or project value.

First of all, Base Case is the fixed investment project. That is sequential compound option including the waiting option or call option of Do (Market Introduction) and the put option of Stop. Secondly, a predetermined project including Indication Expansion is the sequential compound option consisted of the call option of Do after Search and the put option of Stop, in flexibly integrating Search as the predetermined phase without considering the flexibility between Do and Search (Market Introduction).

Then Switching Option is the option of a project which can flexibly select between the base case project (Do) and the predetermined indication expansion project (Search) at the point time after the phase three of clinical trial in the drug development process. It can selectively use the learning option having both the information on the up ratio of the underlying asset value by Search as the indication expansion and the irreversible sunk cost, according to the conditional necessity in addition to Do (market introduction) and Stop.

One of the guideline tools is the Selective Map in the switching option (Table-1). The option value can increase if Search (learning option or Indication Expansion) is inserted between Stop (put option) and Do (Market Introduction or call option). The higher the up ratio of project value by Search, the more the expansion room for rationality of Search without immediately shifting into Do (Market Introduction). And the higher the up ratio of project value (a priori or a posteriori), the more the search rationality, instead of initial decision of stop (Fugire-2).

Main parameters in the Selective Map are the volatility and the up ratio of project value by search (Table-1). That is, the higher the volatility, the more Do (Market Introduction or call option) and Search (learning option) both can increase the project value. The implication of Search and a learning option increases with volatility, favorable condition for higher binominal multiplication of up ratio of project value, and up ratio of project value by Search.

These concepts as decisions of business entry or project abandonment, continuity of R&D as a learning option, and decision deferring can be expected to apply to the decision making for drug development process at biotech start-ups.

IV. APPLICATION OF REAL OPTIONS TO DRUG DEVELOPMENT

Here we apply Sequential Compound Switching Option to the drug development project at a biopharmaceutical start-up, based on an assumed case.

A. Assumption

As two projects of drug development, we classify the base case that it files New Drug Application or Biologic License Application immediately after clinical studies and the indication expansion case that it shifts directly for the indication expansion phase rather than straightaway launching the product on the market. As both projects are subject to the same 20 years patent expiration limit, the equivalent period becomes shortening if the indication expansion project is selected. And both projects are assumed that they have each negative risk adjusted Net Present Value (raNPV). That is, if each stage of drug development is independent, the probability of success (POS) of each stage can be multiplied. By summing the expected present value of cash-out at investment stage and the expected present value of cash-in after tax during the product on the market reflecting the possibility of acceptance by FDA (Food and Drug Administration), the raNPVs of both projects are negative, then the conditions are not appropriate to invest without any additional modifications.

For example, the raNPV of base case is (from Figure-3)

$$raNPV_B = \sum raPV[CF(\ln)] - \sum raPV[CF(Out)] = 23.519 - 23.527 = -0.008 < 0$$

Similarly the raNPV of the indication expansion project is (from Figure-4)

$$raNPV_I = 7.051 - 19.451 = -12.400 < 0$$
Then on this assumption, whichever the base case of drug development or the indication expansion for adding new search is selected, the rNPV is always negative. If this rigorous decision as the present investment or the never investment from now to forever is made, both investment alternatives are rejected.

### B. Application of Real Options

Next, the drug development is practically the sequential compound option as milestone type of flexible decision making process where each stage needs decision whether continuity or stop is suitable for next stage. This is correct for the base case or the indication expansion. Additionally if it is possible to shift for the other development mode, this is called as the sequential compound switching option or...
sequential compound chooser option [3]. Thus we can classify 3 investment types.

Firstly Figure-5 is the base case project as the benchmark without doing the indication expansion, showing the result of application of the sequential compound option to the stages from preclinical trial to market introduction. Each stage of this project is indicating the schedule. From the top in this figure, first block is showing the evolution of project value as the underlying asset. Next block is the evolution of compound option value from 5th option at the top in this block to 1st option at the bottom.

Figure-6 is the expanded part of the area covering the whole value of this compound option as the 1st option in Figure-5. Even if starting this project by investing in preclinical trial stage, the ENPV (Expanded Net Present Value) is zero, while this value received the contribution from the option. That is, unless there is the milestone type of compound option, raNPV as the expected NPV was negative at the base case. Therefore although the expected NPV was improved from negative value $-0.008$ in the case of rigid decision making to zero through the flexibility of decision making on continuity or cancellation at each stage, the value is still not yet positive. Then this condition cannot show the validity for investment without any new modification.

Next, the project which takes a risk to shorten the period of the product on the market by inserting the indication expansion must pay the opportunity cost as the lost revenue if should it launch the product on the market immediately after finishing clinical studies. But this is the aggressive additional investment type in the reduction of uncertainty in search of market expansion. As the additional assumption, the sequential compound option has the binomial process with the up ratio $= 1.1$ and the down ratio $= 1/(1.1)$ for drug value at the indication expansion, is shown as Figure-7. However as Figure-8 shows, under this assumption, the ENPV $= 0$. That is, the NPV as investment criterion was improved from negative raNPV $-12.400$ as the expected present value with rigid decision making to zero due to the flexibility of decision making based on milestone. But it did not still get the positive value, and then it is not possible to find the evidence for investment promotion without any changes.

However, under the same assumption, only if making the sequential compound switching or chooser option with such flexibility as switching option just to select which mode between the base case or the indication expansion case is better, the ENPV as a sort of NPV can be improved into the positive value (Figure-10). The summary of the value evolution of this sequential compound switching option is shown in Figure-9. That is, each mode of both cases cannot support the investment because the ENPV $= 0$. However just after inserting the flexibility of the mode selection in the common process, the integrated investment criterion is ENPV $> 0$, then it is possible to send GO sign for this project. Figure-10 is the guideline on option selection along with the evolution of project value calculated by MS Excel. If following this policy, and calculating the validity of the start of project retroactively by the method of backward induction, the ENPV can be positive.

In short, even if each independent case project is worthless for investment separately, just by adding the autonomous discretion of selecting each mode in the development process according to the condition, this investment scheme able to switch the mode can be accepted. Next, we examine factors and means for this integrated project to further improve the investment performance.
Figure-5 Sequential Compound Option (Base Case)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Drug Tested</th>
<th>Pre-Clin</th>
<th>Ph-I</th>
<th>Ph-II</th>
<th>Ph-III</th>
<th>Ph-IV</th>
<th>Ph-V</th>
<th>Ph-VI</th>
<th>Ph-VII</th>
<th>Ph-VIII</th>
<th>Ph-IX</th>
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<th>Ph- XI</th>
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<td>PVI</td>
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<td>1.09920</td>
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<td>1.49920</td>
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<td>PVI</td>
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<td>1.49920</td>
</tr>
</tbody>
</table>

Figure-6 The Condition of ENPV=0 at Base Case

Payoff = max(S-X, 0)

3068
## Figure-7 Sequential Compound Option of the Indication Expansion

### Table 1: Option Value

<table>
<thead>
<tr>
<th>PV(t)</th>
<th>142.0571</th>
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<tbody>
<tr>
<td>Value</td>
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<tr>
<td>1.0000</td>
<td>31.5406</td>
</tr>
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<td>31.5406</td>
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<td>1.0002</td>
<td>31.5406</td>
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<td>65.4807</td>
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### Table 3: Option Value

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<td>1.0002</td>
<td>65.4807</td>
</tr>
</tbody>
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**Figure-8**

*Figure-8 Sequential Compound Option of the Indication Expansion*
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### Figure-8 The Condition of ENPV=0 at Indication Expansion

<table>
<thead>
<tr>
<th>Stage</th>
<th>Drug-Disc</th>
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<th>Pre-Clin</th>
<th>Ph I</th>
<th>Ph II</th>
<th>Ph III</th>
<th>Ph IV</th>
<th>Ph V</th>
<th>Ph VI</th>
<th>Ph VII</th>
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<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
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<tr>
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</tr>
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</table>

### Figure-9 The Evolution of Option Value at Sequential Compound Switching Option

![Diagram](image)

Figure-10

### Figure-10

Figure-10

Figure-10

Figure-10

Figure-10

Figure-10
C. Characteristics of analyzed results

The base case is considered as a sequence of binomial decision making either on business continuity or cease, to prevent the technological or economical uncertainty by the investment in the development process. On the other side, the mode of indication expansion is evaluated as a sort of decision deferring to search for the opportunity, without shifting into immediate operation after the clinical studies. When mapping from both the binomial value level of underlying asset after the clinical studies and the change of mode selection, this relationship can be understood from the long area of effectiveness of selection deferring as the indication expansion, in addition to the effects of upside opportunity utilization and downside risk hedge (Table-1).

That is, the binomial value change level in the phase III clinical test stage on time point 8 in Figure-11 is equivalent to the vertical axis in Table-1. Along with the up ratio of the indication-expansion project value at the given volatility, each rational selection is equivalent to the shift stage of up ratio of the indication expansion value at the horizontal axis.

As the implications of map, when the up ratio is not so high, following each rational alternative is the product on the market rather than additional search if the product market value is favorably high (close to “a” of binomial value level in Table-1), is the stop if oppositely the product market value is unfavorably low (close to “i” of binomial value level in Table-1), and is explorable decision-deferring as the indication expansion if the area is the mid range between them (condition “f” of in Table-1). However as the up ratio becomes large, while the immediate stop option is still effective, the scope of search thrust becomes enlarged rather than the rush launching of the product on the market on the favorable chance expanding condition. If the up ratio expands further, this table shows the exploration or the decision deferring as the indication expansion is rational even in the unfavorable condition. That is, as the increase of up ratio supports additional search efforts even in the unfavorable condition. Thus basically as the attractive potential expands, the reasonable opportunity of search efforts also enlarges.

**TABLE-1 SELECTION MAP AMONG BASE CASE, INDICATION EXPANSION, AND STOP**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<td>Stop</td>
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<td>Stop</td>
<td>Stop</td>
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</tr>
</tbody>
</table>

Incidentally, even in the mode of the market introduction, as the volatility $\sigma$ enlarges, there is an opportunity to improve the business value by itself (Figure-12). However, if we can preliminarily make index of value increase rate of the indication expansion, by using the binomial value change level on time point 8 at the endpoint of phase III clinical studies (Figure-13) and option selection boundary for volatility (Figure-14), it becomes easier to make decisions for selection among market introduction, indication expansion, or stop. For example, Figure-15 shows, for both “e” and “f”, the value evolution of each M (Market Introduction) and I (Indication Expansion) along with option shift stage based on volatility. There we have to select the option with higher business value between the Market Introduction and the Indication Expansion for each stage of option shift for both “e” and “f”. Furthermore, by adding the line of business value zero for stop option where the scrap value equals to zero because of not out-license, we can rationally select the best decision among three alternatives.

**Figure-13** Evolution of Business Value in Volatility at Market Introduction
Thus the map in Table-1 can be expected to show each highest project-value area in three options of the base case, the indication expansion, and the stop by cross return surface among three axes of the binomial stage, the option selection shift stage, and the project value.

V. CONCLUSION

A sequential compound switching option can be created by combing above two projects, firstly the market introduction project which can enjoy longer period of sales, once the project succeeded in launching the products on the market, and secondly the indication expansion project which has the learning options with decision deferring in addition to two functions as utilizing upside chances and hedging against downside risk while the sales period will be shorten by the additional stage of the indication expansion. This sequential compound switching option can be considered as a method to cope with the irreversibility at investment from a sunk cost under uncertainty. Especially if a project is a promising R&D with the derivation potential at the indication expansion, additionally unless there is any room for simultaneous market introduction, it is more rational to invest the sunk cost in the exploratory ventures from a long-term perspective than the market introduction decision from a short-term point of view. Since high volatility includes not the only risk but also the opportunity, the validity of additional investing in exploration can exist within some extent even in unfavorable condition rather than the decision of stop from just waiting and seeing. In particular, this is also dependent on investment efficiency in exploration to actively reduce the uncertainty. It is the function of the R&D as a learning option to actively reduce the opportunity loss of a waiting option.

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