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JAPAN'S HEALTH-CARE QUALITY AND APPLICATION OF REAL OPTIONS TO THE FLEXIBLE DECISION-MAKING STRATEGY FOR BIOTECH START-UPS

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ABSTRACT

Japan has an aging population as a near future critical problem. One of start-up functions is more rapid commercialization of life science than large corporations do. However, its innovation depends on the inefficiency as the fecundity and many deaths. In Japan, the number of biotech start-ups exceeded more than 300, mainly due to the national reform of the system of technology-transfer from universities. At the same time, the expansion of M&A activities of pharmaceutical corporations can increase the partnership opportunity with them. But so far, only more than ten biotech start-ups achieved the IPOs. Recently the real options theory has attracted attentions about the function of flexibility against uncertainty with start-up activities. Then, this paper will especially examine the survival strategy or approach of drug-discovery start-ups during the Death-valley as a negative cash flow period, from a viewpoint of real options analysis.

Keywords: Real Options, Death-valley strategy, and Biotech start-up.

Introduction

As study backgrounds, there are the production concept, biotech innovation, and start-up. Firstly for an analytic framework, this paper wishes to try a high-dimensional expansion of an input-output system concept, from the standard manufacturing or operations to the product development and further to the incubation. Secondly, the innovation of biotechnology seems to be useful for the quality of healthcare service to aging population:

Q = f(a product/service for customer satisfaction, a system stably producing high quality output, an environmental infrastructure to promote a system evolution, and a luck for an opportunity increase of innovation). Thirdly, a start-up seems a critical method of technology transfer to fulfill a vacancy between the medical schools as investment targets for basic researches by the government and the large pharmaceutical corporations concentrating major resources on the clinical development.

Even if a promising drug discovery is depending on a basic research, it needs a long term and huge cost of development. Then such a start-up is risky project, because its resources are limited. So how can an innovative drug-discovery start-up survive and overcome this critical death-valley, the negative CF (Cash Flow) period?

As main keyword definitions for objective re-evaluation of entrepreneurship instead of a cultural perspective, firstly a biotech start-up is defined as a decision making system about

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risk management, in transforming a research idea of life science into a company. Secondly death-valley is definable as a critical threshold period for affecting the success or failure of a radical innovation.

MOT (Management of Technology) is a framework for a guideline and system for reasonable decision making on the innovative and promising but risky developmental investment as the commercialization of results from basic research. In particular, even if operations management for manufacturing and service did traditionally have the static and incremental improvement measures for productivity as quality, cost and delivery time, it did not so for scales as risk and CF on innovative and radical investment under uncertainty. Therefore as MOT has an aspect as an investment of development projects or patents in transforming a technical idea into a new product or service, operations management and finance had always a necessity to be integrated at innovation. In this article, based on MOT which means production of a sort of service as development, we will examine a theoretical trial on integration between operations management and finance, and a methodological ROA (Real Options Analysis) meaning the application of concepts and tools of financial derivatives to real assets.

As research objectives, through seeking a more clearly decision-making guideline on reasonable tolerance to the negative NPV with an innovative project, we will examine the method that can make a drug-discovery start-up survive during an early critical period and the financial valuation technique to be effective for promotion of the risky but innovative project.

Trial for General Theory of Operations Management including Innovation and Service

As precede main studies, Sipper (1997) on operations management as supply-chain management, Kenny (1986) for biotechnology as emerging industry with academic-private cooperation, and Mun (2003) on Real Options Analysis are useful and representative. But, a connection between operations management and finance seem to be necessary for production of the innovative idea, service, or company. Especially, for survival of start-up as a technology transfer mechanism during death-valley period, the valuation of patent or start-up firm is considered to be possible by using ROA. Then, first of all, theoretical scheme will be examined for new combination of existing elements.

In exploring such approach, this paper examines a theoretical trial of the integration between operations management and finance in the development of a health-care service product, through the application of method of ROA (Kulatilaka, 1988) as a conceptual tool for applying the financial derivatives (Black, 1973, 1976; Merton, 1973; Ross, 2003; Hull, 2006) into the real assets. The research presented in the following section, aimed to gain insights to guide decision-making about reasonable tolerance levels to a negative net present value (NPV) in an innovation project of case study. The method used promotes the survival of a drug discovery start-up during an early critical period, and the financial valuation technique (Rubinstein 1976; Margrabe, 1978; Copeland, 1982; McDonald, 1986; Teisberg, 1994) deemed as effective for the promotion of a risky, but innovative project.

Input-Output Mode (Phase Transition)

When physically transforming input into output, phase transition is possible within a physical energy frontier of 3 phases of Atom, Bit, and Life. In addition, the added value of physical transformation is measured with a common standard of CF at both sides of input and output (see Fig.1). The output/input ratio in specific time horizon is less than 1 in the case of energy, but must be equal or more than 1 () in CF, for survival or growth. But there still remains a problem how to value a long term of high risk but high return project in which NPV is a minus value in the short term, but can become a plus value finally. 1e"*NPV*

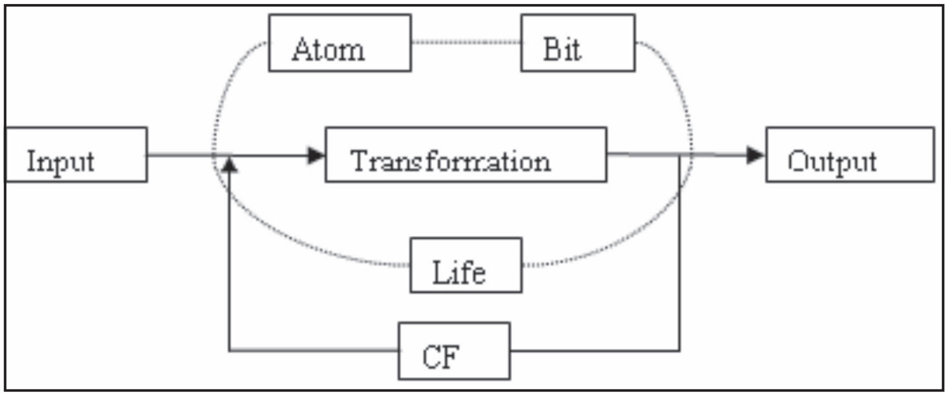

Figure 1: Input-output Model (Phase Transition)

Type of Input-Output System

As each typical pattern of Atom, Bit, Life, or CF, there can be indicated; the steady-state operations based on a manufacturing function transforming materials into products as Atom, the entrepreneurial added value breakthrough based on an imagination function transforming resources into intangible service with sensitivity as Life, the commercial innovation based on a business model transforming an innovative but conceptual idea into a technically feasible information as Bit, and the investment decision maximizing a positive NPV through transforming CF to CF. Even if it is assumed that the manufacturing is included in the service due to finally appealing to the sensitivity of customers, the decision making to control the investment risk in innovation becomes necessary for reasonable productivity improvement within a physical energy frontier.

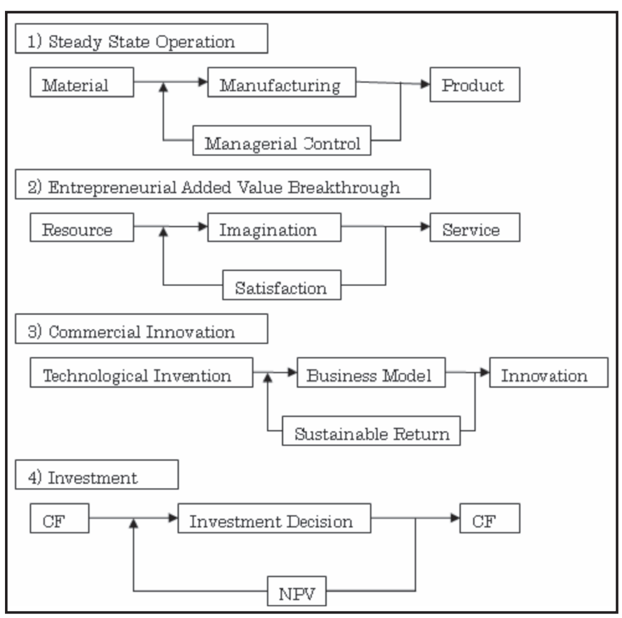

Figure 2: Types of Input-output System

Change Level of Transformation

As each type of productivity improvement in transformation of an input-output system, according to change level, there is, at first, the incremental improvement in an existing transformation system as production system converting materials into a product or service, secondary, the product development transforming an idea into a new product as a radical model change of output, and thirdly, the founding or incubation for transforming an idea into a new firm as innovation of system in itself.

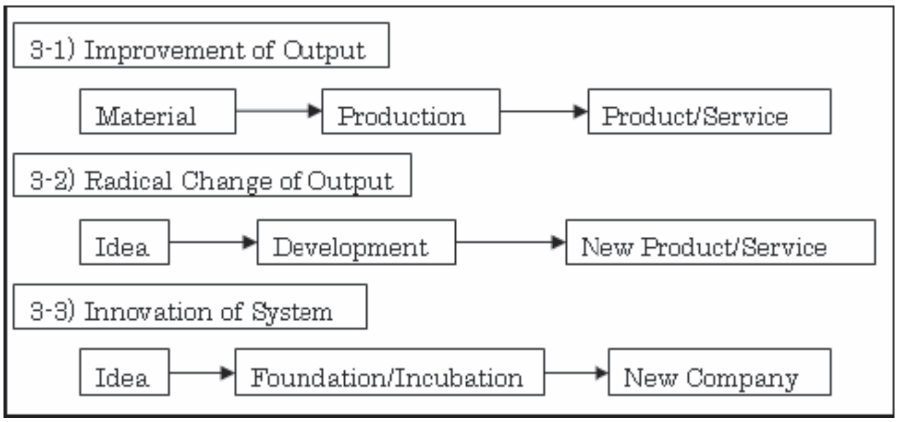

Figure 3: Change Level of Transformation

Drug Development Partnership

As for the drug development to be connected directly with health care service, it becoming the tendency that development is done as the open innovation among some organizations rather than by only one company. For example, in the U.S.A., about 50% of basic research budget are invested into medical schools. Otherwise, large pharmaceutical corporations are seeking more R&D money by M&A and concentrating the resources on later stage of the process as clinical development. The development situations become resemble even in Japan. Then, in this situation, because a blank stage occurs between the basic researches and the later stage of drug development, even for a meaning to mediate such a gap, the application development by biotech start-up including drug discovery becomes inevitable to promote commercial technology transfer.

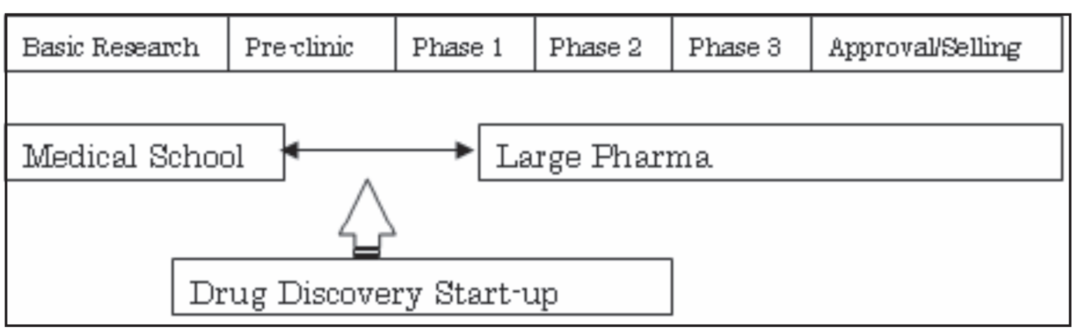

Figure 4: Drug Development

Japan's Population Aging and Quality Sustaining of Healthy Care Service

Population Dynamics

From Japan's population aging, men's average life span is 78.32 years old and women's is 85.23 years old, and a distribution ratio of both genders' equal and more than 65 years old is 18.5%, and its counterpart of equal and less than 14 years old is 14.2% in 2002 (Yano, 2002). Hereafter, even if the second baby boomer period faced the peak, the following problems are still forecasted as the population's aging behind prolongation of an average life span, the declining birthrate by women's society involvement, and the decrease of the whole population. In particular, the aging of population suggests future importance of healthcare industry as a service.

Healthcare Industry as Service

To understand the weight of healthcare industry, from a change of the distribution ratio of work force by industry, the distribution ratio of the first industry (the agriculture, forestry, and marine products industries) in the country suddenly fell after 1955. The second industry (the manufacturing, construction, and mining industries) radically raised the ratio since 1955 to 1970, but afterwards has continued the stable period. The third industry including service (the other industry) has raised the ratio constantly after 1949. As a result, as of 2000, each distribution ratio becomes the first industry 5.1%, the second industry 30.7% and the third industry 64.2% (Yano, 2002).

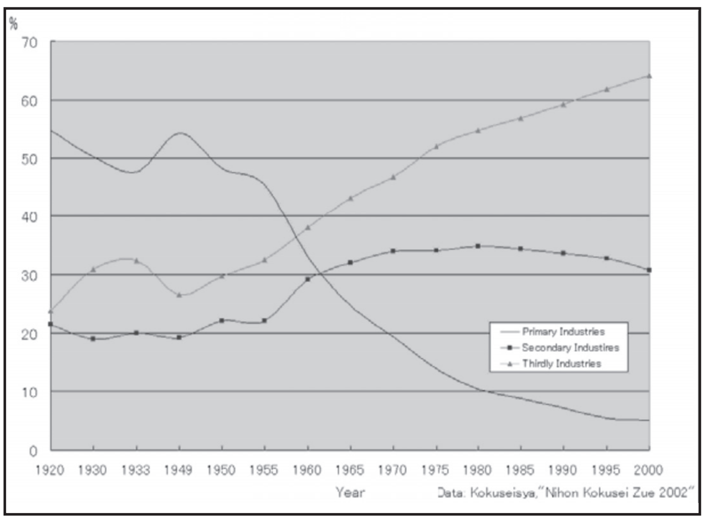

Figure 5: Trend of Japan's Employee Ratio by Industy

The service industry has deep relationship with the third industry. When looking at the distribution ratio by industry of 43,786,000 work force of the third industry in 2001, the three main sub-industries are the service 40.3%, the retail, wholesale, and restaurant business 40.2% and the traffic and communication business 8.6% respectively (Yano, 2002).

By the business area distribution ratio of 12,990,000 workers in 2001, main 5 categories are the health care 24.2%, the education 17.1%, the professional service 14.1%, the cleaning and hair salon 9.5%, and the social insurance and welfare 9.4%. In this way, the healthcare has the possibility to grow up into a main industry, reflecting social needs, even in the service, of which weight of work force is increasing.

Drug Expenditure in the Healthcare

According to the average household expensesÿ331,199 JYN/Month ÿin 2002, the weight of health care expenditure is only 3.2%. However, by the trend of household expenses for 1980-2002, the health care that rose by 1.84 times in 2002 and is anticipated still increasing in the future attracts attention, in addition to the education rapidly rising by 2.19 times by 1992 and afterward being relatively stable, the housing rapidly arriving at a peak to 2.16 times in 1996, then making a sudden drop, and the traffic and communication at the top by 2.16 in 2002 and still of a rise tendency. Thus, a rise of health care is expected in the household expenses.

At a breakdown of medical cost of 30.2 Billion JYN in 2001, drug cost is only 10.8%, in addition to the outpatient treatment costs 42.4%, the hospitalization treatment cost 38.2%, and the dentistry treatment costs 8.6%. However, for a change of 1980-2001 of medical cost, the shift of drug cost rises to 19.93 times in 2001, while a change of each treatment costs of outpatient, hospitalization, and dentistry remains within a range of 2.39-2.03 times. In particular, the drug cost recently soars since 1990.

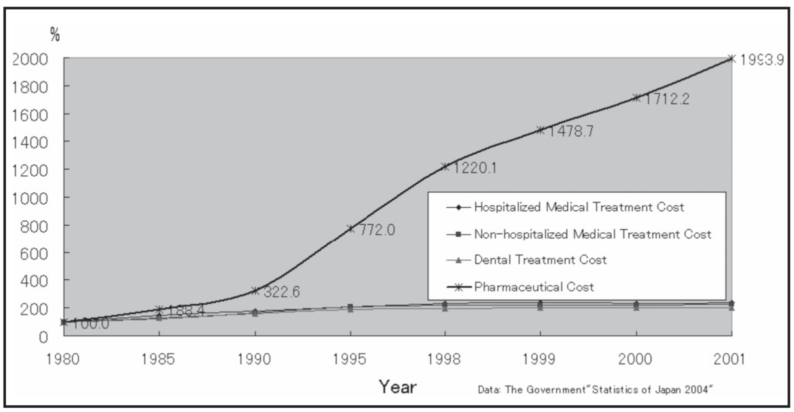

Figure 6: Trend Of Medical Cost

Drug Development Cost

As for the rise of drug cost under the review of standard prices for drugs, the relationship with the new drug development cost is considerable, apart from merely quantitative increase. Both numbers of the application of initial clinical trials during 1993-2001 and each year's application of clinical trials have the falling tendencies (Jiho, 2003). For example, the application of initial clinical trials fell from 160 cases in 1993 to 43 cases in 2001. The application of clinical trials likely fell from 1200 cases of 1993 into 434 cases in 2001 (Jiho, 2003). In particular, the hollowing out of domestic clinical trials is occurring, with the regular price re-calculation of new drugs in 1996, the official announcement for new GCP (Good Clinical Practice) at International Conference of Harmonization (ICH) in 1997, and the full enforcement of new GCP and the receiving expansion of foreign clinical data in 1998 (Jiho, 2003). Reflecting hollowing out of clinical trials of new drugs, the average R&D cost of domestic top ten sales firm rises from 26.3 Billion JYN in 1990 to 48.8 Billion JYN in 2000, and the ratio of R&D cost to sales of these rises from 10.8% in 1990 to 14.3% in 2000 similarly. This means that one of challenges is to restrict the rise of R&D cost.

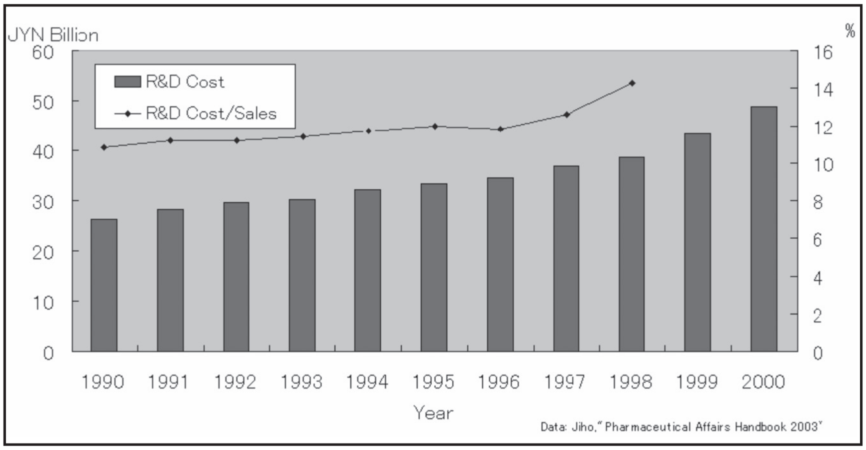

Figure 7: Average R&D Cost Of Pharmaceutical Companies (Japan's Top Sales)

Thus, in order to response to the coming aging, restrict the remarkable rise of drug development costs, and quickly transfer the technology from basic research of life science invested increasingly and considerably by the government into much higher quality level of drugs or medical technologies, it is more urgent matters to pay attentions to start-ups able to challenge a high risk R&D even to niche markets rather than large pharmaceutical firms only focusing on block buster drugs for big markets.

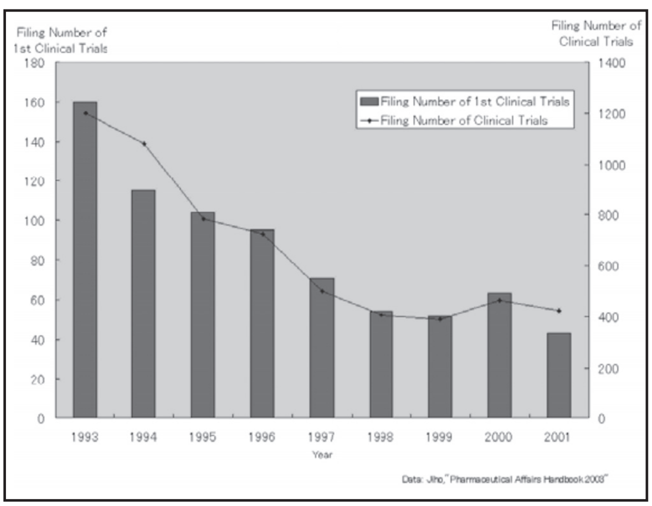

Figure 8: Trend Of Clinical Filing

A Pioneering Case of Academic Biotech Spin-off: AnGes MG

It is said that about 300 companies could achieved IPOs among about 3000 biotech start-up in the U.S.A., and further the number of companies being in the black seems limited to a few dozens of top sales rank. In Japan, the situation is such that only 14 companies achieved IPOs in the about 300 biotech start-ups. In this way, Japan's biotech start-ups are in the process of aiming at catch up to the U.S.A.

Table 1: IPO Biotech Start-ups

Company Name	Date of IPO	Capital Market	Date of Foundation	Business
MBL	Feb.2,1996	JASDAQ	Aug.1983	Clinical Diagnostics
Intec Web and Genome Informatics	Dec.19,2000	Mothers	Mar.1989	Bioinformatics
PPS	Feb.28,2001	Hercules	Jul.1985	DNA Extraction Device
AnGes MG	Sep.25,2002	Mothers	Dec.1999	Gene Therapy
Trans Genic Inc.	Dec.10,2002	Mothers	Apr.1998	Knockout Mouse
MediBic	Sep.18,2003	Mothers	Feb.2000	Bioinformatics
Medinet	Oct.9,2003	Mothers	Oct,1995	Medical Treatment Support Service
Onco Therapy Science	Dec.9,2003	Mothers	Apr.2001	Genetic Cancer Drug Discovery
Soiken	Dec.18,2003	Mothers	July,1994	Test of Functional Foods
DNA Chip Research	Mar.19,2004	Mothers	Apr.1999	DNA Chip
Sosei	Jul.29,2004	Mothers	Jun.1990	Drug Development
LTT Bio-Pharma	Nov.25,2004	Mothers	Apr.198	DDS
Takara Bio	Dec.7,2004	Mothers	May,1995	Gene Therapy
Effector Cell Institute,Inc	Mar.29,2005	Centrex	Jun.1999	Drug Discovery Support Device/Service

In such Japan's biotech public companies, at the summarized information of AnGes MG as a pioneer, employee number is R&D 50, development of research reagents 13, and other management sections 19, among 82 as number of employees (89 as of December 31, 2005). And the company value is about 61.2 Billion JYN.

Three cases of the clinical trial stage in HGF gene therapy projects have alliances with Daiichi Pharmaceutical of Daiichi-Sankyo group. In NFºB decoy oligo projects, two cases of pre-clinical trial stage have alliances with Seikagaku, and one of pre-clinical trial has partnership with Goodman. A HVJ-E vector project, as a chemical reagent on the market for gene analysis, has cooperation with Ishihara Sangyo. For all other projects, potential for partners are open.

Table 2: R&D Projects

Project	Target	Development Status	Corporate Partner
HGF Gene Therapy	Periphery Vascular Disease(Japan)	Phase 3	Daichi Pharmaceutical (Daichi-Sankyo Group)
HGF Gene Therapy	Periphery Vascular Disease(USA)	Phase 2	Daichi Pharmaceutical (Daichi-Sankyo Group)
HGF Gene Therapy	Coronary Heart Disease(USA)	Phase 1	Daichi Pharmaceutical (Daichi-Sankyo Group)
HGF Gene Therapy	Pearkinson's Disease	Pre-clinical	Openness
NFκB DecoyOligo	Atopic Dermatitis	Pre-clinic	Openness
NFκB DecoyOligo	Psoriasis	Pre-clinic	Openness
NFκB DecoyOligo	Arthrosis Rheumatism	Pre-clinic	Seikagaku
NFκB DecoyOligo	Osteoarthritis	Pre-clinic	Seikagaku
NFκB DecoyOligo	Vaso-reconstriction Prevention	Pre-clinic	Goodman
HVJ-E Vector	Reagent for Genetic Analysis	On the Market	Ishihara Sangyou
HVJ-E Vector	DDS	Pre-clinic	Openness

According to the business model, as the input side, this company in-licenses the master patents as basic research results from Osaka University Medical School where a medical professor as founder and a science adviser belongs to, and pays royalty of the compensation. Otherwise, as the output side of process, the business model is specialized in application research, with seeking the upfront money, the fund for development assistance, the milestone money with development alliances through stages such as the pre-clinical trial, clinical trial, and sale approval, and after the sale of products, the royalty by out-license of the sale right.

As main financial indices for 2001-2005, the sales of 1300.6 Million JYN of 2001 rises to 2430.4Million JYN in 2005, but otherwise, the net income of 142.6 Million JYN in 2001 falls in -1905.1 Million JYN in 2004. Then, this drug-discovery start-up faces typical death-valley, as negative cash flow period. But as the market evaluates the technological potential, the cash on hand of 1299.4 Million JYN of 2001 expands into 5179.1 Million JYN in 2004.

Consequently, if drug-discovery start-up faced the death-valley due to its innovative project, the method to appropriately evaluate a technology or a project becomes necessary for continuing a long-term R&D in spite of net loss.

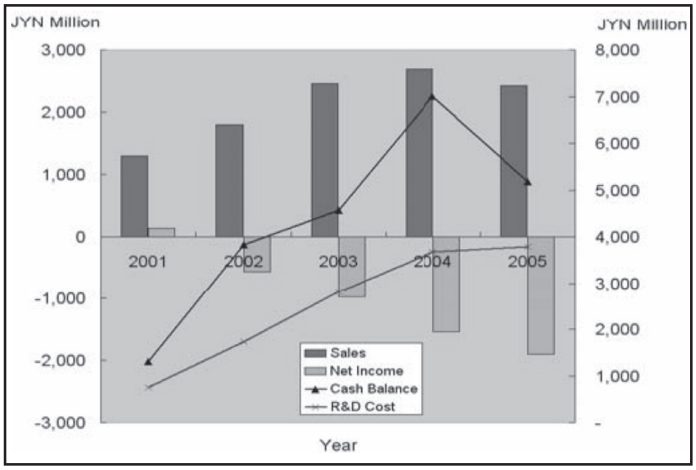

Figure 9: Main Financial Indices of Anges Mg

Model Building for Overcoming the Death-Valley with ROA

As one of the techniques to cope with death-valley, ROA attracts attentions.

DCF model

We start from building a hypothetical DCF model that assumed a start-up as an academic biotech spin-off facing death-valley.

It is supposed that the time horizon is five years, and sale forecasting is calculated by annually multiplying a ratio of 1.37 of 2001 sales/2002 sales by 2430.4 Million JYN of 2005 sales after this year of AnGes MG, for high volatility reflecting potential characteristic of ROA.

Referring Mun's DCF model and considering competition environment as state variables, input data include the competition intensification with rivals, the competition between company projects, and maturity in a market of own product (Mun 2003). Selling cost as commission is assumed as 0.25 of sales, and operating cost is as 0.30 of a gross margin. In order to continue a drug discovery project, it is supposed that an investment of 1100 Million JYN annually is needed, and depreciation 700 Million JYN, and payment interest 100 Million JYN are annually constant.

Based on a business model assumed here, a decision variable is given as the royalty for patents in-licensed from a university. In a contract agreement between both parties, the royalty rate is set with a range of minimum 5% and maximum 10% in the first two years, a range of the minimum 10% and maximum 15% in next two years, and a range of 10% and maximum 20% in the last year. Tentative values for a decision variable are provided as 7.5% in the first two years, 12.5% in next two years, and 15% in the last year.

As the account titles reflecting CF as return, tax shield of royalty processed as expense is considered for the intellectual assets formation to own company's balance sheet, in addition to depreciation. For calculation of NPV, the discount rate of CF as return is given 15%, and the discount rate of inside investment is given risk-free rate 5% as capital cost from an already decided policy of a constant investment of every year. As a result, in this business model, NPV becomes -306 Million JYN or rejected possibility of the investment decision in regardless of sales rise tendency. But since the volatility from logarithm approach to return CF is 9.59 %

and relatively large, there is prospective room of a risk hedge effect depending on an optional design.

Input Parameters	
Discount Rate (Cash Flow)	15.00%
Discount Rate (Impl. Cost)	5.00%
Tax Rate	50.00%

Results	
Present Value (Cash Flow)	¥4,457
Present Value (Impl. Cost)	¥-4,762
Net Present Value	¥-306

Year	**2006**	**2007**	**2008**	**2009**	**2010**
Revenue	¥3,330	¥4,562	¥5,009	¥5,500	¥6,039
Adjustment to Revenue	¥200	¥456	¥902	¥1,293	¥1,751
Cost of Revenue	¥833	¥1,141	¥1,252	¥1,375	¥1,510
Royalties Paid	¥250	¥342	¥626	¥688	¥906
Gross Profit	¥2,048	¥2,623	¥2,229	¥2,145	¥1,872
Operating Expenses	¥614	¥787	¥669	¥644	¥562
Depreciation Expense	¥700	¥700	¥700	¥700	¥700
Interest Expense	¥100	¥100	¥100	¥100	¥100
Income Before Taxes	¥634	¥1,036	¥760	¥702	¥510
Taxes	¥317	¥518	¥380	¥351	¥255
Income After Taxes	¥317	¥518	¥380	¥351	¥255
Non-Cash Expenses	¥825	¥871	¥1,013	¥1,044	¥1,153
Cash Flow	¥1,142	¥1,389	¥1,393	¥1,395	¥1,408
Implementation Cost	¥-1,100	¥-1,100	¥-1,100	¥-1,100	¥-1,100

Adjustment to Revenue:	**2006**	**2007**	**2008**	**2009**	**2010**
Competitive Effects	1.00%	2.00%	3.00%	4.00%	5.00%
Cannibalization Effects	5.00%	8.00%	10.00%	12.00%	14.00%
Market Saturation	0.00%	0.00%	5.00%	7.50%	10.00%

Adjustment to Revenue:	**2006**	**2007**	**2008**	**2009**	**2010**
Royalty Rate	7.50%	7.50%	12.50%	12.50%	15.00%
Minimum Rate	5.00%	5.00%	10.00%	10.00%	10.00%
Maximum Rate	10.00%	10.00%	15.00%	15.00%	20.00%
Maximum Total Rate	50.00%		Minimum Total Rate		20.00%

Volatility Measure:					
Logarithmic Returns		0.1962	0.0029	0.0009	0.0097
Volatility	9.59%				

Modification from Mun (2003)

Figure 10: DCF Model

Two types of Real Options by Binomial Lattice Model

Here, by option value of strategic flexibility (Bower, 1970; Pindyke, 1991; Dixit, 1994; Trigeorgis, 2000), the possibility is examined to change a minus value of original NPV into a positive expanded NPV. The types of real options dealt are a sequential compound option and a chooser option, both based on binomial lattice model (Cox, 1976).

Sequential Compound Option

The option treated here is the compound option as option of options (Geske, 1979), consisted of second option derived from underlying assets, and first option derived from second option. As a unit period for a half year, it is a milestone form of options consisted of the first option with 3 years of maturity, and the second option with later two years of maturity (the fifth year of expiration from start).

Input Assumptions

Present Value of Future Cash Flows (asset)	¥4,457
Implementation Cost (cost)	¥4,762
Volatility (volatility)	9.59%
Maturity (maturity)	5
Risk-Free Rate (rf)	5.00%
Binomial Lattice Steps (steps)	10
Second Phase Implementation Cost (cost 2)	¥238
Time to Second Phase (time 2)	6

Intermediate Calculations

Time Step (dt)	0.50
Up Jump (up)	1.0702
Down Jump (down)	0.9344
Risk-Neutral Probability (prob)	0.6695

Results

Binomial Lattice Result(ENPV)	¥649

Underlying Asset Lattice

¥4,457	¥4,769	¥5,104	¥5,462	¥5,846	¥6,256	¥6,695	¥7,165	¥7,668	¥8,206	¥8,782
	¥4,164	¥4,457	¥4,769	¥5,104	¥5,462	¥5,846	¥6,256	¥6,695	¥7,165	¥7,668
		¥3,891	¥4,164	¥4,457	¥4,769	¥5,104	¥5,462	¥5,846	¥6,256	¥6,695
			¥3,636	¥3,891	¥4,164	¥4,457	¥4,769	¥5,104	¥5,462	¥5,846
				¥3,398	¥3,636	¥3,891	¥4,164	¥4,457	¥4,769	¥5,104
					¥3,175	¥3,398	¥3,636	¥3,891	¥4,164	¥4,457
						¥2,967	¥3,175	¥3,398	¥3,636	¥3,891
							¥2,772	¥2,967	¥3,175	¥3,398
								¥2,590	¥2,772	¥2,967
									¥2,420	¥2,590
										¥2,262

Equity Lattice

¥838	¥1,023	¥1,236	¥1,479	¥1,752	¥2,054	¥2,386	¥2,747	¥3,138	¥3,561	¥4,020
	¥528	¥669	¥839	¥1,040	¥1,273	¥1,540	¥1,838	¥2,165	¥2,520	¥2,906
		¥282	¥376	¥495	¥646	¥831	¥1,054	¥1,316	¥1,611	¥1,933
			¥115	¥162	¥229	¥320	¥443	¥606	¥818	¥1,083
				¥26	¥41	¥62	¥95	¥146	¥223	¥342
					¥0	¥0	¥0	¥0	¥0	¥0
						¥0	¥0	¥0	¥0	¥0
							¥0	¥0	¥0	¥0
								¥0	¥0	¥0
									¥0	¥0
										¥0

Valuation Lattice

¥649	¥820	¥1,023	¥1,258	¥1,525	¥1,822	¥2,148
	¥352	¥471	¥624	¥813	¥1,041	¥1,302
		¥137	¥199	¥287	¥413	¥593
			¥23	¥35	¥53	¥82
				¥0	¥0	¥0
					¥0	¥0
						¥0

Modification from Mun (2003)

Figure 11: Sequential Compound Option

The exercise price of the second option is the present value of a total investment amount of money of a DCF model to get final result of the project. And the exercise price of the first option is arbitrarily supposed as 5% of the exercise price of the second option. Then, at each last node of the second option, whether the difference of the exercise price of second option from the project value as underlying asset corresponding to each state is above or equal zero is the decision standard. In addition, it is a decisive factor of a payoff for each last node of the first option, whether a difference of the value of the second option corresponding to the node from the exercise price of the first option to get it by exercise is positive or not. Furthermore, the initial value of the first option is the payoff to choose bigger value between the holding value of the first option as the discounted expected value calculated backward from the value just after target and the return of immediately exercised time as the difference of the exercise price of the first option from the initial value of the responding second option. This is the expanded NPV by this sequential compound option.

For example, the second option value at the highest and last node is

$$C_{2u^{10}} = \max[u^{10}V_o - X_2, 0]$$

$$\max[1.0702^{10} \times 4457 - 4762,] \qquad (1)$$

$$\approx 04020,$$

Where volatility s=0.959 a unit period of the lattice model *dt = 0.5*, up step-size u=exp (s√dt) = exp (0.0959√0.5) ≈ 1.0702, an initial value of underlying asset V_o*= 4457*, an exercise price of second option = present value of accumulated investment amount of money=4762.

The payoff of second option at the second period from final and highest node, from comparing discounted expected value with exercised performance by hedge portfolio method, is

$$
\begin{aligned}
C_{2u^9} &= [u^9 V_0 - X_2, \{pC_{2u^{10}} + (1-P)C_{2u^9 d}\} \\
&\quad \exp(-rjdt)] \\
&= \max [8206 - 4762, (0.6695 \text{ X } 4020 \qquad (2) \\
&\quad +0.3305 \text{ X } 2906) \text{ X } 0.9753] \\
&\approx \max [3444, 3561] \\
&= 3561,
\end{aligned}
$$

where down step-size d=1/u=exp(-σ√dt)≈0.9344, risk neutral probability $p=\frac{\exp(r_f dt)-d}{u-d}$

$=\frac{\exp(0.05 \text{ x } 05.5) - 0.9344}{1.0702-09344} \approx$ and risk free rate r_f = 0.05.

From this result, the value of second option at initial node is

8382=*C*. (3)

Otherwise, the valuation of first option at final period and highest node is

$$
\begin{aligned}
C_{1u^6} &= \max [C_{2u^6} - X_1 0] \qquad (4) \\
&= \max [2386\text{-}238,0] \\
&= 2148.
\end{aligned}
$$

The payoff of first option of initial node, from hedge portfolio method and the characteristic that underlying asset of first option equals second option, is

$$
\begin{aligned}
C1 &= \max [C2\text{-}X1\{pc1u=(1-p)C1d\} \exp (-rf\ dt)] \\
&= \max [838 - 238, (0.6695 \text{ X } 820 + 0.3305 + 352) \\
&\quad \text{x } 0.9753] \\
&\approx 649 \text{ (Mllion JYN)}
\end{aligned}
$$

This C_1 is responsible to the expanded net present value (ENTV) by such sequential compound option, because of reflection for exercise price with newly enjoying first option in addition to the value of second option by investing in the exercise price to project return as underlying asset. 1*C*1*X*2*X*

Thus, for this sequential compound option, a milestone form of option is set with two periods. As a result, while being one point of estimate method, the expanded NPV reflecting the flexibility with an option could be changed into a plus value from a minus NPV of original project. However, although the exercise price of second option was supposed here as the present value of a total accumulated investment amount of money for the convenience of a calculation, its time value essentially should be changed with each node location.

Chooser Option

Next, it is tried to design the option to choose or chooser option as the scheme of combination of simple options as the expansion, contraction, and abandonment options (Myers, 1990), and including the case of non exercising options.

Comparing with previous sequential compound option, total periods of binomial lattice model were reduced from 10 to 5. Then a unit time was changed into dt=1 As the result, some basic parameters became u=1.1007, d=0.9085, and p=0.7429. The change of underlying asset also became into each middle range value of the final and highest node from $u^{10}V_0$ = 8782 to u^5V_0 = 7200, and of the final and lowest node from $d^{10}V_0$=2262 to d^5V_0=2759 respectively. 1.1007,*u*=0.9085,*d*=7429.0=*p*8782010=*Vu*720005=*Vu*2262010=*Vd*275905=*Vd*

Firstly, at the expansion option as a component of the chooser option, expansion factor=1.38, exercise price=600, secondly, at the contraction option, contraction factor=0.88, exercise price = 2000, and finally at the abandonment option, exercise price = 5930. Among these simple options, expansion option is call option, and contraction and abandonment option are put options.

For ENPV of a two lattice model, after calculation of total return of cash flow through comparing each simple option's payoff at final nodes, the present value of total accumulated investment amount of money is subtracted.

The payoff of chooser option of binomial lattice model at final and highest node is

C = max [Expansion Factor x u^5V_0-Expansion Cost, Contraction Factor X u^5V_o

+ Saving, Salvage]

= max [1.38x7200-600, 0.88+2000, 5930]

= max [9336, 8336, 5930]

= 9,336.

And the payoff at second form final and highest node, including holding option, is

C_{n4} = max [Expansion Factor x u4Vo - Expansion Cost,

Contraction Factor X U4Vo + Saving,

Salvage, {pC_{u5} + (1-P)C_{u4d}} exp (-$r_f$dt)]

= [1.38x6541-600,0.88x6541+200,5930,

(0.7429x9336+0.257x7601)x exp (-0.05 x1)]

= max [8426, 7756, 5930, 8456]

= 8456

Similarly, the selection tree of each option is also showed. The decision tree of option selection locates each selection guideline as the expansion option for favorable conditions, the abandonment option from early time for adverse conditions, and the contraction option for middle range between the expansion and the abandonment options.

As a result, the initial option payoff as return cash flow not including investment cost equals 5955 Million JYN, the option value which subtracted the present value of underlying asset from the value equals 1498 Million JYN, and the expanded NPV which subtracted the present value of the accumulated investment 4762 Million JYN from the initial payoff becomes 1192

Million JYN.

Therefore, even in a chooser option reflecting flexibility, the expanded NPV changed into a plus value from the original negative NPV by one point estimation method after parameter setting including the policy of each option exercise responding to conditional variables.

However, both the sequential compound option and the chooser option here are based on one-point estimation method, still being necessary to inspect the more general-purpose or versatile propriety by simulation.

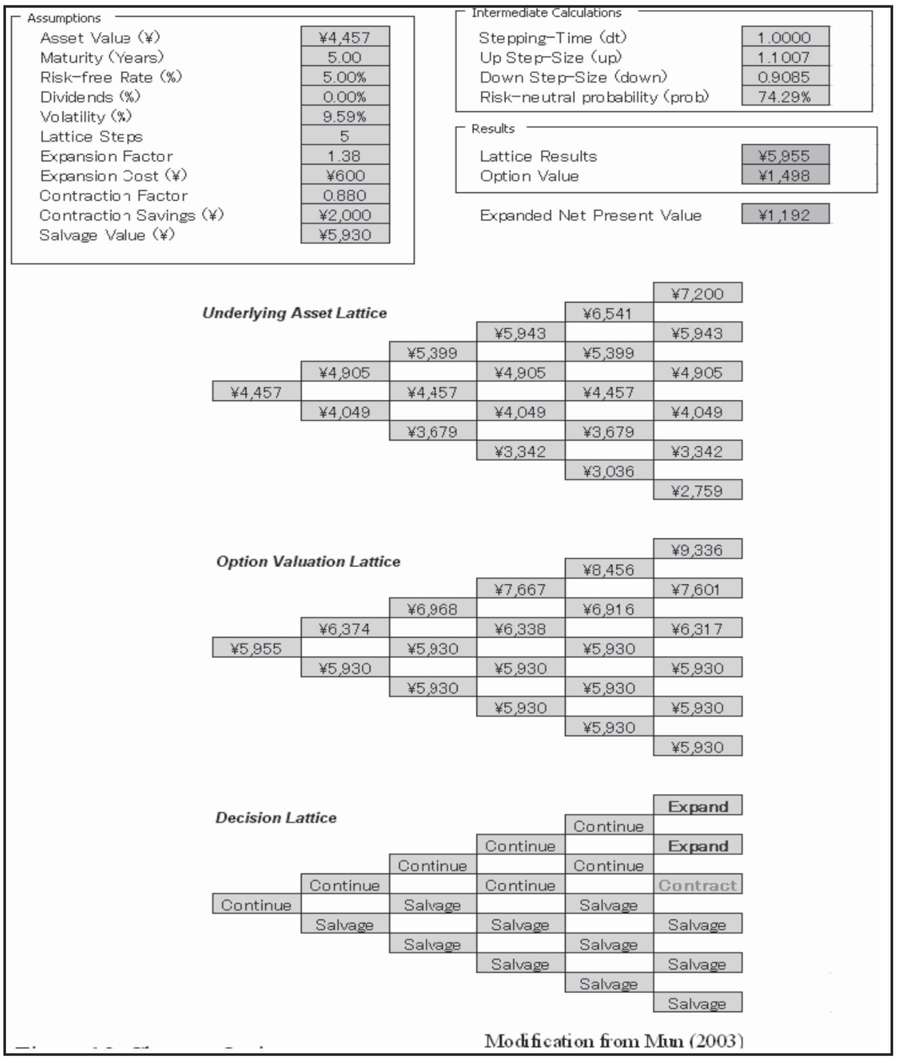

Figure 12: Chooser Option

Evaluation of Option Value by Simulation

Continually, as a result of 100,000 trials of Monte Carlo simulation with Crystal Ball (Mun, 2003; Boyle, 1977), the volatility based on original DCF model became a lognormal distribution. The comparison of distributions among the NPV of a project without options, the ENPV of a project having a sequential compound option and the ENPV of a project to have a chooser option become a following figure 6.14. As a result, the distribution of NPV of a project without options had the average = -301.90 Million JYN, and about 75 per cent of the distribution was confined to the negative area. The distribution of ENPV of the sequential compound option had the average = 727.92 Million JYN. Further, the distribution of the ENPV of the chooser option had a much bigger average = 1,341.39 Million JYN. Fig.13 shows a lognormal distribution of the volatility simulated.

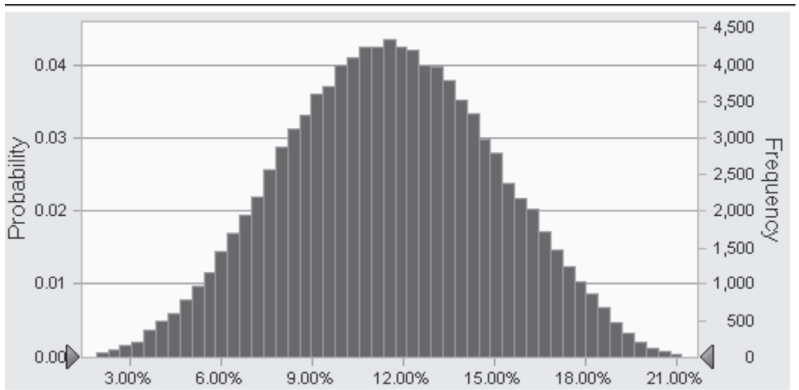

Figure 13: Volatility

The comparison of distributions among the NPV of a project without options, the expanded NPV of a project having a sequential compound option and the expanded NPV of a project to have a chooser option become a following figure as Fig.14.

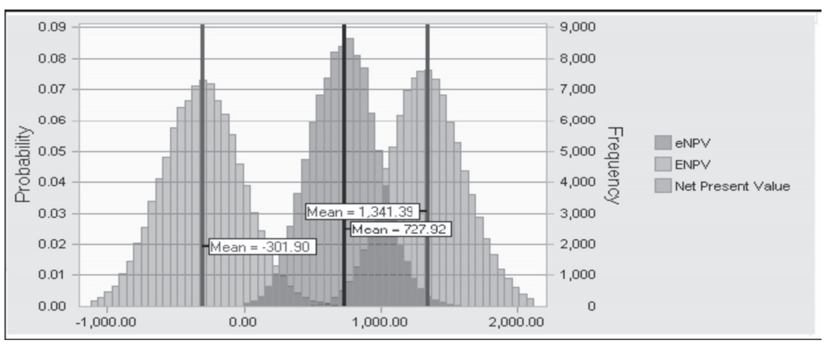

Figure 14: Overlay Chart of 3npvs

As a result, the distribution of NPV of a project without options had the average = -301.90 Million JYN, and about 75% of the distribution was confined to the negative area. The distribution of ENPV of the sequential compound option had the average = 727.92 Million JYN. And the distribution of ENPV of the chooser option had much bigger an average= 1341.39 Million JYN.

In particular, for the comparison between both distributions of the NPV of a project without options and of the ENPV of a project with a chooser option, although major part of original NPV distribution belonged to a negative region, most part of ENPV distribution belonged to a positive region and reduced the standard deviation from 291.65 to 277.24.

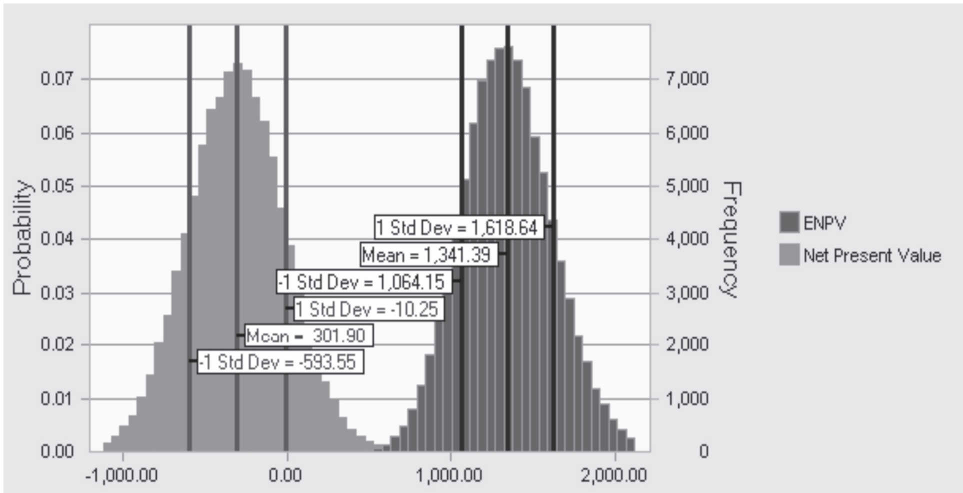

Figure 15: Overlay Chart of 2npvs

In this way, by using ROA, even an innovative but risky project with a minus NPV has a potential to change the EVPV into a positive value and also to reduce the standard deviation as a risk. In other words, ROA makes possible an expansion of return while reducing a risk.

Royalty Payment Decision of ENPV Maximization by Stochastic Optimization

Next, simulation of stochastic optimization of royalty payment as the decision variable is showed, in order to maximize ENPV of a project having a chooser option in a range set as a contract condition, when biotech start-up pays royalty to universities.

Optimization is Complete

Simulation	Maximize Objective ENPV:2 Mean	Requirement Net Present Value 150 <- Percentile (95)	Royalty 2006	Royalty 2007	Royalty 2008	Royalty 2009	Royalty 2010
1	1341.29	158.389	7.5000E-02	7.5000E-02	0.125000	0.125000	0.100000
3	1388.92	159.238	5.0000E-02	0.100000	0.100000	0.150000	0.100000
183	1389.65	159.316	5.0053E-02	0.100000	0.101065	0.148882	0.100000
Best: 210	1389.66	160.870	5.0373E-02	0.100000	0.101557	0.148071	0.100000

Figure 16: Royalty Soluyion

According to a result of simulation of stochastic optimization for 10 minutes, as a method to maximize the ENPV into 1912.88 Million JYN and make original NPV without an option more than 100 Million JYN in 95%, it was found to set the royalty of the first 2006 in 0.050141 and watch the result, then make 0.09930 of royalty in 2007, similarly 0.100147 in 2008, 0.149920 in 2009, and 0.10041 in 2010 respectively.

In addition, it is understood not to expect a solution of a big difference from this result in an objective function, even if there was a deviation from this solution, from a performance graph by a simulation of more than 121 trials. In other words, it is considered that an opportunity cost is small, because the improvement of a solution more than this is almost impossible.

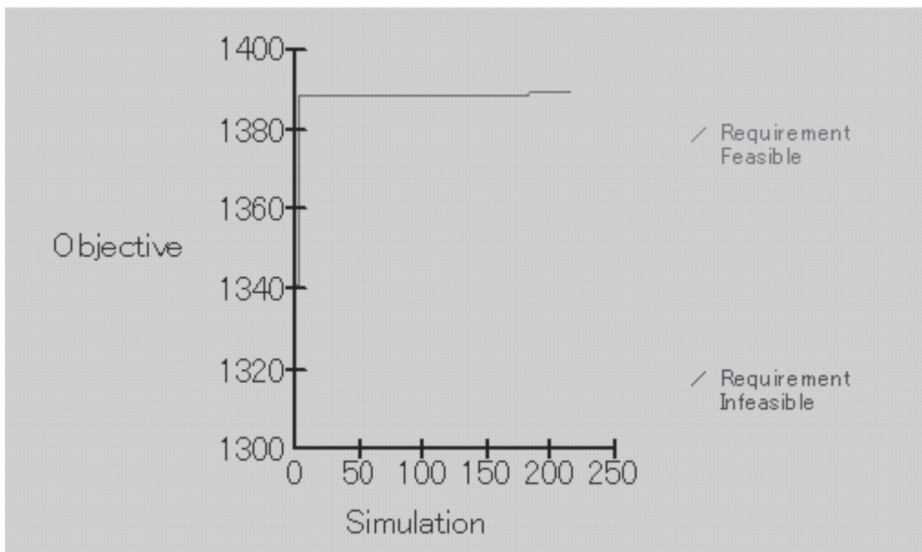

Figure 17: Performance of Stochastic Optimization

Conclusion

When our lives are based on LOHAS(Lifestyles of Health and Sustainability), the academic biotech start-up can become a strategic factor for technology transfer in a meaning to utilize the basic research results as the resource.

ROA can improve, within an extent, the NPV of a project or academic drug-discovery start-up that is innovative but risky then tends to face the death-valley as a negative cash flow period. There is also a case that ROA can simultaneously reduce a risk as volatility. Therefore, ROA has a potential to assist the radical innovation exceeds over the threshold at initial critical period as a death-valley.

As the future prospect, it will be more necessary to study the strategic application of game theory to competitive situations(Smit, 1993; Tirole, 1990), and search more deeply in the possibility that can scientifically solve the practical problems at Technology Licensing Office and Venture Capital (Lerner, 1994).

Thus it may be said that ROA is an important technique of decision making for the improvement of quality and productivity of Japan's health care service to the aging progress.

However, otherwise, there are some skeptical experts in using ROA for the reason that life science has too many assumptions and is changeable in the progress. For practitioners, ROA or Monte Carlo simulation may be considered to be separated from useful and simple technique. However, if the meaning of ROA and its software penetrates and the usage simplifies, the understanding and use may spread over.

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