Welfare Economics of Drug Approval in Japan

- "Willingness to Pay" and Risk Benefit Analysis –

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1 Introduction

Economic analysis of medical care has been largely based on the concept of asymmetric information based on Arrow and Akerlof, and focused on the need of disclosure of information monopolized by medical professionals to patients. However, this approach alone will not be sufficient for welfare economics of medical care; it is necessary to analyze the government regulations which are designed to to ensure the quality of care. The purpose of this paper is to analyze the government approval mechanism of drugs, the product which plays a key role in medical care, using the methodology of cost benefit analysis. It also casts light on the role played by prescribing physicians and the Japanese adverse event relief program. The paper will not discuss the issues of health insurance, which will not affect the conclusions.

2 Japanese Drug Approval Mechanism: Overview

2.1 New Drug Approval and Clinical Trial

New drugs (new active ingredients in particular) may not be sold in Japan before grant of a marketing approval. The approval requirement is more appropriately based on the high information cost, rather than information asymmetry.[1] Efficacy or safety of candidate substances, either chemical substances or biological material, cannot be known, a priori, either by consumers or physicians, unless they are tested through a highly costly process. It is self evident that free sale of new drugs without requiring the expense of tests would only lead to fraud, and there would be no functioning drug market.

To obtain approval in Japan, an applicant is required in principle to submit draft specifications, test methods, toxicology test data, and results of clinical trials in humans, and must successfully complete the review by the Ministry of Health, Labor and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA). The most important among clinical trials is a Phase III large scale (comparative) trial. The trial is performed by setting a patient group which is administered the investigative drug and a control group who is not, in order to generate comparative data between the two groups. The control is usually given an existing drug (comparator) when there is one, and is given placebo when there is no comparator. Sometimes, the control group is administered a different dosage of the investigative drug. Data thus generated serve as the key evidence for a final determination on approval of the drug.[2]

More specifically, the Phase III data must indicate significant superiority in case of placebo, or non-inferiority in case of a comparator, in terms of clinical "end points" (e.g., the ratio of life prolongation, the rate of decrease in tumor size) compared to the control group. In addition, as for safety, the investigative drug must demonstrate that the adverse reaction or other safety concerns is at the "acceptable" or "tolerable" level. Quite often, efficacy data are reviewed by comparing the values in the 95 % confidence interval between the administered group and the control group. For instance, the review report of "Acofide

[1] Danzon & Keuffel (2013)

[2] *See* the PMDA's site for details of the provisions of the law, the approval procedure and clinical trial requirements (http://www.pmda.go.jp/operations/shonin/outline.html).

Tablet 100mg" (Zeria Pharmaceutical) of March 2013 states as follows:[3]

> "Major evaluation items of efficacy were 'the rate of improvement in subjects' impression at the time of final survey during treatment' and 'the rate of disappearance of three symptoms at the time of final survey during treatment'. It was determined that the superiority of the 300mg/day group over the placebo group would be established when a statistically significant difference is observed in both evaluation items between the 300mg/day group and the placebo group. The results are shown in Table 42, and the statistically significant difference is observed in both evaluation items between the groups ($p<0.001$ and $p=0.004$; Fisher's direct probability method, significant level 5% at both ends).

<Table 42: Efficacy at the Last Survey (FAS)>

	Placebo Group (442)	**300mg/Day Group (450)**
Improvements	154	235
Improvement rate of the subjects' impression [95% confidence interval]	34.8% [30.5%, 39.3%]	52.2% [47.6%, 56.7%]
Intergroup difference in the improvement rates	--	17.4% [11.0%, 23.7%]
P*	--	p<0.001
Loss of 3 Symptoms	40	69
Rate of loss of 3 symptoms [95% confidence interval]	9.0% [6.7%, 12.0%]	15.3% [12.2%, 18.9%]
Intergroup difference in the rates of loss of 3 symptoms [95% confidence interval]	--	6.3% [2.1%, 10.5%]
P*	--	p=0.004

*: Fisher's direct probability method, significant level at 5% at both ends.

Fig.1 "Acophide Tablet 100mg" Review Report, P. 60

The "Intergroup difference of the improvement rate" indicates that the administered group showed a better improvement rate by an average margin of 17.4 %, which ranges between 11.0 % and 23.7 % at the 95% confidence interval. This discovery of a positive intergroup difference led to the determination of a significant difference compared to the control group, which was one of the grounds for approving the product. On the other hand, safety data such as the rate of incidence of adverse reaction are compared directly between the administered group and the control group without considering a confidence interval. The report on "Acofide Tablet 100mg" contains a safety data table:

[3] Results of review by the Pharmaceuticals and Medical Devices Agency of Japan are summarized in a report and published online. For "Acofide Tablet 100mg", *see* http://www.info.pmda.go.jp/shinyaku/P201300021/38007700_22500AMX00868000_A100_1.pdf

<Table 43: Adverse Events Observed in 2% or More in Either Group>

	Placebo Group (442)		**300mg/Day Group (450)**	
	Rate of Occurrence	No. of Cases	Rate of Occurrence	No. of Cases
All	60.4%	267	56.0%	252
Increase of blood triglyceride	20.6%	91	18.9%	85
Nasopharyngitis	9.3%	41	8.7%	39
Increase of GTP	6.3%	28	7.1%	32
Increase of blood prolactin	6.8%	30	4.7%	21
Diarrhea	4.1%	18	4.7%	21
Increase of blood bilirubin	4.1%	18	4.2%	19
Increase of ALT	3.8%	17	4.0%	18
Digestion difficulty	3.6%	16	3.8%	17
Increase of white blood cells	4.8%	21	3.1%	14
Vomit	2.5%	11	2.9%	13
Increase of AST	2.9%	13	2.2%	10
Constipation	1.4%	6	2.2%	10
Increase of blood uric acid	2.0%	9	1.8%	8
Nausea	2.5%	11	1.3%	6

Fig. 2 “Acophide Tablet 100mg” Review Report, P. 61

The table shows that the incidence of adverse reaction in the administered group is not necessarily higher than in the control group. This is another reason that the product was approved.

2.2 Evaluation of Clinical Trial Results

Evaluation of efficacy and safety of the Phase III clinical trial results, which is the determinant of the grant of approval, is known as “risk benefit analysis”. The risk benefit analysis is a comparative assessment of efficacy (benefits) and safety (risks) for approval decisions. The table below summarizes the control group, the assessment of efficacy, and the authorities’ risk benefit conclusion for the 15 drugs of new active ingredients approved during the first quarter of 2013. Often, more than one Phase III trials are performed either domestically or overseas with divergent end points or purposes, and the information in the table shows the results of a representative trial referred to in the evaluation report.

Comparative evaluation of clinical efficacy or benefits and risks of adverse reaction of a drug raises important and difficult scientific/moral issues. For example, how and for whom can benefits “exceed” risks, or risks be “tolerated”, of a drug expected to prevent deterioration of cancer conditions which may cause interstitial pneumonia as an adverse reaction which could be fatal? One could avoid facing this difficult issue when a product is compared with an existing comparator: In such a case, benefits of a new drug are assessed compared to the comparator in terms of superiority or non-inferiority, and safety data are then compared. If the new drug is not inferior to the comparator in either of the two key aspects, its benefits logically exceed the risks because the comparator’s benefits are supposed to have exceeded the risks when it was approved. However, this convenient route

is not available for a newly developed active ingredient where there is no appropriate comparator. In such a case the drug will be compared with placebo, and the benefits from the investigative drug must be proven to exceed the risks or the risks must be demonstrated to be tolerable, through some form of direct comparison.

Product	Control Group	Efficacy Finding	Safety Finding	Risk/Benefit Conclusion
Arzerra	[No Phase III trial]	--	--	Tolerable.
Acofide	Placebo	Superior at the 95% confidence interval (intergroup difference)	Lower ADR incidence	Tolerable.
Alabel	Existing treatment (foreign trial)	Superior by Chi-square test	Lower ADR incidence	Clinically tolerable.
Inovelon	Placebo	Superior at the 95% confidence interval (intergroup difference)	Higher ADR incidence	Tolerable.
Evoltra	[No Phase III trial]	--	--	Tolerable.
Onglyza	Placebo	Superior at the 95% confidence interval (intergroup difference)	Higher ADR incidence	Tolerable.
Stribild	Comparator	Equivalent improvement rate	Equivalent ADR incidence	No particular concern of safety
Stivarga	Placebo	Superior at the 95% confidence interval (“hazard rate”)	Higher ADR incidence	Prescription is tolerable
Xeljanz	Placebo	Superior at the 95% confidence interval (intergroup difference)	Higher ADR incidence	Benefits higher than risks
Normosang	[Not controlled]	--	--	Tolerable.
Nouriast	Placebo	Superior at the 95% confidence interval (intergroup difference)	Higher ADR incidence	Risks are tolerable.
Borben	Comparator	Not equivalent at the 95% confidence interval (intergroup difference)	Equivalent ADR incidence	Tolerable.
Metreleptin	[Not controlled]	--	--	Tolerable.
Regtect	Placebo	Not superior at the 95% confidence interval (intergroup difference)	Higher ADR incidence	Tolerable.
Absorbed influenza vaccine H5N1	Comparator	Not superior at the 95% confidence interval (intergroup difference)	Higher ADR incidence	Tolerable.

Table 1: Approved Drugs (New Active Ingredients) during 1st Quarter of 2013

In this weighing process, uncertainty over efficacy and safety becomes problematic. The review report of “Ascofide Tablet 100mg” contains the following graph plotting the rate of symptom disappearance, another end point of the investigation.

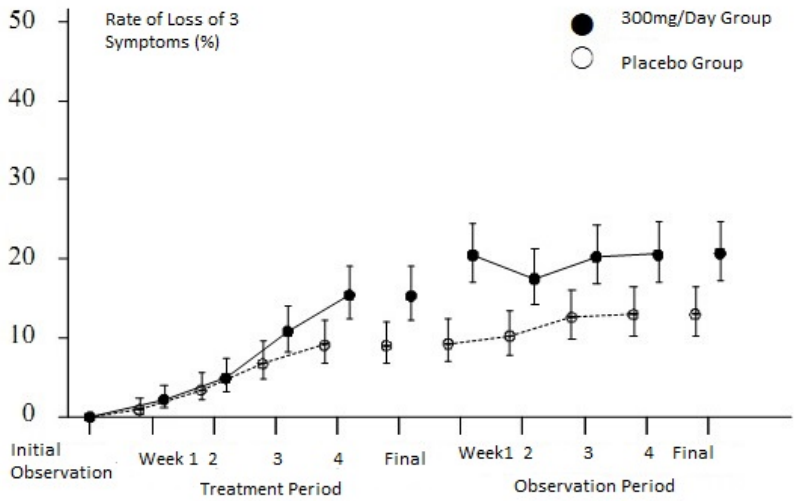


Fig. 3: "Ascofide Tablet 100mg" Review Report, P. 70

The round dots in Figure 3 show the average rates of symptom disappearance in each of the groups, and the vertical section surrounding the dot shows the 95% confidence interval. Notably, there are points in time where the investigative drug is not more efficacious than placebo in terms of this end point. For example, at the third week of the treatment period, the lowest rate of symptom disappearance in the 95% confidence interval of the administered group is lower than the highest rate of symptom disappearance in the 95% confidence interval of the placebo group. Even at the final observation period, values in the confidence intervals are not quite apart. The variance of values (or uncertainty from the patient's viewpoint) may be attributable to stochastic factors or to individual factors, and no definite conclusion can be drawn from the results of the clinical trial alone. Whatever the cause may be, it is evident that patients may or may not expect effects from the investigative drug. Similarly, adverse effects may or may not manifest themselves, and it is generally not known where the variance comes from.

2.3 Approaches to Evaluation of Clinical Trial Results

There is no established approach, either in Japan or overseas, for the risk benefit analysis, or methodology to compare directly benefits and risks of a drug product. Traditionally, the regulatory authorities have made an intuitive decision, on the basis of input from experts, on whether or not the benefits exceed the risks (which are then found "tolerable"), in the approval process. In the review reports of the 15 new drug products, for example, efficacy was first discussed and recognized and safety was then found to be broadly "acceptable". There is no detailed discussion of the basis of this decision.

More recently, there is a growing international trend toward a quantitative and direct comparison of efficacy and safety under the same yardstick. One notable development is the concept of "quality adjusted life years" (QALY).[4] The concept is based on a survey of preference (value) of health, and is used to evaluate the benefits and adverse events of a medicinal product. In practice, QALYs are calculated, for example, on the basis of a trade-off between the length of healthy life years and the indifferent length of years with a disease. The calculation can be made for evaluation of both efficacy and safety, enabling risk benefit comparison and judgment under the same yardstick. When used to value the net

[4] Freeman *et al.* (2003)

benefit of a new drug product, it is called "Incremental Net Health Benefit" (INHB). Under this concept, benefits in terms of recovered health (efficacy) will be measured by the number of health years gained while risks are shown by the number of healthy years lost, and INHB will be given by subtracting the latter from the former. Using this concept, a following simple equation shows a desired risk benefit profile of a drug product:[5]

$$INHB=(B2-B1)-(R2-R1)>0$$

B2, B1, R2 and R1 denote, respectively, benefits found among the administered group, benefits of the control group, risks found among the administered group, and risks of the control group. The above equation means that net benefits from the new drug exceed the net benefits of the control group, and approval of the drug is justified under the condition.

These approaches are yet at the research stage and no government has yet fully adopted them. They are illustrative, however, of the current approval practice in a theoretical, refined form. As discussed, the current practice compares relative benefits and relative risks, and, for approval, finds the latter are "tolerable" implying a value judgment under some yardstick that the benefits exceed the risks. In the process of evaluation, the degree of improvement, the seriousness of the disease, the severity or degree of adverse reaction must be implicitly compared and valued. In this sense, the current practice is not different from the above INHB equation, in terms of its fundamental framework.

3 Welfare Economics of Approval

3.1 Cost Benefit Analysis

We now turn to welfare economic considerations of these approval standards and practices. A most useful analytical tool for the purpose will be cost benefit analysis of the approval mechanism. Specifically, benefits of a drug should be valued in monetary terms and an efficient level of supply would be at the point where the marginal benefit equals the marginal cost of supply. The relevant market is deemed to exist for each product, as drugs are normally protected by patents.

In Figure 4 below, the demand curve is plotted along the level of the amount which each patient is "willing to pay" for the treatment using the drug, with respect to the patient group (n).[6] The monetary benefits of a drug which a patent would receive will be equal to recovery of lost revenues and the value derived from avoidance of death, disabilities and pain. Needless to say, they differ for each individual, and the patients in the Figure are aligned from the highest valuation to the lowest, resulting in a downward sloping demand curve. Risks (damages) can be considered as social costs, however, it would be easier to handle to consider them as negative benefits, and the demand curve represents net benefits, with risks subtracted from gross benefits of a drug product. The marginal cost of supply (including manufacture and dispensation) is assumed to be constant for the sake of simplicity. Evidently, the point O represents a Pareto optimum solution, with the consumers' surplus with the size of α. To achieve Pareto optimality, the solution will be to prescribe the drug up to Patient k, but not beyond the point. If the goal is to meet the Kaldor-Hicks criteria, the approval condition should be $[\alpha+\beta>0]$.

[5] Garrison (2011).
[6] Stokey & Zeckhauser (1978).

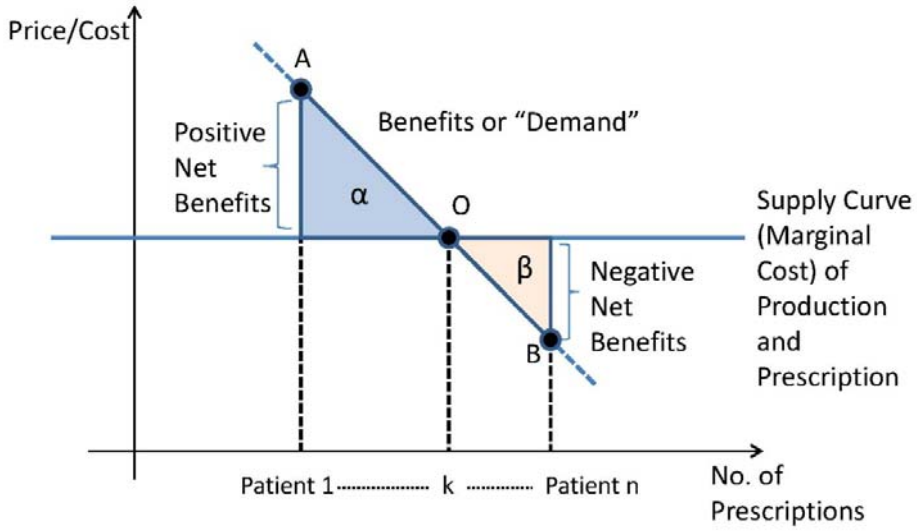


Fig. 4 Cost Benefit Analysis of Drugs by "Willingness to Pay"

There are admittedly several major obstacles to introducing the normal cost benefit analysis into the approval practice. First and foremost, there will be significant social or psychological resistance to the idea of comparing life or heath with the supply costs. Second, it causes serious difficulties to determine how much one would be "willing to pay" for life or health. A consumer survey may or may not be reliable. Moreover, the demand curve must represent the entire patient population, and their willingness to pay need to be estimated on the basis of a survey of a group of limited size (e.g., subjects of a clinical trial). The reliability is not guaranteed, however, as the "willingness to pay" is subject to a decision of the individual concerned. Finally, monetary valuation includes gains from foregone revenues from illness, and the more one earns, the more is he or she likely to value the benefits of a drug. This raises a fairness issue, because benefits of those drugs which treat high-income population tend to be valued higher and be accepted.

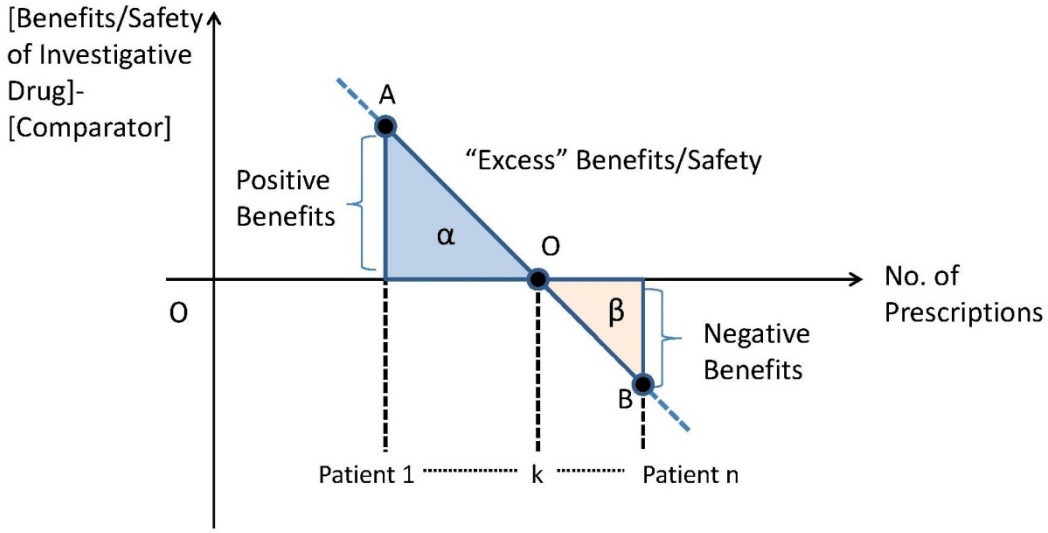
3.2 Risk Benefit Analysis

The risk benefit analysis as incorporated in the approval practice offers significant advantages over the cost benefit analysis. First, by comparing benefits to the health and risks to it, the approach avoids the valuation question, which patients themselves would find difficult. This approach may be justified on the basis of high societal value of life and health; as the production and supply costs of a drug may be viewed as sufficiently small, risks to the health such as adverse reaction should be primarily considered as social cost. In the case of placebo as control, the risk of adverse reaction and other health risks are assessed as social costs against the benefits, whereas in the case of a comparator, net benefits of the comparator are considered as opportunity costs against which the net benefits of the new drug are compared. Secondly, the risk benefit analysis avoids the fairness issue in monetary valuation of benefits where high income earners would tend to value relatively high the net health benefits of a new drug.

One can show the risk benefit analysis of clinical trial results in a graph using a method similar to the "willingness to pay" approach. Since benefits and risks of a drug product are uncertain among the patient group (n), some patients may enjoy benefits exceeding risks whereas others may not, whether for stochastic causes or for individual attributes. Using QALY, we can calculate net benefits for each subject, subtracting further net benefits of a comparator when it is the control, and estimate the net benefits for the entire patients and align them in the decreasing order of the net benefits. They will be either in the order of the

degree of adaptability (if the individual attributes are the cause), or the degree of luck (if the differences are stochastic). Figure 5 shows the "demand curve" using the comparator as the control, similar to Figure 4, which is estimated to be linear for the sake of simplicity.

Fig. 5: Risk Benefit Analysis



There is no supply curve, as the "demand" is net benefits with risks (proxy cost) subtracted. The net benefits are positive up to Patient k, and turn negative beyond that point. Similar to Figure 4, Pareto optimality will be achieved at point O, with the consumer surplus of α (in terms of QALY).

The INHB equation above requires the average net benefits to be positive, which is equivalent of the requirement that the sum of net benefits to be positive. In Figure 5, the sum of net benefits is given by [α+β], and the equation can be rewritten as [α+β >0]. This is the Kaldor-Hicks criteria. If the INHB equation is adopted as the approval standard, new drugs will be approved if its clinical trial results meet the condition, and not if the results fail.

3.3 Analysis of Current Approval Practice

This leads to the issue of the analytical underpinning of the current approval practice in Japan. As noted earlier, the current practice is, while not explicitly using QALY, based on a philosophy similar to the INHB equation. More specifically, the practice does investigate if [B2-B1] is positive at the 95 percent confidence interval, and addresses [R2-R1] qualitatively. The approval decision then states, "In light of [B2-B1], [R2-R1] is tolerable". This can be summarized in the following simple equation:

$$f(\text{B2-B1})-g(\text{R2-R1})>0$$

f and *g* are functions which assign weight to the input for the purpose of benefit and risk evaluation. If patients are aligned according to their [*f* - *g*] value along the X axis, one can generate a downward sloping curve (or line) similar to Figure 5.

Needless to say, the average value of [B1, B2, R1, R2] will not necessarily produce the average value of [*f* - *g*]. This means that the above equation is not identical to [α+β>0]. Nevertheless, the authorities compare the average value of the benefits and then compare the average value of risks to see if risks increase by a new drug product. It will not be

farfetched to say that the current practice reflects Kaldor-Hicks considerations in some undefined form. Indeed, the practice approves a product "Regtect" (see Table 1) which did not show superiority over placebo and shows a right rage of adverse reaction. Evidently, the authorities are not in pursuit of Pareto optimality.

The reason for absence of Pareto optimality element is obvious. It is no easy task to identify personal attributes or stochastic elements which affect the response to a drug product. With the limited number of subjects of a clinical trial (the number is often 1,000 in Phase III), it will be extremely difficult to identify who Patient k is. This makes almost impossible to pursue Pareto optimality. Indeed, in the Iressa case, this ambiguity became a major issue. As a molecular target drug, the innovative product was widely prescribed as a anti-carcinogenic agent. In fact, however, the product was only relatively efficacious for a specific patient group, which was not known at the time of approval. In contrast, conditions are sometimes attached to the approval, physicians are cautioned not to prescribe to an identified group of patients who are likely to suffer from adverse reaction in package inserts, or "discretionary prescription" is recommended. These can be viewed as an attempt to identify Patient k as much as possible and maximize [α+β], approaching the Pareto optimality.

4 Patients' Risk Preference

From patients' point of view, the difficulty of identifying the patient k raises a serious issue, because their most important concern is whether or not he or she lies between 1 and k, regardless of the social benefit of the product. If patients are particularly risk-averse, they may even choose to avoid the use of the drug even if it is approved, and the expected social benefits may not materialize. The current regulation copes with the risk preference problem through two mechanisms.

4.1 Physicians' Role

Physicians play a primary role in the use of new drugs. In our experience, we normally ask physicians' opinion when hear news of a new drug. Those who still wish to use the new drug when physicians are not favorable would be rather a monitory. For the social welfare, it is desirable to recommend the use of a new drug even when it is not certain if the patient would receive net benefits, as long as the product satisfies the Kaldor-Hicks criteria as a whole. This means that a physician has, in addition to the role to identify the disease and confirm conditions for a prescription, the role to expand the social welfare through the use of a drug, even to the possible detriment of the patient's interest.

This social role, however, involves a risk of negative distributional impact for the patient. Notably, whether or not a particular product would bring net benefits to a patient is not always evident even for a physician. Therefore, a significant damage may result from the use of a new drug if the approval is based on the Kaldor-Hicks criteria and the adverse reaction is serious, while the risk is relatively law if the approval seeks Pareto optimality through attached conditions and recommendations in package inserts. The case of Iressa which showed significant benefits to some patients but tended to cause sometimes fatal reaction of interstitial pneumonia can be considered to illustrate this issue. This role may be one of the causes why patients who suffered damages from a drug often file a lawsuit naming the physicians as a co-defendant.

4.2 Drug Health Damage Relief Program

Another mechanism neutralizing the patients' risk preference is the Drug Health Damage Relief Program. To the extent the Kaldor-Hicks criteria is approval standard, it is desirable for the distributional fairness to distribute compensation from the patients who enjoy the

benefits to the patients who did not. The Japanese Drug Health Damage Relief Program should be able to play this distributional rule; the Program, funded by contributions by the manufacturers, provides a flat compensation for health care costs and other damages of the patients who suffered significant damages. However, the Program has a few shortcomings as the distribution mechanism. First, adverse impact must include hospitalization or other seriousness. This may be based on practical considerations of burden of proof or administrative costs, but is not theoretically justifiable. Secondly, income compensation is a fixed amount which is not high. Third, if the manufacturers shift the burden of contribution to patients, the payments are ultimately borne by patients in general including patients who suffered minor adverse reaction, not limited to those who received benefits. Finally, major medicines including anti carcinogen agents are exclude from the Program.[7]

The current Program is obviously insufficient. It is not a distribution from receivers of benefits to those who suffered, and does not provide an adequate level of compensation. While achieving a more direct distribution mechanism may be technically difficult, the insufficiency of compensation may be based on the political concern that a higher contribution would lead to pressure to raise the price. If, however, all patients' earnings are equal, they may suffer all diseases with the same likelihood, the likelihood of damages from a drug is equal and other monolithic conditions are met, the current mechanism is not unreasonable. In this sense, the Program represents very crude justice. Still, exclusion of anticarcinogen agents from the Program is not justifiable. For distributional fairness, a more robust compensation would lead to greater social welfare.

The Program, however insufficient, should give patients a degree of comfort and induce acceptance of prescriptions. It helps neutralize the patients' risk preference and promote realization of social benefits expected under the Kaldor-Hicks criteria. Needless to say, adequate compensation will increase the number of patients who want a prescription. However, the phenomenon does not reflect moral hazard; it is what is anticipated under the approval standard. If, for example, a higher number of prescriptions result in social loss whereas fewer prescriptions would not, it will be because the approval itself failed to meet the Kaldor-Hicks criteria. For greater social welfare, therefore, a more robust Program is desirable.

5 Conclusion and Note on Iressa Case

Using an analytical method similar to "willingness to pay", the current approval standard of new drugs has been found to be similar to the Kaldor-Hicks criteria. This suggests importance of a compensatory mechanism for adverse reaction. Notably, the Supreme Court judgment of the Iressa case includes supplementary opinions by Justices Tahara, Ohtani and Ohashi which emphasizes that relief be given to damages from drug use. The concern is justifiable as the current Relief Program is insufficient. The entire litigation may be viewed as an attempt to realize the element of compensation under the Kaldor-Hicks criteria through reinterpretation of torts law or the concept of "defect" under the product liability legislation. As such, the plaintiffs' claim is justifiable, although the Supreme Court made clear that the current judiciary is not up to the task.

[Cases]

Judgment of Nov. 15, 2011, Tokyo High Ct., 2131 Hanrei Jiho 35 (2012)

Judgment of Apr. 12, 2013, Supreme Ct. (*available at* Supreme Court's website)

[7] *See* http://www.pmda.go.jp/kenkouhigai/help/taisyou/taisyou_seizai.html for the list of exclude products.

[Reference]

Akerlof G.A., The market for “lemons”: Quality Uncertainty and the Market Mechanism, Quarterly Journal of Economics 1970; 84: 488-500.

Amiram G., Willingness-to-pay as a measure of benefits, Medical Care 1991; 29: 1246-51.

Arrow K.J., Uncertainty and welfare economics of medical care, American Economic Review 1963; 53: 941-73.

Danzon P.M., Keuffel E.L., Regulation of the pharmaceutical-biotechnology industry, *paper prepared for NBER “Economic Regulation and its reform: what have we learned?*” (January 2013), *available at*: http://nber.org.

Freeman A.M., Hammitt J.K., Civita P.D., On quality adjusted life years (QAYKs) and environmental/consumer safety valuation, *paper presented at RFF conference “Valuing health outcomes: an assessment of approaches”* (February 2003), *available at*: http://www.rff.org.

Garrison L., Quantifying benefit-risk assessment: health outcomes modeling, presentation for RTI symposium (May 2011), *available at*: http://www.ispor.org:

Mishan E.J., Evaluation of life and limb: a theoretical approach, Journal of Political Economy 1971; 79: 687-705.

Posner R., Economic Analysis of Law 8th ed. NY: Wolters Kluer, 2011

Stokey E., Zeckhauser R., A Primer for Policy Analysis, NY: Norton & Co.,1978