Appropriate Drug Prices in an Aging Society — Striking a Balance Between Containing Medical Care Costs & Promoting Innovation

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As the frontrunner of aging societies, Japan continues to see the cost of its national medical care rise. According to figures published by the Ministry of Health, Labour and Welfare (MHLW) in September 2016, national medical care expenditures in FY2014 topped 40 trillion yen for the second consecutive year — 40.8071 trillion yen to be exact. The national medical care expenditures figure is an estimate of the medical care expenses that qualify under the public insurance system, medical and dental treatment expenses as well as medication charges, dispensary charges and home nursing, among others. Payment for advanced medical care, physical checkups and nonprescription drugs are not included. There is vocal demand for urgent measures to restrain its growth.

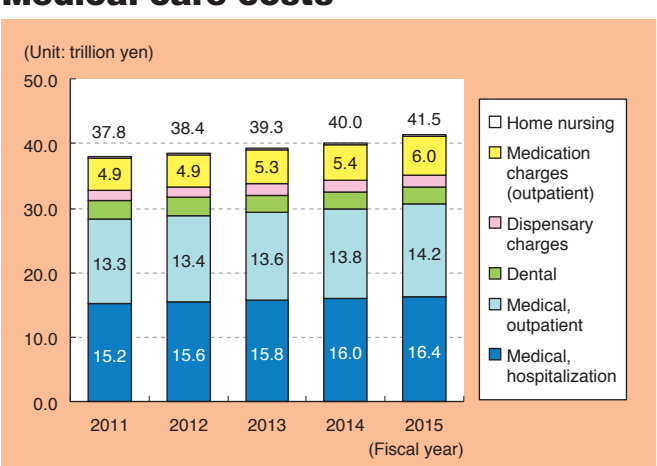
The rise of the over-65 population is given as a cause of the continuous rise of medical care expenditures. According to the government's 2016 *Annual Report on the Aging Society*, there were 33.92 million people 65 or older as of Oct. 1, 2015, a jump of 6.5 million from the previous year that brought their percentage of the total population of 127.11 million to 26.7%. And it is normal for the body to break down as it ages. However, there is a factor that pushes medical care expenditures up even more — the rise of medication charges, that is, payment for drugs.

Payment for Drugs Is Greatest Driver of Healthcare Expenditures

Take a look at *Charts 1 & 2*. According to documents published by the Japan Medical Association (JMA) and the Council on Economic and Fiscal Policy, medical care expenditures (estimate) reached 41.5 trillion yen in FY2015. They grew 3.8% year-on-year, much more than the usual annual increase of 2% more or less. Aging accounted for 1.2 percentage points, while advances in medical care technology accounted for the rest, with medication charges taking the lion's share at 1.4 percentage points. Drug payments, which account for one-fifth of national medical care expenditures, reach 8-9 trillion yen per year. This is a manifestation of the progress in the development of drugs, leading to the widespread use of highly effective but expensive drugs.

CHART 1

Medical care costs



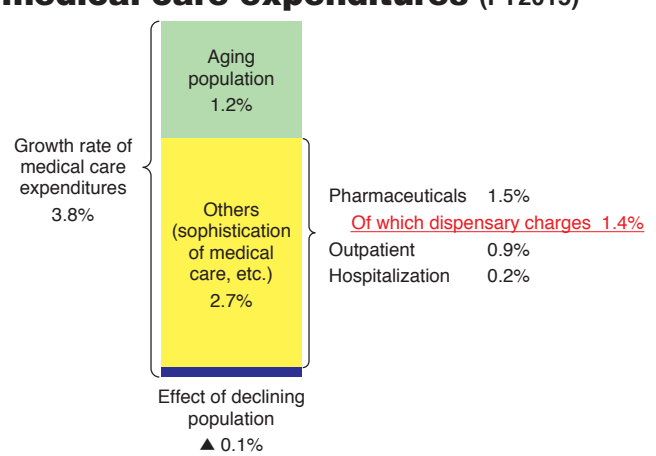
** Created from Medical Care Expenditure Trends in FY2015 and Dispensary Medical Care Expenditure Trends, FY2015 version (both Ministry of Health, Labour and Welfare). Dispensary charges for hospitalized patients and outpatients are included in the respective categories.*

Note: Overall medical care expenditures estimate for 2015 was 41.5 trillion yen, up 3.8% from the previous year.

Source: Material published by the Japan Medical Association (at regular press conference on Sept. 26, 2016)

CHART 2

Breakdown of causes of rising medical care expenditures (FY2015)



Note: Aging accounts for 1.2 percentage points, lower than progress in medical technology (sophistication of medical care, etc.) at 2.7 percentage points. Dispensary charges, at 1.4 percentage points, are the biggest factor in the sophistication of medical care.

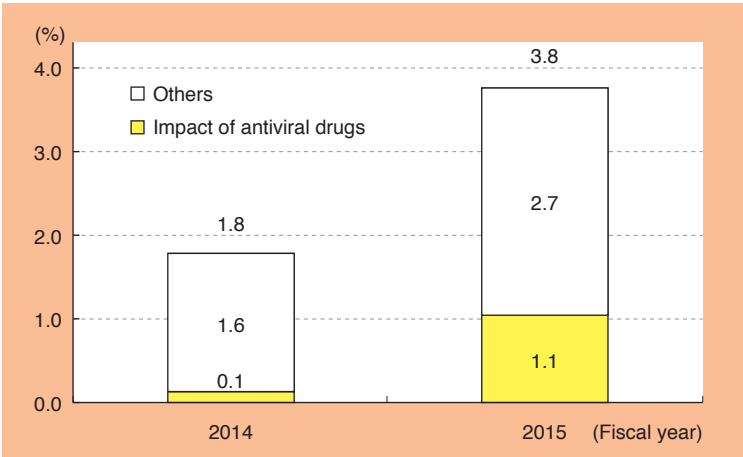
Source: Material submitted to the Economic and Fiscal Policy Council by expert member (Oct. 14, 2016)

Photo 1: Gilead Sciences website

Sovaldi & Harvoni tablets: the hepatitis C wonder drug

CHART 3

Impact of antiviral drugs on the rise in overall medical care expenditures



** According to an estimate by the Japan Medical Association, antiviral drugs such as therapeutic drugs for hepatitis C account for about 1 percentage point of the rise in medical care costs.*

Note: Created from Medical Care Expenditure Trends in FY2015 and Dispensary Medical Care Expenditure Trends, FY2015 version (both Ministry of Health, Labour and Welfare); and State of Progress in Division of Labor in Medical Care (pharmaceutical trends under the public insurance system), Japan Pharmaceutical Association (JPA).

Source: Material published by the Japan Medical Association (at regular press conference on Sept. 26, 2016)

60,000-80,000 Yen per Pill for Type C Hepatitis Drug

Good examples of this are wonder drugs for hepatitis C Sovaldi (generic name "sofosbuvir", used in patients with hepatitis C virus genotype 2 infection) and Harvoni (generic names "sofosbuvir" and "ledipasvir" for genotype 1) from Gilead Sciences, an American company *(Photo 1)*. Interferon had already provided significant progress in treating hepatitis C but Sovaldi and Harvoni offered a dramatic breakthrough, completely healing 98% of the patients. Sovaldi inhibits the function of NS5B polymerase, a protein that the hepatitis C virus needs in order to multiply. Harvoni is a combination drug which adds ledipasvir, an NS5A polymerase inhibitor, to Sovaldi. Each does the job through a 12-week treatment regimen. Launched commercially in 2013, they became global pharmaceutical sensations. They were placed on the Japanese market in 2015, Sovaldi at 61,799 yen per tablet in May and Harvoni at 80,171 yen per tablet in September. A full therapy regimen for Sovaldi and Harvoni costs approximately 5.46 million yen and 6.73 million yen per person respectively.

According to JMA estimates, antiviral drugs for hepatitis C and other ailments accounted for 1.1 percentage points of the FY2015 rise in medical care expenditures *(Chart 3)*. They are a godsend to patients, effective as they are, but the JMA points out that pushing up medical care expenditures runs the risk of threatening universal healthcare itself. It was against this background that the drug prices of Sovaldi and Harvoni, which had led the field in domestic revenue, were reduced by a whopping 31.7% each as of April 1, 2016.

Market Share of Generics in Japan Low at 55%

Another way that the Japanese government is aiming to contain the rise of drug payments in addition to reducing the prices of expensive drugs is to increase the use of cheap generics as the patents for brand-name drugs expire (after approximately 20 years). *Basic Policies 2015* included the quantitative goal of raising the "share of generics to 70% or more by 2017 and to 80% by the earliest possible time between FY2018 and 2020". The share of generic drugs is exceptionally low in Japan compared to other industrialized economies. The share of generics during September 2014 and September 2015 surpassed 90% in the United States, 85% in Germany, and 75% in the United Kingdom, but it was only 55% in Japan *(Chart 4)*. That is why there is a need for a revision of the treatment remuneration system in order to provide incentives to physicians to prescribe generics and normalization that eliminates the gap between listed prices and the actual prices at which they are being sold on the market. There is an 8.8% gap on average between the listed prices and the actual prices in the market *(September 2015 Survey on Pharmaceutical Prices)*.

35 Million Yen per Year per Person & Ramifications

Last year, criticism focused once again on an excessively high-priced anti-cancer drug — Opdivo (generic name "nivolumab"), launched by Ono Pharmaceutical in September 2014. An anti-cancer immunotherapy drug unlike conventional anti-cancer drugs, its initial indication was unresectable malignant melanoma. Ono Pharmaceutical filed the application, forecasting 470 patients taking one intravenous drip infusion every three weeks and annual sales peaking at 3.1 billion yen. The listed drug price based on these assumptions was 729,849 yen for one 100 mg injection.

An anti-cancer drug developed on the basis of research by Dr. Tasuku Honjo, professor emeritus of Kyoto University, it was approved in Japan ahead of the rest of the world as a drug for malignant melanoma, a rare, intractable type of skin cancer. But the focus turned to the issue of drug prices when its indication was expanded to cover other, more common cancers.

In December 2015, non-small cell lung cancer was added to the indication, instantly raising the number of applicable patients to the tens of thousands. With an injection every other week for this, it costs approximately 35 million yen per year per patient. Ono Pharmaceutical revised its FY2016 forecast upward to 126 billion yen as a result of the rise in the number of eligible patients (estimated at a maximum of 15,000). One expert calculated that there were 50,000 eligible patients, and if they each used Opdivo for one year, the medical expenditures would reach 1.75 trillion yen. Given this situation, people thought that the drug price for Opdivo would be reduced in the April 2016 revision of medical treatment remuneration. That did not happen *(Photo 2)*.

Opdivo 4.9 Times More Expensive Than in UK

The decision to leave the price untouched drew criticism from many quarters. The Central Social Insurance Medical Council (*Chuikyo*), which determines drug prices, began considering measures on price reduction for Opdivo and other expensive drugs.

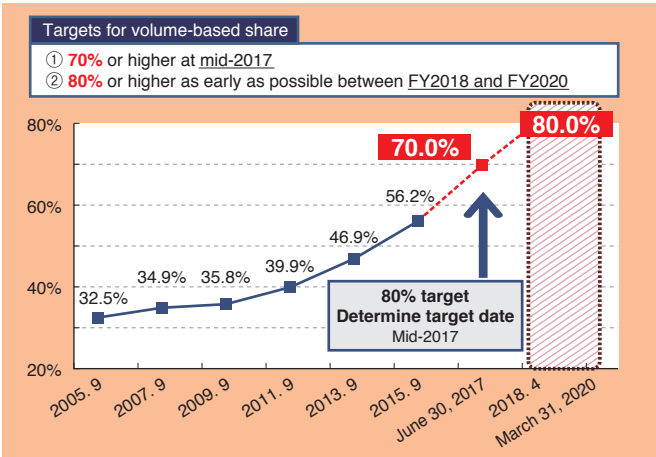
Last September, *Hodanren* (Japanese Medical and Dental Practitioners for the Improvement of Medical Care) pointed out that the Japanese price of Opdivo is dramatically higher than its price in the US and the UK, where the drug was later authorized, and issued an "Emergency Recommendation". The Japanese price of Opdivo was 4.9 and 2.45 times higher than it was in the UK and US respectively *(Chart 5)*.

The Japanese rules for calculating the price of a new drug consist of two main pillars, the "similar efficacy comparison method" (where there are similar drugs and the price is determined by considering effectiveness among others) and the "cost accounting system" (where there are no similar drugs and the price is determined by considering the development costs and the expenses incurred in manufacturing and distribution). Added to this formulation are the "corrective addition" which accounts for innovation by reflecting the superiority from a comparison of its innovativeness, safety and effectiveness and existing medicine, and "average foreign price adjustment" which is added in the case where there is a large gap between the foreign prices of the same product.

Hodanren emphasizes that "the Japanese drug price system and its calculation rules have a problem. Once a high drug price is listed for public insurance, it tends to remain stuck there." In the US, price levels are relatively high, given their free pricing system. But even there, drug prices fluctuate according to the balance between supply and demand in the market, and price negotiations between pharmaceutical companies and insurance companies, falling

CHART 4

Volume-based share of generics in Japan & future targets



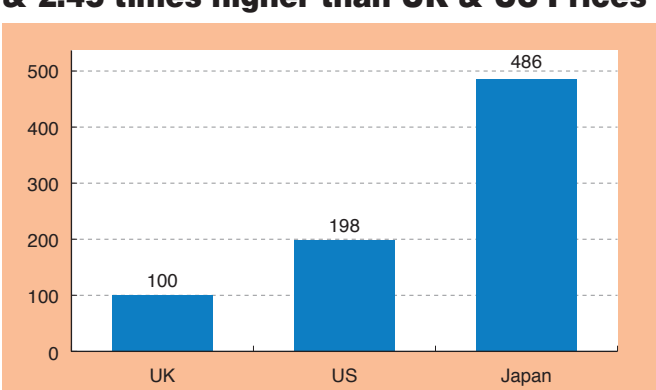
Note: Volume-based share uses the sum of the volumes of brand-name drugs and their generics as the denominator and the volume of those generics as the numerator.
Source: Material published by the Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryou/kouhatu-iyaku/)

Photo 2: Press release from Ono Pharmaceutical Co., Ltd

Opdivo: focus of attention as expensive drug

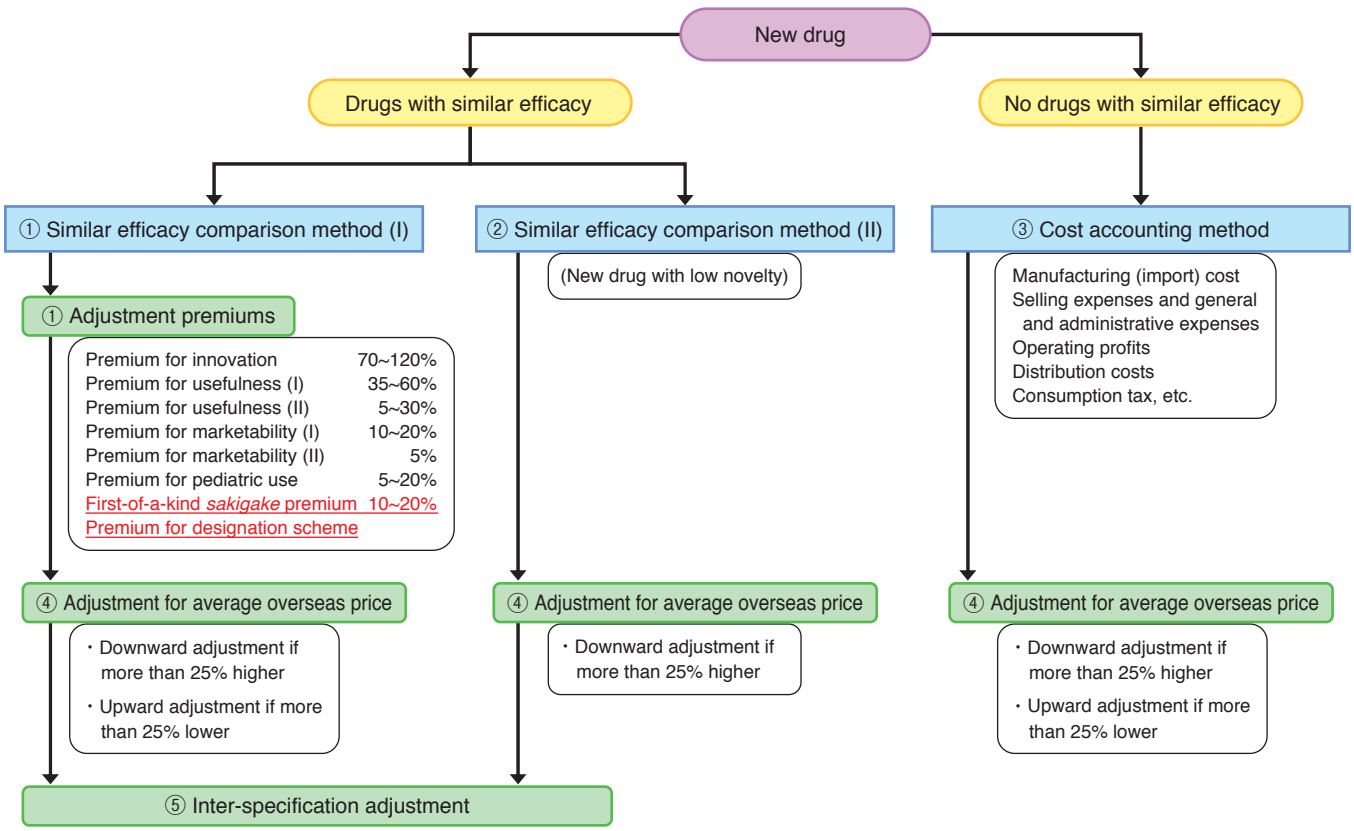
CHART 5

International comparison of the price of Opdivo: Japanese price approximately 5 & 2.45 times higher than UK & US Prices



** $1 = 103.5 yen; 1 GBP = 136.95 yen*
Note: US: Average wholesale price (AWP; Bristol-Myers Squibb Co.). Actually retails at a 20% or so discount from this price. UK: UK List Price (BMS).
Source: Press release by Hodanren (Japanese Medical and Dental Practitioners for the Improvement of Medical Care) on Sept. 6, 2016

CHART 6
Current calculation method for pricing new drugs



Note: For highly useful kit products, a 5% premium is added to the sum of the result of adjustment ⑤ and the material costs for the kit.
Source: Material from the Expert Committee on Drug Prices of the Central Social Insurance Medical Council, Nov. 30, 2016

significantly by price negotiations in response to rising demand between pharmaceutical companies eager to sell more to meet demand and insurance companies eager to keep prices low. In the US, insurance companies can select the drugs to be covered by their policy and pharmaceutical companies prefer their drugs to be used even at cheap prices. However, in Japan, pharmaceutical companies determine prices when they deliver the drugs to medical institutions through pharmaceutical wholesalers, and virtually never give discounts on a new drug. Furthermore, the price for a new drug is topped off by an addition for new drug development, in order to enable the manufacturer to recover the cost of developing new drugs. The addition for new drug development cannot be altered through the drug price revision process until a similar drug is launched, which takes 12.4 years on average. In the meantime, drug prices would not go down. *Hodanren* points to these structural flaws in the drug pricing system and demands improvement *(Chart 6)*.

Recognizing Value of Innovative New Drugs

Low drug prices are not an unqualified boon, however. Developing drugs takes an enormous amount of time, effort and money. And a profit margin must be tacked on, or else corporate funding for research and development and hence innovative new drugs will not be forthcoming. And that will eventually hurt patients, who are the beneficiaries of medical care. In short, drug prices require the perspective of promoting the innovation that supports research and development by pharmaceutical firms as well.

When considering the cost of new drugs, it is necessary to understand the herculean task of their development. The core values of drugs are effectiveness and safety. Effectiveness will be meaningless without safety. That is why time is necessary for verification. Sources say that it takes nine to 17 years from the discovery of a candidate substance to its production and sales.

The first step is “basic research”, the search for candidate substances. In addition to substances contained in plants and produced by microbes all over the world, the structures and properties of synthetized substances are examined using computer technology. Next come “preclinical studies” where the effectiveness and safety of new candidate substances are tested on cell culture products and/or mice and other animals. When these are confirmed,

"clinical trials" on human beings begin. During the clinical trials, tests are repeated on patients and healthy persons at many medical institutions. At this stage, development is often terminated because of the emergence of serious side effects. After enough data showing effectiveness and safety are collected from this process, which takes years, an application for approval is filed with the MHLW. Here it undergoes yet another exacting inspection, and it is often the case that new trials are required due to insufficient data. It is only after this exacting inspection that it is approved and registered in the drug price list. Some say that the probability of a new drug candidate actually making it to a market launch is one in 20,000 to 30,000, at a cost of tens to hundreds of billion yen. The bulk of new drugs had been low molecular weight drugs and the like. However, progress in molecular biology has recently led to a rapid increase in the number of biological drugs, including antibody drugs using genetic recombination technology. And research and development on biological drugs is expensive, resulting in expensive drugs *(Chart 7)*.

Number of Effective but Expensive Biologicals on Rise

Chart 8 "Transition of new drugs" shows that only two of the top 15 drugs in global sales in 2001 were biological drugs, accounting for $5.6 billion in sales, only a little more than one-tenth of low molecular weight drug sales. But in 2014, those numbers rose to eight of the top 15, accounting for $68 billion, a 12-fold leap. Antibody drugs and the like distinguish themselves by their pinpoint precision, attacking cancer cells effectively with minimal side effects.

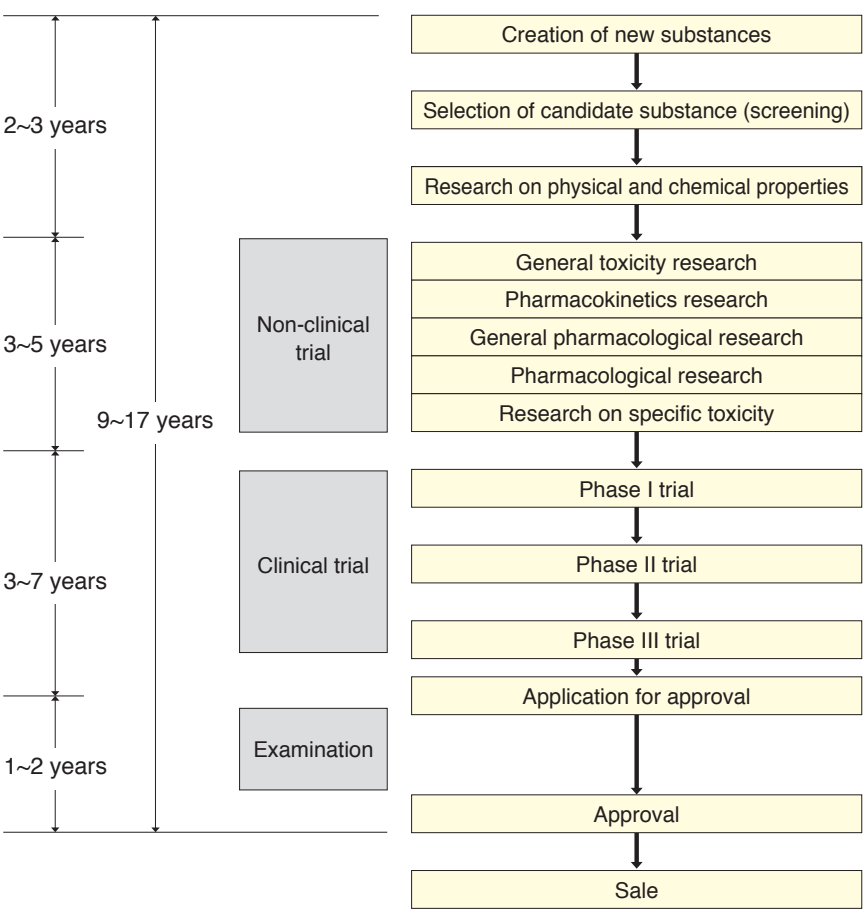
In many cases, a biological drug arrives when a researcher who discovers a candidate substance sets up a startup, which is bought up by a major pharmaceutical company, which manufactures and markets the drug. As the result, blockbuster drugs, a new concept defined as a drug generating more than $1 billion in sales, such as drugs for treating hyperlipidemia, rheumatoid arthritis and so on, are generated by major pharmaceuticals, who have the financial wherewithal.

The world sales rankings of pharmaceutical companies are topped by European and US companies Novartis (Switzerland) and Pfizer (US), while Japanese companies struggle, as Japan's top pharmaceutical companies Takeda Pharmaceutical, Astellas Pharma and Daiichi Sankyo rank 17th, 19th and 24th respectively. Investment in research and development, which accounts for approximately 20% of profits, correlates to the operating profit ratio. A look at the operating profit ratio and sales and R&D expenditures over time highlights the high operating profit ratios of US and European pharmaceuticals as a major reason for the enormity of their research and development expenditures. The operating profit ratio, which shows how much profit is made on drug sales, is almost twice as high for US and European companies than their Japanese counterparts. This gap is reflected in the relative size of their R&D expenditures.

CHART 7

Outline development process with timeline for new drugs

It is said that it takes 9-17 years to develop a new drug and that it costs approximately 50.0 billion yen per item to do so.

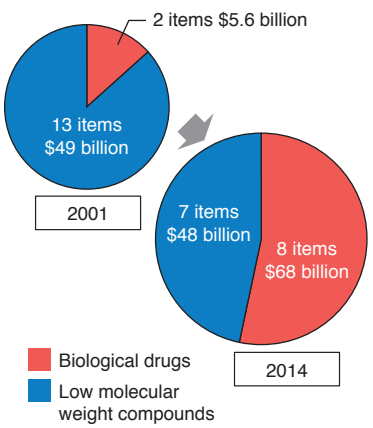


Source: Ministry of Health, Labour and Welfare material

CHART 8
Transition of new drugs

Changes in drug creation trends

Global sales of biologicals by value (World top 15 items by sales value)



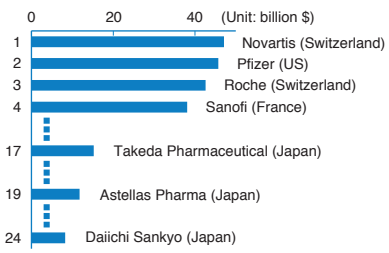
Operating profit ratio and sales

Operating profit ratios of main Japanese, US & European pharmaceutical companies (2014)

United States	Europe	Japan
21.5%	19.2%	11.5%

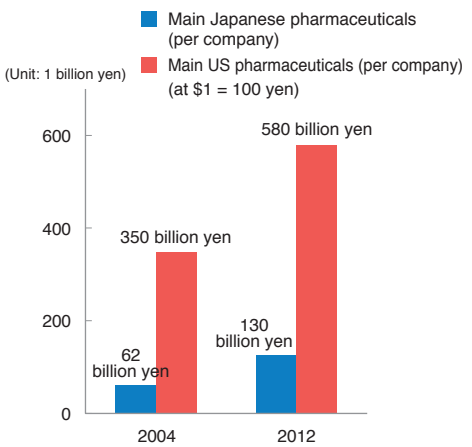
Japan, US and Europe: eight main pharmaceuticals each

Sales of major global pharmaceutical companies (2014)



Ratio of research and development expenditures

R&D expenditures by main Japanese and US pharmaceutical companies



Source: Material submitted on Dec. 7, 2016 to the Economic and Fiscal Policy Council by temporary member Yashuhisa Shiozaki.

Opdivo, a Japanese Innovation

The high price of Opdivo was partly the outcome of efforts to protect drug development in Japan in the harsh environment surrounding pharmaceutical companies. The development of Opdivo was triggered by Dr. Honjo's discovery of programmed cell death-1 (PD-1) on the surface of immune cells that cause apoptosis. PD-1 is expressed widely on immune cells such as T cell and B cell lymphocytes, where it acts as an immune checkpoint molecule, a brake on the immune system to prevent it from overreacting. Cancer cells in particular activate this braking function in order to multiply.

This was an epoch-making discovery that opened the way to new immunotherapy. Previously, immunotherapy consisted of activating immune cells by injecting cancer antigens. But removing the braking function of PD-1 would reactivate immune cells and cause them to begin attacking cancer cells.

The Kyoto University research team discovered PD-L1 as the ligand that activates PD-1. It found that PD-L1 exists on the surface of cancer cells and weakens the immunological response by connecting with PD-1. So, if PD-L1 is suppressed by putting a lid on it with an anti-PD-L1 antibody, the immune cells become active again. The group confirmed the effect of restraining cancer through tests, and filed patent applications jointly with Ono Pharmaceutical in 2002. Joint clinical trials were started with Bristol Myers Squibb, the US pharmaceutical company, in 2006. And this anti-PD-L1 antibody was nivolumab, better known as Opdivo, its brand name.

Opdivo is distinguished by three features: (1) it can be used on a wide range of cancers, (2) nausea, hair loss and other side effects are minimal, and (3) it is sustainably effective in terminal cases. It only helped about 20% of the patients, but cancer cells stopped growing for them, effectively eliminating cancer cells in some. The first new drug developed in Japan in a long while and with no similar drug available, the drug price was determined under the cost accounting method. The operating profit ratio was set at 27%, six-tenths higher than the 17% average for ordinary drugs.

New Rules for Reducing Expensive Drug Prices

There is a rule newly adopted in 2015 for reducing the price of an expensive drug. Applied to the aforementioned top-selling drug Sovaldi among others, the rule calls for the reduction of the publicly listed price of a drug whose annual sales surpass 150 billion yen and the pharmaceutical company's forecast by 30% or more by a maximum of 50% at the once every two years revision of medical service fees. A drug whose annual sales surpass 100 billion yen and the forecast by 50% or more may be reduced by a maximum of 25%.

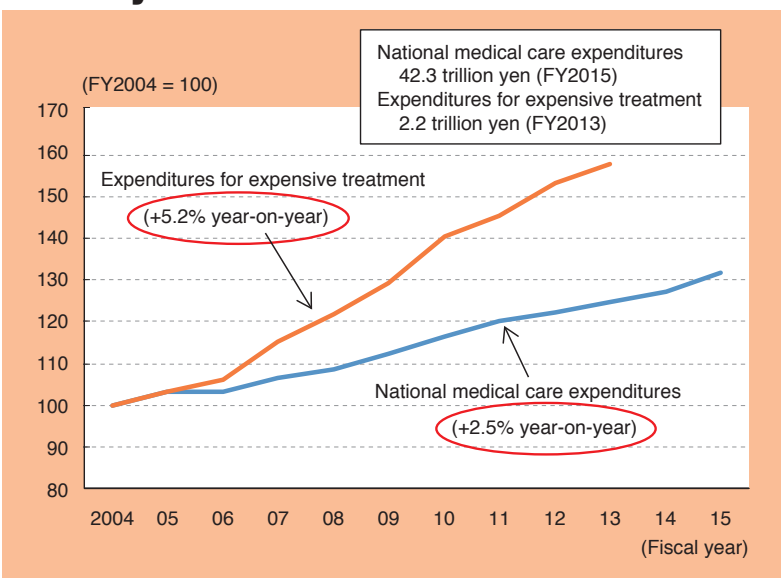
This new rule is applied at the biannual revision of medical service fees. But in light of the Opdivo problem, on Oct. 14 last year, Prime Minister Shinzo Abe took the occasion of the Council on Economic and Fiscal Policy to issue an instruction to the MHLW, stating, "I wish to have specific measures developed to respond to expensive drugs." In response, the MHLW and *Chuikyo* decided to conduct an emergency drug price revision effective as of Feb. 1 this year. It is highly unusual for a drug price to be revised other than at the revision of medical service fees. The price of Opdivo was reduced by 50% to 364,925 yen. The Japan Pharmaceutical Manufacturers Association

(JPMA) and others are protesting, stating that it "could result in reducing willingness to conduct research and development of new drugs."

To deliver effective drugs to patients at appropriate price levels, it is necessary to satisfy two different perspectives, the sustainability of universal healthcare and the promotion of innovation. It was to this end that the Japanese government last year revised the basic principles for calculating drug prices (1) to review the price of a new drug such as Opdivo for which an indication is added subsequently or which is attaining sales beyond original expectations at the quarterly listing of new drugs, (2) to revise drug prices once a year based on market research to see how much the difference is between actually prevailing prices, and (3) in evaluating innovation to introduce cost-benefit analysis and raise the price if the economic effect is confirmed, among others.

CHART 9

Rising cost of expensive treatment - public payment for expensive treatment rising 5% annually



Note: Created from National Medical Care Expenditures and Basic Material concerning Medical Care Insurance (both Ministry of Health, Labour and Welfare). FY2014 and FY2015 figures estimated by multiplying FY2013 national medical care costs by the FY2014 and FY2015 growth rates of the overall medical care expenditures estimate.

Source: Material distributed to the Economic and Fiscal Policy Council (Oct. 21, 2016)

Cost-Benefit Analysis & Annual Revision of Drug Prices

Cost-benefit analysis, through which experts correct the price for drugs by evaluating their economic efficacy, was introduced on a trial basis in April 2016. The yardstick used for this inspection is the "Quality-Adjusted Life Year (QALY)". QALY provides the means for the comprehensive evaluation of how much the quality of life is improved as well as how many years survival is extended. The method was adopted in the UK, where all medical care costs are covered by the state. The National Institute for Health and Clinical Excellence (NICE) was established in 1999 to implement it, an organization with approximately 500 staff members including experts.

QALY is represented by the area representing the number of years of life and the state of health (quality of life = QoL) on a graph. For QoL, perfect health is given a value of 1 and death 0. For example, if QoL remains unchanged at 0.7 during two years of life, QALY = 0.7 x 2 = 1.4. In fact, QoL changes with the symptoms. In the case of the UK, cost-benefit is considered high if the cost per QALY is 20,000-30,000 pounds or lower.

NICE dropped approximately half the anti-cancer drugs from the recommended list as not being cost-effective. Opdivo as a treatment for lung cancer is also currently under consideration.

Continued Debate Towards Appropriate Drug Prices Essential

Japan has a system for expensive therapy in place that restrains copayments even when expensive drugs are used. Under this system, the state takes care of the payment when the monthly outlay exceeds a certain amount that is determined by personal income. This is a very powerful safety net. However, it has a defect. Since this does not impose much of a burden on the individual, there is a tendency to abuse the system by such means as the excessive use of drugs, with the result that a rising proportion of the costs is being borne by the state. Expenditures under the system for expensive therapies are rising dramatically *(Chart 9)*.

It is said that the drug price determination system lacks transparency. It is necessary to increase the transparency of the deliberation on drug prices and develop a framework for reviewing drug prices in response to changes in the environment including the expansion of the market and cost-benefit analysis. Expensive but highly effective drugs will continue to emerge. Drastic measures that give appropriate recognition to the innovation that leads to their development while making major reductions in the drug prices when its indication is expanded will be necessary. It is difficult to get a perfect answer from the beginning. Continuous debate and a highly flexible response that takes this into consideration are required. JS

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