

**New vision for the pharmaceutical industry**  
– Aiming at the industry with international  
competitive power taking the mission of innovation –

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## Table of contents

<b>Introduction</b>	<b>... P 3</b>
1. Changes in 5 years after establishment of the vision in the pharmaceutical industry and concept of establishment of new vision	
(1) Changes in 5 years after establishment of the previous vision	
(2) What is requested for strengthening of the international competitive power and for solving drug lag?	
(3) Direction of measures and policies in the new vision	
2. Those requested in the pharmaceutical industry	
3. Point of this vision for the pharmaceutical industry	
<b>I. Changes in the environment surrounding the pharmaceutical industry</b>	<b>P 9</b>
1. Progression of life science	
(1) Trend of research and development in the life science field and changes in recent years.	
(2) Research and development leading to development of new drugs	
2. Progression of globalization and all-out international competition	
(1) Progression of globalization	
(2) Escalation of international competition in research and development	
(3) Cooperation with Asia	
3. Increase of M&A and changes in capital markets, etc.	
4. Function differentiation in the pharmaceutical-related industries	
5. Increase of medical care expense accompanied by rapid progression, etc. of aging population combined with the diminishing number of children	
6. Change of in citizens' consciousness to medical care	
7. Needs of preventive medical care such as vaccine and future of the industry	
<b>II. Current status and tasks of the pharmaceutical industry</b>	<b>... P 24</b>
1. Characteristics of the market	
(1) Market size	
(2) Market structure	
2. Characteristics of the industry	
(1) Industrial structure	
(2) International competitive power	
(3) Size of company	
(4) Status of technology / research and development	
(5) Sales strength	
<b>III. Mechanism of innovation-centered growth of the pharmaceutical industry and picture of the future industry</b>	<b>... P 33</b>
1. Predominant features, innovation-centered growth and repercussion of the pharmaceutical industry	
2. Picture of the future pharmaceutical industry – Structure of the pharmaceutical	

industry with the international competitive power –

- (1) Direction to which pharmaceutical companies take
- (2) Industries newly generate
- (3) Entry and integration of different industries

3. Picture of the future drug industry

- (1) Current status of drug wholesaling
- (2) Tasks and picture of the future of drug wholesaling

4. Picture of the future drug retailing

- (1) Current status of drug retailing
- (2) Tasks and picture of the future of the drug retailing

**IV. Basic concept of policy for the pharmaceutical industry . . . P 43**

1. Strategic business development by the company
2. The roles of the government
3. Setting of the intensive period and conduct of policy for creation of innovative new drugs
4. Industrial policy for promoting innovation-centered new drug development
5. Industrial policy in recognizing the importance of innovation ripple effects

**V. Concrete measures to be taken during the “Intensive period for creation of innovative new drugs” (within 5 years) . . . P 47**

1. Enhancement and implementation of the efforts in the government
  - (1) Comprehensive response as the whole government
  - (2) Positive approach by the related government ministries and agencies, etc.
2. Action plan for realization of this vision
  - (1) Support to research and development
  - (2) Promotion of clinical trials / clinical researches
  - (3) Speed-up and quality improvement, etc. of the approval examination
  - (4) Future existence of the drug pricing system and drug benefit
  - (5) Fostering of generic market
  - (6) Fostering of proprietary drug market
  - (7) Streamlining and grade-up of distribution function
  - (8) Promotion of proper use of pharmaceutical products
  - (9) Arrangement of the promotion system by the public and private sectors

**Conclusion . . . P 69**

\* On preparing this report, we made reference to many domestic and foreign literatures and survey reports including the “Future Vision of Pharmaceutical Industry – Industry’s missions and challenges toward 2015” (May 2007) by the Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturers Association. We obtained cooperation from many people including Professor Kimura, Donated Course “Pharmacobusiness Innovation”, Graduate School of Pharmacy, The University of Tokyo. We are grateful to all the relevant people.

## Introduction

### 1. Changes in 5 years after establishment of the vision in the pharmaceutical industry and concept of establishment of new vision

#### (1) Changes in 5 years after establishment of the previous vision

- Five years have passed since the first establishment of a vision of the pharmaceutical industry “Hoping for strengthening of the international competitive power of the pharmaceutical industry supporting century of life – Vision for the pharmaceutical industry –“ (hereinafter referred to as the “previous vision”) by the Ministry of Health, Labour and Welfare as the national vision in 2002.
- During this period, along with progression of M&A between pharmaceutical companies, international evolution has progressed mainly in large-scale companies and the foreign sales ratio has increased to the level of nearly 50%. The assistance measures by the government such as activation of clinical trials begin to achieve an effect for example, the number of clinical trial notification turns to increase.
- However, the percentage of Japan-made drugs in new blockbuster drugs in the world has not increased and when the situation is reviewed limitedly after 2000, no new blockbuster drug made in Japan has not appeared. Difference in the scale of research and development expenditure between Japanese companies and European and U.S. companies tends to increase. Accordingly, the international competitive power of Japanese companies is hard to say enough and these are difficult times for Japanese companies.
- On the contrary, the timing of launch of pharmaceutical products in Japan is slow compared with the world level (that is, “problem of drug lag”). Moreover, in the situation that multinational clinical trials by which international development of pharmaceutical products is simultaneously conducted in plural countries become mainstream, with the background of clinical trial environment with relatively high cost, it is pointed out that Japan alone misses out on the wave among the countries developing new drugs. This can also be said that the pharmaceutical market in Japan itself become to lose the international competitive power.
- In the situation that achievement of direction aimed by the vision for the pharmaceutical industry is not sufficient, acceleration of economic growth and promotion of innovation became to position as big political tasks of the whole government since last year.
- Especially, the pharmaceutical industry contributes to improvement of the level of medical treatment for health of citizens and is the industry that can be expected to largely contribute to growth of national economy as a leading industry taking over Japan that aims the nation built on intellectual property. The pharmaceutical industry is considered to play an important role that can be said as the first stage of innovation as the field contributing to creation of innovation that contributes to growth.
- Based on the above-described changes in 5 years after establishment of the previous vision and based on the basic direction of promotion of innovation and acceleration of growth potential that are important political tasks in Japan, in order to try strengthening of the international competitive power of the pharmaceutical industry in Japan and resolution of drug lag, thereby aiming wealthy country that can “supply citizens with safe and high-quality pharmaceutical products meeting medical needs as early as possible at reasonable prices”, we decide to establish a new vision for the pharmaceutical industry.

## **(2) What is requested for strengthening of the international competitive power and for solving drug lag?**

- In the 21st century that is said as “century of life science”, the pharmaceutical industry is the one that is expected not only to contribute to improvement of the level of medical treatment for health of citizens but also to largely contribute to economic growth. Because of such industry, competition is accelerated in the world scale.
- Japan is said to have the power of developing new drugs in the 3rd place following U.S. and U.K. but the domestic market size of pharmaceutical products has relatively decreased to about 10% of the world market. Pharmaceutical companies cannot survive against severe international competition today by targeting at the domestic market alone and cannot take a ride on benevolent cycle of continuing investment to new drug development.
- Also, existence of “drug lag” represents decrease of international appeal of the drug discovery environment and market in Japan and considering that we are the 2nd largest pharmaceutical market in the world by country, increase of the international competitive power will help to introduce up-to-the-second therapeutic drugs in foreign countries rapidly and Japanese patients are considered to be able to rapidly receive medical care of the highest level.
- In order to correspond to these 2 tasks, it is essential to make our drug discovery environment / pharmaceutical market open and internationally consistent. Accordingly, from that point of view, it can be said that attitude of totally checking the policy is required.

## **(3) Direction of measures and policies in the new vision**

- From the above-described viewpoint, the government has worked to establish comprehensive political package and to provide a forum for dialogue between the public and private sectors for conducting discussion between the public and private sectors about such important matters.
- On January 31 2007, under hosting by the minister of Health, Labour and Welfare, the minister of Education, Culture, Sports, Science and Technology, the minister of Economy, Trade and Industry and relevant persons in the pharmaceutical industry and education and research organizations attended and set “Communication between the public and private sectors for innovative pharmaceutical products” for the purpose of having common view on creation of innovation in the pharmaceutical field and strengthening of the international competitive force of the pharmaceutical industry.
- Furthermore, the second occasion of communication between the public and private sectors was held on April 26 2007. On this occasion of communication, we decided the “Five-Year Strategy for Creation of Innovative Pharmaceutical Products and Medical Devices” (the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labour and Welfare and the Ministry of Economy, Trade and Industry) composed of intensive infusion of research fund, fostering of venture companies, etc., arrangement of environment for clinical researches and clinical trials, cooperation with Asia, speed-up and quality improvement of regulatory review and proper rewarding of innovation.
- The concept that was used as the background of this 5-year strategy was as follows: For rapid supply of excellent new drugs in the world to Japanese patients, first of all, Japanese companies increase incentive for research and development and launch in Japan by keeping up with Europe and U.S., foreign companies regard Japan as important market and conduct positive investment to Japan and also speed-up of launch is necessary. For this, it is

important to make Japan to be the place for drug discovery environment enabling simultaneous development with Europe and U.S. and to arrange the environment of the domestic market such that innovative new drugs are properly rewarded.

- In order to properly reward innovative new drugs while harmonizing with sustainability of healthcare financing, further promotion of use of generics and proprietary drugs is also important task.
- This vision is a comprehensive industrial vision prepared by using this 5-year strategy as the basic strategy and also by adding the picture of the future industry, growth of related industries and necessary measures and policies for it.
- This industrial vision should be pursued by the public and private sectors in cooperation based on the common understanding. Those required to the pharmaceutical industry as well as those to be implemented by the government should be pursued by the public and private sectors in cooperation with appropriate role sharing.

## **2. Those requested in the pharmaceutical industry**

- Pharmaceutical products are placed as a part of medical care and have high value and grave social responsibility as life-related products. The industrial vision has the purpose of having common view between the public and private sectors for various points and it is also important to divide and share responsibility between the public and private sectors. Those requested to pharmaceutical companies is not only strengthening of the international competitive power.
- With the time, the structure of diseases in the society has changed. Response to unmet medical needs (medical needs that have not been satisfied yet) in the structure of diseases at that time is important and the pharmaceutical companies that catch the needs rapidly and make successful development of new drugs meeting this needs are expected to get a huge lead on the world pharmaceutical industry in the future.
- There are many pharmaceutical products whose importance of development is recognized though profit performance is low such as therapeutic drugs for incurable diseases for which the therapeutic method has not been discovered, orphan drugs and new vaccine effective for prevention, etc. of new infections.
- As a company whose base is placed in Japan, approach to develop and supply the pharmaceutical products better suiting the domestic or Asian needs as pharmaceutical company is regardable and is very important same as the approach by the government. Furthermore, it is also expected to conduct social and international contributions such as humanitarian support to developing countries with poor access to pharmaceutical products and risk management on onset of unanticipated occurrences including new flu, disasters and bio terrorism, etc.
- It is welcome that pharmaceutical companies place their hub / base for research and development in Japan and develop new drugs made in Japan. Also, support by the government to such companies should be sufficiently examined.

### **3. Point of this vision for the pharmaceutical industry**

- This vision for the pharmaceutical industry is established and published as a new industrial vision by totally reviewing at present the vision for the pharmaceutical industry published in 2002.

#### **(Major environmental changes)**

- First of all, this vision addresses as changes in the environment surrounding the pharmaceutical industry, trend of research and development in the life science field, especially, that after completion of genome sequencing, post-genome research deals understanding of functions in RNA transcript level and understanding of molecular biological disease structure as important themes and that by reflecting these themes, competition in new drug development gets more serious in the pharmaceutical field such as antibody drugs and molecular targeting drugs.
- Also, further progression of globalization is the other important environmental change. It addresses that in the situation that worldwide simultaneous development becomes mainstream in the in the world leading pharmaceutical companies, Japan gets left behind from multinational clinical trials, innovation receives greater recognition in individual countries worldwide and international competition in research and development is progressed in the government level and Japan also starts approach by establishing the “Five-Year Strategy for Creation of Innovative Pharmaceutical Products and Medical Devices”.
- Moreover, it also addresses that merger and acquisition activity in the pharmaceutical industry is further promoted and merger of large-scale companies begins also in the pharmaceutical industry in Japan and various related industries are growing such as flourishing of venture companies and increase of companies conducting various contracts.

#### **(Current status and tasks of the pharmaceutical industry)**

- Based on such environmental changes, the current status and the tasks of the pharmaceutical industry are sorted out. Compared with the status of the industry at the time of the previous vision, the share of pharmaceutical products made in foreign countries increased in the pharmaceutical market in Japan and on the other hand, problem of “drug lag” becomes clear that launch of the pharmaceutical products that have already been marketed in main companies in Europe and U.S. delays in Japan. From the viewpoint of international competitive power of the industry, it is hard to say that there was progression in spite of approach for the past 5 years.
- By sorting out such status surrounding the pharmaceutical industry, it may be no exaggeration to say that in the situation that international competition in new drug development gets more serious also involving the governments, the international competitive power of the pharmaceutical industry in Japan has not increased and the international competitive power (= international appeal) of the environment of drug discovery and the market itself are almost lost. In other word, Japan is in the crisis situation.

#### **(Characteristics of this vision)**

- Based on recognition of such current status, the vision indicates the picture of the future industry and the measures and policies that the government should take in the form of action plan. This is basically the structure same as that in the previous vision but it has new characteristic as described below for the picture of the future industry.

- [1] The picture of the future industry has been refurbished based on the current status of international competition.
- [2] It has been clarified that continuous innovation is essential for growth of the industry.
- [3] Also for drug wholesalers, picture of the future industry is indicated and functionality requirements are shown.

- For the measures and policies that the government should take, the “Five-Year Strategy for Creation of Innovative Pharmaceutical Products and Medical Devices” was summarized in April this year under cooperation of 3 ministries. Mainly based on this strategy, a comprehensive action plan including fostering of generic market, fostering of proprietary drug market and streamlining / grade-up of distribution function was established this time.

#### (Construction of this vision and the follow-up system)

- This vision for the pharmaceutical industry, same as the previous vision, has the construction that while having a look over the industry after 10 years, the period of intensive approach for 5 years is defined, concrete action plan is established and annual follow-up is conducted for various measures and policies by the public and private sectors.
- With regard to the follow-up, since some of the actions plans are the same as those raised the aforementioned 5-year strategy, the “occasion of communication for creation of innovative drugs between the public and private sectors” to be held this year by the Ministry of Health, Labour and Welfare under the participation of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Economy, Trade and Industry will be utilized, and with regard to the entire action plans, the progress status of the policies will be reported at the “Conference for promotion of pharmaceutical industry policies” as before.

#### (Positioning of this vision)

- The industrial vision this time, based on the previous vision as described above, responds to the future environmental changes, further progresses the system of collaboration between the ministries and the system of communication between the public and private sectors and aims a new goal for internationalization / strengthening of the international competitive power. Accordingly, it should be called “a new vision” as establishment of the new vision not only review of the previous vision.
- Importance is increasing in the direction of the industry conducting not only development of pharmaceutical products focused on therapy, etc. but also development of pharmaceutical products with an eye to pharmaceutical products for prevention / therapy such as vaccine. We will respond this in cooperation with “Vaccine Industrial Vision” (by the Ministry of Health, Labour and Welfare in March 2007).

# **I. Changes in the environment surrounding the pharmaceutical industry**

## **1. Progression of life science**

### **(1) Trend of research and development in the life science field and changes in recent years.**

- The 21st century is called “Century of life science” and progression of life science is expected to make contribution in the field directly linked to peoples’ lives such as overcome of diseases that afflict humanity.
- Especially in Japan in which aging society with a falling birth rate and depopulating society are coming, life science research is attracting attention as science and technology that can realize healthy long life of citizens and can realize securing safety of citizens such as treatment of new / repeated infections including new-type influenza and SARS (severe acute respiratory syndrome) as well as that will lead strengthening of the international competitive power of the pharmaceutical industry.
- Life science research has large expectations internationally. Individual countries positively conduct investment of public fund for research of the life science field after 2000 and competition in research and development gets more serious between countries including strategy for intellectual property.
- Human genome sequencing has been progressed, approach to post-genome research has been accelerated and desired result has been achieved. Considering flow of the future life science research, however, it becomes important themes to understand not only gene level of individual human genome but also function of collection of genes such as haplotype, function at the RNA transcript level and molecular biological disease structure in the various levels of expressed protein and metabolites and to deepen understanding of comprehensive complete picture as living matter.
- Especially, for research and development related to drug discovery and medical technology, empirical research is necessary until practical realization. Mechanism that the processes and results of the basic research that has been progressed are smoothly linked to practical realization is important. It is necessary to come to attach in importance to the viewpoint of giving outcome back to citizens and to promote research for bridging to clinical researches and clinical setting.

### **(2) Research and development leading to development of new drugs**

- After human gene has been decoded in the 21st century, development of new drugs by applying genomics and protein science, etc. is progressed in the world.
- By progression of these life science researches, developments have been proceeded for “antibody drug” making use of the nature of “antibody” in the immune function that human originally possesses, “molecular targeting drug” that finds out targets such as specific gene (molecule) and protein exists on the cell surface (high molecule) and selectively attacks (affects) specific cells and genes, etc. and “RNA interference drug” that affects the function of RNA by paying attention to the transcription function of genes. Especially, a hopeful view is taken on these drugs in the anticancer drug field and it is expected as one of the fields of pharmaceutical products that will mostly grow in the future.

- Also the method of narrowing down candidate compounds of pharmaceutical products from the viewpoints of efficacy and toxicity (safety) has been evolved and there are methods such as new toxicity evaluation method “toxicogenomics” in which causes of occurring adverse reactions of drugs and chemical substances are examined based on the information at onset of the adverse drug reactions at genome base (gene level) and “pharmacogenomics” in which genome information (genetic characteristics) of patients is analyzed for searching and developing appropriate pharmaceutical products efficacious and safe in specific disease groups and development of a drug suitable to the disease is aimed.
- Moreover, new biotechnology is closely related to informatics field and for gene discovery from sequence information, structural analysis of biologic molecules and expectation of interaction between proteins, “bioinformatics” conducted by integrating IT and biotechnology is fully used. Practical realization in drug discovery is difficult without these technologies.
- Especially, analysis technology in “in silico” has been markedly progressed that re-creates life phenomena such as the action between proteins related to diseases and pharmaceutical products on computer. These technologies are closely related to development speed in drug discovery and research and development expenditure for bioinformatics business tends to sharply increase in the several years.
- Pharmaceutical products are expected for the following points by these target researches of drug discovery.
  - [1] Through increase of opportunity of finding out target in drug discovery and change from stochastic method to logical and scientific method for research and development process of pharmaceutical products, pharmaceutical products can be developed more effectively than by the conventional drug discovery method.
  - [2] By such “pharmacogenomics” making use of such drug discovery method, more effective and safer pharmaceutical products suitable to dispositions of individual patients are developed and administration of effective and economical pharmaceutical products becomes possible.
- In order to create many pharmaceutical products by these new target researches in drug discovery as outcome that can be given back to medical care and patients by 10 years after, pharmaceutical companies must strengthen capacity for technological development. It is huge task to obtain a leading role in international competition in innovative changes of drug discovery method.
- As biological resources such as genes, cells and experimental animals are indispensable for development of pharmaceutical products, a research resource bank was established by cooperation between the National Institute of Biomedical Innovation and the Japan Health Science Foundation (the bank collects biological resources from individual research institutions such as universities and countries and standardize them, furthermore incubates the resource and gives them to individual research institutions). The bank develops biological resources required in research setting and also conducts research for collecting and keeping various biological resources intact and for stably providing them to research setting.
- In target research in drug discovery that becomes diversified year by year, it becomes the situation that roles of the research supporting facilities and private facilities conducting the basic research for drug discovery should be sorted out in relation with the tasks such as

convergence of resources for research and development defined in the “Five-Year Strategy for Creation of Innovative Pharmaceutical Products and Medical Devices”.

## **2. Progression of globalization and all-out international competition**

### **(1) Progression of globalization**

- Rapid progression of science and technology in the 21st century largely changed the industrial structure, society and the way of life and brought significant benefits such as overcome of many diseases and prolongation of life-span. With rapid changes in means of transportation and IT as backgrounds, it also brought “global age” in which people, things and money rapidly move everywhere and information is shared everywhere.
- In the 21st century in which the industrial activity is also spreading out in a borderless manner in the world market, international competition gets more serious with science and technology as the mean of providing seeds to economic growth and political infusions of taxpayers’ money, investment to research and development in companies and systemic reforms promoting research support are proceeded in individual countries. Also, in Japan, the policy based on reorganization of importance in science and technology is regarded as important field for future investment.
- Above all, in the pharmaceutical industry with high risk of research and development not observed in other industries and many proceedings, etc. related to approval application, etc. of pharmaceutical products, it is very important to effectively utilize the up-to-the-second research outcomes of biotechnology and genome, etc. in which individual countries worldwide engage, to conduct search and research and development of seeds in individual countries in the world at high speed for obtaining approval of pharmaceutical products and to extend distribution activity in individual countries in the world for maximization of profit.
- Actually, all the pharmaceutical companies ranked high in sales amount in the world have deployed the business activities such as research, development and marketing in a borderless manner, and the development and marketing of new drugs are performed simultaneously all over the world as the mainstream. In such situation, though multinational clinical trials are preceded in the world scale in not only Europe and U.S. but also in East Europe and Asia, etc. having potential of becoming new market in which cost for clinical trials is inexpensive, Japan alone is missing out on the wave.
- In the age of such rapid globalization, the importance of “innovation” has become highlighted rapidly in individual countries of the world. For increasing the international competitive power of the pharmaceutical industry of each country, it is necessary to establish such social system, etc. that promotes the processes of invention, technical innovation and practical realization of basic research outcomes, especially at the speed of the global level, in order to rapidly provide the research/development outcomes to the domestic and foreign markets and change the economic and social values of the country.
- Especially in the case of pharmaceutical products, since clinical trials requiring enormous costs are essential for obtaining regulatory approval, harmonization of regulatory review standards is strongly desired. In this connection, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) among Japan, the USA and Europe has been held since 1993. As a result, some regulatory review standards have been unified, and utilization of foreign clinical trial data have become possible to some extent. However, further cooperative relationship among Japan, the USA and Europe in the next stage is necessary such as the common consultation system among the three regions like that tested between the USA and Europe.

- In order that the government rapidly and properly examines pharmaceutical products making use of the state-of-art science and technology such as biotechnology and confirms efficacy and safety after marketing, it is necessary for the pharmaceutical administration itself to catch up with progression of technology and to have regulatory science that enables scientific examination firmly responding marked progression of life science.
- Also in “New Health Frontier Strategy” (World Economic Forum for New Health Frontier Strategy in April 2007), as approach for speed-up, etc. of evaluation of products / technologies in practical realization, that “investigation and research on appropriate evaluation method for efficacy and safety of products using innovative technology are promoted” is mentioned and regulatory science is considered one of key measures and policies in the future.<sup>1</sup>
- For repletion of regulatory science, efforts of the departments and agencies that take charge of the pharmaceutical administration and arrangement of base such as progression of related sciences and repletion of education in the national study and research center and independent administrative agencies for research and development, etc. scientifically supporting the departments and agencies.

## **(2) Escalation of international competition in research and development**

- The life science field is placed as the field with leading force in the economic development in individual advanced countries and is regarded as point field and approach is strengthened as national strategy.
- In U.S., the ratio of NIH (The National Institutes of Health) in the budget for research and development is as high as about one-quarter. Moreover, since 2004, strategic initiative “NIH load map” plan has been deployed for accelerating deployment of the basic research outcome and research outcome to clinical application. Researches are progressed across the organizations as the whole research institutes under NIH in the field such as research for elucidation of complex biologic system difficult to yield results in single laboratory, academic field research and high risk research and reorganization of clinical researches.
- In EU, partnership business between the public and private sectors ”Initiative for Innovative pharmaceutical products” was deployed for accelerating search and development of new drugs and in 2006, “Strategic research agenda” identifying bottleneck in the drug discovery process that is tried to be resolved was summarized. Especially, in U.K., approaches were made such as foundation of partnership for the purpose of promotion of clinical researches in U.K. (U.K. Clinical Research Collaboration: UKCRC) (2004) and foundation of National Institute of Health Research (NIHR) for promotion of research coordination / clinical trial conduct in NHS (2005). Also, in 2006, setting of [1] the central coordination organization for health research (Office for Strategic Coordination of Health Research: OSCHR) and suggestion of [2] furtherance to translational research jointly by Medical Research Conference (MRC) and National Institute for Health and Research (NIHR) (foundation of Translational Medicine Funding Board) were made.

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<sup>1</sup> In the United States, the report of the regulatory authority FDA entitled “Critical Path Opportunity” (2004) states that “In order to resolve the bottle-neck in development, it is necessary to realize “Regulatory Science” (e.g., discovery and utilization of biomarkers using microarray technology which can predict the efficacy and toxicity of a drug without conducting human studies, development of disease model animals showing similarity to human disease and drug evaluation using such animals, etc.)”.

- Based on the Basic Law on Science and Technology, “Basic Plan for Science and Technology” (the 1st period: from 1996 to 2000) was established as the basic policy for comprehensive and intentional promotion of the measures and policies related to fostering of science and technology in the 21st century while aiming “nation built on creativity of science and technology”. In the 2nd period (from 2001 to 2005), the life science field was addressed as the point field and it was continuously handled as the point field also in the 3rd period (from 2006 to 2010). Also, promotion strategy by the field was defined for proceeding selection and convergence of investment for research and development and intensive investment was decided to be conducted to clinical researches linking outcomes of the basic research to drug discovery / bridging researches to clinical practice, etc.<sup>2</sup>
- In April 2007, under the initiative of the minister of Health, Labour and Welfare, Japan participated in the international development / supply system of innovative pharmaceutical products and medical devices and the “Five-Year Strategy for Creation of Innovative Pharmaceutical Products and Medical Devices” was established with the purpose of making the industry of pharmaceutical products / medical devices as a role with leading power in the growth of Japan and the purpose of rapidly supplying citizens with pharmaceutical products / medical devices of the world top level. This strategy was decided to be steadily promoted also in the “Basic Policy for Economic and Financial Reforms 2007” (approved in a Cabinet meeting on June 19, 2007) and it was shown to support the pharmaceutical industry as the national strategy.
- Other than above, putting the period until 2025 in perspective, “Innovation 25” (approved in a Cabinet meeting on June 1, 2007) that is a long-term strategic guidance showing the medium-term and long-term policies to be conducted for research and development, etc., “New Health Frontier Strategy” (April 2007) that promotes prevention-oriented health and supports prolongation of healthy life-span for spending healthy and active life and “Economic Growth Strategic Outline” (June 2007) showing conduct of the above-described 5-year strategy for strengthening of the international competitive power of the industry of pharmaceutical products / medical devices were established.<sup>3</sup>
- As described above, arrangement of systems in which industry, government and academia cooperate for research and development for creating drug discovery technology and make

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<sup>2</sup> Besides, the policies having been implemented and being implemented now as the national strategies include “Millennium Project” (5-year plan from fiscal 2000) aiming at realization of innovative medical care depending on individual characteristics in the aging society, “Medical Frontier Strategy” (5-year plan from fiscal 2001) aiming at improvement of prevention and treatment results for cancer, myocardial infarction, dementia and bone fracture and “Health Frontier Strategy” (10-year plan from fiscal 2005) aiming at a decreased number of patients needing caretaker and 2-year prolongation of healthy life.

<sup>3</sup> In addition, the R&D-supporting systems have also been arranged surely and steadily. Furthermore, promotion of technology transfer by the Technology Licensing Organization Law (TLO Law, 1998) and the Industry Revival Special Measures Law (Japanese version of the Bayh-Dole Act, 1999), promotion of collaborative researches between the public and private sectors by revision of the Research Exchange Promotion Law (1998), creation of new business and new market with high productivity by enactment of the Industry Technical Power Reinforcement Law (2000), and drug patent reinforcement (abolition of 2-year cutback requirements in the patent duration extension system) by revision of the Patent Law (2000) were implemented. In addition, the “Patent Examination Highway System” in which expedited patent application examination through simplified procedures is available by submitting the examination result in a country where the patent application concerned has been approved is tested currently (between Japan and USA: from July 2006; between Japan and Korea: from April 2007,; between Japan and the UK: from July 2007). Besides, a preferential taxation system to encourage study/research (deduction of research/development cost at a certain rate) has been created.

various supports has been largely progressed in the past 10 years. Especially, in the situation that globalization of drug discovery strategy in the industrial arena is progressing, in development of pharmaceutical products with high intensity of intellectual property, liquidation occurs such as transfer of the base for research and development to the regions beneficial for development. When the international competitive power of the industry is considered as a country, importance of measures and policies, etc. for creating innovation conducted by individual countries is increasing.<sup>4</sup>

### **(3) Cooperation with Asia**

- In recent years, it is considered important to cooperate with Asia that is close geometrically and alike ethnically also in research and development of pharmaceutical products.
- In February 2007, the Japanese government agreed “New future-oriented concept of cooperation between Japan and China” between Japan and China. For measures against cancer, with clinical research for establishment of therapy and interchange / fostering, etc. of researchers as important pillars, joint clinical research is decided to promote for developing new drugs made in Asia and effective in Asian. In April 2007, in the meeting between Japanese, Chinese and South Korean Health Secretaries, the Japanese government signed “Memorandum of understanding for joint response to new-type influenza between Japan, China and South Korea” incorporating strengthening of cooperative system in the fields of quarantine, surveillance and therapy. Also, the government agreed to cooperate for collective occupation of clinical data, etc. for early development of excellent pharmaceutical products in the 3 countries.
- By strengthening cooperation with Asia, the effect of contributing to streamlining and speed-up of clinical researches and clinical trials can be expected in Asian regions.

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<sup>4</sup> Recently, also Japanese government and pharmaceutical companies are increasing the research/development budgets and pursuing effective utilization of research/development resources such as collaborative utilization of the world’s leading experimental facilities including SPring-8 (Japan Synchrotron Radiation Research Institute), but not only in the field of medicine and pharmacy, there is an absolute difference in basic research budget between Japan and the USA. In the situation that the USA is in the superior position in intellectual property strategy related to the biological field including genome analysis, it is the urgent issue to reinforce Japan’s basic research power in new drug creation especially in the field of protein analysis in Japan’s line.

### 3. Increase of M&A and changes in capital markets, etc.

- In the international market, M&A (mergers, acquisitions and transfer of business, etc.) had acutely increased by 2000 mainly in Europe and U.S. by liberalization, etc. of the world trade investment. The pharmaceutical industry is no exception and half of the top 20 companies in the world sales ranking merged during this decade (Fig 1).
- As the reason for increasing M&A, in the situation that research and development expenditure will internationally increase acutely by competition of new drug development in the future and the share of generics is increasing worldwide, securement of size of research and development expenditure, supplement of pipeline for preventing profit decline due to income reduction after patent time of original products and aiming increase of sales strength are considered.
- Since 1994, from the viewpoint of strengthening the international competitive power of companies, provision of corporate legislative enabling flexible and various corporate reorganization became political task. Legalization of pure holding companies (1996), foundation of stock exchange / stock transfer system (1999), foundation of corporate divestiture system and corporate divestiture tax system, legalization of treasury stock (2001) and introduction of consolidated return system (2002) were conducted.<sup>5</sup>
- Furthermore, in order to strengthen the industrial technologies supporting innovation, the Industrial Technologies Strengthening Act was revised with the content that control was transferred from AIST for Japanese Bayh-Dole Act that attributes intellectual property right related to research and development contracted by the government to business operators and it shall be the permanent measures (2007).<sup>6</sup>
- With such situation as background, also in Japan, the number of M&A is largely increasing in recent years. Especially, M&A between Japanese companies is largely increasing and M&A between foreign companies and Japanese companies that had been few is also increasing (Fig. 2).
- Also for capital market, by changing from indirect finance to direct finance and by diversifying financing method, etc., cooperate governance by main bank weakened and the ratio of stock holding by foreign investors increased, thereby shifting to “stockholders-weighted operation”.
- Japanese companies have also proceeded “selection and convergence” policy in which managerial resources are focused to the pharmaceutical business unit with high earning capacity based on such changes in the business environment and provision of the laws /

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<sup>5</sup> In 2005, the Company Law was enacted, in which the regulations on organizational restructuring actions have been refurbished. In the case of merger by absorption, it is now admitted to pay the properties of the surviving company other than the stocks thereof (cash or parent company’s stocks) to the stock holders of the expired company as compensation to the stocks of expired company (flexible mechanisms for compensation of merger). This system has enabled the merger in which a foreign company absorbs a Japanese company utilizing its subsidiary company founded in Japan and pays the stocks of the foreign company being the parent company to the stock holders of the expired company (so-called “forward triangular merger”).

<sup>6</sup> Furthermore, for reinforcement of the industry’s technical power supporting innovation, the Industry Technical Power Reinforcement Law was revised (2007) to transfer the Japanese version of the Bayh-Dole Act, in which the intellectual properties related to the researches commissioned by the government are assigned to business owners etc., from the Industry Revival Special Measures Law to be the permanent measure.

systems for smooth conduct of corporate reconstruction. Also as financial standing in pharmaceutical companies is stable, M&A had been rarely conducted until now. However, M&A between companies in the high sales ranking in Japan has become active beginning with Mitsubishi-Tokyo Pharmaceutical Inc. and Welfide Corporation, Chugai Pharmaceutical Co., Ltd. and Roche Japan, followed by Yamanouchi Pharmaceutical Co. Ltd. and Fujisawa Pharmaceutical Co. Ltd. (Astellas Pharma Inc. at present), Sankyo Pharmaceutical Co. Ltd. and Daiichi Pharmaceutical Co., Ltd. (Daiichi Sankyo Company, Limited at present), Sumitomo Pharmaceutical Co., Ltd. and Dainippon Pharmaceutical Co., Ltd. (Dainippon Sumitomo Pharma Co., Ltd. at present) merged (in 2007, Tanabe Seiyaku Co., Ltd. and Mitsubishi Pharma Corporation is planned to merge) (Fig. 3).

- Also, alliance (cooperation) has become active more than ever such that companies jointly attempt research and development and distribution in foreign countries of pharmaceutical products with high risk. As pharmaceutical companies are expected to grow and the ratio of stock holding by foreign investors is increasing, the cases using M&A and alliance are considered to increase in the future as means for management's rationalization and strengthening of the competitive power.

#### 4. Function differentiation in the pharmaceutical-related industries

- The future research and development of pharmaceutical products will require wide and various new technologies including biotechnology especially in the initial stage. On the contrary, as progression of these technologies is rapid and future prospects are unclear, pharmaceutical companies themselves must conduct investment at high risk. Venture companies play an important role in the field of drug discovery in the initial stage of such research and development along with universities and public research facilities and become indispensable for improvement of research and development capacity of the pharmaceutical industry in Europe and U.S.
- However, venture companies are fewer in Japan than in Europe and U.S. and immature. Recently, therefore, various measures to support venture companies have been taken.<sup>7</sup>
- Recently, venture companies that deals with technology of pharmaceutical products derived from tissues / cells of human and animals and DDS (Drug-Delivery System), development of nucleic acid drug, etc. and genetic research using the state-of-art technology such as biotechnology have generated and are expected to increase in the future.
- The National Institute of Biomedical Innovation supplies venture companies conducting research of pharmaceutical products / medical devices at the stage of practical realization with research fund by the Bayh-Dole contract method. Also, the institute delivers grant and supports by instructions and advices, etc. to venture companies for stimulating research and development of orphan drugs for which research and development are difficult to progress due to small number of patients and difficult return of investment for research and development though their medical needs is high.
- Furthermore, as various venture companies and new contract businesses increase, also the pharmaceutical companies that do not conduct from research and development to distribution by themselves but outsource a part of it or receive supply from outside are increasing.
- For example, in research and development, there are cases that clinical trial is contracted out to Contract Research Organization (CRO) or a certain stage of clinical study conducted by bio-venture companies is purchased. Especially, by the revision of the Pharmaceutical Affairs Law (enforced in April 2005), as “authorization of manufacturing” became “authorization of manufacturing and distribution” and “authorization of manufacturing”, there is large influence that pharmaceutical companies become to be able to totally contract out manufacturing to any other company having manufacturing factory without having factory by themselves. Also, in trial institutions, the cases that part of duties for clinical trial (management of trial-related documents and prior informed consent to patients for clinical trial, etc.) is contracted out to Study Management Organization (SMO) are increasing. The market size of Contract Research Organization (CRO) is about 83.1 billion (Fig. 4) and the

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<sup>7</sup> As the recent venture-supporting measures, the environmental arrangements such as enactment of the New Business Creation Promotion Law (1998, 2005, Law Related to New Business Activity Promotion for Small & Medium Enterprises (unified to the Small & Medium Enterprises New activity Promotion Law), creation of the stock exchange markets of “Mothers” and “NASDAQ Japan” (1999-2000), liberalization of stock option by revision of the Commercial Law (2001), admission of new company type by enactment of the Company Law (limited liability company (LLC)) (2005), etc., and the policies such as funding to venture companies by the Organization for Small & Medium Enterprises and Regional Innovation and investment/financing activities by the former Organization for Pharmaceutical Safety and Research were performed.

market size of Study Management Organization (SMO) is about 33.7 billion (Fig. 5), both of which are extending.

- Entry of IT industry is also observed in genetic analysis, etc. For manufacturing, the cases that manufacturing is contracted out in some form are predominant. For activities of supplying information in distribution, service of substituting role of MR by using IT occurs. Furthermore, in recent years, in case that companies want to temporarily increase MR such as at launch of new drugs, the companies that utilize “contract MR” (MR dispatched from Contract Sales Organization (CSO) to pharmaceutical companies or MR belonging to CSO who conducts MR activity by contracting duties from pharmaceutical companies) tend toward increase.

## **5. Increase of medical care expense accompanied by rapid progression, etc. of aging population combined with the diminishing number of children**

- By rapid progression of aging population combined with the diminishing number of children and prolongation of mean life-span, etc., medical care expense for citizens, especially, medical care expense for the elderly acutely increase and further increase is expected in the future (Figs. 6 to 8).
- In such situation and in the situation that the environment surrounding medical care is largely changing such as flagging economic condition, progression of medical technology and change in consciousness of citizens, the Ministry of Health, Labour and Welfare thought that in order that citizens can enjoy good and effective medical care now and in future years, each system constituting the medical care system such as the healthcare system, the medical fee system and the healthcare insurance system are required to be largely changed and presented the “Draft for reform of the medical-care system” in September 2001.
- In March 2003, “Basic policy for reform of the medical-care system” was approved in a Cabinet meeting in which the medical fee system shall be reviewed at each revision and foundation of new medical care system for the elderly and reorganization and integration of insurers shall be realized in 2008.
- By the “Basic policy for economic and fiscal management and structural reforms” (that is, “Large-boned policy” 2005), from the viewpoint of securing sustainability of the social security system in super-aging society, for political target aiming substantial achievement of appropriate medical care expense, while responding that “reform of the medical-care system shall be carried out resolutely in 2006 upon obtaining conclusion in 2005 along with content of concrete measures” and with the aim of concretizing the “Basic policy for reform of the medical-care system”, the Ministry of Health, Labour and Welfare indicated the “Draft for reform of the medical-care system” in October 2005.
- Based on this draft, in December 2005, “Outline of reform of the medical-care system” was summarized by the Medical Council of the government and ruling parties that shows the basic concept concerning securing safe and reliable medical care, comprehensive promotion of weighting prevention and appropriate medical care expense and concerning realization of new healthcare insurance system having a look over super-aging society. The healthcare system bill based on the outline was submitted to the regular Diet and enacted in June 2006. Hereafter, it is necessary to make steady promotions toward preparation of the plan for appropriate medical care expenditures and establishment of the late-stage medical care system for the elderly.
- As the prices of ethical drugs with the sales accounting for 90% or more in the market are fixed by the healthcare insurance system, the influence of reform of the medical-care system is very large for the pharmaceutical industry. As a result of minimizing excess difference in drug price for 10 years, the percentage of drug price in the medical care expense has decreased from about 30% to about 20%. This tendency toward decrease in recent years would have received large influence of drug price revision (reduction) conducted almost every two years but it is the situation that the percentage of drug cost stops to decrease from decrease of drug price difference, repercussion of proper use of pharmaceutical products and appearance of few drugs, etc. Hereafter, the total medical care expenditures are expected to increase due to further aging and progress of medical science, and the drug expenditures are also expected to increase similarly based on the recent situation.

- On the contrary, in the situation that severe healthcare financing will continue in the future, as the volume of production in the whole pharmaceutical industry largely depends on drug benefit cost by medical insurance, in the domestic market, strict rationalization of the whole pharmaceutical industry and change of the industrial structure will be demanded.

## 6. Change of in citizens' consciousness to medical care

- Along with changes in disease structure such as increase of adult diseases by progression of aging, repercussion of informed consent and pursuit of quality of life (QOL), the interest of the people on their health and medical care is raising such as metabolic syndrome. On the contrary, the government declared Healthy Japan 21 in 2000, put the Health Promotion Law into force in 2003 and spelled out the measures and policies for promotion of citizens' health by self-supervision.
- In such situation, "self medication" making use of the OTC drugs at hand under the advices of healthcare professionals such as pharmacists at pharmacies and drug stores is getting more important, and the term of "self medication" has become popular (Figure 9). But, in recent years, the release amount of OTC drugs has rather decreased (Figure 10).
- This is because the types of OTC drugs currently marketed are not sufficient and cannot meet the needs of consumers that their health is protected by themselves (for example, prevention of metabolic syndrome, etc.) Also, we can consider the influence of that citizens who become to feel interest in health and medical care become to positively purchase health foods and supplements, etc. represented by "food for specified health use (FOSHU)" under the label of "food".
- In such situation, citizens' needs are increasing also for information on pharmaceutical products. It is required to supply easily understandable information on indication, adverse drug reactions and intake method, etc. In addition, by recent increase of medical care expense for citizens, increase of burden on patients and increase of the interest in generics, information supply is also requested on prices and equivalency of original products and generics. As further progressions of personalized medical care and evidence-based medicine (EBM) are expected in the future, detailed activities for information on pharmaceutical products reflecting differences in conditions and predispositions, etc. of patients are estimated to further progress.
- Information supply gives the utility not only to patients themselves but also is expected to give the utility to the society such that by many citizens having enough information, development of pharmaceutical products and information supply better meeting patients' needs are promoted and repercussion of self medication using OTC drugs and stable repercussion of generics suppresses increase of medical care expense for citizens.

## **7. Needs of preventive medical care such as vaccine and future of the industry**

- There is a vision that by increase of needs in the field of elderly people and adults, the world vaccine market will grow 3 times or more the current market after 10 years (Fig. 11). On the other hand, critical feeling against international bio terrorism, etc. increases and measures by vaccine have become to attract attention at a rapid rate for several years. As the basic measures against infections, not only use of vaccine for normal preventive inoculation but also use of vaccine for prevention of infections is expected especially in the field where there are no therapeutic drugs or the effect of the therapeutic drug is not sufficiently expected. Securing of production base having the international competitive power, strengthening of research and development capacity that can correspond to risk management observed in discussion on measures against new flu and securing of production and supply system, etc. become huge tasks in the international society.
- In the Western countries, large-scale companies are developing new vaccines continuously, but in Japan, small-scale companies are supporting production/supply of vaccines for prophylactic inoculation. The difference in R&D power is also marked between inside and outside Japan, and furthermore the standard vaccines used worldwide have not been introduced into Japanese market, resulting in the current serious situation. Especially, also in the field in which practical realization of Japan-specialized technology is expected such as new immunoenhancing drugs and vaccines with new administration route, there is the crisis situation that clinical application and industrialization of Japanese technologies developed in national research institute, etc. are not progressed.
- For vaccine technology in Europe and U.S., developments related to DNA vaccine and new administration technique and development, etc. of new immunoenhancing components are progressed, bio-venture companies, etc. enter the development of production technology for new vaccine and proceed active research and development.
- In such situation, we have enacted the “Vaccine Industry Vision” aiming at activation of Japanese vaccine market and securement of the domestic vaccine production system. Since the vaccine industry is the essential industry supporting the national policy against infection, we intend to promote strategic cooperation between the domestic vaccine companies and the domestic/foreign major pharmaceutical companies for arrangement of the domestic system from development and production of vaccine in collaboration of industry, government and academia from the comprehensive aspect including the national vaccination policies.

## **II. Current status and tasks of the pharmaceutical industry**

### **1. Characteristics of the market**

#### **(1) Market size**

- The pharmaceutical market size in Japan is about 7.6 trillion yen (2005) and more than 90% of it is accounted by ethical drugs (Fig. 1). As positioning in the world market, the pharmaceutical market in Japan accounts for about 10% of the world market and the share by country is the 2nd largest market in world following U.S. (2006) (Fig. 2)
- Degree of extension in the market size of ethical drugs is strongly affected by the drug price revision and the reform of the medical-care system (Fig. 3). After 1990 and 1991, the percentage of the drug cost in the medical care expense for citizens has decreased from about 30% to about 20% due to reduction of drug price, etc. but in this 5 years, the percentage of the drug cost slightly takes a favorable turn (Figs. 4 and 5).

#### **(2) Market structure**

- Compared with the current ethical drug market with that 5 years before, “cardiovascular drugs” having the top share of 17% remains to increase the share with the background of aging. Other than this, “other metabolic drugs” including diabetic drugs increase the share due to the influence of adult diseases and “anticancer drugs” also increase the share as development of new anticancer drugs continues. On the contrary, the shares of “digestive drugs” and “antibody preparations” decrease (Fig. 6).
- The share of Japanese companies in the Japanese market is about more than 60% and the share of U.S. companies and European companies is respectively around 20% but of the shipment value in Japan, the shipment value in foreign companies is increasing year by year and becomes to account for about one-third (Figs. 7 and 8). Especially, when we limitedly review pharmaceutical products containing new active ingredients approved in Japan, the percentage of foreign-made products is about 75% and that of Japan-made products is about 25% (Fig. 9).
- From the viewpoint of access to the up-to-the-second medical care, drug lag is observed in new drugs with high usefulness such as antibody drugs and molecular targeting drugs as well as anticancer drugs and also in many launched items common between Japan and main countries in Europe and U.S. Furthermore, though there are various factors, for the items in the world high sales ranking, not only the timing of launch is slower in Japan than in Europe and U.S. but also there are pharmaceutical products that were launched in other countries but are not launched in Japan. Accordingly, Japanese patients cannot use these pharmaceutical products and there are opinions pointing out particularity of Japanese market (Fig. 10).
- Such situation is largely attributable to that the Japanese market has not grown to the place to which individual companies want to launch new drugs preferentially because of weak international competitive power and poor appeal of the drug discovery environment even though there is an aspect of influence of development strategy by individual companies.
- Also, compared with Europe and U.S., Japan has the high share of about more than 60% for the items in which 10 years have passed from their launch (the number of items base / money base). It is considered attributable to that the life cycle is long for the item in which 10 years have passed from their launch (Fig. 11).

- The share of generics is 16.8% (surveyed by the Japan Generic Pharmaceutical Manufacturers Association in 2004) and the share is lower in Japan than in other countries that develop new drugs (Fig. 12). This is considered attributable to that the public healthcare insurance system in Japan differs from that in other countries and that generics companies cannot sufficiently obtain confidence of healthcare professionals, etc. Also from the viewpoints of decreasing the patient's burden and improving the public finances for medical insurance as well as appreciating the innovative new drugs, it is important to promote use of good-quality generic products, and the government is also going to pursue the program to steadily achieve the targeted share of generic products.

## 2. Characteristics of the industry

### (1) Industrial structure

- The number of companies obtaining authorization of manufacturing of pharmaceutical products or manufacturing / distribution of pharmaceutical products is 1,660 companies by “Survey of the Prescription Pharmaceuticals Industry of Japan” (2005) and about 70% of the whole companies are those with capital asset of 300 million yen or less. The breakdown of it is [1] companies mainly manufacturing and distributing ethical drugs: 447 companies (of these, companies mainly manufacturing / distributing generics: 72 companies), [2] companies mainly manufacturing and distributing OTC drugs: 387 companies and [3] companies manufacturing and distributing pharmaceutical products other than OTC drugs: 108 companies (excluding 259 companies having no sales of pharmaceutical products and 429 companies that did not submit the surgery sheet) (Fig. 13).
- Viewed the degree of concentration in the sales amount of pharmaceutical products, the top 5 companies account for 35.5%, the top 10 companies account for 49.8% and the top 30 companies account for 74.9%. Furthermore, viewed the degree of concentration in the sales amount of ethical drugs, the top 5 companies account for 38.4%, the top 10 companies account for 53.7% and the top 30 companies account for 79.6%. Compared with the status 5 years ago, the degree of concentration in the whole industry tends toward further increase (Fig. 14).
- The number of employees related to pharmaceutical products is 238,000 persons (189,000 persons in manufacturing / distribution of pharmaceutical products and 49,000 persons in drug wholesaling) and the percentage of them in people holding jobs in the whole industry is about 0.4% (Fig. 15).
- The self-assessed income of the pharmaceutical industry account for 12% of the national income, ranked third among the manufacturing industries following the automobile industry and electric industry (Figure 16).

### (2) International competitive power

- Balance of visible trade of pharmaceutical products has worsened after peaking in 2000 and it exceeds 620 billion in 2006 (Fig. 17). The index of international competitive power [= (balance of imported and exported amounts) / (exported amount + imported amount)] has been continuously minus since before in the pharmaceutical industry, as distinct from the tendency of getting plus in the other industries (Figure 18). Though tendency toward improvement was observed in the period from 1990 to 2000, the index worsened again during the period from 2000 to 2005.
- On the contrary, technology balance has largely increased in recent years and its surplus is the 2nd highest in the whole industry following automobiles (Fig. 19). But, it is necessary to keep in mind the fact that in the pharmaceutical industry, the international competitive power cannot be simply measured with only trade balance and status of technology licensing in/out.
- Seven products containing 4 components developed by Japanese companies are included in the top 30 items in the world sales ranking by component (Fig. 20). When origins of the top 100 items in the world sales ranking are examined by country of companies, Japan is in the 3rd place following U.S. and U.K. (Fig. 21). Of the world blockbuster products (sales amount: 700 million dollars or more), the share of products originated from Japan has

increased in recent years. Provided, however that blockbuster products are increasing in the world, the shares of both the number of items and the sales amount show almost no change (Fig. 22).

- Japanese companies have become to be able to develop drugs in foreign countries from the late 1990s. Before then, actually there were many cases that pharmaceutical products developed in Japan were derivated to foreign companies and overseas presence was achieved by clinical development by foreign companies.
- In recent years, major companies emphasis on overseas presence and the percentage of the sales amount in foreign countries in the total sales amount is lower in main Japanese companies than in main European companies but is comparable to that in main U.S. companies. Many companies whose percentage of the sales amount in foreign countries increased also increased the total sales amount (Figs 23 and 24). In the situation that the sales in Japan turns flat, for example, whether or not research and development / distribution strategy of pharmaceutical products can be positively proceeded in Europe and U.S. such as conduct of multinational clinical trials is the important point for growth of Japanese pharmaceutical companies.
- Moreover, individual countries in Asia including China in which marked economic development is expected in the future are close geometrically and ethnically compared with the countries in Europe and U.S. and highly likely to become attractive market in the aspect of development and distribution of pharmaceutical products for Japan. After 2000, there is the situation that Europe and U.S. companies have increasingly conducted multinational clinical trials in Asia bypassing Japan and positive business deployment by Japanese companies is expected as core of drug discovery in Asia (Fig. 25).

### **(3) Size of company**

- The international competitive power of companies is not necessarily decided only by the sizes like sales amount but in order to conduct large investment for research and development continuously in parallel with individual countries in the world, it is the fact that a certain sales amount (company size) is necessary.
- Major pharmaceutical companies in Japan had increased the sales amount by progression, etc. of foreign deployment but as major pharmaceutical companies in the world have further increased the sales amount more by merger and market extension in Europe and U.S. Accordingly, at present, at the head of Takeda Pharmaceutical Company Limited in the 16th place in the world (2001: in the 15th place), Astella Pharma Inc (in the 20th place), Daiichi Sankyo Company, Limited (in the 22nd place) and Eisai Co., Ltd. (in the 23rd place) and Otsuka Pharmaceutical Co., Ltd. (in the 25th place) enter their names in the 20s in the world. Pharmaceutical companies of the different types from the conventional pharmaceutical companies caught up with Japanese pharmaceutical companies and begin to take over Japanese companies such that bio-venture companies, AMGen Inc. leaped ahead to the 11th place (2001: in the 20th place) and Genentech, Inc. to the 17th place (2001: in the 31st place) as well as Teva Pharmaceutical Industries Ltd. that is generic company leaped ahead to the 19th place (2001: under the top 30 pharmaceutical companies) (Fig. 26).
- For the share by country in the top 30 pharmaceutical companies in the sales ranking, 12 companies in U.S. account for 43.4% and 2 companies in U.K. account for 14.9%. Other than above, 2 companies in Switzerland and France respectively account for 13.0% and 9.6%. In Japan, 5 companies account for 7.8% and it is the actual situation that many medium-sized companies of the similar size stand cheek by jowl (Figure 27).

- U.S. companies entering in the top 20 ranking in the world had extended the share upon the expanding U.S. market and based on the activity in U.S., they had increased the sales amount in foreign markets. Considering the above, Japanese pharmaceutical companies are also requested to positively expand scale and to have the competitive power comparable to that of foreign companies in the sales share by overseas presence to U.S. market, etc.

#### **(4) Status of technology / research and development**

##### **[1] Situation of investment for research and development, etc.**

- Research and development of pharmaceutical products takes 9 to 17 years from start of research to obtainment of approval and the successful rate by candidate compound is said to be as low as part per 15,622 (0.006%). The development cost per component is said to be about 50 billion including the cost of the components whose development is suspended (Fig. 28).
- For the trend of increase and decrease in the research fund in recent years, it has increased in the pharmaceutical industry exceeding the mean increase in the whole industry (Fig. 29). By major pharmaceutical companies, in comparison between Japan and Europe / U.S. of the operating profit margin, net profit margin and the percentage of research and development expenditure to the recent sales amount, the operating profit margin and net profit margin are lower in Japan than in Europe and U.S. but the percentage of research and development expenditure is comparable between Japan and Europe and U.S. (Fig. 30).
- On the contrary, research and development expenditure per company in Japan is as low as one-sixth that in U.S. In several years, the difference tends to increase and I would have to say that the absolute research fund in Japanese companies is small (Fig. 31). The budget related to life science in the Japanese government is increasing but it is only one-seventh the budget in the U.S. government with difference remaining (Fig. 32).
- The percentage of researchers in employees in the pharmaceutical industry is above 10%, which is 3rd highest following the electric machine industry and the scientific industry (Fig. 33). Research fund per researcher is about 48 million yen (2005) which is highest in the manufacturing field (Fig. 34), indicating that burden of research and development expenditure is large in the pharmaceutical industry.
- As described above, in the situation in which high-cost tendency is progressing in the drug discovery environment, reservation about dwindling pipeline for drug discovery is pointed out. Quality becomes to be challenged in search of effective seeds for drug discovery and bridging the seeds to development as well as development strategic management by the companies related to selection of development items.
- Especially, in the situation that needs specific to companies are difficult to generate to unmet medical needs, importance is increasing in license strategy such as investment to, cooperation / coordination and M&A, etc. with outside companies including venture companies supplying seeds in development strategy by Europe and U.S. companies. Also in Japanese companies, arrangement of such license environment with outside companies is the task.
- Depending on the scale and content of research, joint development is sometimes more effective than research and development by single company. Joint research and cooperation,

etc. are conducted between individual companies as necessary but there is approach by participation of more companies.<sup>8</sup>

- Besides, the number of pharmaceutical companies which include an invention reward system in the wage system to increase the researcher's incentive to new drug creation has been increasing since before, but the revised Patent Law was put into effect in 2005, and it has become a principle to decide the reward to employee's invention through negotiation between the employer and the employee.

## [2] Technology situation and level of research and development

- The number of registrations of patents related to pharmaceutical products in Japan has changed in about 1,300 cases per year for 10 years during the period from 1996 to 2005. On the contrary, though it tends toward decrease in U.S. in recent years after 2002, it is as high as about 6,000 cases per year (Fig. 35). Simple comparison cannot be made as differences in the patent system and content of patents must be considered. However, though the number of the whole patent registrations is comparable between Japan and U.S. (Fig.36), difference is large in the number of patent registrations related to pharmaceutical products between the countries.
- When the situation of patent application by company is reviewed, the number of application is very large in the companies in the high sales ranking in the world such as Pfizer Pharmaceutical Company and GlaxoSmithKline K.K and the number of applications to Japan, U.S. and Europe is large, while the number of applications by Japanese companies is small and most of them were applied to Japan alone. Difference is also observed in the trend of patent application between foreign companies and Japanese companies (Fig. 37). If Japanese companies aim the international deployment, it is necessary to be conscious of global response also for patent.
- Especially, also in the critical technology related to research tool of biotechnology required for technology innovation for realizing development of innovative biotechnologically-based products (gene analysis technology and bioinformatics, etc.) and effective search technology of drug discovery seeds (combinational chemistry, high throughputs screening), main patents are held by U.S. and Japan depends on imports of products and technologies by Europe and U.S.
- When the number of patent applications by company is reviewed limitedly for patents of biotechnologically-based products, also in this field, the number of patent applications is small by Japanese companies (Fig. 38). In the technological field that has not been established in Europe and U.S. such as analysis of disease-related protein possibly leading directly to drug discovery, Japan must regain lost ground. As shown in Celera Genomics, etc. in U.S., in supply of research tool used in drug discovery, fostering of bio-venture

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<sup>8</sup> The examples include a consortium in which 22 member companies of the Japan Pharmaceutical Manufacturers' Association are jointly utilizing the SPring-8 by setting the dedicated beam line for protein structure analysis aiming at drug creation, a consortium in which the National Highly Professional Medical Center and pharmaceutical companies jointly perform "analysis of cancer-related proteins" utilizing the latest mass analysis technology, and a toxicogenomics project in which the National Institute of Biomedical Innovation and 15 pharmaceutical companies are aiming at development of a system to evaluate/foresee safety of drugs at the early stage of drug creation by establishing the data base accumulating the toxicity information and gene information through gene expression analysis after exposing animals and cells to drugs and by utilizing the informatics technology together with the data base.

companies that make technologies in the domestic public research institutes and universities practicable can be said as urgent task.

- In the trend of patent application in post-genome-related technologies, it tends to decrease after peaking in 2000 in Europe and U.S., while it tends to increase in Japan (Fig. 39). By the ranking of applicants, the period of 1991 to 1999 is the time when patent application of genome information began in earnest and there were many patent applications based on gene structure analysis. During this period, major pharmaceutical companies and venture companies were in the high ranking (Fig. 40). During the period from 2002 to 2004, the rank of venture companies lowered and universities and research institutes heaped ahead (Fig. 41). Patent applications by Japanese universities and research institutes tend to increase and it is important to foster companies having the international competitive power by transferring outcomes of the basic research by universities and research institutes to the industrial arena.
- After middle 1990s, in the situation that the influence of drug price reduction and the influences of enforcement of new GCP Ordinance in 1997 and increased acceptance of foreign clinical data in the pharmaceutical affairs rules, the number of domestic clinical trials had been decreased for 10 years. International competition becomes rather serious but after 2000, no new blockbuster drug made in Japan has been launched.
- In order to improve such situation and to strengthen the international competitive power of the pharmaceutical industry, we established the “Five-Year Strategy for Creation of Innovative Pharmaceutical Products and Medical Devices”. After the completion of this strategy period, if Japanese companies have no international competitive power in the true sense, they would suffer a setback from the domestic market and the world market after 10 years when the current researches produce results.

### [3] Technology transfer and the situation of collaboration of industry, government and academia

- In recent years, for economic activation by creation of new industries, etc., return of research outcomes by universities and national study and research institutes, etc. back to the society and collaboration of industry, government and academia become more important. For this, the above-described promotion strategy has been taken and in the future, arrangement of personnel and base, etc. for collaboration of industry, government and academia, support to smooth transfer and practical realization of research outcomes and start of business and promotion, etc. of research and development leading to typing are required. As means for this, there are Technology Licensing Organizations (TLO) approved or certified based on the Technology Licensing Organization Law (TLO law) and the number of patent applications and income of royalty, etc. are increasing (Fig. 42).
- Also, in the drug discovery field, by joint research between the public and private sectors, in order to promote development of innovative and unique pharmaceutical products and pharmaceutical products closely meeting the needs in clinical setting, research related to development of the up-to-the-second and the critical technologies and research and development of AIDS drugs, etc., “Human Science Total Research Business for Drug Discovery” was conducted by public offering method with the main body of the Japan Health Science Foundation. As a result, it become possible to start development of pharmaceutical products by applying outcome related to hypoxia-responding molecules and RNAi having the angiogenic action and possible to apply the research outcome of purification of neurotoxin to formulation of orphan drugs.

- From the year of 2004, in the field related to rare diseases and AIDS, etc. that is politically important but in which research and development are not promoted only depending on self effort of the industry, “Political Drug Discovery Total Research Business” is conducted for development of excellent pharmaceutical products, etc. by joint research between the public and private sectors. For technology transfer, the Japan Health Science Foundation was certified in 2003 as the first TLO by the Ministry of Health, Labour and Welfare and technology transfer of research outcomes by the national study and research institutions, etc. under the Ministry of Health, Labour and Welfare is proceeded and the environment for promotion of collaboration of industry, government and academia has been arranged.

#### [4] Environment for clinical trials

- Clinical trial is an important step for launch of new drugs and the percentage of the cost related to clinical trial is high in the research and development expenditure. In Japan, the number of clinical trial notifications has decreased after establishment of Ordinance on Good Clinical Practice (GCP) (the Ministry of Health, Labour and Welfare Ordinance No. 28 in 1997) also by the influence of increasing acceptance of foreign study results as approval application data and the influence of drug price reduction, etc. (Fig. 43). Accordingly, critical feeling on “Evisceration of clinical trial” (increase of the cases that pharmaceutical companies precede clinical trials in Europe and U.S. than in Japan) has been pointed out.
- Such “Evisceration of clinical trial” is disadvantage in the aspects that [1] patients delay to access the up-to-the-second medical care (new drugs, etc. distributed in foreign countries) and [2] for the pharmaceutical industry, etc., research and development capacity of Japanese companies decreases and creation of new businesses and new employments decrease. [3] For medical institutions and doctors, etc., level-up of technology delays. Accordingly, negative influences are large in the healthcare insurance level and the international competitive power of the industry in Japan.
- The causes of “Evisceration of clinical trial” are that [1] the time required for clinical trial is longer in Japan than in Europe and U.S., [2] the cost for clinical trials is higher in Japan than in Europe and U.S. and [3] excess response exists in quality control (QC) and quality assurance (QA) of clinical trial data, etc.
- As the reasons for occurring such problem, in the environment of clinical research in Japan including clinical trials, [1] incentive is low in persons who conduct clinical trial (doctors, etc.) and subjects (patients) (academic evaluation of clinical trial is low, significance of clinical trial does not percolate and economic incentive is low), [2] it is expensive (the number of subjects per medical institutions is small and proceedings in each medical institution is bothersome), [3] the clinical trial conduct system is poor (there is few medical institutions in which the clinical trial conduct system is arranged and fostering of doctors and trial collaborators [Clinical Research Coordinator: CRC<sup>9</sup>, etc.] is insufficient), etc. are pointed out.
- In order to improve such situation, by approach based on the “Three-Year Plan for Activation of Clinical Trials Nationwide” established by the Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology in April 2003, the clinical trial conduct system was improved such that large-scale network for

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<sup>9</sup> CRC stands for Clinical Research Coordinator. CRC supporting a clinical trial is called “Clinical Trial Coordinator”.

clinical trials was established and fostering of CRC is being conducted. In recent years, a certain achievement is obtained such that the number of clinical trial notifications tends to gradually increase.

- However, it has been pointed out necessary to conduct a clinical trial efficiently by training clinical trial staffs including physicians, improving the quality of CRC staff, etc. with expertise, resolving the quantitative and qualitative deficiency of clinical trial staffs through improvement of incentive to clinical trial including career pass of physician and CRC, unifying the format for documents necessary for clinical trial contract/application and resolving the so-called “over quality” including excessive responses to GCP inspection, etc. In addition, it has been pointed out necessary to take a measure for reinforcement of functions of the medical institution network constructed so far, arrange environments for prompt and efficient conduct of high-quality clinical trial and intensify the conduct system not only for clinical trial but also for entire clinical researches.
- Based on such situation, with the purpose that “excellent and state-of-art medical care is provided to citizens, the conduct system for clinical studies / clinical researches of pharmaceutical products / medical devices that would become the base of the international competitive power is secured and creation of innovation by Japan is aimed”, the Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology established the “New 5-year plan for activation of clinical studies” in March 2007 and put the plan into force from April 2007. They are attempting arrangement of the environment for effective and rapid conduct of clinical trial / clinical research of high quality such that personnel conducting clinical studies / clinical research are intensively infused and as facilities intensifying technology and fostering staffs, core hospitals and base medical institutions are arranged.

## **(5) Sales strength**

- Information on pharmaceutical product and pharmaceutical product are inextricably linked and activity of information supply is essential. Improvement of qualification of MR and proper allocation of MR have been conventionally addressed as tasks. In Japan, unlike foreign countries, in addition to MR in pharmaceutical companies, MS in wholesale companies also conduct activity of information supply and it was pointed out that there were too many MRs. At present, pharmaceutical companies become to put emphasis on the promotion activity of anchor products, they increase employment of MR. Also, in case that pharmaceutical companies want to temporarily increase MR such as at launch of new drugs, they sometime utilize contract MR and the percentage of use of contract MR tends to increase in recent years.
- Most of the major companies that increase the sales amount in foreign countries distribute the products in foreign countries by themselves. How to establish the distribution system in foreign countries is the point to secure high income.

### **III. Mechanism of innovation-centered growth of the pharmaceutical industry and picture of the future industry**

#### **1. Predominant features, innovation-centered growth and repercussion of the pharmaceutical industry**

- In general, for growth of industry, there is “spiral growth” that requires “benevolent cycle of demand and innovation” as follows; new products / new services produced by innovation (technology revolution) generate new demand and in order to meet this demand, competition is conducted in the market. As a result, productivity in the industry increases and new investment for research and development becomes possible, thereby generating further innovation and further demand.
- However, growth of the pharmaceutical industry has the following features based on the specialty of medical care and pharmaceutical products.
  - ◆ As it has the feature of one patent per product, original products after patent time lose market by rapid transfer to generics. Accordingly, companies cannot grow continuously without continuous production of new drugs.
  - ◆ Medical needs of citizens always change such that overcome of one disease clarifies the needs for other disease and innovation is continuously required such that in order to meet new medical needs, discovery of new mechanism of action, etc. is required
  - ◆ The research and development expenditure is getting higher year by year and cost recovery becomes difficult in one country. Furthermore, the particularity of pharmaceutical is getting more conspicuous, in the light of the public insurance system, the world trend toward promoted use of generic products and the development of a target patient-limited drug such as a tailored drug, etc..
- Healthcare insurance and overcome of diseases are felt want of citizens and the role of the government is large in promotion of development of pharmaceutical products. Development of pharmaceutical products itself is the role of the private sector but when whole flow of development of new drugs is reviewed, it has features that there are many portions closely related to the roles the government should play such as promotion of the basic research, bridging outcomes to the private sector, facilitation and speed-up of process to productization and indemnity of cost to patients.
- On the contrary, from the other viewpoint of the whole pharmaceutical industry including related industries, it has also repercussion-growth structure that innovation is affecting activation of market of the whole industry such that research and development / innovation take a lead in the whole industry which become new product group in generic market after termination of patent time.
- Accordingly, growth of the pharmaceutical industry can aim innovation-centered growth of companies dealing with research and development (innovation-centered growth) and repercussion-type growth that it is spreading in the whole market. For growth of innovation which is the key point, industrial vision like this vision and the system of communication between the public and private sectors started this year are essential.

## **2. Picture of the future pharmaceutical industry – Structure of the pharmaceutical industry with the international competitive power –**

- Medical care expense for citizens in Japan is expected to be 44 trillion yen in 2015 even after the system reform conducted in 2006 and expected to be 56 trillion yen in 2025. It is not only due to the influence of aging but also grade-up of medical care such as launch of new drugs is incorporated. If the future increase of the drug cost is comparable to that of the medical care expense, the future pharmaceutical market would become 1.3 times in 2015 and 1.7 times in 2025 that in 2005.
- Looking the world market, the markets in individual countries show increase larger than that in Japan and larger market is expected to appear. In order to grow the pharmaceutical industry in response to this expansion of the market, as described above, continuous development of new drugs, innovation and approach to the international deployment become necessary. If the industrial arena will make a great leap forward based on the “Five-Year Strategy for Creation of Innovative Pharmaceutical Products and Medical Devices” made by the government, Japan will be able to become base of new drug development parallel to Europe and U.S.
- As described above, for proceeding international development while attempting innovation, the scale enable to secure a certain research and development is essential. On the contrary, in the situation that the existing products matured and more targeting development of pharmaceutical products will become necessary in the future, it is pointed out that there is a limitation in the model of the conventional global mega pharma conducting development of mainly blockbuster products while repeating mergers.
- The pharmaceutical industry of Japan will be sufficiently capable of competing with the world major companies in development of new drugs, if successful in adaptation to the new stage of international competition, expansion to an appropriate company size, pursuit for the field in which Japan can lead the world, line-up of competitive products, etc. Hereafter, Japan should continue to be one of the major three regions (Japan, the USA and Europe) in drug creation and lead the drug development in Asia. It is not impossible for Japan to develop at least one-fourth or one-third of the new active ingredients developed in the world. The government is also aiming at such situation that Japan is the world’s base for new drug development.
- On the contrary, pharmaceutical companies other than mega pharma are expected to play a role of supporting Japanese medical care more than ever before under the severer environment of completion by specializing the function by “selection and convergence” making use of their features and expanding the scale.

## **(1) Direction to which pharmaceutical companies take**

- The industrial structure shown in the previous vision is sorted out based on the above environmental changes and market change as well as growth of companies and the following 5 characteristics are clarified:
  - [1] Comprehensive companies for development of new drugs having many world-class pharmaceutical products and achieving a certain status in world market (mega Pharma)  
--- Of these, at least 1 to 2 companies are expected to aim a part of new-type global mega pharma that take a lead in development of pharmaceutical products in the future world in which sales of blockbuster products is not main income.
  - [2] Companies for development of new drugs having research and development capacity that can obtain a certain evaluation in the world in the specialized field (specialty pharma).  
--- They are requested to aim the case that they are growing by making use of outcomes of major research and development even in relatively small-scale companies (global niche pharma) and the cases that the international competitive power is strengthened by targeting research and development into the specialized field (global category pharma).
  - [3] Companies which effectively and stably supply basic, essential or traditional drugs supporting medical care (basic drug pharma)  
--- Reinforcement of corporate constitution is required so that basic, essential or traditional drugs supporting medical care (for example, vaccines, infusion fluids, blood preparations, pharmacopoeia products, Kampo preparations, crude drugs, etc.) can be supplied stably in good quality also hereafter.
  - [4] Companies that stably distribute good and inexpensive generics with repletion of information supply (generics pharma)  
--- In the situation that expansion of market share of generics is political task, needs of good and inexpensive generics is considered to further increase and growth is requested for good-standing major generic companies that contribute to stable supply and improvement of reliability on quality.
  - [5] Companies that correspond to self-medication and mainly develop OTC drugs (OTC pharma)  
--- Considering that the needs for QOL improvement including maintenance and promotion of health and prevention of disease are increasing in people, growth of OTC drug companies is required so that the new needs in people can be met by utilizing OTC drugs including “switch OTC drugs”.
- Among those companies, especially the mega pharma companies representing Japan are expected to make business development exceeding the mere pursuit for short-term corporate profit, and they are required to place their strongholds and bases inside Japan and supply safe and high-quality drugs meeting Japan’s medical needs for contributing to both industry development and improvement of medical service to people and simultaneously playing an important role in Japan’s knowledge-intensive key industries.

- Especially, companies should consider response to unmet medical needs (medical needs that have not been satisfied yet) in disease structure in the age and pharmaceutical products whose development is important though profit performance is low such as therapeutic drug for refractory diseases without therapy, orphan drugs and new vaccine. It is a matter of course that the government supports development of such drugs.

## **(2) Industries newly generate**

### **[1] Pharmaceutical ventures**

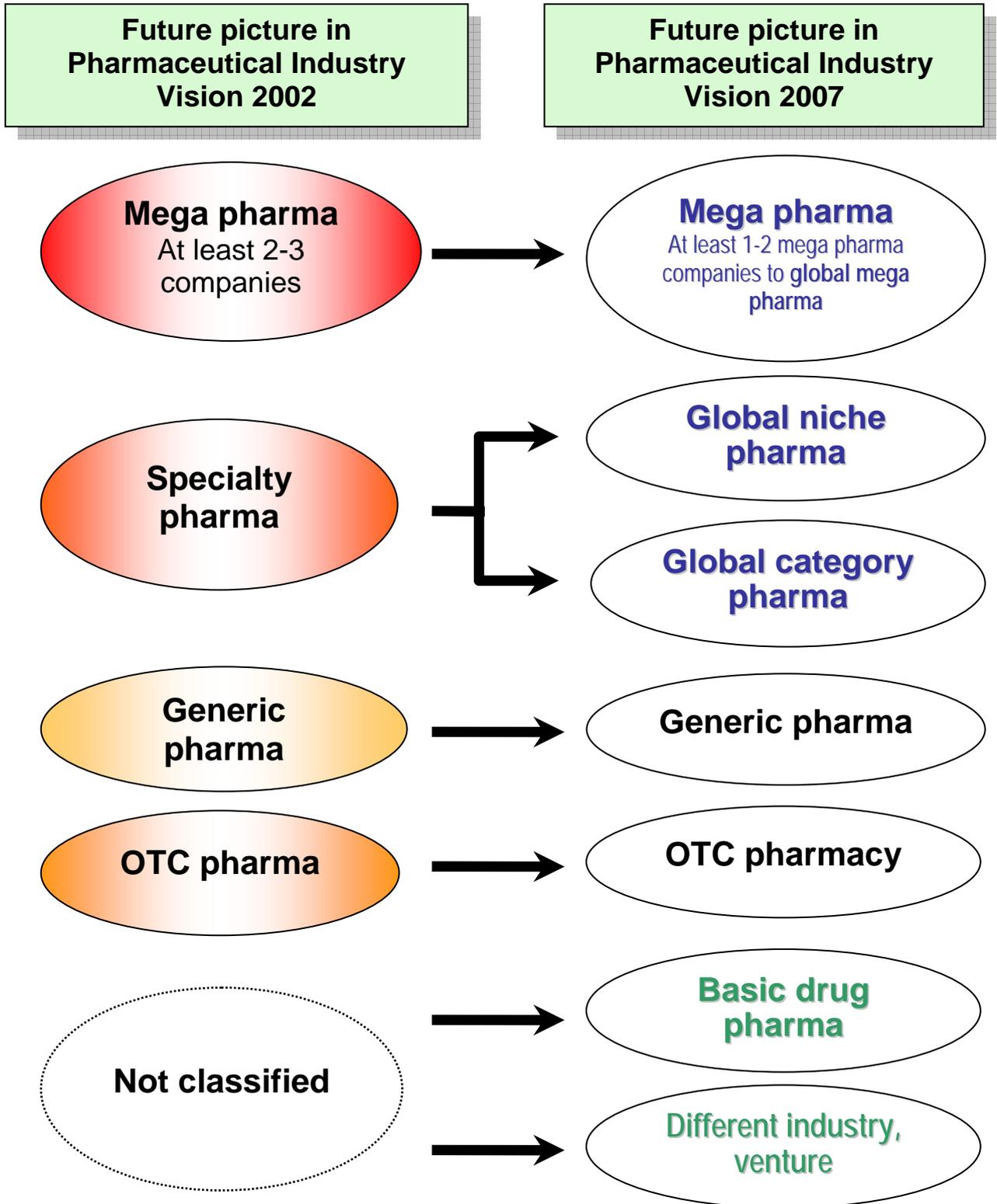
Pharmaceutical ventures that are enterprising companies dealing research and development for drug discovery with biotechnology as the critical technology have not been outstanding in Japan yet but they have become essential existence in Europe and U.S. and are expected to play a role of creating new technologies also in Japan in the future.

### **[2] Related industries expected to grow in the future**

As the industry that support or contract the duties from research and development to manufacturing and distribution in the pharmaceutical industry, new businesses will grow in the future such as gene analysis business, contract research organization, contract manufacturing organization (CMO) (manufacturing organizations which can accept commissioned manufacturing in the whole stage from research/development to commercial production including manufacturing of antibody drugs), PMS contract business, information supply service to medical institutions and contract sales organization (CSO) and are expected to contribute to rationalization and streamlining of the industry structure.

## **(3) Entry and integration of different industries**

- In Japan, companies of different industries without specialty of pharmaceutical products have played a large role of taking development of biotechnology in Japan by aiming positive entry to drug discovery making use of new technology. Also, in the future, the companies of different industries are expected to play a certain role in new-type research and development of pharmaceutical products such as reclamation of new fields by integrating pharmaceutical products and medical devices along with venture companies.



### **3. Picture of the future drug industry**

#### **(1) Current status of drug wholesaling**

- There are 3,349 companies that received the authorization of the first-class wholesaler based on the Pharmaceutical Affairs Law (surveyed by the Japan Generic Pharmaceutical Manufacturers Association in 2005). Of these, 2,378 companies (about 70%) respond the survey. Of the responding companies, those who have the authorization of wholesaler of ethical drugs are 972 companies and most of them are small and medium-sized provider. Moreover, those who make wholesaling of mainly pharmaceutical products are 128 companies admitted in the Federation of Japan Pharmaceutical Wholesalers Association (at the end of 2006) and 64 small-scale companies admitted in the Japan Generics Distribution Associations mainly dealing with generics (as of January 2007).
- For the number of companies admitted in the Federation of Japan Pharmaceutical Wholesalers Association that take a large portion of wholesaling of ethical drugs, reorganization of the industry by M&A, etc., acceleration of business cooperation and upper centralization have been progressed since 1999 by large changes in the situation surrounding wholesalers such as the influences of progression of modernizing distribution of pharmaceutical products and drug price reduction, progression of pharmaceutical duties sharing and spread of IT and movements to joint purchase. As a result, it decreased to 128 companies from 166 companies at the time of the previous vision (at the end of 2006) and the trend continues at present.
- Looking at the management status of the drug wholesalers, in spite of the expansion of sales amount, the gross profit margin tends to decrease due to the government's drug expenditure-containing policies and the pharmaceutical company's high settlement price policy to keep the NHI drug price. In spite of the efforts of decreasing the distribution cost and general management cost (distribution and management cost), the operating profit margin has changed less than 1% since 1999. Moreover, while the selling difference is minus, the sales rebates and allowances tend to increase, suggesting that management stability of drug wholesaler is strongly affected by the sales policy of the pharmaceutical company being the trade partner. (Fig. 1).
- For transaction of ethical drugs in drug wholesalers, concerning uncompleted / provisional invoice price that has been regarded as problem, uncompleted rate has changed in high rate in 2006 ever than before and necessity of improvement of distribution is strongly indicated.

#### **(2) Tasks and picture of the future of drug wholesaling**

<<Stable supply>>

- The primary role of drug wholesaling is to secure stable supply. The wholesalers ensure to deliver extremely many kinds of drugs to medical institutions, pharmacies, etc. accounting for about 220,000 and still increasing with progress of separation of dispensing and prescribing functions to meticulously meet the delicate needs and play the role of so-called "blood capillary-type" distribution function providing and collecting various drug information. As the meticulous responses to delicate needs, they are required to deliver the drugs to even a place inconveniently located in terms of public transportation and also required to actively line up generic products. In recent years, inventory consolidation and expansion of distribution area are attempted by the wholesaling distribution center, and thus sophistication and efficiency of the entire drug distribution are required.

- In addition, for the pharmaceutical stockpile and prompt supply during the crisis of the national scale such as casualties, terrorism and epidemic of infections, the establishment and spread of the risk-managed pharmaceutical distribution system is required. Particularly, in the event of large-scale epidemic of infection such as ordinary influenza or measles, the stable supply of vaccines, infusion fluids and therapeutic agents as well as the prevention of uneven distribution are the important functions of wholesalers. Further, during the epidemic of new influenza, it is critical to improve the system to secure the stable supply of vaccines as well as therapeutic agents under the cooperation between the government and prefectures according to the epidemic situation.

#### <<Implementation of IT>>

- Moreover, it is necessary to implement the standardization and IT of distribution code in order to manage safety and traceability in bearing the distribution of ethical drugs with various risks.
- For the ethical drugs, barcode labeling is required to manufacturers/distributors depending on package unit and type of ethical drug according to the “Implementation of Barcode Labeling for Ethical Drugs” (September 2006) for the purpose of preventing drug-mistaking accidents and securing drug traceability. At the present time point, only for biological products, labeling of expiration date, Batch No. and amount in addition to product code is made essential.
- Meanwhile, the counterfeit drug is a huge social issue in foreign countries, and WHO has initiated a measure as an international issue. It is designed to promote IT to ensure traceability of the drug for this counterfeit drug measure.
- For this global movement, it is necessary to promptly introduce distribution code that meets the international standards for all the items of ethical drugs in our country, and cooperative efforts between the wholesalers and the pharmaceutical companies are required.

#### <<Assessment of the information function>>

- Another important role of the drug wholesaling is the information function. Positive efforts in providing the revised package insert information as well as adverse drug reaction information required by the pharmaceutical companies or in collecting information on post marketing surveillance, etc. to increase the value of wholesale trade are considered necessary for the development of drug wholesaling and it is MS (Marketing Specialist) who is responsible for the information function.
- MS is important from the viewpoint of information provision to medical institutions, etc. On the other hand, it is expected hereafter to improve the MS function quality while promoting the efficiency of the entire distribution. It is conceivable that such MS function will also become a new source of profits.

#### <<Establishment of the primary business role>>

- Further, in recent years, the necessity of primary business role and constitutional strengthening of the wholesaler who is responsible for the drug distribution is strongly required, and the market reorganization has been done due to environmental changes for the recent drug wholesaling. As a result, the business conditions changed from the conventional manufacturer-affiliated wholesale to the full line wholesale, and a system to conduct autonomous and proactive business activities is being developed at last. However, they still have the profit structure that is strongly affected by the business policy of pharmaceutical

companies, and have not yet become independent wholesale distributors in reality and in name.

- While they are in the situation that is expected to have a variety of needs from the pharmaceutical companies as well as medical institutions, etc. and to develop an equal business entity in the future, individual company are required to have criteria for rational pricing in accordance with business terms (such as order-receiving system, number of distribution and payment condition) so that proactive price negotiation can be conducted with medical institutions and pharmacies under the adequate profit control.
- On the other hand, in the drug wholesaling, “unsettlement/shipment with provisional invoice price” that the product is still delivered without the price being determined over long periods and that the payment is received at the tentative price, and “total value price” that the negotiation is done at discount rate in total value and that is set at the flat discount rate for the price by brand name have become problems. These are the transactions that could damage the credibility of the drug price survey and that are inappropriate for the intent of the drug price system by brand name.

#### <<Future vision>>

- On the basis of the current situation of drug distribution, when looking toward the future from the issues in the drug wholesaling mentioned above and the expected roles, the progress of functional differentiation is expected as follows.
  - [1] “Integrated-type” that leads the distribution with a large scale of physical distribution network that covers the nation, and with advanced information service and infrastructure in the full line wholesale emerged from the manufacturer-affiliated wholesale.
  - [2] “Coordinated-type” that is based on a certain area and coordinated with other wholesalers based on other areas and has functions capable of competing with the “integrated-type” wholesalers as a group.
  - [3] “Specific-type” that is specialized in a specific product field such generic field, specific users such as clinics / pharmacies or specific regions, providing distribution network and information service tailored to individual characteristics.
  - [4] “New composite-type” that constitutes horizontal integration (product-type wholesalers) or vertical integration (manufacturer / wholesaler / retailer) exceeding the frame of drug distribution.
  - [5] “OTC drug-specialized-type” that attempts efficient business development by making special dealing of OTC drugs not covered by the health insurance system.
- Amid an expectation of the growth and vitalization of the entire pharmaceutical market, if the establishment of primary business role, the modernization of transactions and the diversification of profit structure by the functional differentiation and functional enhancement by using these wholesale characteristics expand, there is a possibility that the expansion of scale of the wholesale distributors as well as the improved profitability may be expected.
- Consequently, it is important for the government to support the efforts of the entire wholesale distributors with the agreement from relevant parties, focusing on the improvement of distribution.

## **4. Picture of the future drug retailing**

### **(1) Current status of drug retailing**

- According to the revision of the Pharmaceutical Law in 2006, the retail distributors were classified to [1] pharmacies, [2] retail seller and [3] household distributors, from [1] pharmacies, [2] drug sellers with first-class license, [3] drug sellers with second-class license, [4] household distributors and [5] special drug sellers.
- According to the research on the number of pharmaceutical related business (by the Health, Labour and Welfare Ministry at the end of March 2005), there were approximately 51,000 of pharmacies, 11,000 of drug sellers with first-class license, 13,000 of drug sellers with second-class license, 10,000 of household distributors, and about 86,000 of the total which was decreased by about 2,000 compared to the year 2000 (Fig. 2).
- The number of pharmacies is increasing with progress of separation of dispensing and prescribing functions [prescription-receiving rate in 2005: 54.1% (surveyed by the Japan Pharmaceutical Association)]. Although drug sellers with first-class license are increasing associated with the extension of drug store business, the number has been decreasing since 2001. The number of drug sellers with second-class license, household distributors as well as special drug sellers is also decreasing.
- In the revision of the Pharmaceutical Law in 2006, the selling system of non-prescription drugs was reviewed and the improvement of information service and consulting system was made according to the level of risk. This enabled the high-risk pharmaceutical agents in particular with a component that requires safety precaution to be sold only by the pharmacist as is conventionally done, and the registered sellers who were confirmed to have what it takes to engage in the sales of the pharmaceutical drugs could also sell other relatively low risk non-prescription drugs according to the studies conducted by the prefectures.

### **(2) Tasks and picture of the future of the drug retailing**

- In recent years, the pharmaceutical retail distributors with large management capitals called chain pharmacies and chain drugstore are increasing and marketing competitions including the conventional pharmacies and so on are heating up. It is preferable to lead the decline in the selling price and the improvement of service by diversifying the primary business role of the pharmaceutical retail industry and creating competitions.
- Relaxation of regulations on the sales of pharmaceutical products in March, 1999 (the shift of 15 product lines to the quasi drugs) had a tremendous impact on the management of small and medium-sized pharmacies and drugstores. By the further request of relaxation of regulations on the sales of pharmaceutical products from convenience stores as well as general stores, 371 items were shifted from non prescription drugs to quasi drugs in July, 2004. Although relaxation of regulation is implemented for the purpose of revitalization of the nation's economy and improvement of convenience for the consumer, based on the proper use of pharmaceutical products and ensuring safety, continuous and careful approach is needed for the relaxation of regulations on the sales of pharmaceutical products.
- At any rate, pharmacies, etc. are required to set the clear difference with other pharmacies and business competitors and to secure the confidence, adequately responding to the needs of the people in the local community amid the advance in the competition within the industry as well as in the intertype competition due to the relaxation of regulations.

- Specifically, specialists such as pharmacist give an appropriate advice serving as the community-based health station, and contributing to the promotion of self-medication for the people in the local community. That is, it is important for the pharmacy closed to the people in the community to proactively support the health plan for the people in the community including the improvement of symptoms for common and mild disease and the prevention of disease through the sales of non-prescription drugs such as switch OTC drugs as a way of self-medication.
- Further, in consideration of the rapid IT development, it is necessary to discuss a marketing strategy with the use of IT. In the sales of pharmaceutical products, it is quite important to provide patients information such as the direction for the use of medicine and adverse effects, and it is hoped that pharmacies strive to provide and collect such information serving as the health station in the community by using IT. It is also important to use IT in the distribution aspects such as the purchase and inventory control for the management of pharmacies and so on.
- Particularly, for the pharmacy who plays an important role as a base of supply such as pharmaceutical products in the community, it is essential to deal appropriately with fulfillment of their role as a family pharmacy, implementation of high quality pharmaceutical specialization and improvement of health care in the local community, etc. from the viewpoint of medical policy in the community because of the development of pharmaceutical specialization and the health insurance reform.
- From the viewpoint of family pharmacy, pharmacies should actively participate in healthcare service for mild symptoms not only by promotion of proper use of ethical drugs but also by promotion of use of OTC drugs such as switch OTC drugs. In addition, they are expected to play the roles such as appropriate delivery of drugs to patients in a home-care setting and giving drug-taking instructions.
- In addition, the role of the pharmacy is significant in promoting the use of generics. For the patients who provided prescriptions in favor of switching to generics, the pharmacy provides an appropriate information on the relevant generics such as price difference, and in case that the patient preferred for the drugs, the pharmacy is required to give contributions that make possible the improvement of the public finances of medical insurance, reduction of the burden on patients and participation in the choice of medical treatment by prescribing generics.

## **IV. Basic concept of policy for the pharmaceutical industry**

### **1. Strategic business development by the company**

- Industrial development advances in the free competition of each company on the basis of market principles, and this ideology should continue to be the base in the future as well.
- Particularly, in the pharmaceutical industry where international competition is intensified, it is essential to work on the strategic management development such as M&A, alliance and “selection and convergence” and to strengthen the international competitiveness such as the implementation of global and simultaneous development/marketing and the creation of innovative pharmaceutical products under the strong leadership of top management from the perspective of research and development/promotion of innovation that is the key to the growth of the company.

### **2. The roles of the government**

- In general, the roles of the government are :
  - [1] to improve the national systems contributing to development of the industry and to eliminate the conditions and factors that inhibit the fair and appropriate market competition principle from functioning effectively,
  - [2] to create the field where the private business can hardly go into because of unprofitability and the basis that research and development not generating from the competition should be shared
  - [3] to intensively support what the government determines to be necessary from the national strategic perspective.
- The government should play a certain role based on such ideology for the pharmaceutical industry, but in such case, it is necessary to note the feature that doesn't exist in the product of other industries in the following pharmaceutical products.
  - [1] Research and development of the pharmaceutical products take a lot of time and money with the low success rate, and mimicry is easy despite the high risk. In addition, although other products can promote the cross license involving from several hundreds to thousands of patents in one product, as there is one basis patent for the pharmaceutical products as principle, the acquisition of patent have a significant impact on the life to the products.
  - [2] The drug seeds in development and the elemental technologies are supported by the high-level basic research, and the process bridging between the high-level basic research and the practical application is necessary.
  - [3] Clinical trial is necessary before the pharmaceutical products placing on the market, and it is essential to have cooperation from medical institutions as well as the healthcare professionals.
  - [4] As the pharmaceutical products have a critical impact on the public life and health, they are regulated under the pharmaceutical jurisprudence for ensuring the quality, efficacy and safety, and it is also essential to ensure the stable supply and to provide information.
  - [5] The price of the ethical drugs covered by the medical insurance is officially fixed and companies do not have a liberty to set the price.

[6] While the research and development using human tissues/cells are advanced, and establishment of screening standards as well as clarification of safety parameters is required, it is further necessary to receive informed consent from the donor and to give consideration from an ethical aspect.

- Although many of these features are the essential hurdles for the pharmaceutical industry to contribute to improving the public healthcare, it is also true that these hurdles impose a heavy burden on the company. Especially for the various regulations the government placed upon, the government should always note and consider whether these regulations are the minimum in achieving the purpose, and it is important to make efforts to jump over or to improve the hurdles with the government and the industry working together.
- Furthermore, competitiveness in international markets of the pharmaceutical industry is enhanced, developing as a Japanese growing traction industry in the 21st century. In addition, in order to promptly provide the public the world's most advanced pharmaceutical products, it is critical to continued approaching in cooperation with the industry-academia-government as the nation's project from the enhancement of basic research through ensuring of the clinical research system. Such national approach has been already implemented in the United States and Europe.

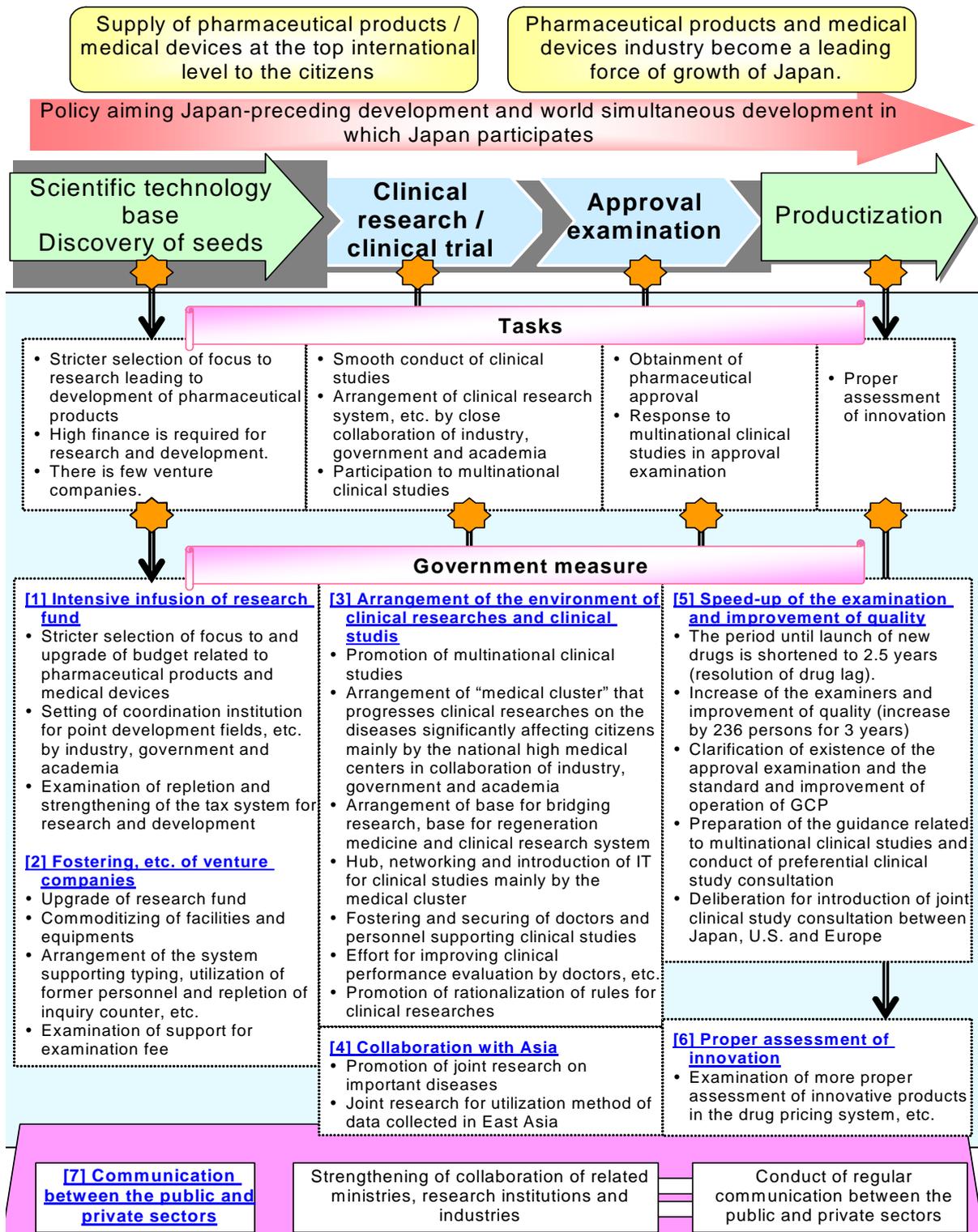
### **3. Setting of the intensive period and conduct of policy for creation of innovative new drugs**

- We have been working for 5 years since the establishment as the “intensive period for the innovation enhancement” in the previous vision for the potential policies that should be implemented by the government on the basis of such arrangement, and from a view of promoting innovation that is the motive force for industrial progress, we need to continue to address by setting the period to intensively work in. Particularly, in order to make up for the lost time in engineering innovation for developing efficient new drug seeds such as biotechnologies, it is necessary to put up industrial policies as soon as possible that the environments of new drug and market make more internationally attractive. For the next five years, we will place the “intensive period for developing innovative new drugs” anew, and implement the necessary policies systematically and gradually.

#### 4. Industrial policy for promoting innovation-centered new drug development

- Various issues between the base research and the launch of the product have to be all solved in order for the company to research and develop an innovative new drug. That is because it affects the final launch of the product if even one stagnation is present.
- Fig.1 shows the problems to be solved for each stage and its countermeasures in promoting the development of innovative new drugs as below.

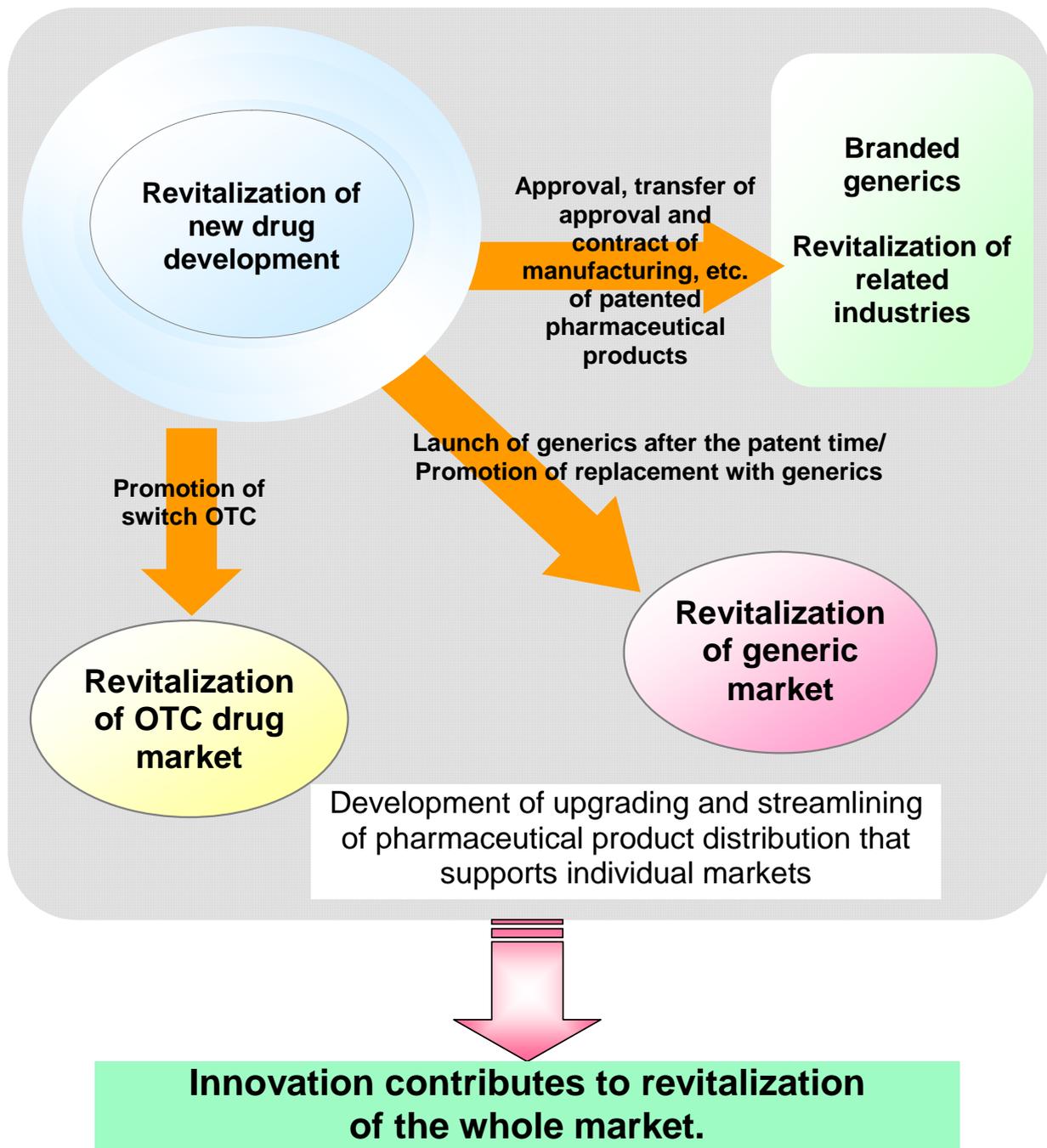
**Fig. 1 [Industrial policy for promotion of innovation-centered new drug development]**



## 5. Industrial policy in recognizing the importance of innovation ripple effects

- From the viewpoint of the entire pharmaceutical industry including the relevant industries, it is considered that activation of new drug development will activate the OTC drug market, the generic drug market and the relevant industries, leading furthermore to sophistication and efficiency of the drug distribution supporting each market. Thus, innovation is considered to contribute to activation of the entire drug market.
- It is necessary to implement such industrial policy in recognizing the importance of innovation ripple effects. Fig. 2 shows the summary as follows.

**Fig. 2 Industrial policy in recognizing the importance of innovation ripple effects**



## **V. Concrete measures to be taken during the “Intensive period for creation of innovative new drugs” (within 5 years)**

### **1. Enhancement and implementation of the efforts in the government**

#### **(1) Comprehensive response as the whole government**

- The government has a enormous role for increasing competitiveness in the international market of the pharmaceutical industry, and it is critical for the government to continuously strengthen and promote comprehensive and strategic efforts.
- In the past, various efforts were engaged under the initiative of the prime minister or the cooperation with Cabinet members (“Strategic outline of biotechnology” in December, 2002 (established during the Koizumi’s administration)), “Strategy of health frontier” (such as secretary general of the ruling parties/ chairman of the Policy Research Council)), and there are great expectations toward the pharmaceutical industry that in recent years, the prime minister firstly illustrated the medical fields as an example for the field that benefits the development of innovation contributing to the economic growth. In 2007, “New strategy of health frontier” and “Innovation 25” (both established during the Abe’s administration) were established. “5 years strategy for development of innovative pharmaceutical products / medical devices” was placed as the policy of the whole government.
- Further, since April, 2006, the first Basic Program for Science and Technology that presents the expansion of investment for research and development during the planned period and the implementation of fundamental science and technology system reforms was established and implemented under the leadership of the prime minister as well as the minister in charge of science and technology policy in the Council for Science and Technology Policy, Cabinet Office for planning and overall coordination of comprehensive and basic science and technology policies.
- Particularly, for the promotion of research in life science, it is necessary to continue to work on an increase of research expenses, more strategic priority in the research field and flexible allocation of research expenses based on the Basic Program for Science and Technology in the Council for Science and Technology Policy, Cabinet Office.
- Furthermore, for intellectual property, the Strategic Council on Intellectual Property was established under the Prime Minister in February 2002, and the “Basic Law on Intellectual Property” was enacted in November. In March 2003, “Intellectual property strategy headquarters” was created in the Cabinet and the “promotion program on the creation, protection and exploitation of intellectual property” was announced in July and the direction of measures for the implementation of intellectual property power was specified. This plan has been updated each year and “promotion program for intellectual property 2007” was summarized in May, 2007.
- The government is further required to continue working on comprehensive and flexible responses so that the assistance requiring in response to the drastic change in the international environment can be provided promptly and adequately.

#### **(2) Positive approach by the related government ministries and agencies, etc.**

- There are many administrations that have an impact on the development of the pharmaceutical industry and that are overseen by other government ministries, and among

the most important are intellectual property system such as patent, education/human resources development and business environmental improvement of the company.

#### [1] Intellectual property protection

- The patent system that protects intellectual property is an extremely important system for pharmaceutical companies and has a great impact on research and development of the pharmaceutical products and the management depending on what it should be.
- In consideration of the characteristics of pharmaceutical products, it is important to obtain a basic patent as far as possible, but since the upstream patent acquisition related to a gene or protein for which the functions are clarified or the patent acquisition related to edge-cutting technology has a marked influence on the downstream drug development, there is a possibility that the research and development may be disturbed if the upstream patent or the edge-cutting technology patent cannot be utilized smoothly.
- Accordingly, how to balance the protection of individual intellectual property and the competition of research and development in the whole industry is the critical issue for the future. As a concrete issue related to this, revision of “restriction on arbitrary license of use-relations” based on the agreement between Japan and the United States in 1994 was pointed out by the pharmaceutical industry, and it is indicated that careful consideration should continue to be given from the perspective of international cooperation, etc. with foreign countries.
- Today, venture companies that handle tissue-engineered medical products such as tissue-engineered skin in addition to engineering innovation such as regenerative medicine, cell and gene therapies are coming into market. Since it is important to promptly grant a patent to such technology for promotion of technology innovation and venture business creation in the edge-cutting medical field, it was clearly stated in the patent examination criteria in 2003 that “The manufacturing methodologies for gene-recombinant drugs or medical devices such as cultured skin sheet can be handled as a target of patent application even when the premise is to return to the same subject”.
- Further, the “promotion program for intellectual property 2007” stated that operation status of patent criteria on technology of “how to produce the effect-efficacy of pharmaceutical drugs for manufacturing and selling of the pharmaceutical drugs” revised in April, 2005 should be observed and that continuous collection and analysis of information should be provided on the technology trend in the advanced medical field as well as the trends of international discussion regarding the patent protection since 2007. Furthermore, the same program includes reinforcement of the investigation system related to intellectual property policies (such as policies for genetic resources) and also includes investigations related to arrangement of the rules to restrict author's rights on the occasion for the drug manufacturer/distributor to provide formation related to proper use of drugs, etc. to healthcare professionals.
- The needs for the companies to obtain patent rights are increasing in the foreign companies along with the globalization of the economy, and applications with the same content are submitted in order to obtain patent rights in the several countries. Under such circumstance, for efficient patent examination and prompt patent granting, international cooperation in patent examination is implemented between Japanese Patent Office and each country's Patent Office. For example, the program of “Patent Examination Highway” has been initiated as the inter-Patent Office cooperation frame work.

## [2] Education and human resources development

- Although pharmaceutical companies should proactively conduct research for development of new drugs, the role to be played by the government such as universities and national research institutes is also important for the promotion of basic research and improvement of the basis of research and development. How to recruit excellent researchers is an important key in order to research and develop fine pharmaceutical products. It is necessary to recruit the best researchers from around the world in our research centers and institutions for the improvement of attractive research environment, etc. but it is also important to foster young and excellent personnel in the educational institutions of universities.
- In the future, the effort of educational research cooperating with medical science, pharmaceutical sciences, science and engineering, and biostatistics are required in addition to the development of human resources in individual fields of clinical pharmacology, science and engineering, and bioinformatics. In addition, at universities, etc., it is necessary to secure and increase clinical research-related education opportunities for medical service staffs such as physicians, pharmacists and nurses.
- Furthermore, as the presence of specialists who support the implementation is also important in clinical studies and trials, it is necessary to educate specialists such as clinical study coordinators and biostatisticians who support clinical studies. In addition, it is important to improve the medical environment where various pharmaceutical products developed can be properly used, and in consideration that pharmacotherapy, explanation to patients and instruction on dosage and administration in addition to the improvement of medical facilities can be adequately conducted, human resources development is also necessary for healthcare professionals such as physicians and pharmacists.

## [3] Business restructuring and environmental improvement for industrial reorganization

- By the development of Special Measure Law for Reviving Industrial Vitality, etc., it is necessary for the companies to flexibly promote the strategic allocation and the concentrated investment of management resources, and facilitate the business restructuring, and the industrial reorganization that leads to the strength of competitiveness.
- Further, in the perspective of developing venture companies that play an important role for the discovery of new drug seeds, etc., it is necessary to implement assistance measures of the venture companies in aspects of finance, human resources and systems.

## 2. Action plan for realization of this vision

### (1) Support to research and development

Initiatives based on Action Plan for previous Vision

- Progress has been made with healthcare-focused basic research, in particular through the implementation under industry-university-government collaboration of the 'Disease-related Protein Analysis Project' and the 'Toxicogenomics Project'.
- Technology transfers and industry-university-government tie-ups have been promoted through actions such as the establishment of the Institute of Basic Pharmaceutical Research and the conversion of the Health Sciences Foundation to an authorized TLO.

- In addition to the introduction of a Japanese version of the Bayh-Dole system, the Institute of Basic Pharmaceutical Research (from fiscal 2004 the Pharmaceuticals and Medical Devices Agency) has been conducting contract research projects to commercialize the outcomes of advanced research including those given to venture firms and pharmaceutical companies etc. through technology transfers.
- The bank of research samples set up to acquire human tissue and other research resources has been making efforts to increase year by year the quantity of resources stored and also the number of sample donor medical institutions.
- The support package for corporate research initiatives has included the establishment of a tax relief scheme for total experimental research costs and for the experimental research costs for orphan drug and similar research.

<h3>Action Plan for New Drug Industry Vision</h3>
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[1] Budgetary prioritization and increase to promote drug development  
(‘Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices’)

- It has been pointed out that the life sciences-related budget in Japan is smaller than in Europe and the US. As well as increasing this budget and, in particular, prioritizing and expanding the pharmaceutical fields covered, priority should also be given as follows according to their content: a) Clinical research and applied research (including bridging studies for clinical application), b) Cancer, neuropsychiatric disorders, refractory and other major diseases, rare diseases, c) New technologies (biomarkers, creation of disease models, tailor-made medicine, regenerative medicine etc.) (Fiscal 2007 ~ ) .

[2] Increase and review of competitive research funds (‘Five-Year Strategy for Creation of Innovative Drugs and Medical Devices’ etc.)

- Basic research under a competitive environment has been boosted through the ‘Third Phase of the Science and Technology Basic Plan’ (agreed by the Cabinet on March 28 2006), the ‘Innovation 25’ project and the ‘Increase in Competitive Funds and Promotion of System Reform’ (Expert Panel on Basic Policy, Council for Science and Technology Policy, June 14 2007). In addition, the following initiatives concerning health and labour grants-in-aid for scientific research and other competitive research funds have been agreed upon with a view to promoting cutting-edge and high-risk research.
  - a) To increase the competitive funds in order to enhance the quality of research under the principle of competition (Fiscal 2007 ~ ) .
  - b) To review as a matter of urgency the assessment process in the screening of highly-rated researchers who are actively engaged in global as well as domestic research (Fiscal 2007 ~ )
  - c) To transfer the competitive funds allocation function to an independent agency (in principle an independent administrative agency) (Fiscal 2007 ~)
  - d) To set as soon as possible at 30% the fixed portion of research costs allocated for the indirect expenses of the organization to which a researcher who has acquired competitive funds belongs. (This is the provision for the administrative and other expenses of the research facility incurred for the conduct of the research) (Fiscal 2007 ~ ) .

- e) In particular, to extend the eligibility of researchers to pay out of competitive funds the personnel costs essential for the conduct of clinical research. In addition, to encourage research institutions to take voluntary initiatives such as giving financial awards to competitive fund acquirers and persons achieving excellent research outcomes. (Fiscal 2007 ~ ).

[3] Reinforcement of role of research-related independent administrative agencies

- The allocation of research resources by the government or other agencies should be rationalized through promoting and prioritizing the efficient and effective use of such resources. Measures to this end include prioritization of the fields for drug and medical device development covered by the life sciences-related budget.
- As an independent administrative agency, the Institute of Basic Pharmaceutical Research also undertakes the role of a research support agency, for example allocating funds for basic research in the healthcare field based on the Bayh-Dole contract system, providing research funds to venture firms etc. conducting research at the drug or medical device commercialization stage and giving grants-in-aid for the development of orphan drugs. This is expected to reinforce the support framework for drug and medical device research funding.
- At the same time, the Institute of Basic Pharmaceutical Research is expected to play some part in promoting the use of drug discovery techniques through establishing the pharmaceutical research infrastructure. This will take the form of support for pharmaceutical ventures through the offer of consultations and knowledge on capitalization and drug development etc., support packages for facility and equipment-sharing ventures etc. and other support for public-private co-researches.
- The role division with research-backing public interest corporations etc. should be clarified and a framework that will ensure consistency in the implementation of the respective initiatives to establish the pharmaceutical research infrastructure should be discussed. These initiatives include the intellectual property licensing by national research and other organizations, studies of trends in life sciences and the role of fund allocation agencies in the development and training of biotechnology firm human resources and research funding. (Fiscal 2008 ~ )

[4] Promotion of exploratory research into drug discovery biomarkers and research projects on bioresources and drug discovery animal models

- Advances in genome and post-genome research are expected to reveal new drug discovery targets through higher-function analysis of genes, proteins and sugar chains etc. In particular, rapid progress is anticipated in the search for and functional analysis of disease-related genes based on analysis of patient-derived genomes and drug response-related genes and proteins linked to pharmaceutical action; in the establishment of animal disease models and elucidation of their link with human diseases; and in efficient drug efficacy and safety evaluations based on biomarker searches.
- Exploratory research into drug discovery biomarkers to help elucidate the higher function of proteins and establish the regulatory sciences infrastructure data shall include searches for disease-related proteins and analyses of their structure and function and the analysis of transcriptomes.. (Fiscal 2008 ~ )

- In addition, to promote the development by animal development centers of new animal disease models in areas where this is desirable, such as cancer, myocardial infarction, stroke and dementia, and to apply these animal disease models effectively to drug discovery research, research projects on bioresources and drug discovery animal models shall be promoted through the creation of databases of such animal disease models. The expansion of these bioresources is expected to contribute to drug discoveries and new medical technologies. (Fiscal 2008 ~ )

#### [5] Development of second-generation vaccines

- While the development of new vaccines is gathering pace in Europe and the US, in Japan, notwithstanding that vaccine seeds are likely to exist in universities and national research institutions, they do not progress to the commercialization stage due to the history of harm suffered from inoculations and to the high risks involved.
- Nevertheless, hopes are gathering for vaccines for disorders such as cancer and dementia as well as for infections, and the global demand for vaccines is estimated to at least treble the current level in the next ten years. If this situation persists, Japan will be left behind in the global competition. The 'Vaccine Industry Vision' should be pushed ahead to allow new vaccine development targets to be set, including the prevention and treatment of Alzheimer's and similar disorders, the prevention and treatment of cancer and similar disorders, the prevention of new infectious diseases in adults and the elderly and the fight against new types of influenza. Second-generation vaccine research should be promoted whereby, in addition to conventional injection-based inoculation techniques, the development and clinical evaluation of new production and pharmaceutical techniques, such as efficient culture methods and antigen protein manufacturing processes, leads to the development of vaccines with transnasal or other new routes of administration and also of effective DNA vaccines. (Fiscal 2008 ~ )
- In addition, bio-venture firms and major pharmaceutical companies are expected to participate in these researches as the leaders of the new vaccine industry. Hopes of achieving preventive medicine in the 21<sup>st</sup> century through the development of these second-generation vaccines are also increasing.

#### [6] Nurture of venture firms ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- Advances in genome and post-genome techniques have made it necessary for pharmaceutical companies to incorporate biotechnology and other unconventional new techniques into the drug discovery process, but, unlike drug discovery techniques to date, the biotechnology field has specific characteristics, such as a high degree of technological originality and individuality and a segmented market for the prospective application, which also make the path to commercialization highly risky.
- For the development of such drug discovery seeds and elemental technologies to be entirely undertaken in-house alone incurs problems such as further increases in research expenditure and the deterioration of investment efficiency in the eyes of investors. Therefore, in the US, the number of pharmaceutical company alliances and M & A with venture firms in possession of unique innovative biotechnologies has been increasing in recent years. However, since bioventures in Japan are few in number and lack maturity, Japanese pharmaceutical companies mainly form alliance partnerships with US bioventures. But the nurture of venture firms is vital to enhance the future global competitiveness of Japan's drug industry.

- Accordingly, the infrastructure to facilitate the creation of technologies with greater application potential is required through the implementation of a support package or similar measures for venture firms. Policies to nurture venture firms would include an increase in their research funding, the promotion of facility and equipment sharing and co-research with venture firms, the establishment of a framework allowing former players with expert knowledge of pharmaceuticals to be utilized in advising venture firms, and other measures to support the commercialization of embryonic technologies. (Fiscal 2007 ~ )

#### [7] Facilitation of patent use in research

- Although universities and similar institutions and the private sector own research tool patents for processes such as the screening of genetically modified animals and plants, they cannot readily use these in research. The Council for Science and Technology Policy therefore agreed (in March 2007) on the 'Guidelines to facilitate the use of research tool patents in life sciences' with a view to facilitating their use in research by universities and similar institutions and the private sector.
- In response to this the necessary measures shall be taken (fiscal 2007 ~ ) in respect of actions agreed upon by the relevant ministries to promote the Guidelines (including publicity campaigns, handling of public applications for research, practical assistance with costs). In addition, to promote the use of research tool patents in life sciences, an integrated database shall be created to facilitate the release and collective search of information on research tool patents and tangible patented materials etc. (type of research tool, patent number, conditions of use, term of license, license charges etc.) that are owned and are transferable by universities and similar institutions and the private sector. (Fiscal 2008 ~ )

#### [8] Expansion and consolidation of research and development tax incentive scheme ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- Under the tax scheme for total experimental research costs established in 2003 (the research and development tax incentive scheme allowing fixed rate tax relief on total experimental research costs; made a permanent measure in 2006) the maximum relief is 20% of current term corporation tax, but the scheme is underused since the majority of pharmaceutical companies are fully up to this limit. Furthermore, although in 2006 the relief rate for the incremental tax scheme for experimental research was reduced, allowing the tax scheme for total experimental research costs or other schemes to be topped up, this measure is similarly underused due to the constraint of the 20% maximum corporation tax relief.
- Under the current research and development tax incentive scheme, the support package given when companies proactively seek to undertake research and increase their research expenditure is inadequate. In view of the massive research funding that is characteristic of drug development, discussion on expanding and consolidating the tax scheme for research and similar operations is called for. (Fiscal 2007)

#### (2) Promotion of clinical trials / clinical researches

Initiatives based on Action Plan for previous Vision
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- The 'Three-Year Nationwide Clinical Trial Promotion Plan' was formulated and the following measures implemented to accelerate and improve the quality of clinical trials.
  - a. Efforts have been made to establish the 'Mega Clinical Trial Network', which (as at March 2007) is comprised of 1,312 medical institutions. In addition, the network

conducts investigator-initiated trials on drugs unapproved in Japan, pediatric drugs and orphan drugs etc., some of which are currently pending approval.

- b. By fiscal 2006 approximately 5,000 CRCs, who help to improve the quality of clinical trials, had completed their training. In addition, the clarification of the status and operations of SMOs has facilitated the outsourcing (including to SMOs) of part of the duties of clinical trial medical centers.
  - c. To assist patients to enrol in clinical trials, efforts have been made to publicize clinical trials through posting information on the significance etc. of clinical trials on the 'Clinical Trial Website'.
- Investigator-initiated clinical trials have been institutionalized and the 'Ethical guidelines for clinical research' and the 'Guidelines for clinical research using human stem cells' formulated.

Action Plan for New Drug Industry Vision
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[1] Development of Medical Clusters ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices' etc.)

- Based on the 'New Health Frontier Strategy' and the 'Five-year Strategy for the Creation of Innovative Drugs and Medical Devices', 'Medical Clusters' shall be developed led by the National Centers for Advanced and Specialized Medical Care to promote clinical and applied research through close industry-government-university collaboration. The aim is to develop and commercialize pioneering technologies, goods and systems for disorders that have serious adverse effects on the public (major and rare diseases). Further, with the conversion of the National Centers for Advanced and Specialized Medical Care to independent administrative agencies in 2010, these centers shall be able to fulfil their respective roles more competently. (Fiscal 2008 ~ )
- To facilitate close industry-government-university collaboration, the 'Medical Clusters' shall be the basis for providing such items as clinical research beds and experimental medical devices, promoting co-researches through the intake of corporate and overseas researchers and other measures, and building up a pool of business organizations and university and other research institutions.
- These 'Medical Clusters' form open-style research bases that act as a bridge between basic research and the process of commercialization of the clinical application and between the clinical stage and development, and also nurture Japanese ventures etc. to supply promising drug discovery seeds. As such there are great expectations of their being used as a new supply source of seeds for the pharmaceutical industry in drug development.

[2] Infrastructure for core hospitals and medical bases ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- Although the clinical trial network has been formed under the 'Three-Year Nationwide Clinical Trial Promotion Plan' and other plans, it is clear that this alone has failed to promote clinical trials and clinical researches fully. The formation and support of the clinical trial network built up to date should be supplemented with core clinical trial/research hospitals and medical bases having specialist areas, medical center tie-ups or similar characteristics.

- To this end, in accordance with the 'New Five-Year Clinical Trial Promotion Plan', clinical trial/research human resources shall be intensively channelled into around 40 core hospitals and medical bases in order to centralize skills and train staff, and at the same time a liaison framework shall be established to facilitate efficient and speedy multinational clinical trials and clinical researches. Specifically, assistance shall be given for the respective provision of 10 medical institutions as core hospitals and 30 as medical bases. (Fiscal 2007 ~ )

[3] Improvement of clinical trial/research framework in medical institutions etc.

('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices', 'New Five-Year Clinical Trial Promotion Plan')

- It has been pointed out that the majority of trained CRCs are not directly engaged in clinical trial/research duties and that there are inadequate training opportunities for physicians and other medical personnel to improve their clinical trial/research skills. These are issues that affect the conduct of high-quality clinical trials/researches. Accordingly, it is imperative to facilitate the conduct of clinical trials/researches through qualitative improvement of physicians, CRCs and other personnel, and to provide incentives for these persons to undertake such work. (Fiscal 2007 ~ )
- Specifically, measures such as the following are called for:
  - a. To provide and increase the opportunities for physicians, pharmacists, nurses and other medical personnel to be given clinical research training in universities or other institutions (Fiscals 2007 ~ 2011)
  - b. To take actions to improve the assessment of the clinical performance of physicians etc. (including the setting of target assessment criteria to improve the quality of clinical research, such as the number of papers on clinical researches in Japan contributed to leading overseas journals) (Fiscal 2008 ~ )
  - c. To train CRCs and other clinical research support specialists. A further 3,000 CRCs shall be developed. (Fiscals 2007 ~ 2011)
  - d. To assess the clinical research/trial performance of researchers and their involvement in biostatistics or other specialist professions when selecting clinical researches for public funding. (Fiscal 2008 ~ )
- In addition, to speed up clinical trials and reduce their costs, IT-based inter-facility networks shall be established and clinical trial document formats standardized. (Fiscals 2007 ~ 2011)

[4] Support package for patient participation in clinical trials ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- In setting up the clinical trial framework to date strong calls have emerged for more positive recognition of experienced clinical trial operators, for "information on the status of clinical trials" and for "a proper explanation from the medical personnel at the clinical trial enrolment stage". Further campaigns to publicize clinical trials are needed in response to demands from the general public and patients concerning clinical trials.
- Specifically, measures such as the following shall be implemented:
  - a. To provide a portal site for a clinical research registration database (Fiscal 2007 ~ )
  - b. For medical institutions and pharmaceutical companies etc. to encourage trial subjects to take actions such as continuing with treatment where this is found to be effective in clinical trials or following up approval information on the trial drug

(Fiscal 2007 ~ )

- c. To encourage the set-up of a 'Patient advisory service' in core hospitals and medical bases to promote communication between patients and medical personnel (Fiscal 2007 ~ )

[5] Development of regenerative medicine bases ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- Japan is the global leader in the field of regenerative medicine technologies and the 'New Health Frontier Strategy' also has expectations of their development and dissemination as part of advanced preventive, diagnostic and therapeutic techniques. It is the universities and venture firms etc. that support regenerative medicine technologies, but many of the universities do not possess cell processing centers, which impedes commercialization or makes it difficult to share facilities with venture firms etc.
- With the aim of extending the researcher base in this field, providing a more competitive environment for applied research and increasing the number of regenerative medicine technologies originating in Japan, measures such as the following shall be implemented:
  - a. To develop and create a network of pro-commercialization hospital bases (with specialist regenerative medicine clinical research beds and labware and analytical equipment etc.) (Fiscal 2008 ~ )
  - b. To promote world-leading technological developments (the development of commercialization-focused technologies for manipulating and applying stem cells, the establishment of a stem cell bank, nanotechnologies, the promotion of material engineering tie-ups and other initiatives) (Fiscal 2008 ~ )

[6] Promotion of multinational clinical trials ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- The participation of Japanese medical institutions too in multinational clinical trials will enable phase III studies etc. to be initiated simultaneously with other countries and large amounts of study data to be gathered speedily from wide-ranging areas, facilitating the comparison of regional variations. The conduct of clinical trials based on joint protocols provides advantages such as greater efficiency and effective application through the elimination of data duplication and allows new drugs developed both in Japan and elsewhere to be delivered to the public either first in the world or simultaneously, thus correcting the delay in public access to cutting-edge medical care.
- To this end, the following actions shall be taken to facilitate the conduct of multinational clinical trials in Japan:
  - a. Establish the infrastructure for inclusion in multinational clinical trials by increasing case numbers and reducing the cost of clinical trials through the consolidation of tie-ups with core hospitals and medical bases and other measures. (Fiscal 2007 ~ )
  - b. Take actions to develop the human resources required for the conduct of multinational clinical trials (personnel familiar with the clinical trial rules in other countries etc.) (Fiscal 2007 ~ )
  - c. Draft the basic philosophy on multinational clinical trials in the approval process (Fiscal 2007 ~ )

[7] Asian alliances ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- Given the importance in simultaneous global developments of alliances with Asian countries, which have large populations and markets and fewer ethnic differences with Japanese people than Westerners, measures such as the following shall be implemented:
  - a. Take initiatives to promote co-researches with Asian countries on drugs for cancer and other major diseases (Fiscal 2007 ~ )
  - b. Conduct co-researches on methods of evaluating and applying clinical data gathered in East Asia (Fiscal 2007 ~ )

[8] Review of clinical research ethical guidelines ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- It has been pointed out that the current 'Ethical guidelines for clinical research' do not provide a mechanism for official checks on the quality of clinical research and also fail to protect trial subjects. Therefore, with ongoing reference to the current clinical status and other relevant matters, the guidelines should be reviewed and discussed, including the legal aspect and the introduction of a system of notification on commencing clinical research. (Fiscal 2007). However, in doing so care should be taken to prevent clinical research being hindered.

**(3) Speed-up and quality improvement, etc. of the approval examination**

Action Plan based on previous Vision

- The Pharmaceuticals and Medical Devices Agency was established and systematic review staff increases planned to expedite approval reviews and reinforce the system. In addition, targets for reducing the administrative processing time for reviews were set and reviews have been conducted with a high degree of transparency. Furthermore, priority clinical trial consultations are also held for drugs highly needed in medical care.
- The approvals and licensing system has been revised to allow across-the-board contracting for product manufacture as in Europe and the US.
- To assure the quality and safety of biological and autologous products, as well as regulatory reinforcement through the reclassification of 'biological products' and 'specified biological products' in the Pharmaceutical Affairs Law, efforts have been made to give guidance and advice at the development stage.
- The collection and analysis of post-marketing data on adverse reactions, decisions on safety assurance and other system criteria were set as requirements for the marketing authorization license.

Action Plan for New Drug Industry Vision

[1] Acceleration of approval reviews and system reinforcement ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- In view of the calls to eliminate the 'drug lag', the targets for the approval process for new drugs are to reduce the development time and approval review time respectively to 1.5 years

and 1 year by 2011, which will reduce the drug lag by a total of 2.5 years and bring new drugs to the market at the same time as in the US. (Fiscals 2007 ~ 2011)

- It has been pointed out that the framework for the clinical trial consultations and approval reviews conducted by the Pharmaceuticals and Medical Devices Agency lacks human resources, in particular those that will promote approval efficiency and physicians and biostatisticians with clinical experience. This is held to be one of the reasons for the delays in clinical trial consultations and approval reviews. The following measures are necessary to solve this problem and to expedite and promote the efficiency of clinical trial consultations and approval reviews:
  - a. To double the number of new drug reviewers (an increase of 236 persons) (Fiscals 2007 ~ 2009)
  - b. To improve clinical trial consultations qualitatively and quantitatively ( ~ fiscal 2011)
  - c. To expedite reviews and otherwise expand and improve the review operations through measures such as the introduction of a preliminary application assessment system and an increase in the review teams (in conjunction with discussion of the overall review framework including the two-track system of separate teams for priority and ordinary reviews) (Fiscal ~ 2011)
  - d. To discuss the status of the use of former private sector players (Fiscal 2007 ~ )

[2] Approval criteria for new technologies ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- Europe and the US are leading the way in research into surrogate biomarkers of drug efficacy and safety in relation to disorders and new imaging processes and other diagnostic techniques to promote efficient drug development. The US FDA refers to such studies to promote the efficiency and speed of drug development through these new drug evaluation and other processes as 'critical path research'.
- In addition, in Europe drug studies on humans are conducted using very low dosages and the European Medicines Evaluation Agency is actively investigating the use of the microdosing technique to study internal pharmacokinetics. Europe anticipates that this will significantly reduce the number of new drug dropouts in phase I studies and also new drug development costs. Guidelines on microdosing have already been published in Europe and the US, and the ICH also started to discuss microdosing in the fall of 2006.
- In Japan too the toxicogenomics database and other globally unprecedented studies into drug discovery biomarkers are progressing. However, the major challenges for the future are to rationalize the drug development process and promote efficient and speedy scientific evaluations in reviews through the development and application of other biomarkers and diagnostic techniques and also of animal disease models. Research on product evaluation processes using these new methods and the formulation of review criteria for these new techniques is urgently called for. (Fiscal 2007 ~ )

[3] Application of compassionate use system (CU system)

- Given the likelihood of the medical frontline seeking to use in times of emergency drugs under development and pending national approval or drugs approved overseas, the lifting of the ban to a limited extent on the manufacture, import and marketing etc. of unapproved

drugs (the CU system) should be considered in cases such as critical illness where no alternative therapy is available.

- In the EU, which has already introduced the CU system, the basic objective is to give relief to patients with life-threatening illnesses using investigational drugs as well as approved drugs from other countries. In the US, although in principle under drug regulations the distribution of unapproved drugs is banned unless notification is filed with the FDA, a CU system has been established whereby the distribution of unapproved drugs is permitted through special case procedures if certain conditions are fulfilled.
- In Japan too it has been held that with a view to introducing the CU system the 'Panel for the Prompt Supply of Effective and Safe Drugs' should consider, with continued adherence to the principle of government approval once the necessary domestic clinical trials have been conducted, such matters as the basic philosophy of this system (the scope of unapproved drugs to be covered and the target patients), the respective roles of the government, pharmaceutical companies and physicians, and the handling under medical insurance. (Fiscal 2007 ~ )

[4] Multinational clinical trial-geared approval reviews ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')

- The conduct of multinational clinical trials also requires corresponding approval review measures, including the effective use of domestic and overseas clinical trial data as well as provision of the domestic clinical trial infrastructure. At present it has been agreed to implement measures such as the following, but the further measures necessary should be discussed.
  - a. To draft the basic philosophy on multinational clinical trials for approval reviews (Fiscal 2007)
  - b. To conduct priority clinical trial consultations for multinational clinical trials with multinational participation (Fiscal 2006 ~ )
  - c. To discuss the introduction of joint clinical trial consultations between the regulatory authorities in Japan, the US and Europe (Fiscal 2008 ~ )

[5] Improvement of clinical trial consultations system

- The clinical trial consultations conducted by the Pharmaceuticals and Medical Devices Agency are not on a level with those in Europe and the US as expected. Their content also cannot be described as fully satisfactory to the companies concerned and the system is far from being the timely and precise one needed for corporate operations.
- To establish a clinical trial consultation system capable of timely responses to all consultations, the Pharmaceuticals and Medical Devices Agency shall take initiatives to set targets including guidance for a new consultation and review framework, a substantial increase in the consultations quota, reduction in the application waiting time, improved consultation options and preliminary evaluation of application details. (Fiscal 2008 ~ )

[6] Regulatory status of autologous cell and tissue products

- Autologous cell and tissue products carry inherent risks such as a) Concomitant infections in the processing, b) Carcinogenesis or other efficacy and safety risks from the processed product per se, c) Consistency of quality. At the same time, since the final product, having

undergone various manufacturing processes, will essentially differ from the original cells and tissue, certain public health controls are considered necessary.

- The following actions to provide a short-term commercialization package based on these views are in progress.
  - a. The formulation of safety and other evaluation criteria for autologous cell and tissue products (the formulation of evaluation criteria reflecting the characteristics of autologous products in requiring these to present no problems of donor-derived infections or immunity compliance) (Fiscal 2007)
  - b. The conduct of fine-tuned clinical trial consultations by the Pharmaceuticals and Medical Devices Agency (with improvements such as the provision of additional categories for autologous cell and tissue products) (Fiscal 2006 ~ )
  - c. The rationalization of clinical trial procedures (elimination of duplication in the attached data required for the final application and clinical trial protocol notification, procedural rationalization and expedition etc.) (Fiscal 2006 ~ )
  - d. Regulatory provision for manufacturing and quality control (formulation of regulations for the manufacturing and quality control of autologous cell and tissue products (GMP) based on the respective product characteristics, together with consolidation of GMP status at the clinical trial stage) (Fiscal 2007)
- It is held that while continuing with the above actions, the 'Panel on the Prompt Supply of Effective and Safe Drugs' should discuss as and when necessary the status of the appropriate regulations for cell and tissue products with reference to advances in regenerative medicine.

[7] **R Revision of Ordinance on the Standards for the Implementation of Clinical Trials (GCP Ordinance)** ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices', 'New Five-Year Clinical Trial Promotion Plan' )

- It has been pointed out that the GCP Ordinance requires more implementation documents than the global standard (ICH – GCP). In the interest of promoting efficient clinical trial administration and the conduct of multinational trials, the parties concerned are also seeking its rationalization insofar as matters such as the protection of trial subjects are not affected. With reference to this situation, discussion shall be held with a view to improving the implementation of the GCP Ordinance and facilitating the conduct of clinical trials. (Fiscal 2007)

**(4) Future existence of the drug pricing system and drug benefit ('Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')**

Action Plan based on previous Vision
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- The successive efforts to revise the drug pricing rules and promote their transparency with reference to the discussions by the Central Social Medical Insurance Council (Chuikyo) have produced certain results for Japan's drug pricing system in the form of a substantial reduction in the drug price gap and in the drug price ratio.
- In the fiscal 2002 drug pricing reforms measures were implemented including the price rationalization of original drugs and greater rewards for innovative new drugs etc. through increases in the corrective premium rates.

- In the fiscal 2006 drug pricing reforms, the breakthrough and usefulness premium requirements were relaxed, premium rates increased and the graduated allocation of corrective premiums was revised. At the same time a new 'pediatric' premium category was established.

Action Plan for New Drug Industry Vision
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- Acceleration of approval reviews The problems with the drug pricing system in terms of promoting and expanding the drug industry have been referred to. These include the impediment to healthy competition of a system in which prices fall continuously under the drug pricing criteria and special case reductions of original drugs etc. that are independent of market prices.
- These points are based on the philosophy that, to deliver high quality drugs to patients, it is vital to value innovation fairly and also to secure adequate profits and research funding to expedite the development of innovative and high quality drugs. On the other hand, the health insurance system, which includes the current drug pricing system, serves as a financial guarantee of access to healthcare by the whole nation and it can also be argued that in terms of system sustainability there are natural limits to the burden it shoulders.
- However, reform of the clinical trial infrastructure and review system and aspirations for a globally competitive market environment are crucial for the elimination of the drug lag.
- From this perspective, given the situation under the present drug pricing system where, even during the patent life, drug prices are structured to fall continuously and moreover are used for comparison in the calculation of drug prices, even the corrected prices of new drugs are likely to fall below the level in the major European countries and the US, leading to more increases rather than reductions on the application of the foreign price adjustment. In respect of drugs which thus are expected to be more highly priced abroad than in Japan, it has been pointed out that launch overseas gives more favorable drug pricing and that the pricing system has become unfavorable to domestic lead-off development.
- With reference to the above points, to assure a fair valuation of innovation, a globally competitive market and the sustainability of health insurance finances, discussion should be held on a mechanism for achieving returns during the patent life commensurate with the risks and innovation and allowing steady generic substitution on patent expiry and completion of the reexamination period. (Fiscal 2007)

Matters such as the stable supply of drugs should be considered in conjunction with the review and implementation of the drug pricing system.

**(5) Fostering of generic market**

Action Plan based on previous Vision
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- The promotion of generic drugs requires the establishment of the respective medical fees infrastructure. In the fiscal 2002 revision, measures such as the following were taken: ① Higher assessment for prescriptions that include generic drugs, ② Dispensing fee premiums for pharmacies dispensing and supplying information on generic drugs. In the fiscal 2006 revision, the prescription format was changed to facilitate the decision by physicians to switch to generic drugs.

- As a support package to enhance the reliability of generic drugs: ① An overview of 'Medical fees for generic drugs' was supplied on the MHLW Web site and ② Generic drug manufacturers have been instructed to make efforts to ensure stable supplies, improve the package insert information, provide an information supply framework and supply relevant information promptly

Action Plan for New Drug Industry Vision

- While innovative new drugs promote the quality of healthcare, the use of high quality and reasonably priced generic drugs reduces the financial burden and rationalizes health insurance finances. It follows that a balanced distribution of original and generic drugs is vital. The current status of the drug market does not allow generic drugs to fulfil their potential role.
- The reasons given for this include ① That the full trust of medical professionals cannot be won due to the existence of generic drug manufacturers with deficiencies in stable supply, information supply and other respects, ② That the doubts over the quality of frontline medical professionals have to be dispelled and ③ That pharmacies are concerned about matters such as the increase in stockpiles and dead stock and in the time spent on supplying information to promote generic drugs.
- The MHLW will therefore implement an overall package of measures, including initiatives to tackle issues such as stable supply and information supply, to ensure the steady achievement of the target of at least a 30% generic market share (double the current) by fiscal 2012 (16.8% by volume (fiscal 2004)) set out in the 'Program to Improve the Quality and Efficiency of the Medical and Nursing Services' (MHLW May 2007) (Fiscal 2007 ~ )

**(6) Fostering of proprietary drug market**

Action Plan based on previous Vision

- In areas where self-medication is anticipated, the use as non-prescription drugs of suitable products shall be approved as appropriate with reference to the recommendations in the 'Status of Non-prescription drugs in Self-medication' (the interim report from the Panel on the Rationalization of Non-prescription Drug Approval Reviews). The aim is to promote the OTC drug market while ensuring global consistency through measures such as switching to OTC drugs those that the nation can use correctly of their own accord under the proper advice of a pharmacy or drugstore pharmacist or other specialist.

Action Plan for New Drug Industry Vision

- Although to pursue the concept of self-medication further it is vital to promote the effective use of non-prescription drugs, in recent years their market has been shrinking. Meanwhile, the market for drugs for specified health use has been increasing, which is inferred to be linked to the purchasing of health foods and supplements etc. as public concern is directed at disease prevention and promotion of health.

- On the other hand, given the further increasing ratio of elderly to the total population and also the diversification of the healthcare needs of the public, promotion of the effective use of non-prescription drugs calls for the development of non-prescription drugs, quasi-drugs and switch OTC drugs capable of responding to the new needs of the public.
- In particular, the promotion of 'switch OTC drugs' through the conversion of ethical drugs and the development of OTC drugs with new indications is expected to produce products with indications and effects beyond those required of conventional non-prescription drugs and thus to respond to the new health consciousness and other public trends (for example, the prevention of the metabolic syndrome, skincare benefits). Meanwhile, for the original developers of ethical drugs, conversion to switch OTC drugs enables consumers to purchase these drugs freely, expands their market and ordinarily imposes a three-year period of safety surveillance after acquisition of marketing approval. Therefore in terms of the new drug life cycle, this is considered to be an attractive market sector and further promotion of switch OTC drugs can be expected.
- Nevertheless in view of the high development risks involved with switch OTC drugs, the conversion to non-prescription drugs of the active ingredients of ethical drugs is currently not progressing smoothly, as is evident from the limited number of products approved as new switch OTC drugs over the last five years.
- Therefore, in compliance with the scheme deliberated and approved by the MHLW Committee on Non-prescription Drugs in March of this year for the conversion to non-prescription drugs of the active ingredients of ethical drugs, the conversion, while ensuring the transparency of the process, of those periodically considered suitable shall be actively promoted through discussion and publication by the Council on Drugs and Food Sanitation following requests to drug-related medical societies for draft summaries and hearings of their views. (Fiscal 2007 ~ )
- In addition, the stumbling blocks in the filing of applications for the approval of switch OTC drugs and the provision of a highly prompt and transparent review system for their early launch should be discussed.
- Furthermore, the support of the public is vital for popularizing self-medication and expanding the OTC drug options, and the collaborative industry-government-university infrastructure required for this should also be discussed.

## **(7) Streamlining and grade-up of distribution function**

Action Plan based on previous Vision
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- To address issues such as the rationalization of drug distribution and inventory management, the computerization of medical institution and pharmacy operations and lot number labelling for the safety assurance of biological or similar products, the introduction of IT and standardization in the drug distribution sector has been promoted and implementation guidelines on the bar-coding of ethical drugs to prevent drug mix-ups and secure product traceability have been formulated.
- The 'Council for the Improvement of Ethical Drug Distribution' (established in June 2004) compiled an 'Interim Report' (December 2004) and the 'Handling of Returns' (March 2006) concerning the correction of inappropriate drug trade practices such as pending price settlements and provisional deliveries. In addition, the Outline of Fiscal 2006 Drug Pricing

Reform (approved by Chuikyo) set out the plans to correct these long-term practices, to which end a guidance notification based thereon was issued to NHI medical institutions, NHI pharmacies, drug wholesalers and the heads of other related organizations. Updates on the situation have been made through status surveys of price settlements and requests for improvement have been made to the respective trading parties.

Action Plan for New Drug Industry Vision
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[1] Actions to rationalize ethical drug distribution and correction of inappropriate trade practices

- To correct inappropriate trade practices such as pending settlements, provisional deliveries and global pricing, which could undermine the trust in the current drug pricing system and surveys, the 'Council for the Improvement of Ethical Drug Distribution' shall hold itemized discussions with a view to compiling further remedial measures. (Fiscal 2007)
- In addition, the Council shall regularly conduct status surveys of price settlements etc., publish the results and request remedies from the respective trading parties based thereon. (Fiscal 2007 ~ )

[2] Further promotion of IT and standardization

- Standardization of ethical drug code labels will assure medical safety through post-marketing product traceability and the prevention of drug mix-ups. Bar-coding on a per package basis by manufacturers and marketers is also called for to rationalize drug distribution and inventory management.
- The 'Implementation Guideline for Bar-coding of Ethical Drugs' was set out in September 2006 concerning ethical drug code labelling, and efforts are being made to publicize the requirement in principle for proper bar-coding with the mandatory label items for all products shipped with effect from September 2008. Further guidance shall be given on the actions to be taken, such as surveys on the implementation status of pharmaceutical companies. (Fiscal 2008 ~ )
- In addition, in terms of anti-counterfeit drug measures, product recalls and other distribution management rationalization measures, surveys of voluntary label items shall also be conducted to check their bar-coding status, application and other actions taken. Pharmaceutical companies shall be encouraged to take early action to implement this voluntary labelling on a per retail package basis and subsequent expansion of the scope of labelling shall be discussed. (Fiscal 2008 ~ )

**(8) Promotion of proper use of pharmaceutical products**

Action Plan based on previous Vision
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- With reference to the recommendations of the 'Council on Drug Information Supply', the Pharmaceuticals and Medical Devices Agency prepared and released a 'Supply of Information on Drugs and Medical Devices Website' to supply safety information and evaluations thereof to medical professionals, patients and the public. In addition, this

website also gives the latest package insert information and drug guides for patients and the public.

Action Plan for New Drug Industry Vision
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- To ensure the safe supply of drugs, the Pharmaceutical Affairs Law imposes duties on manufacturers and marketers such as the inclusion of necessary particulars in package inserts etc. In addition, the collection of package inserts etc. should allow the optimum treatment for patients to be selected at the medical frontline.
- Pharmaceutical companies are primarily responsible for supplying the medical frontline with the necessary information on drugs through package inserts etc., and the 'Panel for the Prompt Supply of Effective and Safe Drugs' holds that for the post-marketing safety of drugs care should be taken to make the information given therein as clear as possible. To this end the following actions are necessary:
  - a. To modify the warnings in package inserts to ensure that the necessary details are clearly and plainly understood in proportion to the effect on the patient, through giving prominence or fine-tuning the "Warnings of potentially life-threatening adverse effects on patients"
  - b. To supply information to patients through the further constructive preparation and use of 'Drug guides for patients'. (Fiscal 2007 ~ )

**(9) Arrangement of the promotion system by the public and private sectors  
(Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices')**

Action Plan for New Drug Industry Vision
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[1] Public-private dialogue

- On January 31 2007 hosted by the Minister of Health the 'Public-private dialogue for innovative drugs' was inaugurated and attended by the Minister of Education, Culture, Sports, Science and Technology, the Minister of Economy, Trade and Industry and representatives from the pharmaceutical industry and educational and research institutions etc. The aim of the dialogues is to gain a common perception on the creation of innovation in the drug field and enhancement of the global competitiveness of the drug industry. A second public-private dialogue was also held, on April 26 2007, at which the 'Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices' was agreed. These dialogues shall continue to be held around once or twice a year, and progress checks on the Five-Year Strategy shall be carried out regularly. (Fiscal 2007 ~ )
- In addition, a subordinate liaison unit shall be established by the relevant ministries, research institutions and industry, which shall also carry out functions such as coordinating the views on the subjects of priority areas for drug and medical device research, the policies for the nurture of venture firms and the provision of the clinical research and trials infrastructure. Where necessary a forum for public-private dialogue at all levels shall also be provided, since discussions on the future status of the drug industry should also be considered. (Fiscal 2007 ~ )

## [2] Establishment of research framework

- To push ahead with this Vision and the 'Five-Year Strategy for the Creation of Innovative Drugs and Medical Devices' the Health, Labour and Welfare administration shall consolidate the framework for promoting drug and medical device research and commercialization and for enhancing the global competitiveness of the industry. (Fiscal 2008 ~ )

## **Conclusion**

Since the drugs supplied by the drug industry have a major impact on the life and health of the nation and also have a bearing on medical insurance finances, an even higher level of ethics, reliability and transparency is called for from this industry than from industries in general. Further, the drug industry is now attracting unprecedented attention, as evidenced last year by the changes in the national perception of drugs and the industry and the expectations placed on it by the government as a growth industry. Greater political correctness in corporate behaviour, an open business structure, compliance with the code of practices and other efforts to maintain the trust of the public are called for. The government should also support the drug industry and implement public-focused policies to ensure the prompt delivery of world-leading drugs to the nation.