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A New Movement in Drug Development Technology — Microdosing and its challenges —

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1 Introduction

The use of pharmaceuticals, whether these are cold medicines sold at drugs stores or cancer drugs that cost hundreds of thousands of yen per ampule, provides us with great benefits, such as the treatment of sickness and the alleviation of symptoms. Though to the people who use them, it seems to be a given that such medicines are effective and without serious side effects, for the developers, it is difficult to develop such compounds, even with the latest scientific technology.

Figure 1 (a) shows the simplified process of normal drug development. Drug development starts with compound synthesis and optimization using knowledge from basic research, following which a few candidate compounds are selected by repeated test tube and animal experiments in the nonclinical test stages. Out of these candidate compounds, the ones that are estimated to possess the best qualities proceed to clinical trials, which is the stage in which the safety and efficacy of the compound on humans is verified. More than a few of them, however, cause unexpected side effects or show no effect on humans. As if to tease, "pharmaceutical companies have more than enough drugs, if you want to treat a lab rat," it is very difficult to narrow down the results obtained in nonclinical studies to compounds that are safe and effective for humans, and more solid methods for doing this have been needed for a long time.

Microdosing trials were proposed as an effective technique at the beginning of this century (Figure 1(b)). Microdosing is a technique to narrow down the candidate compounds with the highest viability for clinical trials by administering them to humans at extremely low doses to examine their metabolism and tissue distribution when multiple candidate compounds remain after nonclinical trials. At these extremely low doses, there is a low risk of side effects, and therefore, this method enables the performance of candidate compounds in humans to be evaluated safely and in a short period of time.

This report introduces the trend of the microdosing technique in Japan and around the world in the context of recent drug development, and discusses the challenges facing the actual application of microdosing in the future.

2 Problems with Drug Development and the Significance of Microdosing

The development of a new drug generally takes about 15 years and costs tens to hundreds of billion yen. Commonly sold and used drugs are created through an overwhelming process in which a single compound is selected from among hundreds of thousands of candidate compounds. Pharmaceutical companies usually take the main role in drug development, but currently, they rarely undertake all of the processes. In many cases, the evaluation of candidate compounds and clinical trials are referred to contract research organizations (CROs). CROs verify the safety and efficacy of candidate compounds by tests done in test tubes and with animals as nonclinical tests.

Animal experimentation is essential to today's drug development. From the past to the present, a large number of animal studies have been conducted to obtain important data at the organism level that cannot be revealed by molecular and cellular tests. However, it is not a versatile method, since results vary due to species-specific differences between animals and humans. Figure 2 shows a comparison of bioavailability—the fraction of an orally administered dose of a drug that reaches systemic circulation and circulates in the body after the compound is absorbed

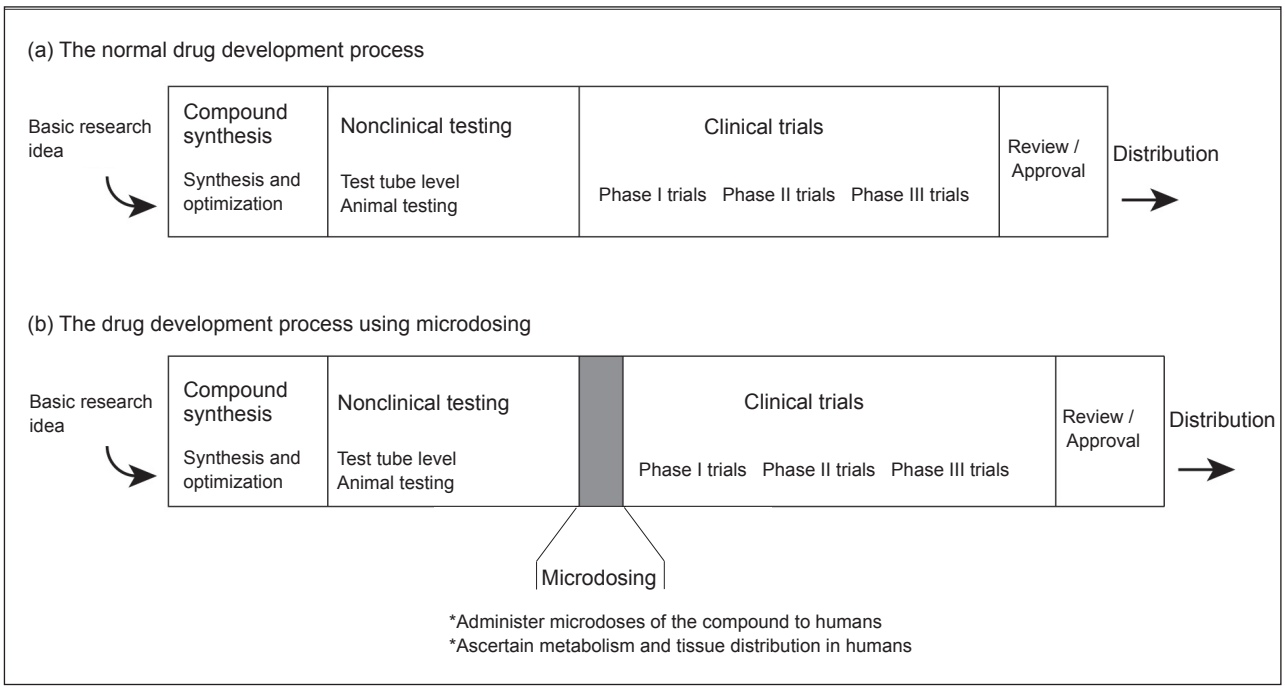

Figure 1 : The Drug Development Process

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by the digestive tract—between humans and animals. Various drugs were tested in this experiment, and the results of each drug are plotted for comparison between humans and monkeys, humans and rodents, and humans and dogs. If the bioavailability of humans and the animals are proportional to each other, the results should plot along a linearly increasing line, whereas in reality, the plot points are scattered randomly. This means that there is little correlation between the bioavailability of humans and that of each animal, clarifying the difficulty of estimating human bioavailability from animal experiments.[1]

In drug development, several candidate compounds are selected in the nonclinical stage of the development and proceed to the clinical trials. As mentioned earlier, it is extremely difficult to select compounds in the nonclinical stages of development that will be safe and effective in humans, and the reality is that the probability of the compounds selected for clinical trials being approved as drugs in the end is low. Reasons for their disqualification vary; for example, the compound cannot be absorbed after oral administration and therefore does not reach circulation, it produces toxic metabolites when metabolized in the liver, it does not reach the target organ or tissue, it gets transferred to organs and tissues that trigger side effects, or it does not get metabolized in the body and actually exhibits toxicity. These are problems related to the pharmacokinetics, in other words, absorption, distribution, metabolism, and excretion, and take up a large proportion of the reasons for disqualification. Other factors contributing to disqualification include unwanted interactions with other drugs, as well as pharmacokinetics that vary from person to person or symptom to symptom.

Figure 3 shows the proportion of the compounds that make it to distribution out of the candidate compounds entering Phase I, the first stage, of clinical trials. Approximately 11% actually make it onto the market. When development is terminated at the level of clinical trials, various actions need to be taken, such as another set of clinical trials using other candidate compounds, and this is extremely inefficient, extending the development period and boosting up the costs.[2]

If candidate compounds are disqualified for pharmacokinetic reasons, the success rate in clinical trials can be increased by selecting candidates based on their good pharmacokinetic properties in humans. This is how microdosing came along. Microdosing can reveal whether the candidate compounds' metabolic rate is too fast or too slow, or if they reach the target organs or tissues in humans. If candidate compounds are selected with these data in mind, their viability will increase dramatically. In other words, improved viability means reducing losses from costs and time wasted on testing non-viable compounds, and as a result, reducing the development time. Of

course, microdosing also requires a certain amount of time and costs. However, both the costs and the time needed are slight compared to normal clinical trials, and considering the current viability of 11%, the overall time and cost for getting the drug onto the market can be drastically reduced (Figure 4). As shown here, microdosing has drawn attention as a technique to improve the efficiency of drug development. In addition, it is believed to be useful in allowing a company to find which of their drugs are candidates for having the highest sales among those with the same mechanisms of action (Best-in-Class drugs), by comparing them with drugs that other companies have already come out with, and it is also said to be effective in allowing a company to re-evaluate its own candidate compounds.

3 The State of the Japanese Pharmaceutical Industry

Japan has contributed to a significant proportion of global drug development as one of the few countries that can develop new drugs domestically. At the same time, the country continues to move toward a "super-aging" society, and with the most common cause of death being cancer, and with neuropsychiatric diseases such as dementia increasing rapidly, development of drugs to treat these illnesses is an urgent task. In addition, unmet medical needs, meaning medical needs with no existing effective treatments, must also

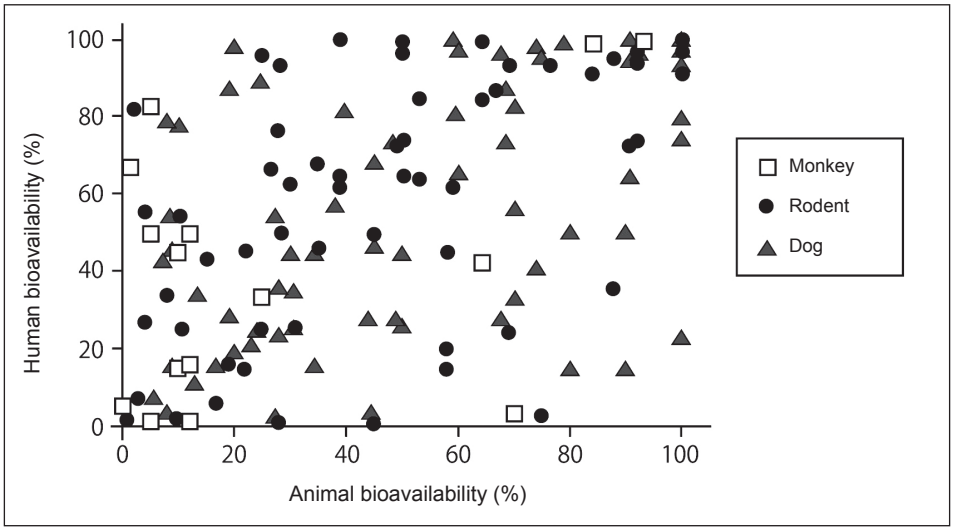

Figure 2 : Comparison of bioavailability between human and animals

Produced at the STFC based on Reference[1]

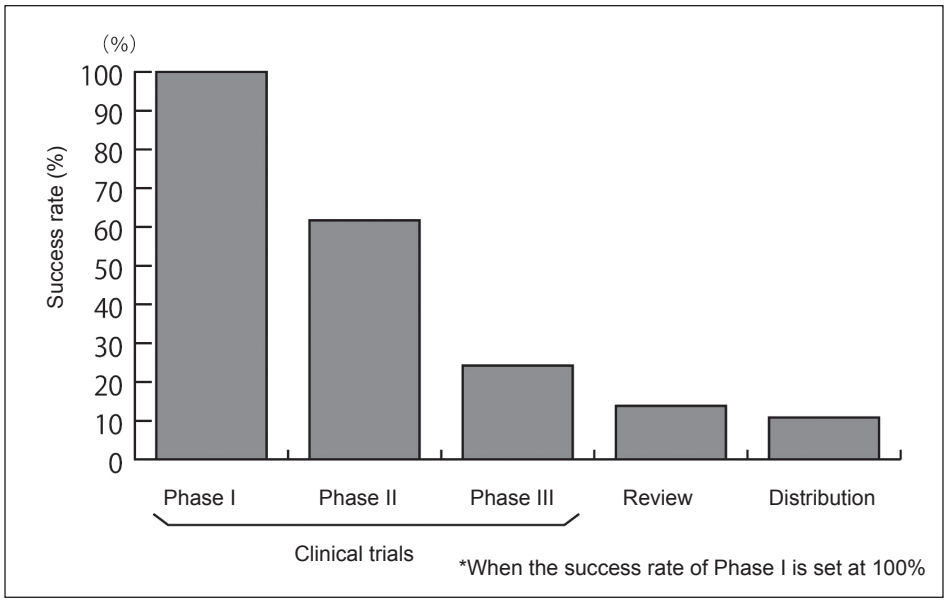

Figure 3 : Success rate of drug development in the top 10 U.S. pharmaceutical companies (1991–2000)

Produced at the STFC based on Reference[2]

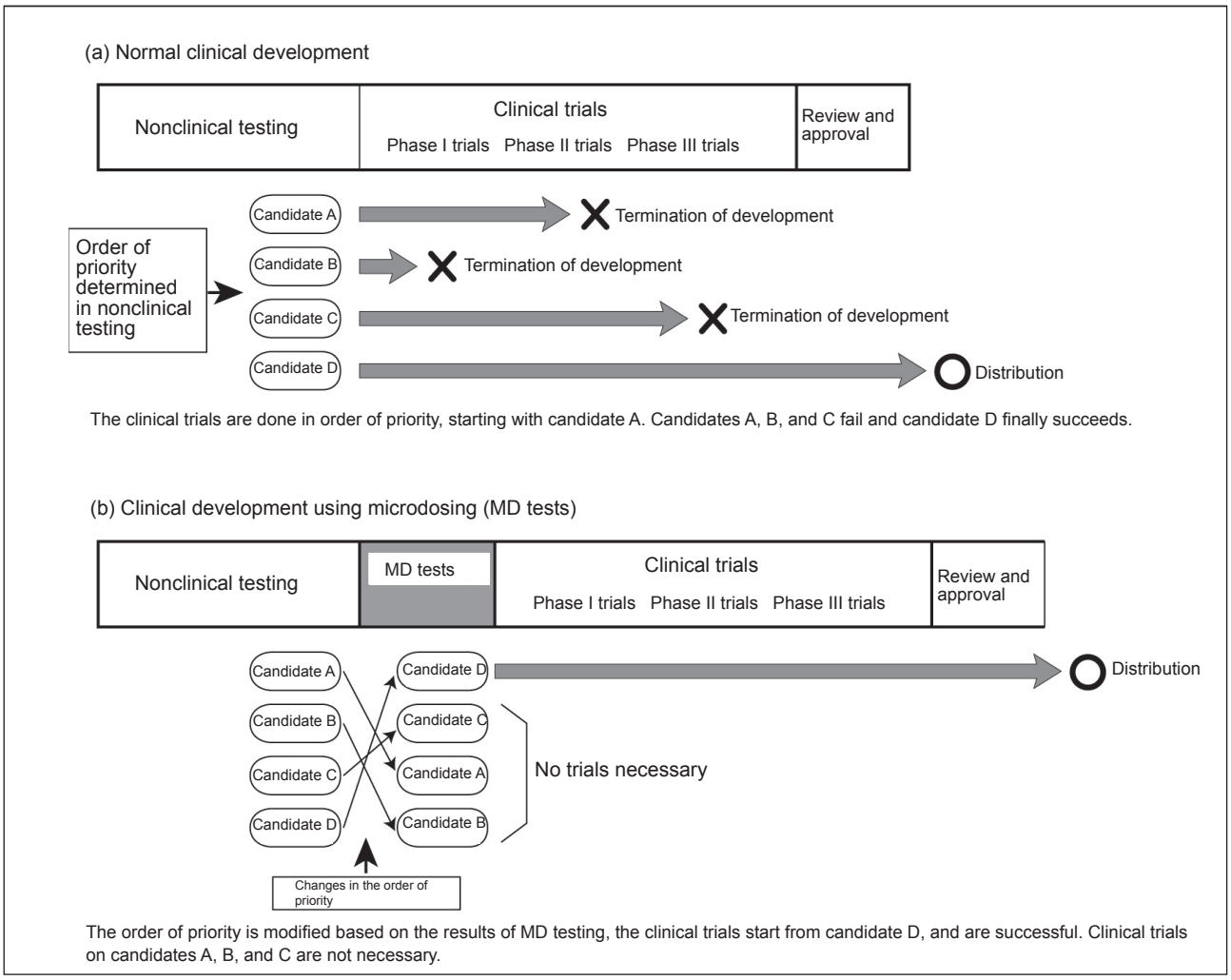

Figure 4 : Normal clinical development and clinical development using microdosing

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be dealt with.

New drugs need to be developed; however, the number of new drugs developed in Japan has a decreasing tendency. Figure 5 shows the changes in the number of manufacturing approvals for new drugs, including those with new active ingredients, in Japan. This number starts to decrease in the later half of the 1990s, and it has notably not exceeded 10 per year after 2001.[3] A similar decrease can be observed in the U.S., albeit to a milder extent than in Japan.[4] In addition, the U.S. has increased its proportion of development of innovative drugs, meaning the first drug to be discovered that uses a certain mechanism (a new class of drug), whereas Japan has decreased here also.[5]

The decrease in the number of newly approved drugs causes the increase of development costs as a result. The average annual cost of research and development among 10 major pharmaceutical companies in Japan was 43.3 billion yen in 1999, whereas in 2008, it increased more than 3 times to 133 billion yen (Figure 6). This caused development costs to exceed 20% of sales in 2008, and caused net profits to drop to 5%.[3] One of the biggest factors in these increasing costs is the low viability of compounds in clinical trials, as mentioned earlier. When development is terminated at the half way point, most of the costs invested up to that point are wasted, and the loss gets bigger as the termination occurs later on in the development. Consequently, it starts to appear as an increase in development costs for the company as a whole.

The United States is one of the biggest markets for Japanese pharmaceutical companies, and the country's safety review of new drugs became stricter with the Food and Drug Administration (FDA) reform bill in 2009. With this, development costs are expected to increase further with the increase that this has caused in the number of subjects and extended period that will be necessary in future clinical trials.[4]

Japan is one of the few countries that develop drugs domestically, as mentioned earlier, however, in the balance of trade, Japan has an excess of imports

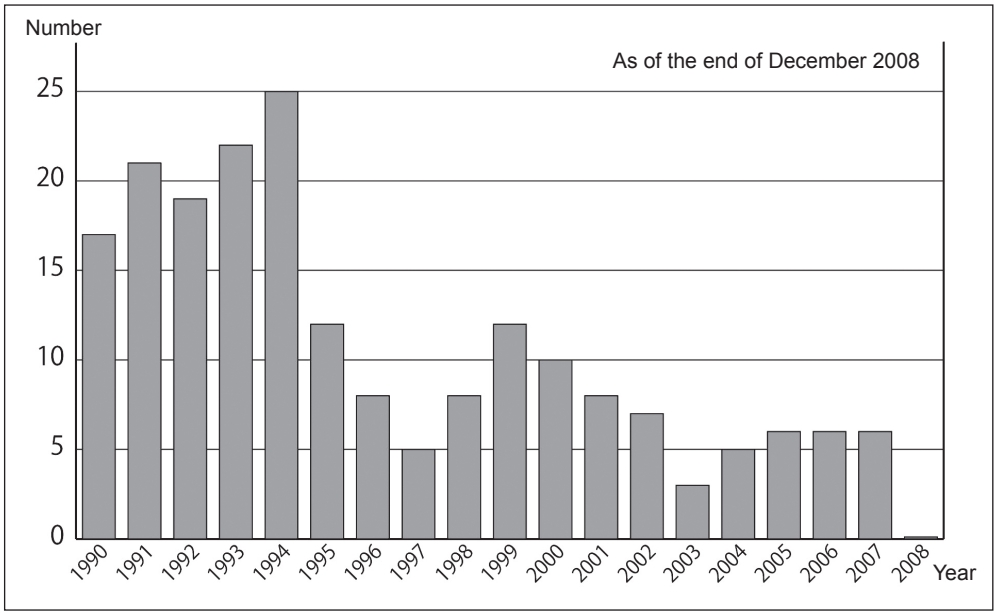

Figure 5 : Number of manufacturing approvals of drugs with new effective contents in Japan

Prepared at the STFC based on Reference[3]

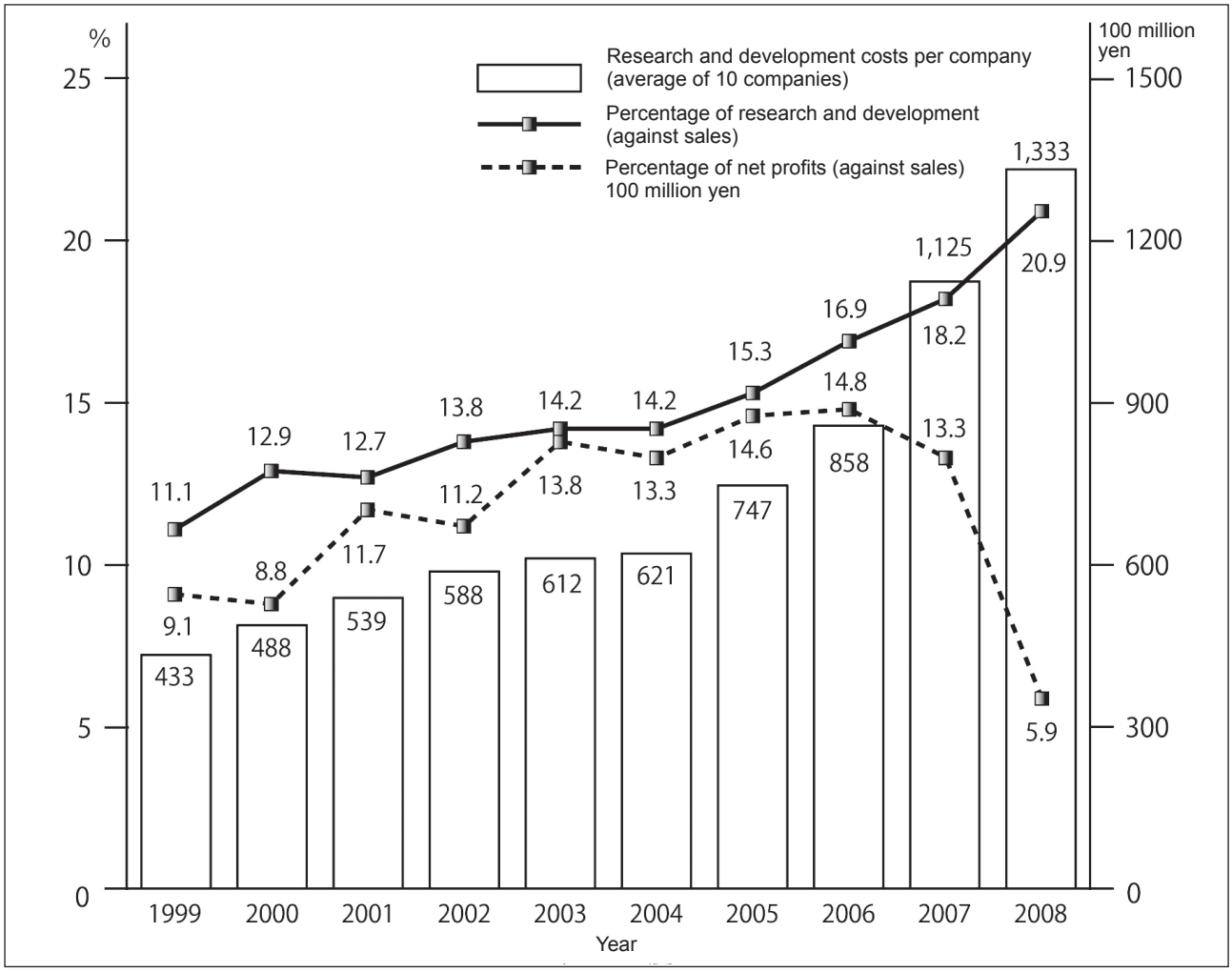

Figure 6 : Changes in research and development costs and the proportion of profit over sales at 10 major pharmaceutical companies in Japan

Prepared at the STFC based on Reference[3]

over exports on the pharmaceutical industry. When comparing 2000 and 2008, exports increased slightly, whereas imports almost doubled, making imports more than triple of exports in 2008, and creating a deficit of 780 billion yen in the 2008 balance.[6] Japan is moving toward a super-aging society, and further increases in medical costs are expected. Developing drugs in Japan not only benefits its citizens, but also helps the trade balance by increasing proportion of purely domestic drugs. However, Japanese companies are at a disadvantage in innovating new drugs. They are relatively small companies by global standards, as evidenced by Takeda Pharmaceutical, which has the highest domestic drug sales, and is ranked only 17th in the world.[7] Mega-pharmaceutical companies in the U.S. and Europe may be able to run clinical trials one after another with their abundant financial resources. Small-scale pharmaceutical companies in Japan, therefore, should be more efficient in drug development, such as through the use of microdosing, to compete with these mega companies.

4 Advocacy of Microdosing and International Guidelines

Low viability and increases in development costs are not unique to drug development by Japanese pharmaceutical companies, but are, in fact, a global problem. One of the methods to solve this problem is microdosing.

The concept of microdosing first appeared in the position paper of the European Medicines Agency (EMEA) in 2003. In addition, the FDA issued a Critical Path Report in 2004, indicating the importance of conducting exploratory clinical trials before normal clinical trials, and further developing this idea later on. In response, though delayed, the MHLW (Ministry of Health, Labour and Welfare) in Japan released its Guidance on Microdosing in June 2008. Guidelines on drug development allow for more efficient development when standardized internationally. Therefore, the Non-clinical Safety Studies for the Conduct of Human Clinical Trials guideline of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), was revised and agreed upon among the EU, the U.S., and Japan, and publicized domestically in February 2010.[8] This has provided a way for microdosing to be conducted based on internationally standardized guidelines.

The Guidance on Microdosing, in addition to prescribing technical guidelines such as the administering dose of the compound, toxicity tests on the compound, the compound quality, measurement methods, and evaluation of internal exposure, also prescribes the formation of protocol for the clinical trials, formation of a review board, and the notification of the relevant government agencies, and requires that microdosing studies actually being conducted adhere to all of these guidelines, as well as the ethical aspects of such testing.

5 Implementation of Microdosing Studies and Measurement Technology

Microdosing studies are trials where less than 1/100 of an effective dose totaling less than 100ug of a candidate compound is administered once or multiple times (up to 5 times) to humans. Since the dosage is so small, there is little risk of side effects even when studies are done on humans. In addition, the toxicity testing that is carried out on animals before these studies can be completed more easily and in a shorter time than before normal clinical trials. In actuality, CROs commissioned by pharmaceutical companies conduct these studies, by administering microdoses of candidate compounds to several healthy male subjects and taking measurements. For measurement, one method is usually selected from 3 major methods (Table 1).

5-1 Accelerator Mass Spectrometry (AMS)

Accelerator mass spectrometry (AMS) is a method used for dating, and has a characteristic high sensitivity. In microdosing, candidate compounds are labeled with ^{14}C. After administering a microdose of labeled compound to a human subject, samples such as blood, urine, and feces are analyzed using AMS. Since ^{14}C-labeled compounds are administered, a small amount of radiation is released. The amount, however, is much less than the annual exposure to natural radiation, thus the radiation from the study is believed to have no effect on the subjects' health, and the labeled compounds are not legally regarded as radioactive isotopes due to their small doses. It is useful for investigating how the compound is

Table 1 : Measuring techniques used for microdosing

Measuring method	Labeling of testing material	Characteristics
Accelerator Mass Spectrometry (AMS)	Radioactive isotopes with a long half life, such as ^{14}C	*Extremely high sensitivity *Capable of constructive analysis of the metabolites of the compound *Requires large facilities and equipment
Liquid Chromatograh Mass Spectrometer (LC/MS/MS)	No labeling required	*Capacity for profile prediction of the medicinal properties of a compound *Suitable for cassette dose test
Positron Emission Tomography (PET)	Positron-emitting nuclide with a short half life, such as ^{11}C, ^{13}N, ^{18}F, ^{15}O	*Capacity to measure distribution and concentration of the compound in the body *Requires large facilities and equipment

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absorbed, metabolized and excreted as a whole. In other words, by measuring the concentration of the administered candidate compound in the blood, urine, and feces chronologically, the pharmacokinetics of the candidate compound, as well as its metabolites in the human body, can be found. Since drugs become active and consequently act as drugs after becoming metabolized in the body in many cases, a low concentration of active metabolite in the measurement causes the compound to be given a low evaluation. In addition, the use of ^{14}C labeled compound enables the discovery and/or identification of new metabolites, allowing for a separate toxicity test of the metabolite later. Since there is a difference between some metabolic enzymes in humans and in animals, there is a possibility that a metabolite that is toxic specifically in humans may form. If the strong toxicity is revealed beforehand, the candidate compound can be eliminated from the list, and wasteful clinical trials can be prevented.

Highly sensitive AMS analytic methods are already being used in the U.S. and Europe, and are applied to many microdosing trials. There are also private analytical companies that are equipped with AMS and possess high analytical techniques in Japan.

5-2 Liquid Chromatograh Mass Spectrometers (LC/MS/MS)

A liquid chromatograph mass spectrometer (LC/MS/MS) is a device that combines a high-performance liquid chromatograph (HPLC) and a mass spectrometer (MS), and is able to quantify materials in a highly sensitive manner, as well as to detect blood concentrations of a drug at the order of pg/ml. As for its use in microdosing, it does not require labeling since it does not use radioactive isotopes. In addition, since it does not require a large facility, it can be used at a small scale organization or company.

One characteristic of LC/MS/MS is its effectiveness for cassette dose tests. The cassette dose test is a method to test multiple compounds simultaneously on one subject, enabling the comparison of the compounds under the same conditions, which provides valuable information that can not be obtained from the test of each compound. This means that it enables the compound with the best drug properties to be selected from multiple candidate compounds with similar expected effects, and also cuts costs by reducing the number of subjects required.

5-3 Positron Emission Tomography (PET)

Positron emission tomography (PET) is a method that is commonly used for cancer diagnosis in medical institutions. It measures the distribution and chronological changes of gamma waves emitted by a radioactive tracer labeled with a positron emitting nuclide with a short half-life (^{11}C, ^{13}N, ^{18}F, ^{15}O, etc). In microdosing studies, the distribution and the concentration of the compound can be detected chronologically as imaging data by labeling the testing compound with a positron emitting nuclide and using it as the radioactive tracer. This is a superior characteristic particular to PET. The two methods introduced earlier can measure the time and concentration from the time of administration until its collection, however, they can not reveal the course the compound took. PET can show important information about whether a compound is transferred to the target organs or not. For example, there are more than a few examples of compounds targeting the brain that could not reach the human brain in clinical trials. This is due to the blood-brain barrier in the human brain, which blocks the unnecessary components of the blood from entering the brain. The use of PET enables it to be clearly seen whether a candidate compound reaches the brain, providing important information for the evaluation of the compound. In addition, PET enables the measurement of the occupancy of receptors

(how much of the compound is bound to a particular receptor) that are involved in treatment or in side effects.

As seen up to this point, PET has big advantages; however, it comes with disadvantages as well. Since PET uses radioactive isotopes, it requires strict management of the labeled compounds, necessitates assessments on the safety of the subjects' exposure. In addition, it requires a large facility and equipment including cyclotron, automatic synthesizing apparatus, and PET scanner, requiring a big investment of several billion yen for its construction. In addition, there are some technical problems remaining, especially the existing difficulties with the efficient labeling techniques of candidate compounds with positron-emitting nuclides in extremely short periods of time. In addition, since it is necessary to develop a synthetic method for labeling each individual compound, it is hoped that a universal synthetic method will be developed that can be applied to almost all compounds.

6 Research Trends of Microdosing

Microdosing is a relatively new method in the history of drug development, and its effectiveness had not been confirmed when it was first proposed. In particular, since the method involves taking measurements after very small doses of drugs are administered, there was no proof that measurements would be correlated (linear) to these when a therapeutic dose was administered, and this needed to be confirmed. In addition, many aspects of the measuring techniques were underdeveloped, and the establishment of a methodology, including the management of the overall study was necessary. Because of this, validation projects have been conducted to evaluate the effectiveness and problems of microdosing studies, using existing drugs whose safety and dosages have been confirmed in normal clinical trials, with England playing the central role.

One of the projects was the Consortium for Resourcing and Evaluation AMS Microdosing (CREAM) test conducted by four pharmaceutical companies led by a British CRO, Excelleron Corporation, in collaboration with Eli Lilly, Roche, and others, and its results were reported in 2006.[9] In this study, five existing drugs were used, out of which three maintained linearity, and two did not show enough linearity. However, it was determined that it was possible to predict the causes for disrupted linearity in the two samples using other information.[10]

Another project was the European Union Microdosing AMS Partnership Programme (EUMAPP), which began in January 2006 with the EU's public support. In this study, the aforementioned Excelleron Corporation took charge of coordination, and nine EU private companies and members of academia participated in evaluating seven major compounds that had caused problems in animal studies. As a result, in a study in which microdoses of the target compounds were injected intravenously, the microdoses were confirmed to maintain linearity with the therapeutic doses. On the other hand, the data from oral administration did not maintain linearity to the same extent as it did with intravenous administration, however, they concluded that most of the causes for the disruption could be predicted by the compounds' chemical properties.[11]

These two research projects were groundbreaking in the sense that they clarified the effectiveness and problems of microdosing studies. In addition, by moving forward with these studies, the know-how for conducting microdosing was accumulated and human resources were trained in European CROs such as Excelleron Corporation.

A validation project for microdosing is being conducted in Japan also, namely, the NEDO project, which started in October 2008, entitled Development of Innovative Drugs Using Microdosing Studies: Based on the Quantificational Prediction Technology of Drug Properties and Efficacy. This project is more ambitious than those conducted in the UK or in Europe, as it aims to develop innovative technology that will support drug development, by fusing microdosing studies that use various measurement techniques, including molecular imaging by PET, with kinetic analysis methods related to the prediction of a compound's dynamics in the body, dramatically improving the effectiveness and applicability of microdosing.[12] The abovementioned projects in the UK and the EU used only AMS, but this project values measurements by PET, as well as high-performance LC/MS/MS. In addition, it is attempting to enable wider predictions to be made from the data obtained in microdosing studies, by combining test tube and animal experiment data, such as data on the drug transporters and metabolic enzymes that are involved in transporting a drug in and out of the

cell, and the influence of polymorphism on the genes related to them, and by constructing mathematical models from this combined data. The final results of the project are scheduled to be published in 2011, and they are expected to surpass those of the projects in Europe.[13]

7 Use of Microdosing Studies and the Status of CROs

Corporate activity, particularly information on drug development by pharmaceutical companies, is rarely publicized, making it extremely difficult to grasp the overall picture of the microdosing studies being implemented. An investigation by the Pharmaceutical Research and Manufacturers of America (PhRMA) reported that in the nine participating U.S. pharmaceutical companies they had surveyed, a total of 16 such studies had been implemented from 2006 to 2007 and another 16 had taken place from 2008 to 2009. However, it is noted that a larger number of such studies were actually being implemented.[14] In the UK, at first, many microdosing studies were being implemented for candidate compounds developed by startup companies, however, with the improvement of the measurement technology with PET and LC/MS/MS, major pharmaceutical companies such as GlaxoSmithKline, Servier, Merck, Sanofi-Aventis, and Amgen, started to conduct these studies as well. Especially from 2009 to 2010, conditions changed dramatically, with some reporting that the number of commissioned microdosing studies had almost doubled.[14]

PET is one of the most powerful tools in microdosing, and with the recognition that imaging technology provides valuable information on the direction of drug development, GlaxoSmithKline founded a research institution, the Clinical Imaging Center, at Imperial College London's Hammersmith Hospital in the UK, in 2008. This institution has two PET scanners and two MRI scanners, and has announced its use of imaging technology in approximately 40% of the drugs developed by the end of 2010.[15] As seen here, major pharmaceutical companies in the U.S. and Europe seem to be incorporating microdosing studies as a part of drug development. This is backed by the fact that the previously-mentioned validation studies on microdosing have provided training to the CROs, which makes it easier for the pharmaceutical companies to commission them.

On the other hand, operational experience with microdosing in Japanese pharmaceutical companies is comparatively scarce, with few reports on this topic. Mid-sized Ono Pharmaceutical has reported to have commissioned a British CRO to implement microdosing studies, and decided to continue with development using the results it obtained on bioavailability. Astellas Pharma has applied the accumulated knowledge of many years of PET studies to found their own facility and research institution (Bioimaging Institute) with PET and MRI, and it is believed that it will start running microdosing trials.

There are various CROs for different stages of drug development in Japan, creating a market of over 200 billion yen, and their ability and quality are regarded as extremely high compared to CROs in the U.S. and Europe. They have traditionally evaluated the safety and properties of candidate compounds using animal experiments, however, in recent years, there is a movement to actively incorporate procedures that connect the animals and humans, with an increasing number of CROs conducting tests using human cells. Some of these CROs are participating in the abovementioned NEDO project, and though it is a validation project using existing drugs, it provides the opportunity to advance the know-how and training of human resources for running microdosing studies. In the future, when the use of microdosing gains momentum, the techniques for handling microdose compounds and metabolites will improve, and the CROs will mature to the level of Western CROs. Microdosing studies using PET are harder to tackle than those that use AMS and LC/MS/MS from the perspective of the facilities involved, meaning that only a portion of incorporated administrative agencies, universities, and corporations are able to use PET in reality. Because of this, those that cannot will need to collaborate with CROs to conduct studies using PET in the future.

8 Problems with Microdosing Studies in Japan and Their Solutions

We have discussed microdosing and its techniques, the state of drug development, and domestic and international companies and research trends. As a result of validation studies on micordosing in Europe, microdosing is believed to be a useful technique that will be used more in the future. In the U.S. and Europe, this technique has been taken on by both startup companies and major pharmaceutical companies, and is already being used for drug development.

On the other hand, though delayed from the European projects, the NEDO project has started in Japan. Pharmaceutical companies and CROs are participating in this project, learning measuring and analytical techniques and training personnel by actually conducting microdosing studies. However, Japanese pharmaceutical companies have yet to commission domestic CROs to conduct microdosing studies, and tend to commission CROs abroad for this. Though microdosing is not necessary for all drugs being developed, persistence of the current state will create a large gap in the efficiency of Japan's drug development compared to the U.S. and Europe, causing a decline in the Japanese pharmaceutical industry.

To solve this, policies should be developed to construct a system for carrying out microdosing studies domestically based on the NEDO project results. Considering the validation projects that have already been implemented and the existence of experienced CROs in the U.S. and Europe, it is necessary to train human resources in domestic CROs with even higher techniques for microdosing studies to be conducted in Japan. Fortunately, domestic CROs are participating in the NEDO project, and higher levels of predictive techniques are starting to take shape under its ambitious goals. In order for Japanese pharmaceutical companies to commission domestic CROs rather than those abroad, these CROs need to accumulate experience. To do this, microdosing should be primed by the government (such as Ministry of Economy, Trade and Industry) by providing financial support to pharmaceutical companies to conduct microdosing studies, creating a virtuous circle in which pharmaceutical companies repeatedly commission CROs. Participating companies can be recruited publically, giving the opportunity for bioventures, universities, and incorporated administrative agencies, in addition to mid-sized pharmaceutical companies, to participate. Through this, pharmaceutical companies and CROs will receive actual experience with microdosing studies, resulting in the development of technology, personnel training, and upgrades in management ability, as well as the construction of a system for developing new drugs using microdosing within pharmaceutical companies.

In addition to the construction of a domestic system, it is also important to develop foundational technology, led by MEXT (Ministry of Education, Culture, Sports, Science and Technology). Microdosing is a barely 10-year old method, and upgrading is needed in all areas, such as sampling and sample processing. Testing by PET, in particular, has extremely high potential as a molecular imaging technique for distinguishing tissue distribution as well as for determining the efficacy of future treatments. Since compound labeling is important in microdosing studies using PET, efficient labeling methods should be established in order to construct a domestic system that can respond to a large volume of demand. Since PET studies are more difficult in terms of the facilities required, it is desirable for NIRS (National Institute of Radiological Sciences) and RIKEN, which promote molecular imaging research, to provide the technology and facilities, and collaborate with CROs in implementing microdosing studies.

In recent years, many biomedicines such as antibody drugs, peptides, and nucleic acid drugs have appeared and increased in significance. The technology for testing these biomedicines by microdosing still needs to be established.

As mentioned earlier, drug development requires knowledge in various academic fields, and this has been one of Japan's strong suits. In recent years, however, drugs in Japan are often introduced after their development abroad, creating concerns of the loss of substance in drug development in the country. If microdosing studies can be conducted outside of the country, more information on drug development will flow overseas, possibly worsening this situation. On the other hand, if a system through which microdosing studies can be conducted is established in Japan and uses better techniques than the U.S. and

Europe, pharmaceutical companies inside and outside of Japan will want to conduct their studies in Japan. Microdosing is a desirable tool for Japan to lead global drug development, and will allow many drugs to be developed efficiently to save people suffering from illness all over the world.

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References

[1] Grass and Sinko, DDT Vol.6, No.12 (Supple), 2001

[2] Kola I, Landis J: Nat Rev Drug Discov 3, 711-715, 2004

[3] Public Relations Committee, Japan Pharmaceutical Manufacturers Association, DATA BOOK 2010, 35-56, 2010

[4] Katsumi Hibi, 2010 Issues and prospects in the pharmaceutical industry, Monthly Economic Report, July 2009 http://www.fukoku-life.co.jp/economic-information/index4.html

[5] Shuji Onozuka, National Institute of Science and Technology Policy News (Office of Pharmaceutical Industry Research), 29, 16-19, 2010

[6] Public Relations Committee, Japan Pharmaceutical Manufacturers Association, DATA BOOK 2010, 1-26, 2010

[7] Public Relations Committee, Japan Pharmaceutical Manufacturers Association, DATA BOOK 2010, 58-70, 2010

[8] Guidance on the implementation of nonclinical safety tests for applications for clinical trials of drugs and manufacturing and distribution approval, Pharmaceutical and Food Safety Bureau 0219No.4, February 19, 2010

[9] Lappin G et al. Clin Pharmacol Ther 80, 203 - 217, 2006

[10] Bertino JS et al., J Clin Pharmacol 47, 418 - 422, 2007

[11] Hiroshi Mayahara, Achievements of EUMAPP-Comparative studies of drug properties at microdoses and effective doses, Idenshi Igaku MOOK, supplementary volume "New development from microdosing to PET molecular imaging," 84-95, 2010

[12] Yuichi Sugiyama et al, Development of drug innovation technology using microdosing, Idenshi Igaku MOOK, supplementary volume "New development from microdosing to PET molecular imaging," 28-38, 2010

[13] Kazuya Maeda, Development of a variable prediction method for drug properties by drug interaction, Idenshi Igaku MOOK, supplementary volume "New development from microdosing to PET molecular imaging," 63-73, 2010

[14] Chieko Kurihara, Global trend of policies and guidelines on microdose PET molecular imaging, Idenshi Igaku MOOK, supplementary volume "New development from microdosing to PET molecular imaging," 188-195, 2010

[15] Masaru Iwasaki, Reports from England, a leading country in MD and PET – approach at GlaxoSmithKline –, Idenshi Igaku MOOK, supplementary volume "New development from microdosing to PET molecular imaging," 224-229, 2010

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