**Provisional Translation (as of January 27, 2014)***

November 15, 2013

Pharmaceuticals and Bio-products Subcommittees, Science Board

# Summary of Discussion on Non-clinical Pharmacology Studies on Anticancer Drugs

The objective of non-clinical pharmacology studies (primary pharmacodynamics) in drug development is to investigate the efficacy and a mechanism of action of a pertinent drug at a non-clinical level in an exploratory manner. During the review process of new drugs, while evaluating efficacy, based on the results of clinical studies as a basis, the results of non-clinical pharmacology studies are evaluated from the point of view of "proof-of-concept," that is, whether or not a potency of the drug is supported by pharmacology data demonstrating a mechanism of action. Therefore, study reports of "mechanism of action" and "efficacy against indicated cancer types" are required to be filed as a part of non-clinical pharmacology studies for the regulatory review of anticancer drugs in Japan.

Based on the issues raised by the Pharmaceuticals and Medical Devices Agency (PMDA), the Working Group for the Evaluation of Pharmacology Studies on Anticancer Drugs discussed the following points: (1) the current status of non-clinical studies on anticancer drugs, and the concept of evaluation in regulatory review and (2) the role and contribution of non-clinical pharmacology studies in the development of anticancer drugs, taking into account of the recent progress of personalized medicine.

## 1. Current status of non-clinical pharmacology studies on anticancer drugs and the concept of evaluation in regulatory review

### (1) Necessity of non-clinical pharmacology studies on the efficacy for indicated cancer types

Phase I studies of anticancer drugs are usually conducted in patients with various types of cancer for which no standard therapies exist. For this reason, in actual status, non-clinical

pharmacology studies have not been conducted for every cancer type of those patients prior to conducting clinical studies. Furthermore, in the subsequent clinical studies, development process proceeds by targeting on cancer types that have responded to the treatment in phase I studies, and there are some cases where the new drug applications have been filed without having conducted non-clinical studies on the cancer types indicated for the treatment. It has been pointed out that it is not reasonable to conduct non-clinical pharmacology studies on cancer types indicated for the treatment only for regulatory submission purpose.

Non-clinical pharmacology studies on anticancer drugs generally include *in vitro* studies using human tumor-derived cell lines and *in vivo* studies using xenograft models. However, the former has a possibility of selection bias to occur during the establishment of cell lines, and the properties of the cells may change during passage cultures after establishment. Therefore, it is unclear to what extent the cell lines possess the properties of the cancer type for which the drug is indicated. Also, since a level of responsiveness to drugs differs depending on cell lines even when the cells are derived from the same cancer type, there are inherent limitations to evaluate the significance of efficacy based on non-clinical pharmacology studies using limited types of cell lines. Even for *in vivo* studies using xenograft models, there are some cases where the evaluation results obtained using immune-compromised animals (e.g., nude mice) have not been consistent with the results of the subsequent clinical studies. Use of genetically engineered animals that more accurately characterize the pathology of the target cancer type may be an effective method to resolve this problem, but applicable animal models are limited for pharmacology studies. In addition, for cancer types with absence of or with unknown driver mutation, such as those generated by acquisition of malignant phenotypes due to accumulation of several genetic abnormalities, it is practically impossible to generate animal models or cells that reproduce the molecular pathology.

These technical limitations do not by themselves mean that non-clinical pharmacology studies are unnecessary in the development of anticancer drugs. However, for a drug whose efficacy for the target cancer has already been demonstrated in clinical studies, data obtained in the clinical studies in human subjects are considered to provide more direct and significant information than those obtained in non-clinical pharmacology studies with

various limitations. Based on the above, it is not considered necessarily significant to conduct non-clinical pharmacology studies to evaluate efficacy against indicated cancer types solely for regulatory submission purpose.

**(2) Appropriateness of submitting published literature as application data**

In Japan, instead of submitting the results of non-clinical pharmacology studies on "mechanism of action," published literature are permitted to be submitted, whereas results of studies on "efficacy against indicated cancer types" are required to be submitted as application data with reliability assurance, such as the accessibility to raw data, instead of published literature. In the United States and Europe, in contrast, as non-clinical pharmacology study data are not essential as application data; instead, published literature may be submitted for non-clinical pharmacology data. Should published literature be accepted as application data in Japan as well?

Taking into account of the fact that the Pharmaceutical Affairs Act requires non-clinical studies to conform to the integrity standards but does not require compliance with the GLP, it is appropriate to require submission of data for evaluation with reliability assurance, if any, in the context of the significance of non-clinical pharmacology studies on efficacy against indicated cancer types described in the above section (1). Published literature (limited to peer-reviewed one) may be considered acceptable in certain cases, however it should be noted that, since they are not prepared for the purpose of application data, the quality and content of information may be insufficient from the point of view of regulatory review. To address such cases effectively, the applicant should foster a relationship of mutual trust with authors of the published literature, e.g., persons in charge of drug development, medical professionals and researchers, so that the PMDA may make inquiries as necessary to the authors on raw data and details on conditions of the study, etc., through the applicant.

**(3) Effects on the development of anticancer drugs by altering the scope of non-clinical pharmacology data to be submitted and accepting the submission of published literature for application data**

If it were not required to conduct non-clinical pharmacology studies on "efficacy against indicated cancer types" solely for regulatory submission purpose, provided that the

efficacy of a drug has been demonstrated by clinical studies, how would it affect the development of anticancer drugs? What if published literature as application data is accepted for submission?

The former case would not even exempt non-clinical pharmacology studies of a drug that are necessary and feasible for indicated target cancer type during the development before clinical studies. Therefore, this measure is considered to have a limited effect on future development of anticancer drugs.

Regarding the latter case, it would be difficult for PMDA to confirm credibility of the published literature directly and integrity of the data. Therefore, there would be greater requirement for drug developers and medical professionals to conduct studies according to their scientific conscience, to make efforts to ensure the reliability of the published literature, and to have its scientific consistency reviewed by experts without conflict of interest in the relevant field. In addition, PMDA would be required to collect and evaluate information from multiple aspects when reviewing the application that utilizes the published literature. Currently, since published literature are not accepted for the regulatory submission in Japan, there is a concern that filing and review of applications for anticancer drugs developed through global clinical trials without non-clinical pharmacology studies will be difficult for PMDA to proceed, thus leading to the problem of “drug-lag” faced in this country. Therefore, if published literature are accepted for submission of application data, preceding issue will be resolved.

## 2. Role and expectations for non-clinical pharmacology studies in future development of anticancer drugs (role of non-clinical pharmacology studies and their contribution to the development of anticancer drugs, taking into account of the recent advancement of personalized medicine)

### (1) Development of anticancer drugs targeting “driver mutations”

In recent years, there have been advancements in the development of anticancer drugs that are expected to have high level of efficacy by the combination with companion diagnostics. Although ALK fusion gene is recognized as a driver mutation, it has not been clarified on which types of gene mutations are generally recognized as driver mutations. In addition, regarding the development of anticancer drugs that target driver mutations, it

should be discussed at this stage whether or not it is necessary to follow the conventional process of the anticancer drug development, which is specified by each target organ, and what type of non-clinical and clinical data should be obtained.

Prior to the discussion, Dr. Saya (Professor, Keio Univ.) presented a review on the modifications in the strategy of cancer treatment based on genome sequencing data obtained by the next generation sequencer (NGS), as outlined below.

- Genome analysis using NGS is useful for estimating the etiology of cancer, but is only less frequently able to identify druggable mutations.
- A potentially workable strategy will be to integrate the genomic mutation data with those of mRNA expression, gene copy number, DNA methylation, etc., thereby to identify a pathway that has abnormalities, and to target a specific site on this pathway.
- Due to the heterogeneity of tumor cells, there may be cells that are maintained by the activation of different pathways.

The proposed criteria for selecting driver mutations include sites with frequent mutations on DNA sequences and misssense mutations caused by base substitution (for tumor suppressor genes, the sites of mutations are diverse, resulting in inactivation of the genes). On the other hand, as shown in the presentation by Prof. Saya, for cancers with mutations that vary from patient to patient and for “hyper mutation-type” cancers with numerous mutations, it will be difficult to identify driver mutations, and even if a driver mutation is identified, dependency of cancer cells on the pertinent mutation may be low. This could be contradictory to the fact that the genes, such as *EML4-ALK* fusion gene and *BCR-ABL* fusion gene, generated by chromosomal translocation have potent driver activities, and inhibitors to these genes exhibit marked antitumor effects. For cancers without such pre-eminent driver mutations or for cancers of which the driver mutation has not been identified, signal pathways, metabolic pathways and epigenomic changes specific to the cancer may become new targets for treatment.

In the development of anticancer drugs that target driver mutations, the significance of the conventional anticancer drug development specified for each organ will decrease with the

ubiquitous use of NGS. It is expected that appropriate selection of patients based on presence or absence of the driver mutation, without adhering to the concept of “indicated cancer types (organs)”, will ensure more robust scientific evidence and improvement in development efficiency and success rate of anticancer drugs. For this purpose, it is essential to prove efficacy of a drug based on the mechanism of action in a non-clinical pharmacology study using cell lines (or genetically engineered mice) introduced with the gene with a driver mutation. Also, since disease classification based on driver mutation tends to practically cause fractionation of patients into minor groups, it will be necessary to be aware of the positive mutation rate and mutual exclusivity with other known driver mutations in advance at a clinical level. Furthermore, development of companion diagnostics will be critical.

**(2) Prospect for the future development of anticancer drugs**

New anticancer drugs that are expected to be developed include those targeting nucleic acids such as non-coding RNA. In particular, the clinical development of microRNAs is being advanced and is targeted at diseases such as hepatitis C. Not only an approach that suppresses disease target microRNAs but also use of microRNAs as replacement agents or as diagnostic biomarkers is expected to be beneficial in the future.

Progress will also be seen in the development of drugs that activate cellular immunity in an antigen-specific manner, such as peptide vaccines, and of drugs that activate tumor immunity by blocking immune checkpoint molecules. As an example of the latter approach, ipilimumab, an anti-CTLA-4 antibody, was approved in the United States in 2011, which is followed by other drugs such as anti-PD-1 antibody and anti-PD-L1 antibody, which are under clinical development. Drugs targeting immune checkpoints may possibly be applicable to cancers with unknown driver mutations as well.

Non-clinical pharmacology studies on these nucleic acid drugs and immune-targeted drugs should be designed, considering the difference between humans and test animals (human CTLA-4 transgenic mice were used in the non-clinical pharmacology study on ipilimumab) in nucleic acid sequences and immune systems.

[Reference data] Working group members and process of deliberations

1. Working group members (Honorifics omitted)

○ Tatsuro Irimura, Director, Clinical Innovation Division, St Luke's International Medical Center

○ Atsushi Ohtsu, Director, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center

Takahiro Ochiya, Division Head, National Cancer Center

Ikuo Saiki, Professor, Division of Pathogenic Biochemistry, Institute of Natural Medicine, University of Toyama

Hideyuki Saya, Professor, Division of Gene Regulation, Institute for Advanced Medical Research, Graduate School of Medicine, Keio University

Hiroyuki Seimiya, Director, Division of Molecular Biotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research

Haruhiko Sugimura, Professor, Department of Tumor Pathology, Hamamatsu University School of Medicine

○ Tomoki Naoe, President, Nagoya Medical Center, National Hospital Organization

(○: members of Pharmaceuticals Subcommittee)

2. Process of deliberations

(1) Meeting schedule

○ First WG meeting

Date, time, and place of meeting: April 23, 2013, at Meeting Rooms 8-9 of PMDA

Members in attendance: Irimura, Ohtsu, Ochiya, Saiki, Saya, Seimiya, Sugimura, and Naoe (8 in total)

Agenda: Discussion was held on the topic presented

Topic: "On pharmacology studies on anticancer drugs" presented by Office of New Drug V, PMDA

○ Second WG meeting

Date, time, and place of meeting: July 9, 2013 at Meeting Rooms 8-9 of PMDA

Members in attendance: Irimura, Ohtsu, Ochiya, Saiki, Saya, Seimiya, Sugimura, and Naoe (8 in total)

Agenda: Discussion was held on the topics presented

Topic: "Role of pharmacology studies, questionnaire to industries" presented by Office of New Drug V, PMDA

"Genome analysis using the next generation sequencer" presented by Saya

○ Third WG meeting

Date, time, and place of meeting: October 29, 2013, Meeting Rooms 8-9 of PMDA

Members in attendance: Irimura, Ohtsu, Saiki, Saya, Seimiya, and Sugimura (6 in total)

Agenda: Compilation of opinions on pharmacology studies on anticancer drugs

Discussion on topics presented by WG members

Topic: "Topics expected for future discussion" presented by Ohtsu, Saiki, Saya, Seimiya, and Sugimura

○ Report to the Pharmaceuticals and Bio-products Subcommittees

Date, time, and place of meeting: November 15, 2013, at Meeting Rooms 1-5 of PMDA

Details: The summary of discussion on non-clinical pharmacology studies on anticancer drugs was approved upon review.

(2) Opinions contrary to the results of deliberation (WG meeting summary)

None