

Administrative Notice
December 26, 2013

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

From: Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Technical Guidance on Development of In Vitro Companion Diagnostics and
Corresponding Therapeutic Products

We have recently received from the Pharmaceuticals and Medical Devices Agency a report on the topic mentioned above as shown in the corresponding attached document. Please inform the relevant manufacturers and sellers under your jurisdiction to use this report as a reference in their business operations.

PMDA Notification No. 1224029

December 24, 2013

To: Director of Evaluation and Licensing Division
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Chief Executive
Pharmaceuticals and Medical Devices Agency

Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products

The handling of in vitro companion diagnostics and corresponding therapeutic products has been described in the “Notification on Approval Application for In Vitro Companion Diagnostics and Corresponding Therapeutic Products” (PFSB/ELD Notification 0701-10, by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated July 1, 2013) and other relevant documents. The Pharmaceuticals and Medical Devices Agency has recently developed a technical guidance containing approaches to, and points to consider in, the development of in vitro companion diagnostics and corresponding therapeutic products, as well as Questions and Answers (Q&A) regarding this guidance, which are shown in Attachment 1 and Attachment 2, respectively, and reported.

Please note that this guidance and Q & A only represent a summary of our basic approaches based on the current scientific knowledge, and are not necessarily intended to require strict compliance with the approaches described therein.

Attachment 1

**Technical Guidance on Development of In
Vitro Companion Diagnostics and
Corresponding Therapeutic Products**

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4. Explanation of Terms

1. Introduction

1.1. Background

With the advancement of human genome and proteome analysis owing to the development of science and technology, biological molecules involved in diseases have been identified and analyzed. Currently, target molecules involved in the growth of malignant tumors, etc., are being identified. Using these molecules, so-called personalized medicine has been developing in recent years, such as: the research and development of therapeutic products based on the expression of, or mutations in, these molecules; and the identification of patient population to be treated with a certain therapeutic product by making use of a biomarker such as relevant biological molecule. Under these circumstances, the national government has shown positive attitudes as seen in the mentioning of the promotion of personalized medicine in the “Strategic Market Creation Plan” under the “Japan Revitalization Strategy” approved by the Cabinet on June 14, 2013 from such viewpoints as “extending the nation’s healthy life expectancy.”

Of the types of personalized medicine, the identification of patient population to receive a certain therapeutic product by using a biomarker related to the target disease or condition would require use of an in vitro diagnostic (hereinafter referred to as an “IVD”) before using that therapeutic product. An IVD that contributes to personalized medicine by being used in such settings as the selection of a therapeutic product is referred to as an “in vitro companion diagnostic.” The efficacy and safety of the relevant therapeutic product is directly affected by the performance of the in vitro companion diagnostic. Therefore, in order to achieve the simultaneous availability of a therapeutic product and the corresponding in vitro companion diagnostic in clinical settings while ensuring the efficacy and safety of the therapeutic product and the performance of the in vitro companion diagnostic, it is important to ensure appropriate cooperation between the developer of the therapeutic product and that of the in vitro companion diagnostic by sharing considerations in the development activities between them, as well as to ensure necessary cooperation between them in the approval review.

Basic concepts of in vitro companion diagnostics are described in the “Notification on Approval Application for In Vitro Companion Diagnostics and Corresponding Therapeutic Products” (PFSB/ELD Notification No. 0701-10, by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated July 1, 2013; hereinafter referred to as the “Director Notification”) and “Questions and Answers (Q&A) on In Vitro Companion Diagnostics and Corresponding Therapeutic Products” (Administrative Notice from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated July 1, 2013).

1.2. Objectives

In the context of development of therapeutic products related to biomarkers and of in vitro companion diagnostics, this guidance aims to facilitate the development and the approval review of these therapeutic products and in vitro companion diagnostics by

organizing current specific technical information, such as points to be considered by both developers of these therapeutic products and those of in vitro companion diagnostics in the development of their respective products. Specifically, this guidance describes points to consider in relation to clinical trials for therapeutic products related to in vitro companion diagnostics and our view on the timing of validation of in vitro companion diagnostics, as well as the clinical significance of in vitro companion diagnostics and our view on concordance studies of in vitro companion diagnostics. In the context of approval review, strict compliance with the approaches described in this guidance will not necessarily be required. It is recommended that developers of these therapeutic products or in vitro companion diagnostics have consultations with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) as appropriate, on a case-by-case basis and in a timely, appropriate manner.

1.3. Scope

The scope of this guidance includes in vitro companion diagnostics and corresponding therapeutic products as defined in the Director Notification.

Section 2.1 of this guidance assumes cases where patient population to receive a certain therapeutic product are identified mainly by using a corresponding in vitro companion diagnostic based on knowledge obtained thus far, etc. Of these cases, sections 2.1.1 and 2.1.3 assume cases where molecular targeted drugs, etc., are used. Even so, we consider that the approaches described in these sections are applicable to cases other than those specified, such as in vitro companion diagnostics intended to optimize the dosage or administration of a therapeutic product or to help make decisions on discontinuation of treatment.

1.4. Basic principle

When filing an application for an in vitro companion diagnostic intended to measure a biomarker, data supporting the performance of the in vitro companion diagnostic are required. When filing an application for a therapeutic product related to an in vitro companion diagnostic, the required data include those showing the clinical utility of the in vitro companion diagnostic, whose performance has been warranted, in identifying patient population to be treated with a certain therapeutic product.

2. Clinical Trials for Development of Therapeutic Products Related to In Vitro Companion Diagnostics

2.1. Points to consider in identifying patients using a biomarker

Described below are points of particular consideration in clinical trials for therapeutic products that involve the identification of patient population to receive a certain therapeutic product mainly by using a biomarker, based on knowledge obtained thus far, etc. For the terms “biomarker-positive” and “biomarker-negative” specified below, the result determined based on the clinical cut-off was described.

2.1.1. Handling of biomarker-negative patients in early development phase of molecular targeted drugs, etc.

In the development of a molecular targeted drug, i.e., a drug targeted to a particular biomarker involved in the relevant disease, there are cases, for instance, where patient population to be treated with the drug is limited to positive cases only, based on the results of biomarker measurements using an in vitro companion diagnostic. Theoretically, a molecular targeted drug is expected to show higher utility in biomarker-positive patients. However, the exclusion of biomarker-negative patients in early development phase and thereafter would make it difficult to make comparisons and analysis between biomarker-positive and negative patients to find out any difference in risk-benefit balance between them, due to the unavailability of data to determine the validity of the clinical cut-off for the biomarker or an inability to determine whether or not the target patient population in which treatment with that drug will be effective has been appropriately identified.

Therefore, it is important to establish a development strategy for a therapeutic product which reflects the necessity of analyzing biomarker-negative patients from early development phase. For instance, in clinical trials in early development phase, such as exploratory dose-response studies, both biomarker-positive and negative patients should be included in principle. However, this does not apply to cases where there is good reason not to include biomarker-negative patients in clinical trials, such as cases where it is extremely unlikely that the therapeutic product will show efficacy in biomarker-negative patients from non-clinical or clinical trial data (including retrospective analysis results), or where the therapeutic product is highly toxic, strongly suggesting a safety concern that treating a wider range of patients with it would expose them to unreasonable risk.

The handling of biomarker-negative patients in each stage of a clinical trial should be considered based on information obtained before the start of the clinical trial. In considering the trial design, it is recommended to consult PMDA.

2.1.2. Necessity to conduct prospective confirmatory clinical trials

When verifying the efficacy and evaluating the safety of a therapeutic product related to a biomarker, it is necessary, in principle, to conduct prospective randomized controlled trials, as is the case with a common therapeutic product. If it is necessary to evaluate the qualification of a biomarker in the course of development of such a therapeutic product, retrospective analysis may be conducted using stored samples from clinical trials that were conducted in the past. While this kind of analysis is encouraged, the retrospective analysis to evaluate the biomarker merely represents an exploratory analysis. If the results of the retrospective analysis suggest the utility of the therapeutic product only in biomarker-positive patients, it is desirable to separately conduct prospective randomized controlled trials in biomarker-positive patients. In conducting prospective randomized controlled trials, it is desirable to elaborate the trial design so that not only the efficacy of the therapeutic product can be verified but also

the biomarker qualification can be evaluated.

On the other hand, examples of cases where it is difficult to conduct prospective randomized controlled trials include the following three cases:

- (i) Cases where it is difficult to verify its qualification by prospective randomized controlled trials from an ethical point of view, such as cases where it has been suggested that the safety biomarker is associated with extremely serious adverse events.
- (ii) Cases where it is difficult or inappropriate to verify its qualification by prospective randomized controlled trials, such as cases where restricting patient population to be treated based on the status of the efficacy biomarker would make it extremely difficult to conduct a randomized controlled trial from the viewpoint of sample size.
- (iii) Cases where evaluation of the biomarker based mainly on the results of the retrospective analyses is acceptable even after considering potential biases arising from the retrospective analyses, such as cases where the retrospective analyses meet all of the following conditions:
 - The retrospective analysis derives from randomized controlled trials which were appropriately planned and conducted and in which data were obtained, in principle, from all registered subjects wherever possible.
 - The retrospective analysis uses measurement methods which have undergone certain analytical test validation.
 - An appropriate hypothesis and statistical analysis on the biomarker had been defined before analyzing data.
 - Statistically appropriate analysis in terms of multiplicity adjustment, etc., has been planned and conducted.
 - Consistent analytical results have been obtained from results of two or more independent clinical trials each of which meets all of the above four conditions.

In any of the above cases, it is recommended to consult PMDA on such matters as the procedure for development based on retrospective analyses.

2.1.3. Points to consider in conducting prospective confirmatory clinical trials

It is expected that randomized controlled trials in biomarker-positive patients will be planned, assuming that, as described in section 2.1.1, an analysis including biomarker-negative patients had been performed before confirmatory clinical trials are conducted. Based on non-clinical and clinical data obtained before planning randomized controlled trials, an appropriate trial design needs to be selected. For instance, a preliminary exploratory analysis including biomarker-negative patients may indicate potential utility also in biomarker-negative patients, in which case it may be

decided that biomarker-negative patients should remain a target population for the drug development, separately from the population of biomarker-positive patients. Thus, there may be cases where a trial including both biomarker-positive and negative patients is conducted. In such case, it is necessary to previously specify in the protocol a trial plan including randomization and blinding methods as well as an appropriate analytical plan based on the interpretation of results (including definition of hypothesis, sample size design, multiplicity adjustment, etc.), since analytical results will be obtained from each of the overall population, the population of biomarker-positive patients and that of biomarker-negative patients.

2.2. Development of therapeutic products and timing of validation of in vitro companion diagnostics

If a clinical trial is conducted using an in vitro companion diagnostic that has not been fully validated, the intended purpose of the trial may not be achieved due to such reasons as a failure to appropriately identify patient population to be treated. A confirmatory study should use an in vitro companion diagnostic which has undergone certain analytical test validation as well as clinical test validation in terms of the clinical cut-off for the biomarker to be used to identify eligible patients, and which is, in principle, intended for a regulatory submission. However, if it is difficult to previously set a clinical cut-off based on exploratory study results, due to such reasons as an extremely small sample size, then it is recommended to consult PMDA on such matters as the study design, before conducting the confirmatory study.

Clinical test validation including the validity of the clinical cut-off is evaluated mainly in the approval review process of the therapeutic product, while analytical test validation is evaluated mainly in the approval review process of the in vitro companion diagnostic. During the approval review of the therapeutic product, it is required that the validity, etc., of the clinical cut-off for the in vitro companion diagnostic be justified by presenting reasons. The applicant of the therapeutic product and that of the in vitro companion diagnostic should cooperate and collaborate with each other in filing their respective applications. For points to consider in analytical test validation, see section 3.3, “Analytical test validation of in vitro companion diagnostics.”

3. Evaluation of In Vitro Companion Diagnostics

In cases where patient population to receive a certain therapeutic product is identified by using a biomarker, the efficacy and safety of the therapeutic product is directly affected by the performance of the in vitro companion diagnostic. As major considerations in the development of in vitro diagnostics, this section describes the clinical significance of in vitro companion diagnostics, concordance studies, and analytical test validation.

3.1. Clinical significance of in vitro companion diagnostics

Evaluation of the clinical significance and the clinical cut-off for an in vitro companion diagnostic is generally performed using the results of clinical trials for the corresponding

therapeutic product conducted in patients identified by using the in vitro companion diagnostic. For this reason, the company developing the in vitro companion diagnostic needs to cooperate and collaborate with the company developing the therapeutic product including obtaining in advance information on such results from the company. In this regard, the clinical significance and the clinical cut-off for the in vitro companion diagnostic may be explained at the time of filing an approval application, using a summary of the clinical trial results for the corresponding therapeutic product, including the name of the investigational therapeutic product(s) used in the clinical trials, titles and methods of the trials, and a summary of their results.

3.2. Concordance studies of in vitro companion diagnostics

3.2.1. Basic concept on the necessity of concordance studies

If the in vitro companion diagnostic for which an approval application is to be filed is not used in the confirmatory clinical studies, it is necessary to evaluate the concordance between the measurement method used in the clinical trials and the proposed in vitro companion diagnostic. If there is any standard method that may be used as a control (such as a normative method employed by public agencies¹ or standardization bodies²), it is necessary, in principle, to conduct a concordance study between such method and the in vitro companion diagnostic, in order to evaluate the validity of the determination or measurement results obtained using the in vitro companion diagnostic. In such a case, a scientifically justifiable control method needs to be selected based on the standards and other requirements for operation, determination method and performance specified by the relevant public agencies, standardization bodies, relevant academic societies, etc.

3.2.2. Considerations in conducting concordance studies

Concordance studies of an in vitro companion diagnostic should basically be conducted using samples collected from subjects included in clinical trials for the corresponding therapeutic product. However, if for any reason it is difficult to use samples from subjects included in those clinical trials, concordance studies may be separately conducted using samples collected and stored according to inclusion criteria equivalent to those for such clinical trials, subject to the appropriate management of samples in terms of the timing of their collection, the nature of the lesion, and post-fixation condition and storage conditions of the samples, among others. In such case, it is recommended to consult PMDA in advance.

In concordance studies, the range of detection and measurable range need to be found out. Of particular importance are the predictive values of determination results

¹ World Health Organization (WHO), etc.

² Joint Committee on Traceability in Laboratory Medicine (JCTLM), Clinical and Laboratory Standards Institute (CLSI), Japanese Committee for Clinical Laboratory Standards (JCCLS), etc.

around the cut-off³ or the lower limit of measurements and concordance evaluation of measured values. If it is difficult to evaluate these items based solely on samples collected in clinical trials for the therapeutic product, it is necessary to conduct a concordance study separately from those clinical trials.

In addition, since the performance of an in vitro companion diagnostic directly affects the efficacy and safety of the corresponding therapeutic product, it is generally required that an in vitro companion diagnostic shows good performance in terms of both positive and negative predictive values, and that discrepant cases be fully discussed scientifically. On the other hand, there may be cases where, depending on the characteristics of the product, an in vitro companion diagnostic with not poor positive or negative predictive value is still acceptable. Therefore, it is recommended to consult PMDA if it is difficult to clinically evaluate concordance study results. The positive or negative predictive value required for an in vitro companion diagnostic to be found appropriate as such needs to be considered based on the nature of the target disease, number of target patients (i.e., number of actually evaluable patients), confidence intervals, etc. With respect to the validity of such a value, it is recommended to consult PMDA.

3.3. Analytical test validation of in vitro companion diagnostics

For in vitro companion diagnostics, the following details should be clarified in connection with the validity of the evaluation method for, and results of, analytical test validation, as is the case with common IVDs. For our view on the appropriate timing of validation, see section 2.2, “Development of therapeutic product and timing of validation of in vitro companion diagnostics.”

- Accuracy
- Precision including repeatability, intermediate precision, and reproducibility, and factors, etc., that reduce precision
- Factors, etc., that affect reaction specificity (cross reactivity, effects of coexisting materials, non-specific reaction, effects of inactivation, effects of anticoagulants when using plasma samples, etc.) and measurements or determination results
- Range of measurements, such as quantitation range or detection limit, and linearity
- Analytical cut-off
- Reference standard or reference substances for calibration
- Information on samples to be collected, such as methods for collecting, processing, and storage of samples and storage period.
- Reaction conditions and other assay conditions, and any possibility of and inhibition method for non-specific reaction
- Possibility of false positive or false negative results due to contamination, and measures to eliminate such false results

If any change is to be made to the measurement (detection) system specified by this

³ In this context, the cut-off refers to the analytical cut-off and/or clinical cut-off.

analytical test validation, the applicant needs to give an appropriate explanation of the concordant ability of the system to perform measurements (detection) before and after the intended change, by presenting results of the required validation items.

4. Explanation of Terms

- Biomarker

A characteristic that is measurable as an indicator of a normal biological process, pathogenic process and/or pharmacological reaction to therapeutic intervention, etc.

- Clinical utility

In this guidance, clinical utility means any improvement in the efficacy or safety of a therapeutic product achieved by measuring the relevant biomarker using an in vitro companion diagnostic. In other words, clinical utility means the value of an in vitro companion diagnostic, which is that it improves benefit-risk balance of the corresponding therapeutic product.

- Biomarker qualification

In this guidance, biomarker qualification means the nature of a biomarker based on which the biomarker can be relied upon to adequately reflect a response after dosing, and support use of the biomarker at the dosing. See the ICH E16 guideline.

- Analytical test validation

To prove that a certain analytical test is reliable and suited for its intended purpose, by verifying that its precision is managed appropriately, that it is capable of measuring the analyte precisely, and that it is capable of producing expected results with high reproducibility.

- Clinical test validation

To prove that a certain analytical test is capable of accurately predicting the presence or absence of a certain disease or phenotype, based on such information as sensitivity (a positive rate in subjects with the disease or phenotype) and specificity (a negative rate in subjects without the disease or phenotype).

- Clinical cut-off

In this guidance, a clinical cut-off means, in the context of treatment with a therapeutic product, a value set by taking a risk-benefit balance of the therapeutic product into account, above which subjects are considered to be biomarker-positive and below which they are considered to be biomarker-negative. Treatment decisions will be made with respect to the groups divided by such a clinical cut-off.

- Concordance study

A study for evaluating the concordance of predictive values or measurement results between the IVD of interest and an appropriate control IVD (such as a normative measurement method or the measurement method used in clinical trials), in order to ensure the detection (measurement) precision of the IVD of interest.

Questions and Answers (Q&A) on
“Technical Guidance on Development of In Vitro
Companion Diagnostics and Corresponding
Therapeutic Products”

2.1.1. Handling of biomarker-negative patients in early development phase of molecular targeted drugs, etc.

Q1: While “biomarker-positive” is mentioned as a patient inclusion criterion, biomarker-negative patients may be selected for some drugs (e.g., KRAS gene mutations in anti-EGFR antibody therapy). The guidance is written on the premise that after a certain biomarker is measured, positive patients are included in clinical trials. If, to the contrary, negative patients should be included, can the guidance be simply read in the inverse sense?

A1: That is correct.

2.1.2. Necessity to conduct prospective confirmatory clinical trials

Q2: Does the term “confirmatory clinical trials” refer to phase III randomized controlled trials?

A2: The term “confirmatory clinical trials” generally refers to phase III randomized controlled trials. However, if phase II trials are the most important trials in the data package for application due to such reasons as a difficulty in conducting phase III randomized controlled trials, then the term may refer to such phase II trials in this guidance.

Q3: Does the phrase “all registered subjects wherever possible” mean all subjects diagnosed, whether positive or negative? Does “data from registered subjects” mean data from both positive and negative subjects?

A3: That is correct. Data from both positive and negative subjects are required.

2.2. Development of therapeutic products and timing of validation of in vitro companion diagnostics

Q4: Prior to conducting a clinical trial for a therapeutic product, specifically to what extent does analytical test validation of the relevant in vitro companion diagnostic to be used need to be done?

A4: We consider that it is sufficient if, prior to conducting a clinical trial for the therapeutic product, the items of analytical test validation that are necessary to achieve the intended purpose of the clinical trial (such as accuracy, precision, measuring range, analytical cut-off, etc.) have been confirmed as appropriate. Reaction specificity, information on samples, assay conditions, etc., should be evaluated to some extent prior to conducting a clinical trial for the therapeutic product. In case of doubt in specific cases, it is recommended to consult the Pharmaceuticals and Medical Devices Agency (PMDA).

3.2. Concordance studies of in vitro companion diagnostics

Q5: Please list points to note in handling clinical samples used for the simultaneous development of a therapeutic product and the relevant in vitro companion diagnostic and in retrospectively re-using samples collected in an existing trial.

A5: If the protocol for the existing trial mentions the collection of clinical samples and if subjects' consent has been duly obtained with the review and approval of the Institutional Review Board or the Ethics Committee, then it is generally not necessary to obtain re-consent for the re-measurement. If the linking capability is maintained, it is advisable to allow the results to be disclosed at the request of subjects. If a concordance study is planned, it is necessary to appropriately store both positive and negative samples since it is important to evaluate both positive and negative predictive values.

The morality and reliability of a concordance study need to be fully ensured. Therefore, we consider that the samples to be used in the concordance study should be evaluated in terms of the details and validity of the collection procedure, storage conditions, and application to the concordance study, particularly in the following points:

- (i) Prior to conducting the concordance study, the following have been made clear: the collection procedure for the samples to be used in the study; that the approval of the Institutional Review Board or Ethics Committee has been obtained; and that the subjects' consent has been obtained.
- (ii) The fact that the clinical samples were used has been made clear. Background information on the samples has been made clear, such as clinical information on the subjects from whom the samples were collected, the procedure for preparing the samples, and the storage conditions.
- (iii) Background information on the conduct of the trial in which the samples were

collected has been made clear, such as the site(s) at which the samples were collected, the principal investigator, and trial period. The fact that the verification performed in the trial using human-derived samples was in compliance with currently applicable ethical guidelines, etc., has been made clear.

3.2.2. Points to consider in conducting concordance studies

Q6: Do “subjects included in clinical trials” not always have to be Japanese?

A6: Samples from non-Japanese subjects may be used, subject to the appropriate management of the samples in terms of the timing of their collection, the nature of the lesion, and post-fixation condition and storage condition of the samples, among others. Note that this does not apply to certain biomarkers such as those which represent a genetic mutation or expression, etc., that is specific to the Japanese population or which are significantly affected by external environmental factors.

Q7: What are the specific cases where a concordance study has to be conducted using samples not used in clinical trials?

A7: One example would be in vitro diagnostics whose nature requires that samples be tested promptly following collection, i.e., cases where it is difficult to use stored samples for testing. Specific examples include certain kits for fluorescence activated cell sorter (FACS) analysis using peripheral blood or other cells.

Q8: The guidance requires that an in vitro companion diagnostic “shows good performance in terms of both positive and negative predictive values.” What specifically is supposed to be good performance? What are the points to consider in performing evaluation?

A8: A common in vitro diagnostic is used in a position to support a diagnosis and a treatment decision which are made in a comprehensive manner based not only on results obtained by the diagnostic but also on those obtained by other relevant tests and on clinical symptoms, etc. On the other hand, an in vitro companion diagnostics has an extremely high association with the decision as to whether or not the corresponding therapeutic product should be administered, and there may be cases where such a decision is made based solely on results obtained by that diagnostic. Therefore, considering that an in vitro companion diagnostic is used in a position to ensure the efficacy and safety of the corresponding therapeutic product or to dictate the decision as to whether or not the corresponding therapeutic product should be administered, it is desirable that in a concordance study for an in vitro diagnostic, evaluation criteria for predictive values be set at a more favorable level than those in a concordance study for a common in vitro diagnostic.

Regarding evaluation criteria for good predictive values to be employed in a concordance

study, no specific guide for such predictive values can be given since a decision should be made on a case-by-case basis by taking into consideration such factors as the characteristics of the therapeutic product (such as whether or not it is associated with serious adverse reactions) and the measuring principle for the in vitro diagnostic. Appropriate evaluation criteria for predictive values should be determined by taking the aforementioned factors into account. In the concordance evaluation of an in vitro diagnostic, discrepant cases should be examined by scientific analysis to find the reason for discrepancy. Once the limitations of the diagnostic's performance are made clear, any points to note in ensuring good screening precision should be reminded in the package insert.

3.3. Analytical test validation of in vitro companion diagnostics

Q9: Please explain terms used in the evaluation of analytical test validation by referring to the notification, "Points to consider in Filing Applications for In Vitro Diagnostics," which describes the handling of an in vitro diagnostic in filing application (PFSB/ELD/OMDE Notification No. 0216005, dated February 16, 2005; hereinafter referred to as the "Notification No. 0216005").

A9: Terms used in the current notification differ from those used in Notification No. 0216005 or are not found in Notification No. 0216005 are explained in the table below.

Term used in the guidance	Explanation
Accuracy	"Accuracy" in Notification No.0216005
Precision	The closeness of agreement (or degree of scatter) in results obtained by measuring the same samples. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.
Repeatability	"Repeatability" in Notification No.0216005
Intermediate precision	Within-laboratories variations: different days, different analysts, different equipment, etc.
Reproducibility	The precision between laboratories.
Quantitation limit/range	The range of concentration of analyte in a sample which can be quantitatively determined with suitable accuracy and precision. Quantitation limit/range is evaluated in relation to a quantitative measurement method.

Detection limit	The lowest amount of analyte in a sample which can be detected. A detection limit may be outside the quantitation limit/range.
Analytical cut-off	The boundary value for analytical determination of a qualitative item.

Other matters

Q10: The guidance is titled, “Technical Guidance on Development” Please explain its positioning with respect to related notifications, such as “Notification on Approval Application for In Vitro Companion Diagnostics and Corresponding Therapeutic Products” (PFSB/ELD Notification No. 0701-10, dated July 1, 2013).

A10: This guidance presents PMDA’s concept on the simultaneous development of an in vitro companion diagnostic and the corresponding therapeutic product based on the current regulations and cases, and does not necessarily require strict compliance with the approaches described in it. For any case that is not covered by this guidance, it is recommended to consult PMDA appropriately. The guidance will be revised appropriately based on new cases.

Q11: For cases where an application for a therapeutic product and that for the relevant in vitro companion diagnostic are submitted at the same time, please indicate a review timeline intended to achieve the simultaneous availability of both the product and the diagnostic in clinical settings.

A11: Regarding a review timeline intended to allow simultaneous approval, a review timeline for a therapeutic product is usually presented at some time between the initial meeting and the Expert Discussion. For an in vitro companion diagnostic, the fact that no total review period has been specified for in vitro companion diagnostics makes it difficult to present a review timeline for it in the same manner as for the corresponding therapeutic product. However, if the company which filed an application for an in vitro companion diagnostic promises PMDA that it will take measures according to the review period for the corresponding therapeutic product, such as by making responses to PMDA’s inquiries according to the review timeline for the therapeutic product, then PMDA will take measures according to the review timeline for the therapeutic product. The applicant for the therapeutic product and that for the in vitro diagnostic are both requested to perform applications in full cooperation with each other.