Topics on regulation of drug development with companion diagnostics

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- The views and opinions expressed in the following PowerPoint slides are containing those of the individual presenter as well as PMDA.

In vitro companion diagnostic devices WG

About this WG

We organize the problems involved in companion diagnostics (CoDx), and create the necessary guidance.

What we did

- We developed a technical guidance indicating points to consider in the development of CoDx and corresponding therapeutic products.
- We assisted MHLW to prepare the relevant notifications.

Principal regulatory guidance in Japan

Publication Date	Title
July, 2013	Notification on approval application for in vitro companion diagnostics and corresponding therapeutic products
July, 2013	Questions and answers (Q&A) on CoDx and corresponding therapeutic products
Dec., 2013	Technical guidance on development of in vitro companion diagnostics and corresponding therapeutic products (technical guidance and questions and answers (Q&A))
Feb., 2014	Notification on approval application for in vitro diagnostics used as companion diagnostics
Mar., 2014	Questions and answers (Q&A) on “Notification on approval application for in vitro diagnostics used as companion diagnostics”

Agenda

1. Definition of CoDx
2. General principles and technical consideration on the drug development with CoDx
3. Current regulatory challenges

Agenda

1. **Definition of CoDx**

2. **General principles and technical consideration on the drug development with CoDx**

3. **Current regulatory challenges**

Notification describing how to handle CoDx

- ✓ Notification on approval application for *in vitro* companion diagnostics and corresponding therapeutic products
- ✓ Questions and answers (Q&A) on CoDx and corresponding therapeutic products

Main contents

- Definition of CoDx
- Points to consider on approval application
- Points to consider on clinical trial notification
- PMDA's review system

Definition of CoDx (1/2)

A CoDx is essential for using the pertinent therapeutic product, and corresponds to either of the following [except in vitro diagnostic agents or medical devices intended simply for disease diagnosis (see next slide), etc.]:

- that is used to identify patients who are expected to respond better to a specific therapeutic product.
- that is used to identify patients who are likely to be at high risk of developing adverse events associated with a particular therapeutic product
- that is necessary for optimizing the treatment including dose, schedule, and discontinuation of a particular therapeutic product

Definition of CoDx (2/2)

Q: What examples are there of "*in vitro* diagnostic agents or medical devices intended simply for disease diagnosis" ?

A: Examples may include *in vitro* diagnostics that are used for either of the following:

- bacterial or viral identification and susceptibility tests for infections.
- biochemical assays related to organ functions such as AST and ALT level.
- tests used to check the treatment effect in routine clinical practice such as CEA level.

However, diagnostics of these types may also be judged as CoDx depending on the clinical necessity, etc.

Agenda

1. Definition of CoDx

2. **General principles and technical consideration on the drug development with CoDx**

3. Current regulatory challenges

Technical guidance and Q&A

✓ Technical guidance on development of *in vitro* companion diagnostics and corresponding therapeutic products (technical guidance and Q&A)

Main contents

1. Background
2. Points to consider on drug development with CoDx
3. Points to consider on evaluation of CoDx
4. Explanation of terms

Points to consider on drug development

Main discussion points on drug development with CoDx

① Handling of biomarker-negative patients in clinical trials

② Retrospective analyses on biomarkers

③ Development of drug and timing of validation of CoDx

Biomarker-negative patient (1/2)

Handling of biomarker-negative patient in clinical trials

- It is important to establish a development strategy for a drug which reflects the necessity of analyzing biomarker-negative patients from early development phase.

- In clinical trials in early development phase, such as exploratory dose-response studies, both biomarker-positive and negative patients should be included in principle.

Biomarker-negative patient (2/2)

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 drug will show efficacy in biomarker-negative patients from non-clinical or clinical trial data (including retrospective analysis results),

- or where the drug is highly toxic, strongly suggesting a safety concern that treating a wider range of patients with it would expose them to unreasonable risk.

Retrospective analyses on Biomarker (1/5)

Handling of the retrospective analyses

- To conduct retrospective analyses of biomarkers with stored specimens of clinical studies conducted previously is useful. However, such retrospective analyses of biomarkers are exploratory.

- It is necessary in principle to conduct prospective randomized controlled trials.

Retrospective analyses on Biomarker (2/5)

Examples of cases where it is difficult or inappropriate to conduct prospective randomized controlled trials include the following three cases:

① Cases where it is difficult to conduct 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.

② Cases where it is difficult or inappropriate to conduct prospective randomized controlled trials for a limited number of patients as the result of patient selection with biomarkers.

Retrospective analyses on Biomarker (3/5)

Examples of cases where it is difficult or inappropriate to conduct prospective randomized controlled trials include the following three cases:

③ 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 (next slide).

Retrospective analyses on Biomarker (4/5)

Evaluation of the biomarker based mainly on the results of the retrospective analyses is acceptable if the retrospective analyses meet all of the following conditions (1/2):

- 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.

(continued on next slide)

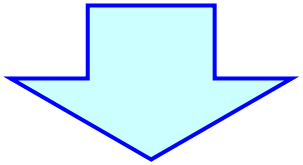
Retrospective analyses on Biomarker (5/5)

Evaluation of the biomarker based mainly on the results of the retrospective analyses is acceptable if the retrospective analyses meet all of the following conditions (2/2):

- 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.

Timing of validation of CoDx

- If a clinical trial is conducted using an in vitro diagnostic (IVD) 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 CoDx which has undergone certain analytical validation as well as clinical validation, and which is, in principle, intended for a regulatory submission.

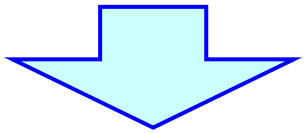
Validation of CoDx

- Analytical Validation
  (Accuracy, Precision, Range of measurements, Analytical cut-off, etc.)

  } Evaluated mainly in the review of the CoDx

- Clinical Validation
  (Clinical cut-off, etc.)

  } Evaluated mainly in the review of the drug



The applicant of the drug and that of the CoDx should cooperate and collaborate with each other in filing their respective applications.

Concordance study of CoDx (1/2)

If the CoDx for which an approval application is to be filed is not used in the confirmatory clinical trial, it is necessary to conduct a concordance study between the clinical trial assay (CTA) and the proposed CoDx.

An example (Gene mutation detection kit)		CoDx		Agreement
		Mutation detected	Not mutation detected	
CTA	Mutation detected	95	5	PPA: 95% NPA: 95% OPA: 95%
	Not mutation detected	5	95	

PPA: Positive percent agreement, NPA: Negative percent agreement,
OPA: Overall percent agreement

Concordance study of CoDx (2/2)

Examples of points to consider on concordance study

- Concordance study of a CoDx should basically be conducted using samples collected from subjects included in clinical trials for the corresponding drug.
- It is generally required that a CoDx shows good performance in terms of both positive and negative predictive values.
- Discrepant cases should be examined by scientific analysis to find the reason for discrepancy.

Agenda

1. Definition of CoDx

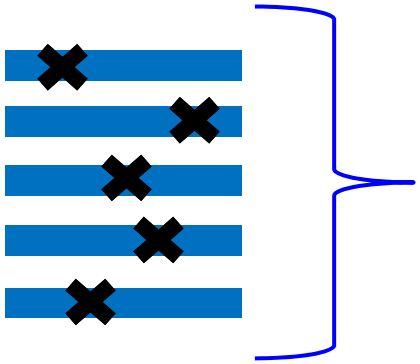
2. General principles and technical consideration on the drug development with CoDx

3. **Regulatory challenges**

Multiplex diagnostics (1/2)

Examples of cases where multiplex diagnostics such as next generation sequence (NGS) are used in clinical trials

① Multiplex diagnostics for measurement of one biomarker are necessary because there are many mutation sites in the biomarker such as *BRCA* gene mutation

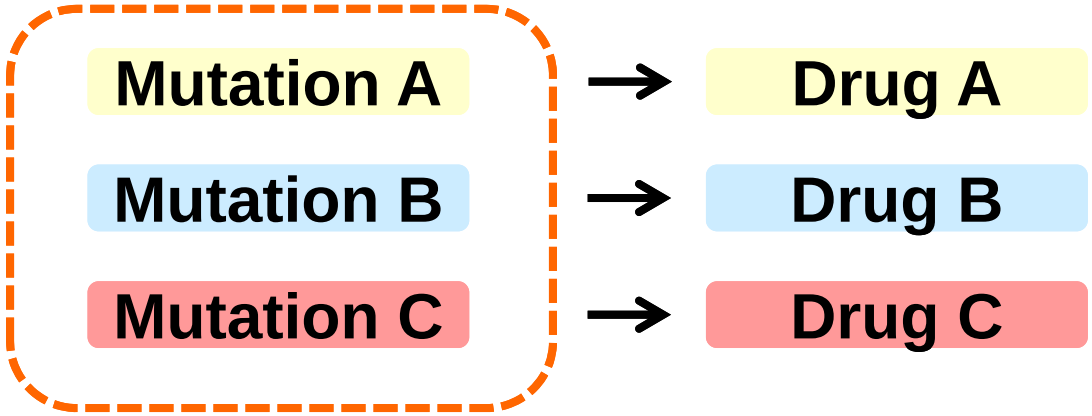


Mutations for use of the corresponding drug

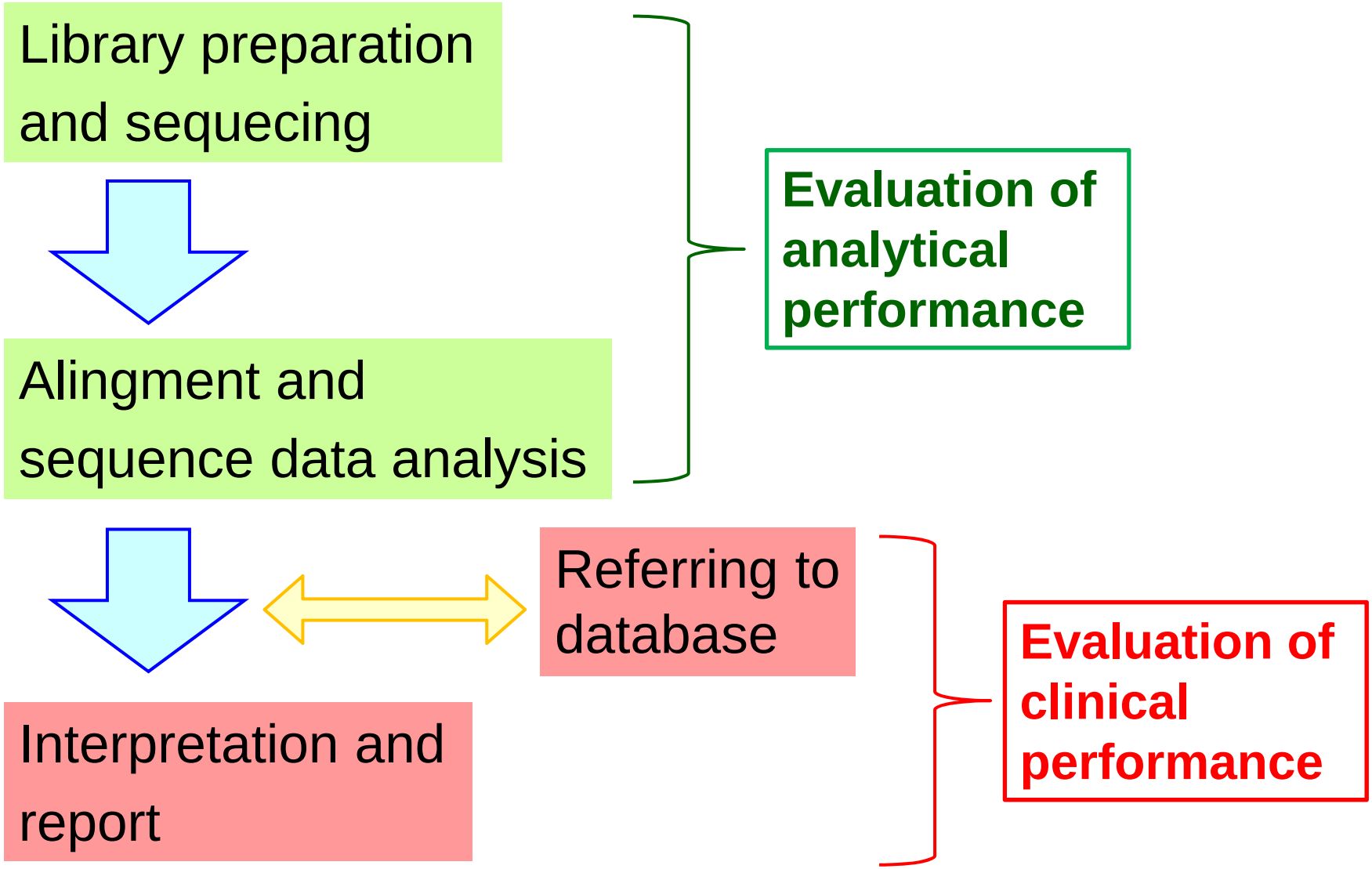
Multiplex diagnostics (2/2)

Examples of cases where multiplex diagnostics such as NGS are used in clinical trials

② Measurement of many biomarkers is necessary because there are many biomarkers with corresponding molecular targeted therapy such as EGFR and ALK etc. in lung cancer (umbrella trial in master protocol)



NGS overview



Main discussion points regarding NGS

Examples regarding review of approval applications

- Is each component of NGS medical device or IVD ?
- How to evaluate analytical performance of NGS
- How to define “patients with X mutation as detected by approved NGS” as indication of corresponding drug (clinical performance of NGS as CoDx)
- How to ensure quality of clinical database
- How to handle update of clinical database after marketing authorization of NGS (and corresponding drug)

PMDA's activity

- We will organize the problems involved in the current regulatory challenges such as NGS and create the necessary guidance.
- The new drug review team and the CoDx review team in PMDA are coordinated adequately (clinical trial consultation during the development and review).

Acknowledgment

- Current and former members of in vitro companion diagnostic devices working group in PMDA

(HP in English)
https://www.pmda.go.jp/english/rs-sb-std/standards-development/cross-sectional-project/0005.html

(HP in Japanese)
http://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0013.html