4th of Joint Conference of Taiwan and Japan
on Medical products regulation

In Vitro Companion Diagnostic Devices

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Agenda

I. What is Companion Diagnostics ?

II. Discussions on CoDx evaluation

III. Recent Topics

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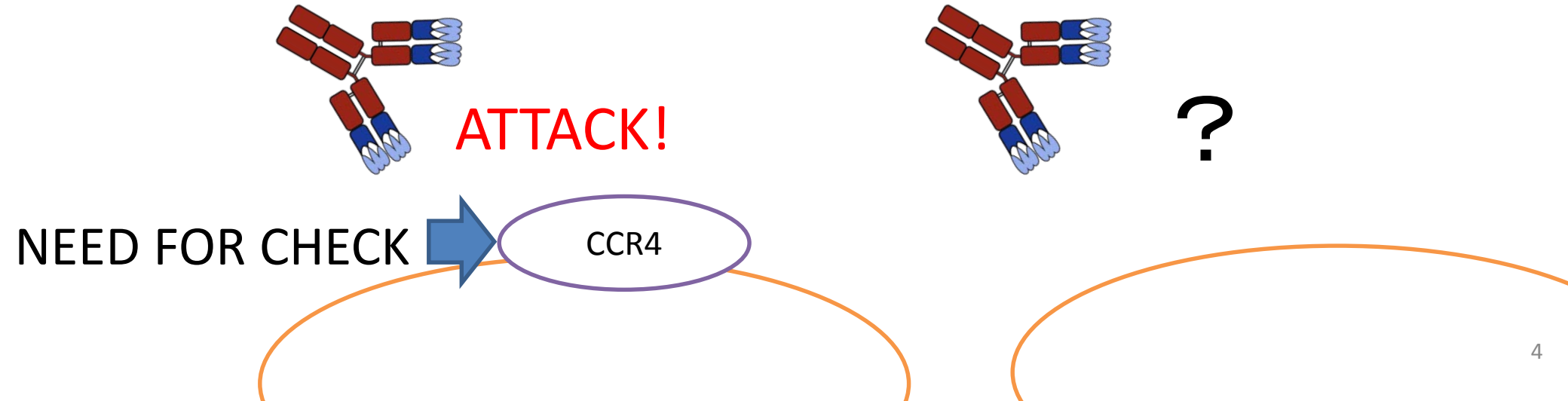
Example

- Mogamulizumab & CCR4 detection kit for ATL

Mogamulizumab : monoclonal antibody for CCR4
CCR4: found on T-lymphocyte in ATL patients

Mogamulizumab can effective only for ATL patients who have CCR4+ cells



Definition of CoDx in Japan(1(Simple))

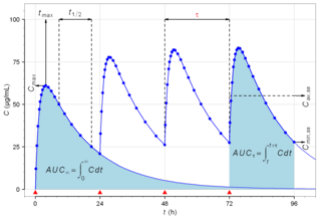
- **Essential for using a pertinent medicine**
- **To increase safety or effectiveness**
- **Except simple diagnostics**

Three types of CoDx

- To identify
  - GOOD RESPONDER/ Target of the medicine

  - HIGH RISK of Side Effect/ Avoid use of the medicine

- To optimise dose/ decide discontinue



Definition of CoDx in Japan(1)

A companion diagnostics(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, 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

July 2013; Notification on Approval Application for *In Vitro* Companion Diagnostics and Corresponding Therapeutic Products

Why It is So Hot ? (Background)

- Advance in the medicine

  We found

  - ✓ more specific target (molecular level)
  - ✓ Polymorphism (and its‘ effect on macro)

- Dream for “perfectly fit medicine”

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What is important for evaluation of CoDx?

Companion diagnostics (CoDx) Project

Founded in April, 2012

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

- ✓ From many divisions of PMDA
- ✓ Discuss points to consider
- ✓ Issue Guidelines and concept papers
- ✓ Support issuing notifications
- ✓ Disseminate concepts

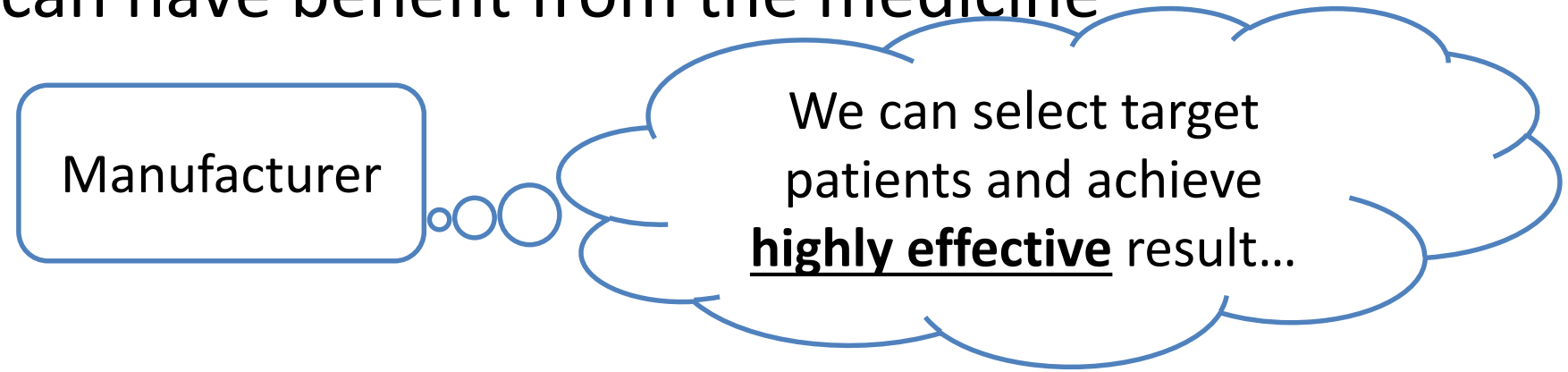
What is important for regulation of CoDx?

- Simultaneous application with the pertinent medicine
  - ✓ To make available CoDx from the start of use of the medicine

- Need for cooperation of companies (medicine/ IVD)
- Need for cooperation of review sections (medicine/IVD)
- Clear connection between CoDx and the pertinent medicine (declaration in package inserts each other)

Pit hole of CoDx?

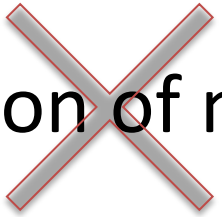
- Considerations for CoDx
  - ✓ It may unnecessarily reject patients who actually can have benefit from the medicine



  - ✓ It may create patient group who seem to have benefit from the medicine by retrospective research

Need for consideration

- Biomarker Negative patients



✓ Early exclusion of marker negative patients

✓ To include both biomarker negative and positive to early stage of clinical trials

(not mean to treat negative patient as positive nor mean obligation of clinical trial targets negative patients!)

This helps consideration of the cut-off value and evaluation of comparison of balance of risks and benefits between biomarker negative and positive

Possibility of the Effect

Even if Biomarker negative patients, the pertinent medicine may be effective because…

- ✓ Off-target effect
- ✓ CoDx may fail to detect the truth
- ✓ Samples might be degraded
- ✓ Intra-tumor heterogeneity

Be careful for retrospective evaluation

Retrospective evaluation might be accepted only

- ✓ Consent of participants of clinical trials
- ✓ Proper preservation of samples
- ✓ Supported by prospective research

(exceptions)

- ✓ For Safety marker, the side effects are very serious
- ✓ Difficult to prospective research because of number of patients
- ✓ Coherent in multiple clinical trials etc.

Clinical performance study for CoDx

- ✓ If the CoDx is used in the confirmatory clinical trials, the test data (including negative case, invalid result, information of sample and patient's background etc.) should be submitted as a clinical performance study.
- ✓ If the CoDx is not used in the confirmatory clinical trials, it is necessary to evaluate the concordance with the clinical trial assay.
- ✓ In either case, if there are any standard method (such as a normative method employed by public agencies or standardization bodies), in principle, it is necessary to conduct a concordance study with such method.
- ✓ If the clinical cut off is defined in the exploratory clinical trial, such data should be submitted as a clinical performance study.

*These should be considered individually, so it is recommended to consult PMDA

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Multiplex diagnostics

There are cases where multiplex diagnostics such as next generation sequencing are used in clinical trials.

- ✓ Multiplex diagnostics for measurement of one biomarker are necessary because there are many mutation sites in the biomarker.

- ✓ Measurement of many biomarkers is reasonable because there are many biomarkers with corresponding molecular targeted therapy.
  e.g. lung cancer, gastrointestinal cancer

Discussion Points of NGS Regulation

- Is each component of NGS MD or IVD reagent in Japan?
  (oncology panels, universal kit, sequencer, programs…)
- How to evaluate analytical performance of NGS
- How to define validated mutations as an indication of corresponding drug
- How to deal with update of clinical database after marketing authorization
  (and corresponding drug)
- How to review panels used for multiple drugs
- How to regulate/control the information of unknown mutations

Concept paper has been issued
https://www.pmda.go.jp/files/000214302.pdf

Thank you for your attention!