Clinical/Non-clinical Review of Diagnostic Radiopharmaceuticals in Japan

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Outline

- Characteristics of Diagnostic Radiopharmaceuticals
- Non-clinical evaluation
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
- Clinical evaluation
  - Clinical overview
  - Case study

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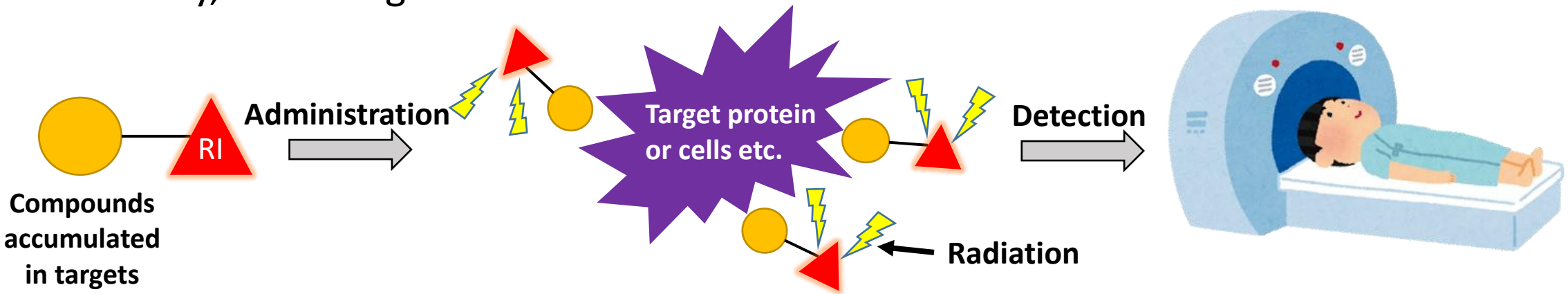
Characteristics of Diagnostic Radiopharmaceuticals

- Diagnostic radiopharmaceuticals include compounds that accumulate in target proteins/cells and radioisotopes (RI) that bind to those compounds.
- Clinical diagnosis is performed by detecting radiation emitted from RI bound to compounds accumulated in targets and examining its distribution.

- Single dose administration

- Basically, the dosage is a microdose.



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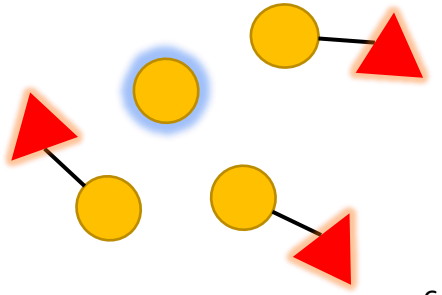
Pharmacology

Study for MAA	
1 Primary pharmacodynamic studies e.g., Binding to target	○
2 Secondary pharmacodynamic studies e.g., Binding to various receptors	○
3 Safety pharmacology studies e.g., Effects on cardiovascular, respiratory and central nervous systems	○
4 Pharmacodynamic drug interaction studies e.g., Drug interaction with respect to binding to targets	△

⇒Ref. ICH S7A, ICH S7B

Due to the manufacturing process of RI-labeling compounds, it is assumed that unlabeled compounds will be included in the evaluation.



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Pharmacokinetics

Study for MAA	
1 Absorption	○
2 Distribution	○
3 Metabolism	○
4 Excretion	○
5 Pharmacokinetic Drug Interaction	○

⇒Ref. ICH S3A, ICH M12

Diagnostic radiopharmaceuticals are characterized by low concentrations, making it difficult to measure the concentration of the drug. The radioactivity was calculated as the ratio of tissue radioactivity to administered radioactivity (%ID/g) instead of measuring the concentration.

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Toxicology

Study for MAA	
1 Single dose toxicity studies	○
2 Repeated dose toxicity studies	○
3 Genotoxicity testing	×
4 Carcinogenicity studies	×
5 Reproduction toxicity studies	×
6 Local tolerance studies	○
7 Other toxicity studies e.g., Qualifying impurities and degradants	△

⇒Ref. ICH M3 (R2), ICH M7 (R2)

However, reproductive toxicity and genotoxicity must also be evaluated.

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Clinical overview

● Diagnostic radiopharmaceuticals are evaluated from two perspectives.

1. Appropriate test performance

In general, test performance of diagnostic radiopharmaceuticals is evaluated based on the sensitivity and specificity.

2. Clinical benefit of the diagnostic test

e.g., Provide appropriate treatment options, Determine treatment efficacy

How to show benefits

- Evaluation of clinical benefit based on the clinical trial results
- Explanation of the clinical significance of the test based on the clinical guidelines (Clinical trials are not necessarily required)

Evaluation of test performance

● When evaluating test performance, the following points should be considered.

1. **The purpose of the diagnostic test**
   - Diagnosis of disease
   - Identification of disease site

2. **How to position the diagnostic agent**
   - Replace existing tests of established clinical significance
   - Add on to existing tests of established clinical significance
   - No existing test method

Evaluation of test performance
- Standard of truth

- Standard of truth（SOT） is an indicator that can assess the true state of the disease or condition that the investigational medicinal products are intended to assess, independent of the investigational medicinal products.

  e.g., Pathology of cancer

  Diagnostic results from existing tests that have been validated

  Follow-up survey results（When the passage of time will ensure the results of the diagnosis）

Evaluation of test performance - Sensitivity

- Sensitivity is the ability to detect that a person is ill (positive) .

$$\text{Sensitivity} = \frac{a}{a+c}$$

True state of disease (SOT)

Diagnostic Results from Investigational medicinal products	+	−	Total
+	a (True Positive)	b (False Positive)	a＋b
−	c (False Negative)	d (True Negative)	c＋d
Total	a＋c	b＋d	a＋b＋c＋d

Evaluation of test performance - Specificity

- Specificity is the ability to detect a person who is not ill (negative).

$$\text{Specificity} = \frac{d}{b+d}$$

		True state of disease (SOT)		
		+	−	Total
Diagnostic Results from Investigational medicinal products	+	a (True Positive)	b (False Positive)	a＋b
	−	c (False Negative)	d (True Negative)	c＋d
	Total	a＋c	b＋d	a＋b＋c＋d

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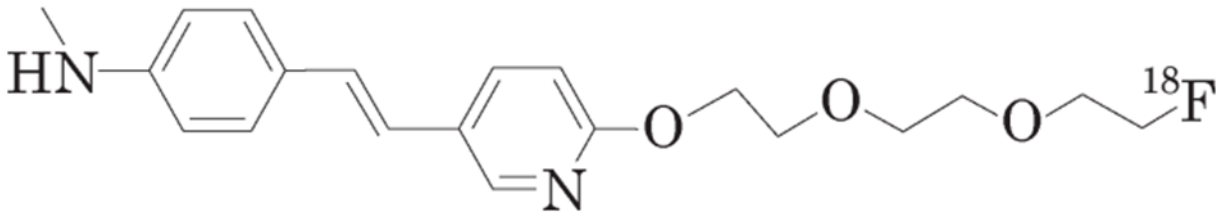
E.g., 1. Amyvid® (Florbetapir (^{18}F))



Source: IF of Amyvid®

- A radiopharmaceutical diagnostics agent for PET imaging
- This new drug was first approved December, 2016
- Indication and Usage (First approved)
  - Imaging of the brain to estimate β-amyloid (Aβ) neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.
- Dosage and Administration
  - Administer 370 MBq as a single intravenous bolus imaging is started 30-50 minutes after administration. The imaging time should be 10 minutes.

Major clinical trial

	A16 (Global Phase 3 study)
Study population	Autopsy brains of subjects who have consented to brain donation
Subjects number	59 subjects
Evaluation of efficacy	Test performance (sensitivity and specificity) of PET imaging when the pathology is SOT

Test performance

Consistency between Amyvid PET imaging and amyloid pathology

		Amyloid pathology (modified CERAD)[a]		Total[a]	Sensitivity [95%CI][b]	Specificity [95%CI][b]
		+	−			
PET imaging[a]	+	36	0	36	$\frac{36}{39}$ = **92.3%** [78%, 98%]	$\frac{20}{20}$ = **100%** [80%, 100%]
	−	3	20	23		
Total		39	20	59		

a : number of subjects
b : Wilson's score

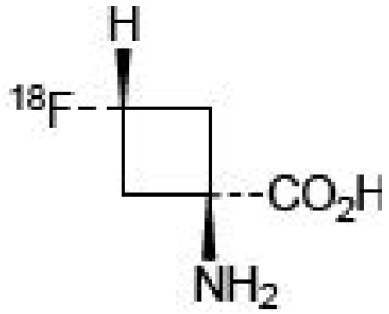
Sensitivity and Specificity were prior to the reference standard (80%).
The clinical study showed substantial test performance of Amyvid.

Clinical significance

- It is described in the Clinical Practice Guidelines for Dementia that obtaining information on the accumulation of Aβ in the brain is useful in the diagnosis of dementia.

- The test results by Amyvid will provide the information on whether the patient is eligible for AD therapy or not.

E. g., 2. Axumin® (Fluciclovine (^{18}F))



Source: IF of Axumin®

- A radiopharmaceutical diagnostics agent for PET imaging
- This new drug was approved March, 2021.
- Indication and Usage
  - Imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment
- Dosage and Administration :
  - Generally, one vial (87-270 MBq) of the drug is administered intravenously, and imaging is started 10-50 minutes after administration.

Major clinical trials

	P301 (Domestic Phase 3 study)	P302 (Domestic Phase 3 study)	
Study design	Open-label, uncontrolled study	Open-label, compared study	
Study Population	Japanese patient with clinically suspected glioma and scheduled for brain tumor resection		
Number of subjects (FAS)	36 subjects Meged analysis of P301 15 subjects + P302 21 subjects Excluding 3 cases of no information on tissue collection site, etc.	Axumin group 24 subjects	※Plan the site of tissue collection and extent of tumor resection with reference to MRI images for navigation and PET images of Acumin.
		Control group 23 subjects	※Plan the site of tissue collection and extent of tumor resection with reference to MRI images for navigation
Evaluation of efficacy	Positive predictive value (PPV) when the pathology in areas determined to be contrast (-) PET (+) by central image determination was SOT (reference standard 70%) ⇒Evaluation of test performance	9-month Progression-Free Survival (PFS) in patients with suspected high-grade glioma ⇒Evaluation of clinical significance (turning point)	

Test performance

Consistency between Axumin PET imaging findings in glioma and tumor pathology

		Tumor pathology contrast (-) PET (+) region[a]		Total	PPV [95%CI][b]
		+	−		
PET imaging[a]	+	**22**	3	**25**	$\frac{22}{25}$ = **88.0%** [75.3%, 100%]
	−				
Total					

a : number of tissue
b : Wald's method

Patients with suspected high-grade glioma : **88.9%** (16/18 tissue)

Patients with suspected low-grade glioma : **85.7%** (6/7 tissue)

PET imaging with Axumin was shown to identify tumors outside the high-signal region of contrast-enhanced T1-weighted MRI images with substantial accuracy, irrespective of the grade of the tumor.

Evaluation of clinical significance

	Axumin group [95%CI]	Control group [95%CI]
9-month PFS rate	33.3 (4/12 subject) [9.9,65.1]	46.7 (7/15 subject) [21.3,73.4]

- It was not shown that improved tumor removal rate based on PET test using Axumin improved prognosis.
- PMDA considered the possibility that the study result did not adequately reflect the relationship between PET scan (the removal of more tumors based on PET) and PFS due to the extremely limited number of subjects.

Clinical significance

- According to brain tumor practice guidelines, the higher the degree of surgical removal in glioblastoma, the better the prognosis for life.

- The clinical study showed PET imaging with Axumin can identify tumor tissue in areas undetectable by MRI imaging.

- Therefore, it is significant to provide Axumin to the medical community because it is expected to increase the tumor volume to be removed and to contribute to improved prognosis when evaluated with Axumin.

Take-Home Message

- Diagnostic radiopharmaceuticals are evaluated from two perspectives
  - Appropriate test performance
  - Clinical benefit of the diagnostic test

Q&A