Overview of PMDA Review Process including Radiopharmaceuticals

Itsuki KOMINATO

Office of New Drug II, PMDA

Outline

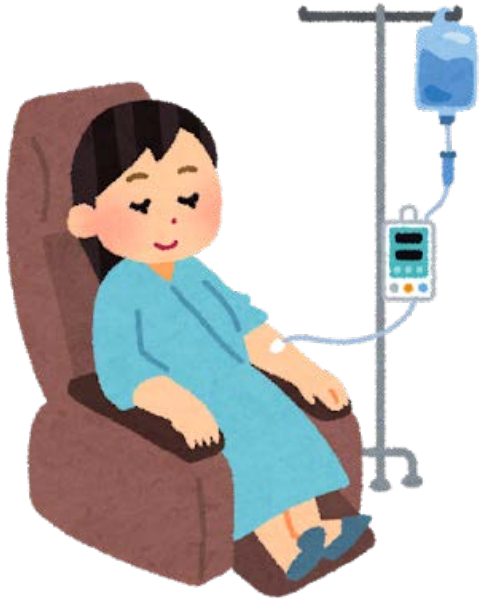
- What are Radiopharmaceuticals?
- Review Process of Diagnostic Radiopharmaceuticals in Japan
- Points to Consider in the Review of Diagnostic Radiopharmaceuticals

Outline

- **What are Radiopharmaceuticals?**
- Review Process of Diagnostic Radiopharmaceuticals in Japan
- Points to Consider in the Review of Diagnostic Radiopharmaceuticals

What are Radiopharmaceuticals?

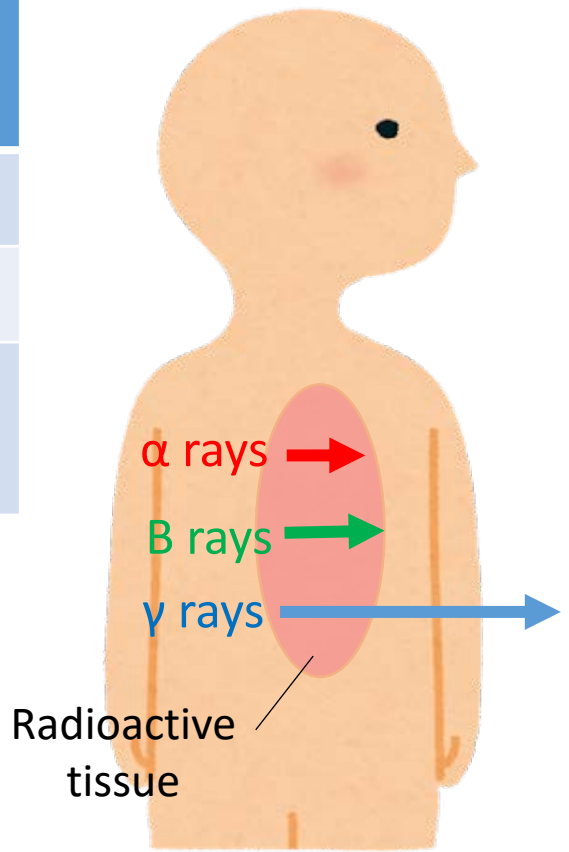
- Drugs that have radioisotopes (RI) as a structural element and emit radiation
- Used for diagnosis and treatment of disease



What are Radiopharmaceuticals?

- Three types of radiation are used for radiopharmaceuticals.

	Penetrating power	Half-life	Main nuclides
α rays	Low	Long	^{223}Ra
β rays	↕	↕	^{131}I, ^{177}Lu, ^{90}Y
γ rays	High	Short	^{18}F, ^{81m}Kr, ^{99m}Tc, ^{123}I, ^{111}In, ^{201}Tl, ^{67}Ga,



What are Radiopharmaceuticals?

- Because radiopharmaceuticals have short half-lives, some radiopharmaceuticals need to be radiolabelled in the hospital using a radionuclide generator or cyclotron just before use.

Radionuclide Generator

Devices that contain parent nuclides with long half-life(e.g. ^{81}Rb). The daughter nuclides(e.g. ^{81}mKr) decayed from the parent nuclides can be obtained using the eluates.

Nihon Medi-Physics Co., Ltd. Krypton (^{81m}Kr) generator
https://www.nmp.co.jp/member/list/02_08.html

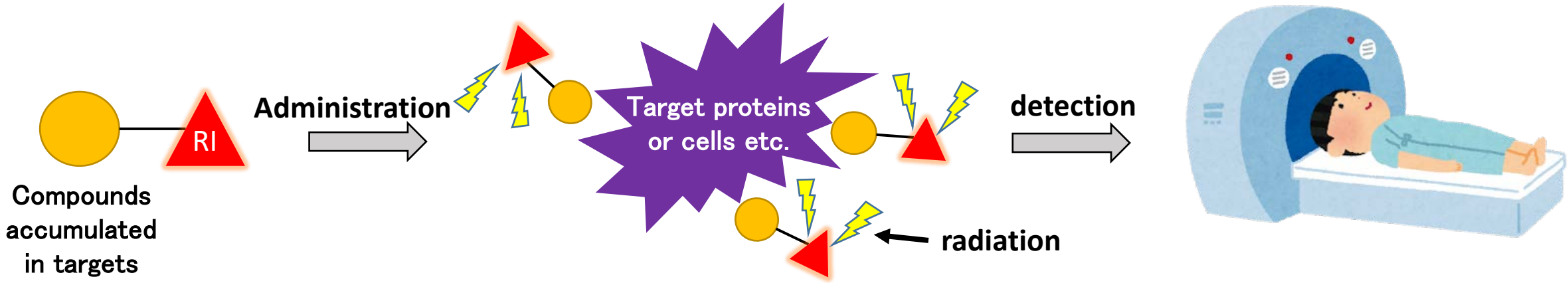
Cyclotron

Devices that produce the nuclides by causing a nuclear reaction.

Sumitomo Heavy Industries, Ltd. PET Cyclotron System
https://www.shi.co.jp/products/machinery/cyclotron/index.html

Diagnostic Radiopharmaceuticals

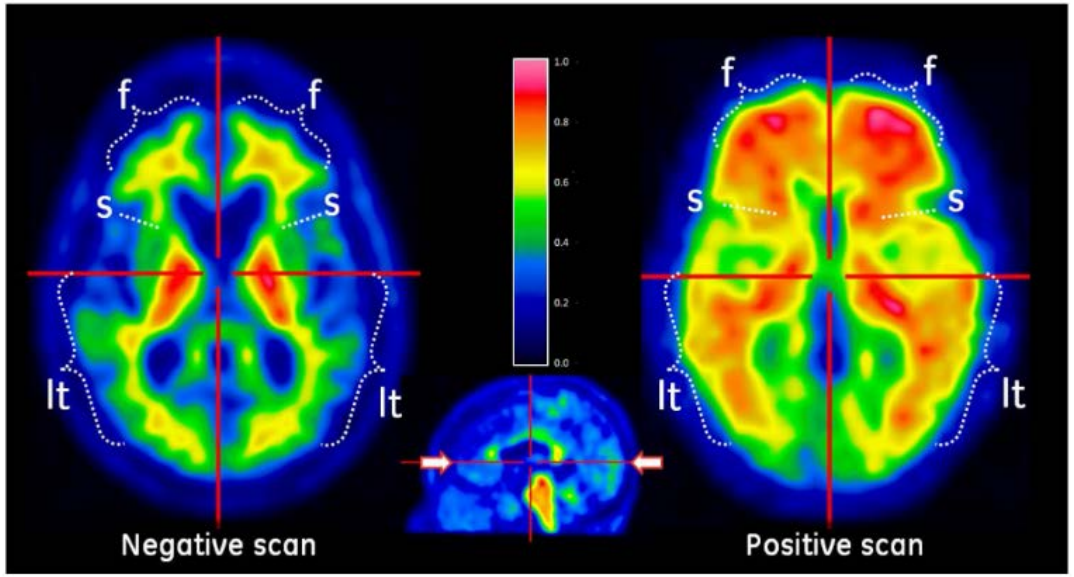
- Radiopharmaceuticals used for diagnosis
- Clinical diagnosis is performed by detecting radiation emitted from RI bound to compounds accumulated in targets and examining its distribution.
- Nuclides with the following characteristics are often used:
  - ➢ High-penetrating γ rays are emitted to make radiation detectable from outside the body.
  - ➢ A half-life is short to minimize radiation exposure during diagnostics.



Example of Diagnostic Radiopharmaceuticals

VIZAMYL

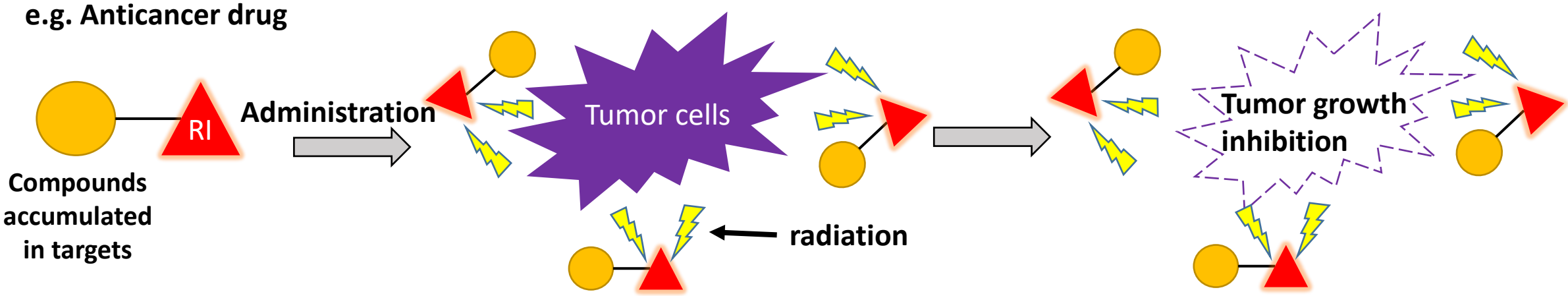
- Overview: A diagnostic agent aimed at visualizing Aβ plaques in the brain
  Flutemetamol, which specifically binds to Aβ, is labeled with ^{18}F
- Nuclide : ^{18}F
- Radiation type: γ rays
- Half-life: 109.8 minutes



Application Summary of VIZAMIL

Therapeutic Radiopharmaceuticals

- Radiopharmaceuticals used for treatment
- The mechanism of action for radiopharmaceutical therapy is radiation-induced killing of cells.
- Nuclides with the following characteristics are often used :
  - ➢ Low-penetrating α or β rays are emitted to minimize exposure outside the target
  - ➢ A half-life is longer than that of the nuclides used in diagnostic radiopharmaceuticals



Example of Therapeutic Radiopharmaceuticals

LUTATHERA Intravenous

- Overview : Anticancer drug targeting neuroendocrine tumors expressing somatostatin receptors

  Somatostatin analogues that bind to somatostatin receptors are labeled with ^{177}Lu.

  The β-rays emitted from ^{177}Lu damage the tumor cells, inhibiting tumor growth.

- Nuclide : ^{177}Lu
- Radiation type: β rays (and γ rays)
- Half-life: 6.64 days

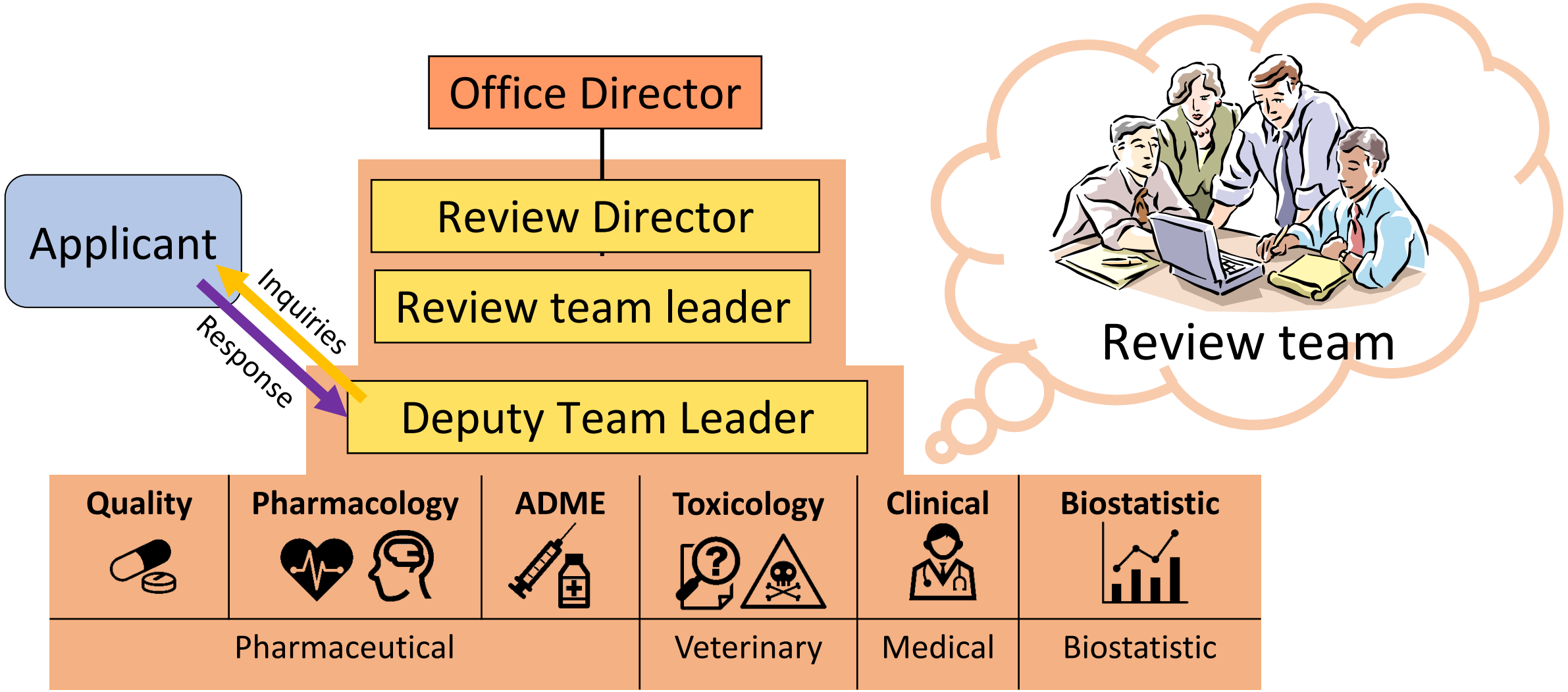
Review Categories of New Drugs in PMDA

Office	Review Category	Products
Office of New Drug I	Team 1 Team 6-2	Gastrointestinal drugs, Dermatologic drugs Hormone drugs, Drugs for metabolic disorders
Office of New Drug II	Team 2 Team 5 Radiopharmaceuticals In vivo diagnostics	Cardiovascular drugs, Antiparkinsonian drugs, Antithrombotic, Anti-Alzheimer's drugs Reproductive system drugs, Drugs for urogenital system, combination drugs Radiopharmaceuticals Contrast media
Office of New Drug III	Team 3-1 Team 3-2	Central/peripheral Nervous system drugs (excluding anesthetic drugs) Anesthetic drugs, Sensory organ drugs (excluding drugs for inflammatory diseases), Narcotics
Office of New Drug VI	Team 4 Anti-AIDS drugs Team 6-1	Antibacterial drugs, vermifuge, Antifungal drugs, Antiviral drugs (excluding AIDS drugs) Anti-HIV agents Respiratory tract drugs, Anti-allergy drugs (excluding dermatologic drugs), Sensory organ drugs for inflammatory diseases
Office of New Drug V	Oncology drugs	Antineoplastic drugs
Office of Cellular and Tissue-based Products	Bio-CMC Cellular and tissue-based products Gene therapy products	Quality of biologics, Biosimilars Cellular and tissue-based products Quality and safety of gene therapy products
Office of Vaccines and Blood Products	Vaccines Blood products	Vaccines, Antitoxic serum Globulin, blood coagulation factor products

Outline

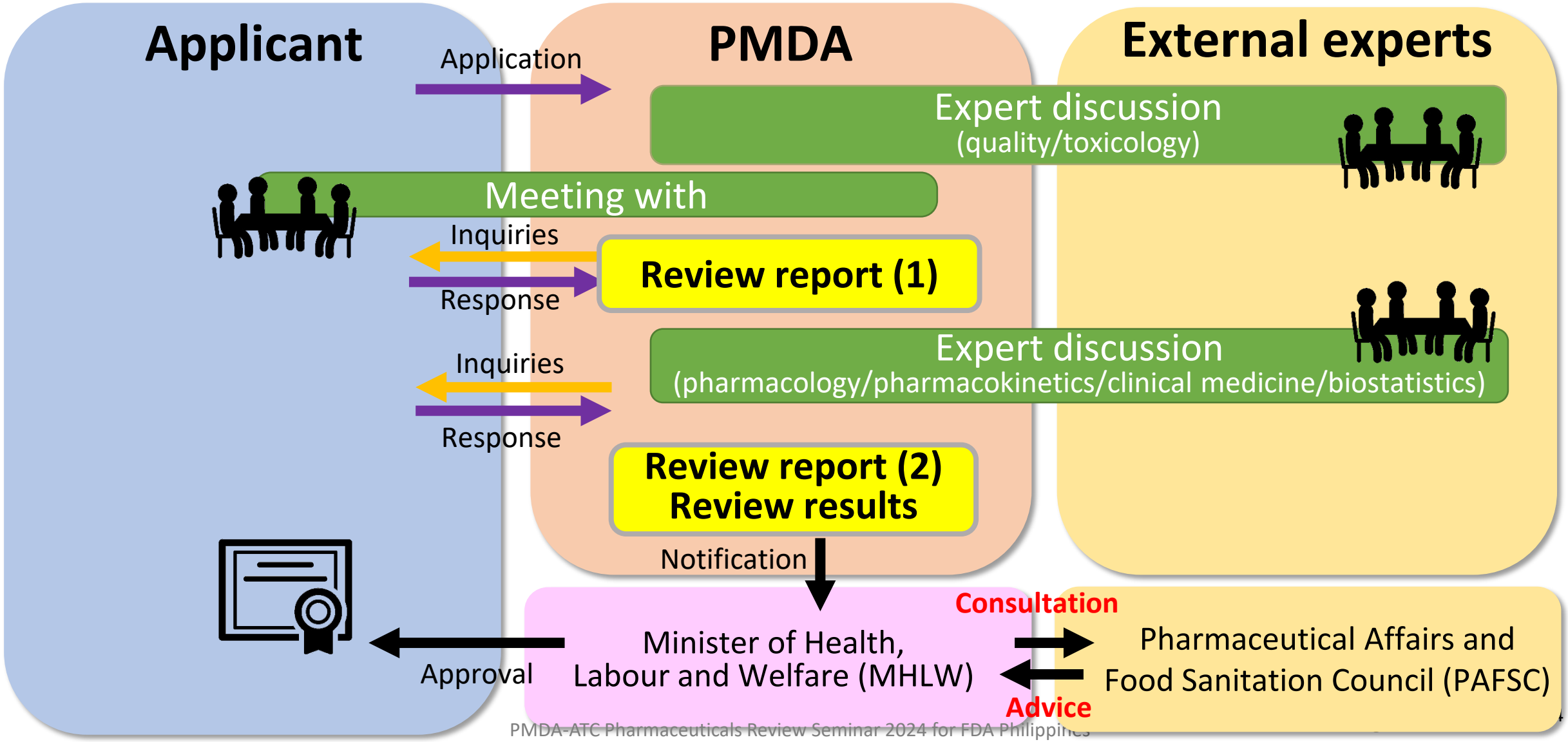
- What are Radiopharmaceuticals?
- **Review Process of Diagnostic Radiopharmaceuticals in Japan**
- Points to Consider in the Review of Diagnostic Radiopharmaceuticals

Review Team for New Drug

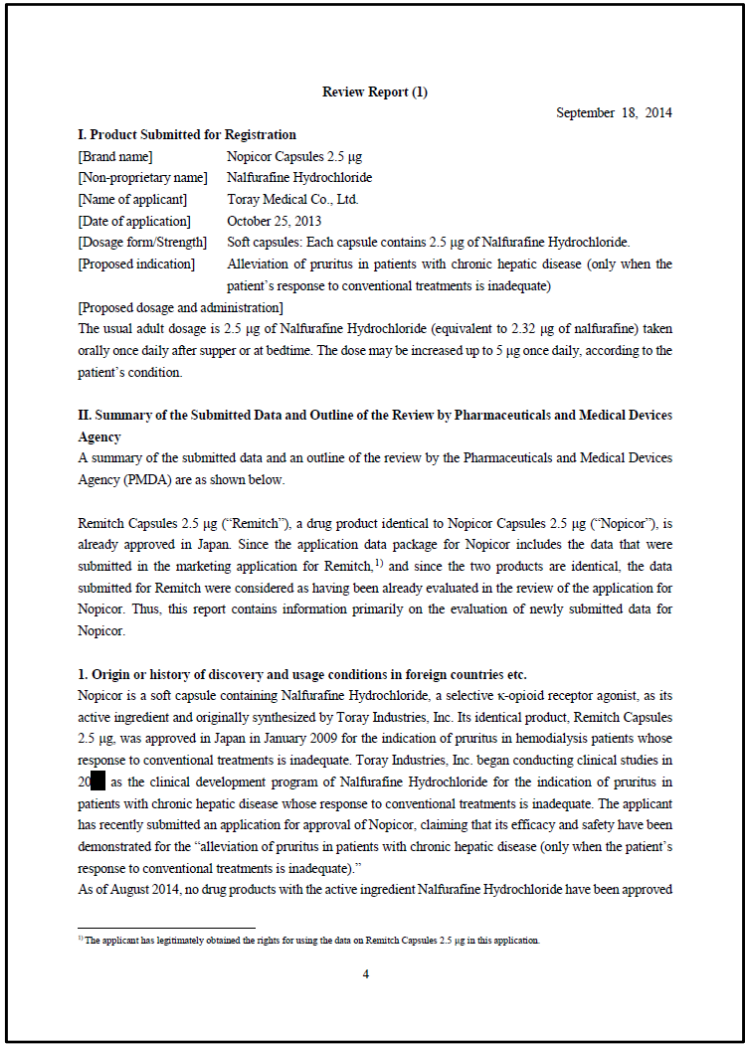


Review Process of MAA* for New Drugs in Japan

* : marketing authorization application



Review Report Format



Review Report (1)

September 18, 2014

I. Product Submitted for Registration

[Brand name]	Nopicor Capsules 2.5 μg
[Non-proprietary name]	Nalfurafine Hydrochloride
[Name of applicant]	Toray Medical Co., Ltd.
[Date of application]	October 25, 2013
[Dosage form/Strength]	Soft capsules: Each capsule contains 2.5 μg of Nalfurafine Hydrochloride.
[Proposed indication]	Alleviation of pruritus in patients with chronic hepatic disease (only when the patient's response to conventional treatments is inadequate)

[Proposed dosage and administration]
The usual adult dosage is 2.5 μg of Nalfurafine Hydrochloride (equivalent to 2.32 μg of nalfurafine) taken orally once daily after supper or at bedtime. The dose may be increased up to 5 μg once daily, according to the patient's condition.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

Remitch Capsules 2.5 μg ("Remitch"), a drug product identical to Nopicor Capsules 2.5 μg ("Nopicor"), is already approved in Japan. Since the application data package for Nopicor includes the data that were submitted in the marketing application for Remitch,[1)] and since the two products are identical, the data submitted for Remitch were considered as having been already evaluated in the review of the application for Nopicor. Thus, this report contains information primarily on the evaluation of newly submitted data for Nopicor.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Nopicor is a soft capsule containing Nalfurafine Hydrochloride, a selective κ-opioid receptor agonist, as its active ingredient and originally synthesized by Toray Industries, Inc. Its identical product, Remitch Capsules 2.5 μg, was approved in Japan in January 2009 for the indication of pruritus in hemodialysis patients whose response to conventional treatments is inadequate. Toray Industries, Inc. began conducting clinical studies in 20[redacted] as the clinical development program of Nalfurafine Hydrochloride for the indication of pruritus in patients with chronic hepatic disease whose response to conventional treatments is inadequate. The applicant has recently submitted an application for approval of Nopicor, claiming that its efficacy and safety have been demonstrated for the "alleviation of pruritus in patients with chronic hepatic disease (only when the patient's response to conventional treatments is inadequate)."

As of August 2014, no drug products with the active ingredient Nalfurafine Hydrochloride have been approved

1) The applicant has legitimately obtained the rights for using the data on Remitch Capsules 2.5 μg in this application.

4

1. Origin or History of Discovery, **Use in Foreign Countries** , and Other Information
2. Data Relating to **Quality** and Outline of the Review Conducted by PMDA
3. **Non-clinical Pharmacology** and Outline of the Review Conducted by PMDA
4. **Non-clinical Pharmacokinetics** and Outline of the Review Conducted by PMDA
5. **Toxicity** and Outline of the Review Conducted by PMDA
6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, **Clinical Pharmacology** , and Outline of the Review Conducted by PMDA
7. **Clinical Efficacy and Safety** and Outline of the Review Conducted by PMDA
8. Results of **Compliance** Assessment Concerning the Application Data and Conclusion Reached by PMDA
9. **Overall Evaluation** during Preparation of the Review Report (1)

Review Report (1)

- The review team summarizes its review process and considerations before expert discussion (pharmacokinetics/clinical medicine/biostatistics).

- A review report consists of two parts:
  - Summary of the submitted data
  - Outline of the review by PMDA

- Based on the report, the review team clarifies discussion points for the expert discussion.

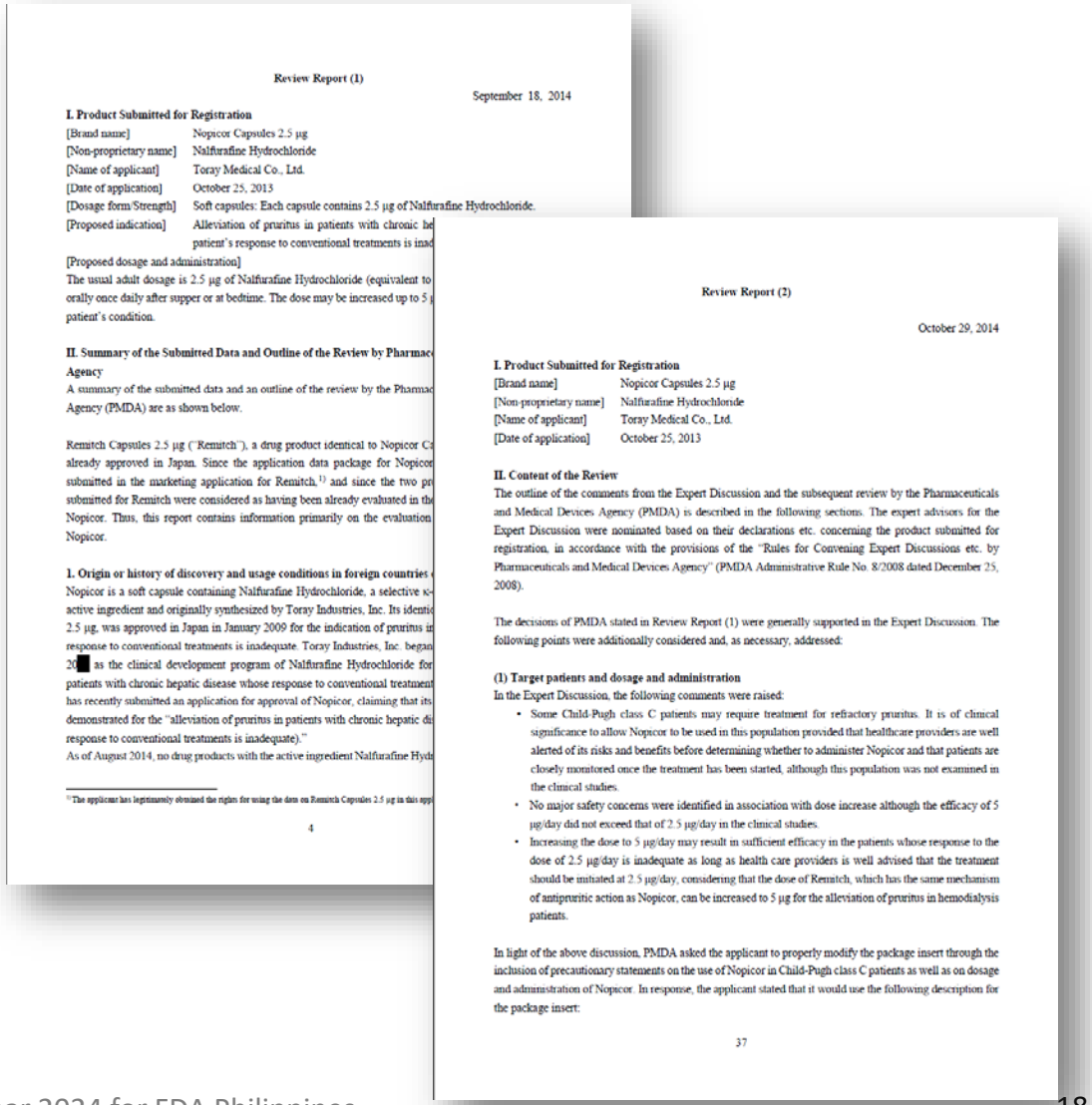
Review Report (2)

- The review team summarizes results of the expert discussion and the applicant's plan for post-marketing risk management.
- The review team states PMDA's final conclusion about whether the product is approvable.

Publish the Review Reports

Review reports can be found at https://www.pmda.go.jp/PmdaSearch/iyakuSearch/

Some of the reports have been translated in English http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html



Review Report (1)

September 18, 2014

I. Product Submitted for Registration

[Brand name] Nopicor Capsules 2.5 μg
[Non-proprietary name] Nalfurafine Hydrochloride
[Name of applicant] Toray Medical Co., Ltd.
[Date of application] October 25, 2013
[Dosage form/Strength] Soft capsules: Each capsule contains 2.5 μg of Nalfurafine Hydrochloride.
[Proposed indication] Alleviation of pruritus in patients with chronic he
patient's response to conventional treatments is inad
[Proposed dosage and administration]
The usual adult dosage is 2.5 μg of Nalfurafine Hydrochloride (equivalent to
orally once daily after supper or at bedtime. The dose may be increased up to 5
patient's condition.

II. Summary of the Submitted Data and Outline of the Review by Pharmac
Agency

A summary of the submitted data and an outline of the review by the Pharmac
Agency (PMDA) are as shown below.

Remitch Capsules 2.5 μg ("Remitch"), a drug product identical to Nopicor Ca
already approved in Japan. Since the application data package for Nopicor
submitted in the marketing application for Remitch,[1] and since the two pr
submitted for Remitch were considered as having been already evaluated in th
Nopicor. Thus, this report contains information primarily on the evaluation
Nopicor.

1. Origin or history of discovery and usage conditions in foreign countries
Nopicor is a soft capsule containing Nalfurafine Hydrochloride, a selective κ-
active ingredient and originally synthesized by Toray Industries, Inc. Its identic
2.5 μg, was approved in Japan in January 2009 for the indication of pruritus in
response to conventional treatments is inadequate. Toray Industries, Inc. began
20[redacted] as the clinical development program of Nalfurafine Hydrochloride for
patients with chronic hepatic disease whose response to conventional treatment
has recently submitted an application for approval of Nopicor, claiming that its
demonstrated for the "alleviation of pruritus in patients with chronic hepatic di
response to conventional treatments is inadequate)."
As of August 2014, no drug products with the active ingredient Nalfurafine Hyd

[1]The applicant has legitimately obtained the rights for using the data on Remitch Capsules 2.5 μg in this app

4

Review Report (2)

October 29, 2014

I. Product Submitted for Registration

[Brand name] Nopicor Capsules 2.5 μg
[Non-proprietary name] Nalfurafine Hydrochloride
[Name of applicant] Toray Medical Co., Ltd.
[Date of application] October 25, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

The decisions of PMDA stated in Review Report (1) were generally supported in the Expert Discussion. The following points were additionally considered and, as necessary, addressed:

(1) Target patients and dosage and administration

In the Expert Discussion, the following comments were raised:

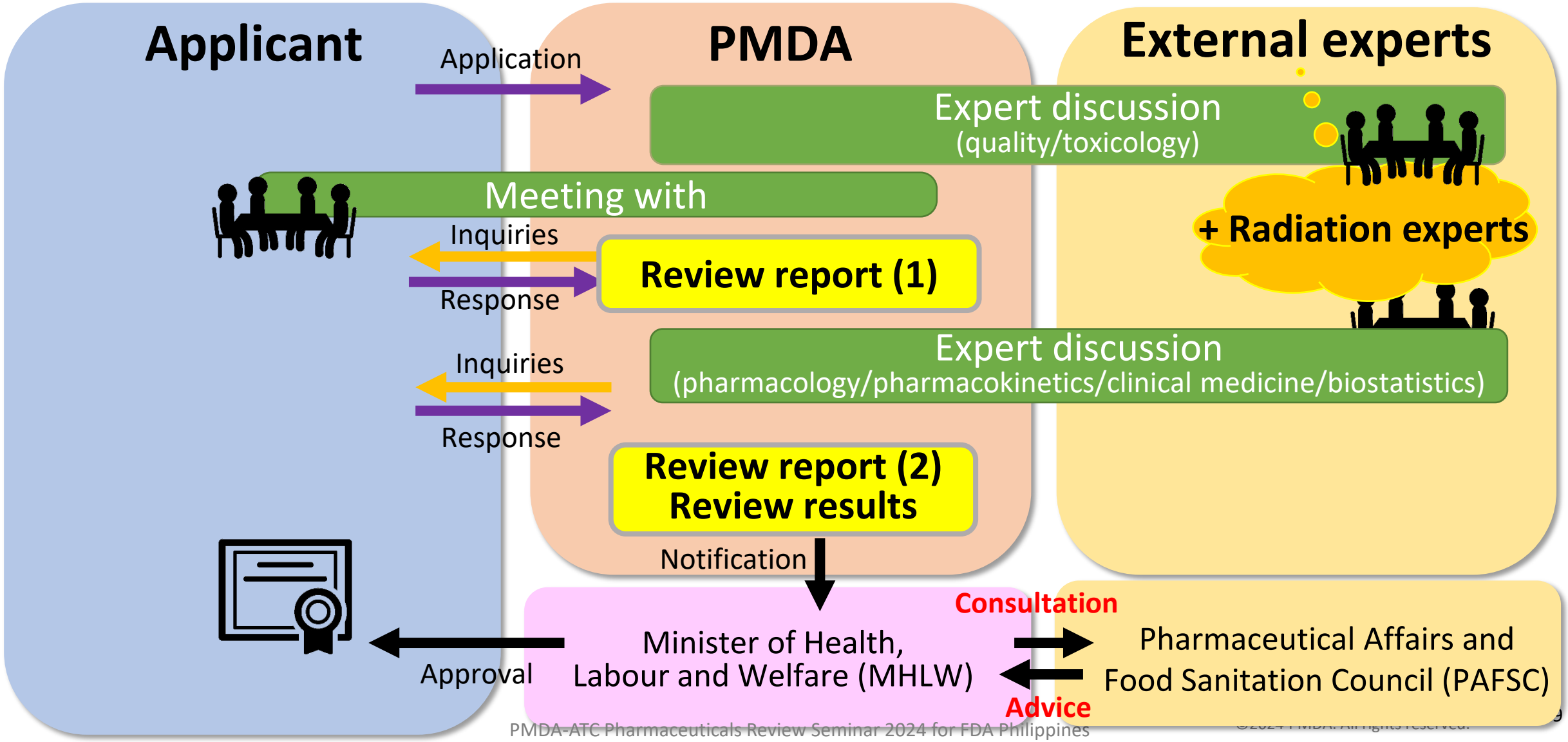
- Some Child-Pugh class C patients may require treatment for refractory pruritus. It is of clinical significance to allow Nopicor to be used in this population provided that healthcare providers are well alerted of its risks and benefits before determining whether to administer Nopicor and that patients are closely monitored once the treatment has been started, although this population was not examined in the clinical studies.
- No major safety concerns were identified in association with dose increase although the efficacy of 5 μg/day did not exceed that of 2.5 μg/day in the clinical studies.
- Increasing the dose to 5 μg/day may result in sufficient efficacy in the patients whose response to the dose of 2.5 μg/day is inadequate as long as health care providers is well advised that the treatment should be initiated at 2.5 μg/day, considering that the dose of Remitch, which has the same mechanism of antipruritic action as Nopicor, can be increased to 5 μg for the alleviation of pruritus in hemodialysis patients.

In light of the above discussion, PMDA asked the applicant to properly modify the package insert through the inclusion of precautionary statements on the use of Nopicor in Child-Pugh class C patients as well as on dosage and administration of Nopicor. In response, the applicant stated that it would use the following description for the package insert:

37

Review Process of MAA* for Diagnostic Radiopharmaceuticals in Japan

* : marketing authorization application



Review Process of Diagnostic Radiopharmaceutical in Japan

- For a radiopharmaceutical with a new active ingredient, “The Minimum Requirements of Radiopharmaceuticals" are established in parallel with the approval review.

○What are “The Minimum Requirements of Radiopharmaceuticals" ?

- Standards that compile the manufacturing methods, properties, quality, storage, etc. of radiopharmaceuticals approved in Japan.
- Radiopharmaceuticals are designated as drugs that require special care under Japanese law, and minimum standards are set and published for each item.

Outline

- What are Radiopharmaceuticals?
- Review Process of Diagnostic Radiopharmaceuticals in Japan
- **Points to Consider in the Review of Diagnostic Radiopharmaceuticals**

Characteristics of Diagnostic Radiopharmaceuticals

- Diagnostic agents in which RI is bound to compounds that accumulate on a target. After administration to a human, the radiation emitted from the RI is detected by a PET scan or other means, and the distribution is examined to enable diagnostic imaging.

- Single dose administration

- Basically, the dosage is a microdose.

These characteristics must be taken into consideration when developing and reviewing diagnostic radiopharmaceuticals.

Guideline

- In Japan, the following guideline is used as reference in the development and review of diagnostic radiopharmaceuticals.

  ➢**Guideline for clinical evaluation of diagnostic radiopharmaceuticals**

  - Guideline summarizing non-clinical test items and the planning, implementation and evaluation methods of clinical trials required for the development of diagnostic radiopharmaceuticals

Quality and Clinical/Non-Clinical Review

Quality Review

- In manufacturing process and quality control, consideration of radioactivity decay due to short half-life is required.

Clinical/Non-clinical Review

- An evaluation based on the characteristics of diagnostic radiopharmaceuticals is required.
- Diagnostic radiopharmaceuticals are evaluated from two perspestives:

➢ Appropriate test performance must be obtained.

➢ Patients obtain tangible benefits from the diagnosis.

Each point will be explained in detail in the following lectures.

Take-Home Message

- **Radiopharmaceuticals are used for the diagnosis and treatment of diseases.**
- **The review process for diagnostic radiopharmaceuticals is the same as that for general new drugs.**
- **For a radiopharmaceutical with a new active ingredient, the Radiopharmaceuticals Standards is established in parallel with the approval review.**
- **There are several points to consider in the review that are based on the characteristics of diagnostic radiopharmaceuticals.**

Thank you

Q&A