Quality Review of Diagnostic Radiopharmaceuticals

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Outline

1. Objectives of quality review in the new drug approval process
2. Outline of quality review of Diagnostic Radiopharmaceuticals
    1. Manufacturing process
    2. Specifications and Test procedures

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What is the quality review?

"The drug has claimed efficacy with minimal safety concerns in terms of quality."

Development phase

Phase 3 study drug

New Drug Application

Post-marketing phase

Marketing product?

Does the marketing product have similar efficacy and safety as the phase 3 product?

Objectives of Quality Review

- To ensure that every marketing lot of the drug has claimed efficacy with minimal safety concerns, a drug of required quality should be produced consistently.

- To achieve the objective, we review **the manufacturing process and specifications**.

- We also review stability data to confirm that the shelf life and the storage condition of the drug are appropriate.

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    1. Manufacturing process
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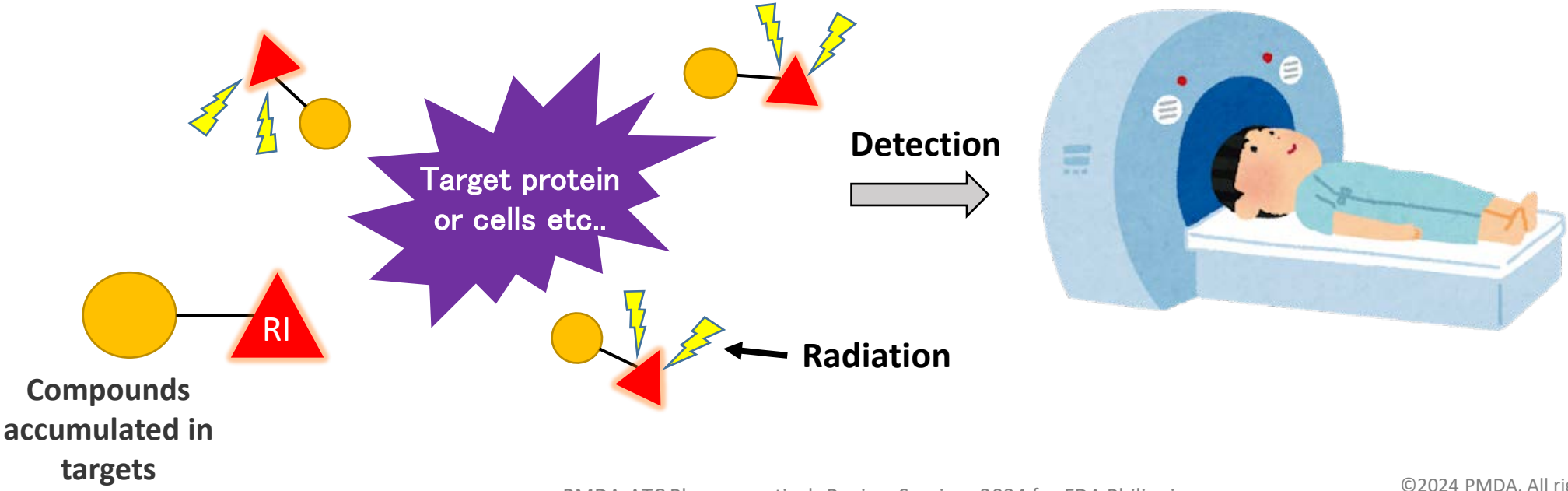
Diagnostic Radiopharmaceuticals

- Diagnostic radiopharmaceuticals include compounds that accumulate in target proteins/cells and radioisotopes(RI) that bind to those compounds.
- Radiation emitted from RI after administration to humans can be detected by PET/SPECT, and imaging can be performed by examining its distribution.



Manufacturing process

- The goal of manufacturing process development is to establish a commercial manufacturing process that can consistently produce a drug substance and a drug product of the intended quality.
- Diagnostic radiopharmaceuticals use **nuclides with short half-lives** to reduce the adverse effects of patient exposure to radiation.

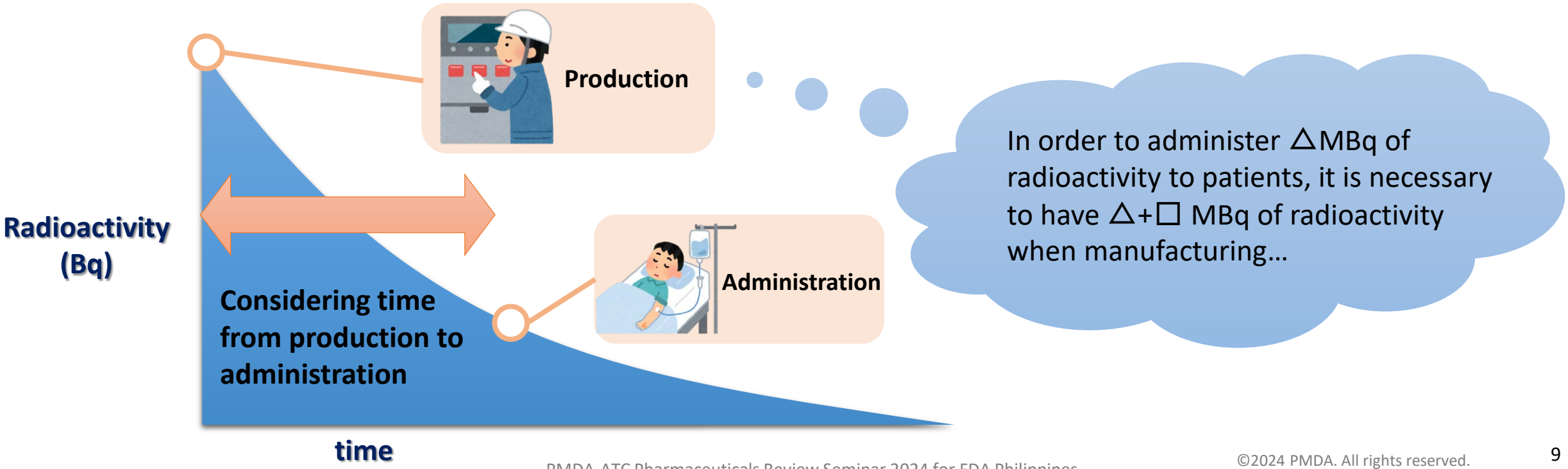
Nuclides	Half-lives($T_{1/2}$)
^{11}C	20.39 m
^{13}N	9.97 m
^{15}O	2.04 m
^{18}F	109.77 m
^{81}Rb	4.58 h
^{99m}Tc	6.02 h
^{123}I	13.22 h
^{99}Mo	2.75 d
^{111}In	2.80 d

Rf : https://www.mhlw.go.jp/file/05-Shingikai-10801000-Iseikyoku-Soumuka/0000191780.pdf

What is needed to ensure the quality of radiopharmaceuticals?

Manufacturing process

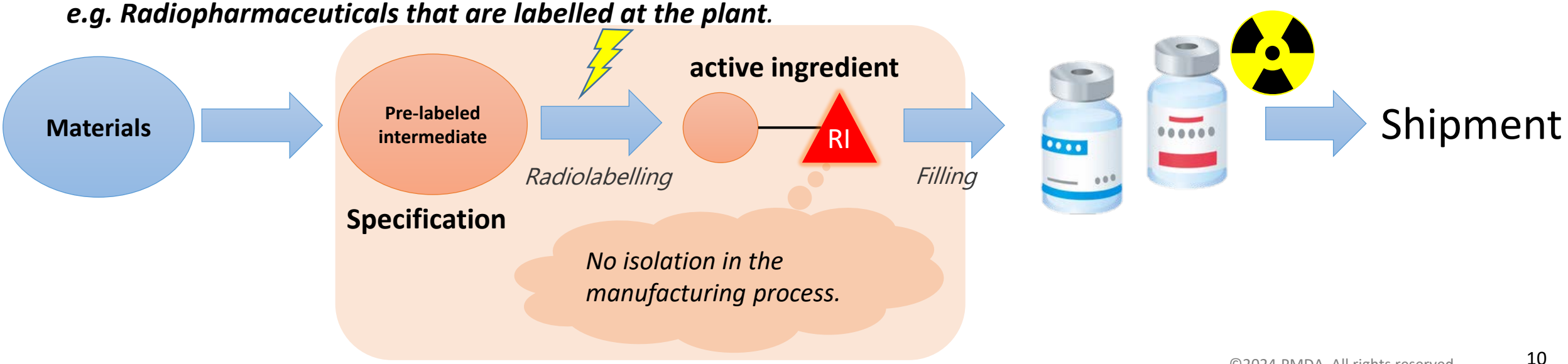
- Diagnostic radiopharmaceuticals must contain **"radioactivity."**
- In the manufacturing process, the radioactivity is adjusted in consideration of the time from production to administration.
  - The immediate post-production radioactivity is higher than at the time of use in medical practice.



Manufacturing process

- In the manufacturing process of a general drug product, specifications are established for the active ingredient(AI).
- The AI in radiopharmaceuticals is a radiolabeled compound that uses short-half-life nuclides, and it is often formulated **without isolation in the manufacturing process.**
  - Specifications are established for pre-labeled intermediates instead of radiolabeled AI.

e.g. Radiopharmaceuticals that are labelled at the plant.



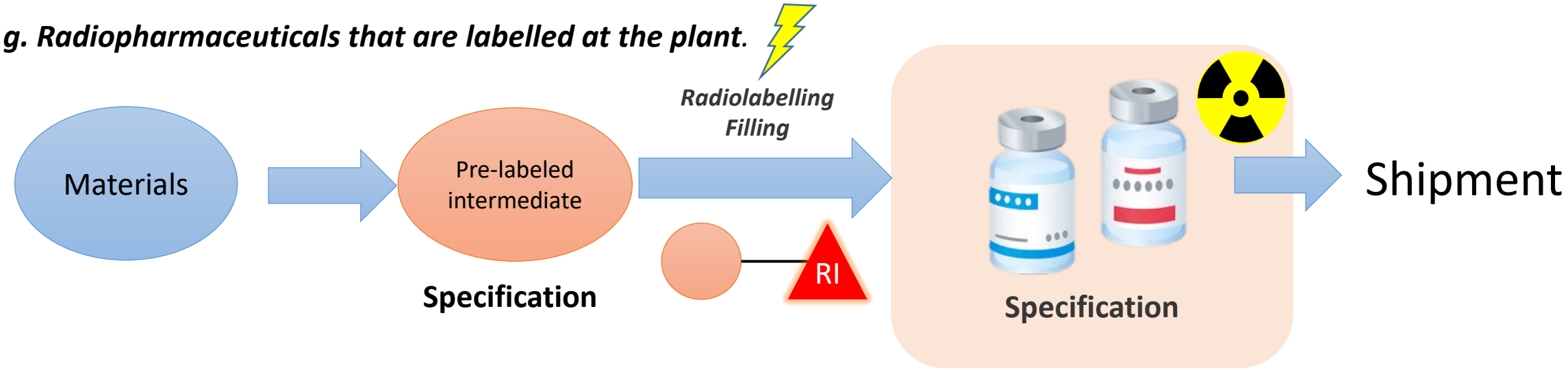
Specifications and Test procedures

- Specifications and test procedures characteristic of the radiopharmaceutical product

I. Content: Specified by radioactivity

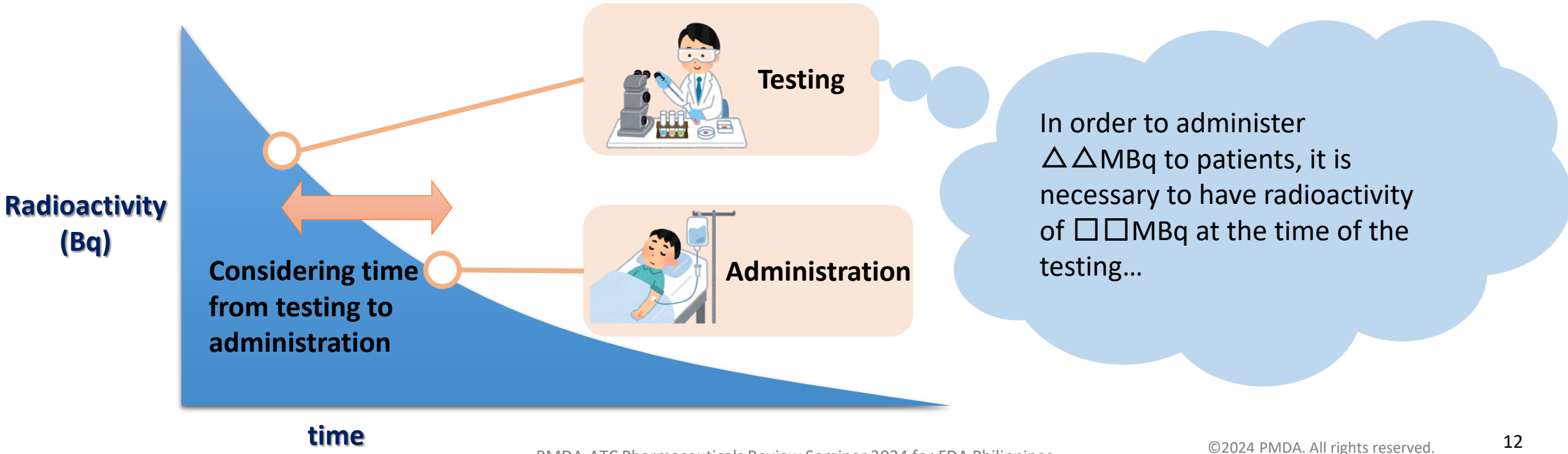
II. Purity: Radiochemical purity and Radionuclidic purity

e.g. Radiopharmaceuticals that are labelled at the plant.



Content (Radioactivity)

- The content of radiopharmaceuticals is specified in Radioactivity (Unit; Bq).
- Because radioactivity decays over time, the radioactivity required at the time of testing is determined, considering the time from testing to administration.

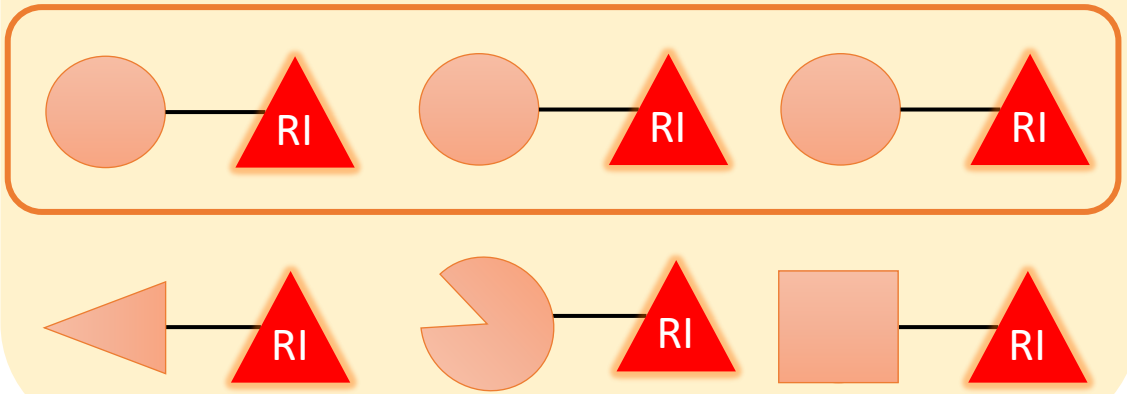


Radiochemical purity and Radionuclidic purity

- The purity tests characteristic of radiopharmaceuticals include “Radiochemical purity” and “Radionuclidic purity”.

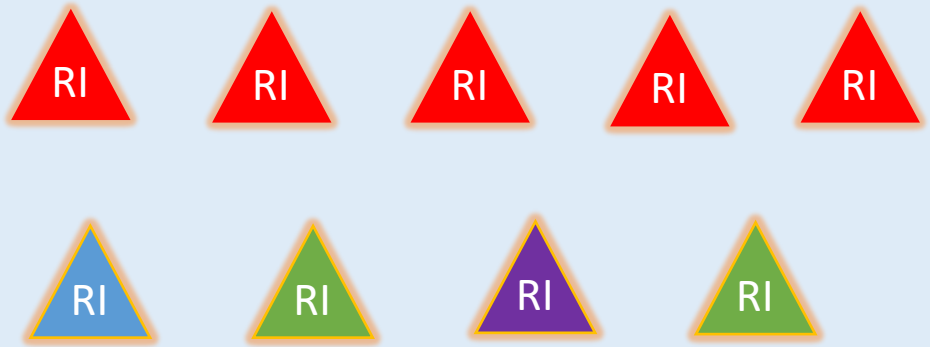
Radiochemical purity

- Ratio of radioactivity of the desired labeled compound to total radioactivity of the nuclide

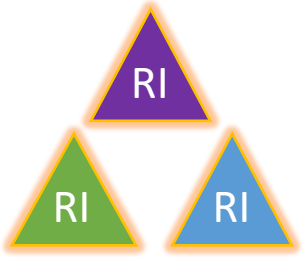


Radionuclidic purity

- Detection/quantification of different nuclides from target nuclides



:The same radionuclide as the Labeled Compound

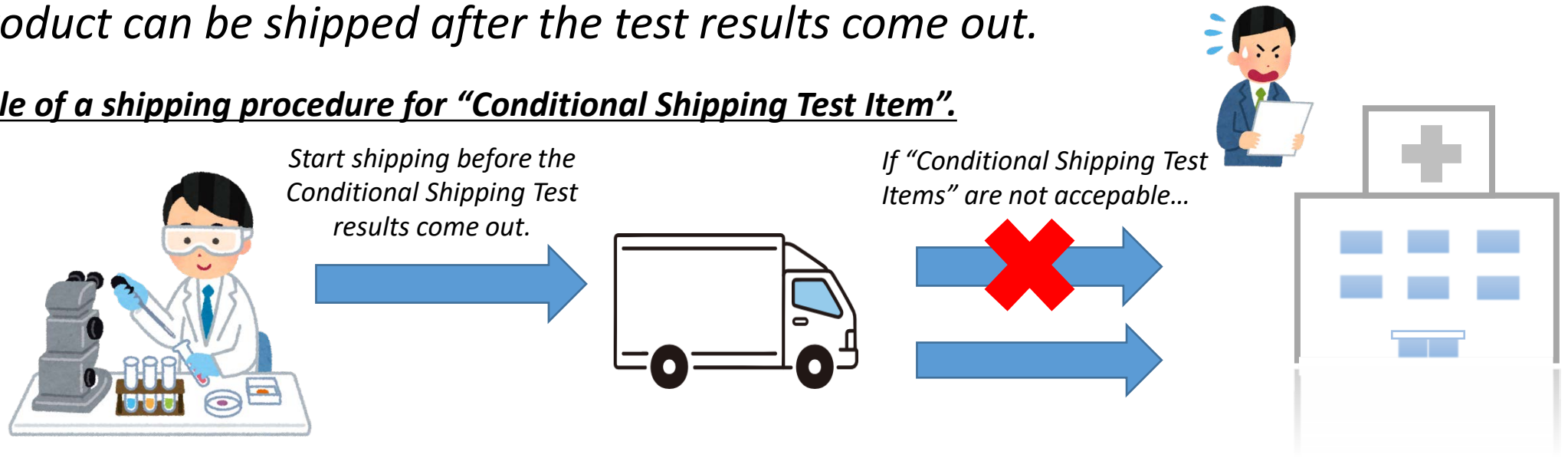


:Radionuclides different from the Labeled Compound

Radiopharmaceutical Shipments in Japan

- **Sterility test**:
  The product can be shipped and administered to the patient before the test results come out.
- **“Conditional Shipping Test Item”**:
  The product can be shipped before the test results come out but cannot be administered to patients before the results come out.
- **Other test items**:
  The product can be shipped after the test results come out.

An example of a shipping procedure for “Conditional Shipping Test Item”.



Others

- Specifications and test procedures for newly approved radiopharmaceuticals are listed in the official standard "Minimum Requirements of Radiopharmaceuticals" in Japan.
- **Shelf life and recommended storage conditions** are established based on the stability studies of radiopharmaceuticals.

Take-Home Message

- **The following control of Radiopharmaceuticals** is carried out in consideration of the attenuation of radioactivity caused by the short half-lives of nuclides.
  1. In manufacturing process, the radioactivity is adjusted to take into account the time to use.
  2. Specification are established with consideration of radiopharmaceutical characteristics.
  3. The shipping system is in place that allows the radiopharmaceuticals to be delivered to medical institutions in a short time.

Thank you.

PMDA is pleased to share our knowledge and experience.