

The use of existing knowledge in pediatric drug development

- Pediatric extrapolation
- Utilization of foreign data

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My Self Introduction

<My Current Job>

- Post-marketing safety measures
- Review and consultation of anti-cancer drugs for pediatric cancer
- Leader of the PMDA Pediatric Drugs Working Group
- ICH E11A Expert Working Group: Deputy Topic Leader of the PMDA/MHLW

<My Background>

- Pediatrician
My area of expertise: pediatric oncology and hematopoietic stem cell transplantation
- I have been working at the PMDA since 2010

The use of existing knowledge in pediatric drug development From E11 (R1)

- This knowledge includes:
 - evidence already or concurrently generated in adult and pediatric populations with similar or other relevant diseases or conditions
 - nonclinical data, data about related compounds, disease pathophysiology, consideration of the developmental physiology, and clinical data from the pediatric population or subgroup.

The use of existing knowledge in pediatric drug development From E11 (R1)

- Use of such information may optimize pediatric programs without reducing the standards for pediatric authorization.
- Any uncertainties related to its use must be identified and managed prospectively.
- As data is generated through the drug development cycle, assumptions may need to be revisited to take new information into account, which will continue to inform the strategy and present an opportunity to further address uncertainties.

Pediatric Extrapolation

Definition from E11 (R1)

“Pediatric Extrapolation” is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that **the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.**

Points to consider related to the process of pediatric extrapolation

- Factors which may result in different drug responses:
 - Intrinsic factors (e.g., developmental)
 - Extrinsic factors (e.g., geographic)that could impact on the extrapolation of data from one population to the other.

- Factors that support the assumptions of similarity of disease and similarity of response to therapy between the pediatric and the reference populations:
 - Disease pathogenesis
 - Criteria for disease diagnosis and classification
 - Measures of disease progression
 - Pathophysiological, histopathological, and pathobiological characteristics

Points to consider related to the process of pediatric extrapolation

- A thorough understanding of the differences between pediatric and reference populations relative to :
 - pathophysiology of the disease
 - available biomarkers/endpoints
 - physiology of organ systems (i.e., renal, hepatic, central nervous system, skeletal, and immune systems)
 - clinical context of available therapeutics
 - the mechanism of action of the drug and its pharmacological behavior

As new information is generated, the process of pediatric extrapolation should be reviewed and confirmed.

Similarity of disease and response to therapy

- Support for the assumptions may be derived from
 - existing data about the use of the drug
 - published literature
 - expert panels and consensus documents
 - previous experience with other products in the same therapeutic class
- All data and information gathered can either confirm the extrapolation approach or inform how it might be improved.
- The exercise should identify if there is sufficient data to support pediatric extrapolation, or if additional clinical information is needed.

A new guideline about Pediatric Extrapolation (ICH E11A) is in process of creation

- ❑ A Step2 Draft guideline was released in April 2022 and public consultation was conducted in several countries and regions.
- ❑ A hypothetical case example was also released.
- ❑ Step3 regional consultation was completed in October 2022.

Objectives

- Address and align terminology related to pediatric extrapolation
- Provide information on various approaches that can be utilized to support the use of pediatric extrapolation
- Discuss a systematic approach on the use of pediatric extrapolation
- Discuss study designs, statistical analysis, modeling and simulation analyses and respective methods

ICH E11(A) : Pediatric Extrapolation Guideline

Key Principles

- ✓ Development of a Pediatric Extrapolation Concept
- ✓ Development of a Pediatric Extrapolation Plan
- ✓ Statistical/modeling methods that can be used to support a Pediatric Extrapolation Concept and Plan
- ✓ Discussion of safety considerations in the Pediatric Extrapolation Concept and Plan including the Extrapolation of Safety
- ✓ Discussion of timing of adolescent patient enrollment in the context of a Pediatric Extrapolation Plan

https://database.ich.org/sites/default/files/ICH_E11A_Step_2_Presentation_2022_0404_0.pdf

3 subgroups

{ Similarity of Disease
Modelling & Simulation
Statistics

Japanese Situation

- ✓ In the EU and the US, pharmaceutical companies have to submit the Paediatric Investigation Plan (PIP) (EU) or the Pediatric Study Plan (PSP) (US) to regulatory authorities at an early stage of the drug development for adults.
- ✓ Therefore, foreign information about pediatric drug development can often be gained when pharmaceutical companies start to consider pediatric drug development in Japan.
- ✓ It is sometimes difficult to accumulate evidence on pediatric drug development based only on Japanese children's data.



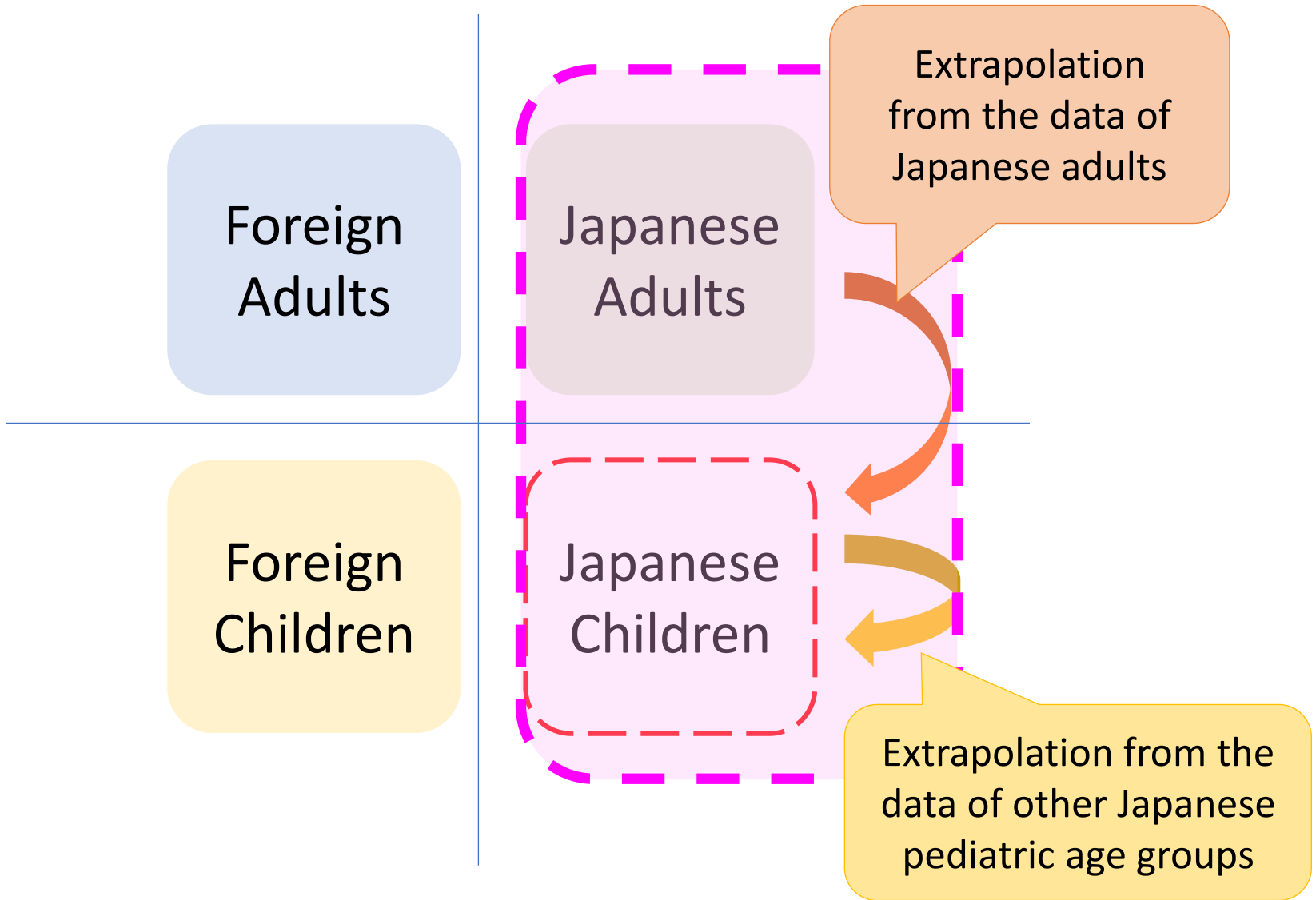
In Japan when Japanese adults' data and foreign children's data are available, both are effectively utilized in pediatric drug development.

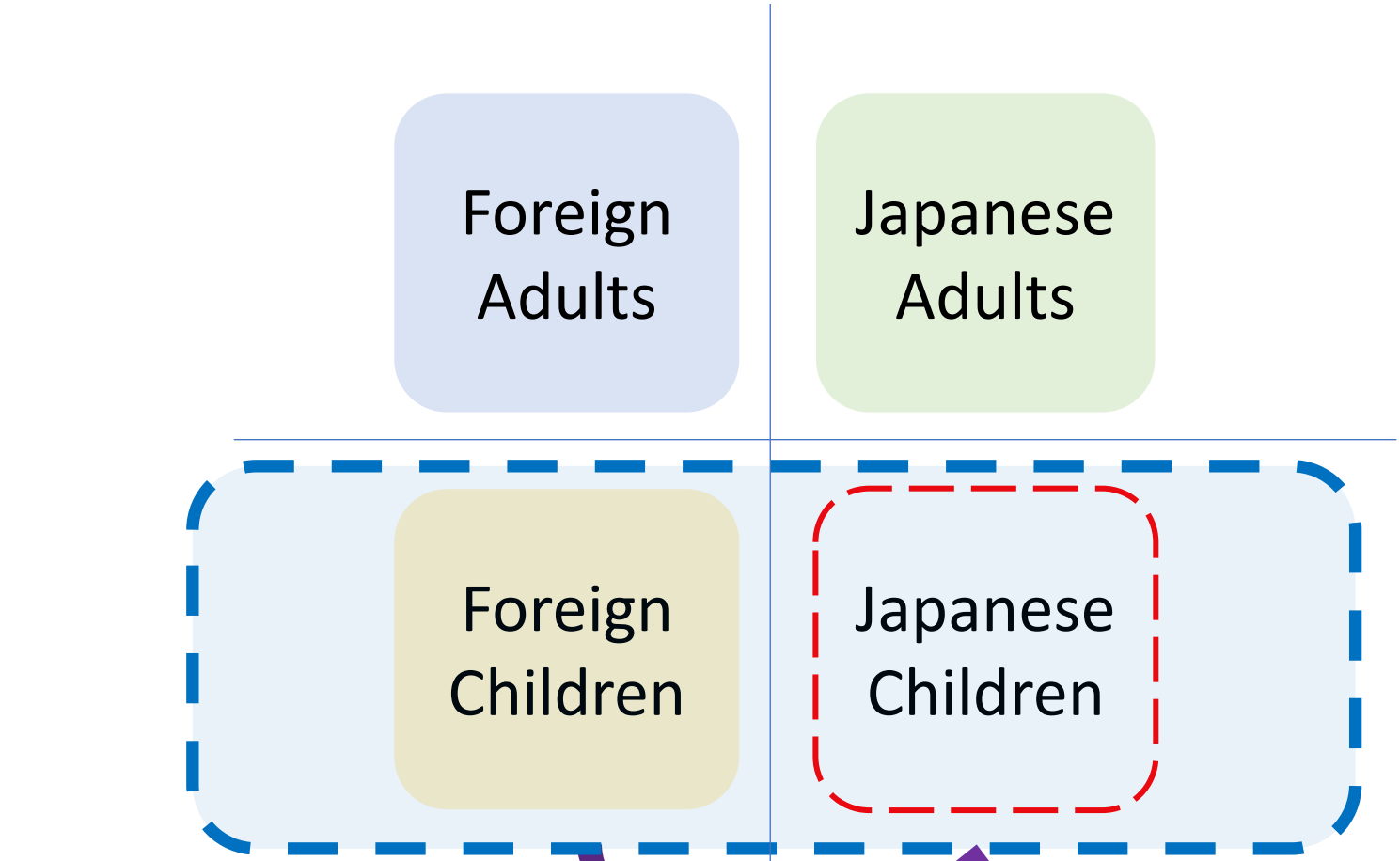
Foreign
Adults

Japanese
Adults

Foreign
Children

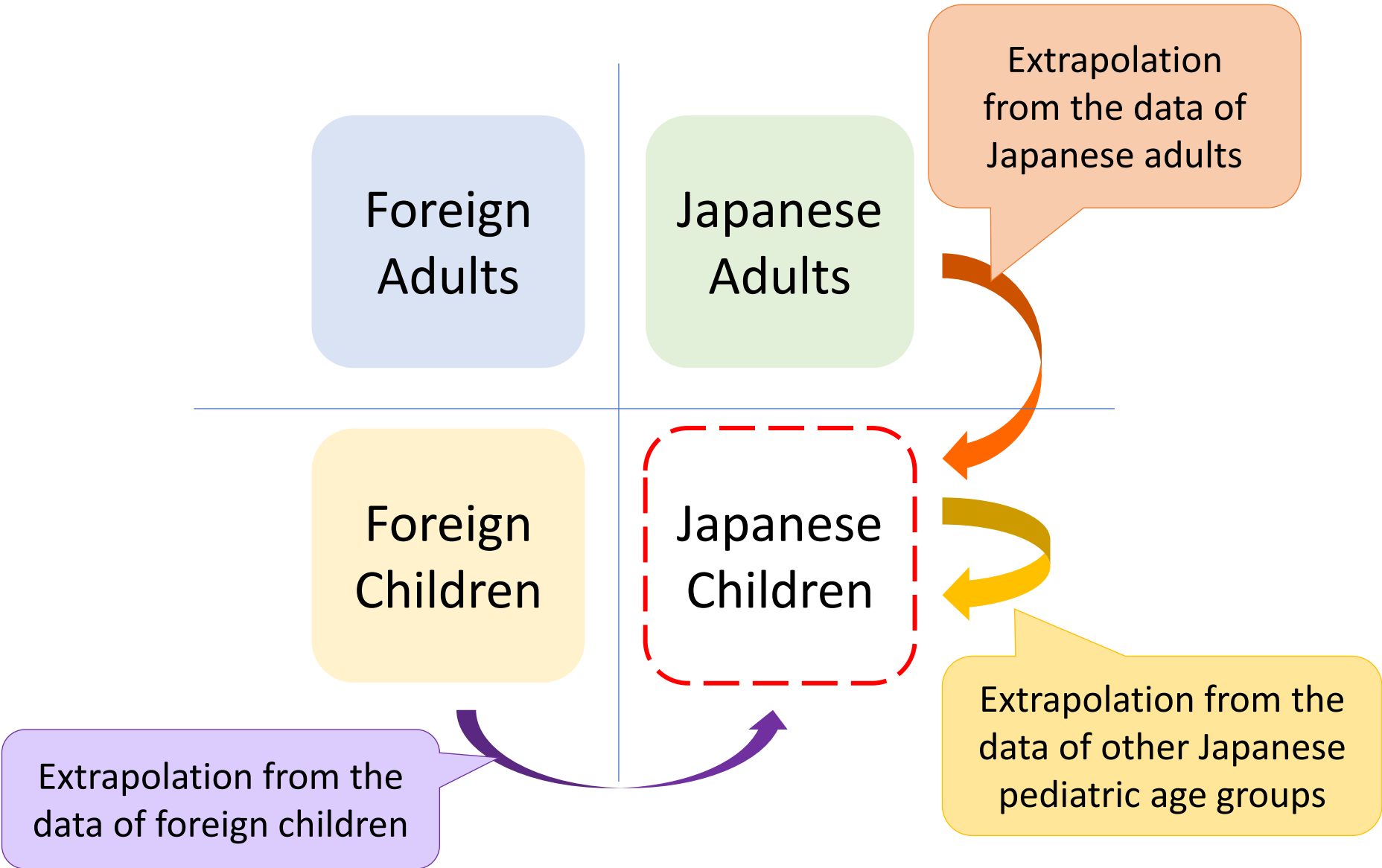
Japanese
Children





Extrapolation from the data of foreign children

This is NOT "Pediatric Extrapolation"



Thank You For Your Attention!