独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

FDA/ISoP Workshop
Optimizing Dosages for Oncology Drug Products: Using Modeling and Simulation to Evaluate Effects of Intrinsic and Extrinsic Factors
October 16, 2023

PMDA Experience with Dosage Selection

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Disclaimer

- The contents of this presentation represent the view of this presenter only, and do not represent the views and/or policies of the PMDA

Objectives

Compare and contrast regulatory framework and current approaches implemented to select dosages in Japan, Europe and USA

Discuss how model-informed approaches is used to select dosages in Japan

Outline of the Presentation

The presenter conducted a survey on clinical data packages, approved dosages, etc. regarding New Molecular Entities (NMEs) for Oncology area approved in Japan from 2020 to 2022.

Compare and contrast regulatory framework and current approaches implemented to select dosages in Japan, Europe and USA

- The status of clinical data packages (assessing MTD and/or DLT, implementation region of pivotal clinical trials) for NDA submission in the Oncology Drugs in Japan.
- The status of consideration of Ethnicity (Japanese vs Non-Japanese and/or Asian vs Non-Asian).

Discuss how model-informed approaches is used to select dosages in Japan

- What kind of quantitative approach was used to select dosages in Japan.

Outline

- Survey on approved Oncology drugs in Japan
  - Clinical data package - Dose-finding study
    - Designed to identify the MTD based on DLT
    - Region that the pivotal clinical study conducted
  - Differences in Dosage and Administration on labels
  - Assessing influence of Ethnic Factor
  - Status of use of model-informed approaches for considerations of dosage and administration
- Conclusion

About the Survey on approved Oncology drugs in Japan

- Targets **24 NMEs** approved in Japan from **April 2020 to May 2022**
  - Excluding drugs containing drug substances of approved drug that is different formulation
- The Survey based on public information

☐ Approval information in Japan
From “医療用医薬品 情報検索” (Japanese only)
https://www.pmda.go.jp/PmdaSearch/iyakuSearch/

☐ Approval information in United States
From Drugs @FDA
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

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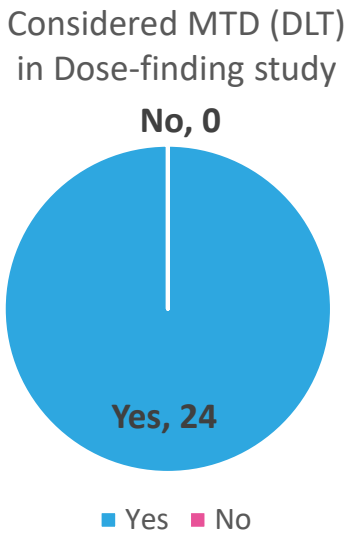
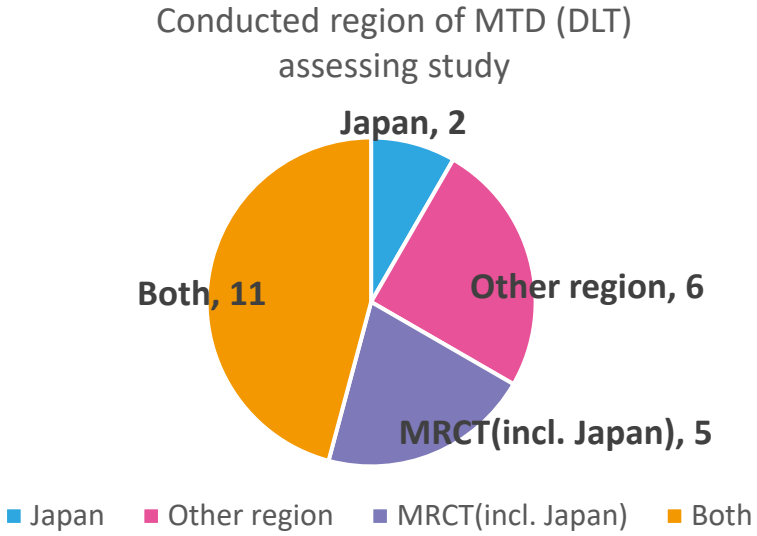
Clinical data package - Dose-finding study

- Designed to identify the MTD based on DLTs
  - Dose-finding trials (e.g., 3 + 3) are designed to identify the maximum tolerated dose (MTD) based on dose-limiting toxicities (DLTs)





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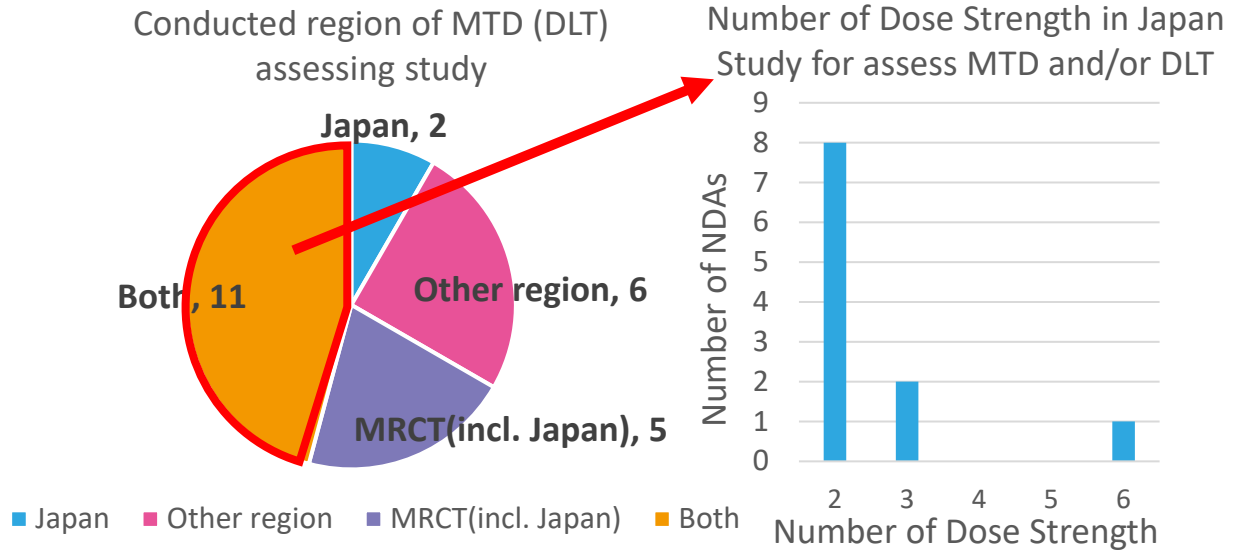

- 10 of the 11 drugs in "Both" were studied in Japan at three or fewer dose strength.
  - ✓ Small-scale trials in Japan confirm tolerability and safety of RP2D confirmed in Other region.
  - ✓ The RP2D was often decided on similar strategy as other region.

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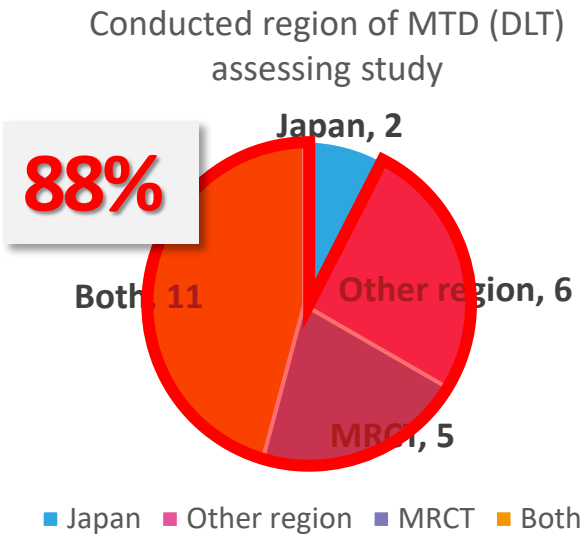
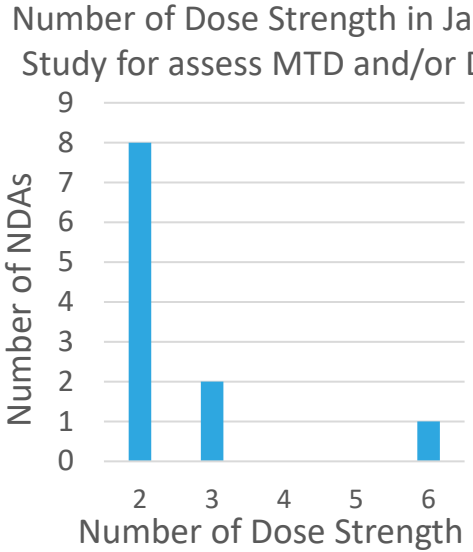
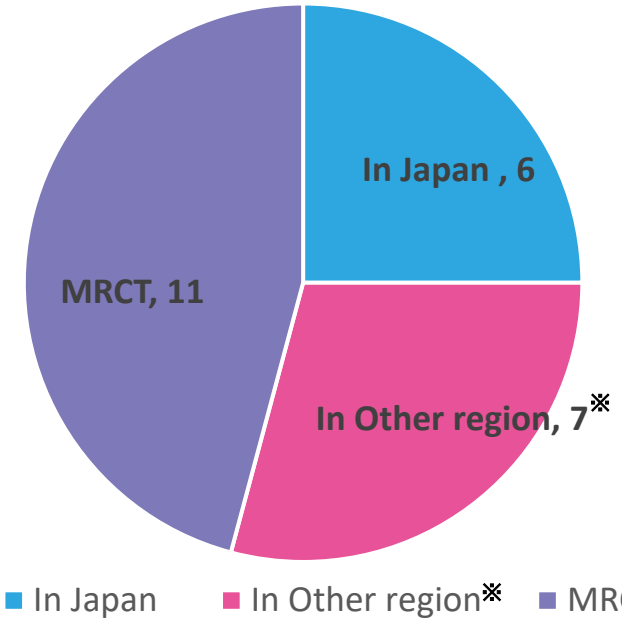




- Of the 24 drugs, 21 drugs include ”Other region”, "MRCT", and "Both" as Japanese studies with 3 or fewer dose strength.
- Therefore, it is thought that approximately 88% of the RP2D for Japan was determined using the similar strategy as the Other region.

Clinical data package - Pivotal study

- Where was the pivotal clinical study conducted?



※: Pivotal studies were conducted in other region and Japan, and study results from other regions were extrapolated to Japan.

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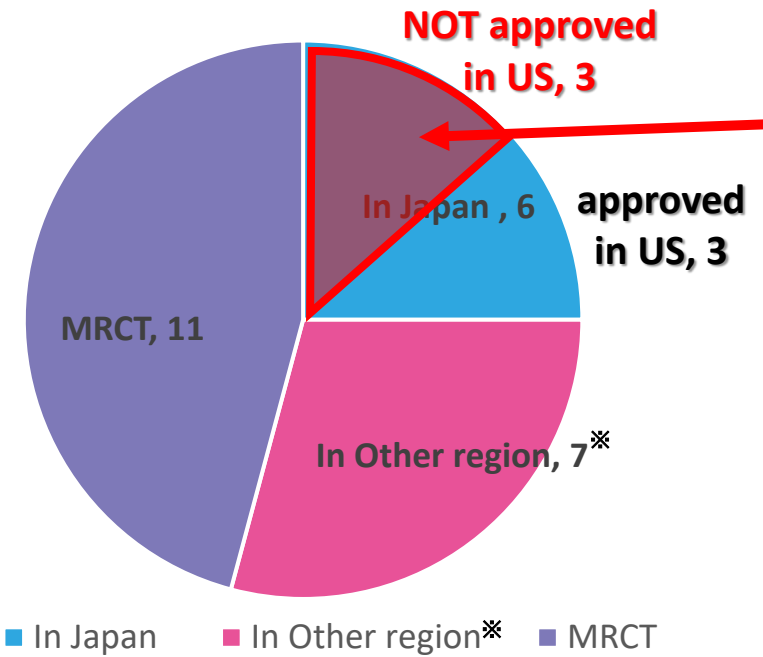

- ☐ 3 of 6 drugs for which pivotal studies were conducted in Japan is not approved in US.

- ☐ 16 of 19 drugs approved in both Japan and US were "MRTC" or "In Other region".
  - ✓ It is likely that the pivotal studies for many drugs in Japan were same as those in the US.

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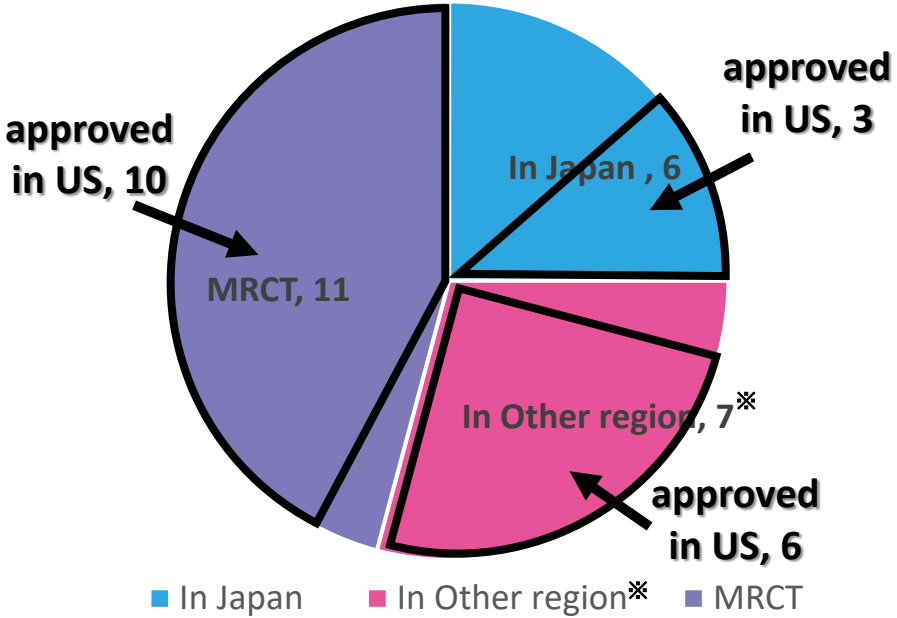

☐ 3 of 6 drugs for which pivotal studies were conducted in Japan is not approved in US.

☐ 16 of 19 (84%) drugs approved in both Japan and US were "MRTC" or "In Other region".

✓ It is likely that the pivotal studies for many drugs in Japan were same as those in the US.

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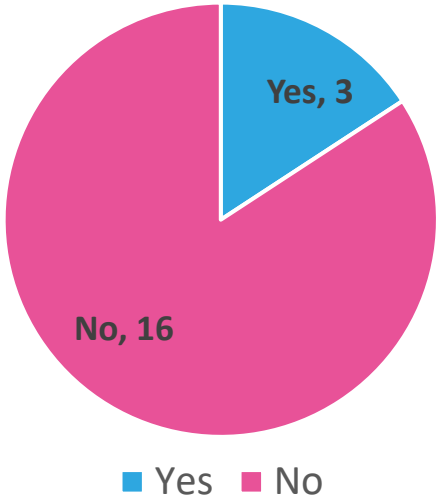
Differences in Dosage and Administration on labels

- Are there any essential differences in Dosage and Administration on labels between Japan and the United States?



《Yes: 3 drugs》
1 drug:
✓ Because Japan conducted a dose finding study based on its own MTD and conducted a pivotal study at a different dose than in other regions.
2 drugs:
✓ Difference in MIDD strategy (due to different dosage and administration from the pivotal study)

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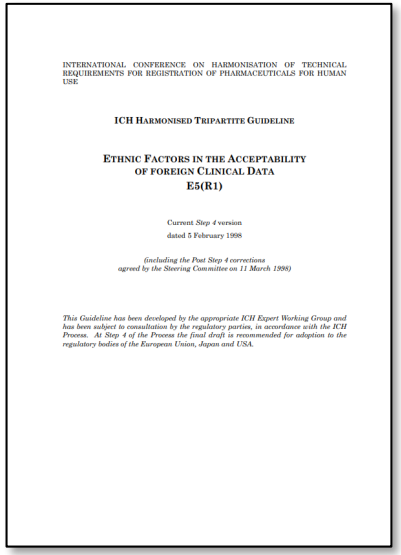
Assessing influence of Ethnic Factor

Ethnic Factors in the Acceptability of Foreign Clinical Data

ICH E5(R1)



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA
E5(R1)

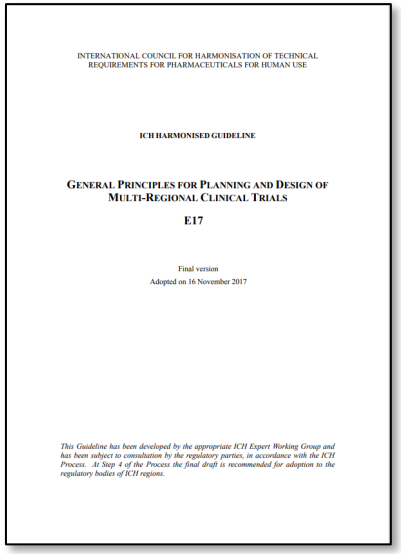
Current *Step 4* version
dated 5 February 1998

(including the Post Step 4 corrections agreed by the Steering Committee on 11 March 1998)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

General Principles for Planning and Design of Multi-Regional Clinical Trials

ICH E17



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR PLANNING AND DESIGN OF MULTI-REGIONAL CLINICAL TRIALS

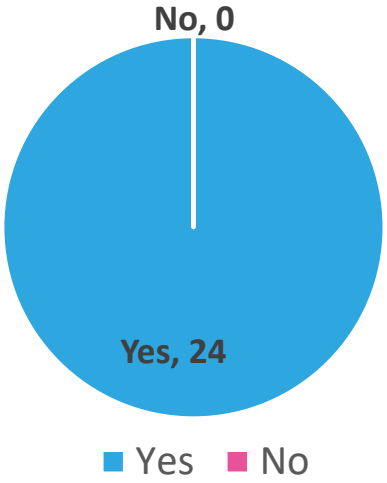
E17

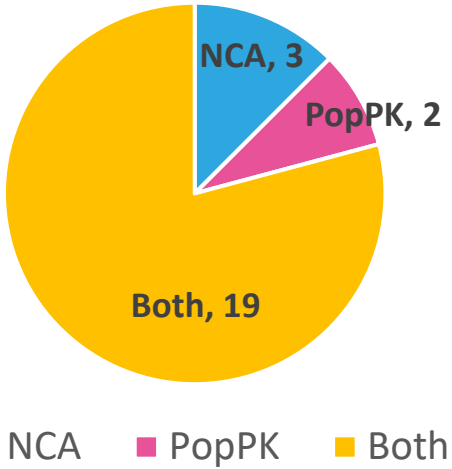
Final version
Adopted on 16 November 2017

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

Assessing influence of Ethnic Factor: PK

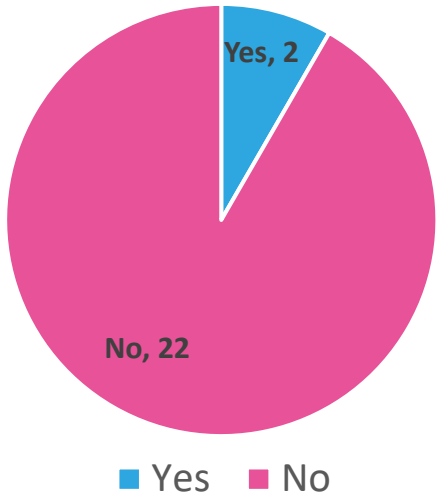
- Has a Japanese and Non-Japanese (Asian and Non-Asian) comparison of PK been considered?
- What technique was used?





Assessing influence of Ethnic Factor: PK/PD or E-R

- Has a Japanese and Non-Japanese (Asian and Non-Asian) comparison of PK/PD or E-R been considered?



- PPK/PD was conducted for the 2 drugs with “Yes”.
- E-R modeling may be difficult to compare Japanese and Non-Japanese from a feasibility perspective, given the number of subjects and the "Response" marker.
- If the use of mechanistic quantitative approaches, e.g. using biomarkers, increases in the future, it may be possible to support the reliability of comparison results of ethnic factor from PD or E-R.

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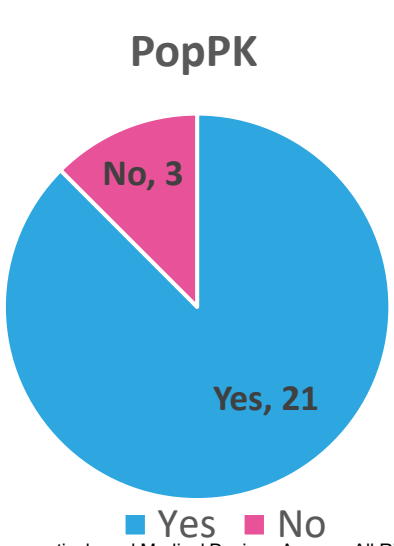
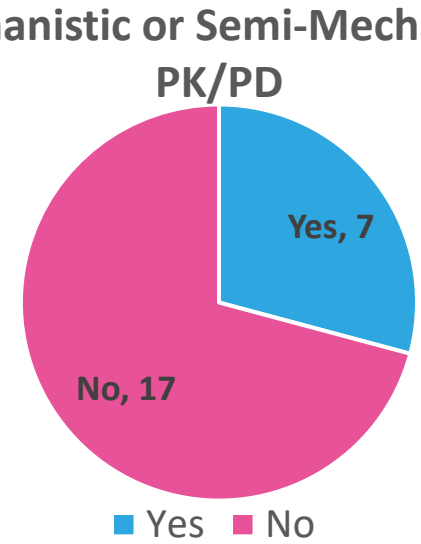
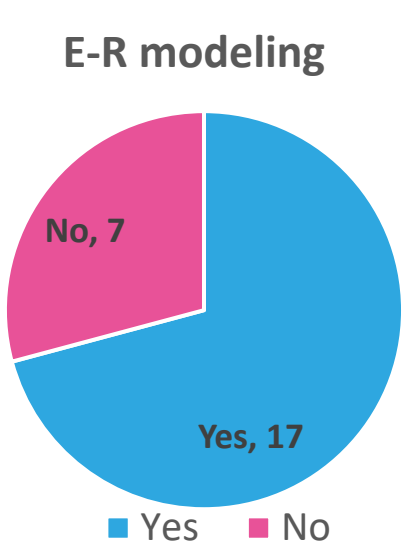
PMDA Experience with Dosage Selection on Oncology Drugs

- Status of use of model-informed approaches for considerations of dosage and administration
  - Includes both the dose finding stage and dose justification after pivotal study.
  - Judged from the explanation in CTD.







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Conclusion

Regulatory framework and current approaches implemented to select dosages in Japan

- MTD based approach was considered for all drugs
- Based on MRCT and extrapolation, RP2D in Japan was considered to be similar to that in US.
- With some exceptions, the Dosage and Administration on the Japanese and US labels were similar.

How model-informed approaches is used to select dosages in Japan

- In assessing ethnic factors, especially in PK, a model-based approach has been almost an indispensable technique.
- Model-based approaches are also essential for dose finding and justification in Japan.

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Thank you !