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Global Collaboration in Cardiovascular Medicine Development

PMDA Perspectives: Global Development Plans, Regional Challenges & Asian Patient Populations

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Global Collaboration: PMDA's Approach

① International Regulatory Cooperation

PMDA actively engages in international harmonization through ICH, ICMRA, and bilateral dialogues with FDA, EMA, and other agencies.

These partnerships align evaluation frameworks and promote consistent global drug development.

② Sharing PMDA's Clinical Evaluation Framework

PMDA proactively shares its clinical evaluation thinking with industry and regulatory authorities worldwide. As one key tool, Early Considerations (ECs) are published in English on PMDA's website and shared with overseas regulatory authorities, enabling globally aligned development before formal submissions.

③ Promoting Global Development in Pediatric & Rare CV Diseases

For rare CV diseases, international MRCT participation is essential. PMDA also prioritizes sharing its evaluation thinking with global stakeholders on pediatric and orphan drug development:

- Clinical evaluation based on the totality of evidence
- Use of real-world data (RWD) as external control

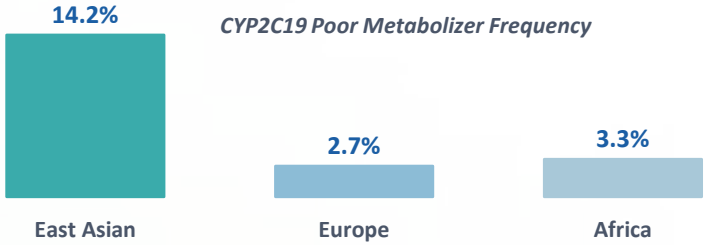
Key Message: Transparent, proactive sharing of PMDA's scientific thinking supports efficient, globally-aligned cardiovascular drug development.

Regional Challenges: Ethnic Factors in Cardiovascular Medicines

Case Study: Mavacamten (oHCM)

CYP2C19 Poor Metabolizers:

~14% in East Asians vs ~3% in Europeans



Result: Japan starting dose 2.5 mg (vs 5 mg in US/EU)

E.g. Japanese stroke centers, such as the National Cerebral and Cardiovascular Center (NCVC), use CYP2C19 metabolizer status to guide antiplatelet therapy selection for stroke prevention.

East Asian Paradox

Anticoagulant/antiplatelet therapy: East Asians show similar/lower ischemic event rates yet higher bleeding risk vs Europeans. Different optimal therapeutic windows apply.

Dosing Differences (Label-Based)

Warfarin

Japan label: Initial 1–5 mg/day; adjust to target PT-INR
US label: Initial 2–5 mg/day; adjust to target INR
(Genetic factors — CYP2C9, VKORC1 — affect dose requirements)

Prasugrel

Japan label: Maintenance 3.75 mg/day
US label: Maintenance 10 mg/day
(Driven by PK, PD, and body weight differences)

Intrinsic & extrinsic ethnic factors must be assessed from early development to ensure appropriate dosing for Asian patients.

PMDA Highlights: Early Consideration on Cardiovascular Medicines

Three Early Considerations issued to date — providing transparent, science-based guidance to facilitate global and regional cardiovascular drug development.

PAH

Pulmonary Arterial Hypertension

Development strategy guidance for PAH therapies.

- **Early entry into international MRCTs recommended**
- **M/M composite endpoint preferred**
- **Parallel pediatric development plans encouraged**
- **PVR or 6MWD as alternatives when M/M not feasible**

ATTR-CM

Transthyretin Amyloid Cardiomyopathy

Clinical endpoints and global development alignment.

- **All-cause mortality or composite (mortality + CV hospitalization) as primary endpoint**
- **Evolving disease landscape reflected in design**
- **Each component of the composite should individually support efficacy**
- **Exercise tolerance/QoL alone not recommended**

HCM

Hypertrophic Cardiomyopathy

Guidance on clinical development for HCM therapies.

- **Separate trials for oHCM and nHCM recommended**
- **Peak VO_2 recommended as primary endpoint**
- **KCCQ-CSS as key secondary endpoint**

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PMDA Key Messages

01 Global Development is Essential

Especially for rare cardiovascular diseases (PAH, ATTR-CM, HCM). PMDA supports MRCT strategies and early regulatory alignment across regions.

02 Asian Patients Need Specific Attention

Ethnic factors — CYP2C19 PMs (~14% in East Asians), body weight, East Asian Paradox — significantly impact dosing and safety. These must be addressed from early development.

03 PMDA's Early Consideration

Three ECs issued for PAH, ATTR-CM, and HCM — providing transparent, science-based guidance to facilitate global and regional cardiovascular drug development.

Strengthening Japan–EU Collaboration

PMDA looks forward to deepening its partnership with EMA and European stakeholders in cardiovascular drug development. Through joint scientific discussions, aligned regulatory guidance, and shared commitment to patient access, we aim to build a stronger Japan–EU collaborative framework for the benefit of patients worldwide.

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Thank you for your attention!