Navigating Clinical Trial into Japan

Regulatory Circumstance in Japan

PMDA approval time

- Japan is now 2nd fastest for NDA approval time amongst all major regulatory agencies
- Average approval now down to ~10 months (twice as fast as 2010)

PMDA: Pharmaceuticals and Medical Devices Agency
NDA: New Drug Application
Source: Centre for Innovation in Regulatory Science (CIRS) , 2020, R&D Briefing 77

Trend for Japan to join multi-regional clinical trials (MRCT)

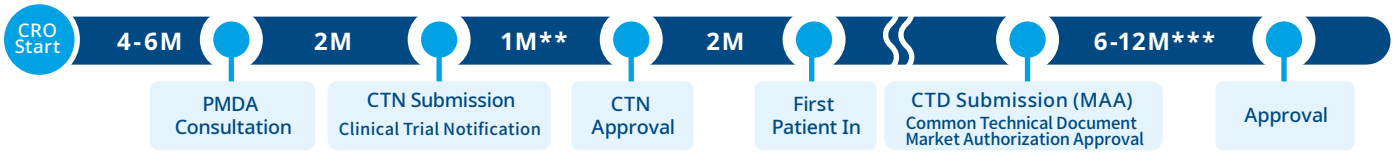
Being more efficient, cheaper and faster for getting approval,
>50% of clinical trials in Japan are MRCT compared to 15% 10 years ago.

Typical clinical development strategy

Phase I | **Global Phase II** and/or **Global Phase III**

- ☑ Recommend including Japanese subjects as part of a global development plan. Japanese patients would be enrolled in a global phase II and/or phase III studies after Japanese phase I trial.
- ☑ Local development plan also possible but recommended to include Japan in a multi-regional development plan
- ☑ **Recently PMDA sometimes accepts Japanese patients directly enrolling in Phase III global study without Japanese Phase I data for diseases with high medical unmet needs**

*Standard Timeline from CRO start to Market in Japan



*It is depending on study design/situation/**30 days after initial notification, 14 days after subsequent notifications
***The review period is depending on review system

Accelerated Review System

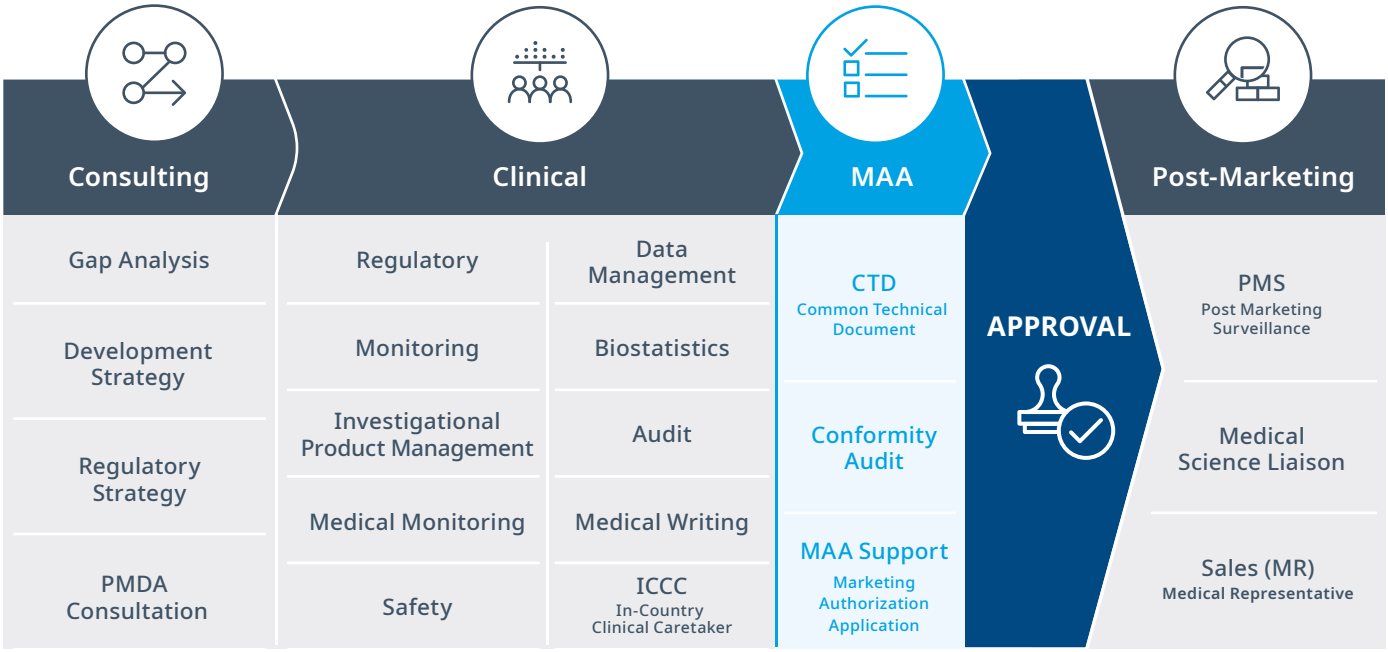
Japanese Regulatory Agency, PMDA, strives to speed up the review process by setting target review times

Type	Designation Criteria	
Basic Review		Clinical Trial (Exploratory) → Clinical Trial (Confirmatory) → MAA → Review **12M** → MA → Re-examination Period: (Exclusivity Period) **8years**
Priority Review	Severe Disease	Clinical Trial (Exploratory) → Clinical Trial (Confirmatory) → MAA → Review **9M** → MA → Re-examination Period: (Exclusivity Period) **8-10years**
Products Targeting Orphan Diseases	Orphan Disease : No. of Pts < 50,000	Clinical Trial (Exploratory) → Clinical Trial (Confirmatory) → MAA → Review **9M** → MA → Re-examination Period: (Exclusivity Period) **10years**
Conditional Early Approval	Insufficient feasibility to do confirmatory clinical trial	Clinical Trial (Exploratory) → MAA → Review **9M** → MA → Re-examination Period: (Exclusivity Period) **8-10years**; Post approval survey based on conditions for approval
Sakigake Forerunner Designation	• Innovative products • Serious disease • World's first development & NDA in Japan	Clinical Trial (Exploratory) → Clinical Trial (Confirmatory) → MAA → Review **6M** → MA → Re-examination Period: (Exclusivity Period) **8-10years**; Priority Consultation; Prior assessment; Support by Concierge

MAA: Marketing Authorization Application
MA: Marketing Authorization
Source: https://www.pmda.go.jp/files/000226208.pdf

IQVIA Japan's End to End Support

IQVIA's experienced regulatory expertise can bring your asset successfully from Molecule to Market



IQVIA Japan's experienced consultants to lead your negotiation with PMDA successfully

Regulatory Consultation Experience in IQVIA Japan

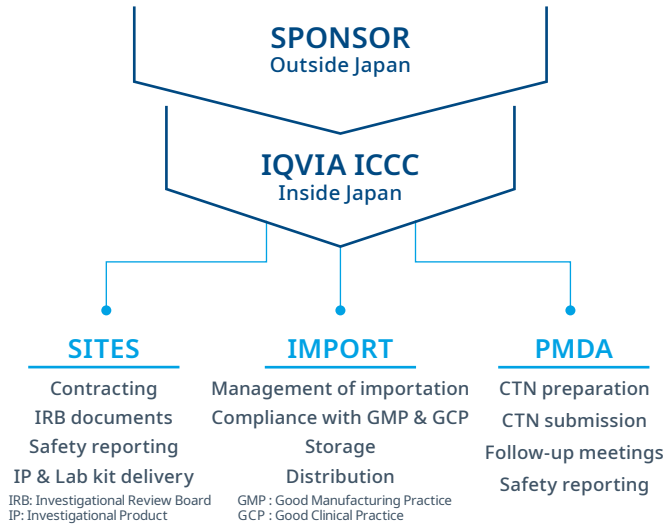
PMDA Consultation	Gap Analysis	Others*
>50	>20	>50

*Others including Strategy development, Clinical development plan, NDA related activities, Orphan Drug Designation, KOL management, and, etc.

ICCC Experience >100 protocols

IQVIA Japan successfully passed all inspections and contributed to getting Sponsor products approved for marketing

Streamlined ICCC Process



It is mandatory for a pharma company based out of Japan intending to perform clinical studies in Japan, to appoint an eligible partner (ICCC, In-Country Clinical Caretaker) as their representative to sponsor that clinical trial, to make sure the procedures are followed as per regulations.

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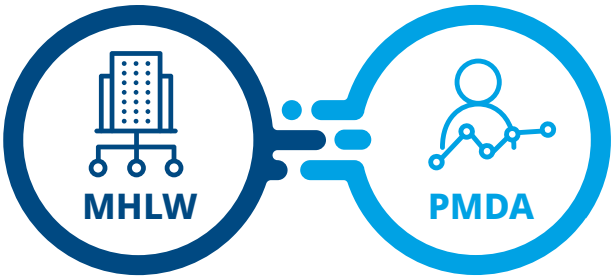
PMDA Consultation

What is PMDA Consultation?

Regulatory Authority



Final Authorization of applications

MHLW: Ministry of Health Labour and Welfare

- Approval Review
- GCP, GMP Inspection
- Consultation on Clinical Trials

Source: https://www.pmda.go.jp/files/000226208.pdf

The Purpose of PMDA Consultation

In clinical trial consultations for new products, PMDA checks whether a proposed clinical trial properly complies with the requirements for regulatory submission, taking into consideration the ethical and scientific aspects and reliability of the clinical trial as well as the safety of trial subjects, and also gives advice to facilitate the improvement of the clinical trial.

Source: https://www.pmda.go.jp/english/review-services/consultations/0002.html

Pre-Meeting and Official PMDA Consultation

Pre-meeting with PMDA → **PMDA Consultation**

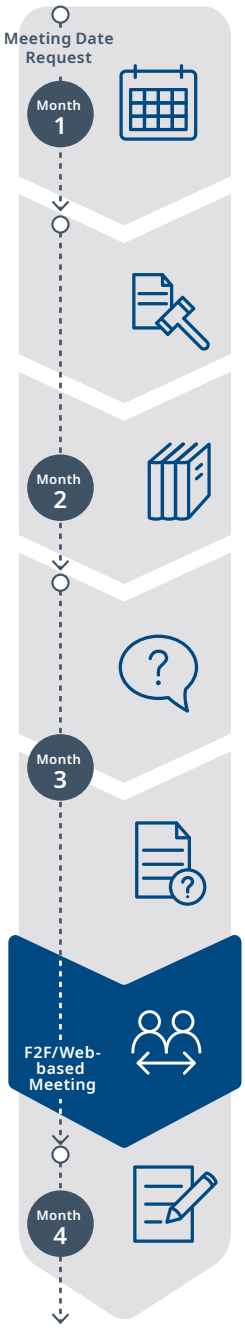
Types of PMDA consultations

For example:

- Safety (non-clinical)
- Quality (CMC)
- Pre-Phase 1
- Pre-early Phase 2
- Pre-late Phase 2
- End of Phase 2
- Pre-NDA
- Post-marketing clinical studies plans, and etc.

Source:https://www.pmda.go.jp/files/000157641.pdf

PMDA Consultation Standard Procedure



Meeting Date request

- 1st working day - 2 months before the meeting
- Meeting date notification (within 5 working days from the request)

Pre-meeting

Official Application & Consultation Fee

- Within 15 working days from the meeting date notifications

Document Submission

- 5 – 6W before the meeting
- BD, IB, Protocol, etc.
- Electrically submission

Questions & Answers

- Questions from PMDA (3 – 4W before the meeting)
- Answers to PMDA within 1W

PMDA Opinion

- 1-2W before the meeting
- Response to opinion (within 3 – 5 days)

F2F/Web-based Meeting

- 2 hours meeting
- Max.15 from applicant
- 20 min presentation

Meeting Minutes

- ~2W: Draft Minutes
- Review / comments
- ~4W: Final Minutes

Source: https://www.pmda.go.jp/files/000157641.pdf

PMDA Consultation Package

Briefing Document (40 – 70 pages)

- Introduction
- Development History / Background
  - Regarding target indication / disease, standard treatments, unmet medical needs, etc.
- Quality Development
- Nonclinical Development
- Clinical Development
  - Planned Clinical Development Plan in Japan
- Consultation Questions and Company Position
- References

Other Documents

- Investigator's Brochure
- Clinical Trial Protocol (or Protocol Synopsis)
- Meeting minutes with other authorities
- References Cited

And

- Informed Consent Document (if available)
- Summary Table of Nonclinical Studies
- Summary Table of Clinical Trials (completed, ongoing and planned)

Source: https://www.pmda.go.jp/files/000157641.pdf

IQVIA

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