



Japanese submission/approval from programming perspective

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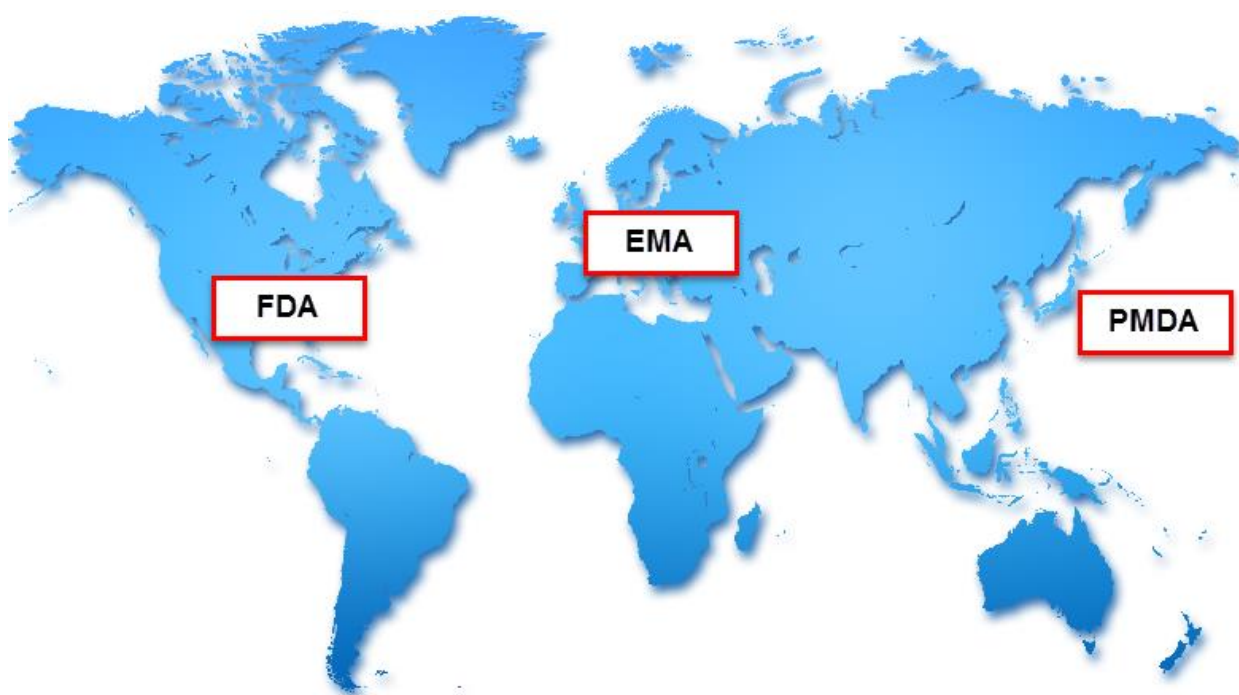
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Agenda

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2. Overview of submission and review/approval processes
 - Japan new drug application
 - Major differences
 - Global study and simultaneous submission
 - Application review
3. Programming tips
4. Other Japan-specific programming requirements
5. Conclusion

1. Introduction

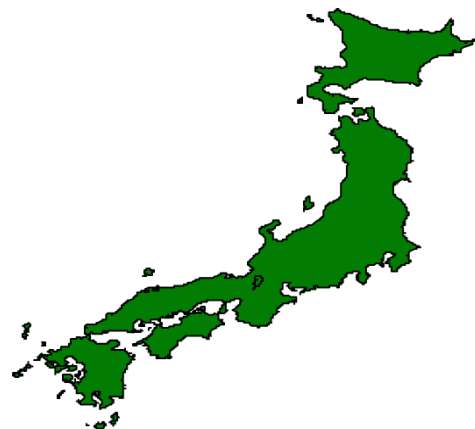
Three major markets and health authorities



1. Introduction

- The goal is to help programmers to understand:

1. Japan-specific submission requirement of programming
2. Review/approval process in Japan
3. Advantages of early planning



- Japan is the 2nd largest market as a single country.

- Population: 125 million
- Capital: Tokyo (Metro area 37 million)
- One of the most aging country
- PMDA (Pharmaceuticals and Medical Devices Agency)

1. Introduction

■ The link of “Medical package insert” from PMDA site:

http://www.info.pmda.go.jp/downfiles/ph/PDF/300242_4291023F1020_1_15.pdf

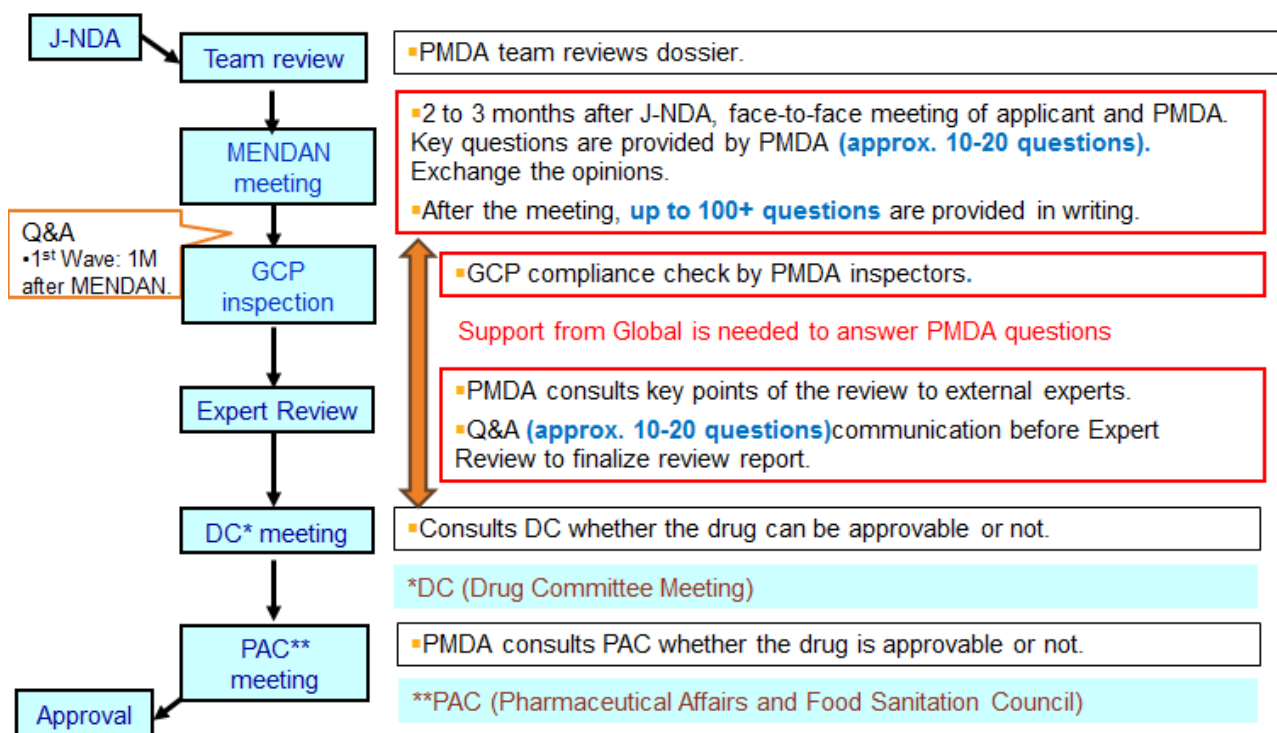
エストロゲン受容体 (estrogen receptor、ER) 陽性かつ HER2陰性でレトロゾール又はアナストロゾールに抵抗性の局所進行性又は転移性の閉経後乳癌患者を対象とした第Ⅲ相国際共同臨床試験において、本剤投与482例（日本人71例を含む）中、副作用は465例（96.5%）にみられた。主な副作用は、口内炎（口腔内潰瘍等を含む）309例（64.1%）、発疹163例（33.8%）、疲労115例（23.9%）、食欲減退96例（19.9%）、下痢94例（19.5%）、味覚異常92例（19.1%）、悪心85例（17.6%）、感染症77例（16.0%）、肺臓炎72例（14.9%）、体重減少66例（13.7%）、貧血55例（11.4%）、鼻出血54例（11.2%）、高血糖51例（10.6%）、血小板減少症50例（10.4%）、そう痒症48例（10.0%）等であった。

その他の副作用

	頻度不明	10%以上	1%～10%未満	1%未満
血液・リンパ	－	－	リンパ球減少症	－
代謝・栄養	血中カリウム増加	食欲減退、高コレステロール血症	低リン酸血症、脱水、低カリウム血症、高トリグリセリド血症、高脂血症	鉄欠乏、低血糖症、低比重リポ蛋白（LDL）増加
精神・神経系	激越	味覚異常、頭痛	不眠症	味覚消失、攻撃性、痙攣
眼	－	－	眼瞼浮腫	結膜炎
心血管系	－	－	高血圧	うっ血性心不全
呼吸器	－	咳嗽、鼻出血	呼吸困難	喀血、咽頭の炎症

2. Overview of submission and review/approval processes in Japan

■ Japan new drug application



PMDA : Pharmaceuticals and Medical Devices Agency

2. Overview of submission and review/approval processes in Japan

■ Major differences of Japanese and EMA/FDA submissions

1. Sub analyses of Japanese patients of key efficacy/safety results
2. Japan CTD
3. Pooling safety analyses for medical package insert can be different from SCS global pooling.

Note: CDISC format is not mandated until 2016.

CTD: (Common Technical Document)

SCS: (summary of clinical safety)

2. Overview of submission and review/approval processes in Japan

■ 1. Sub analyses of Japanese patients:

- ☐ The **most important point for programmers.**
- ☐ Sub analyses of JP(Japanese) patients of key safety/efficacy TFs (tables/figures) are always requested by PMDA.
- ☐ The TFs of JP patients can be same as the shells in global SAP.
- ☐ If number of JP patients is small (15-20 pts), only few AE summary and key efficacy may be enough.
- ☐ **Strongly recommend to use same SAS pgms/macros** to create Japanese TFs to keep consistency.

SAP: Statistical Analysis Plan

2. Overview of submission and review/approval processes in Japan

■ 2. Japan CTD (Common Technical Document)

- ☐ The main difference is that for the key results, **Japanese data are summarized and discussed.**
- ☐ Results for all patients are also summarized.
- ☐ The contents and structure are similar to the global CTD.
- ☐ If results of primary/key secondary are inconsistent between the whole and JP populations, the inconsistencies will be discussed.
- ☐ Key messages/conclusion of J-CTD should be aligned with the global CTD.

2. Overview of submission and review/approval processes in Japan

■ 3. Pooling safety analyses for medical package insert:

The following requirements for filing and update can be requested before approval.

- ☐ Summary tables of AE with suspected relationship to study drug.
- ☐ Specific pooling (it's **not always the same** as global SCS pooling)
- ☐ Pooling of multiple studies of **all indications** in the same compound

Snapshot of the Medical package insert obtained from PMDA web site is in introduction slide.

2. Overview of submission and review/approval processes in Japan

- Global study and simultaneous submission:
 - Pivotal ph III submission, including JP patients
 - ❑ The requirement for Japanese submission to be included in global SAP or separate SAP.
 - ❑ J-CTD summarize results of JP data in addition to results of all patients.
 - ❑ Global CSR will be included in J-CTD. No Japan CSR is needed.
 - Simultaneous submission:
 - ❑ Japan/PMDA try to shorten drug lag.
- If SAP incorporates Japan requirements, and keys results of JP patients are available at same time as global
- >> Simultaneous submission is possible to reduce drug lag.**

2. Overview of submission and review/approval processes in Japan

- Application review
 - Review period after filing:
 1. 12 months for standard review.
 2. 9 months for “Orphan Drug Designation”.
- Key milestones for programmers
 1. **PMDA questions** after face to face meeting (sponsor/ PMDA).
 2. GCP compliance inspection by PMDA.
 3. **PMDA questions** before “Expert review”/”Drug committee” meeting.

3. Programing tips

☐ Same pgms vs. additional pgms for JP sub analyses

Same pgms/macros: Recommended

- Always consistent between all/JP
- Early set up is recommended
- Efficient

Additional pgms/macros: Not Recommended

- Programming change for both all/JP pgms
- Difficult to keep consistency and manage many pgms
- Not efficient

QC pgms: Recommended to use same QC pgms for same reasons.

☐ Working with programmers in Japan

- If global programming team has not enough experience of JP submission, better have a JP programmer in a team
- Coordinate JP submission in parallel with supporting global team

4. Other Japan-specific programming requirements

- ☐ “Guide for appropriate use of medication”
 - Additional safety analyses might be needed depends on safety profile of the drug.
- ☐ J-RMP (Japan Risk Management Plan)
 - Sub analysis of Japanese patients is not required.
 - Risks global defines and PMDA defines can be different.
- ☐ Validation level of listings
 - Quality needs to be good to facilitate proper review and approval.
- ☐ Analyses for PMDA questions
 - Based on review schedule, we can secure resources for questions
 - Similar to EMA/FDA process.
 - Few examples of PMDA questions in backup slide.

5. Conclusions



Key messages:

- ☐ Understanding the specificities of a Japanese submission is key.
- ☐ Sub analyses of JP patients is core of the requirements.
- ☐ **Early** planning of SAP and preparation of SAS pgms/macros to incorporate Japanese requirements is important.
- ☐ **Highly recommended to use same SAS pgms/macros** to produce TFs of JP patients.
- ☐ Overall submission and review/approval processes are similar to those of FDA and EMA.

Questions?



Thank you for your attention!

Any questions?

Backup

■ Acronyms

CDISC	Clinical Data Interchange Standards Consortium
CSR	Clinical Study Report
CTD	Common Technical Document
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
JP	Japan/Japanese
J-CTD	Japan Common Technical Document
J-NDA	Japan New Drug Application
J-RMP	Japan Risk Management Plan
NDA	New Drug Application
PMDA	Pharmaceuticals and Medical Devices Agency
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
US	United States of America

Backup



❑ Strongly recommend to use same SAS pgms/macros to create Japanese tables/figures to keep consistency.

Note: Statistical adjustments may be required for several efficacy analyses, e.g. stratified test vs. unstratified test, depending on the number of Japanese patients.

If number of JP patients is small, unstratified method is often used.

Backup



■ Other analyses (more details)

- ☐ Safety analyses for “Guide for appropriate use of medication”.
 - This document will be used by doctors.
- ☐ Validation level of listings
 - The CSR listings will be checked by PMDA during GCP inspection.
 - Data listed up to the cut-off date will be reviewed by PMDA.
 - Listings to be sorted by country and site for reviewers.
 - **PMDA plans to mandate CDISC format along with SDTM in 2016.**

Backup

■ Other analyses (cont.)

□ Analyses for PMDA questions

- Examples of questions which EMA/FDA normally don't request
 - Ethnic sensitivity related questions. e.g. summary of key safety data of Japanese/non-Japanese patients
 - Detailed questions about listings.
 - AE tables by time period. The below table is from J-CTD format guide line from PMDA web site:

<http://www.pmda.go.jp/operations/notice/2011/file/jimu20110117.pdf>

発現時期	合計	本剤				
		～3ヵ月	4ヵ月～6ヵ月	7ヵ月～9ヵ月	10～12ヵ月	13ヵ月～
評価例数	100例	100例	92例	85例	80例	76例
全有害事象	68 (6.8%)	13	○	○	○	○
死亡例数	○ (○%)	○	○	○	○	○
死亡以外の 重篤な有害 事象例数	○ (○%)	○	○	○	○	○
中止例数	○ (○%)	○	○	○	○	○
鼻咽頭炎	○ (○%)	○	○	○	○	○
頭痛	○ (○%)	○	○	○	○	○
.....						
.....						