Incentives and Regulatory Considerations in Orphan Drug/Medical Device Development - Situation in Japan -

MHLW/PMDA, Japan

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User fee in the following presentation is the fee in Mar 2014.

1. Incentives

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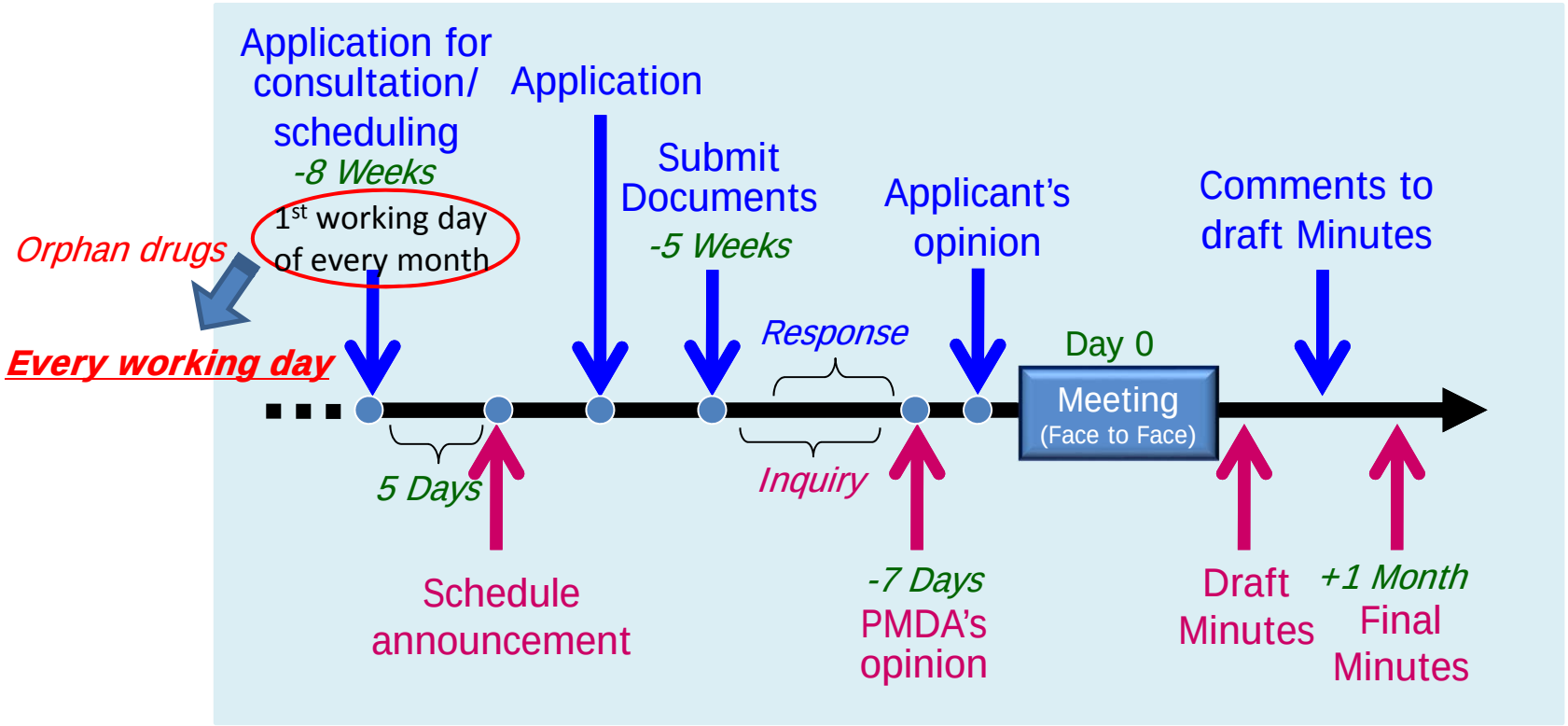
- There are five major incentives for development of orphan drugs/medical devices in Japan.
  - (1) Subsidy payment
  - (2) Consultation
  - (3) Preferential tax treatment
  - (4) Priority review
  - (5) Extension of re-examination period

1.(1) Subsidy payment

- Orphan drug/medical device applicants can receive subsidies through the National Institute of Biomedical Innovation (NIBIO) to reduce the financial burden of product development.
- The total budget for financial year 2012 was 880 million yen (5.1 million GBP/6.3 million EUR/8.6 million USD).

1.(2) Consultation

- PMDA provides a priority consultation system.
- In case of orphan drugs, PMDA always accept "Application for consultation" from sponsor.



1.(2) Consultation

- Lower user fee categories for PMDA's consultation are applicable to designated orphan drugs . (about 25% discount)

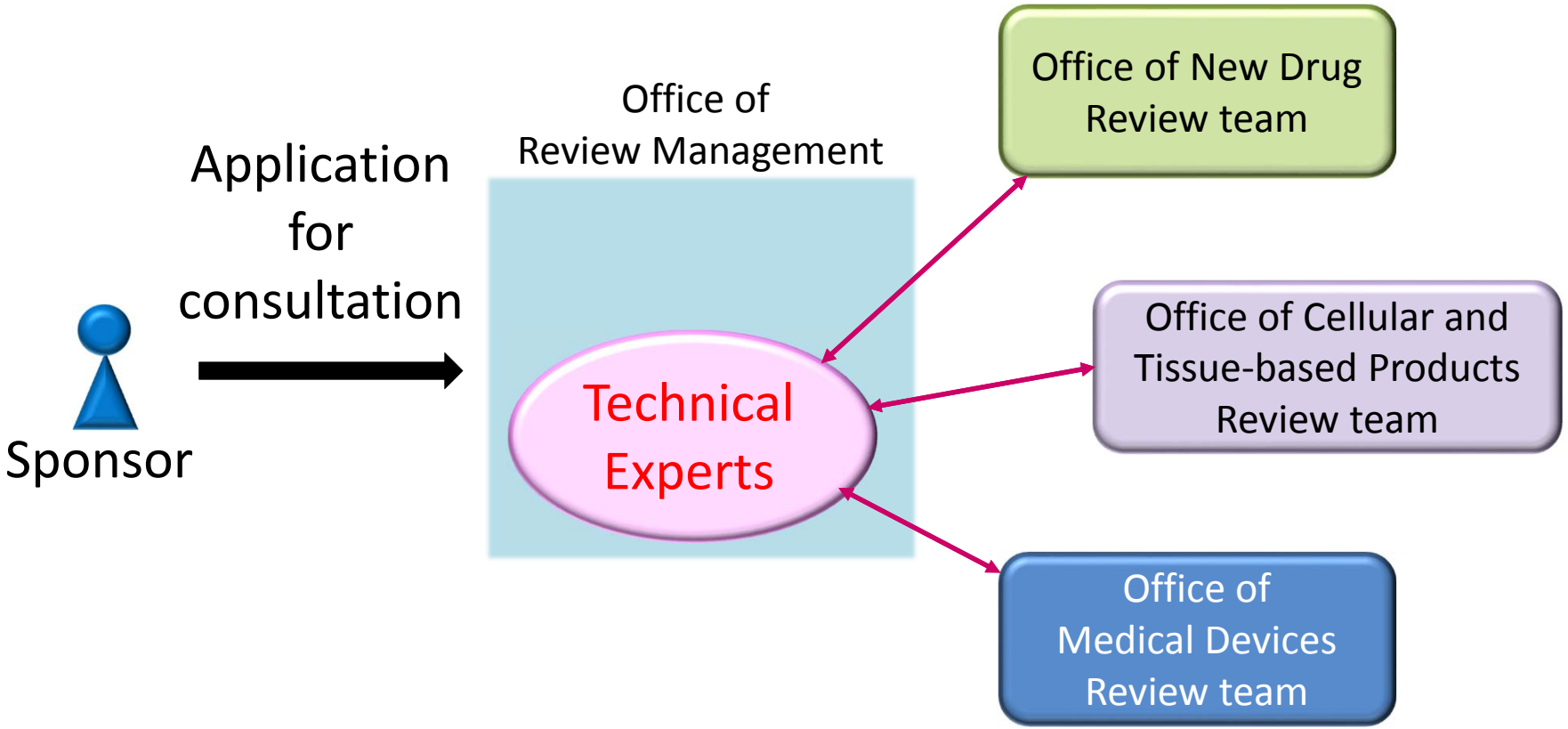
Categories of Scientific Consultations	User Fees for Non-orphan Drugs (per consultation)	User Fees for Orphan Drugs (per consultation)
Consultation before start of phase I study	4,239,400 yen	3,186,100 yen
Consultation before start of early phase II study	1,623,000 yen	1,222,500 yen
Consultation before start of late phase II study	3,028,400 yen	2,274,200 yen
Consultation after completion of phase II study	6,011,500 yen	4,515,700 yen
Pre-application consultation	6,011,400 yen	4,513,000 yen
Additional consultation	2,675,600 yen	2,010,400 yen
Consultation on GLP/GCP compliance	2,875,500 yen	2,157,200 yen

Note: 0.006GBP = 1 JPY
0.007EUR = 1 JPY
0.01USD = 1 JPY

1.(2) Consultation

- PMDA started “Pharmaceutical Affairs Consultation on R&D strategy” in 2011.
- Target of this new consultation category,
  - Regenerative medicine (cellular and tissue-based product)
  - Product for cancer
  - Product for orphan disease, rare disease
  - Product for children
  - Other innovative product

- Review team and Technical Experts (i.e. non-clinical trial, intellectual property strategy) suggest effective development plan.



- Sponsor can contact Technical Experts after the consultation to clarify unclear points.
- Example of question/discussion point
  - Tentative spec of active pharmaceutical ingredient and dosage
  - Non-clinical dataset to initiate first-in-human trial
  - Protocol assistance in non-clinical study
  - Protocol assistance in clinical trial (from first-in-human to proof-of-concept study)
  - Development strategy

Pharmaceutical Affairs Consultation on R&D strategy

- Lower user fee categories are applicable to small company and researcher of college/research institute*. (about 90% discount)

  * Small company: meeting all the following conditions
    1) employee ≤ 300 or capital fund ≤ 300,000,000 yen
    2) any another company doesn't occupy a half of stake/stock.
    3) any other companies don't occupy two third of stake/stock.
    4) no profit in the current term (or no operating revenue when posts current profit)

  Researcher: meeting all the following conditions
    1) Grant from government; drugs ≤ 90,000,000 yen
       medical devices ≤ 50,000,000 yen
    2) no R&D fund from company

	User Fees for Large company / researchers (per consultation)	**User Fees for Small company / researchers (per consultation)**
Drugs	1,498,800 yen	149,800 yen
Medical devices	849,700 yen	84,900 yen

Note: 0.006GBP = 1 JPY
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0.01USD = 1 JPY

1.(3) Preferential tax treatment

- 12% of study expenses for orphan drug/medical device incurred (not including subsidies granted by National Institute of Biomedical Innovation (NIBIO)) during the NIBIO subsidy payment period can be reported as a tax credit.

1.(4) Priority review

- PMDA provides a priority review system.
  - Standard review time (median)

    Non-orphan drug : 12 month

    Orphan drug : 9 month

- Lower user fee is applicable in NDA of orphan drug. (about 25% discount)

  Non-orphan drug : 30,347,700 JPY/application

  Orphan drug : 23,220,100 JPY/application

Note: 0.006GBP = 1 JPY
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0.01USD = 1 JPY

1.(5) Extension of re-examination period

- Exclusive period (“Re-examination period” in Japan) is extended for orphan drugs.

  Non-orphan drug : 8 years (NME)

  Orphan drug : 10 years (NME)

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1. Incentives

	JAPAN	EMA	FDA
Grants from regulatory competent authorities	from NIBIO	from European Commission and other sources	Orphan products grants program
Scientific advice (protocol assistance and/or consultation for development)	yes	yes	yes
Special incentives for SME sponsors	Pharmaceutical Affairs Consultations on R&D Strategy	yes	small business assistance
Financial incentives	Tax Exemption Law 12% of expenses	Member states incentives	50% federal Tax credit for clinical research
Accelerated review in Marketing authorization	yes	yes	yes
Fee reduction for marketing-authorization application	yes	yes	yes
Market exclusivity	10 years	10 years	7 years

2. Orphan drug development in Japan

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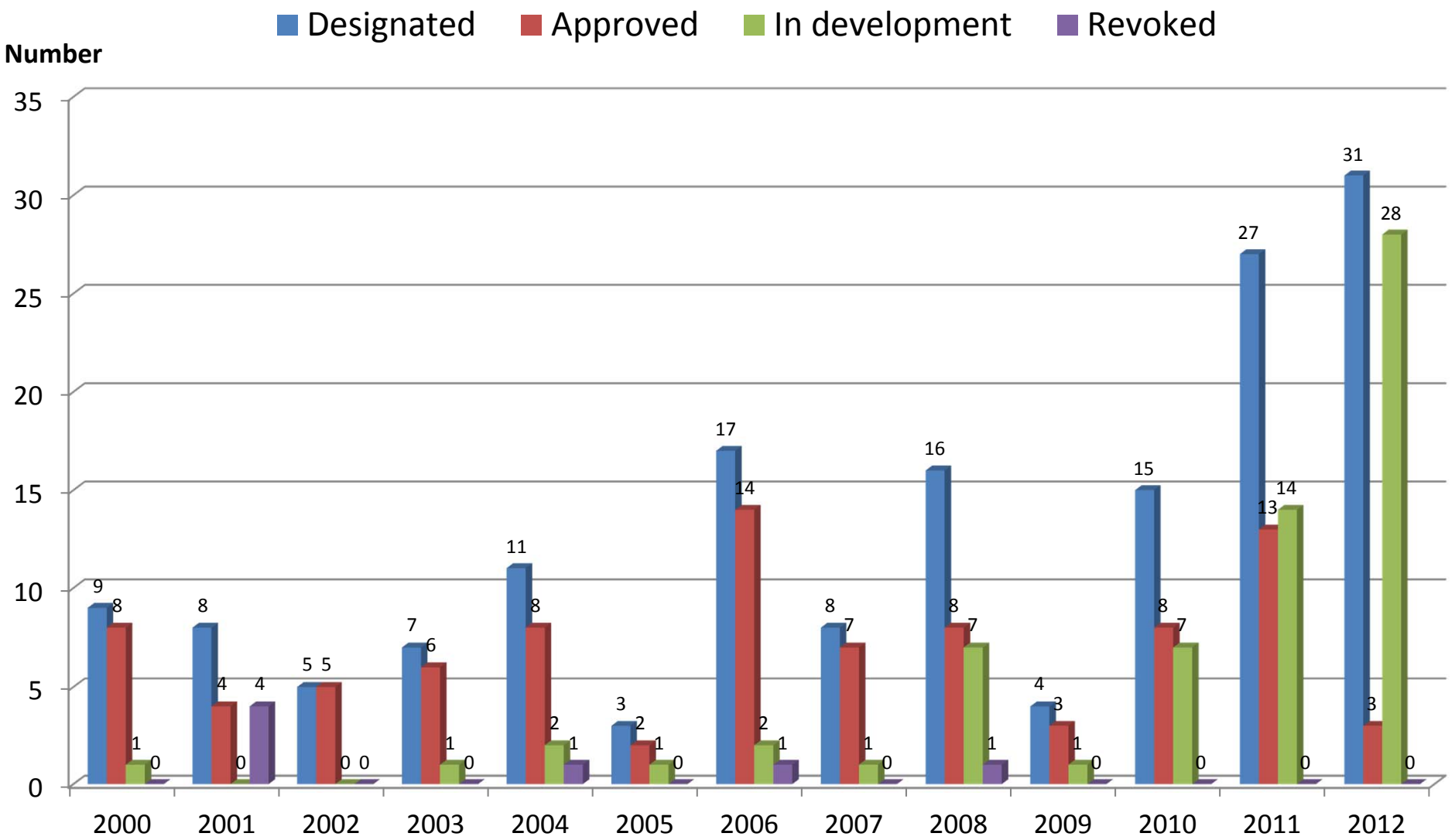

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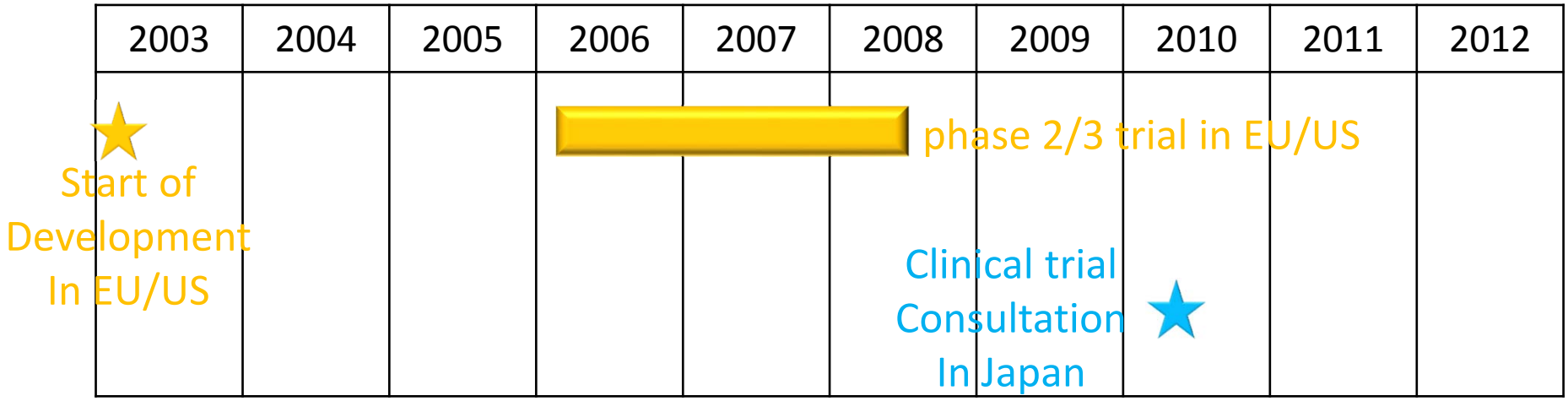
2. Orphan drug development in Japan

- In Japan, there is no documented guidance/guideline for developing orphan drugs.
- Clinical data package is discussed in each product, considering about number of patients, severity of disease, existing treatment, feasibility, extent of establishing efficacy/safety data, and so on.
- To the present, time to start development lag behind EU/US in almost all product.
- In many cases, domestic clinical trials for designated orphan products have been conducted.

2. Orphan drug development in Japan

Typical example of orphan drug development in Japan

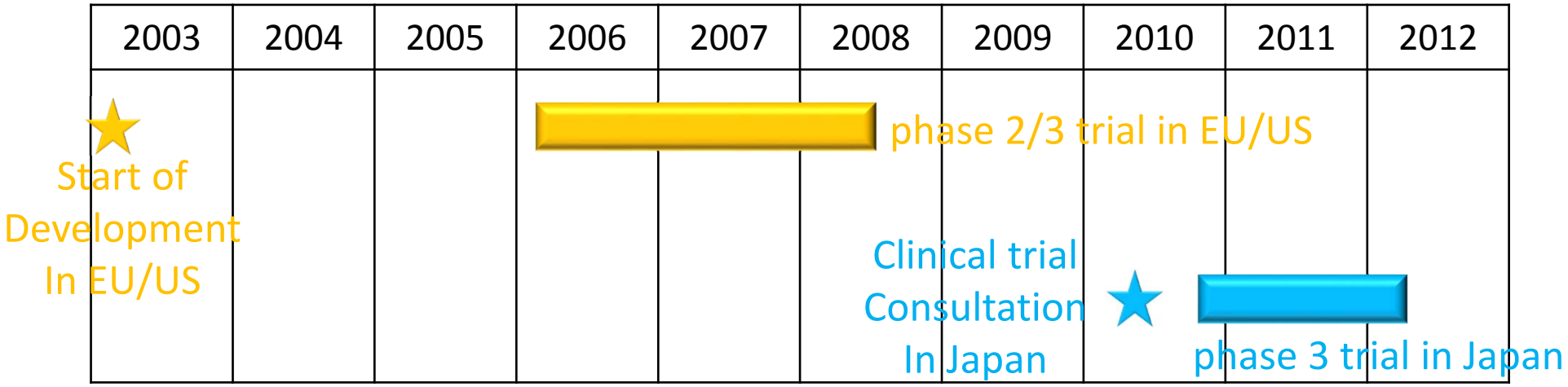
- Indication: severe, progressive inherited disease
- Patient number: about 150 (in Japan)
- There is phase 2/3 trial in EU and US evaluating clinical function, in 18 month.



2. Orphan drug development in Japan

Typical example of orphan drug development in Japan

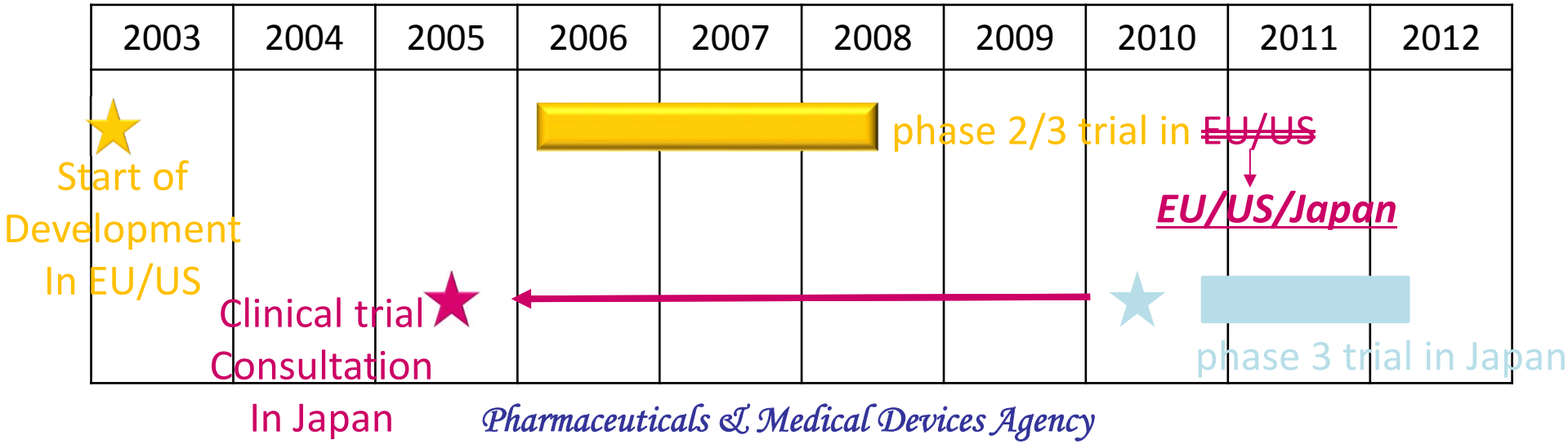
- Phase 3 trial in Japan was conducted to confirm the safety of Japanese patients and similarity of efficacy between Japanese and EU/US patients.



2. Orphan drug development in Japan

- Japan would like to contribute to the establishment of efficacy and safety of new drugs in the world.

Please remember and consider to recruit Japanese patients for global trial.

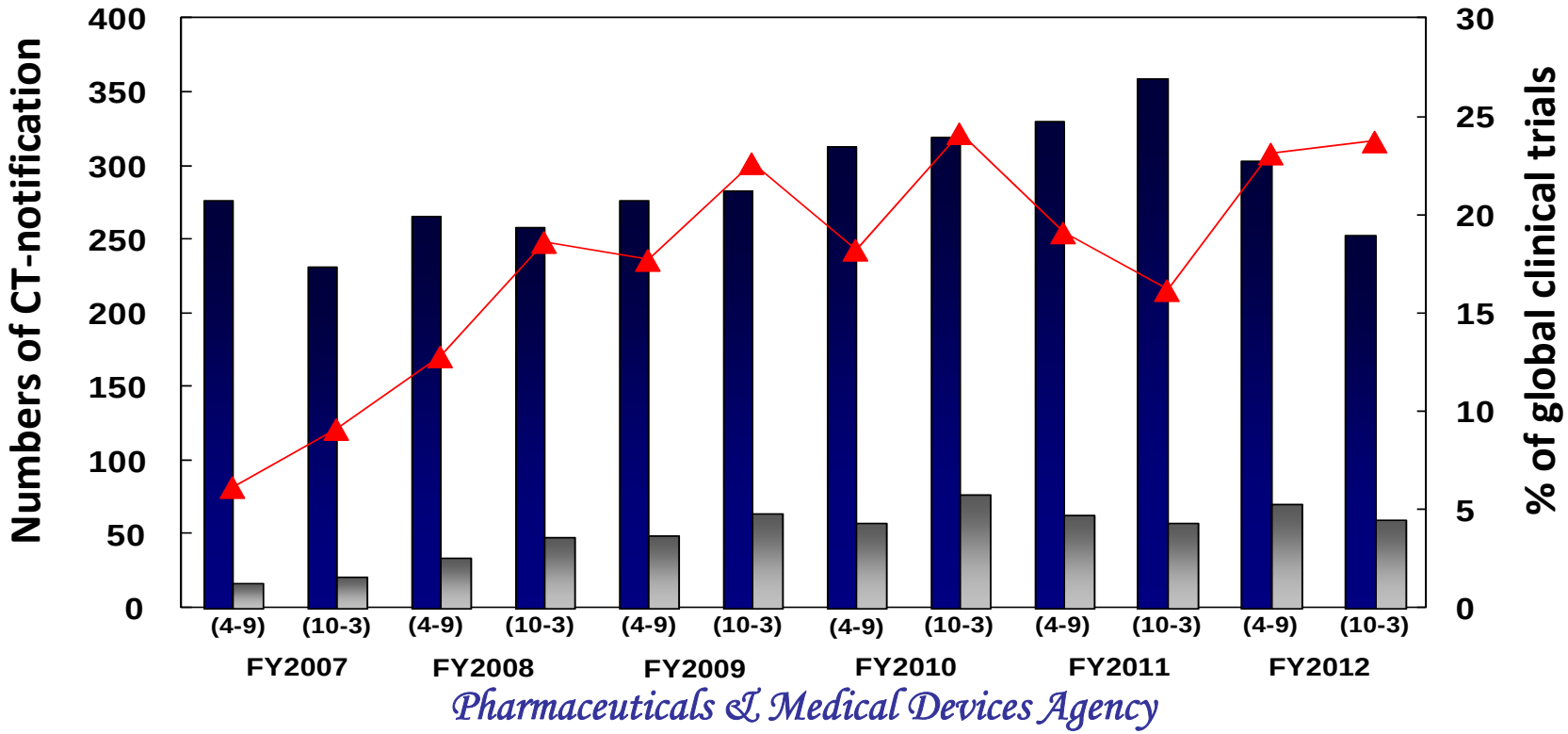


2. Orphan drug development in Japan

- Japanese guidance document “Basic Principles on Global Clinical Trials” (2007)

  English version : http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf

- Number of global clinical trials is increasing.



Thank you for your attention.

Information

- PMDA Orphan Working Group
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