Overview of Consultation System in Japan

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March, 22, 2012

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Contents

- Clinical trial consultation system

New Challenges

- Priority Assessment Consultation（July 2011～）
- Consultation on eligibility for priority review products（Oct 2011～）
- Pharmaceutical Affairs Consultation on R　& D strategy（July 2011～）

Clinical trial consultation system

Background

October, 1994

Increase in the number of innovative drugs.

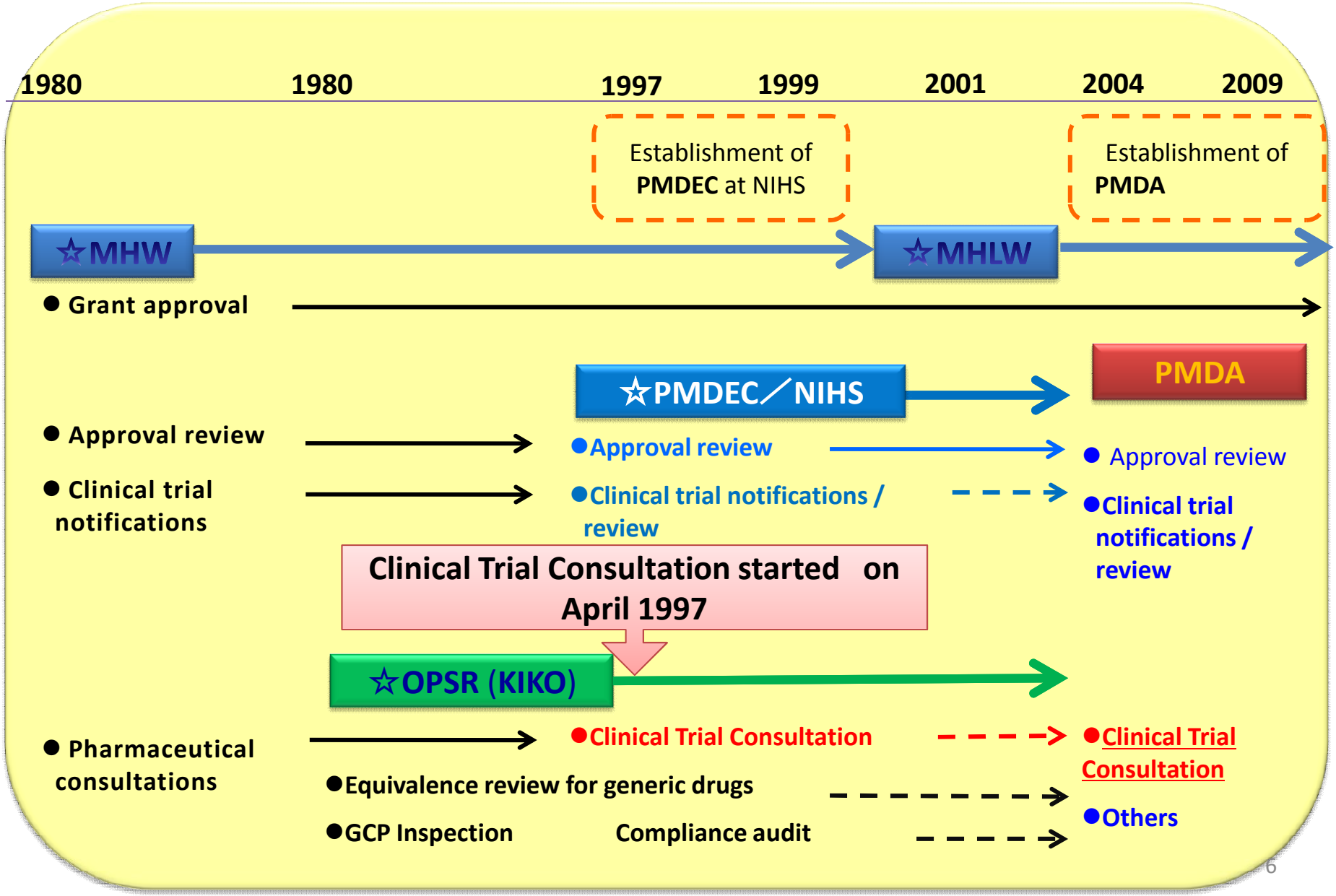
→ Needs for improvement of drug safety

- **Strengthening the responsibility of pharmaceutical companies**
- **Taking comprehensive measure for pharmaceuticals**

June, 1996 Publication of the revised Pharmaceutical Affairs Act
April, 1997 Enforcement of the revised Pharmaceutical Affairs Act

1. **Reinforcement of consultation/guidance on clinical trials**
2. Reinforcement of approval review
3. Strengthening of post-marketing measures
4. Others

History of JP clinical trial consultation system



Purpose of clinical trial consultations

Purpose

By implementation of consultation in development stage

- Secure the ethical and scientific appropriateness of clinical trials
- Share common views of the issues in clinical development between applicants and regulatory agency
  - Reduce application preparation time and cost
  - Avoid critical problems found during NDA review

Consultations tailored for a range of needs

1997
OPSR/Kiko

①Consultation **before IND**
②Consultation **after completion of phase II study** for drug
③ **Pre-application** consultations
④ **Individual** consultation

Expansion of the consultation category

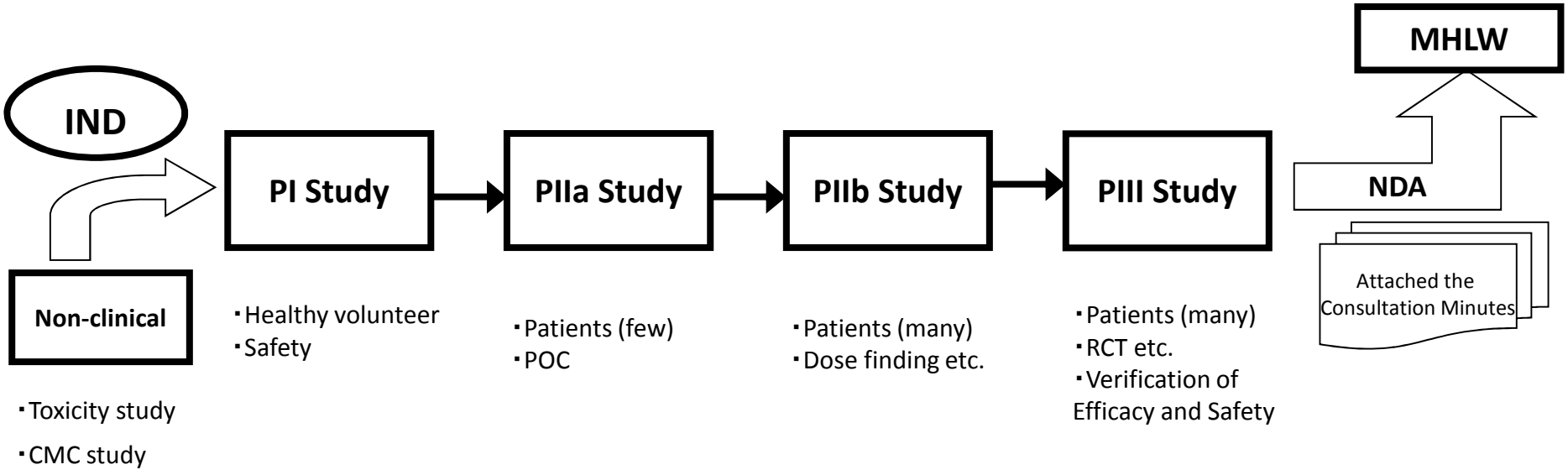
2012
PMDA

Charged !

① Consultation **Pre-phase I study** for drugs
② Consultation **Pre-phase IIa study** for drugs
③ Consultation **Pre-phase IIb study** for drugs
④ Consultation after **End of phase II study** for drugs
⑤ **pre-application** consultation
⑥Additional consultation
⑦ Consultation on **the protocols of clinical trials for reevaluation and re-examination** of drugs
⑧Consultation at completion of clinical trials for reevaluation and re-examination of drugs

① Application procedure consultation
② Quality consultation
③ Safety consultation
④ Consultation on bioequivalence testing, etc. for drugs
⑤ GLP/GCP compliance (for priority review)
⑥ Consultation on document maintenance of Cell-and-tissue-based products
⑦ Pharmacogenomics (PGs)/Biomarker consultation

Clinical trial consultation System at PMDA



[Clinical trial consultation System at PMDA]

Pre-PI Additional **Pre-PII** Additional **End-of-PII** Additional **Pre-Application** Additional

Safety Additional （Consultation only for Toxicity and Pharmacology）

GLP/GCP Compliance

Quality Additional （Consultation only for CMC）

Bioequivalence testing

Procedure Procedure （Consultation for Pharmaceutical Affairs Procedures）

Document maintenance of Cell-and tissue-based products

PGx/ Biomarker

Implementation status of each consultation

Total number of each IND scientific consultation about the new medical products (case)

	FY2005	FY2006	FY2007	FY2008	FY2009	FY2010	FY2011 (～Oct)
Total（Storing number）*	215	327	303	337	332	355	253
Consultation **Pre-phase I study** for drugs	42	73	65	48	47	64	44
Consultation **Pre-phase IIa study** for drugs	2	5	13	12	14	13	6
Consultation **Pre-phase IIb study** for drugs	47	67	67	62	40	44	29
Consultation **End of phase II study** for drugs	33	67	63	110	109	96	88
Pre-application consultations	41	42	24	38	34	27	30
Additional consultation	31	35	20	28	45	42	31
Consultation on **the protocols of clinical trials for reevaluation and re-examination** of drugs	2	3	2	2	2	2	2
Consultation at **completion of clinical trials for reevaluation and re-examination** of drugs	0	0	0	0	0	1	0
Application **procedure** consultation	2	17	16	7	7	22	4
Quality consultation	5	8	23	8	14	24	10
Safety consultation	5	6	5	7	13	12	6
Consultation on **bioequivalence testing**, etc. for drugs	3	4	5	10	6	8	2
Consultation on **GLP/GCP compliance**(for priority reviews)	2	0	0	1	1	0	0
Consultation on document maintenance of Cell-and-tissue-based products			0	4	0	0	0
Pharmacogenomics (PGx)/ Biomarker consultation					1	1	1

***：including a withdrawal**

Consultation Pre-phase I study for drugs

Based on available data of non-clinical tests, approvals and experiences in other countries, information of similar drugs…

- The validity of applying the drug to a person for the first time
- Clinical study design of Phase I *etc.*

For example…

Q：Are non-clinical tests data sufficient at the beginning of a phase I trial ?

Q：Are the initial safe dose and subsequent dose escalation schemes acceptable in a phase I trial?

Q： Are the safety parameters for clinical monitoring acceptable ?

Consultation Pre-phase IIb study for drugs

Based on results from phase I trials, approvals and experiences in other countries, information of similar drugs…

- Clinical study design of phase II etc.

For example…

Q：Are the selection of doses in dose-finding study rationale ?

Q： Are the selection of endpoints in dose-finding study acceptable ?

Consultation End of phase II study for drugs

Based on available data of clinical trials…

- Clinical study design of phase III etc.

For example…

Q：Are dose-response assessment and recommended dose appropriate ?

Q：Are the selection of control products and endpoints in the confirmatory clinical trials acceptable ?

Q：Are the data analysis such as the method of sample size calculation suitable ?

Q：Dose the design of long-duration trials meet the related GL ?

Q：Can foreign clinical data be extrapolated ?

Q：Is Japanese population in multi regional trials sufficient ?

Pre-application consultation

Based on available data of clinical trials…

- The way for compiling the application document
- Sufficiency of the application document

For example…

Q : Are the non-clinical and clinical data sufficient for the application ?

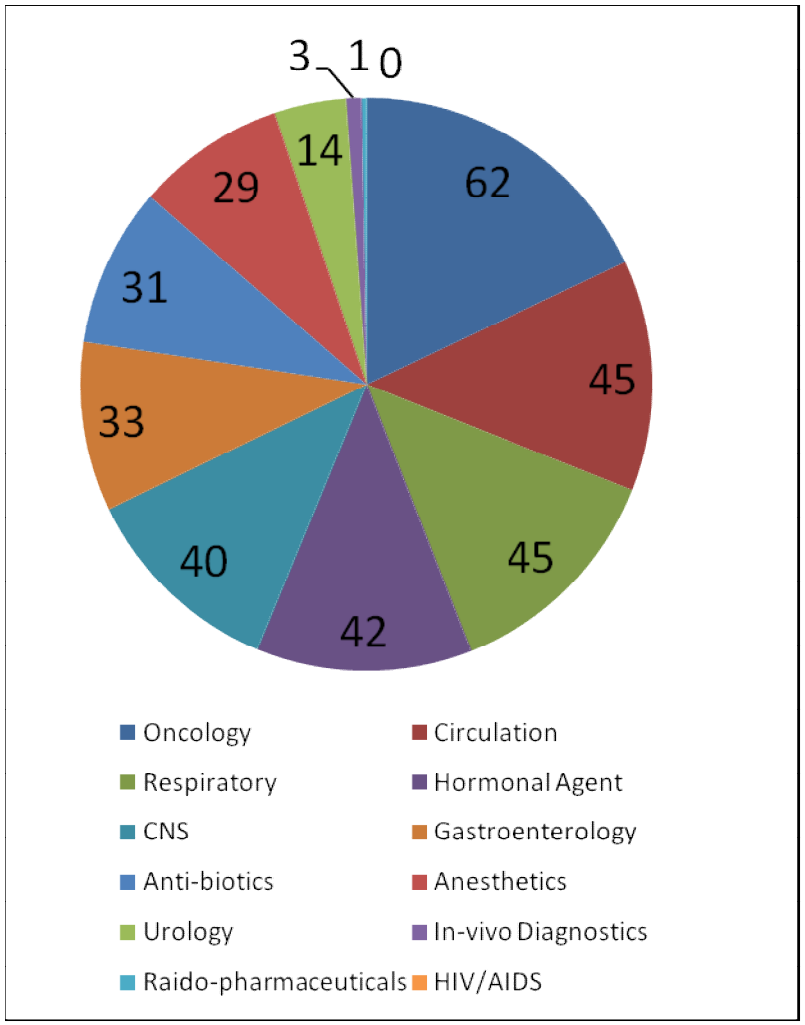
Q : Are Dosage & Administration, and Indication appropriate ?

Q : Is it acceptable that the results of clinical studies in non-Japanese are treated as the evaluation data ?

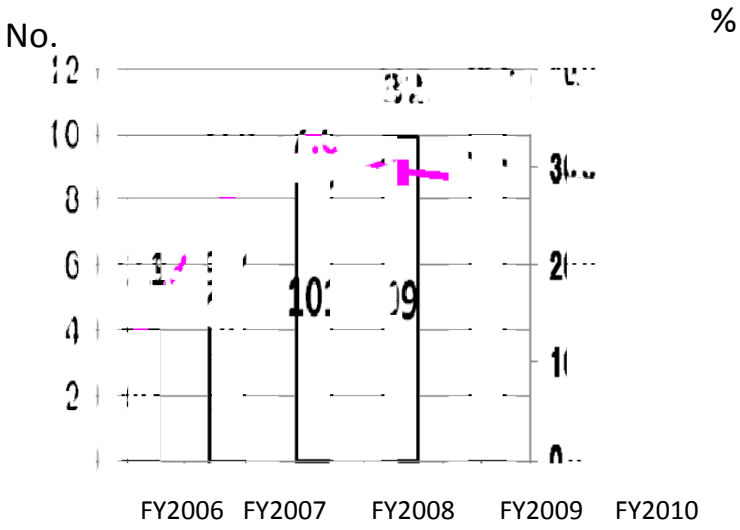
Q : Is the data package including foreign clinical data acceptable ?

Trend of Clinical trial Consultation (FY2010)

Diseases



Global clinical trial consultations



☐ No. of Global Clinical Trial Consultations

■ % of Global Clinical Trial Consultations

Consultation for Global Clinical trials

For example…

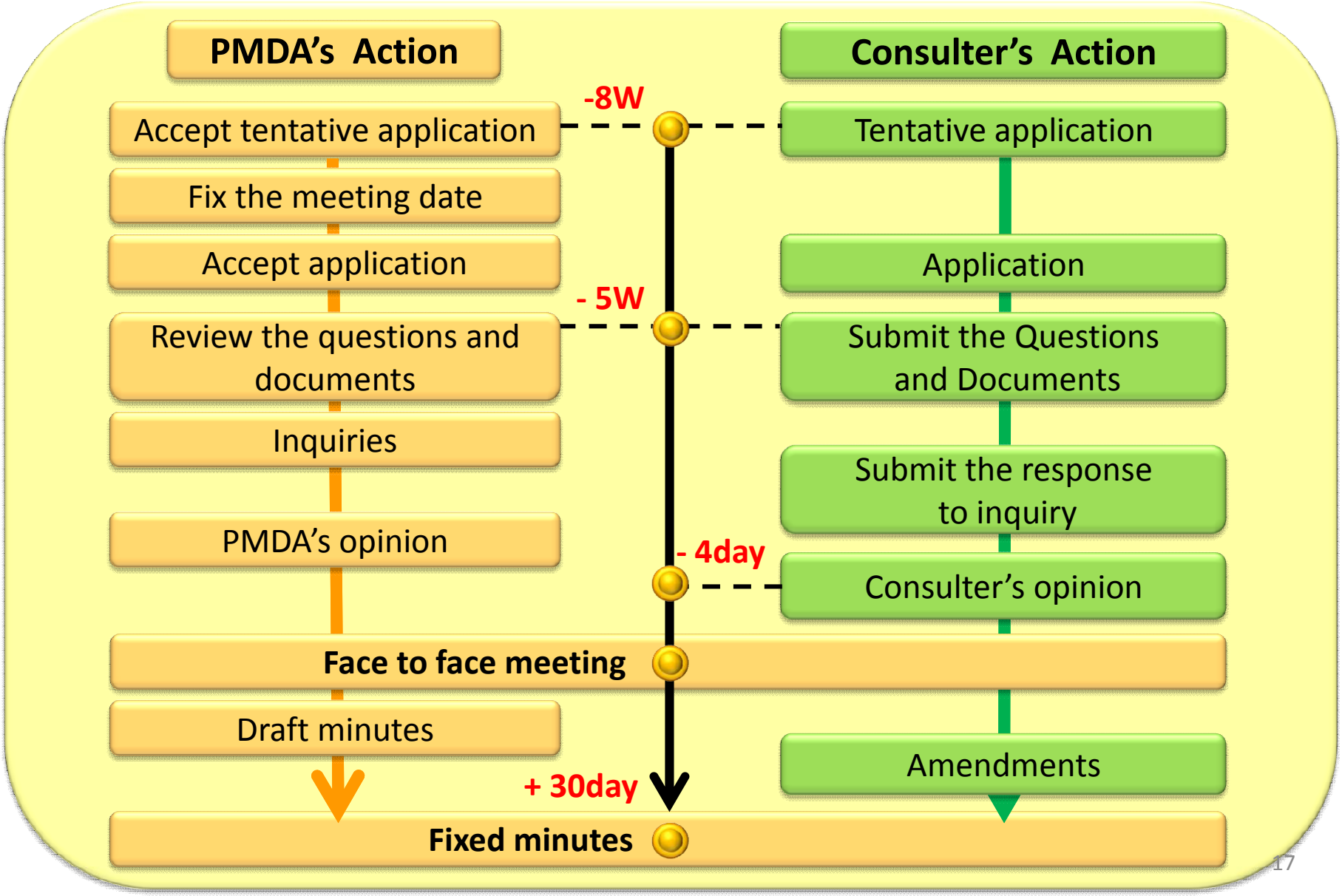
Based on “Basic principles on Global Clinical Trials”,

Q：Is it appropriate to participate in the global trial based on intrinsic and extrinsic ethnic factors ?

Q：Is a development program acceptable in which Japanese subjects are included only from a phase III trial without conducting any dose-finding study in Japan?

Q：How to determine a sample size and a proportion of Japanese subjects in global clinical trial ?

Flow of clinical trial consultation



Documents required for clinical trial consultation

① Background and concept of the IND development
- Existing treatment for the disease
- Problems of the existing treatments and expected benefits of the IND

② Draft of protocols

③ The latest Investigator's Brochure
- List of clinical trials
- List of toxicity studies

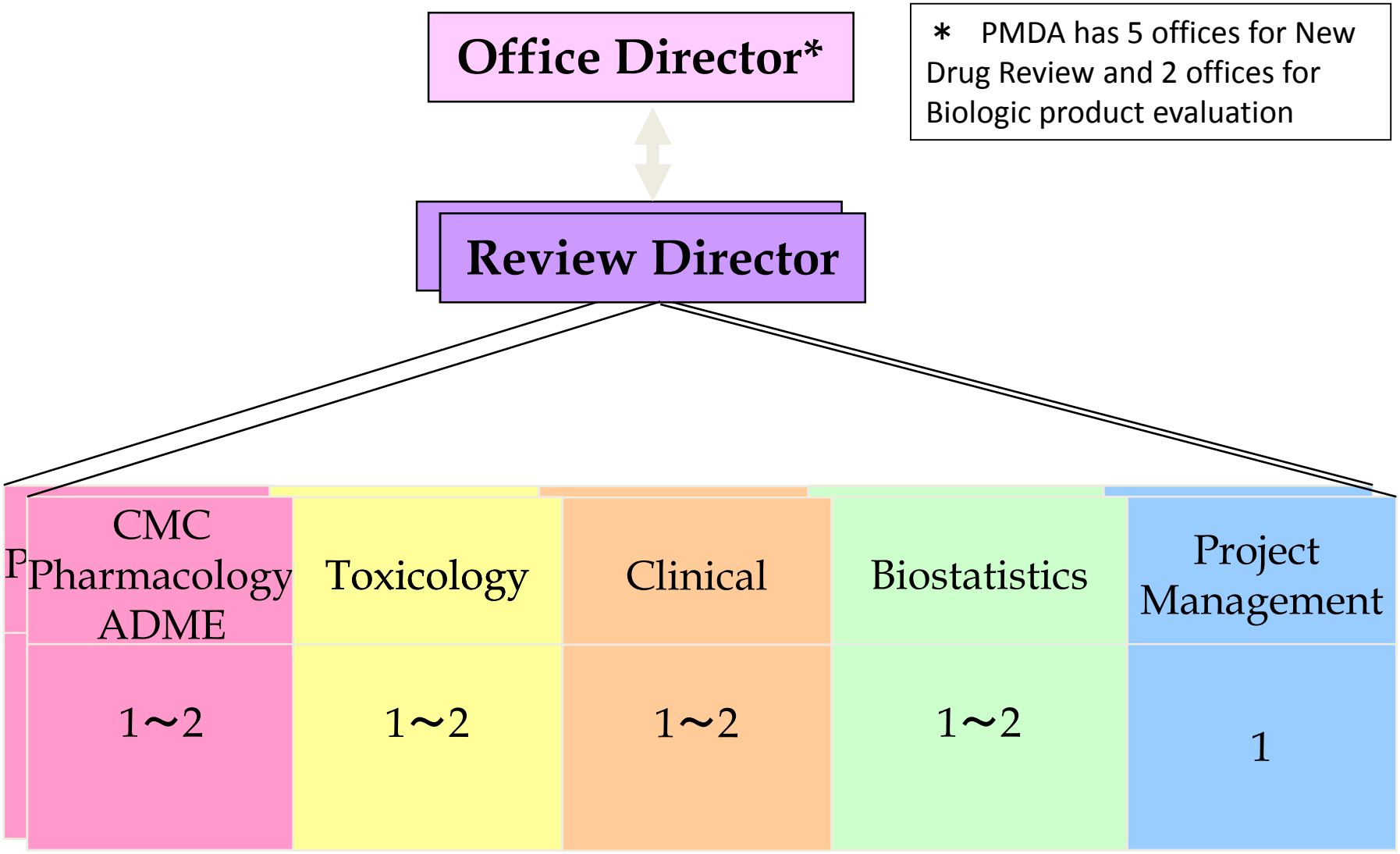
④ Development status in other countries

⑤ References

⑥ Past consultation's minutes

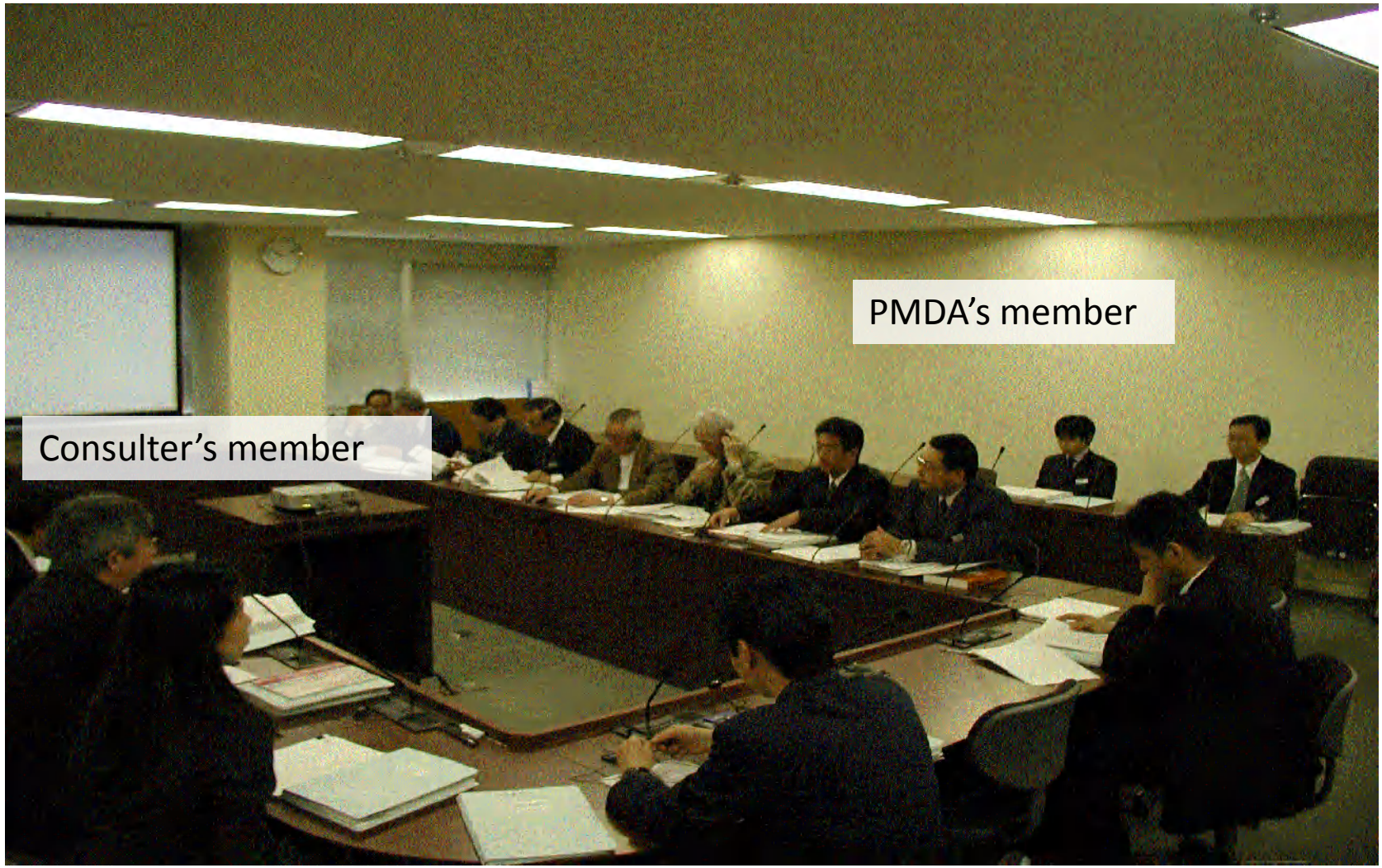
etc.

Composition of Consultation Team



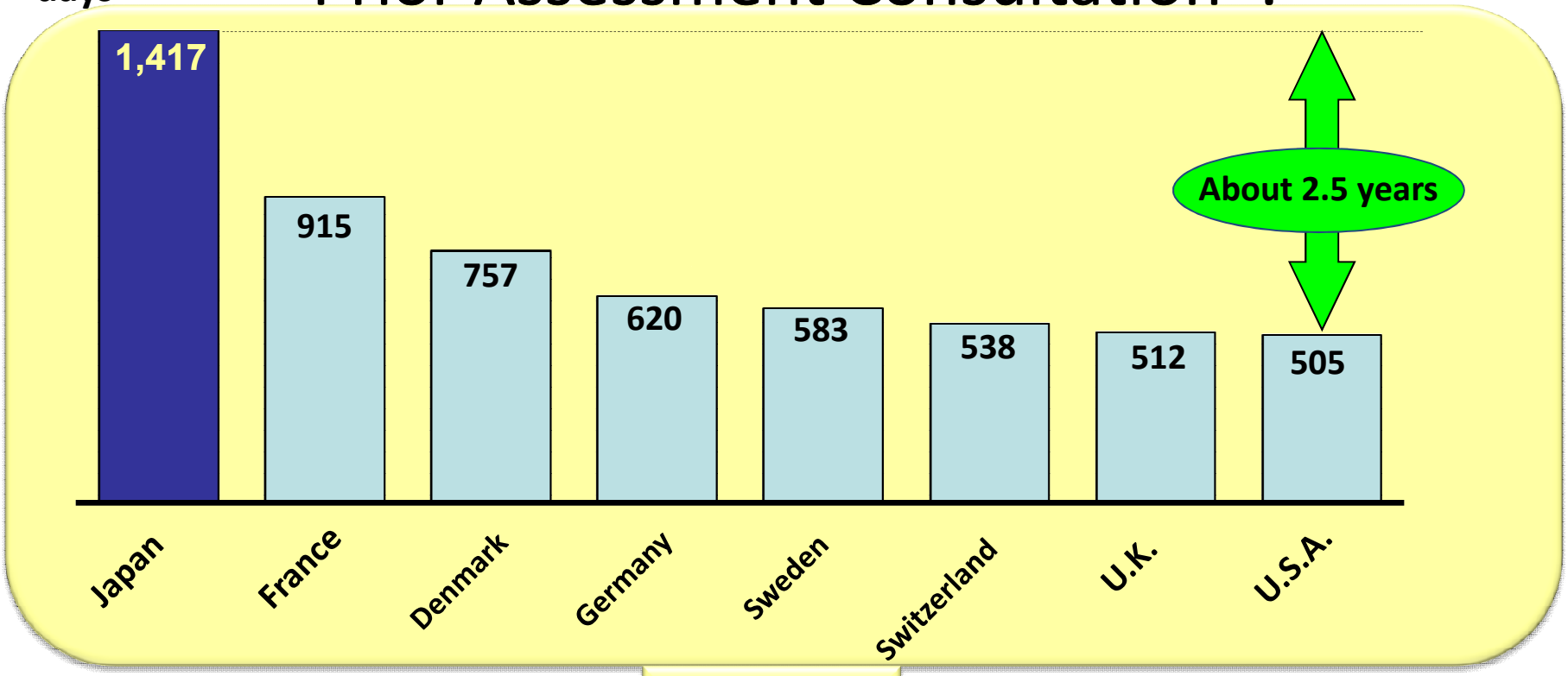
＊ PMDA has 5 offices for New Drug Review and 2 offices for Biologic product evaluation

Scene of Face-to-face Meeting



Prior Assessment Consultation

Why did we introduce "Prior Assessment Consultation"?



"How to eliminate drug lag ? "

The source : JPMA The Office of Pharmaceutical Industry Research
Research Paper No.31（May 2006）

Targets :To reduce the "drug lag" by a total of 2.5 years

	Development time	Approval review time
Measures	***Expansion of the Consulting Service*** - Increase the number of staff about 236 approximately in 3 years -Give adequate training	***Expansion of the Review System*** - Increase the number of staff - Give adequate training
	Improve the quality and quantity of consultations - Advise on overall development strategy to improve development time - Reduce the application preparation time through stepping up the pre-application consultations	***Enhancement and improvement of the Review System*** - Introduce a prior assessment, and reduce applicant workload. - Improve productivity of reviews through measures such as the standardization and Streamlining of the review process
	Clarify the review criteria - Further promote Global Clinical Trials - Draft a guideline on cutting-edge technologies	***Liaise more closely with the FDA and other overseas regulatory authorities***
Targets (by 2011)	**1.5 year reduction of development time**	**1.0 year reduction of approval review time**

Target review time (New Drugs)

(Months)

	FY	2007	2008	2009	2010	2011
Standard review Products (Median)	**Total review time**	21	20	19	16	12
	Regulatory review time	13	13	12	11	9
	Applicant's time	8	8	7	5	3
Priority review Products (Median)	**Total review time**	12	11	11	10	9
	Regulatory review time	6	6	6	6	6
	Applicant's time	6	5	5	4	3

Regulatory and Applicant's work in collaboration to tackle a goal !

Purpose of prior assessment consultation

Purpose

By implementation of consultation before formal NDA

- Shorten NDA review time
  - Identify major discussion points and tasks for NDA submission
  - Help applicants to prepare a good CTD with the inclusion of PMDA's view points

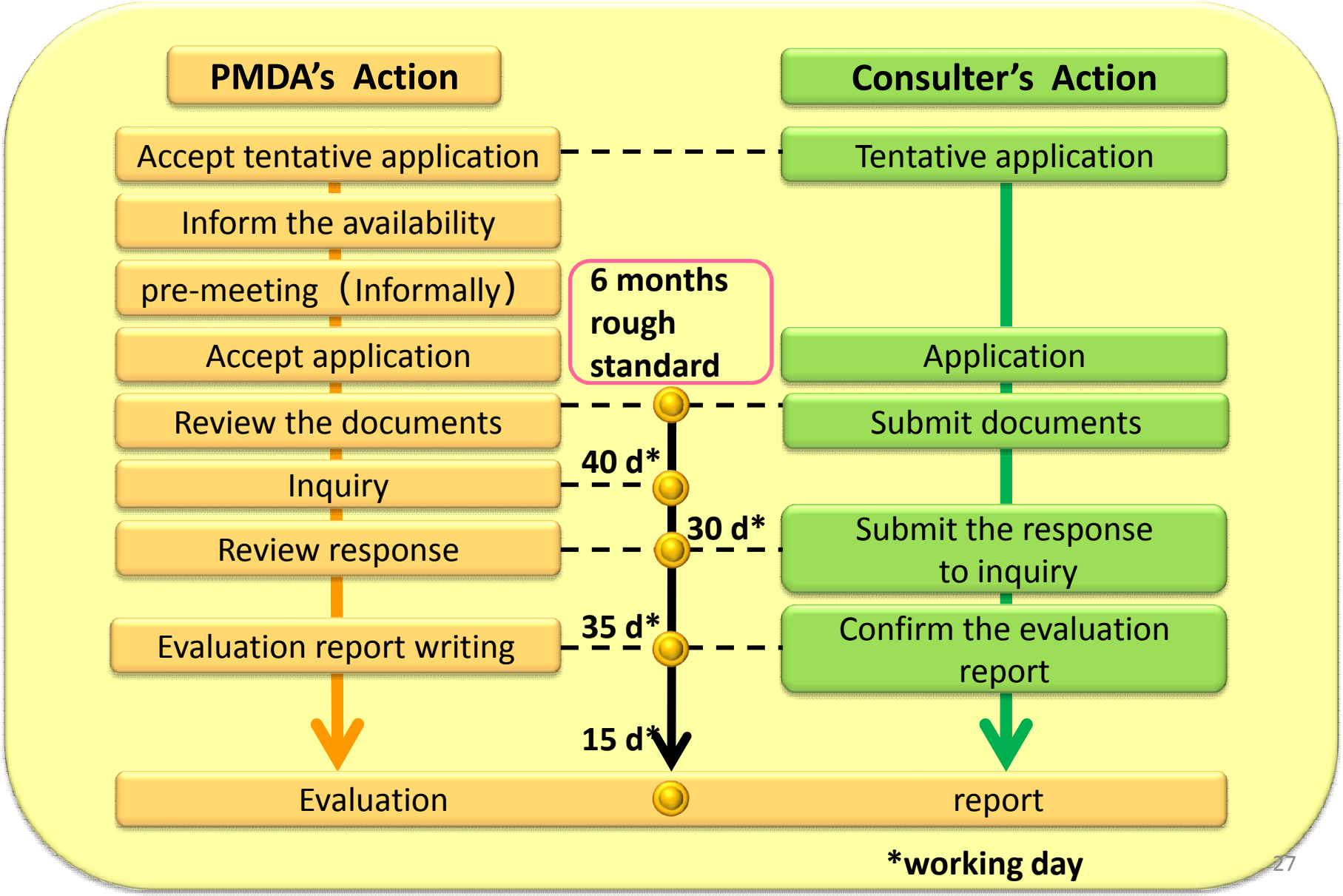
Contents of prior assessment consultation

Consultation contents

- Quality
- Toxicity（non-clinical）、Pharmacology(non-clinical)、Pharmacokinetics(non-clinical)
- Phase I study、Phase II study、Phase II/III study

  - Data evaluation before a formal NDA submission
  - PMDA provides a prior-assessment report for the submitted data/study

Prior assessment consultation Flow



Implementation status of prior- assessment consultation

(FY)		Status of acceptance		Status of consultation (Numbers of category)			Status of review (Number of the ingredient)
		Total of the ingredient	Total of the acceptance	Before consultation	on going	completion	Approval
2009		7	33	0	0	33	6
2010		9	30	0	0	30	1
2011	First half	3	9	0	9	0	0
	Second half	7	24	8	16	0	0

※Data: the end of January 2012

Consultation User Survey Summary - Ⅰ

Q: Consultation Items were resolved or cleared ?

Resolved or Cleared	**7**
Relatively cleared	**7**
Neither	2
Relatively Not cleared	0
Not resolved or Not cleared	0

Generally cleared

Q: How can you conclude a value of the consultations ?

Very useful	**5**
Useful	**9**
Neither	2
Not useful	0

Generally found the value

Q: Unexpected problems are found for application?

Found	**10**
Not found	6

Thought of as advantages

Consultation User Survey Summary – Ⅱ

Q: Number of inquiries after the application will be decreased ?

Clearly decreased	**4**
Perhaps decreased	**12**
No change	0
Perhaps increased	0
Clearly increased	0

Expect the decrease of inquiries

Q: Become helpful in submission data?

Very helpful	**5**
Helpful	**9**
Neither	1
Not very helpful	0
Not helpful	1

Generally helpful

Consultation User Survey Summary – Ⅲ

Q: Review become more efficient ?

Very efficient	**2**
efficient	**4**
Neither	0
inefficient	0
Very inefficient	0

Q: Shortened the review time ?

Considerably shortened	**2**
Shortened	**3**
Neither	1
Extended	0
Considerably extended	0

Q: As at the application, remaining tasks resolved ?

Resolved	**3**
Nearly resolved	**2**
Neither	1
Nearly unsolved	0
Unsolved	0

Q: Did you spend more time for a weighty discussion (dosage and administration, effect-efficacy etc.) ?

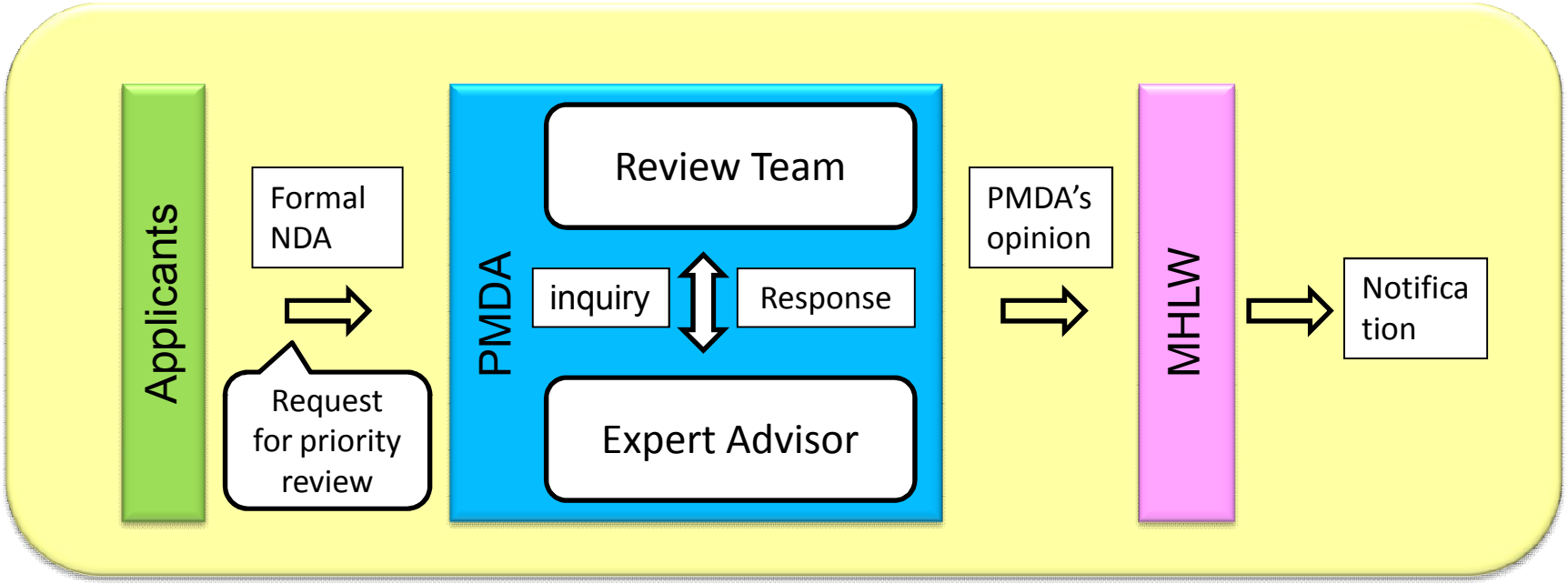
Very fulfilling discussions	**1**
Spend more time for discussion	**2**
Neither	1
Conventional	2
Rather, non-fulfilled	0

Consultation on eligibility for priority review products

Priority review

Reviews of approval applications for orphan drugs and other drugs that are regarded as having particularly high medical need ※ were conducted on a priority basis as priority review products.

※ i.e., drugs for serious diseases with distinctly superior efficacy or safety to existing drugs or therapies



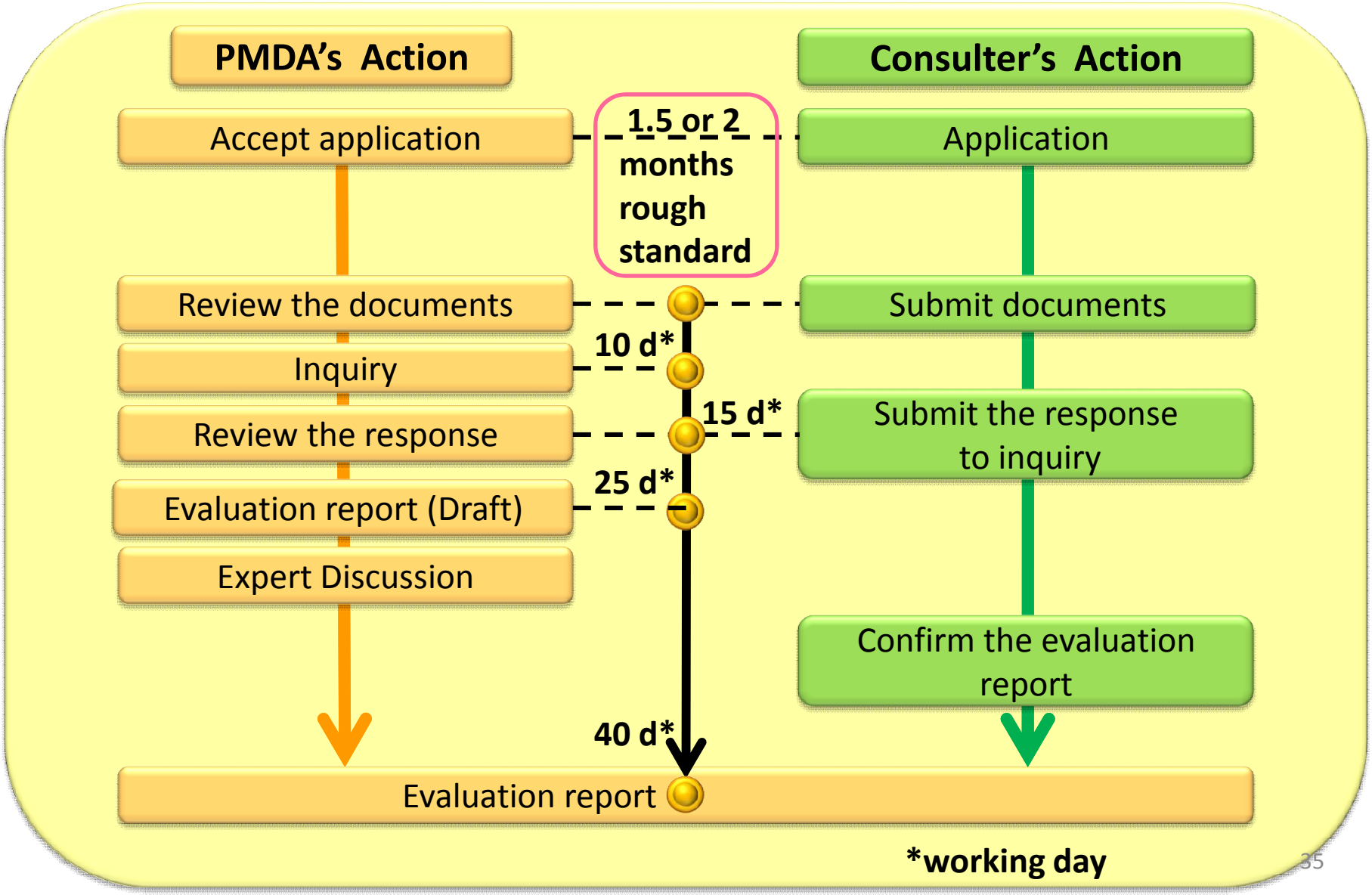
Purpose of consultation on eligibility for priority review products

Purpose

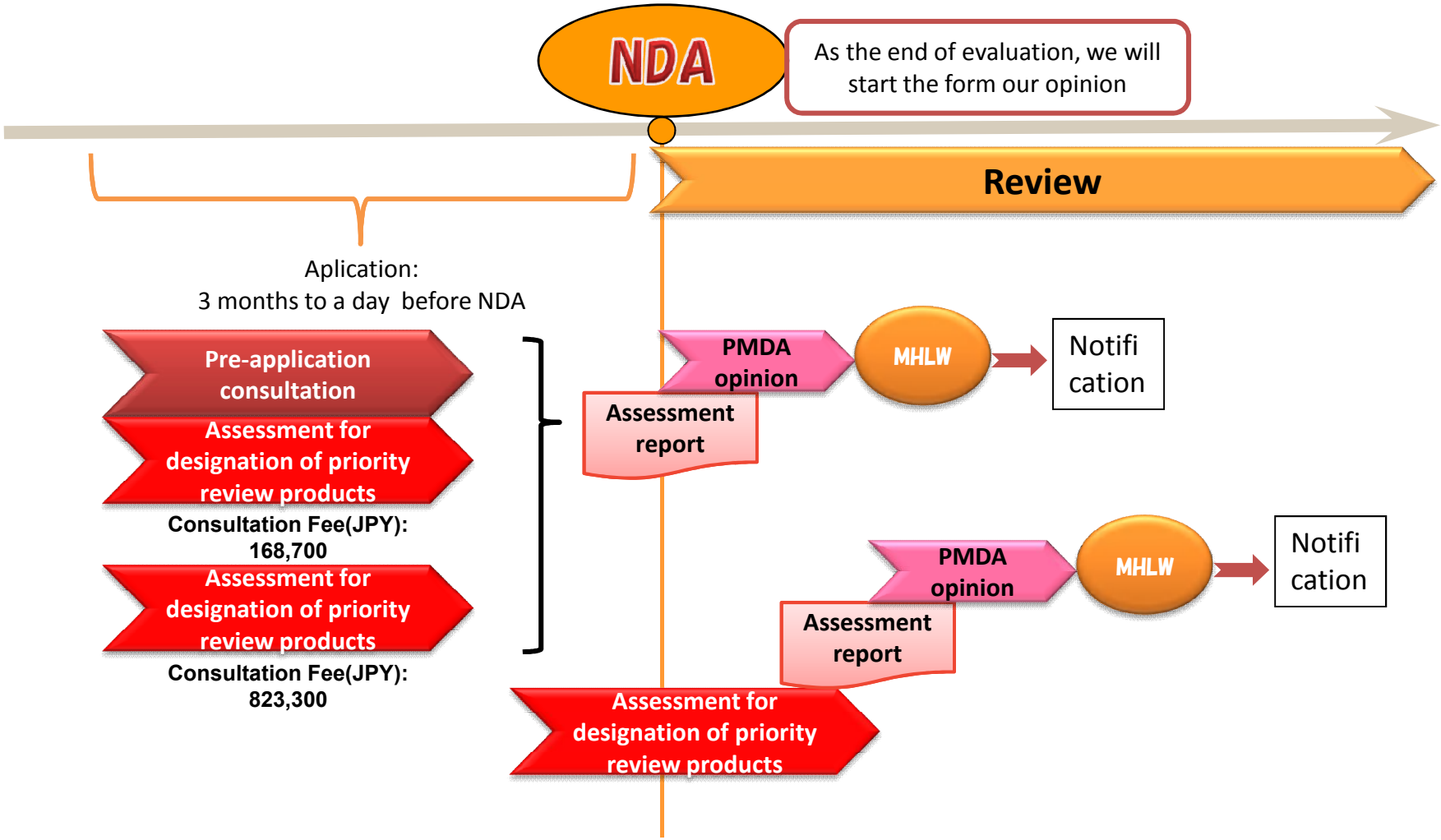
By evaluating the eligibility for priority review products before formal NDA

- Expect to shorten the priority review time
  - Form a PMDA ‘s opinion immediately after formal NDA
  - Spend more time for NDA review
- For applicants, it is beneficial to be clear the product may be eligible for priority review products or not before formal NDA

Flow of consultation on eligibility for priority review products



Consultation on eligibility for priority review products



Pharmaceutical Affairs Consultation on R & D strategy

Policies

○ New Growth Strategy (Cabinet decision in June 2010)

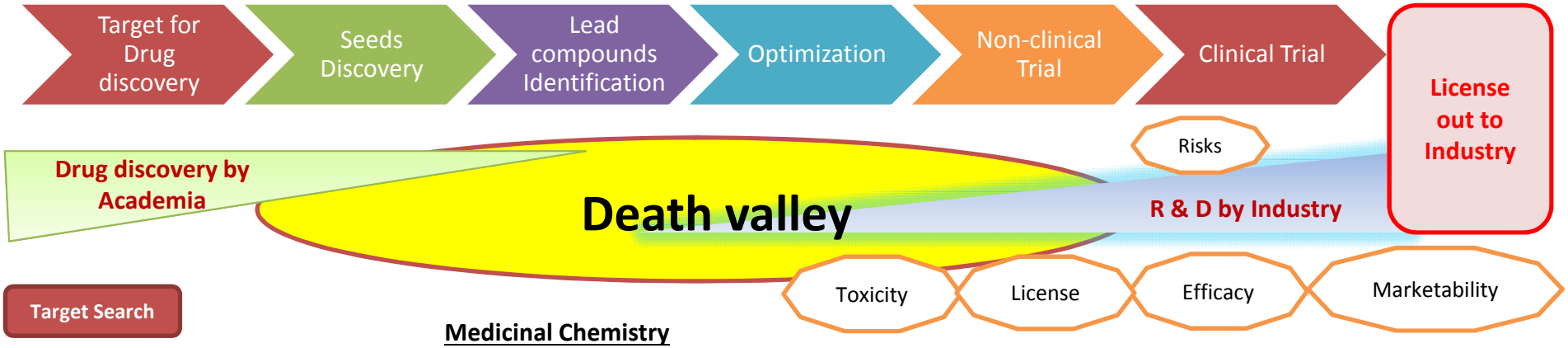
(2) Health power strategy through "Life Innovation"

Promoting research and development of innovative pharmaceuticals and medical and nursing care technologies from Japan

We will **promote research and development of highly safe, superior, and innovative pharmaceuticals and medical and nursing care technologies from Japan**. We will promote unified approaches among industry, government, and academia, **foster drug development ventures, and promote research, development, and application in a number of fields**. These include new drugs, regenerative medicine and other state-of-the-art medical technologies, remote medical treatment systems making full use of information and communications technologies, use of manufacturing technologies to improve personal mobility for the elderly, and medical and nursing care robots. To this end, we will work to resolve the urgent drug and device lag issue, improve the clinical testing environment, and **expedite drug approval decisions**.

New Growth Strategy

Current status in New Drug Research and Development Originated by Academia in Japan



Target Search

Screening (HTS, etc)

-Target Evaluation
-Screening technology Increasing
-Cost Increasing
-Lack of facilities

Medicinal Chemistry

From Seed compounds to Lead compounds

-Research structure activity correlation by medicinal chemist
-Property, Manufacturing process
-Cost burden
-Lack of Researchers

IMP Production (GMP) Drug Formulation (GMP)

-Cost burden
-Possible to outsource
-Production for anti-body drug

Pharmacology, Toxicity ADME (non GLP)

-Planning
-Evaluation
→**Optimization**
-Cost burden
-Possible to outsource

Pharmacology, Toxicity ADME (GLP)

-Planning
-Cost burden
-Possible to outsource

Clinical Trial by Company

Investigator's Initiate Trial

Clinical research

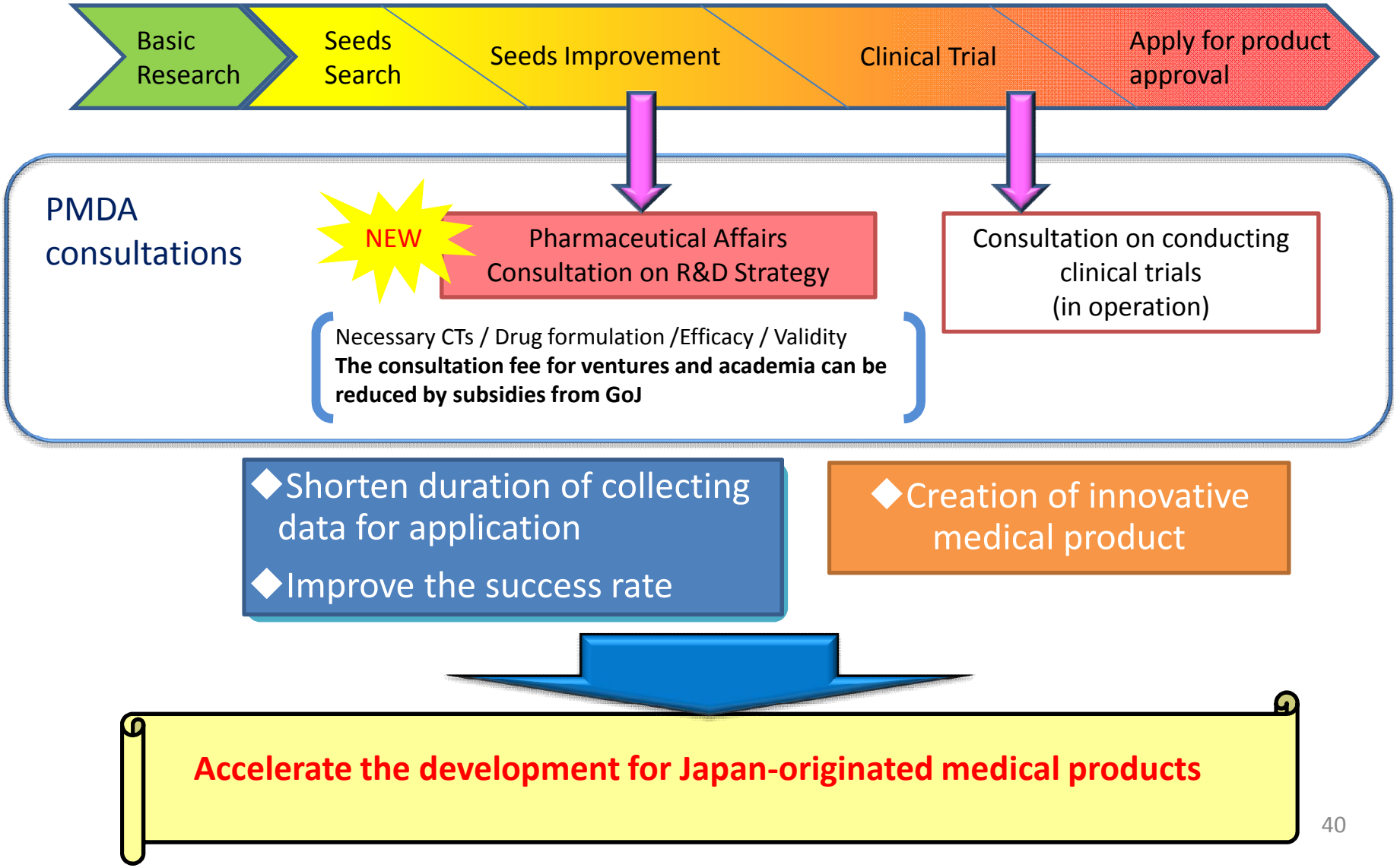
-Impossible to use NDA
-Site
-Quality

Cost Speed Quality Global

Intellectual property

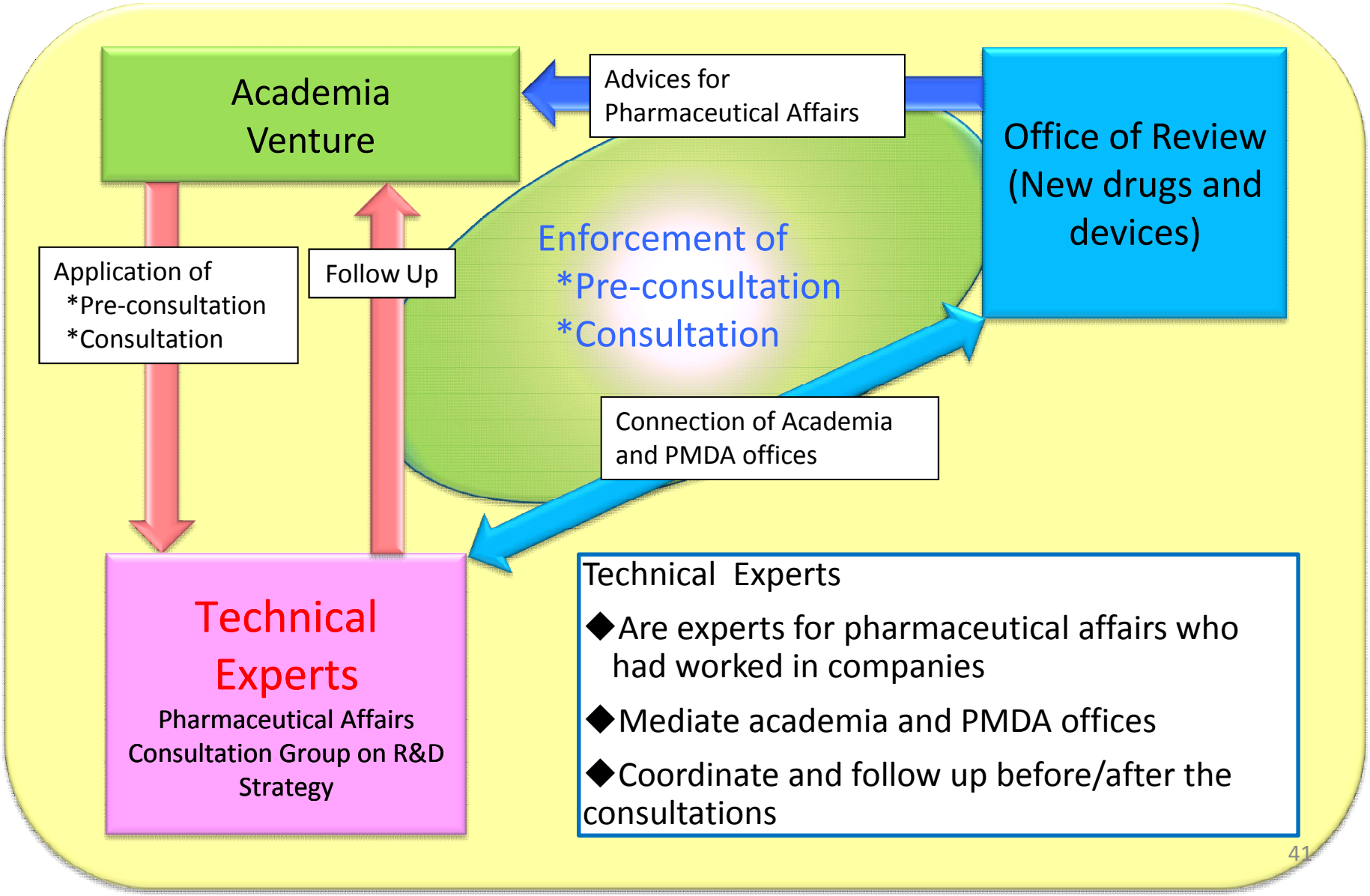
Pharmaceutical Affairs Consultation on R&D Strategy

-To accelerate the development of Japan-originated medical products –

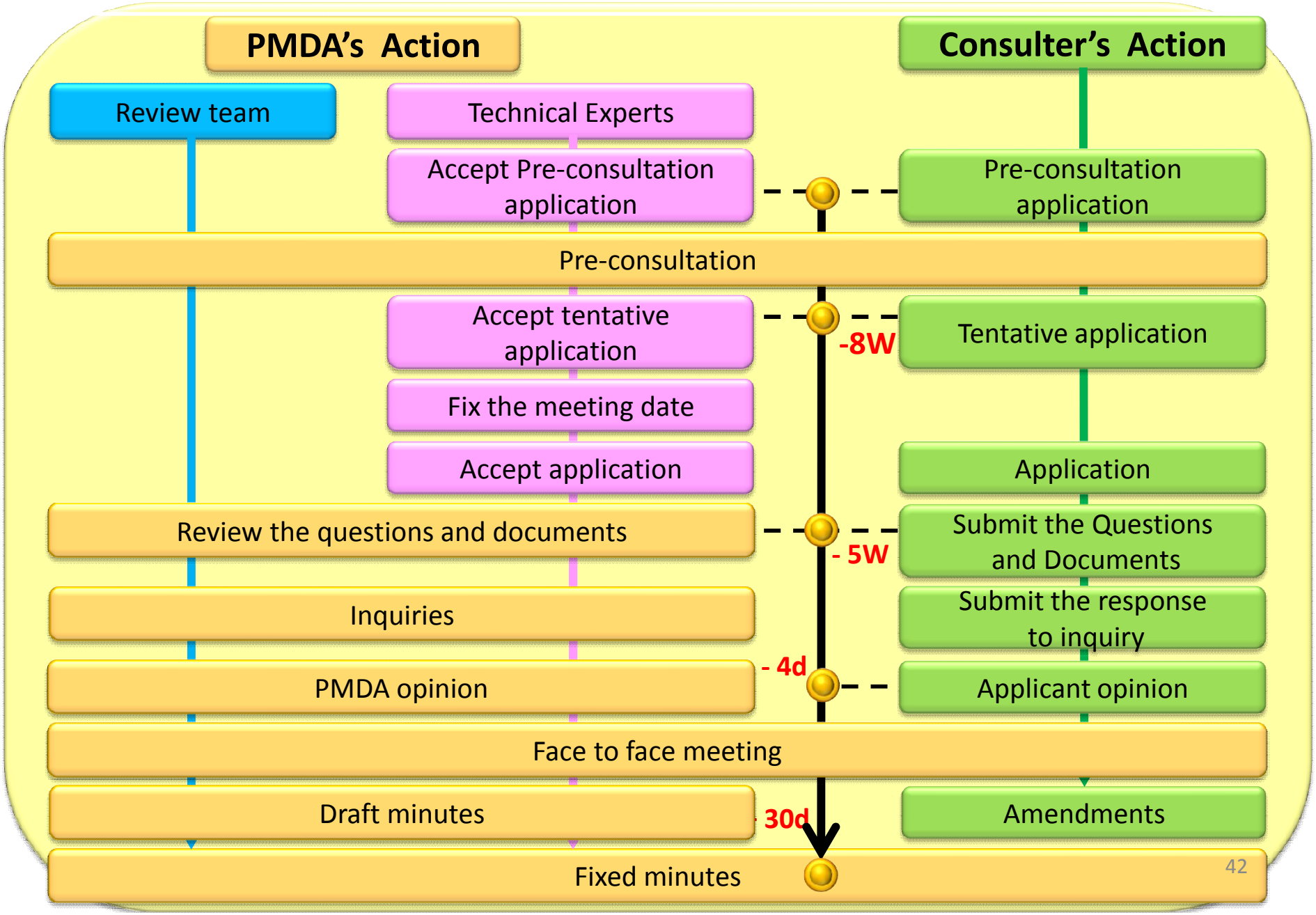


Pharmaceutical Affairs Consultation Group on R&D Strategy

July 2011 started



Flow


PMDA's Action
Consulter's Action
Review team
Technical Experts
Accept Pre-consultation application
Pre-consultation application
Pre-consultation
Accept tentative application
-8W
Tentative application
Fix the meeting date
Accept application
Application
Review the questions and documents
- 5W
Submit the Questions and Documents
Inquiries
Submit the response to inquiry
- 4d
PMDA opinion
Applicant opinion
Face to face meeting
Draft minutes
30d
Amendments
Fixed minutes

Scope of the Pharmaceutical Affairs Consultation on R&D Strategy

Innovative Products in following priority area

- Regenerative medicine (cell- and tissue- based products)
- Cancer
- Incurable disease and orphan disease
- Pediatrics
- Other area, products utilizing particularly innovative technologies

(Note) Regardless of the order among the areas.

The number of each consultation

consultation	Pharmaceutical	Medical device	Regenerative medicine	total
Academia	11	1	2	14（54%）
Venture	0	1	2	3（11%）
Other	5	0	4	9（35%）
total	16（61%）	2（8%）	8（31%）	26（100%）

Pre-consultation	Pharmaceutical	Medical device	Regenerative medicine	total
Academia	33	8	8	49（50%）
Venture	4	8	15	27（28%）
Other	8	6	8	22（22%）
total	45（46%）	22（22%）	31（32%）	98（100%）

Summary

- Consultation system in Japan is the important tool to support and encourage drug development for regulatory approval.
- PMDA provides consultations tailored for a range of needs and challenges to make the better consultation systems for each other.

Thank you for your attention !