Clinical Trial Application and Consultation Systems in East Asia with Expected Improvements in China and Japan from an Industry Point of View

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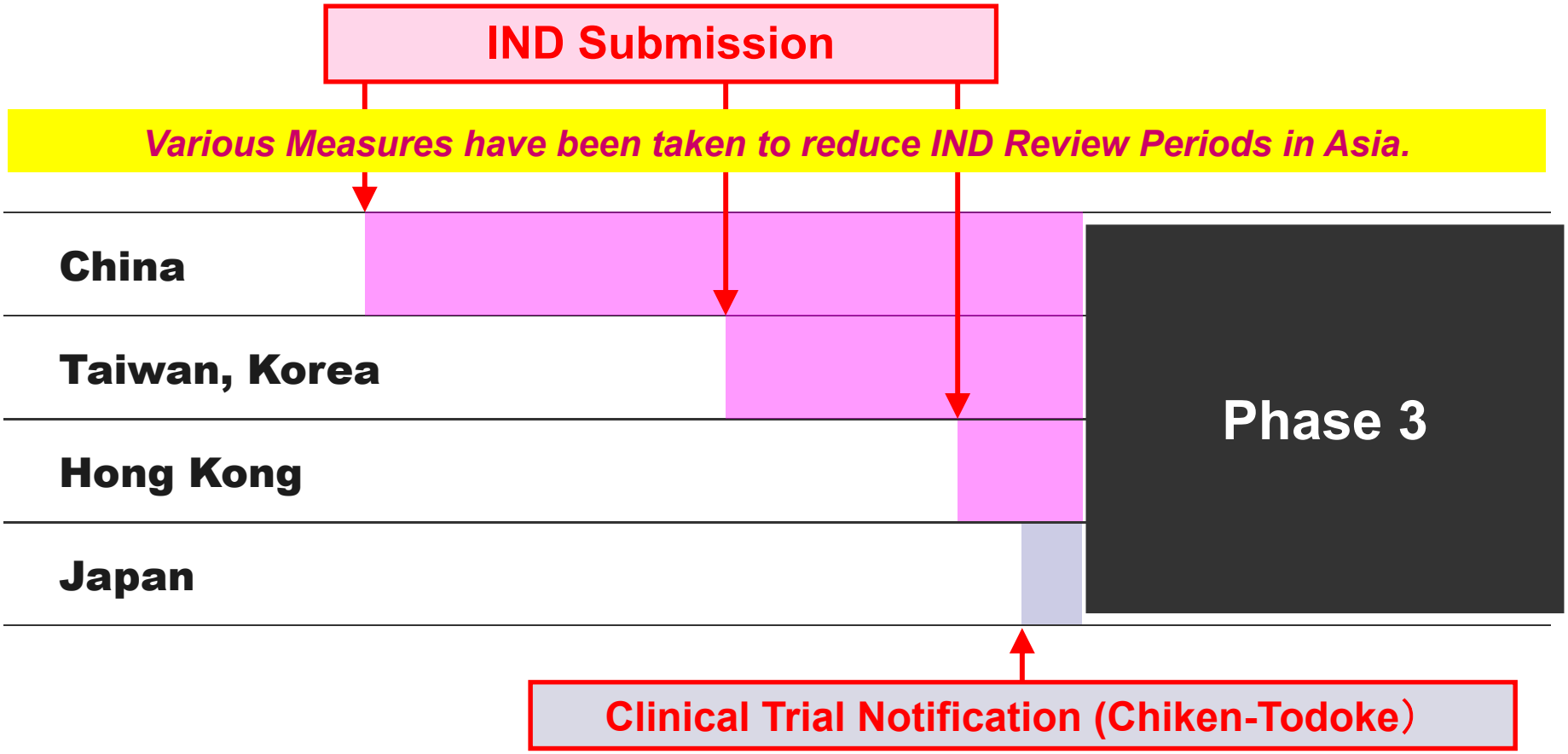
Contents

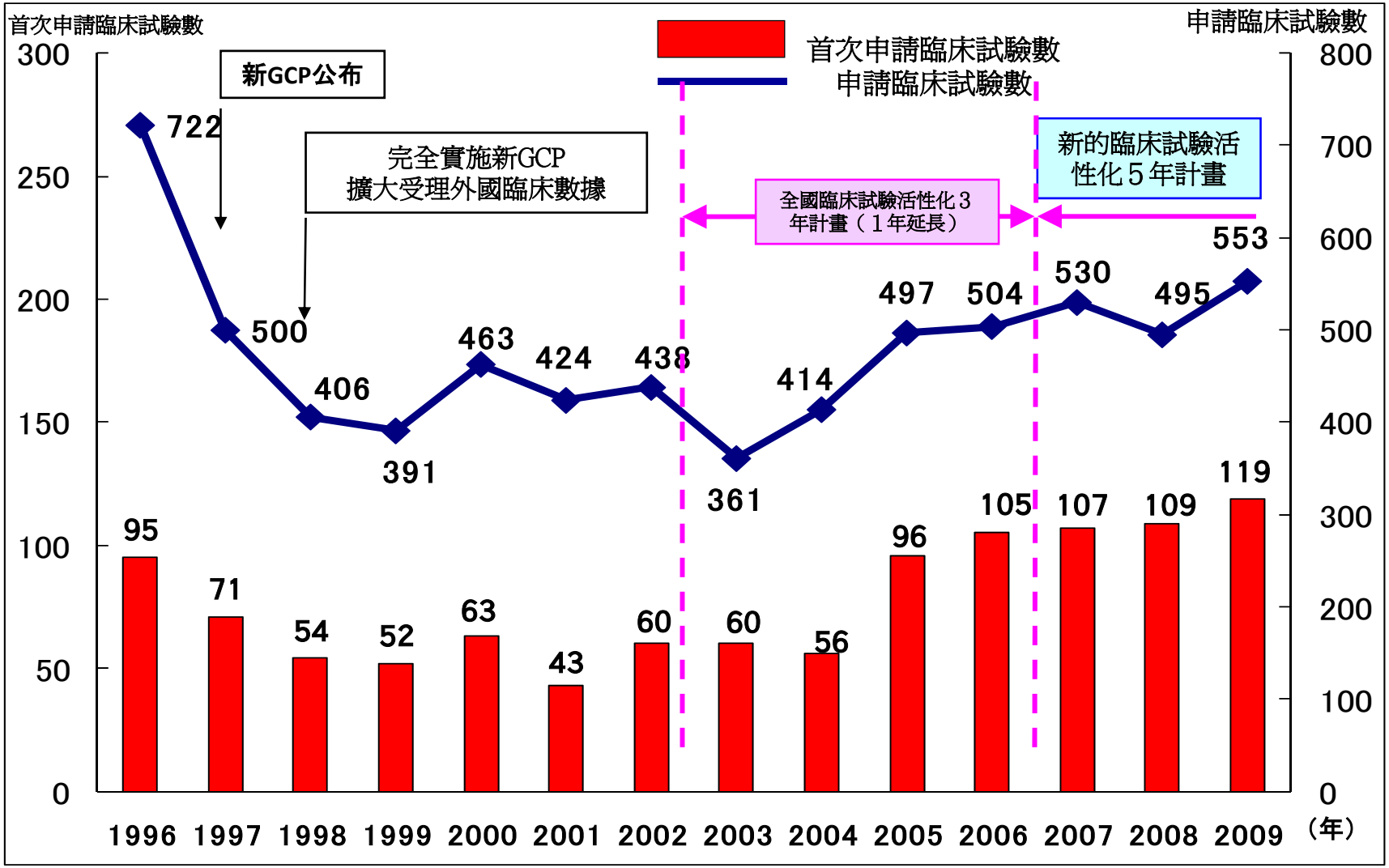
Timing of IND Submissions in Asia

If you need Simultaneous First Patient Enrollment .....



申請臨床試驗計畫數量之推移 (Japan)

出處:厚生勞動省



MultiNational Clinical Trial Notification (CTN) Scheme in Taiwan (18/Aug/2010-)

- MNCT protocol approved by one of the 10 reference countries: US, UK, France, Japan, Switzerland, Canada, Australia, Belgium, Sweden, Germany
- At least one of Taiwan's medical centers joins the trial together with sites of reference countries
- Only administration reviewed by TFDA, no technical evaluation from CDE unless regarded as high risk
- TFDA reserves the right to amend the trial during trial conduction

Herng-Der Chern, Taiwan CDE, 5th Japan-Taiwan Joint Seminar (10/Dec/2010)

CTN in Taiwan (18/Aug/2010 – 31/Jan/2011)

Month	Reg. Review No.	CTN No.	Reg. Review Time	CTN Review Time
18-31 Aug.	6	0	39.3 d	-
Sept.	21	5	43.0 d	15.2 d
Oct.	10	3	38.6 d	20.7 d
Nov.	14	3	26.8 d	20.7 d
Dec.	17	4	29.9 d	15.5 d
Jan. 2011	17	2	29.4 d	18 d
Total / Ave.	85	17	34.5 d	17.5 d

Herng-Der Chern, Taiwan CDE, Workshop for Clinical Trial Professionals (22/Feb/2011)

Characteristics of CTN Cases in Taiwan

- Ph I: 1, Ph II: 6, Ph III: 10
- From 8 big pharma and 1 domestic company
- Indication: Cancer 6, DM 3, Hepatitis 2, Psoriasis 2, Asthma 2, Major Depression 1, Ophth. 1, Orphan Disease: 1
- Join with other Asian countries: Japan 7, China 1, Korea 9, Hong Kong 7
- No case regarded as high risk

Herng-Der Chern, Taiwan CDE, Workshop for Clinical Trial Professionals (22/Feb/2011)

Potential Future Impact of CTN in Taiwan

- ✓ Most MNCT will be CTN cases
- ✓ Short and predictable review time
- ✓ More time for competitive subject enrolment
- ✓ Increase Ph I-II trials, first in Caucasian/Asian strategy for big pharm and domestic companies
- ✓ Regulatory consultation via Pre-IND, End of Ph II meeting to build "IND Process"

Herng-Der Chern, Taiwan CDE, 5th Japan-Taiwan Joint Seminar (10/Dec/2010)

Guidance on IND approval in Korea

- Title: Guidance on IND approval (KFDA notification)
- The date of enforcement: Aug. 25th, 2010
- Pre-IND consultation has practically been implemented in Korea.
  - Mandatory for Phase I with healthy subjects (adults) only except for cell therapy products, gene therapy products and preventive vaccines
  - Taking 24 WDs to get the written results from KFDA
  - Based on the results of pre-IND consultation, the review period for the IND application could be 14 WDs only for Phase I with the healthy subjects

Before	After
– Optional, but rarely used – Period : 50 WDs	– Mandatory for Phase 1 with healthy subjects (adult) only – Period : 24 WDs for Phase I 50 WDs for Phase II & III

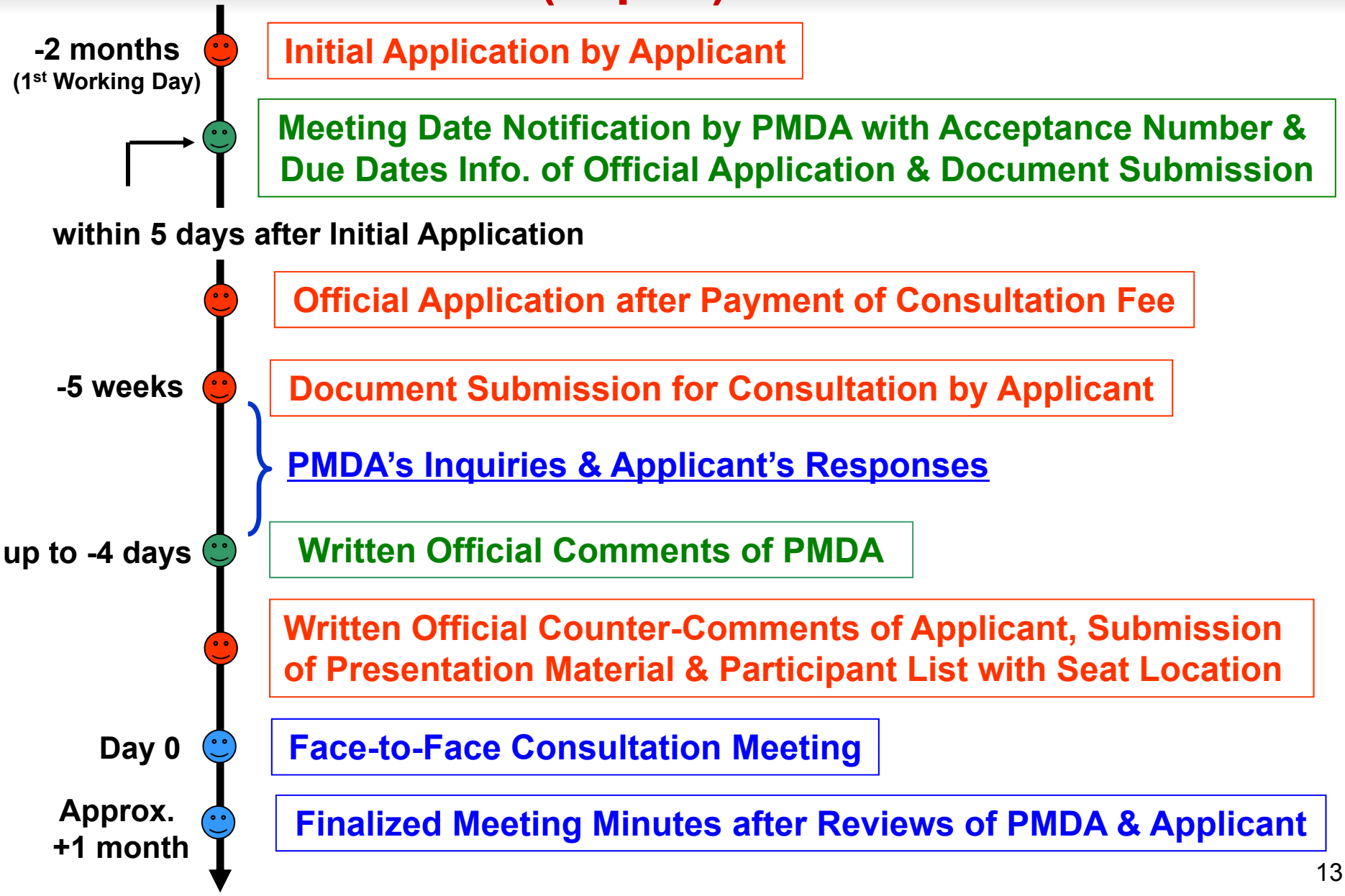
Contents

Types of Consultations with PMDA for Medicinal Products (Japan)

Consultations	Fees (JPY)
1. Application Procedure Consultation	139,800
2. BE Study Consultation	556,000
3. Safety Consultation	1,782,800
4. Quality Consultation	1,478,300
5. Pre-PI Consultation	4,239,400
6. Pre-PIIa Consultation	1,623,000
7. Pre-PIIb Consultation	3,028,400
8. End of PII Consultation	6,011,500
9. Pre-NDA Submission Consultation	6,011,400
10. Pre-Post Marketing Study for Re-evaluation or Re-examination Consultation	3,320,600
11. End of Post Marketing Study for Re-evaluation or Re-examination Consultation	3,319,400
12. Additional Consultation between the Stages above	2,675,600

(Source: PMDA Website)

Timeline for Consultation with PMDA for Medicinal Products (Japan)



Number of PMDA Consultations in FY2009 by Category for Medicinal Products (Japan)

Category	Consultations
Category 1 (Gastrointestinal drugs)	35
Category 6-2 (Hormone drugs)	35
Category 2 (Cardiovascular drugs)	52
Category 5 (Drugs for urogenital system)	19
In vivo diagnostics	1
Radiopharmaceuticals	5
Category 3-1 (Central/peripheral nervous system drugs)	42
Category 3-2 (Anestheteic drugs)	22
Category 4 (Antibacterial agents)	35
AIDS drugs	0
Category 6-1 (Respiratory tract drugs)	32
Anti-cancer drugs	54
Blood products	8
Bio-CMC	11
Biological products	16
Cell- and tissue-based products	1
[Re-listed] Prior assessment (pre-NDA review)	33
Pharmacogenomics and biomarkers	1
GLP/GCP compliance (for priority reviews)	1
Total	370
Withdrawn	23
Grand total	393

(Source: Profile of Services, FY 2010, PMDA)

Expected Number of PMDA Consultations in May 2011 by Category for Medicinal Products (Japan)

Category	Exp. No.
Category 1 (digestive system agent, dermatological preparation)	3
Category 2 (cardiovascular agent, antiparkinsonian drug , brain circulation drug, metabolic improvement drug, anti Alzheimer drug)	3
Category 3-1 (agents affecting the central nervous system, peripheral nervous system drug excluding anesthetic agent)	3
Category 3-2 (anesthetic agent, sensory organ drug excluding those relating to inflammatory disease, narcotic drug)	1
Category 4 (antibacterial agent, antivirus (infestant) agent excluding anti AIDS drug), Anti HIV infectious drug	4
Category 5 (genitourinary tract disorder agent, drugs for anal, ethical combination preparation), Diagnostic product, Radioactive agent	1
Category 6-1 (respiratory drug, allergy drug, sensory organ drug (gastrointestinal inflammatory condition drug))	4
Category 6-2 (hormonal agent, metabolic disease agent excluding combination preparation)	3
Anticancer drug	6
Hematological drug	1
Quality of biotechnology-based drug including gene therapy drug	0
Biological product	2
Cell therapy drug	0
Total	31

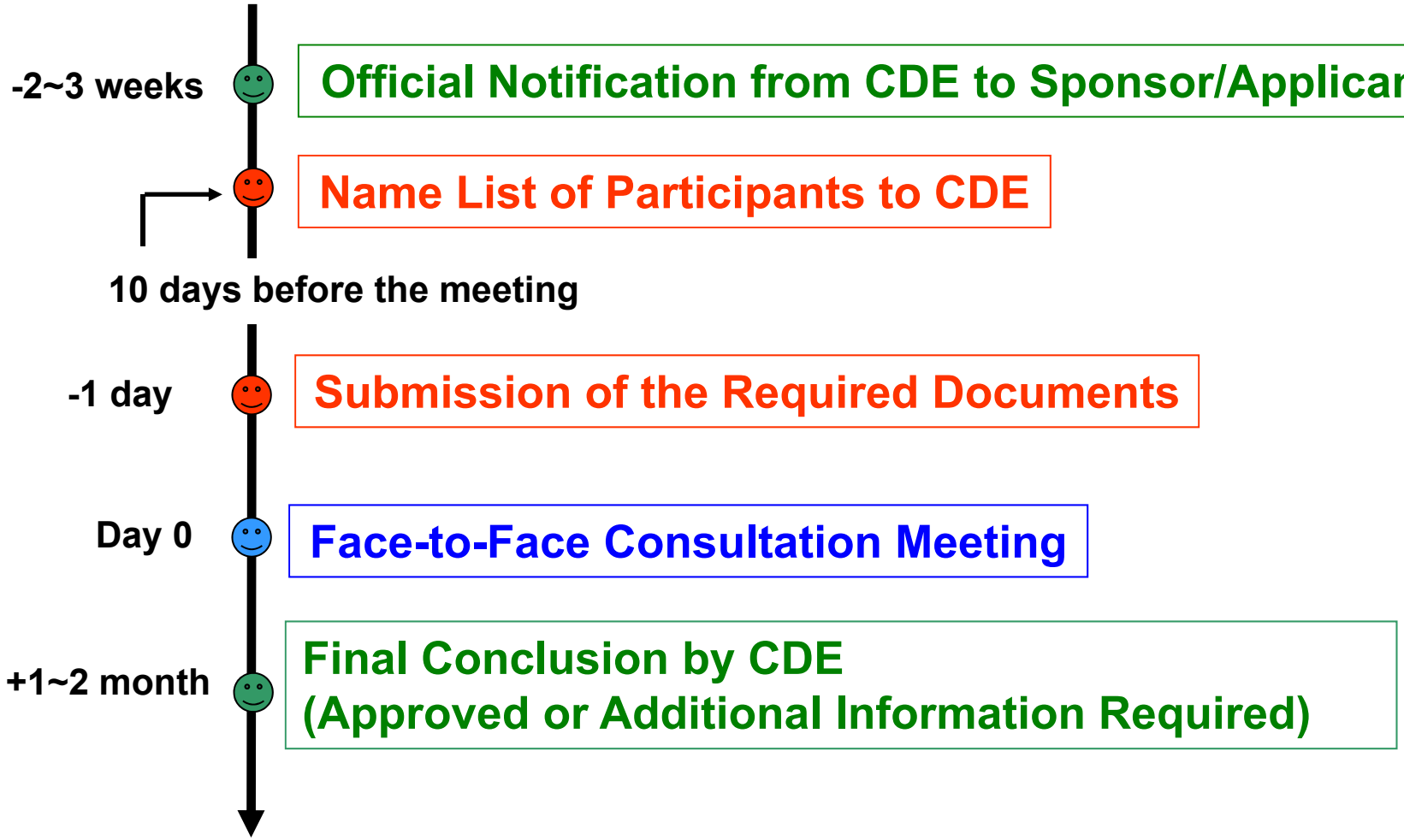
(Source: PMDA Website with Unofficial Translation)

Types of Consultations with SFDA/CDE for Medicinal Products (China)

Consultations		Aims for Consultation	Official/un-official	Time	Fees (RMB)
General consultations for medicinal products to SFDA (Chemical Drug Division/General Division)	Raised by applicants to SFDA	Applicants consult for regulation, application procedure, etc.	Unofficial, no meeting minutes	The 2nd and 4th Tuesday of the month	no
Pre-CTA submission consultations for NCE medicinal products (only for special review process)	Raised by applicants to CDE	Applicants have questions on special review process, technical issue, etc.	Official, but maybe only for domestic applicant up to now?	Determined by CDE	no
Pre-NDA submission consultations for NCE medicinal products to CDE	Raised by applicants to CDE	Applicants have questions on important technical issues, etc.	No information up to now	no	no
CDE-initiated consultation meeting for medicinal products (mainly for NCE drugs)	Raised by CDE to domestic applicants	CDE has technical issues to discuss with sponsors/applicants	Official, with meeting minutes	Depends on CDE review progress	no
	Raised by CDE to external experts	CDE has technical issues to consult with external experts, and needs explanations from applicants	Official, with meeting minutes	Depends on CDE review progress	no
Follow-up consultations for medicinal products to CDE	Raised by applicants to CDE	After dossier submission, applicants consult for technical questions or review progress.	Unofficial, no meeting minutes	Every Wednesday	no

Timeline for CDE-initiated Consultation Meeting for Medicinal Products (mainly for NCE Drugs) (China)

If the Sponsor/Applicant is Invited by CDE .....



Consultations with KFDA for Medicinal Products (Korea)

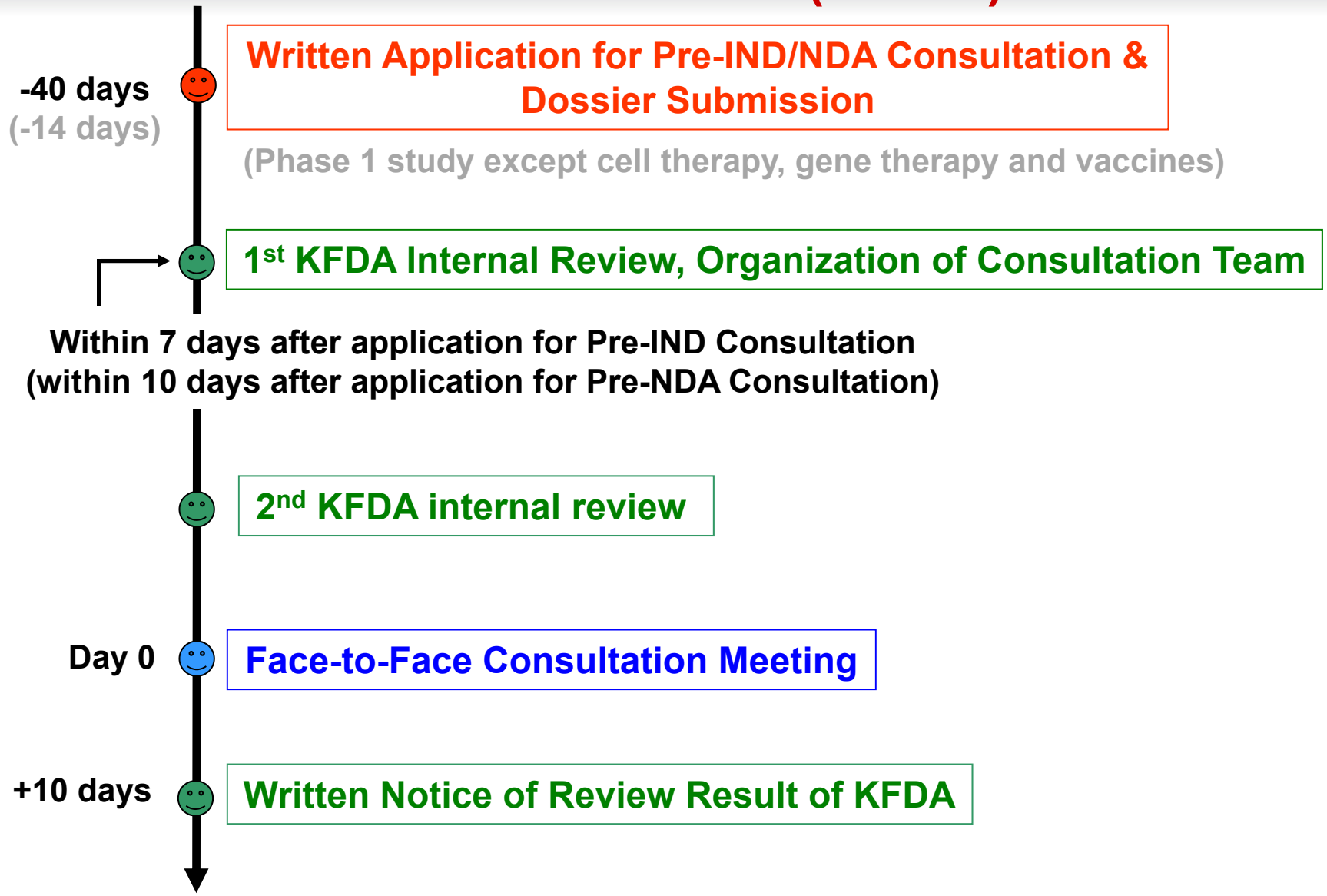
- **No user-fee system on KFDA Consultations**

  - **Pre-IND Consultation**
    - In accordance with 'Guidance on IND approval (KFDA notification)'
    - Written application form and consultation outcome
    - All IND dossier required
    - Face-to-face basis

  - **Pre-NDA Consultation**
    - In accordance with 'Operational guidance on pre-review request for pharmaceutical product (announced by Pharmaceuticals Safety Strategy Division)'
    - Written application form and consultation outcome
    - All NDA dossier required
    - Face-to-face basis

  - **Consultation on Applicant's Request (before submission)**
    - Handled by Center for Drug Development Assistance
    - Email-basis communication (application and response)
    - Face-to-face meeting is possible if KFDA needs
    - No legal binding force about the consultation outcome

Timeline for Pre-IND/NDA Consultation with KFDA for Medicinal Products (Korea)



Consultations with TFDA/Taiwan CDE for Medicinal Products (Taiwan)

- **TFDA entrusts Center for Drug Evaluation (CDE) to handle consultations**
- **No user-fee system on Consultations with CDE**
  - **Pre-IND Consultations**
    - Synopsis and background information/reference required
  - **Consultations on Applicant's request**
    - R & D Consultation (for Strategy)
    - CMC Consultation for Domestic Pharma
    - Clarify NDA Deficiency Letter
    - Bridging Study Consultation (when Bridging Study is required)
  - **Response in writing (e-mail/fax/letters), telephone communication or face-to-face meetings could be determined by CDE**
  - **No legal binding force for above consultation outcome**

Timeline for Consultation with Taiwan CDE for Medicinal Products (Taiwan)

Contents

Challenging Comparative Charts in East Asia (1 of 2)

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China	Data	Note
No. of Consultation	N/A	
No. of Clinical Trial Application	1,419	in 2009
No. of NDA (Application)	6,428	in 2009
No. of CDE Reviewers	94	as of Jan. 2011
Registration Fee	45,300 RMB (for CTA of MRCT or CTA&NDA)	for Import Drug

Japan	Data	Note
No. of Consultation	393	in FY2009
No. of Clinical Trial Notification	553	in FY2009
No. of NDA (Approval)	15 (Priority Review) 92 (Standard Review)	New Drug in FY2009
No. of PMDA Reviewers	389	as of Apr. 2010
Registration Fee	Free (for CTN) > 30,000, 000 JPY (for NDA of New Drug)	

Challenging Comparative Charts in East Asia (2 of 2)

JPMA

Korea	Data	Note
No. of Consultation	N/A	
No. of Clinical Trial Application	400	in 2009
No. of NDA (Approval)	48	NME in 2010
No. of KFDA Reviewers	> 150	(estimation)
Registration Fee	Free (for CTA) 4,239,000 KRW (for NDA incl. DMF)	

Taiwan	Data	Note
No. of Consultation	N/A	
No. of Clinical Trial Application	187	in 2009
No. of NDA (Sub. / Approval)	28 / 20	NCE in 2010
No. of Reviewers (TFDA / CDE)	80 / 100	(estimation)
Registration Fee	15,000 NTW (for CTA) 600,000 NTW (for NDA of NCE)	

Contents

Expected Improvements in China toward Simultaneous Global Development

JPMA

1. **Remodeling of Clinical Trial Application System (Separation of CTA and NDA with Shortening of CTA Review Period)**
   leads to **Elimination of Very Tough Enrollment Plan Environments in China (such as Chinese FPI just before Global LPI)**
2. **Enlargement of Human Resources of SFDA and CDE with Budget System Change**
   leads to **Establishment of Efficient Consultation System**
3. **Science-based Major Revision of Drug Registration Regulation (e.g. discarding 100/arm for Chemical and 300/arm for Biological)**
   leads **China to Real Global Major Player**

Expected Improvements in Japan toward Simultaneous Global Development

1. Acceleration of Penetration in Japanese Citizen about Correct Understanding of Necessity of Earlier Start of Early-phase Clinical Trial in Japan with Mutual Respectful Cooperation among Industry/Agency/Academia and Media
   leads to Elimination of Drug Lag at Development Stage in Japan
2. Environmental Improvement of PMDA Organization (e.g. Further Clarification of Role Sharing with MHLW, Further Power Sharing, Staff Status Protection)
   leads PMDA to More Confident Global Major Agency
3. Acceleration of East Asian Joint R&D to relieve Japanese Citizen's Persistence in Japanese Data
   leads Japan to Survived Global Major Player

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谢谢!

Win-Win Relationship between China and Japan

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Acknowledgment

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