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Outlook of Orphan and Pediatric Drug Development from Regulatory Perspectives

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Agenda

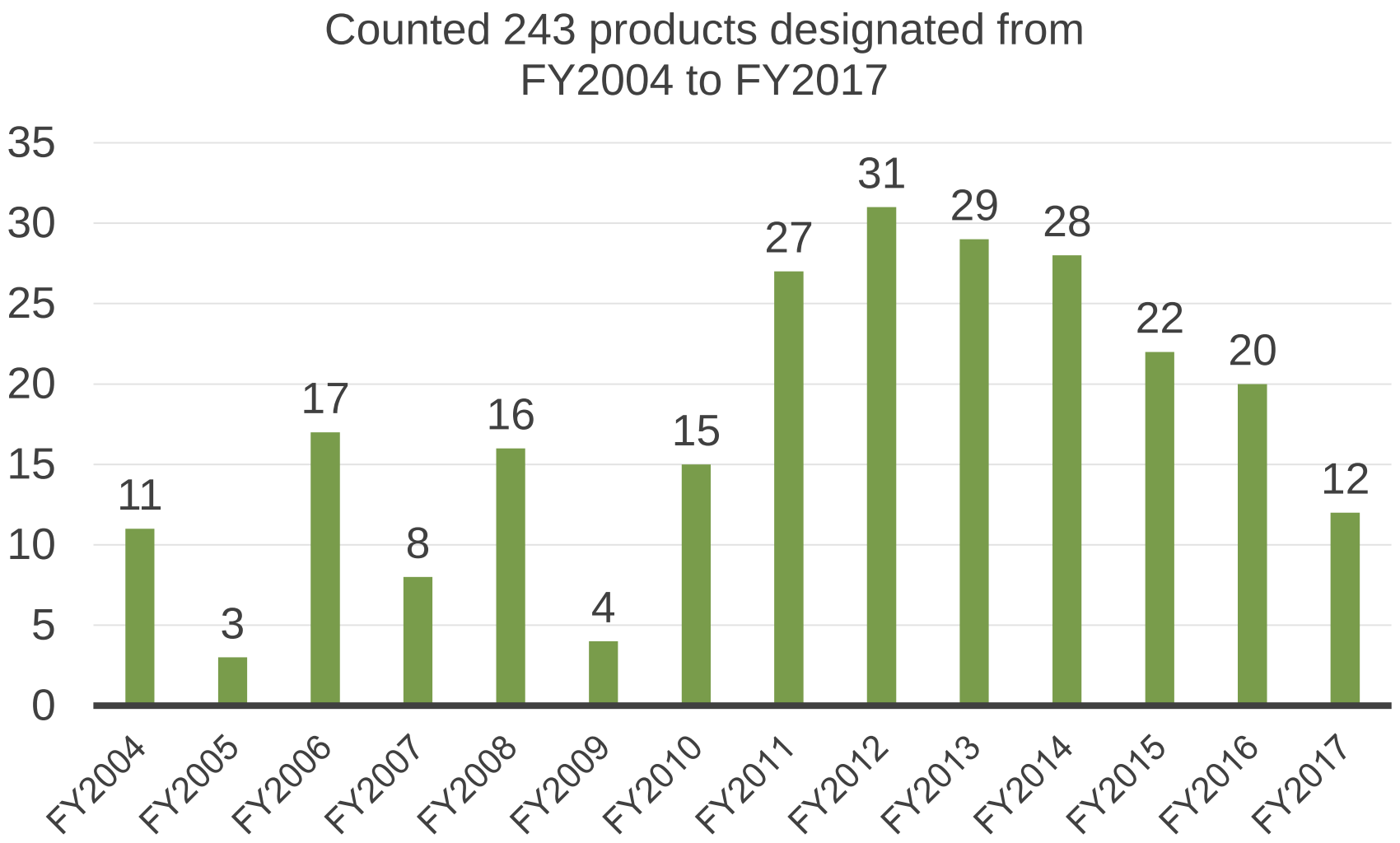
- Trends of orphan and pediatric drug in Japan
- Case study
  - Spinraza® (Nusinersen)
- Future prospects
- Summary

Trends of orphan and pediatric drug in Japan

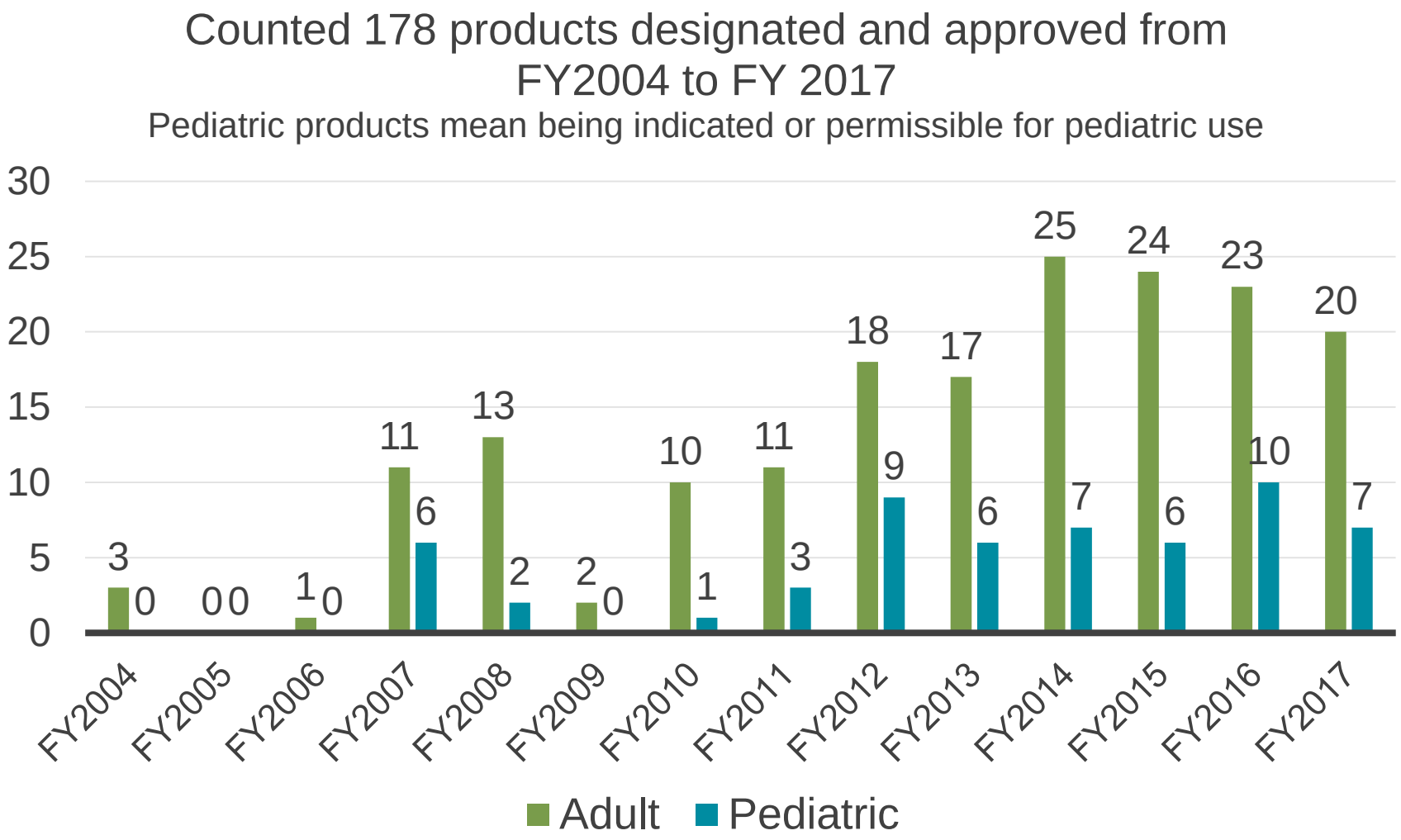
PMDA Orphan Drug Working Group

- Review and analyze the problems surrounding development of orphan drug.
- Propose new perspectives and approaches for orphan drug development driven by advancement of science.
- Promote orphan drug development without a time-lag between domestic and international approval.
- Strengthen collaboration with other regulatory agencies for development of orphan drug.
  - Terms of reference between PMDA and EMA (2012)

Trend of designation of orphan drugs in Japan



Trend of approval of orphan drugs for adult and pediatric in Japan



Case study

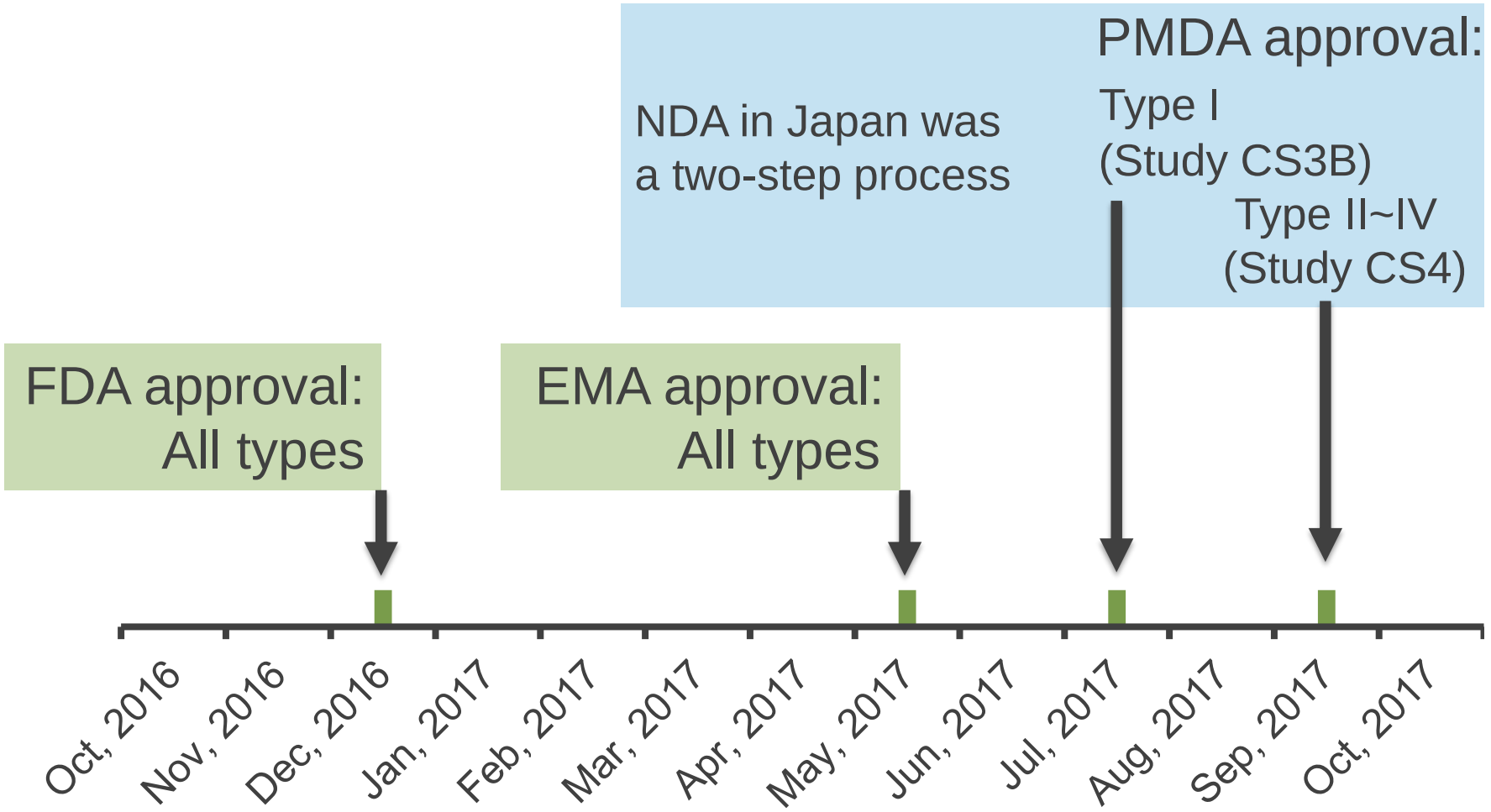
Case study: Spinraza® (Nusinersen)

- Spinraza® (Nusinersen)
- Type: New molecular entities, Antisense oligonucleotide
- Applicant: Biogen Japan Ltd
- Indication: Spinal muscular atrophy (SMA)
- The number of target patients: Less than 1000 in Japan
- Orphan drug (designated on Nov 24, 2016)
- Mechanism of action:
  - Increases the proportion of exon 7 inclusion in *SMN2* mRNA transcripts by binding to an intronic splice silencing site found in intron 7 of the *SMN2* pre-mRNA.

SMA type and characteristics

SMA Type	Age of Onset/ Functional Milestone Achievement	*SMN2* Copies	Estimated Prevalence
Type I	Onset within first 6 months/ Never sit, rapid progression	1-3	58%
Type II	Onset 6-18 months of age/ Sit, but never walk	3	29%
Type III	Onset > 18 months of age/ Walk, but with difficulty	3-4	13%
Type IV	Onset at adult age/ Increasing disabilities after onset	≥ 4	-

Timeline of global approval



Study CS3B: Design

- Study Population
  - Symptomatic infants ≤ 7 months of age at the time of first dose, diagnosed with SMA (symptom onset before 6 months of age).
- Study Intervention
  - Sham-procedure or nusinersen 12 mg (adjusted by age in days) were administered on study days 1, 15, 29, 64, 183, and 302.

Study CS3B: Design

- Global Phase III trial
- Study Population
  - **Planned:** 111 Subjects (Sham-procedure 27 subjects, nusinersen 74 subjects including **8 Japanese subjects**).
  - **Actual: 3 Japanese subjects were enrolled** and allocated to 1 subject in sham-procedure and 2 subjects in nusinersen. At the time point of the interim analysis, 1 subject in sham-procedure is used.
- Primary Efficacy Endpoint (Interim Analysis)
  - Proportion of motor milestone responders (Section 2 of the Hammersmith Infant Neurological Examination [HINE])

Study CS3B: Result

Arm	Subjects	Proportion of motor milestone responders [a] (Section 2 of the HINE (%)	Difference [95%CI] [b]	P-value [c]
Sham-procedure	27	0	41.2 [18.2, 61.2]	<0.0001
Nusinersen	51	41.2 (21)		

a) Proportion（The number of subjects）
b) The exact confidence interval for the difference of proportions
c) Fisher exact test (alpha level for the interim analysis: 0.032)

Study CS4: Design

- Study Population
  - 2 to12 years of age, symptom onset after 6 months of age, can sit independently, but has never be able to walk.
- Study Intervention
  - Sham-procedure or nusinersen 12 mg were administered on study days 1, 29, 85, and 274.

Study CS4: Design

- Global Phase III trial
- Study Population
  - **Planned:** 117 Subjects (Sham-procedure 39 subjects, nusinersen 78 subjects including **8 Japanese subjects**).
  - **Actual: 8 Japanese subjects were enrolled** and allocated to 3 subjects in sham-procedure and 5 subjects in nusinersen.
- Primary Efficacy Endpoint (Interim Analysis)
  - Change from baseline in Hammersmith Functional Motor Scale – Expanded (HFMSE) score at 15 months.

Study CS4: Result

Arm	HFMSE score		Change [a,b]	Difference [95% CI] [c]	P-value [b,c]
	Baseline	15 Months			
Sham-procedure	19.9 ± 7.23 (42)	19.9 ± 8.13 (19)	-1.9 ± 0.97	5.9 [3.7, 8.1]	0.0000002
Nusinersen	22.4 ± 8.33 (84)	24.9 ± 10.64 (35)	4.0 ± 0.56		

Mean ± SD (number of subjects)
a) Least squares mean ± SE
b) Based on ANCOVA with treatment as a fixed effect and adjustment for each subject's age at screening and HFMSE at baseline
c) Alpha level for the interim analysis: 0.025

Japanese subjects enrollment in study CS3B: Applicant's explanation

- Based on the information of the SMART Consortium [a)], enrollment of 8 to 12 Japanese subjects was expected.
- Because there were no effective treatment, it was anticipated that an informed consent would be obtained smoothly.
- However, due to very low prevalence of SMA, it was difficult to identify potential subjects even though using the SMART Consortium.
- Low awareness of SMA in Japan delayed the diagnosis and resulted in disease progression, therefore some patients did not fulfill the inclusion/exclusion criteria.
- Even if patients were diagnosed in early stage, some patients could not take the screening examination due to SMA worsening.

a) SMA Research & Treatment Consortium

Japanese subjects enrollment in study CS3B: PMDA's discussion

- The applicant should have prepared the clinical trial with promoting enlightenment activities about SMA and setting up the system to ensure the enrollment of Japanese subjects.
- The number of the Japanese subjects is limited and make it difficult to evaluate the consistency between the Japanese population and the entire population.
- However, considering the drug's mechanism of action, the intrinsic and/or extrinsic ethnic factors affecting the drug, it is possible to assess efficacy and safety using the CS3B study as a global clinical trial.

Including SMA type IV in the indication

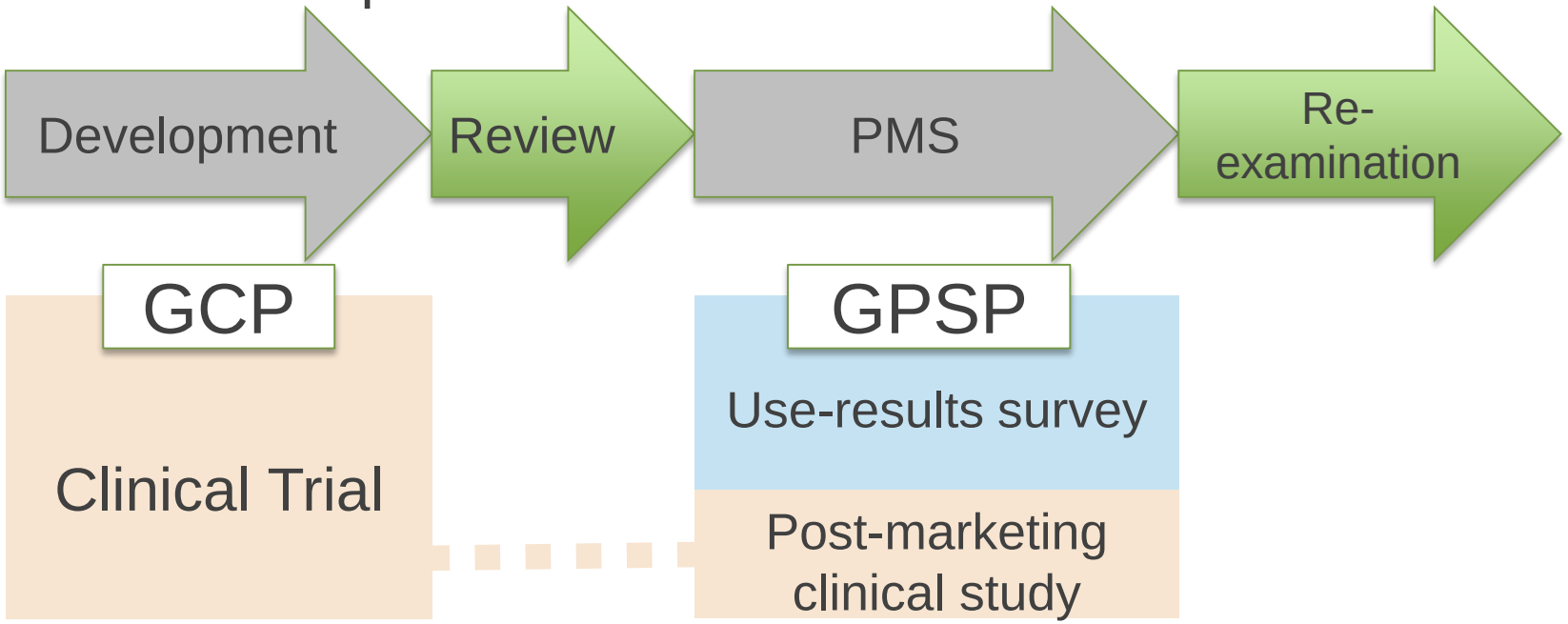
- No SMA type IV patient was enrolled in the study CS4
- PMDA’s discussion
  - The proposed indication, "Spinal Muscular Atrophy" including type IV, is acceptable considering the drug's mechanism of action, the common disease characteristics among SMA types and the low feasibility of conducting clinical trial of SMA type IV.
  - The information about the enrolled SMA types in clinical trials should be included in the package insert, and the PMS should collect a relationship between the SMA type and the drug's efficacy/safety.

Future prospects

Applying real-world data to orphan drug

- Utilizing disease registry data

  From development to re-examination

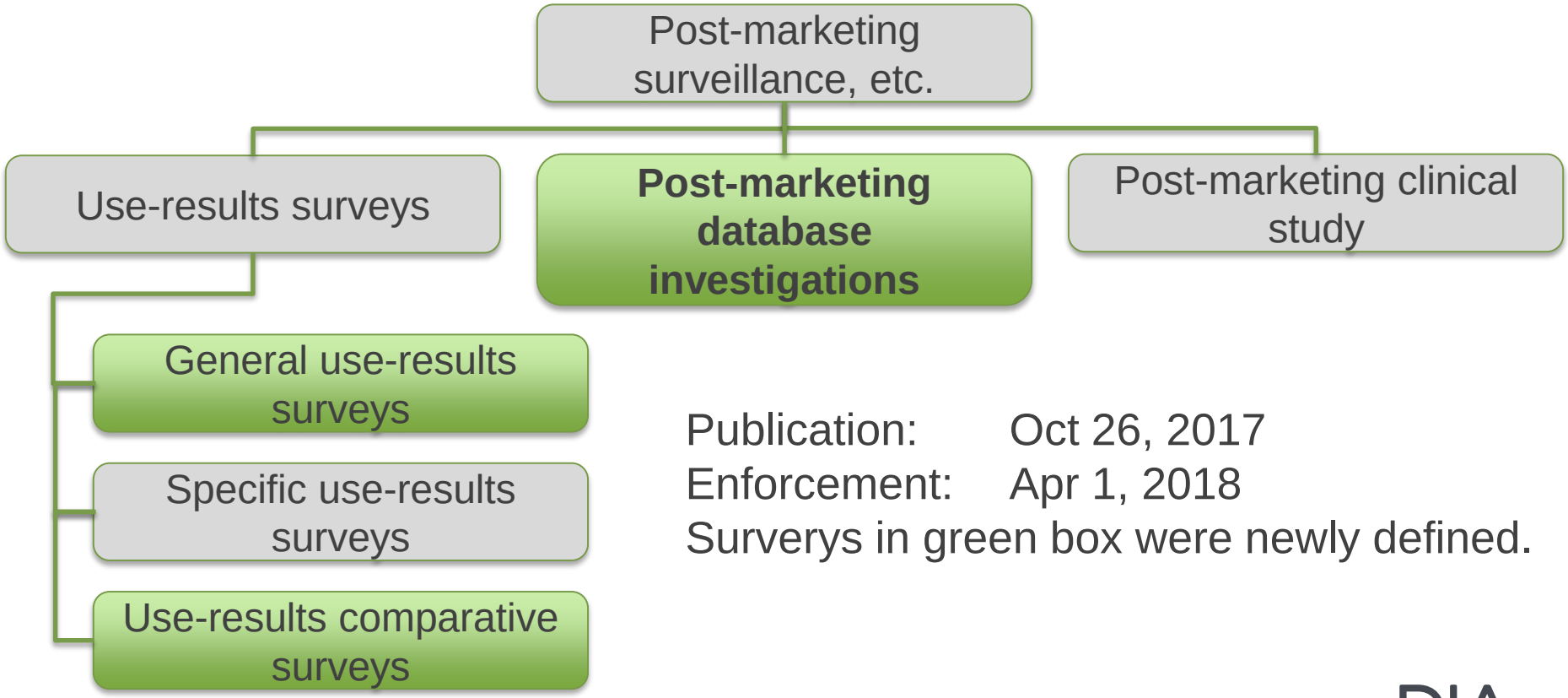


e.g. Clinical trials for rare disease which is difficult to conduct randomized control study

e.g. Conducting survey or study in a more efficient manner

Revision of the GPSP Ordinance

- To ensure the reliability in case a survey utilizing the medical information database is used as data submitted for re-examination, the GPSP Ordinance was revised.

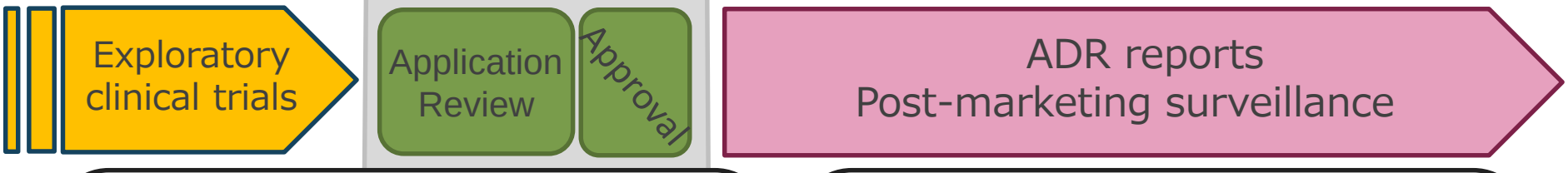


Publication: Oct 26, 2017
Enforcement: Apr 1, 2018
Surverys in green box were newly defined.

Conditional Early Approval System for Pharmaceutical Products

Standard regulatory review process

Conditional Early Approval System



- Early application through confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials
- Shorten overall review times for priority review products

Setting conditions for approval(e.g.)

- Reconfirmation of post-marketing efficacy and safety (including using real-world data)
- Setting requirements such as facility requirements if needed for proper use

Conditional Early Approval System for Pharmaceutical Products: Eligibility

Meet the all requirements from 1 to 4 listed below

1. Seriousness of indications
   - Diseases which have significant impact on lives (life-threatening diseases)
   - Progress of disease is irreversible and the disease has a significant impact on daily lives
   - Others
2. Medical usefulness
   - No existing remedies, preventive therapies or diagnostics
   - Medical usefulness is better than that of existing remedies, preventive therapies or diagnostics in terms of efficacy, safety, and patient's physical and mental burden
3. Being difficult to conduct confirmatory clinical trials or considered to take considerable time to complete trials because of a limited number of patients
4. Considered to have of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials

Support from academia and funding agency

- “Research of drug selection to promote new drug development for pediatric”: AMED research project
  - Japan Pediatric Society (JPS), National Center for Child Health and Development.
  - Based on information of development items submitted from pharmaceutical companies, the research project shall select a drug which should be listed on the Priority List, and support its clinical trials along with the JPS and relevance academic society.
- CiCLE (Cyclic Innovation for Clinical Empowerment): AMED grant program
  - Featuring a multi-years contract up to 10 years and a large budget up to 10 billion yen per individual project.
  - The AMED waivers the charges for research results to be paid to the AMED regarding a project which is listed on the JPS Priority List or designated as an orphan drug.

Summary

Summary

- Development and approval of orphan drugs including for children have shown steady growth over a recent decade in Japan.
- Even targeting rare pediatric disease, a drug with innovative mechanism of action would benefit from global clinical trials.
- Use of the real world evidence and/or refine of the accelerated approval pathway are expected to advance orphan drug development.