外資系企業における承認品目の傾向
～PhRMA/EFPIA合同調査結果より～

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1 米国研究製薬工業協会（PhRMA）、 2 欧州製薬団体連合会（EFPIA）
所属は調査開始時のもの、またPhRMA, EFPIA双方に加盟している場合は本調査における主な活動母体を示している

COI開示：演題発表内容に関連し、発表者らに開示すべき利益相反はありません。

PhRMA/EFPIAで実施した2021年度の合同調査結果は以下の通りであった

- 2020年度には医薬品57品目、再生医療等製品1品目、バイオシミラー（臨床試験なし）2品目計60品目*が承認された
- 承認品目（医薬品）の審査期間は総合機構の審査期間目標値である通常審査品目12ヵ月、優先審査品目9カ月（80パーセンタイル）を達成した
- 優先審査品目、希少疾病品目の割合はそれぞれ31%、26%であり、先駆け指定品目及び条件付き早期承認制度利用品目はなかった
- これらの承認品目の米国の審査においては迅速審査制度が幅広く活用されていた
- 新有効成分19品目中、米国が世界初の承認となった品目は12品目と最多を占めた日本が世界初の承認となった品目は3品目、EUは1品目であった
- PMSは承認品目58品目中（医薬品57品目、再生医療等製品1品目）、39品目（67%）で実施され、うち全例調査は11件（27%）であった。製造販売後データベース調査は6件でPMS全体の15%であった

*特例承認の2品目を除く

PhRMA-EFPIA Joint Survey 2021

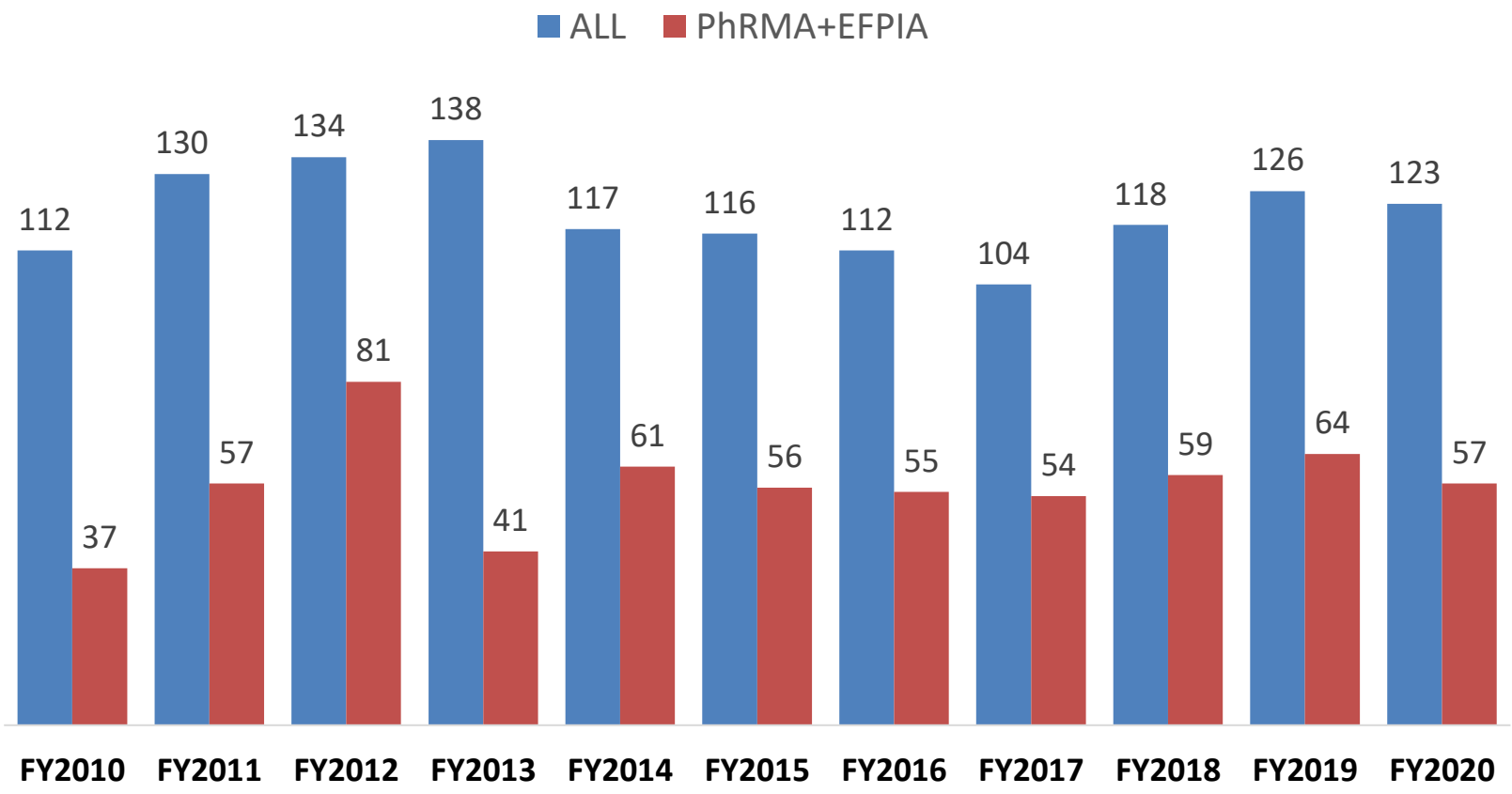
- Review Period
  - Review time for new drug approvals in FY2020
  - Utilization of expedited program
  - Submission/approval lag
- PMS
  - PMS in approved new drugs in FY2020
  - Use of electronic approval/signature in PMS operation
- Clinical Studies and Development Plan
  - Projects ongoing in FY2020
  - Submission lag
  - Development status in China
  - Global and local studies ongoing in FY2020
  - Interaction with the agency for global studies
- CDISC for NDA
- Use of real world data

Participating companies:

- PhRMA (10 companies)
  - Abbvie, Amgen, Biogen Japan, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, MSD, Pfizer, and Gilead Sciences
- EFPIA (15 companies)
  - AstraZeneca, Bayer, CHUGAI, CSL Behring*, Ferring, GlaxoSmithKline, Janssen, LEO, Lundbeck, Merck Biopharma, Boehringer Ingelheim, Novartis, Novo Nordisk, Sanofi, and UCB

* Joined PhRMA from 2021 but FY2020 data is categorized as EFPIA data

The Number of New Drug Approvals in Japan

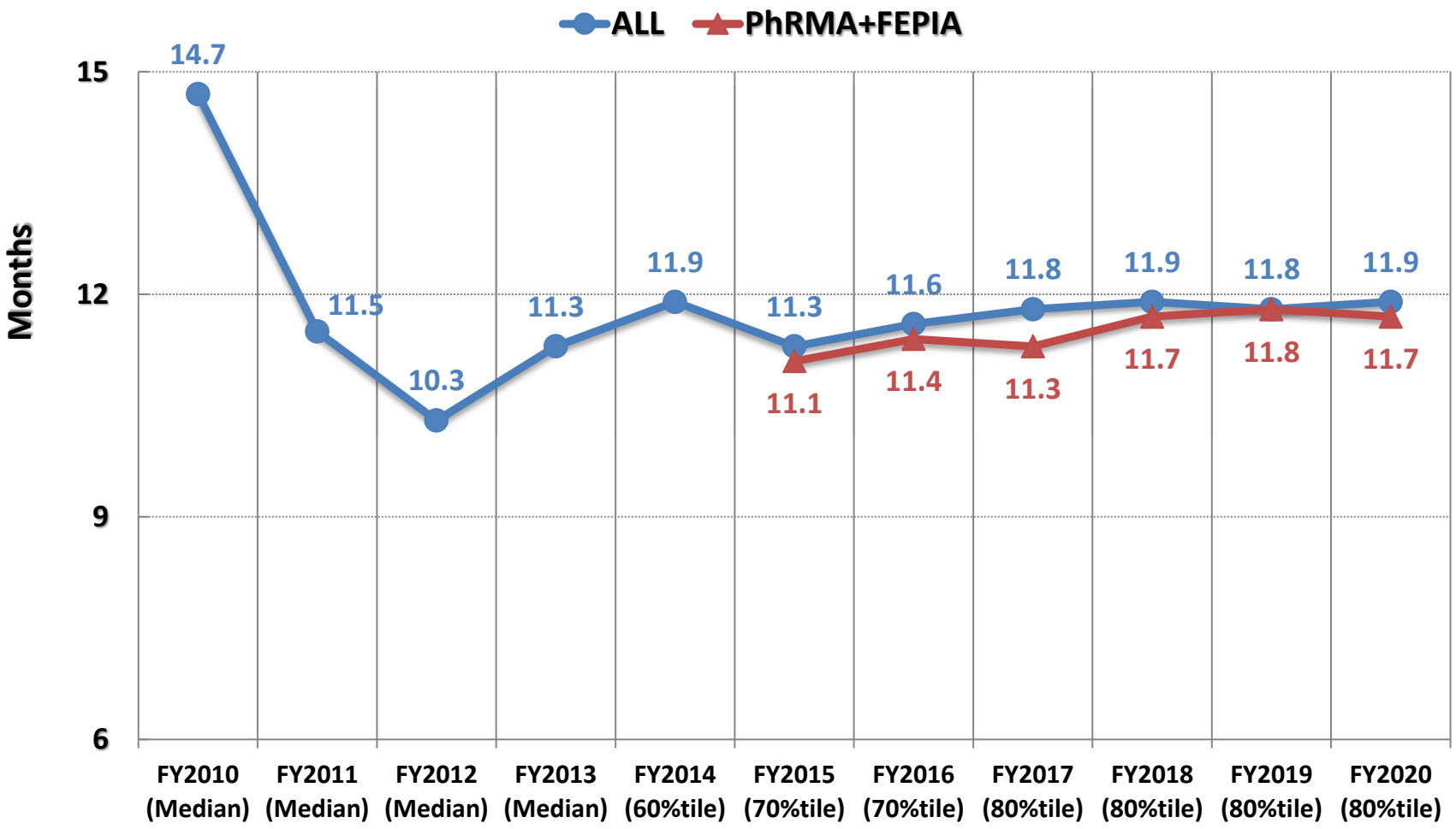


Around half (46%) of drug approvals were EFPIA + PhRMA's in FY2020

Note: Total 60 compounds were approved.
Two cases of exceptional approvals, one regenerative medicine and two biosimilar w/o clinical studies were excluded from FY2020 PhRMA+EFPIA

Duration of JNDA Review for Standard Review

PhRMA + EFPIA (N=40)

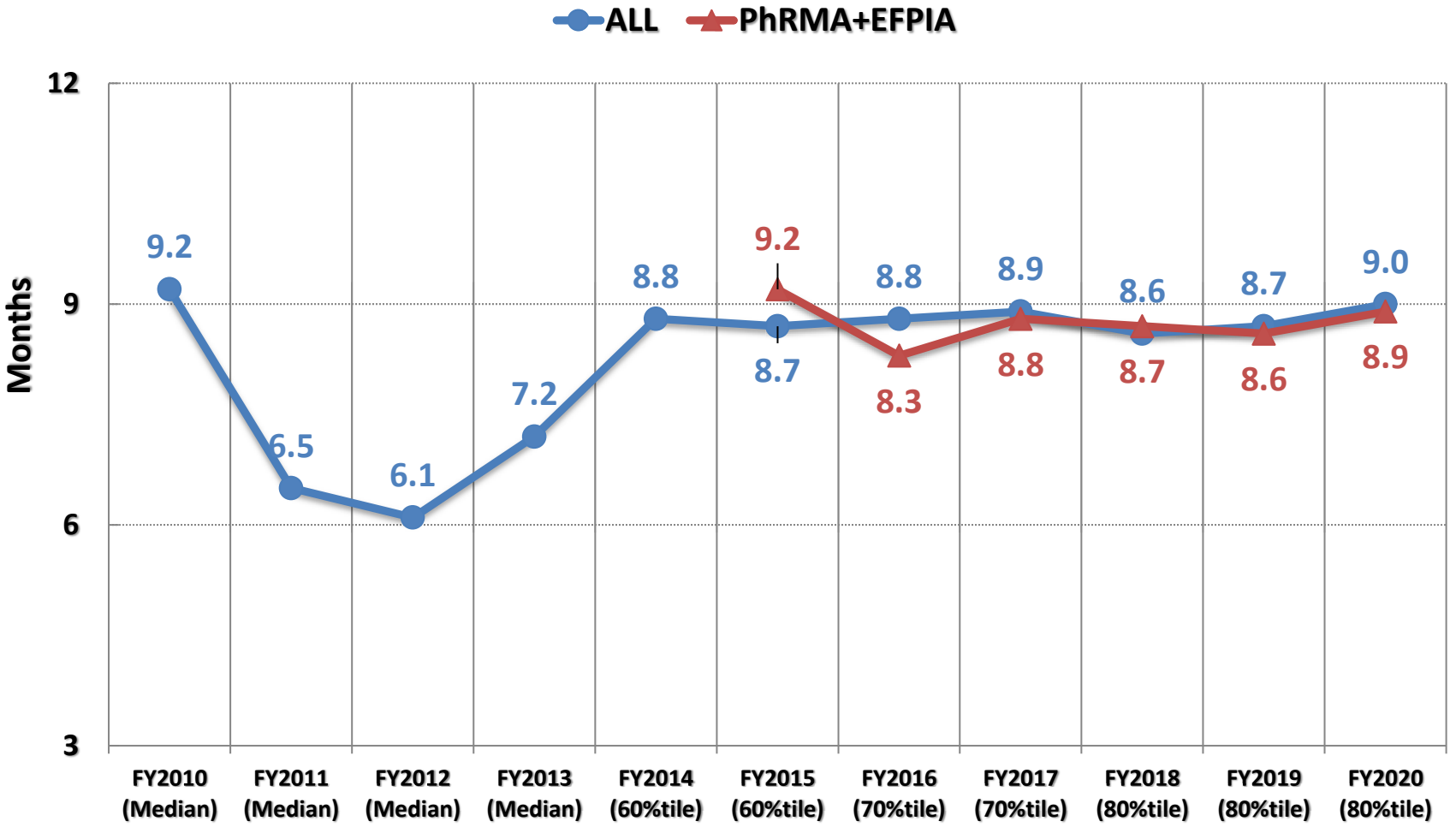


Duration of JNDA Review for "Standard Review" in FY2020 was less than 12 months in 80%tile

Duration of JNDA Review for Priority Review

Including Paper JNDAs

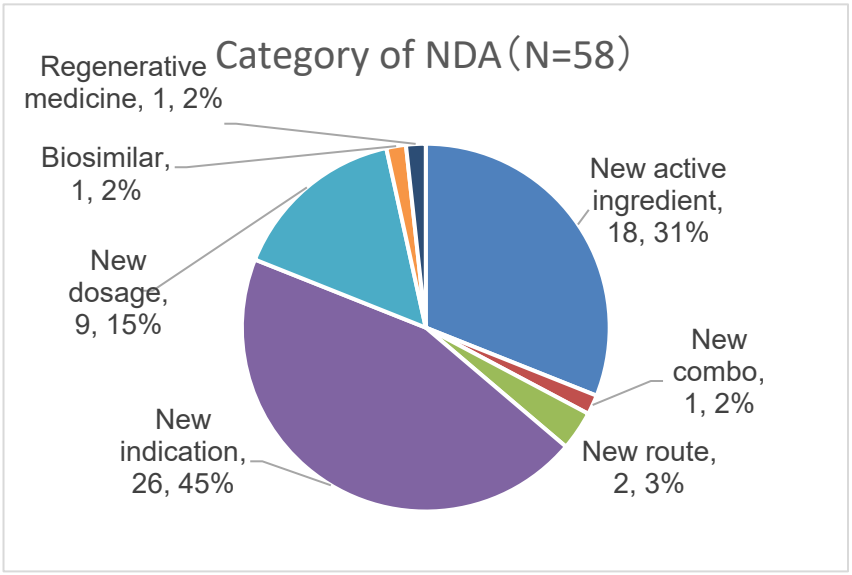
PhRMA + EFPIA (N=17)

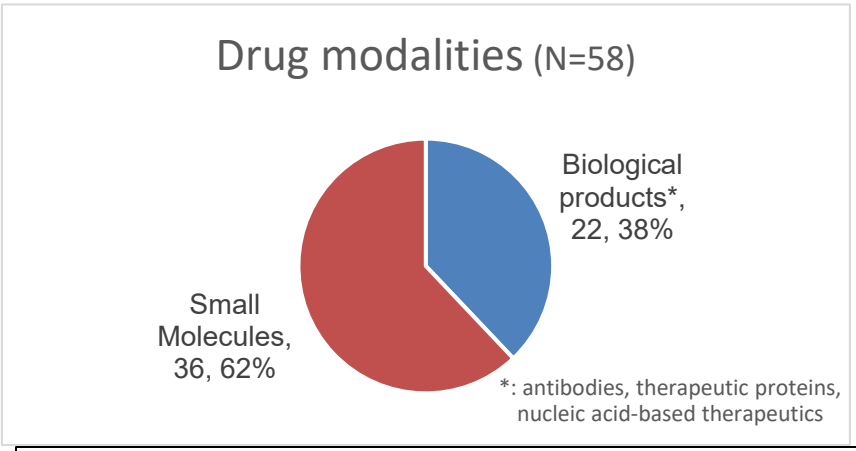


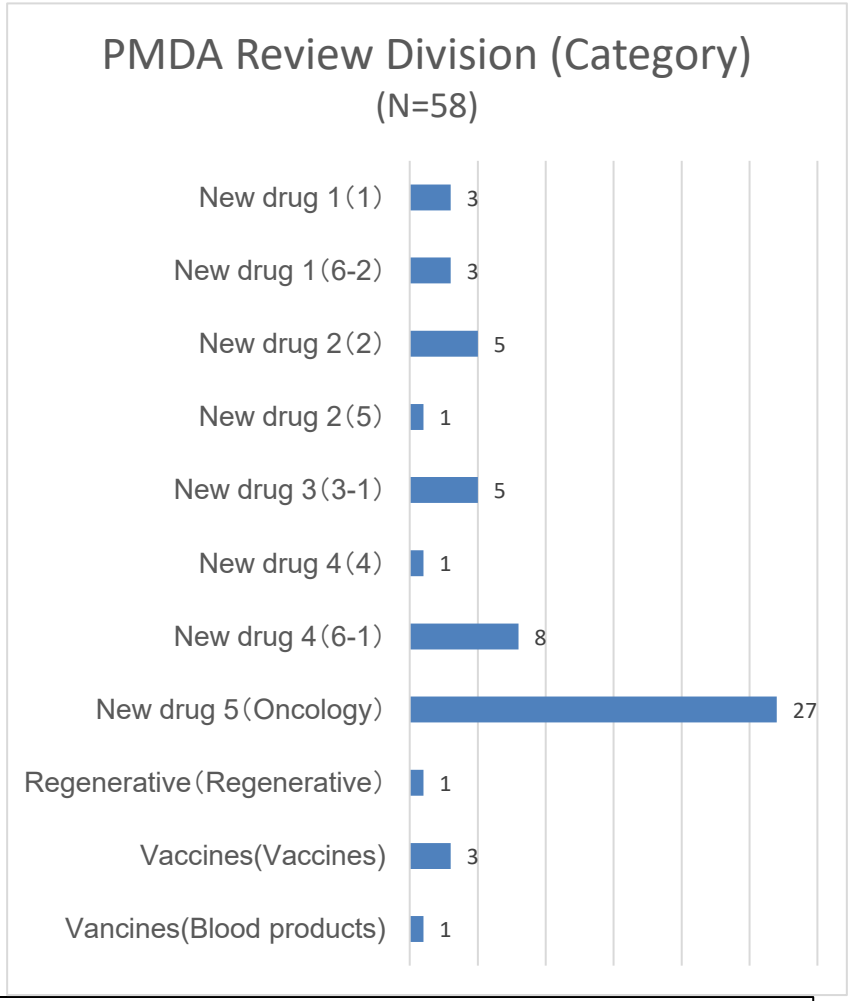
Duration of JNDA Review for “Priority Review” in FY2020 was 9 months in 80%tile

Background of Approved Products PhRMA + EFPIA (N=58*)

*: 57 drugs and 1 regenerative medicine



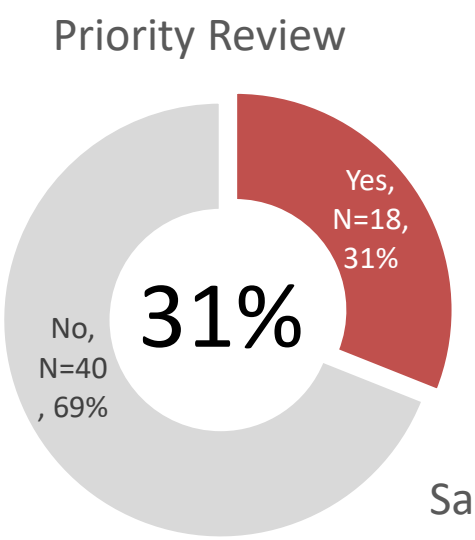


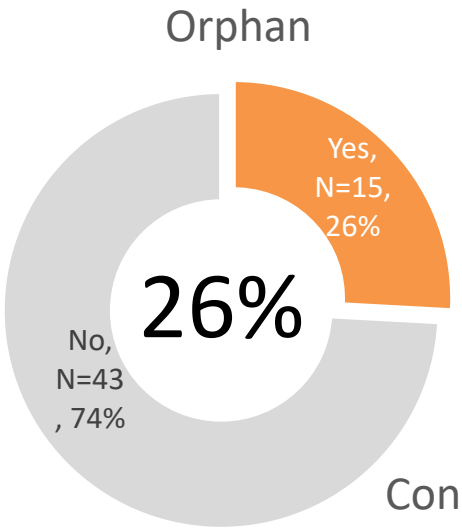


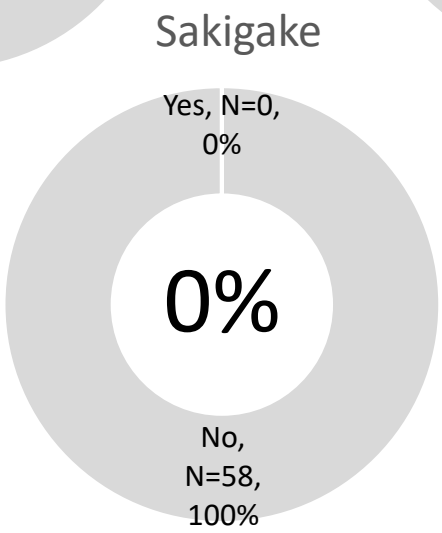
- “New indication” (45%) and “new active ingredient” (31%) were the majority of the JNDA
- Small molecules accounted for 62%, and the remaining 38% was Biological products.
- Oncology (27/58=47%) was the largest number of the division category in FY2020 (It was 35% in FY2019)

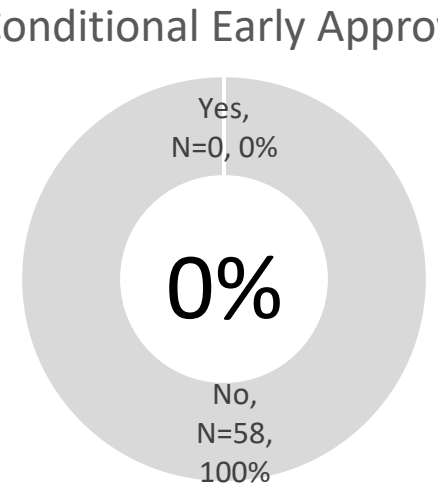
Utilization of Expedited Program

PhRMA + EFPIA (N=58)





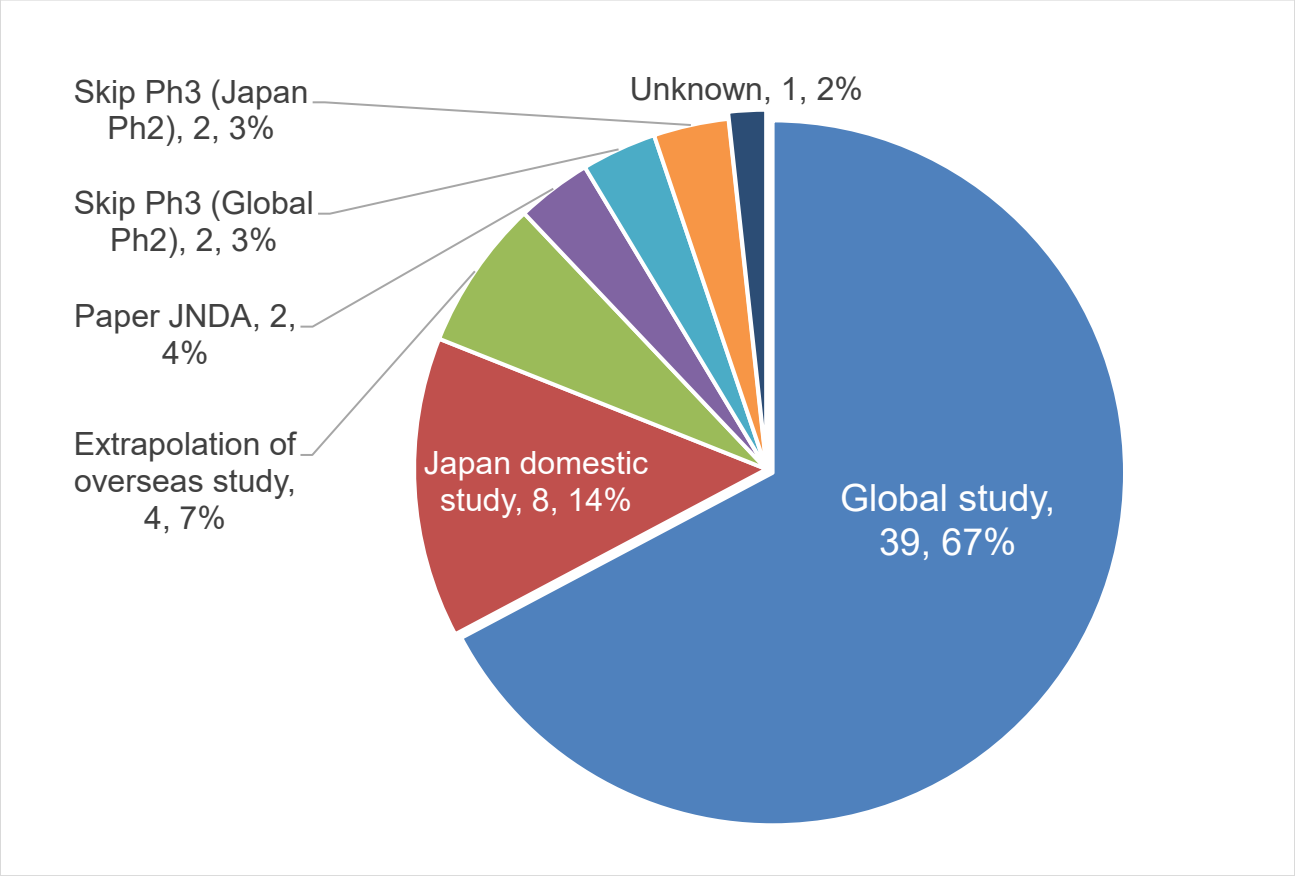




- In FY2020, 31% of products were approved through the Priority review and 26% were the Orphan drug review
- No Sakigake case, No Conditional Early Approval in FY2020

Type of Phase 3 Study in Clinical Data Package

PhRMA + EFPIA (N=58)



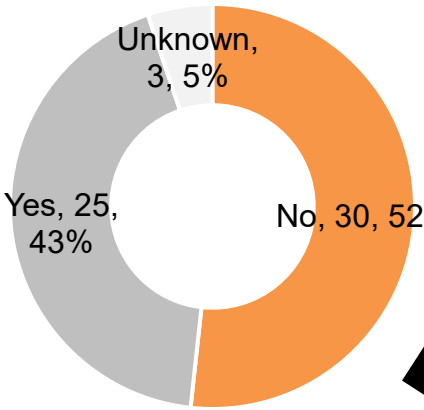
Type of Phase 3 study in Clinical Data Package are mainly:

1) "Global studies" 67% (FY2019: 54%)
2) "Japan domestic studies" 14% (23%)
3) "Extrapolation of overseas study" 7% (14%)

Simultaneous JNDA filing

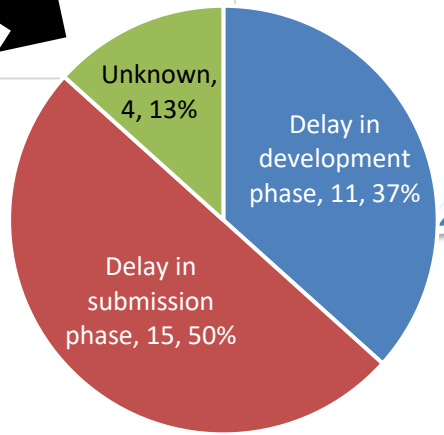
PhRMA + EFPIA (N=58)

Result of simultaneous JNDA filing (within 3 months) (N=58)



52%

Reason why simultaneous application could not be made (N=30)



Delay in submission phase

- Preparation of Japanese Module 2.3 or approval application (1)
- Wait for stability test results (1)
- Preparation of Table of CTD (1)
- Prioritize overseas (2)
- For company's convenience (free description)(4)
- Others(6)

Delay in development phase

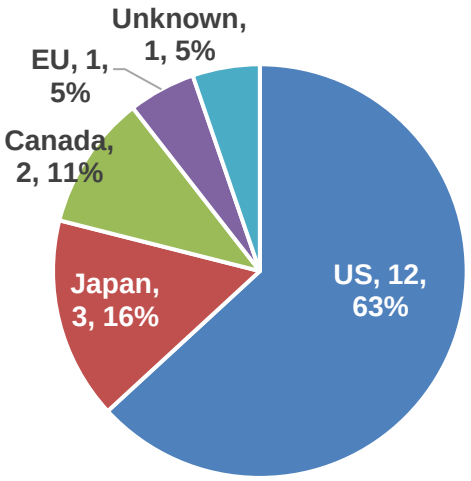
- Japan stand alone development (1)
- Already approved overseas (2)
- Japan could not join the MRCT(verification study) as it was already started (1)
- Japanese dose-finding study became necessary before join in MRCT (1)
- Others(5)
- Unknown (1)

Of the 52% of products that were not filed for JNDA simultaneously, 50% were delayed during the submission phase and 37% were delayed in the development phase.

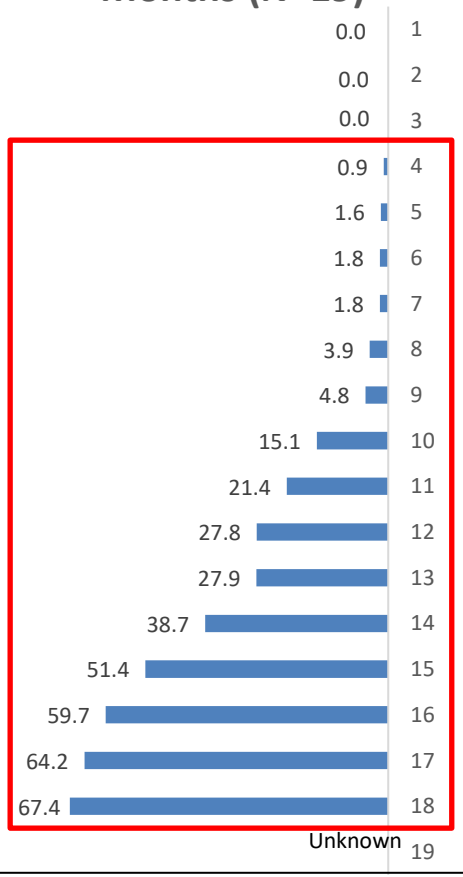
Drug lag for NME (New Molecular Entity)

PhRMA + EFPIA (N=19)

Country of the IBD (International Birth Date)



Approval Lag by Months (N=19)



What is the cause that Japan approval was delayed? Excludes products no Approval Lag (N=15)

Development start lag • Japan could not join the MRCT as it was already started (2) • Japanese dose-finding study was needed before joining MRCT (1) • Others(4)	7 (47%)
Submission lag • Preparation of Japanese Module 2.3 or approval application (1) • For company's convenience (3) • Others (2)	6 (40%)
Review lag • Expedited review was used in overseas (2)	2 (13%)

- Of these 19 NMEs, 12 were approved first (international birth date) in the US, 3 in Japan, two in Canada, and 1 in the EU.
- Cause of drug-lag in Japan : Development start lag 47%, Submission lag 40%, Review lag 13%

Utilization of Expedited Program

		PMDA (N=35)		FDA (N=30)							EMA (N=29)			
		Priority Review	Orphan	Breakthrough Designation	Accelerated Approval	Fast Track	Priority Review	Orphan	RTOR	Assessment Aid	Orbis	PRIME	Conditional Marketing Authorization	Accelerated Assessment	Orphan
Onc	1	PR	Orphan	BTD	AA	FT	PR	Orphan		Ass Aid				AA	
	2	PR	Orphan	BTD	AA		PR	Orphan				PRIME	CMA	AA	Orphan
	3	PR	Orphan	BTD	AA		PR	Orphan					CMA	AA	Orphan
	4	PR	Orphan	BTD				Orphan				PRIME			Orphan
	5	PR	Orphan		AA		PR								
	6	PR	Orphan									n/a	n/a	n/a	n/a
	7	PR	Orphan	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	8	PR		BTD			PR		RTOR	Ass Aid	Orbis				
	9	PR		BTD			PR		RTOR	Ass Aid	Orbis				
	10	PR		BTD					RTOR						
	11		Orphan				PR			Ass Aid					
	12			BTD	AA	FT	PR	Orphan	RTOR	Ass Aid	Orbis				
	13			BTD			PR								
	14			BTD					RTOR	Ass Aid					
	15				AA										
	16						PR	Orphan		Ass Aid				AA	
	17						PR	Orphan							
	18						PR			Ass Aid					
	19						PR								
	20							Orphan							Orphan
	21							Orphan							
	22														Orphan
	23								RTOR	Ass Aid		n/a	n/a	n/a	n/a
	24								RTOR	Ass Aid	Orbis	n/a	n/a	n/a	n/a
		10	8	10	6	2	13	9	7	10	4	2	2	4	5
Non-Onc	25	PR	Orphan	BTD		FT		Orphan							Orphan
	26	PR	Orphan				PR								Orphan
	27	PR	Orphan				PR								
	28	PR	Orphan												
	29	PR	Orphan	n/a	n/a	n/a	n/a	n/a							
	30	PR	Orphan	n/a	n/a	n/a	n/a	n/a							
	31	PR	Orphan	n/a	n/a	n/a	n/a	n/a				n/a	n/a	n/a	n/a
	32	PR		n/a	n/a	n/a	n/a	n/a				n/a	n/a	n/a	n/a
	33					FT								AA	
	34					FT	PR								
	35						PR								
		8	7	1	0	3	4	1	-	-	-	0	0	1	2

- Japan's expedited review system tends to depend on priority review (and orphan) and could not utilize another pathway
- Expedited program is widely granted in oncology projects by FDA

PhRMA+EFPIA's PMDA approvals in FY2020

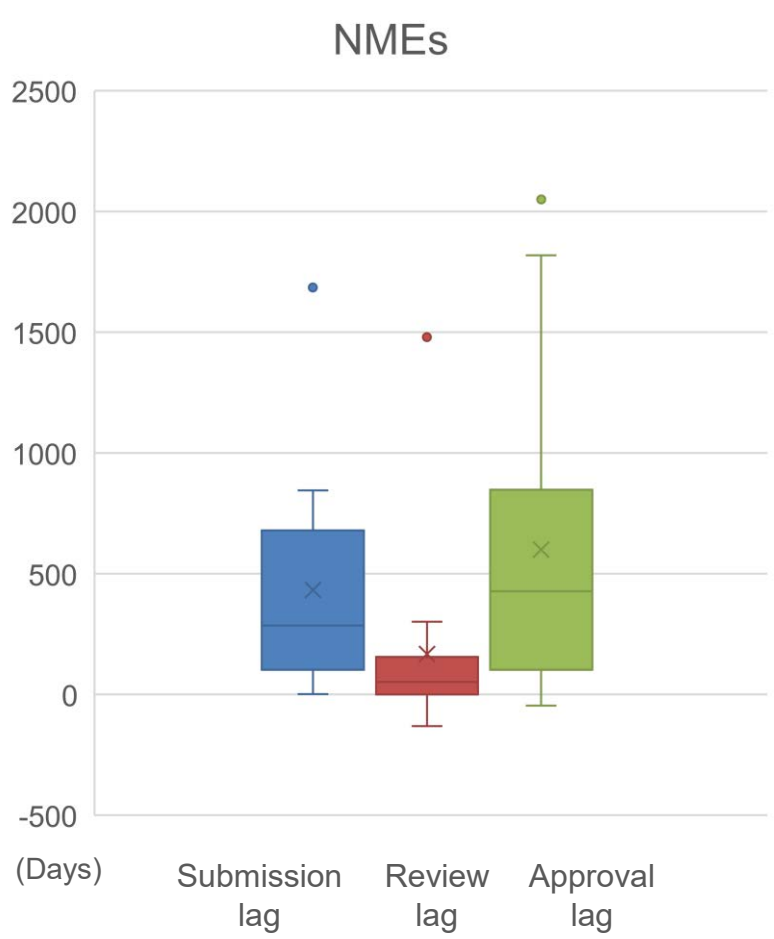
N=35

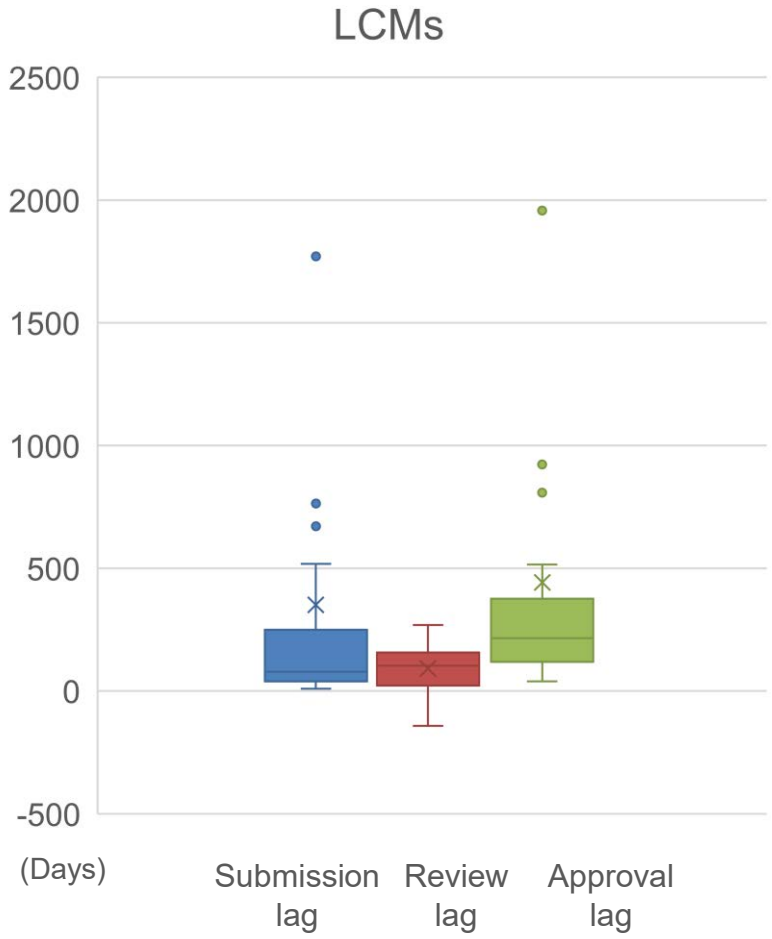
Products which granted expedited pathways by PMDA, FDA, EMA
Onc: 28 → 24
Non-Onc: 30 → 11

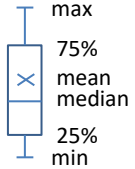
NOTE
Excluded expedited pathways
PMDA:
- No case to be granted for Sakigake, Conditional Early Approval

EMA:
- No case to be granted Exceptional Circumstances

Submission / Review / Approval Lag (vs FDA)



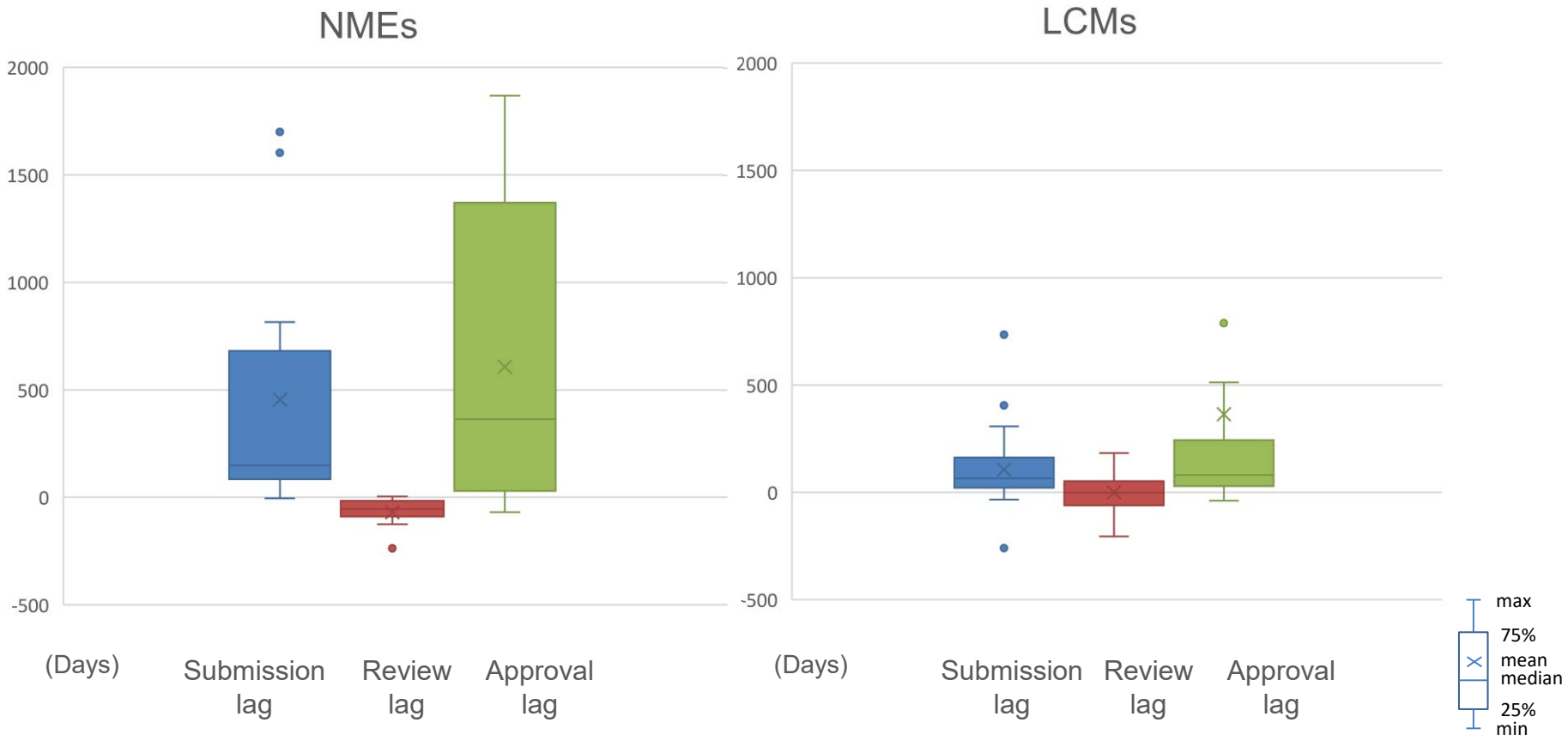




- Review time lag is limited and submission lag led to approval lag due to variations of submission timing
- LCMs were submitted and approved faster than NMEs

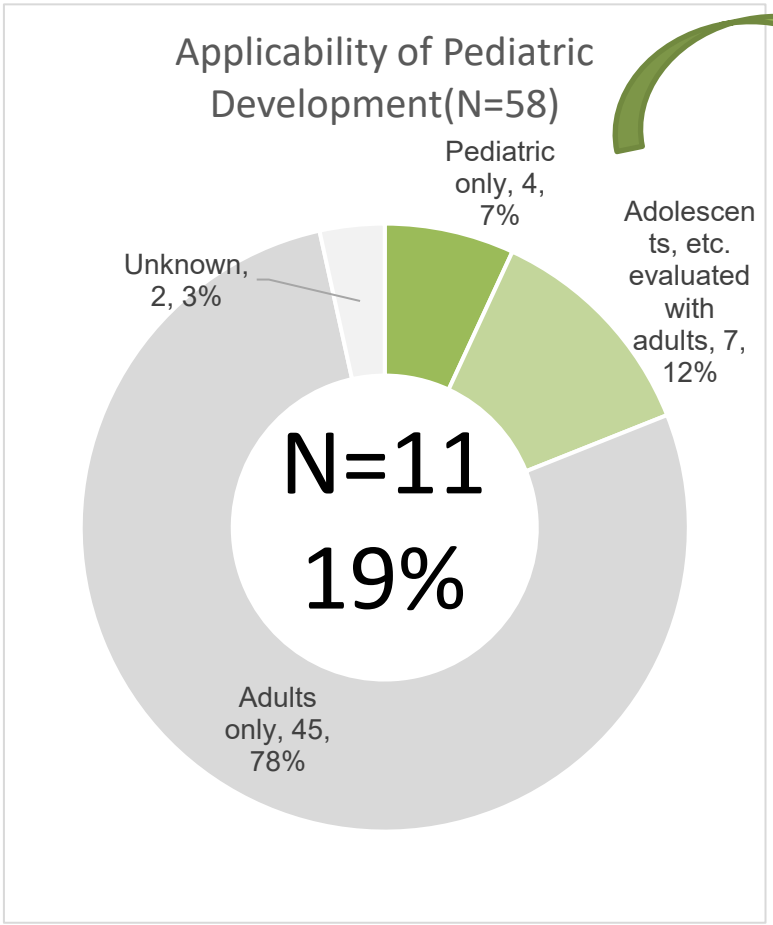
* One outlier over 10 years is excluded from the figure of LCMs

Submission / Review / Approval Lag (vs EU)



- Review time lag is limited and submission lag led to approval lag due to variations of submission timing (number of samples for each lag is different because of missing data)
- LCMs were submitted and approved faster than NMEs

Pediatric Development PhRMA + EFPIA (N=58)

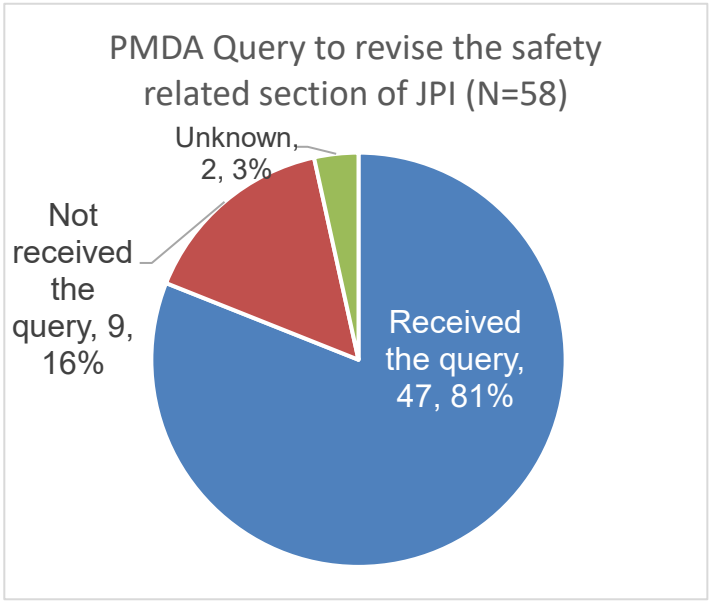


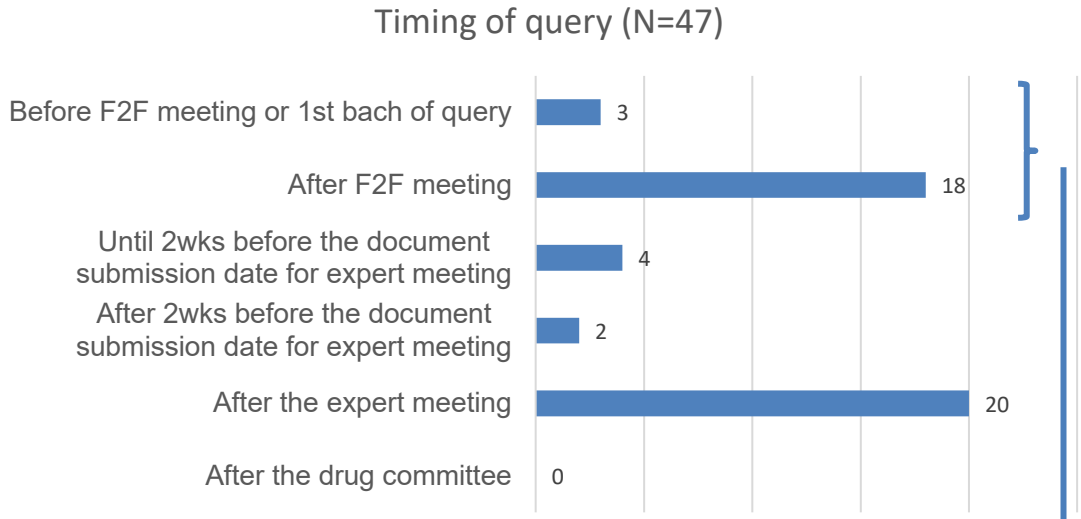
Clinical Data Package for Pediatric Development (N=11)

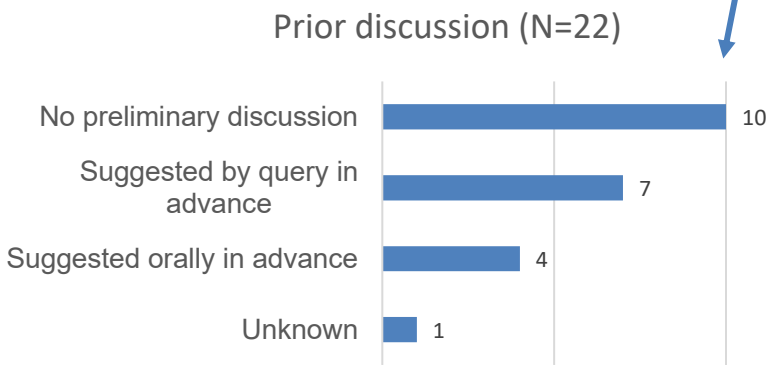
• Global Study including Japanese	5 (45%)
• Global study including Japanese & Japanese PK study	2 (18%)
• Global Study including Japanese & Japanese study (other than PK study)	1 (9%)
• Japanese study (other than PK study)	1 (9%)
Others • Overseas study & domestic study (1) • Paper JNDA(1)	2 (18%)

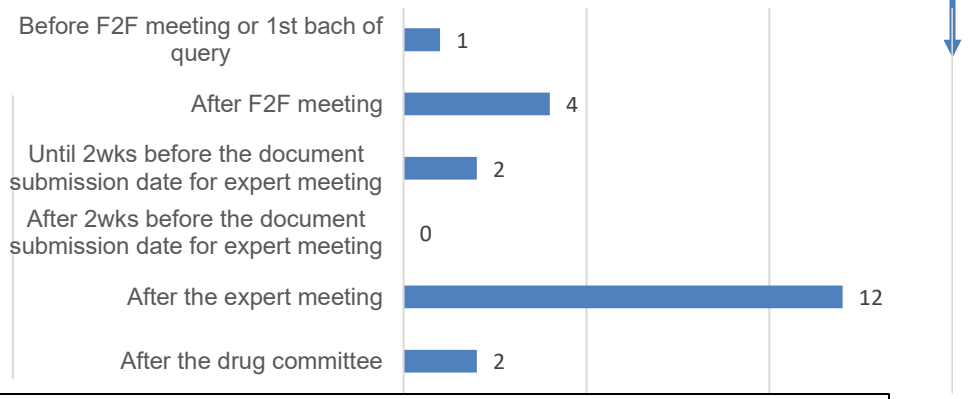
- Pediatric development was undertaken for 19% of products, including pediatric only (7%), and adolescents evaluated with adults (12%)
- Clinical data package for pediatrics come from mainly global studies

PMDA Query to revise the safety related section of JPI



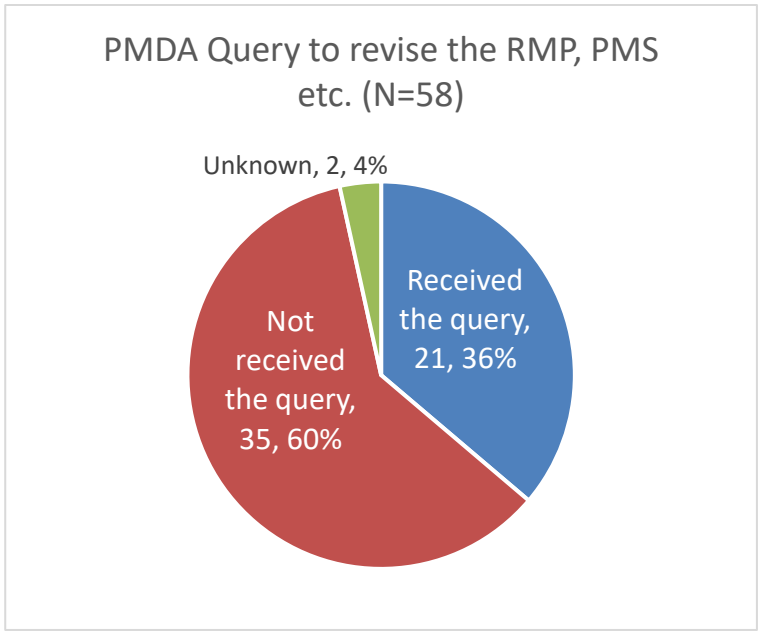


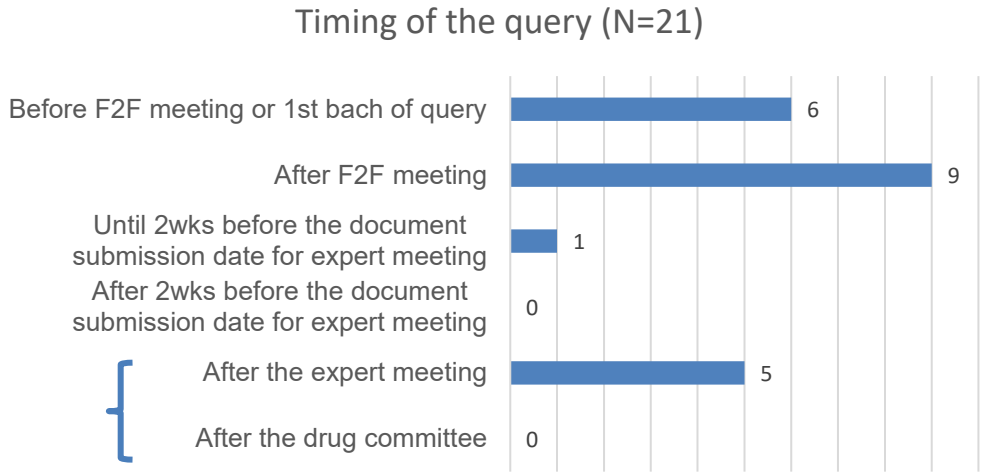


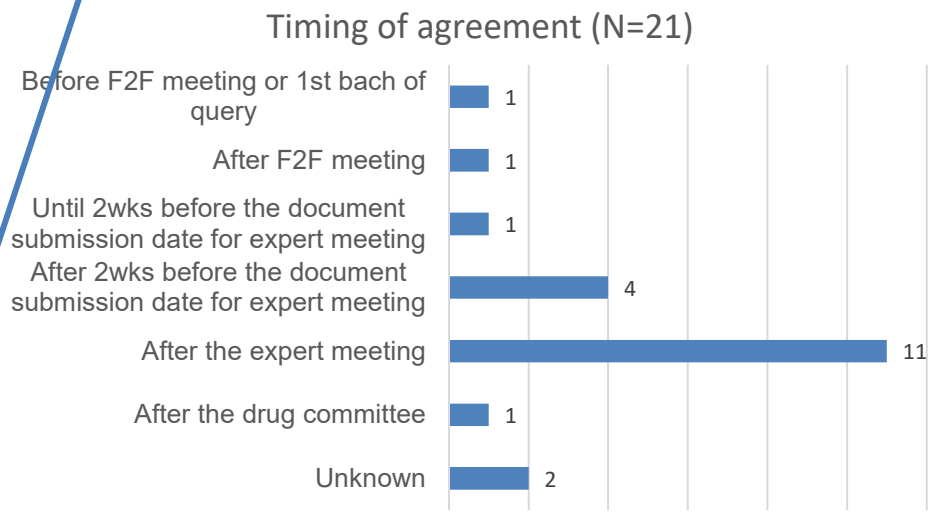


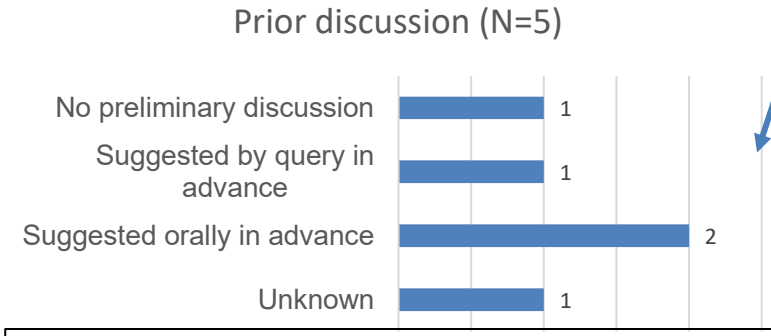
- Of 47 products with request from PMDA to revise safety section of JPI, approximately in half of these products, query to the section was raised prior to or after F2F meeting.
- However, in 22 out of 47 products, query was raised at later stage of review process and in case of 10 products, no preliminary discussion occurred prior to the query.

PMDA Query to revise the RMP, PMS





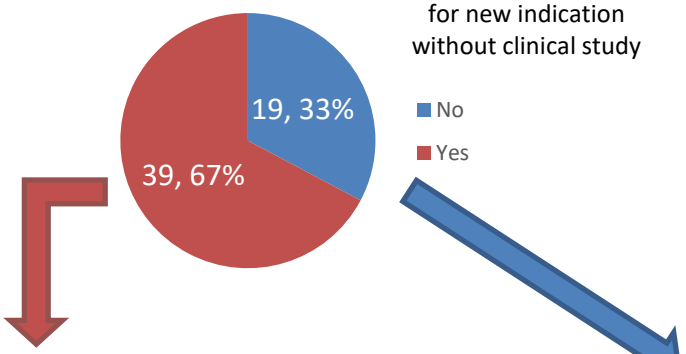




- Of 58 approved product, the number of products with request from PMDA to revise RMP and PMS was 21.
- In the majority of products, query to RMP/PMS was raised prior to or after F2F meeting.
- In approximately half of the products, agreement on RMP/PMS was made after expert meeting.

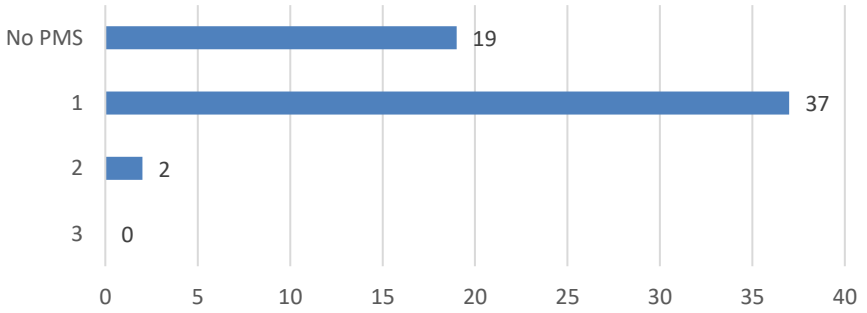
PMS

Approved Products with/without PMS (N=58*)

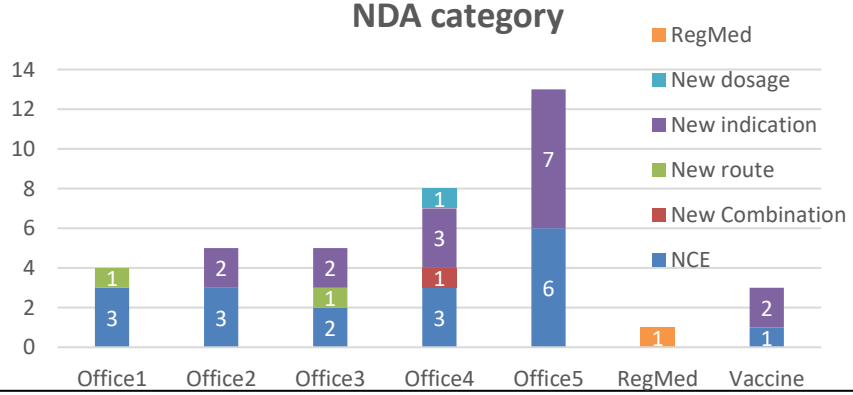


* Excluding biosimiar for new indication without clinical study

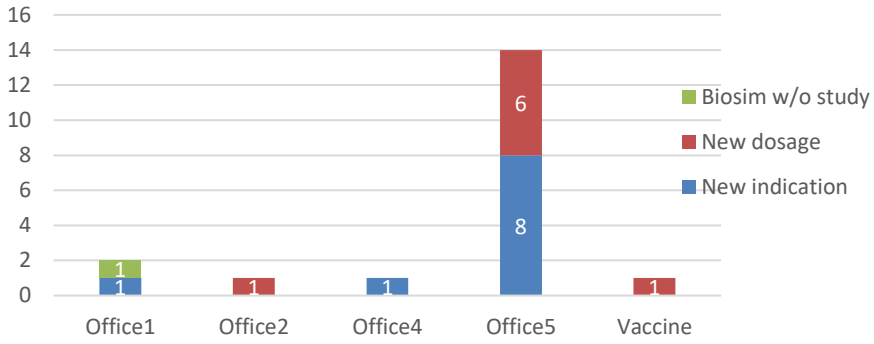
Number of PMS per Product (N=58)



Product with PMS by PMDA Review Office & NDA category

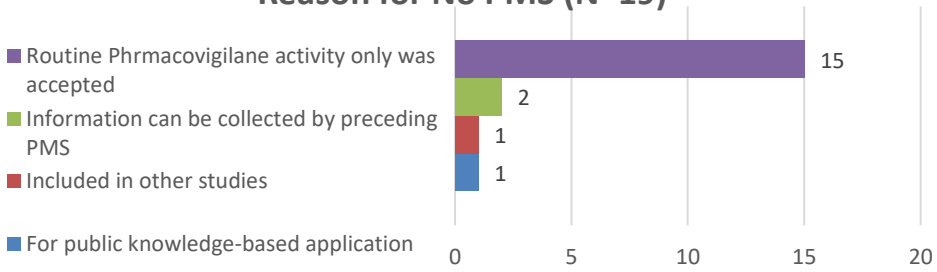


Product without PMS by PMDA Review Office & NDA category

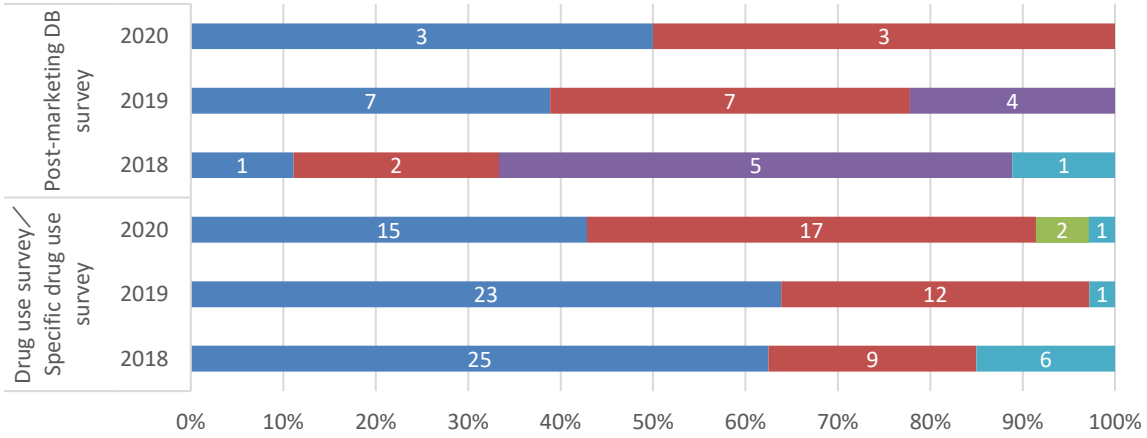


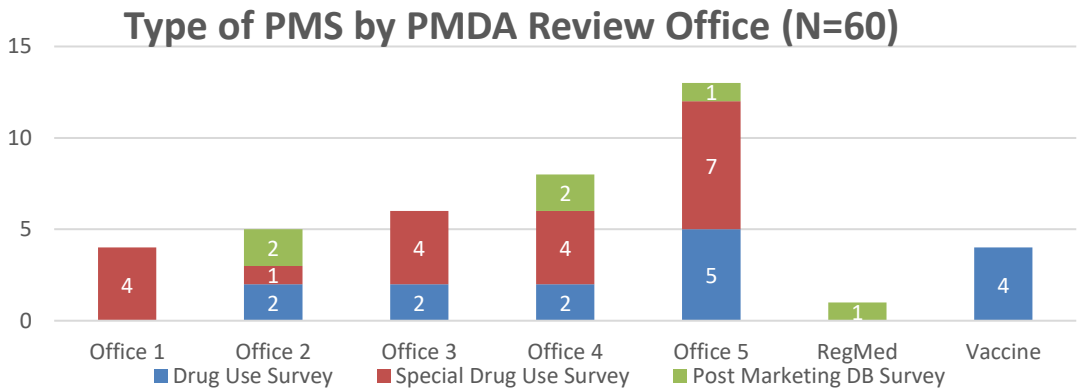
- PMS is conducted for all NCE products approved
- Products without PMS are predominately those approved for new indication and new dosage.
- For most approved products, one PMS is conducted.
- For most products without PMS, it was accepted that routine pharmacovigilance activities suffice.

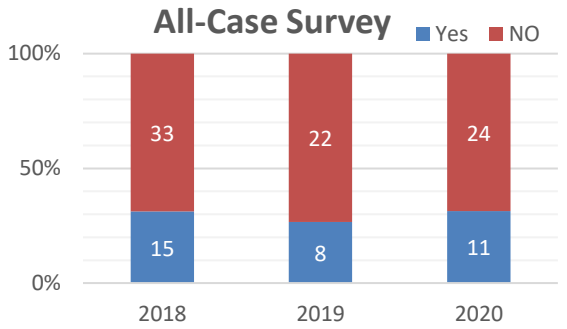
Reason for No PMS (N=19)

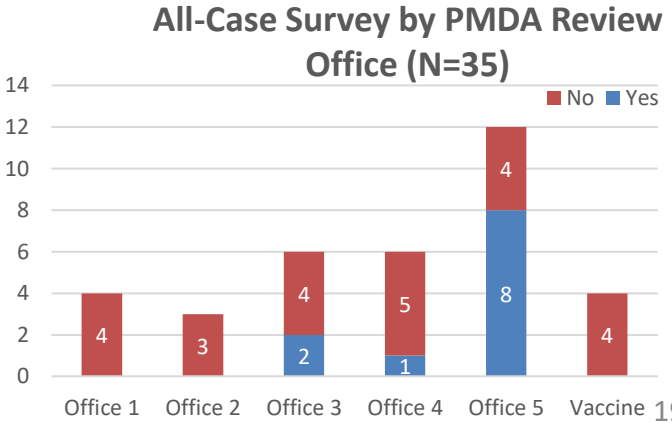


Background of PMS



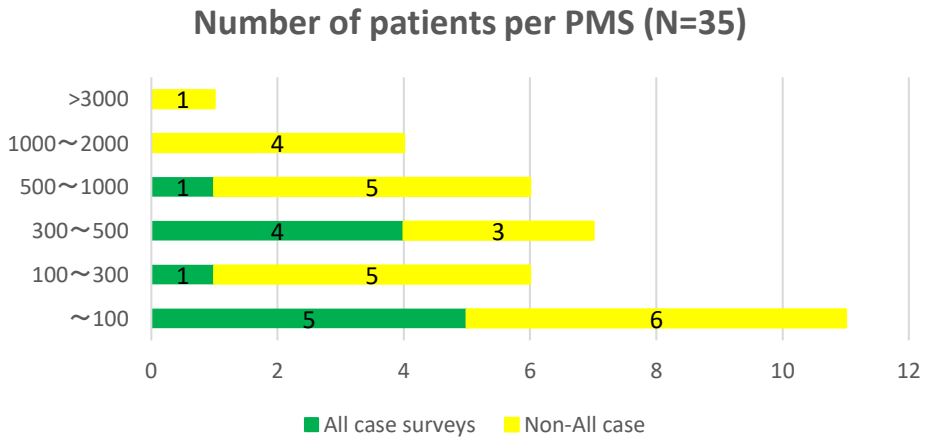


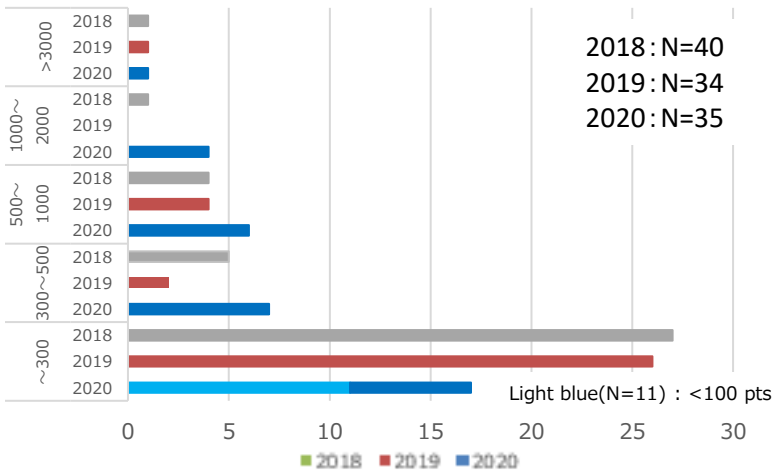


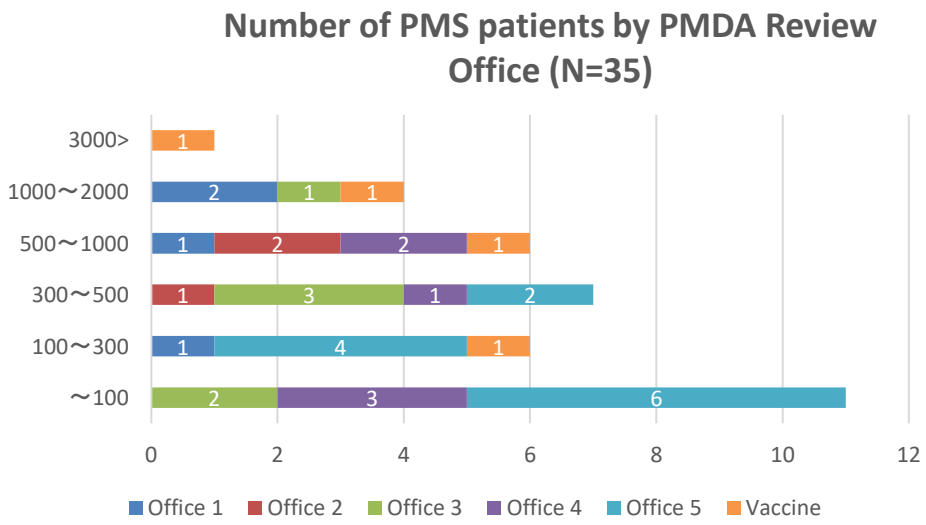


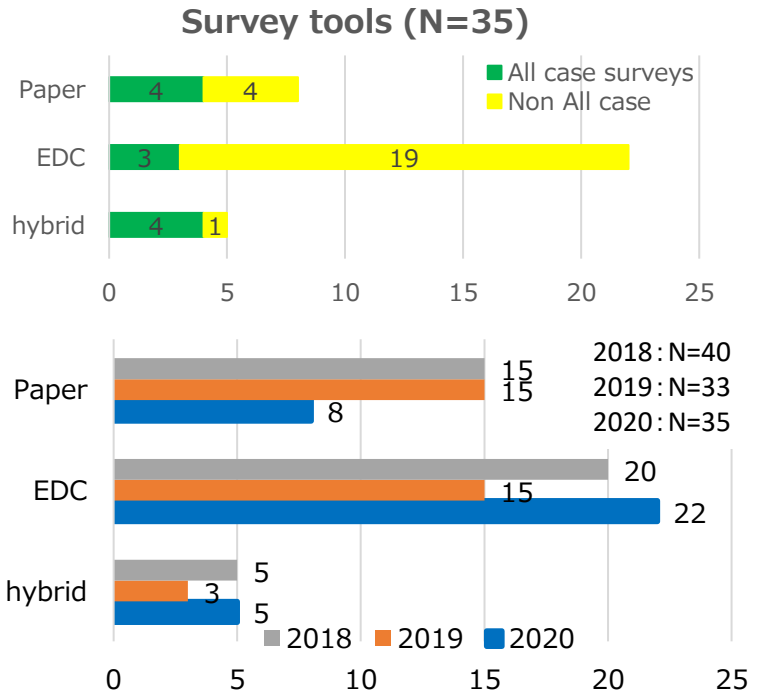
- In FY 2020, 44% of PMS was proposed from applicants and accepted as planned. However, PMS was ultimately decided to conduct in a further 49% of cases (31%, 2019).
- DB survey was only 15% (6 surveys).
- The ratio of all-case survey has remained unchanged since 2018.

Details of PMS (Drug Use Survey and Specific Drug Use Survey)

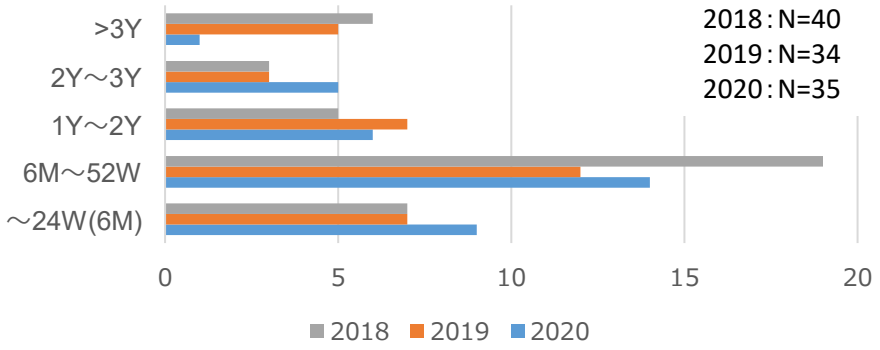




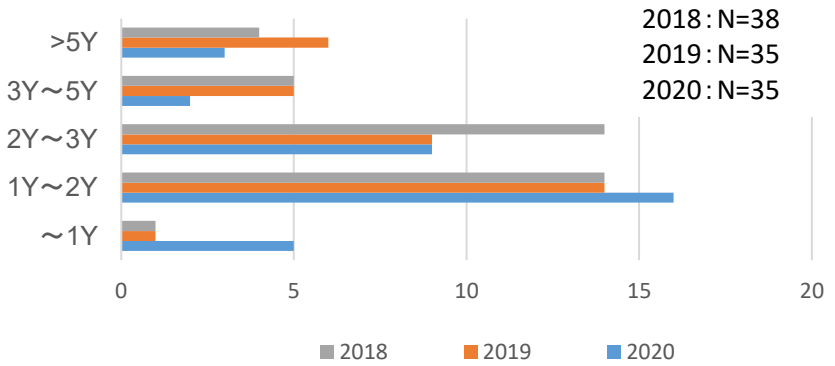




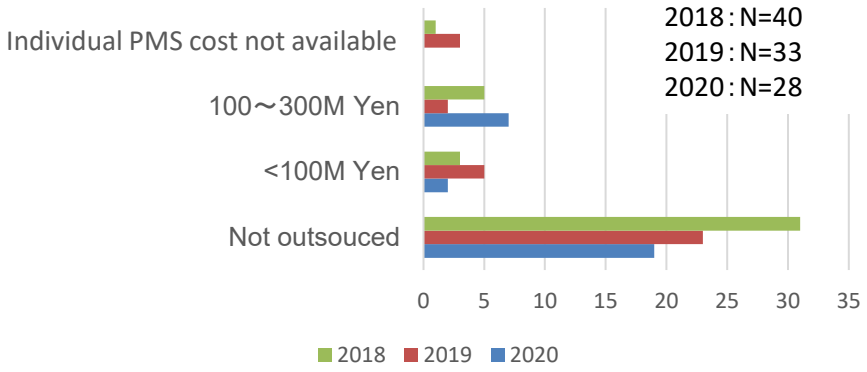
Observation Period per Patient



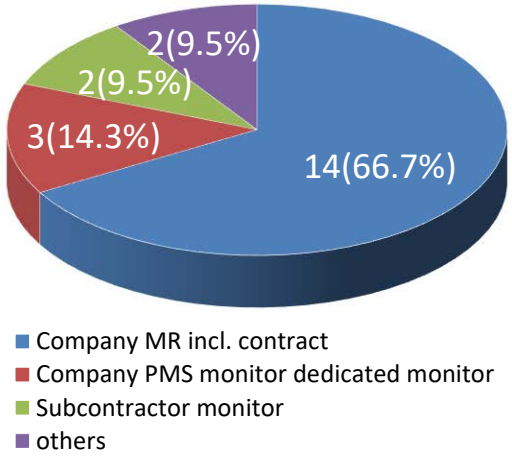
Enrollment Period



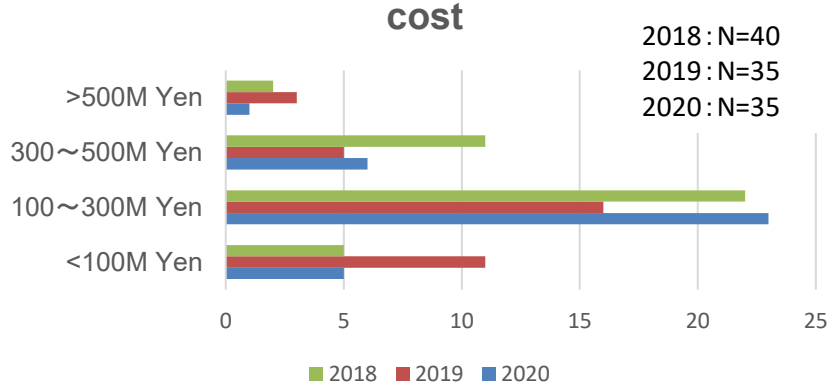
Cost of Outsourced PMS Monitoring



Who mainly conducts PMS Contract/Enrollment/CRF Collection



Cost of PMS excluding monitoring cost



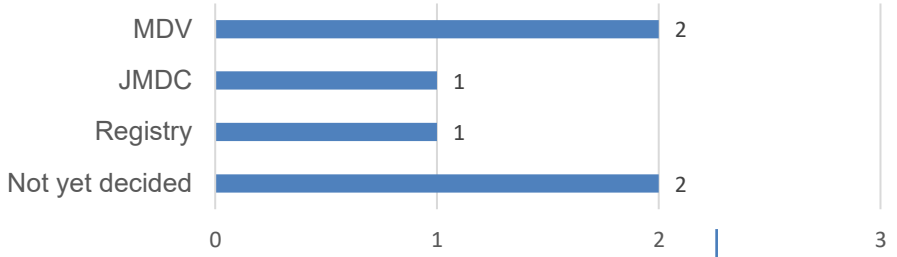
- Just as last year, Less than 300 patients in size(especially less than 100 patients), 6 month to 1 year observation period and 1-2Y year enrollment period are most frequently seen among all PMS.
- AS survey tools, Paper was decreased, and EDC was increased.
- PMS with cost of 100 – 300 M Yen marked highest number.

Post-Marketing Database Survey

Reason for Database Survey Planned (N=6)

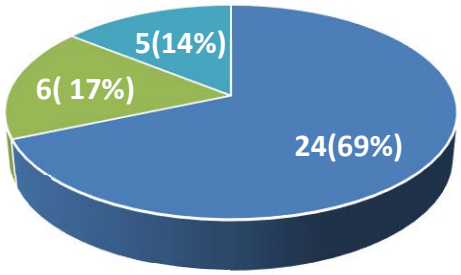
Suitable DB available for the disease and risk	4
DB enables comparison	1
Reduce resources	1

Database used for DB Survey (N=6)



Reason for "Not yet decided"
- Confirming if the required data can be collected: 2

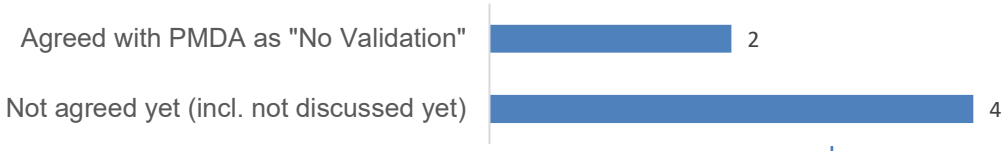
Reason for DB Survey Not Considered



2020 (N=35)

- Data can not be collected through DB
- DB is not suitable to evaluate specific risk
- Others

Necessity of Outcome validation (N=6)

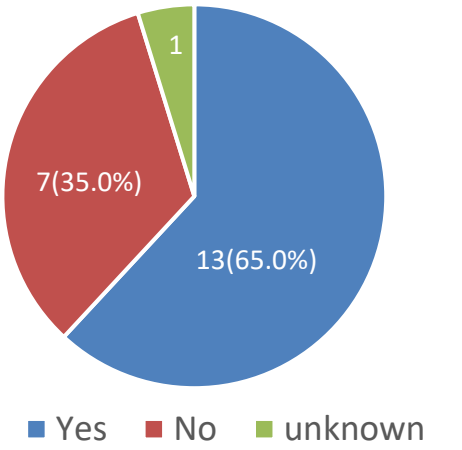


Details for "Agreed with PMDA as No Validation"
- Agreed with PMDA in pre-meeting: 2

- The main reasons DB survey was planned were "DB could be suitable to evaluate the diseases and risks".
- The main reasons why DB was not considered were "Data can't be collected through DB" or "DB is not suitable to evaluate specific risk". The combined proportion of these two reasons is 86%.
- MDV(2), JMDC(1) and Registry(1) is planed and no plan for MID-NET.
- 2 DB survey have reached as no necessity to plan outcome validation in pre-meeting. Rest of 4 DB survey have not reached arrangement yet.

Electronic approval (electronic signature)

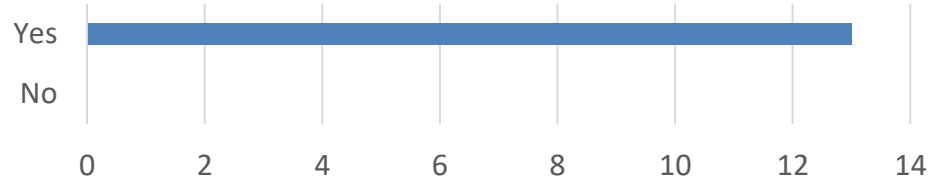
Adoption (even partial) electronic approval (electronic signature) for operations in PMS



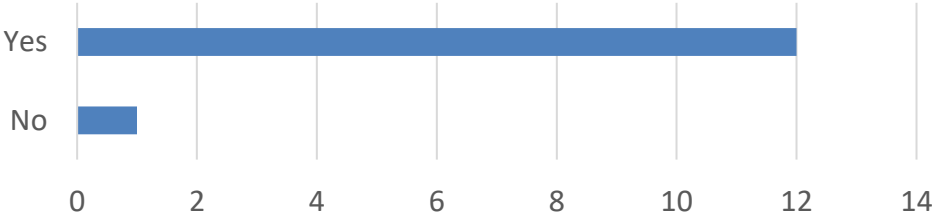
- Due to the impact of Covid-19, **more than half of the companies** have already implemented electronic signatures.
- Company documents and those with external suppliers such as CROs are almost **always signed electronically**.
- PMS contracts with medical institutions **have not yet progressed** because of the need to coordinate with medical institutions.

Range of documents adopted (N=13)

1:Company forms as defined by SOPs (documents that are internally generated and not submitted to external parties, including CROs)



2:Documents with external parties such as CROs (excluding contracts with medical institutions)



3:PMS contracts with medical institutions