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

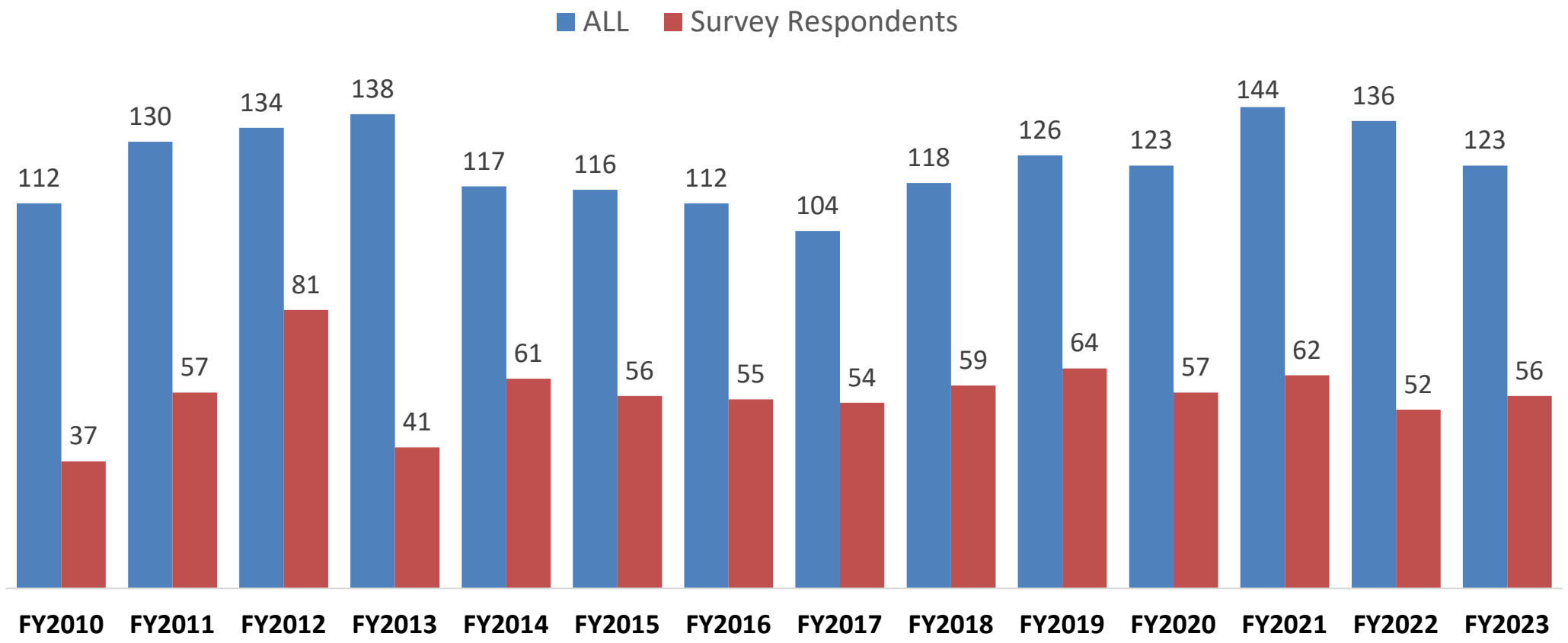
○卜部陽子（ブリストル・マイヤーズ スクイブ）[1]、太田雪（グラクソ・スミスクライン）[1]、中島啓行（ジェンマブ）[2]、日高正泰（ブリストル・マイヤーズスクイブ）[1]、本間麻里子（バイエル薬品）[2]、奥野弘明（日本イーライリリー）[1]、砂村一美（ファイザーR&D）[1]、伊藤美穂子（ルンドベック・ジャパン）[2]、岩崎直子（ノバルティスファーマ）[2]、高橋明子（サノフィ）[2]、竹岡晶子（アレクシオンファーマ）[2]、塚本修（CSLベーリング）[2]、藤直喬也（ブリストル・マイヤーズスクイブ）[1]、綿引友博（ヤンセンファーマ）[1]、来栖克典（フェリング・ファーマ）[2]、平井寛二（MSD）[1]

1：米国研究製薬工業協会（PhRMA Japan）　2：欧州製薬団体連合会（EFPIA Japan）

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。

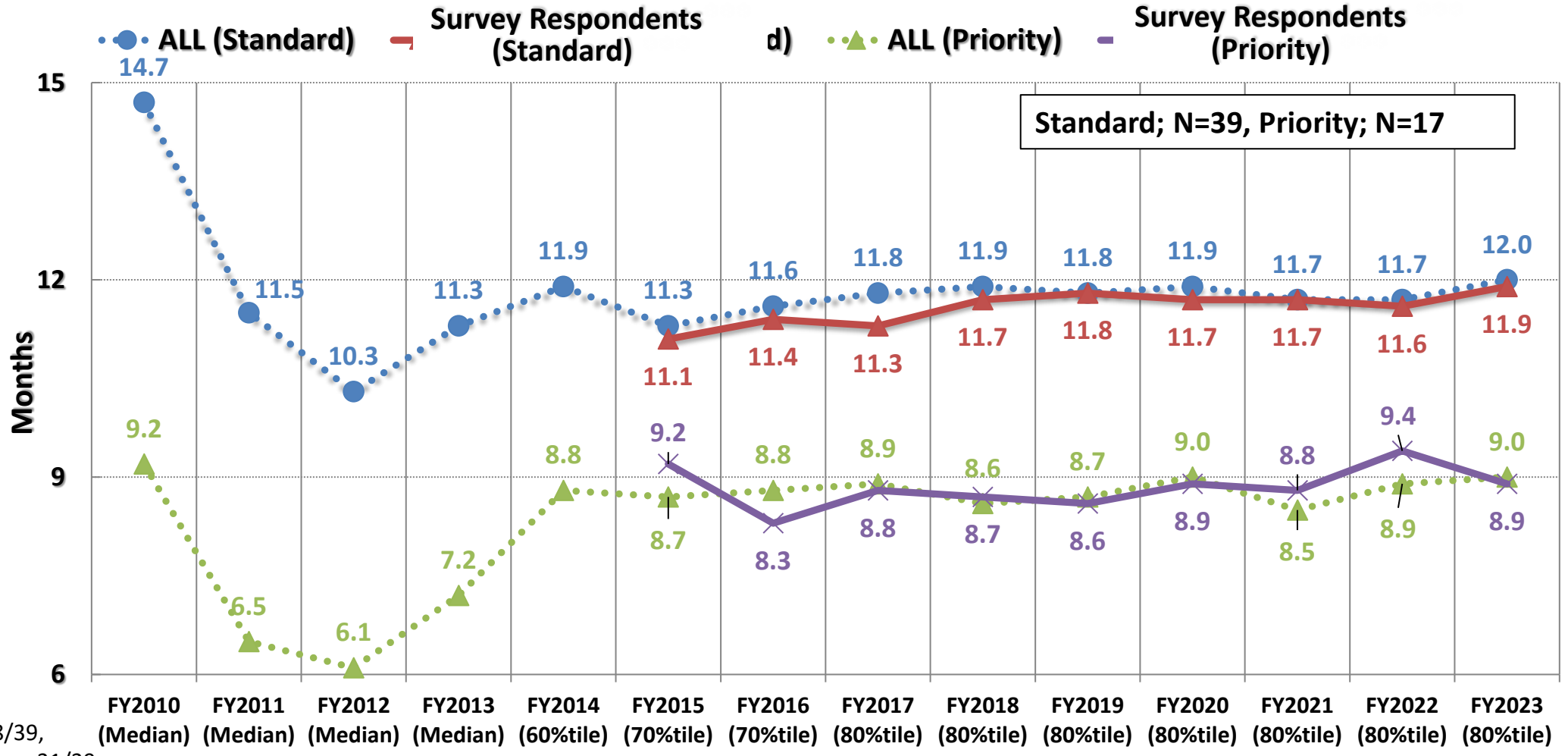
- PhRMA又はEFPIA Japan Japan加盟会社25社を対象に、2023年度（2023年4月～2024年3月）の承認品目（新医薬品）についてアンケート調査を実施し、回答が得られた56品目について分析した。
- 審査期間（80パーセンタイル）は、通常審査品目が11.9カ月（総合機構の審査期間目標値は12カ月）、優先審査品目が8.9カ月（同9カ月）であった。
- 優先審査品目、希少疾病品目の割合はそれぞれ30%、29%であり、先駆的医薬品指定品目及び条件付き承認制度利用品目はいずれもなかった。
- 臨床データパッケージにおけるピボタル試験は、国際共同第3 相試験が64%、国際共同第2 相試験が5 %であった。
- 56品目のうち、海外で承認申請した又は申請予定である品目は51品目（91%）であり、そのうち21品目（41%；21/51品目）において日本が最初に申請又は同時申請（最初の国の申請から3ヵ月以内）を達成した。
- 承認適応が小児を含んでいない28品目のうち、小児開発を別途行う予定があるのは8品目（29%；8/28品目）であった。

The Number of New Drug Approvals in Japan



The survey respondents accounted for 46% (56/123) of the total new drug approvals in Japan in FY2023.

Review Time for Standard Review and Priority Review



Note:

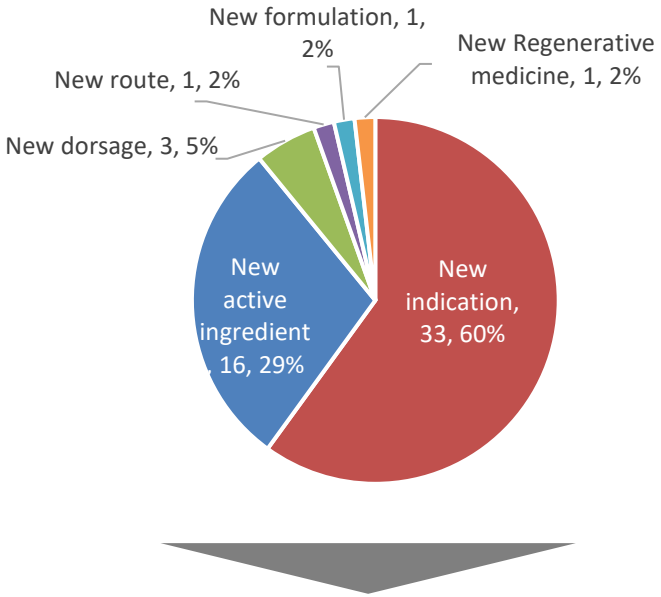
Standard
- Oncology: 8/39,
- Non-oncology: 31/39

Priority
- Oncology: 5/17,
- Non-oncology: 12/17

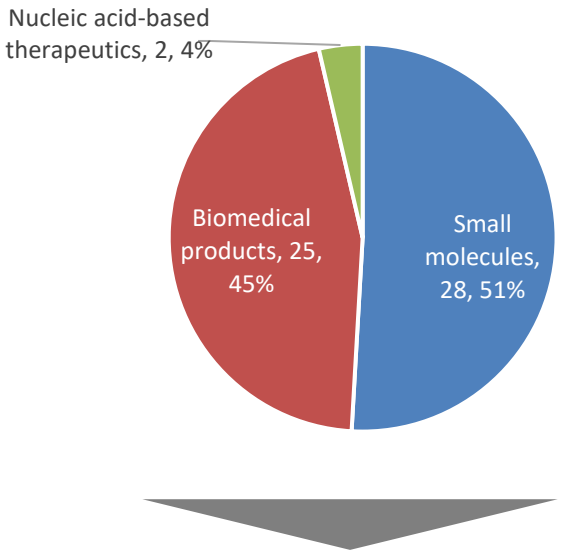
- Duration of JNDA Review for "Standard Review" in FY2023 was 11.9 months (80th percentile).
- Duration of JNDA Review for "Priority Review" in FY2023 was 8.9 months (80th percentile).

Category of Approved Drugs

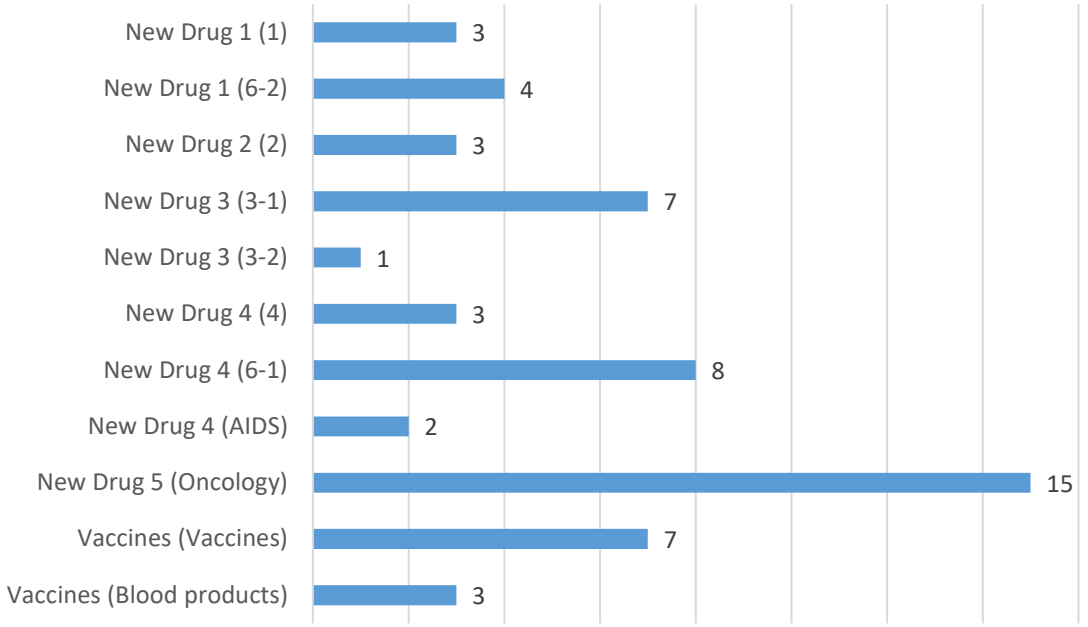
Category of J-NDA in FY2022 (N=55)



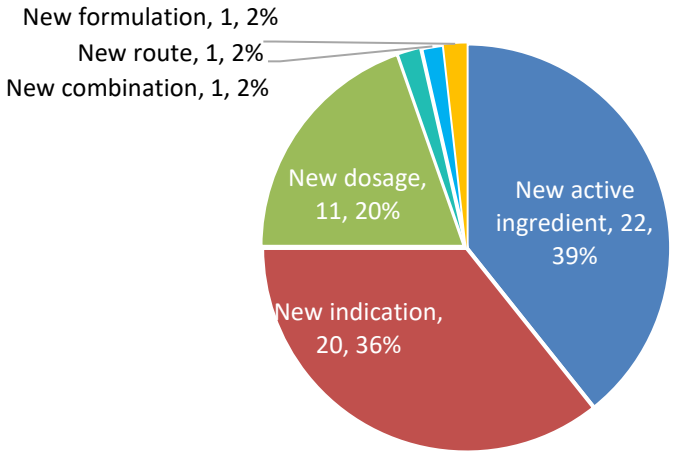
Drug Modalities in FY2022 (N=55)



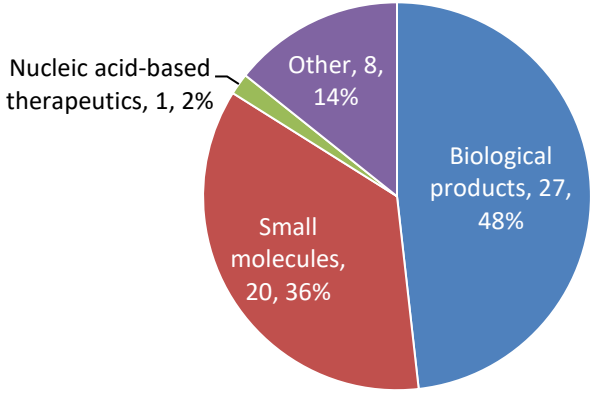
PMDA Review Division (Category) (N=56)



Category of NDA in FY2023 (N=56)



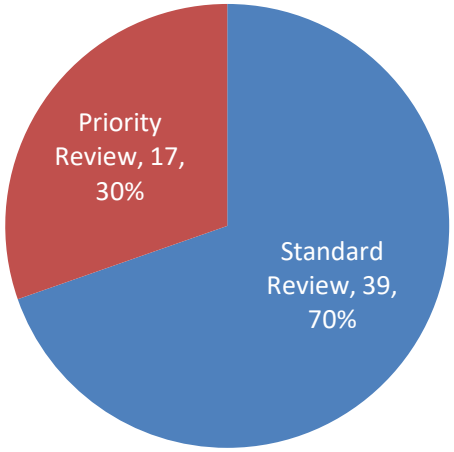
Drug Modalities in FY2023 (N=56)



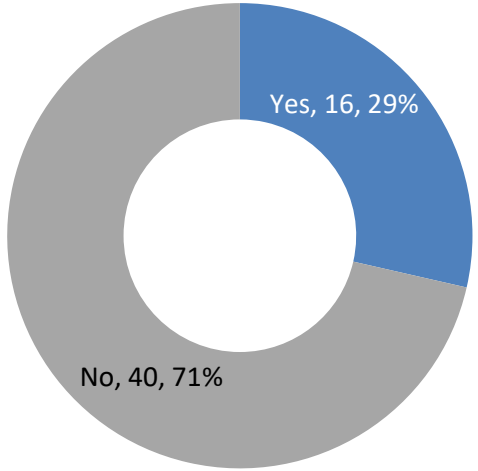
- Different proportions were observed in “New active ingredient” (22/56; 39%), “New indication” (20/56; 36%)“ and New dosage” (11/56; 20%) compared to FY2022.
- Biological products (48%; 27/56) were larger than small molecules (36%; 20/56) in FY2023.
- 15 of the 56 approved products (27%) were for oncology (the largest divisional category).

Utilization of Expedited Program

Review Category (N=56)

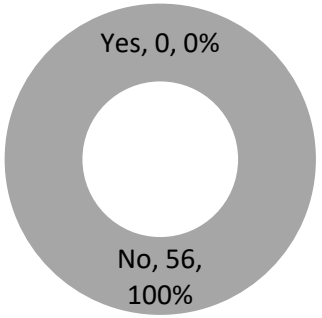


Orphan (N=56)

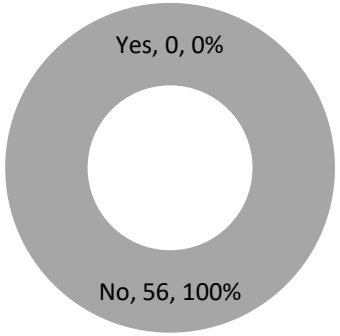


Note:
Oncology: 5/16
Non-oncology: 11/16

Sakigake (N=56)



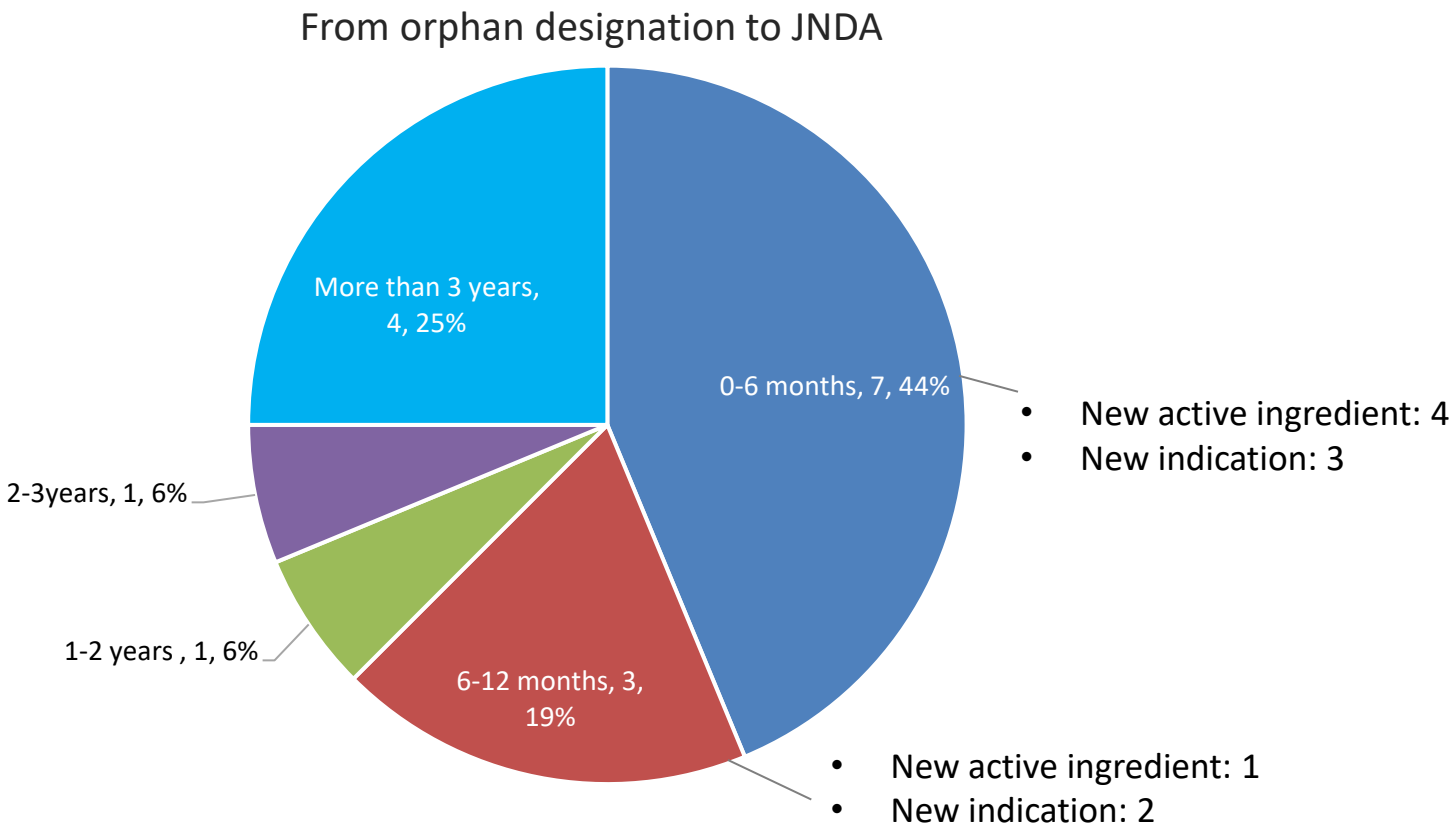
Conditional Approval (N=56)



- In FY2023, 17 products (30%) were approved through the Priority Review and 16 (29%) were approved through the Orphan Drug Review.
- There was no product approved under the Sakigake pathway; none were approved through Conditional Approval.

Timing of Orphan Drug Designation (N=16)

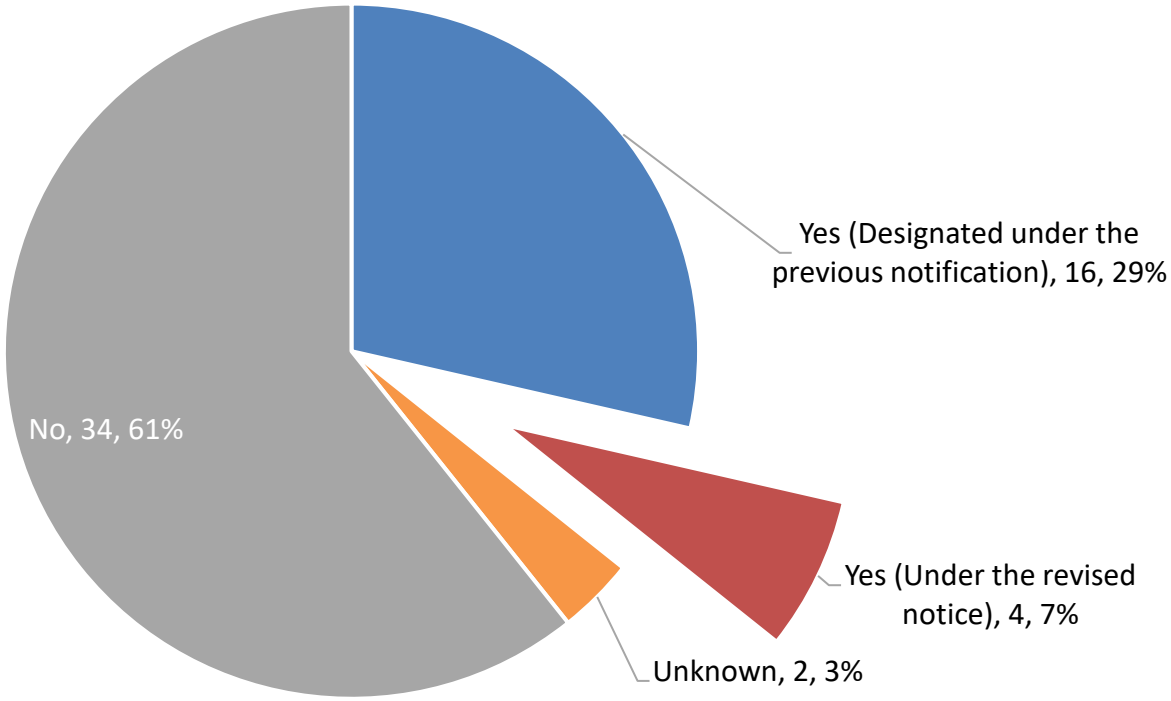
Note: JNDA category (N=16)
- New active ingredient: 6
- New indication: 6
- New dosage: 3
- New combination: 1



- Orphan Drug designation within 12 months before JNDAs accounted for the majority of the timing.
- The JNDA categories of the drugs with orphan designation “More than 3 years before submission” were “New dosage” and “New combination”.

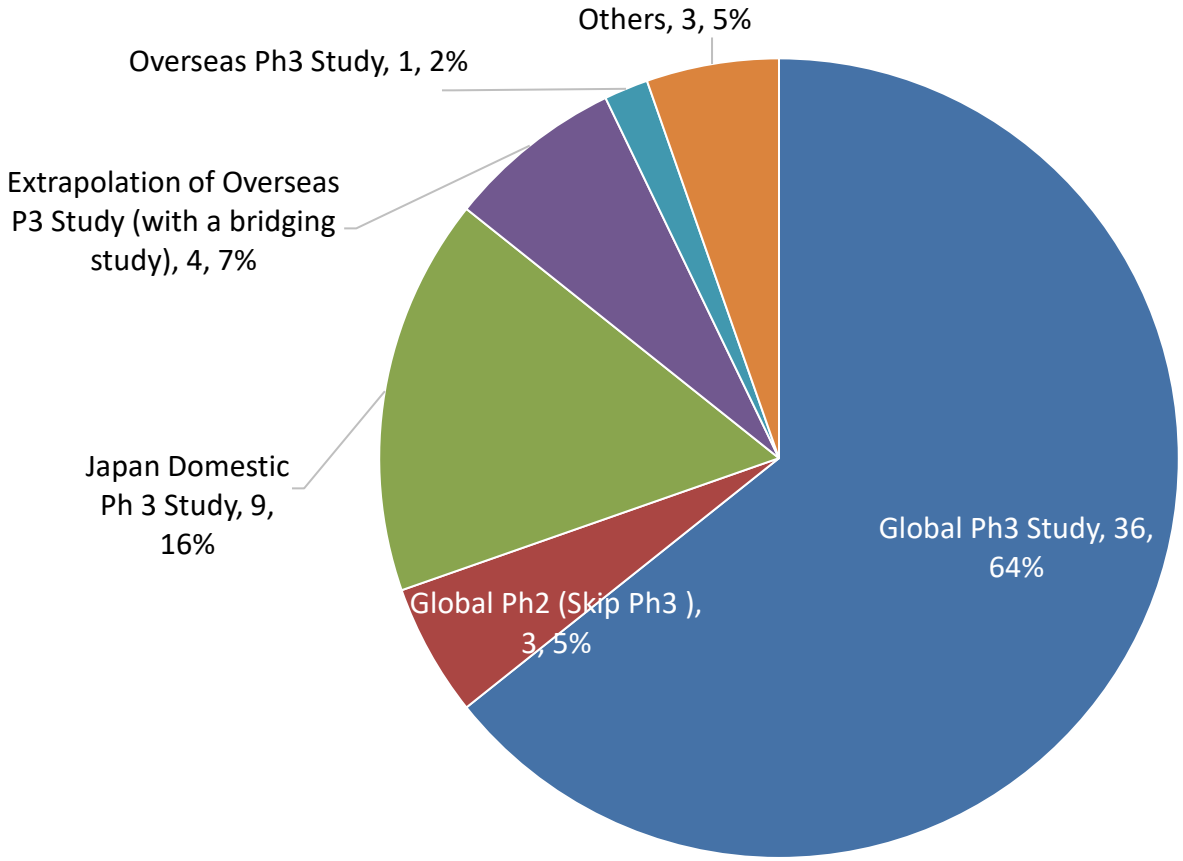
Impact of the Revised Notice on Orphan Designation (N=56)

According to the revised notice on the designation of orphan drugs on January 16, 2024, could it be considered an orphan drugs?



- 4 additional approved products (7%) would have the potential to meet the criteria of the orphan drug designation under the revised notice.
- The revised notice on the designation of orphan drugs (issued on Jan 16 ,2024) may lead to an increase in the earlier designation of orphan drugs in the future.

Pivotal Study in Clinical Data Packages (N=56)

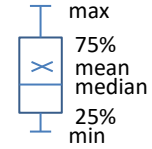


Pivotal study in Clinical Data Package were:

1) mainly “Global study (Ph3 or Ph2 study)”: 39 cases; 69% (FY2022: 67%)
2) “Japan Domestic Study”: 9 cases; 16% (FY2022: 13%)
3) “Extrapolation of Overseas Study with a bridging study”: 4 cases; 7% (FY2022: 8%)

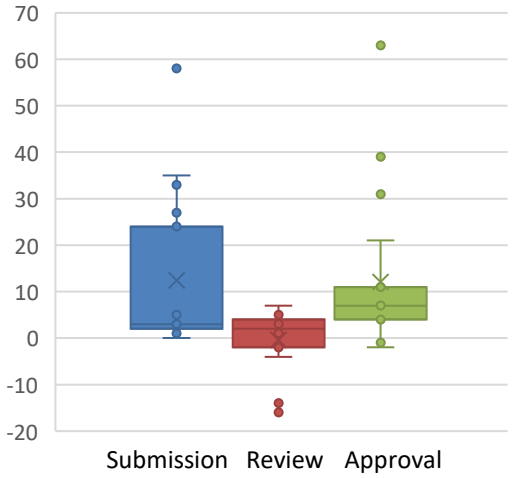
Submission / Review / Approval Lag (vs. US** & vs. EU***)

** approved in US *** approved in EU incl. UK



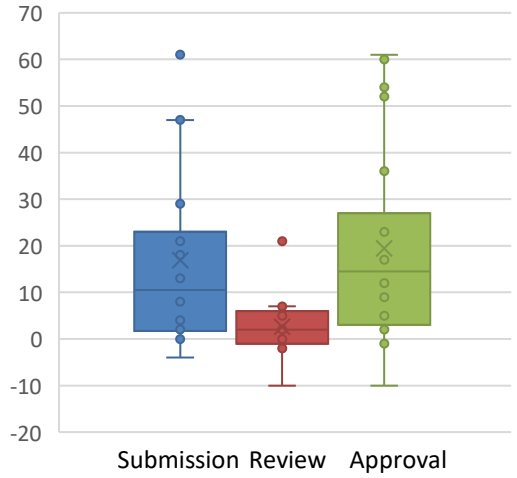
(Months)

NMEs (vs. US) *1*2
N=19



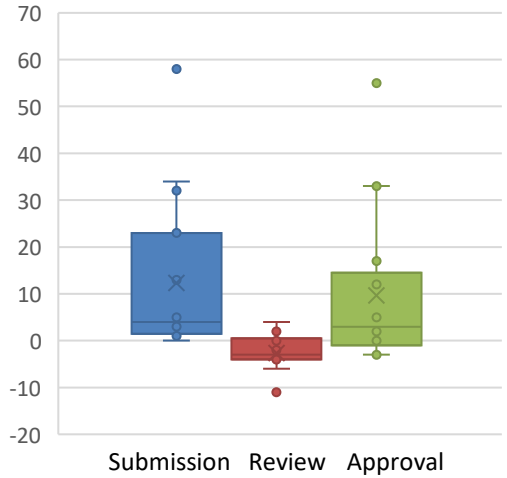
(Months)

LCMs (vs. US) *1*3*4*5
N=22



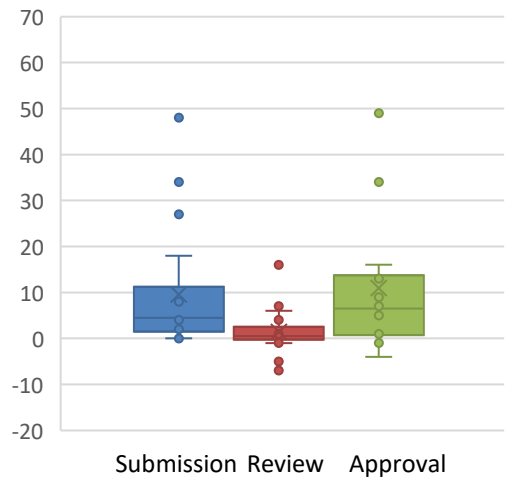
(Months)

NMEs (vs. EU) *6*7
N=17



(Months)

LCMs (vs. EU) *8*9
N=18



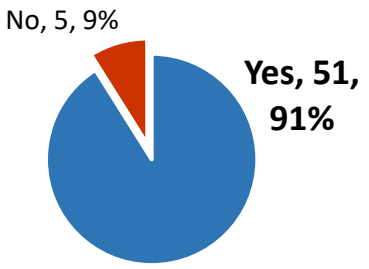
*1 NME is defined as “new active ingredient” in category of J-NDA and LCM is defined as other categories.
*2 Exclude 3 cases under review in US
*3 Exclude 1 case under review in US
*4 Exclude 1 case of submission/approval date unknown
*5 Exclude 2 cases of ＞100 months of submission/approval lag

*6 Exclude 4 cases under review in EU
*7 Exclude 1 case of submission/approval date unknown
*8 Exclude 3 cases under review in EU
*9 Exclude 3 cases of ＞100 months of submission/approval lag
Note: Calculated with 30 days per month

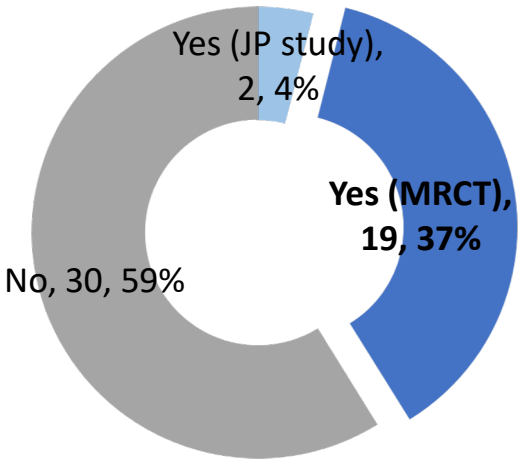
- The following trends were observed, which were similar to those in FY2022.
  - Review duration lag tends to be limited.
  - Overall, submission lag is presumed to be the main reason for approval lag.
- For NMEs, submission/approval lag (median) was smaller in both US and EU compared to FY2022.

Simultaneous J-NDA Filing within 3 Months

Submission in Countries/Regions Other than Japan (N=56)



JNDA Filed Simultaneously (within 3 months) (N=51)



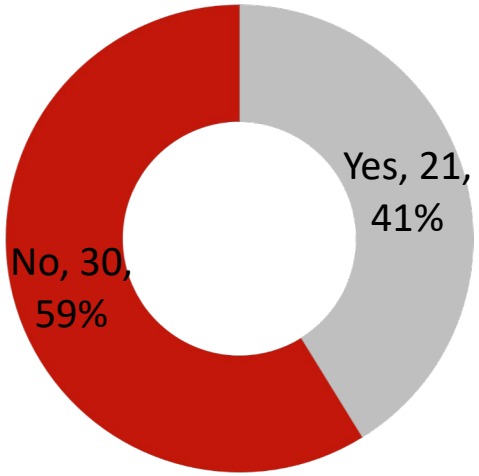
Reasons for Simultaneous J-NDA Filing (within 3 months) based on MRCTs (N=19; multiple answers allowed)

There was a business decision to prioritize Japan	17 (89%)
The standard process that allows the application within 3 months has been established	16 (84%)
It was a partial change application for the indication and dosage/administration, and there was no need to prepare materials for Japan such as CMC	5 (26%)
Others	2 (11%)

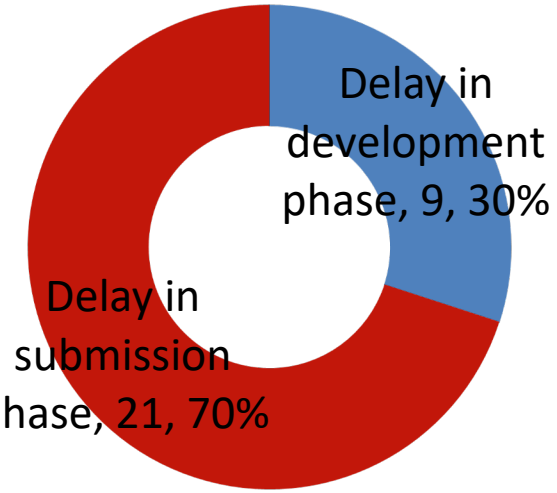
- Of the 51 products that achieved or planned submission globally, 21 J-NDAs (41%) were filed first in JP or simultaneously.
- Primary reasons for these simultaneous applications tend to be the same as last year; “there was a business decision to prioritize Japan” (17 cases, 89%) and “the standard process that allows the application within 3 months has been established” (16 cases, 84% of the applications).
- Five cases (26%) were partial change applications which need no preparation of materials for Japan such as CMC.

Simultaneous J-NDA Filing: Submission Lag More than 3 Months

Number of JNDAs Filed Simultaneously (within 3 months) (n=51)



Reasons for not Filing Simultaneously (within 3 months) (N=30)



- Of the 51 products that achieved or planned submission/approval globally, 30 J-NDAs (59%) were **NOT** filed simultaneously.
- Reasons for not filing simultaneously (i.e., within three months) consist of “delays in the submission phase” in 21 cases (70%), which increased from 14 (54%), and “delays in the development phase” in 9 cases (30%), which decreased from 12 (46%), compared to the previous year.

Simultaneous J-NDA Filing: Submission Lag More than 3 months

Reasons for the Delay in Development Phase (N=9: multiple answers allowed)

Already approved overseas	5 (56%)
Did not consider Japan development due to license-in product	5 (56%)
Japan was unable to join the MRCT (verification study) as it had been already started	4 (44%)
Japanese phase 1 study became necessary before joining MRCT	1 (11%)
Japanese dose-finding study became necessary before joining MRCT	1 (11%)
Others	3 (33%)

Reasons for the Delay in Submission Phase (N=21: multiple answers allowed)

Preparation of Japanese Module 2.3 or approval application	4 (19%)
Conducted additional analysis for consideration of consistency between Japanese and entire population	3 (14%)
Pricing strategy	3 (14%)
Preparation of tables for CTD	2 (10%)
Preparation time for e-data submission	2 (10%)
Interim results were not accepted	1 (5%)
Expedited review in overseas	0 (0%)
Waited for stability test results	0 (0%)
Waited for long-term safety data	0 (0%)
Others	13 (62%)

Main reasons for the delays were:

- Development phase: “already approved overseas” and “licensed-in product” in 5 cases (56%), “unable to join MRCT” in 4 cases (44%)
- Submission phase: not limited to technical/regulatory ones. Submission lags could derive from business/strategic decisions in certain cases.

Simplification of internal processes such as development planning, CTD preparation and review contributed to minimization of the submission lag. Reduction/elimination of Japan-specific requirements related to CMC, CDx, and consistency evaluation was suggested as one of possible measures to promote simultaneous submissions.

Utilization of Expedited Approval Pathways/Novel Regulatory Programs (Oncology)

NME (N=6)	Japan		US								EU					Review Period (Mo)		
	PR	ODD	BTD	AA	FT	PR	ODD	RTOR	AAid	Orbis	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1								✓								10	8	Under Review
2						✓										11	6	14
3						✓			✓	✓						11	4	11
4				✓		✓			✓				✓		✓	9	8	11
5	✓	✓		✓	✓	✓	✓			✓			✓			9	8	11
6																12	6	11

LCM (N=7)	Japan		US								EU					Review Period (Mo)		
	PR	ODD	BTD	AA	FT	PR	ODD	RTOR	AAid	Orbis	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1	✓	✓		✓		✓				✓						8	9	NA
2	✓	✓														8	9	NA
3	✓	✓	✓	✓		✓	✓									6	8	NA
4	✓	✓		✓		✓				✓						8	9	NA
5																10	NA	NA
6																12	5	5
7						✓										18	11	12

PR: Priority Review, ODD: Orphan Drug Designation, BTD: Breakthrough Therapy Designation, AA: Accelerated Approval (US); Accelerated Assessment (EU), FT: Fast Track, RTOR: Real-Time Oncology Review, AAid: .Assessment Aid, PRIME: Priority Medicines, CMA: Conditional Marketing Authorisation, EC: Exceptional Circumstances , NA: Not Applied

Utilization of Expedited Approval Pathways/Novel Regulatory Programs (Non-Oncology)

NME (N=16)	Japan		US					EU					Review Period (Mo)		
	PR	ODD	BTD	AA	FT	PR	ODD	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1	✓	✓				✓	✓					✓	8	6	12
2						✓			✓				11	8	9
3	✓	✓	✓		✓	✓							2	18	13
4													12	8	NA
5	✓	✓	✓			✓	✓					✓	13	Under Review	Under Review
6			✓		✓	✓	✓					✓	24	8	Under Review
7							✓						9	Under Review	Under Review
8													10	24	11
9			✓										12	6	16
10	✓	✓	✓				✓	✓				✓	8	12	14
11			✓										10	Under Review	13
12	✓	✓	✓		✓	✓							2	18	13
13			✓		✓			✓					13	10	9
14													10	12	14
15			✓			✓			✓				11	8	8
16							✓						9	11	13

PR: Priority Review, ODD: Orphan Drug Designation, BTD: Breakthrough Therapy Designation, AA: Accelerated Approval (US); Accelerated Assessment (EU), FT: Fast Track, PRIME: Priority Medicines, CMA: Conditional Marketing Authorisation, EC: Exceptional Circumstances, NA: Not Applied

Utilization of Expedited Approval Pathways/Novel Regulatory Programs (Non-Oncology)

LCM (N=27)	Japan		US					EU					Review Period (Mo)		
	PR	ODD	BTD	AA	FT	PR	ODD	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1			✓			✓	✓						11	4	10
2	✓	✓	✓			✓	✓						30	9	14
3			✓			✓			✓				10	8	8
4													11	Under Review	Under Review
5													11	6	11
6													12	NA	21
7						✓							12	6	8
8													12	NA	11
9													12	10	9
10	✓	✓				✓	✓					✓	7	8	14
11	✓												9	NA	NA
12													11	8	Under Review
13						✓							11	6	NA
14													12	NA	11
15													11	8	11

PR: Priority Review, ODD: Orphan Drug Designation, BTD: Breakthrough Therapy Designation, AA: Accelerated Approval (US); Accelerated Assessment (EU), FT: Fast Track, PRIME: Priority Medicines, CMA: Conditional Marketing Authorisation, EC: Exceptional Circumstances, NA: Not Applied

Utilization of Expedited Approval Pathways/Novel Regulatory Programs (Non-Oncology)

LCM (N=27)	Japan		US					EU					Review Period (Mo)		
	PR	ODD	BTD	AA	FT	PR	ODD	PRIME	AA	CMA	EC	ODD	Japan	US	EU
16													7	NA	NA
17	✓	✓											8	NA	NA
18	✓	✓											8	8	Under Review
19													12	10	12
20													11	13	NA
21													4	12	13
22													11	NA	10
23													9	19	9
24	✓	✓											9	3	14
25			✓			✓							8	9	8
26	✓	✓											7	NA	8
27													12	10	13

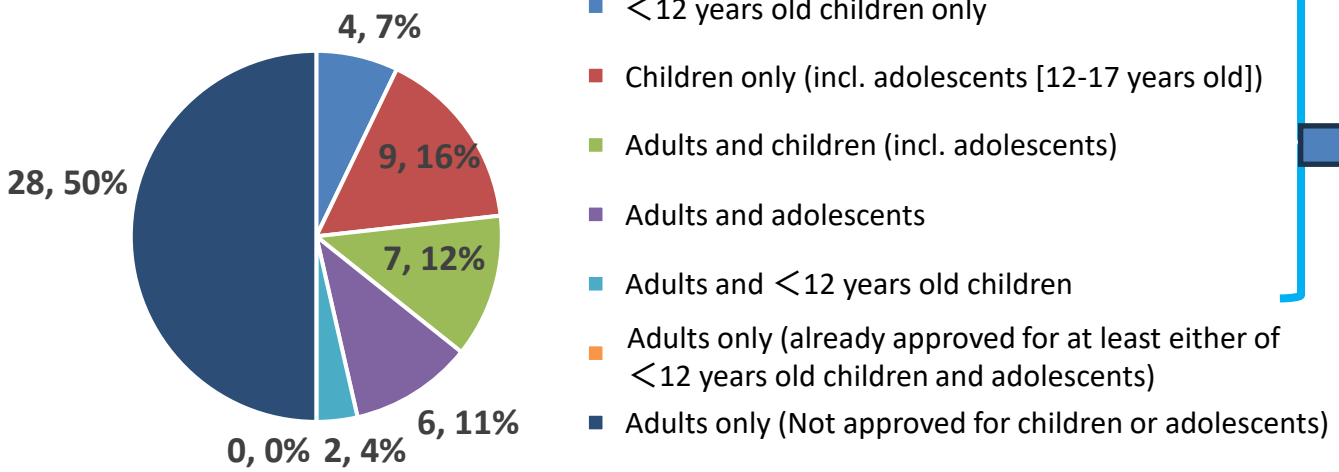
PR: Priority Review, ODD: Orphan Drug Designation, BTD: Breakthrough Therapy Designation, AA: Accelerated Approval (US); Accelerated Assessment (EU), FT: Fast Track, PRIME: Priority Medicines, CMA: Conditional Marketing Authorisation, EC: Exceptional Circumstances, NA: Not Applied

Findings

- Almost all products which applied for priority review in Japan were designated as orphan drugs
- Expedited program is widely granted to oncology projects by FDA.
- EU's expedited review system was not widely utilized compared to the U.S. and Japan
- Review gap with more than a 4-month b/w US and Japan is
  - Oncology: 38% (5/13)
  - Non-oncology: 19 % (8/43)

Pediatric Development

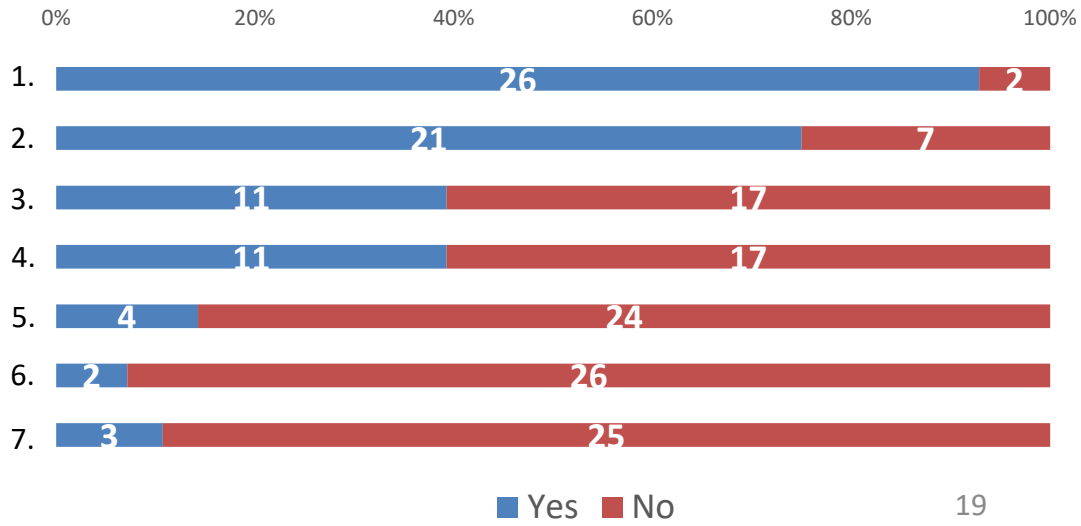
Target of the approved indication (N=56)



(N=28)

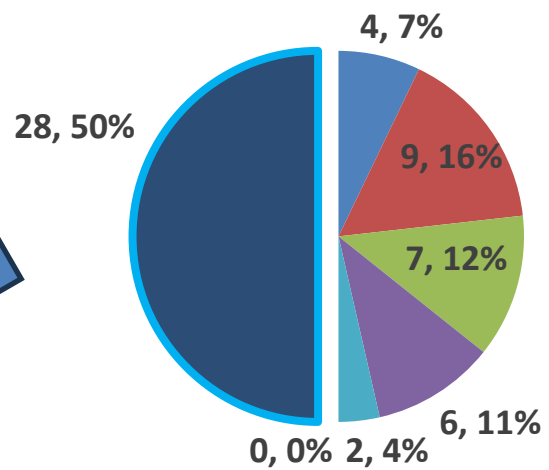
The reason of development for pediatrics (multiple answers allowed)

1. For therapies (drugs) for diseases including children
2. To align with the global development schedule
3. For therapies (drugs) that can be evaluated with adults
4. Because the pediatric premium can be obtained
5. Because the re-examination period for adults can be expected to be extended
6. Because the request from the Evaluation Committee on Unapproved or Off-label Drugs or academic societies, etc.
7. Others



Pediatric Development

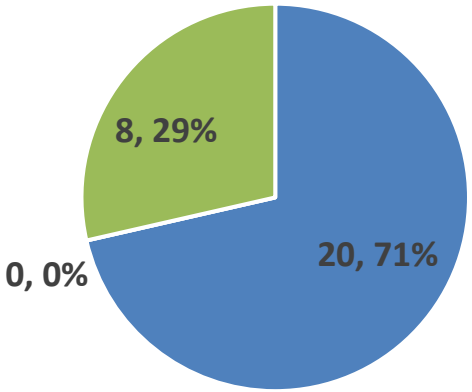
Target of the approved indication (N=56)



- ＜12 years old children only
- Children only (incl. adolescents [12-17 years old])
- Adults and children (incl. adolescents)
- Adults and adolescents
- Adults and ＜12 years old children
- Adults only (already approved for at least either of ＜12 years old children and adolescents)
- Adults only (Not approved for children or adolescents)

(N=28)

Planning of pediatric development of approved indication only for adults



- No plan for pediatric development
- Pediatric development is planned with PMDA confirmation by the end of review for adults
- Pediatric development is planned without PMDA confirmation by the end of review for adults

- 28 (50%) of the 56 products were approved including pediatric use, with disease characteristics and global development being the primary reasons for pediatric development.
- Of the 56 products, 28 (50%) have only been approved for adults. 8/28 (29%) are planning for pediatric use, and no development plan for pediatrics was confirmed with PMDA by the end of review for adults.
- The new notice on the pediatric drug development (issued on Mar 29 ,2024) may lead to an increase of and early development of pediatric drugs in the future.