外資系企業における承認品目の傾向
～PhRMA/EFPIA合同調査結果（2021年度）より～

〇川村純司（ブリストル・マイヤーズ スクイブ）[1]、池田晶子（ヤンセンファーマ）[1]、秋本美紀（ブリストル・マイヤーズ スクイブ）[1]、岩森智子（ノバルティス ファーマ）[2]、太田雪（グラクソ・スミスクライン）[2]、奥野弘明（日本イーライリリー）[1]、北岡伸太郎（バイエル薬品）[2]、来栖克典（フェリング ファーマ）[2]、砂村一美（ファイザーR&D）[1]、関喜史（アッヴィ）[1]、塚本修(CSLベーリング）[2]、中谷優子(バイオジェン）[1]、平井寛二（MSD)[1]、古舘直典（ルンドベック・ジャパン）[2]、本多基子（ヤンセンファーマ）[2]、本間麻里子（バイエル薬品）[2]、綿引友博（ヤンセンファーマ）[1]

[1]米国研究製薬業協会（PhRMA）、[2]欧州製薬団体連合会（EFPIA）

- 2021年度（2021年4月～2022年3月）にPhRMA及びEFPIA加盟会社で承認された新医薬品は63品目（医薬品62品目、再生医等製品1品目）であった。
- 通常審査品目は31品目（50%）であり、審査期間は80%tileで11.7ヵ月であった。優先審査品目は19品目（31%）で、80%tileで8.8ヵ月であった（再生医療等製品を除く）。特例承認品目は8品目（13%）であった。
- 希少疾病品目は18品目（29%）であり、先駆け指定品目は1品目（2%）、条件付き早期承認制度利用品目はなかった。
- 臨床データパッケージにおける第3相試験として、40品目（63%）が国際共同試験に参加していた。また、RWDを活用した承認申請が3件あり、いずれも有効性に対する評価又は参考資料として用いられていた。
- 63品目のうち海外で承認申請予定又は実施した品目は、50品目（79%）あり、そのうち25品目（50%；25/50品目）において同時申請（最初の国の申請から3ヵ月以内）を達成した。また、日欧米のうち日本が最初に承認となった品目は9品目（18%；9/50品目）であった。
- 日欧米のいずれかで迅速審査制度が活用された品目は、全63品目中39品目（62%）であり、特に米国の審査においては1品目に対し複数の迅速審査制度が活用されていた。抗がん剤領域では、13品目中10品目（77%）において日本と米国で4ヵ月以上の審査期間の差が認められた。
- 中国の開発状況として、63品目中少なくとも8品目が中国で承認を取得し、日本より中国において早く申請され、承認が得られている品目が2品目あった。審査期間に関しては、いずれも日本の方が短かった。
- 小児開発は全63品目中19品目（30%）で実施され、そのうち11品目（58%; 11/19品目）で国際共同試験に参加していた。

PhRMA-EFPIA Joint Survey 2022

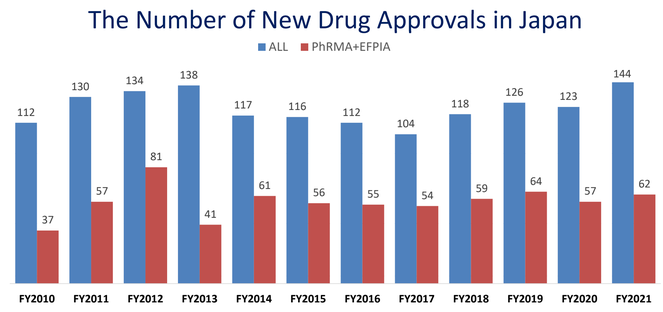
1. ***Review Time***
   - The Number of New Drug Approvals in Japan, in FY2021
   - Review Time for Standard Review and Priority Review
2. ***Category of Approved Product***
   - Background of Approved Products
   - Utilization of expedited program
3. ***Clinical Data Package***
   - Type of Phase 3 Study in Clinical Data Package
   - Utilization of RWD in Clinical Data Package
4. ***Submission/Review/Approval Lag***
5. ***Utilization of Expedited Program***
6. ***China Development***
7. ***Pediatric Development***

These results of analysis are based on the following companies, and the result of three overlapping companies are counted as one time

Participating companies:

- PhRMA (11 companies)
  - Abbvie, Amgen, Biogen Japan, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline*, Janssen*, MSD, Pfizer, Gilead Sciences and CSL Behring*
- EFPIA (15 companies)
  - AstraZeneca, Bayer, CHUGAI, CSL Behring*, Ferring, GlaxoSmithKline*, Janssen*, LEO, Lundbeck, Merck Biopharma, Boehringer Ingelheim, Novartis, Novo Nordisk, Sanofi, and UCB

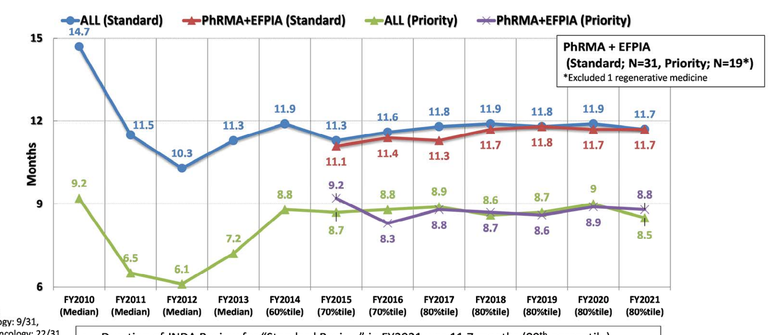
The Number of New Drug Approvals in Japan



The survey respondents from PhRMA and EFPIA accounted for 43% (62/144) of the total new drug approvals in Japan in FY2021

Note: Total 63 compounds were approved.
One regenerative medicine was excluded from the FY2021 survey data

Review Time for Standard Review and Priority Review



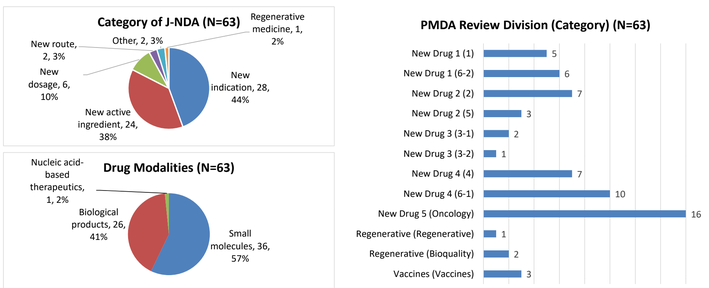
Note:
Standard
- Oncology: 9/31,
- Non-oncology: 22/31

Priority
- Oncology: 7/20,
- Non-oncology: 12/20

- Duration of JNDA Review for "Standard Review" in FY2021 was 11.7 months (80th percentile)
- Duration of JNDA Review for "Priority Review" in FY2021 was 8.8 months (80th percentile)

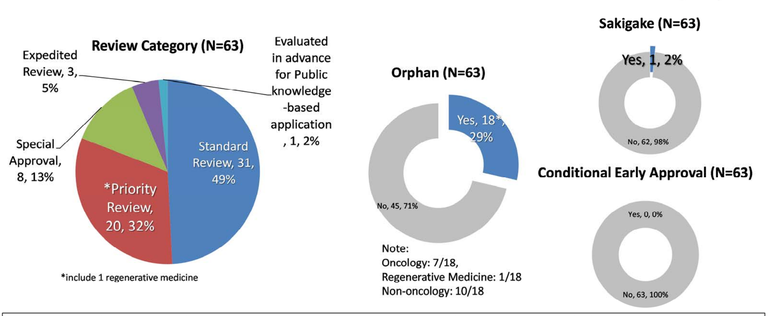
Background of Approved Products PhRMA + EFPIA (N=63*)

* 62 drugs and 1 regenerative medicine



- "New indication" (28/63; 44%) and "new active ingredient" (24/63; 38%) accounted for the majority of the JNDA
- Small molecules accounted for 57% (36/63) and Biological products for 41% (26/63)
- 16 of the 63 approved products (25%) were for oncology (largest divisional category), compared to 47% in FY2020

Utilization of Expedited Program PhRMA + EFPIA (N=63)

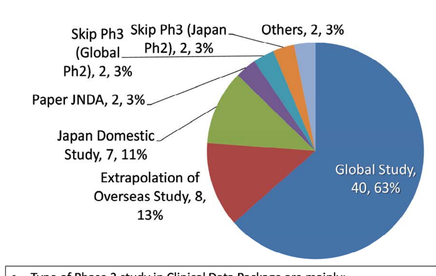


Note:
Oncology: 7/18,
Regenerative Medicine: 1/18
Non-oncology: 10/18

- In FY2021, 20 products (32%) were approved through the Priority review and 18 (29%) were through the Orphan drug review
- There was one product approved under the Sakigake pathway; none were approved through Conditional Early Approval
- 8 products (13%) were approved through special approval, all of which were COVID-19 related drugs

Type of Phase 3 Study in Clinical Data Package

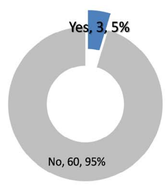
PhRMA + EFPIA (N=63)



- Type of Phase 3 study in Clinical Data Package are mainly:
1) "Global studies": 40 cases; 63% (FY2020: 67%)
2) "Extrapolation of overseas study": 8 cases; 13% (FY2020: 7%), 5 out of 8 cases were special approval cases
3) "Japan domestic studies": 7 cases; 11% (FY2020: 14%)
- Skip Ph3 (Global Ph2) and Skip Ph3 (Japan Ph2) were Oncology Development only

Utilization of RWD in Clinical Data Package

Utilization of RWD



Objective to utilize the RWD (n=3: Multiple answers allowed)

Efficacy as Evaluation Material	2 (67%)
Efficacy as Reference Material	3(100%)
Safety as Evaluation Material	0 (0%)
Safety as Reference Material	0 (0%)

Background to use of RWD

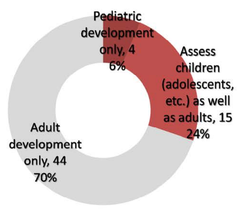
Used as part of the clinical data package upon agreement with PMDA prior to J-NDA submission	2 (67%)
Used as part of the clinical data package at company's (Japanese corporation) discretion without agreement with PMDA	1 (33%)

- In FY2021, there were 3 products (all for oncology) that used RWD (both foreign and Japanese)
- The objectives of RWD utilization were for efficacy data as evaluation or reference materials, not for safety data
- Two of the three involved "Skip Ph3 (Japan Ph2)" in "Type of Phase 3 Study in Clinical Data Package"
- Two of the three were with the agreement of the PMDA prior to JNDA submission

Pediatric Development

PhRMA + EFPIA (N=58)

Relevance of pediatric development (Is the product developed for pediatric use?)



Clinical Data Package for Pediatric Development (N=19)

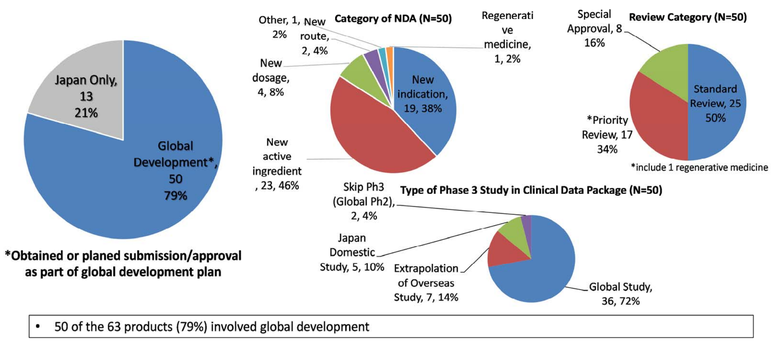
Global Study including Japanese	8 (42%)
Global study including Japanese & Japanese PK study	1 (5%)
Global Study including Japanese & Domestic study (other than PK study)	2 (11%)
Domestic study and PK study	0 (0%)
Domestic study (other than PK study)	0 (0%)
Others	8 (42%)

The reason for conducting pediatric development in Japan (N=19; Multiple answers allowed)

It was planned to be developed by Global	15 (79%)
There was an incentive for a re-examination period	1 (5%)
There were incentives for drug prices	1 (5%)
Others	5 (26%)

- Pediatric development was undertaken for 19 products (30%), including pediatric only (4 cases; 6%), and adolescents evaluated with adults (15 cases; 24%)
- Clinical data package for pediatrics come from mainly global studies
- The reasons to conduct pediatric development was "it was planned to be developed by global" (15 cases; 79%), incentive for a re-examination period (1 case, 5%) and incentives for drug prices (1 case, 5%)

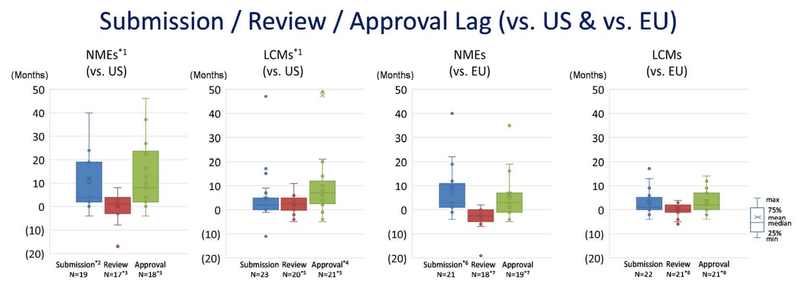
Global Development*



*Obtained or planed submission/approval as part of global development plan

- 50 of the 63 products (79%) involved global development

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



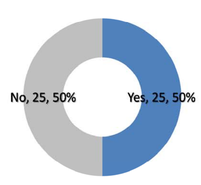
*1 NME is defined as "new active ingredient" in category of JNDA and LCM is defined as other categories
*2 One outlier 63 months is excluded from Submission lag in the figure of NMEs
*3 Exclude 2 cases under review in FDA
*4 One outlier 838 months is excluded from Approval lag in the figure of LCMs
*5 Exclude 3 cases under review in FDA
*6 One outlier 54 months is excluded from Submission lag in the figure of NMEs
*7 Exclude 3 cases under review in EU
*8 Exclude 1 case under review in EU

- Variability in Review duration lag in NMEs and LCMs was limited, and there were faster cases than US or EU review period
- The variation in the NME submission lag was greater than the variation in the LCM submission lag. In addition, the magnitude of the submission lag led to variations in the approval lag.
- LCMs were submitted and approved faster than NMEs

Simultaneous JNDA filing within 3 months

PhRMA + EFPIA (N=50)

Number of JNDA Filed Simultaneously (within 3 months) (n=50)



Reasons for simultaneous JNDA filing (within 3 months) (n=25; multiple answers allowed)

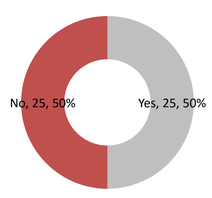
The standard process that allows the application within 3 months has been established	17 (68%)
There was a business decision to prioritize Japan	12 (48%)
It was a partial change application for the indication and dosage and administration, and there was no need to prepare materials for Japan such as CMC	5 (20%)
Others	10 (40%)

- Of the 50 products that obtained or planned submission/approval globally, 25 (50%) of the JNDA were filed simultaneously
- Primary reasons for these simultaneous applications included "the standard process allows for applications to be filed within 3 months" (17 or 68% of the applications) and "there was a business decision to prioritize Japan" (12 or 48% of the applications).

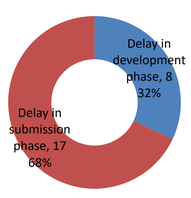
Simultaneous JNDA filing More than 3 months

PhRMA + EFPIA (N=50)

Number of JNDA Filed Simultaneously (within 3 months) (n=50)



Reasons for not filing simultaneously (i.e. within 3 months) (n=25)



- Of the 50 products that obtained or planned submission/approval globally, 25 (50%) of the JNDA were **NOT** filed simultaneously
- Reasons for not filing simultaneously (i.e., within three months) included delays during the submission phase" (17 or 68% of the applications) or "delays in the development phase" (8 or 32% of the applications)

Simultaneous JNDA filing More than 3 months

PhRMA + EFPIA (N=25)

The reasons for delay in development phase (n=8: Multiple answers allowed)

Already approved overseas	4 (50%)
Japan could not join the MRCT(verification study) as it was already started	3 (38%)
Japan stand alone development	1 (13%)
Japanese phase 1 study became necessary before join in MRCT	1 (13%)
Japanese dose-finding study became necessary before join in MRCT	1 (13%)
Did not consider Japan development due to license-in product	1 (13%)
Others	3 (17%)

The reasons for delay in submission phase (n=17: Multiple answers allowed)

Preparation of Japanese Module 2.3 or approval application	3 (18%)
Wait for stability test results	3 (18%)
Preparation time for e-data submission	3 (18%)
Prioritize overseas	3 (18%)
For company's convenience	3 (18%)
Preparation of Table of CTD	2 (12%)
Not accepted interim results	2 (12%)
Conduct additional analysis for consideration of consistency between Japanese and entire population	2 (12%)
Pricing Strategy	2 (12%)
Wait for Long term safety data	0 (0%)
Expedited review in oversea	0 (0%)
Others	6 (35%)
Unknown	2 (12%)

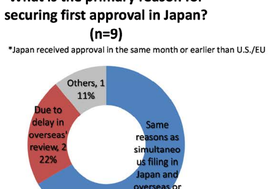
- The reasons for delays in the development phase: 4 cases (50%) was "already approved overseas and 3 cases (38%) could not join MRCT
- The reasons for delays in the submission phase: There were various reasons not only technical and regulatory, but also external factors such as priority, convenience and pricing strategies.

Approval lag

1st approval*

What is the primary reason for securing first approval in Japan? (n=9)

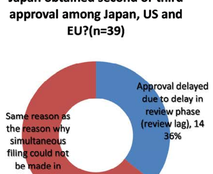
*Japan received approval in the same month or earlier than U.S./EU



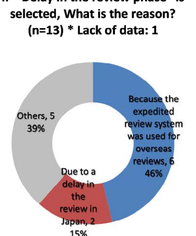
- Of the 50 products that obtained or planned submission/approval globally, 9 products were approved first in Japan
- In 6 of these cases (67%), Japan happened to approve first following a simultaneous filing and in 2 cases (22%), the overseas review had been delayed.

2nd or 3rd approval

What is the primary reason, if Japan obtained second or third approval among Japan, US and EU?(n=39)



If " Delay in the review phase" is selected, What is the reason? (n=13) * Lack of data: 1



- Of the 50 products, which obtained or planned submission/approval globally, 39 products were approved in Japan second or third behind the U.S. and/or EU
- In most of these cases (25 or 64%) the applicant had been unable to file simultaneously in Japan and in 14 cases (36%) due to a delay in the review phase in Japan.
- These delays of the review in Japan were either relative to the expedited review overseas (6 cases or 46%) or actual delays in the Japanese review process (2 cases or 15%)

Utilization of Expedited Program (Oncology)

NME (N=3)

	Japan			US								EU					Review Period (Mo)		
	PR	ODD	Sakigake	BTD	AA	FT	PR	ODD	RTOR	AAid	Orbis	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1	✓	✓		✓	✓		✓	✓						✓			**9**	**5**	14
2	✓	✓		✓	✓	✓	✓	✓	✓		✓			✓			**9**	**5**	13
3	✓	✓		✓	✓	✓	✓	✓	✓	✓			✓			✓	7	4	Under Review

LCM (N=10)

	Japan			US								EU					Review Period (Mo)		
	PR	ODD	Sakigake	BTD	AA	FT	PR	ODD	RTOR	AAid	Orbis	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1	✓	✓						✓	✓		✓						**7**	**2**	10
2									✓	✓							11	10	17
3							✓	✓	✓	✓	✓						**11**	**5**	11
4	✓	✓															**8**	**4**	8
5							✓		✓	✓							**10**	**6**	8
6					✓												**11**	**6**	NA
7									✓	✓	✓						**11**	**<1**	7
8	✓	✓															7	NA	NA
9	✓	✓		✓	✓		✓	✓						✓			**9**	**5**	14
10								✓									**11**	**6**	8

- Japan's expedited review system tends to depend on orphan and could not utilize another pathway
- Expedited program is widely granted in oncology projects by FDA resulting in a review lag between Japan and the U.S.
- In ten instances (77%; 10/13) there was more than a 4-month review gap between Japan and the U.S.

PR: Priority Review, ODD: Orphan Drug Designation, BTD: Break-through Designation, AA: Accelerated Approval (US); Accelerated Assessment (EU), FT: Fast Track, RTOR: Real Time Oncology Review, AAid: .Assessment Aid, CMA: Conditional Marketing Authorization, EC: Exceptional Circumstances

Utilization of Expedited Program (Non-Oncology)

NME (N=15)

	Japan			US					EU					Review Period (Mo)		
	PR	ODD	Sakigake	BTD	AA	FT	PR	ODD	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1	(SA)						✓			✓				**1**	Under Review	1
2	✓	✓				✓	✓	✓	✓	✓			✓	**8**	**11**	8
3							✓							9	8	Under Review
4	(SA)										✓			3	NA	1
5	✓	✓	✓	✓				✓	✓				✓	**6**	Undisclosed	Undisclosed
6	(SA)										✓			1	1	1
7	✓	✓											✓	8	NA	Under Review
8	(SA)										✓			**<1**	**2**	1
9	✓	✓		✓	✓			✓			✓			**13**	**30**	32
10								✓				✓	✓	10	6	13
11						✓	✓							16	8	15
12								✓					✓	12	Under Review	12
13	✓	✓				✓								12	8	15
14						✓	✓							12	8	14
15				✓			✓							**9**	**17**	15

- Japan's expedited review system tends to depend on priority review (and orphan)
- Expedited program is widely granted in non-oncology projects in U.S./EU. However, review period GAP for non-oncology products was lower than that in oncology. And several projects had a shorter review period in Japan than in the U.S. and EU.

PR: Priority Review, SA: Special Approval, ODD: Orphan Drug Designation, BTD: Break-through Designation, AA: Accelerated Approval (US); Accelerated Assessment (EU), FT: Fast Track, CMA: Conditional Marketing Authorization, EC: Exceptional Circumstances

Utilization of Expedited Program (Non-Oncology)

LCM (N=11)

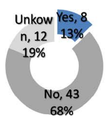
	Japan			US					EU					Review Period (Mo)		
	PR	ODD	Sakigake	BTD	AA	FT	PR	ODD	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1		✓												12	11	12
2	✓	✓			✓		✓	✓	✓	✓			✓	9	4	7
3	(SA)											✓		2	<1	1
4	✓						✓				✓			**4**	Under Review	Under Review
5	(SA)						✓				✓			**1**	Under Review	1
6	✓			✓		✓	✓							8	5	9
7	✓	✓		-		-	-							9	NA	NA
8	(SA)											✓		2	<1	1
9	✓						✓						✓	**1**	Under Review	5
10	✓	✓		-	-	-	-							7	NA	NA
11	✓	✓		✓				✓						8	6	NA

- Japan's expedited review system tends to depend on priority review (and orphan)
- Expedited program is widely granted in non-oncology projects in US/EU. However, review period GAP for non-oncology products was lower than that in oncology. And a couple of projects had a shorter review period in Japan than in the U.S. and EU.

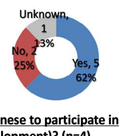
PR: Priority Review, SA: Special Approval, ODD: Orphan Drug Designation, BTD: Break-through Designation, AA: Accelerated Approval (US); Accelerated Assessment (EU), FT: Fast Track, CMA: Conditional Marketing Authorization, EC: Exceptional Circumstances

China Development (Approved Case)

Already Approved in China?



China joins/ed global study (incl. Asia study)?



What was the initial timing for China to join the global development (n=5)

From phase 2	1 (20%)
From phase 3 (incl. 2/3)	3 (60%)
Unknown	1 (20%)

Has a phase 1 PK study been conducted for Chinese to participate in global development (including Asian development)? (n=4)

Chinese Ph1 study in China	1 (25%)
Chinese Ph1 study Overseas	0 (0%)
No	1 (25%)
Unknown	2 (50%)

Has a dose-response study been conducted in Chinese subjects in China? (n=3)

Yes	0 (0%)
No	1 (33%)
Unknown	2 (67%)

*Excluded one case: China joined from phase 2 study

- There were at least 8 instances in which the products were already approved in China
- In at least 5 of these 8 cases, China joined global studies from phase 2 or phase 3 (incl. 2/3)

China Development (Approved Case)

NME (N=4)

		Japan		China				Submission lag	Review Period lag (Mo)			Approval lag
		PR	ODD	BT	CA	PR	SA	Lag	Japan	China	Lag	Lag
6	New Drug 3 (3-1)	✓	✓	UNK	UNK	UNK	UNK	UNK	8	UNK	UNK	UNK
18	New Drug 4 (4)	SA			✓		UNK	1	1	2	-1	0
40	New Drug 2 (2)					✓		**14**	10	12	-2	**12**
63	New Drug 4 (6-1)					✓		-1	9	15	**-6**	-7

LCM (N=4)

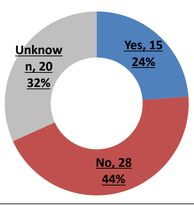
		Japan		China				Submission lag	Review Period lag (Mo)			Approval lag
		PR	ODD	BT	CA	PR	SA	Lag	Japan	China	Lag	Lag
3	New Drug 4 (6-1)							-1	10	15	-5	-6
32	New Drug 4 (6-1)							-1	11	15	-4	-5
38	New Drug 2 (2)							**7**	10	14	-4	**3**
45	New Drug 4 (6-1)			UNK	UNK	UNK	UNK	UNK	9	UNK	UNK	1

- There were a couple of cases where there was a large Submission lag and/or Approval lag between Japan and China
- The review period in Japan is generally shorter than in China

PR: Priority Review, SA: Special Approval, ODD: Orphan Drug Designation, BT: Breakthrough, CA: Conditional Approval

China Development (Approved and on-going)

China joins/ed global study (incl. Asia study)?



What was the initial timing for China to join the global development (n=15)

From phase 2	1 (7%)
From phase 3 (incl. 2/3)	13 (87%)
Unknown	1 (7%)

Has a phase 1 PK study been conducted for Chinese to participate in global development (including Asian development)? (n=14)

Chinese Ph1 study in China	6 (43%)
Chinese Ph1 study in Oversea	0 (0%)
No to conduct	3 (21%)
Unknown	5 (36%)

Has a dose-response study been conducted in Chinese subjects in China? (n=13)

Conduct Chinese study	0 (0%)
Not to conduct Chinese study	8 (62%)
Unknown	5 (38%)

*Excluded one case: China joined from phase 2 study

- There were at least 15 cases where China was part of a global study (incl. Asia study)
- In 13 of these 15 cases (87%), China joined global studies from phase 3 (incl. 2/3)
- Responses were split on whether a Chinese phase 1 study had been conducted (43% - yes; 21% - no)
- There were no instances in which a dose-response study was conducted in China, although there was a case to join from phase 2. Will need to keep an eye on future trends.