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）

- 2022年度（2022年4月～2023年3月）に調査参加企業（PhRMA 11社、EFPIA 16社）で承認された新医薬品は55品目（医薬品52品目、再生医療等製品3品目）であった。
- ·希少疾病品目は17品目（31%）であり、先駆的医薬品・先駆的再生医療等製品指定品目、条件付き早期承認制度・条件及び期限付き承認制度利用品目はいずれもなかった。
- ·医薬品52品目のうち、通常審査品目は29品目（56%）であり、審査期間は80%tileで11.6ヵ月であった。優先審査品目は18品目（35%）で、80%tileで9.4ヵ月であった。
- ·医薬品の臨床データパッケージにおける主要な第3相試験として、34品目（65%）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1件あり、有効性及び安全性の評価資料として用いられていた。
- ·医薬品のうち、海外で承認申請した又は申請予定の品目は48品目（92%）あり、そのうち22品目（46%）は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。また、日欧米のうち日本が最初に承認を取得した品目は10品目（21%；10/48品目）であった。
- ·承認適応が小児を含んでいない医薬品38品目のうち、小児開発を別途行う予定があるのは6品目（16%）であり、うち5品目（83 %） は国際共同試験を予定していた。

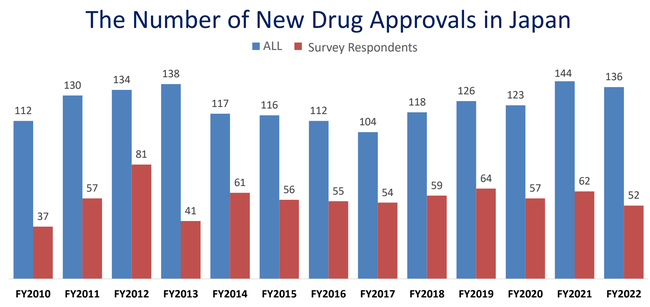
PhRMA/EFPIA Joint Survey 2023

1. ***Review Time***
   - The Number of New Drug Approvals in Japan, in FY2022
   - 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. ***Evaluation of Submission Lag***
6. ***Utilization of Expedited Program***
7. ***Pediatric Development***

Participating companies:
- PhRMA (11 companies)
  - Amgen, Biogen Japan, Bristol-Myers Squibb, CSL Behring*, Eli Lilly, Gilead Sciences, GlaxoSmithKline*, Incyte Japan, Janssen*, MSD, and Pfizer
- EFPIA (16 companies)
  - Alexion, AstraZeneca, Bayer, CHUGAI, CSL Behring*, Ferring, Genmab, GlaxoSmithKline*, Janssen*, LEO, Lundbeck, Boehringer Ingelheim, Novartis, Novo Nordisk, Sanofi, and UCB

* Companies which participate in both PhRMA and EFPIA. For these three companies, survey answers from PhRMA and EFPIA were integrated into single answers.

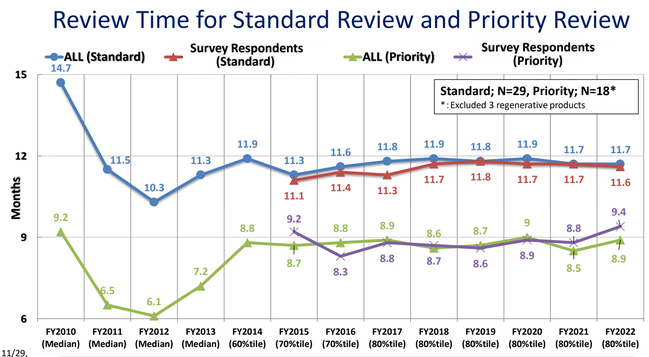
The Number of New Drug Approvals in Japan



The survey respondents accounted for 38% (52/136) of the total new drug approvals in Japan in FY2022

Note: Total 55 products were approved.
Three regenerative products were excluded from the FY2022 survey data.

Review Time for Standard Review and Priority Review



Note:
Standard
- Oncology: 11/29,
- Non-oncology: 18/29

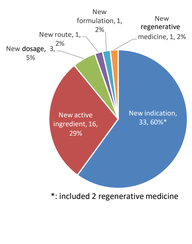
Priority
- Oncology: 8/18,
- Non-oncology: 13/18

- Duration of J-NDA Review for “Standard Review” in FY2022 was 11.6 months (80th percentile)
- Duration of J-NDA Review for “Priority Review” in FY2022 was 9.4 months (80th percentile)

Background of Approved Products (N=55*)

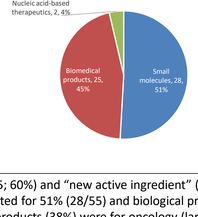
* 52 drugs and 3 regenerative medicine

Category of J-NDA (N=55)

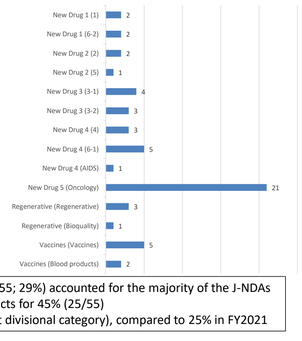


*: included 2 regenerative medicine

Drug Modalities (N=55)



PMDA Review Division (Category) (N=55)

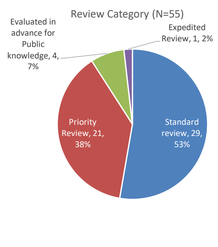


- “New indication” (33/55; 60%) and “new active ingredient” (16/55; 29%) accounted for the majority of the J-NDAs
- Small molecules accounted for 51% (28/55) and biological products for 45% (25/55)
- 21 of the 55 approved products (38%) were for oncology (largest divisional category), compared to 25% in FY2021

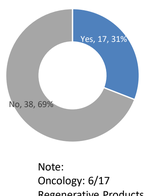
Utilization of Expedited Program (N=55*)

* 52 drugs and 3 regenerative medicine

Review Category (N=55)

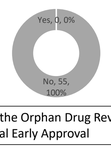


Orphan (N=55)



Sakigake (N=55)

Conditional Early Approval (N=55)

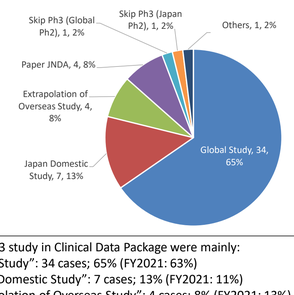


Note:
Oncology: 6/17
Regenerative Products: 3/17
Non-oncology: 8/17

- In FY2022, 21 products (38%) were approved through the Priority Review and 17 (31%) were through the Orphan Drug Review
- There was no product approved under the Sakigake pathway; none were approved through Conditional Early Approval

Type of Phase 3 Study in Clinical Data Package (N=52*)

* Excluded 3 regenerative products



- Type of Phase 3 study in Clinical Data Package were mainly:
  1) “Global Study”: 34 cases; 65% (FY2021: 63%)
  2) “Japan Domestic Study”: 7 cases; 13% (FY2021: 11%)
  3) “Extrapolation of Overseas Study”: 4 cases; 8% (FY2021: 13%)
- “Skip Ph3 (Global Ph2)” was orphan designated drug and “Skip Ph3 (Japan Ph2)” was nucleic acid-based therapeutics.

Utilization of RWD in Clinical Data Package

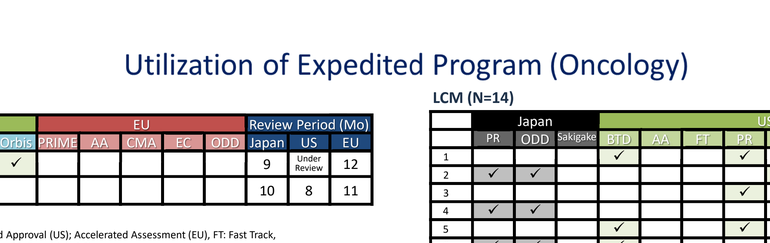
Utilization of RWD (N=52*)

*: Excluded 3 regenerative products

- In FY2022, there was 1 product that used RWD (foreign data)
- The objectives of RWD utilization were for efficacy and safety data as evaluation materials
- Used as a part of the clinical data package upon agreement with PMDA prior to J-NDA submission
- Global natural history data was used as a control in the local Ph3 study in Japan
- This drug is a nucleic acid-based therapy and designated as Orphan Drug

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

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



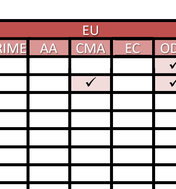
*1 NME is defined as “new active ingredient” in category of J-NDA and LCM is defined as other categories.
*2 Exclude 2 cases under review in US
*3 Exclude 1 case of >500 months of submission/approval lag
*4 Exclude 1 case under review in US
*5 2 cases of >70 months of submission lag are not shown.
*6 2 cases of >70 months of approval lag are not shown.
*7 Exclude 1 case under review in EU
*8 2 cases of >70 months of submission lag are not shown.
*9 3 cases of >70 months of approval lag are not shown.

- Review duration lag tends to be limited, and many cases were shorter than EU review period in the NME.
- Overall, submission lag is presumed to be the main reason for approval lag.
- There were several cases in the LCM that have quite large submission/approval lag in both vs. US and EU.

Simultaneous J-NDA filing within 3 months

Number of J-NDAs Filed Simultaneously (within 3 months) (N=48)

Submission in countries/regions other than Japan (N=52)



Reasons for simultaneous J-NDA filing (within 3 months) (N=20; multiple answers allowed)

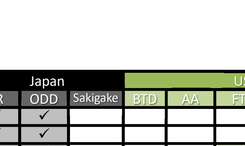
The standard process that allows the application within 3 months has been established	18 (90%)
There was a business decision to prioritize Japan	17 (85%)
It was a partial change application for the indication and dosage/administration, and there was no need to prepare materials for Japan such as CMC	14 (70%)
Others	1 (5%)

- Of the 48 products that achieved or planned submission globally, 22 J-NDAs (46%) were filed first in JP or simultaneously.
- Fourteen cases (70%) were partial change applications which need no preparation of materials for Japan such as CMC.
- Primary reasons for these simultaneous applications were “the standard process allows for applications to be filed within 3 months” (18 cases, 90% of the applications) and “there was a business decision to prioritize Japan” (17 cases, 85%).

Simultaneous J-NDA filing: Submission lag more than 3 months

Number of J-NDAs Filed Simultaneously (within 3 months) (N=48)

Reasons for not filing simultaneously (within 3 months) (N=26)



- Of the 48 products that achieved or planned submission/approval globally, 26 J-NDAs (54%) were **NOT** filed simultaneously.
- Reasons for not filing simultaneously (i.e., within three months) consist of “delays in the submission phase” in 14 cases (54%) and “delays in the development phase” in 12 cases (46%).

Simultaneous J-NDA filing: Submission lag more than 3 months

Reasons for the delay in development phase (N=12: multiple answers allowed)

Already approved overseas	7 (58%)
Japan was unable to join the MRCT (verification study) as it had been already started	4 (33%)
Did not consider Japan development due to licensed-in product	3 (25%)
Japanese phase 1 study became necessary before joining MRCT	1 (8%)
Japanese dose-finding study became necessary before joining MRCT	0 (0%)
Others	4 (33%)

Reasons for the delay in submission phase (N=14: multiple answers allowed)

Preparation of Japanese Module 2.3 or approval application	4 (29%)
Conducted additional analysis for consideration of consistency between Japanese and entire population	3 (21%)
Preparation time for e-data submission	2 (14%)
Preparation of tables for CTD	2 (14%)
Expedited review in oversea	1 (7%)
Waited for stability test results	1 (7%)
Pricing strategy	0 (0%)
Waited for long-term safety data	0 (0%)
Interim results were not accepted	0 (0%)
Others	7 (50%)

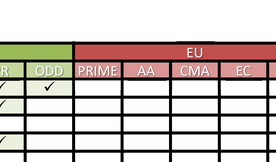
Reasons for the delays were:
- Development phase: “already approved overseas” in 7 cases (58%), “unable to join MRCT” in 4 cases (33%), and “licensed-in product” in 3 cases (25%)
- Submission phase: various reasons, not limited to technical/regulatory ones

Acceptance of English CTDs as well as reduction/elimination of Japan-specific requirements related to M2.3 and approval application form was suggested as one of possible measures to stimulate simultaneous submissions.

Pediatric Development

Summary of products which planned pediatric development after approval for adults

Pediatric development for the approved indication (N=52)

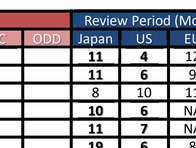


The purpose of development for pediatric （N=6）

Purpose	A	B	C	D	E	F
Pediatric Indication	✔					
Dose and administration	✔	✔	✔	✔	✔	✔
New formulation for pediatric		✔	✔	✔	✔	

Japanese data in the planned clinical data package for J-NDA (N=6)

Status of the extension of re-examination period (N=6)



Conclusion
- 38% (20 products) of the approved products were developed/planned for pediatric indications.
- 11% (6 products) planned pediatric development after the approved adult indication.
  - All the 6 products planned to add dosage and administration for pediatrics.
  - In most cases (80%, 4/6), the purpose included development of new formulation.
  - MRCTs were planned in most cases (83%, 5/6).
  - 3 products planned the extension of re-examination period and 2 products had been already extended the period by 2 years based on the latest notification.

Utilization of Expedited Program (Oncology)

NME (N=2)

	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	Under Review	12
2							✓	✓									10	8	11

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

LCM (N=14)

	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				✓			✓		✓	✓	✓					✓	**10**	**2**	13
2	✓	✓						✓						✓		✓	8	10	6
3							✓				✓						**11**	**5**	7
4	✓	✓															8	NA	NA
5				✓			✓		✓	✓	✓						**12**	**2**	7
6	✓	✓		✓													**8**	**4**	9
7							✓		✓	✓	✓						**11**	**4**	12
8	✓	✓		✓				✓									8	6	NA
9							✓	✓									**10**	**6**	10
10							✓		✓	✓	✓						**11**	**5**	11
11							✓										**11**	**2**	6
12	✓	✓					✓		✓	✓							9	6	8
13	✓								✓		✓						8	11	12
14	✓	✓					✓	✓		✓	✓					✓	9	6	8

Findings in Oncology
- Majority of products which were applied priority reviews in Japan were designated as orphan drugs
- Expedited program is widely granted to oncology projects by FDA resulting in a review lag between Japan and the U.S.
- In eight cases (50%; 8/16) there was more than a 4-month review gap between Japan and the U.S.
- EU's expedited review system was not widely utilized compared to the U.S. and Japan.

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RTOR: Real Time Oncology Review, AAid: .Assessment Aid, CMA: Conditional Marketing Authorization, EC: Exceptional Circumstances, NA: Not Applied

Utilization of Expedited Program (Non-Oncology)

NME (N=9)

	Japan			US					EU					Review Period (Mo)		
	PR	ODD	Sakigake	BTD	AA	FT	PR	ODD	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1	✓	✓											✓	3	21	17
2	✓	✓					✓	✓					✓	9	9	22
3	✓	✓				✓		✓					✓	8	8	18
4	✓	✓					✓							9	53	24
5	✓	✓		✓				✓					✓	26	23	13
6				✓			✓							11	8	13
7	✓										✓			**13**	**<1**	1
8				✓			✓							**16**	**8**	16
9	✓	✓					✓	✓			✓		✓	9	7	15

PR: Priority Review, 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

LCM (N=8)

	Japan			US					EU					Review Period (Mo)		
	PR	ODD	Sakigake	BTD	AA	FT	PR	ODD	PRIME	AA	CMA	EC	ODD	Japan	US	EU
1							✓	✓						**11**	**4**	12
2				✓			✓							**11**	**6**	9
3	✓	✓												8	10	11
4							✓							**10**	**6**	NA
5	✓													**11**	**7**	NA
6							✓							**19**	**6**	8
7						✓								**10**	**6**	11
8	✓	✓												7	NA	NA

Findings in Non-Oncology
- Majority of products which were applied priority reviews in Japan were designated as orphan drugs
- In eight cases (47%; 8/17) there was more than a 4-month review gap between Japan and the U.S., and the review gap was larger in LCM
- EU's expedited review system was not widely utilized, and the review period in Japan was shorter than that in EU in most cases

PR: Priority Review, 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, NA: Not Applied