外資系企業における開発品目の傾向
～PhRMA/EFPIA合同調査結果より～

本多基子(ヤンセンファーマ)[2]、青木勇(ブリストル・マイヤーズ スクイブ)[1]、秋本美紀(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]、今井景子(ヤンセンファーマ)[2]、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]、小川嘉正(フェリング ファーマ)[2]、春日井正文(アムジェン)[1]、川村純司(ブリストル・マイヤーズ スクイブ)[1]、北岡伸太郎(バイエル薬品)[2]、来栖克典(サノフィ)[2]、斉藤江理子(メルク)[2]、砂村一美(ファイザー)[1]、関佳史(アッヴィ)[1]、仙田雅之(サノフィ)[2]、武澤恵美子(ブリストル・マイヤーズ スクイブ) [1]、武部恭子(ヤンセンファーマ)[1]、塚本修(CSLベーリング)[2]、塚本はるな(日本イーライリリー)[1]、鶴田嘉代子(日本イーライリリー) [1]、中谷優子(バイオジェン ジャパン)[1]、花久恭子(ルンドベック ジャパン)[2]、穂積香織(アッヴィ) [1]

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年度は714件のプロジェクトから回答が得られた。疾患領域では昨年に引き続き抗悪性腫瘍薬が最も多く、52%を占めていた
- 先駆的医薬品指定制度の利用は検討中も含めて5%であった
- 欧米における承認制度利用ではRTOR及びBreakthroughが26～29、PRIMEが12プロジェクトあり、これらはAssessment Aid及びProject Orbisと共に利用されているケースも多かった
- 全804試験のうち、多くの品目で海外との同時開発が進められており、国際共同試験の実施が84%を占めていた
- 世界最初の申請から3ヵ月以内で本邦の申請を予定している品目は約50%であった
- 申請ラグの原因としてCTDの日本語化及び日本特有の品質データに加えて本年は日本特有の申請電子データの問題が挙げられた
- CDISC対応には6ヵ月以上また1千万円以上のコストを要しているとの回答もみられた一方で、CDISCが審査に活用されていると実感している企業は14%に留まった
- リアルワールドデータの活用に関しては検討中・未検討がそれぞれ約半数を占め、その理由として規制要件の不確定要素、エビデンスレベルの問題、社内体制が整っていないことが挙げられた
- 今回新たに調査した中国における開発状況については、国際共同試験に参加しているとの回答が29件(92件中)あり、従来1年以上を要していたINDの承認についても6ヵ月未満、1年未満で承認されたとの回答も散見され審査期間の短縮傾向がみられた

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:

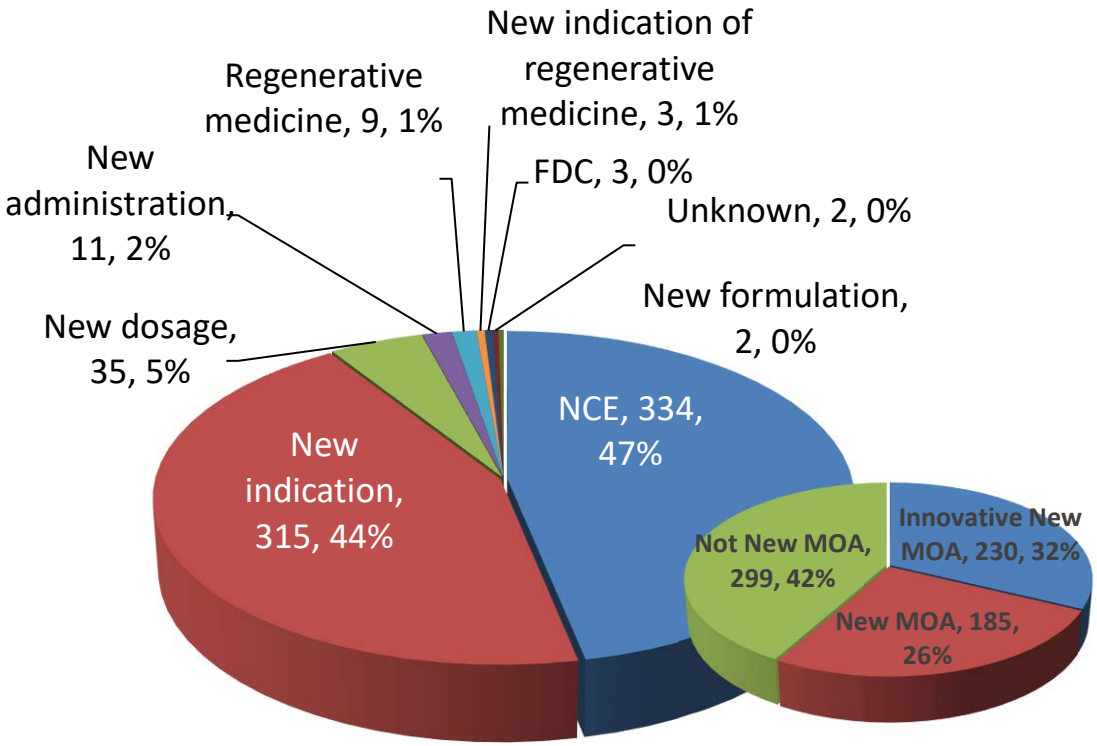
- PhRMA (10 companies)
  - Abbvie, Amgen, Biogen Japan, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, MSD, Pfizer, and Gilead Sciences
- EFPIA (15 companies)
  - AstraZeneca, Bayer, CHUGAI, CSL Behring*, Ferring, GlaxoSmithKline, Janssen, LEO, Lundbeck, Merck Biopharma, Boehringer Ingelheim,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

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

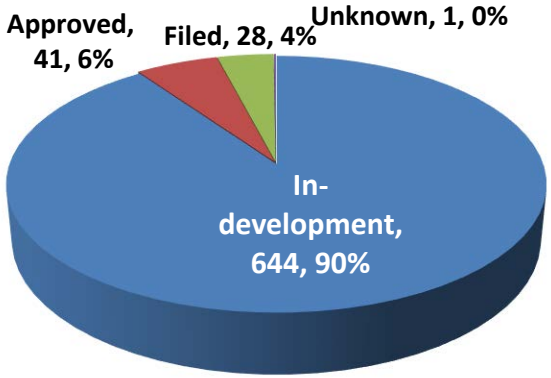
Total Projects in FY2020

EFPIA + PhRMA 714 projects

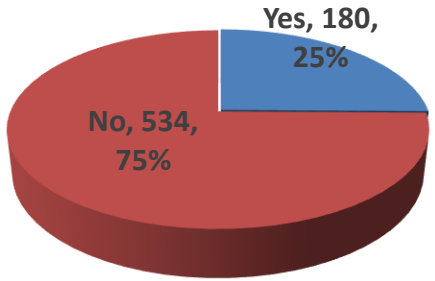
Projects by Planned filing Category



Development Status

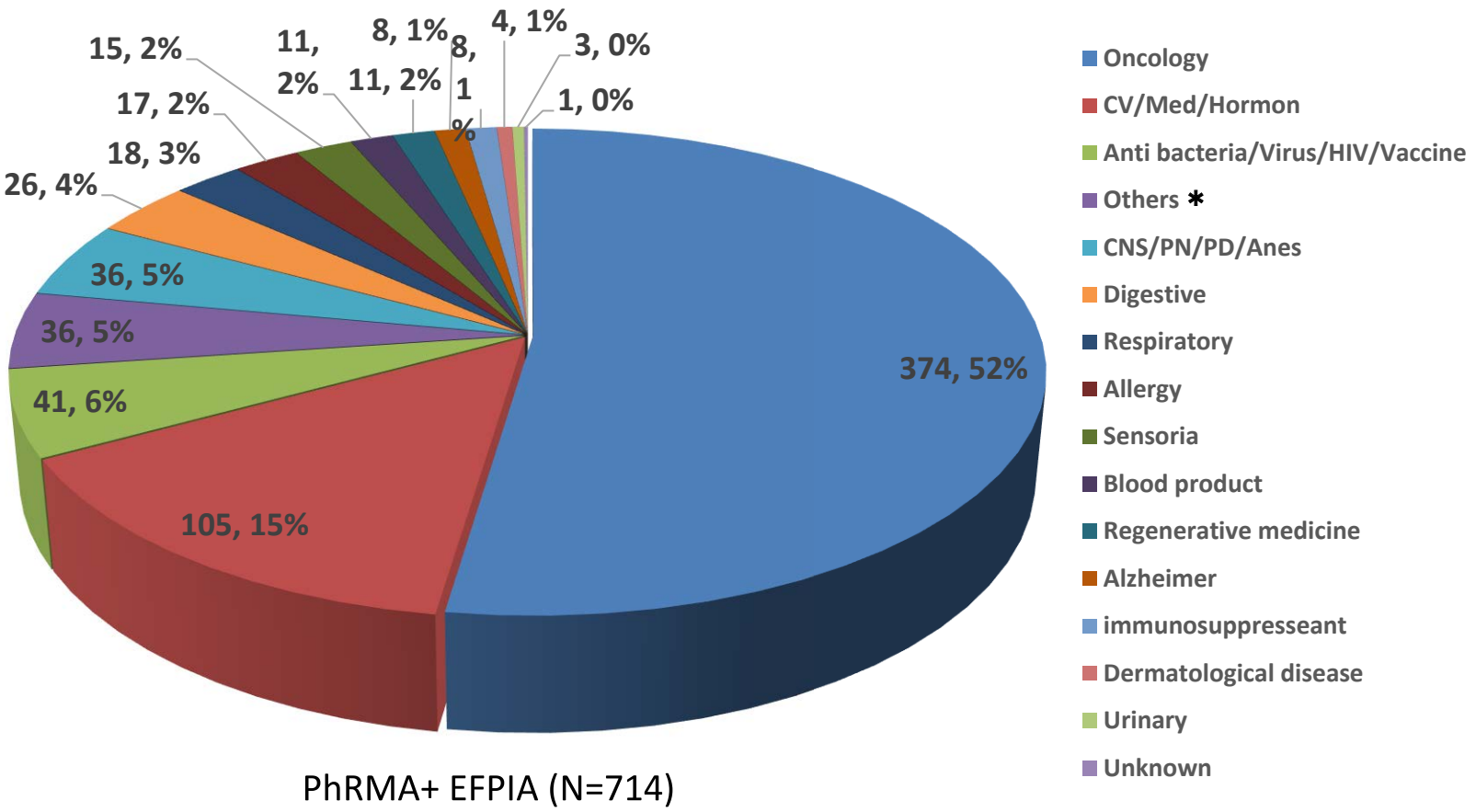


In-license product



- In FY2020 the total number of ongoing projects are 714 (90%) in total are in-development product.
- The ratio of new MOA products is as many as 58%, of which innovative new MOA products (products with significantly different pharmacological effect compared to existing drugs) are 32%.

Therapeutic Area for Projects in FY2020



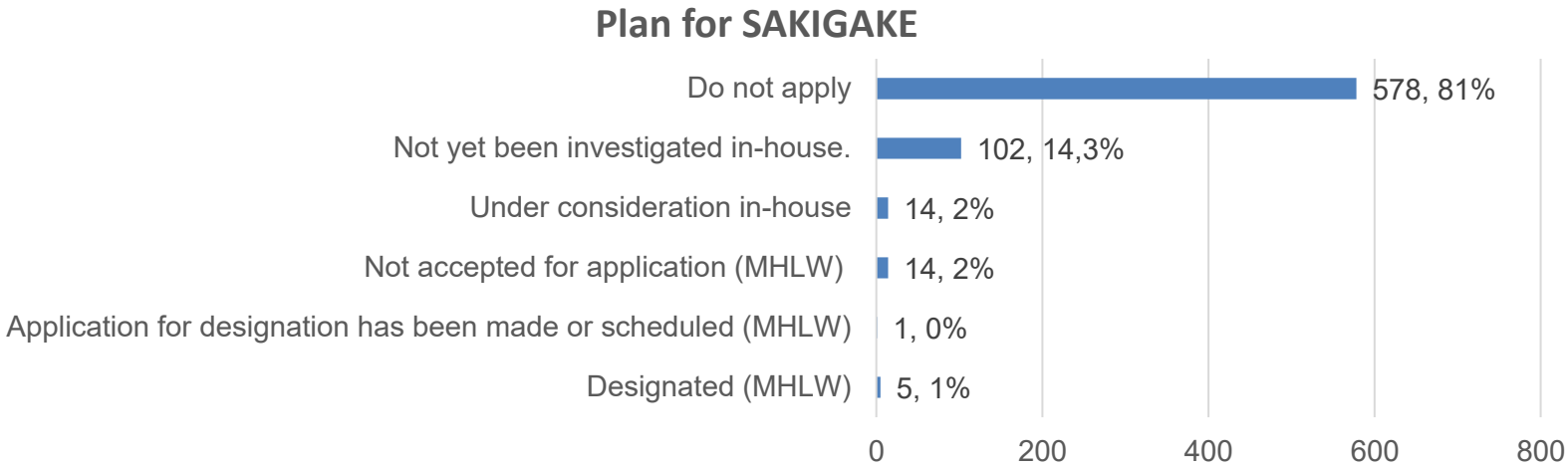
PhRMA+ EFPIA (N=714)

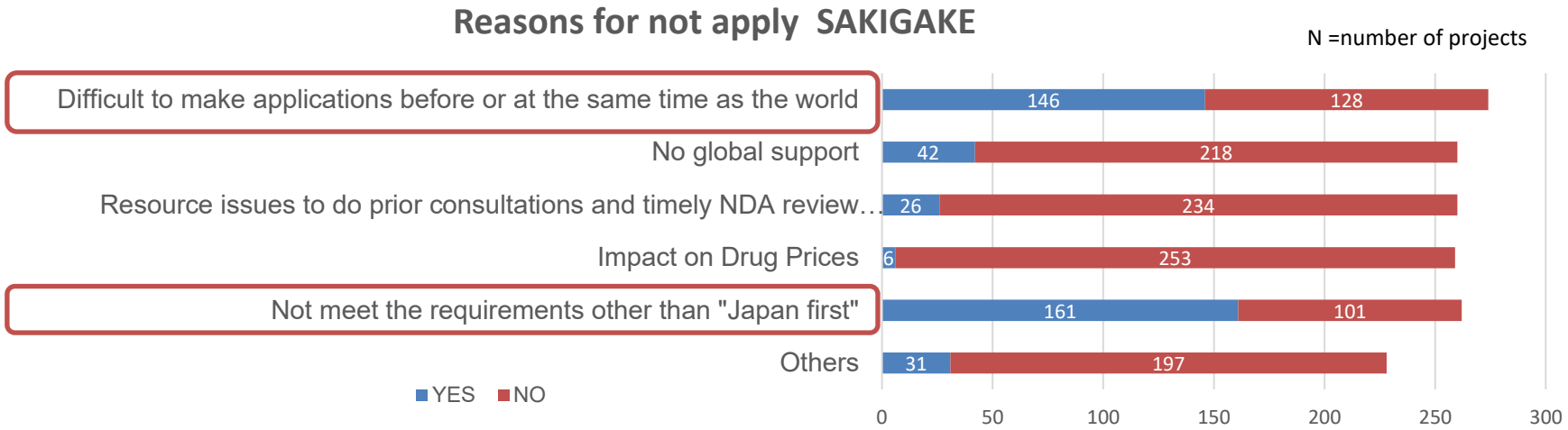
Oncology is a major focused area and the proportion of projects regarding oncology accounts for 52% of the total projects in FY2020 .

＊ : Include Contrast

Plan for SAKIGAKE

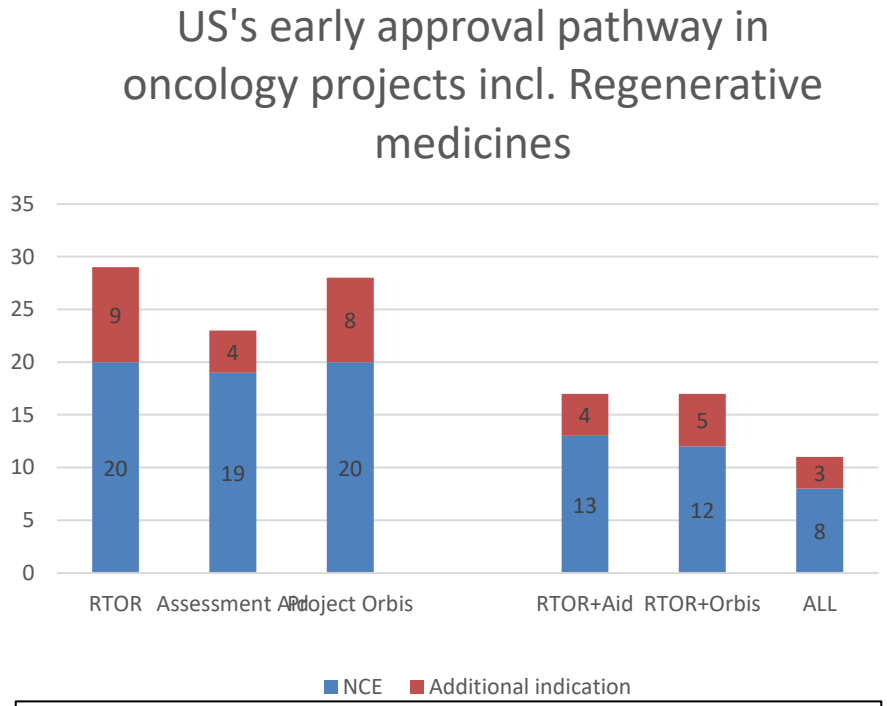
EFPIA + PhRMA 714 projects





Plan for SAKIGAKE was 34 (5%) of the total projects, including those under consideration. The main reasons for not apply SAKIGAE were not meet the requirements and difficult for Japan to make applications before or at the same time with the world.

Use of Early Approval Pathway

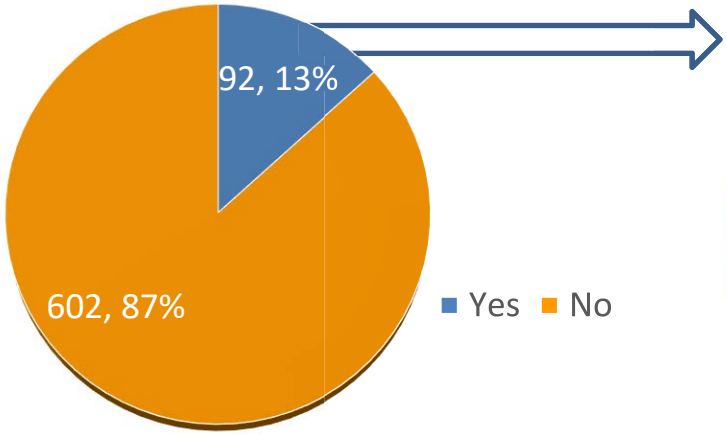


- Projects using Project Orbis (12→28) and Assessment Aid (17→23) were increased and no change in projects using RTOR (30→29), vs 2020.
- There is a trend that the projects to use not only one early approval pathways but several pathways.
- Early approval pathways were utilized by BT and/or PRIME. However, number of sakigake was extremely limited.
- NCE projects are more than half of all projects using these pathways.

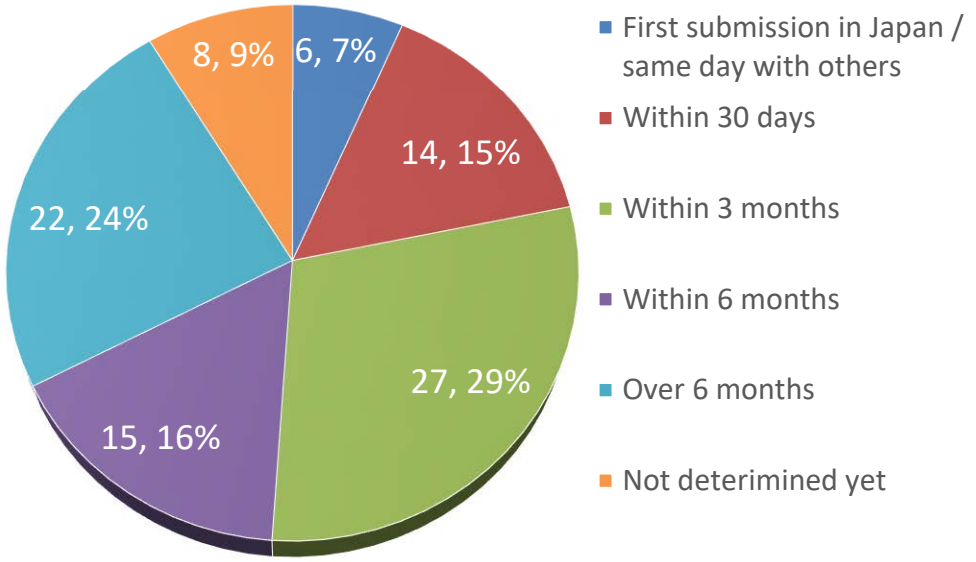
Application Type	Status	RTOR	Assessment Aid	Project Orbis	BT	PRIME	Sakigake
NCE	Being developed	1.YES	1.YES	1.YES	1.YES	1.YES	Not considered yet
NCE	Being developed	1.YES	1.YES	1.YES	1.YES	2.NO	Not considered yet
NCE	Being developed	1.YES	1.YES	1.YES	1.YES	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	1.YES	2.NO	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	1.YES	1.YES	2.NO	Not intended
New Indication	Under review	1.YES	1.YES	1.YES	2.NO	2.NO	Not intended
New Indication	Under review	1.YES	1.YES	1.YES	2.NO	2.NO	Not intended
New Indication	Being developed	1.YES	1.YES	1.YES	2.NO	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	1.YES	2.NO	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	1.YES	2.NO	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	1.YES	1.YES	2.NO	Not considered yet
New Indication	Under review	1.YES	2.NO	1.YES	2.NO	2.NO	Not intended
New Indication	Being developed	1.YES	2.NO	1.YES	2.NO	2.NO	Not intended
NCE	Being developed	1.YES	2.NO	1.YES	1.YES	2.NO	Not intended
NCE	Approved	1.YES	2.NO	1.YES	1.YES	2.NO	Designated
NCE	Being developed	1.YES	2.NO	1.YES	1.YES	1.YES	Intend to apply or being considered
NCE	Being developed	1.YES	2.NO	1.YES	1.YES	2.NO	Not intended
NCE	Being developed	2.NO	1.YES	1.YES	1.YES	1.YES	Not intended
NCE	Being developed	2.NO	1.YES	1.YES	1.YES	1.YES	Not considered yet
NCE	Being developed	2.NO	1.YES	1.YES	1.YES	1.YES	Not intended
NCE	Being developed	2.NO	1.YES	1.YES	1.YES	1.YES	Abandoned as a consequence with interaction with MHLW
NCE	Being developed	2.NO	1.YES	1.YES	1.YES	1.YES	Not intended
NCE	Being developed	2.NO	1.YES	1.YES	1.YES	1.YES	Not intended
New indication	Approved	1.YES	1.YES	2.NO	1.YES	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	2.NO	1.YES	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	2.NO	1.YES	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	2.NO	1.YES	2.NO	Not intended
NCE	Being developed	1.YES	1.YES	2.NO	1.YES	1.YES	Not intended
NCE	Being developed	1.YES	1.YES	2.NO	1.YES	1.YES	Not intended
New indication	Being developed	2.NO	2.NO	1.YES	2.NO	2.NO	Not intended
New indication	Being developed	2.NO	2.NO	1.YES	1.YES	2.NO	Not intended
New indication	Being developed	2.NO	2.NO	1.YES	2.NO	2.NO	Not intended
NCE	Being developed	2.NO	2.NO	1.YES	2.NO	2.NO	Not intended
NCE	Being developed	2.NO	2.NO	1.YES	2.NO	2.NO	Not intended
NCE	Being developed	1.YES	2.NO	2.NO	1.YES	1.YES	Not intended
RegenMed new indication	Being developed	1.YES	2.NO	2.NO	2.NO	2.NO	Abandoned as a consequence with interaction with MHLW
NCE	Being developed	1.YES	2.NO	2.NO	1.YES	1.YES	Not intended
NCE	Being developed	1.YES	2.NO	2.NO	1.YES	2.NO	Not intended
New indication	Being developed	1.YES	2.NO	2.NO	2.NO	2.NO	Not intended
RegenMed new indication	Being developed	1.YES	2.NO	2.NO	1.YES	2.NO	Abandoned as a consequence with interaction with MHLW

Submission lag (1)

Currently filed or scheduled to be filed by the end of March 2022 based on the results of a global clinical trial (N=694)



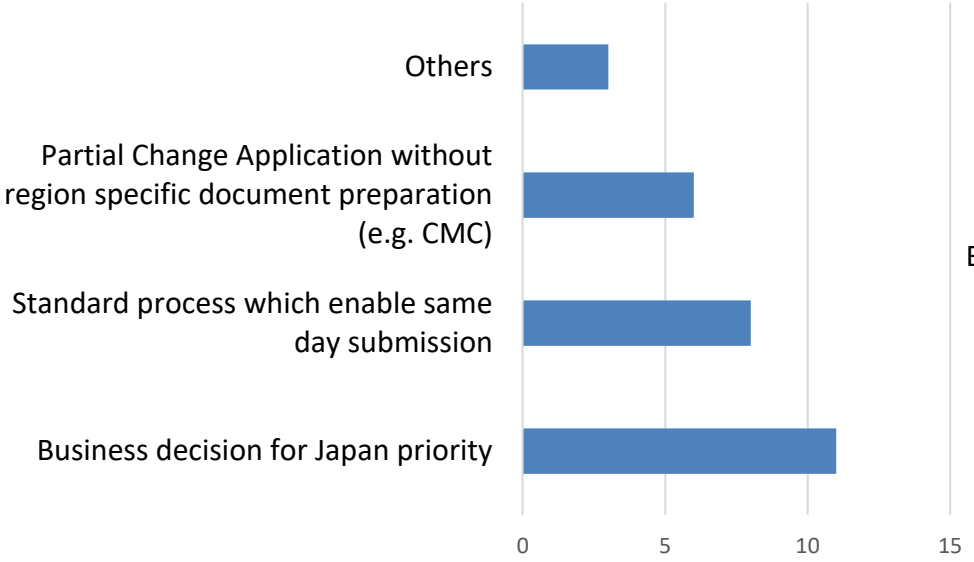
Time lag from the 1st Submission in the World (N=92)



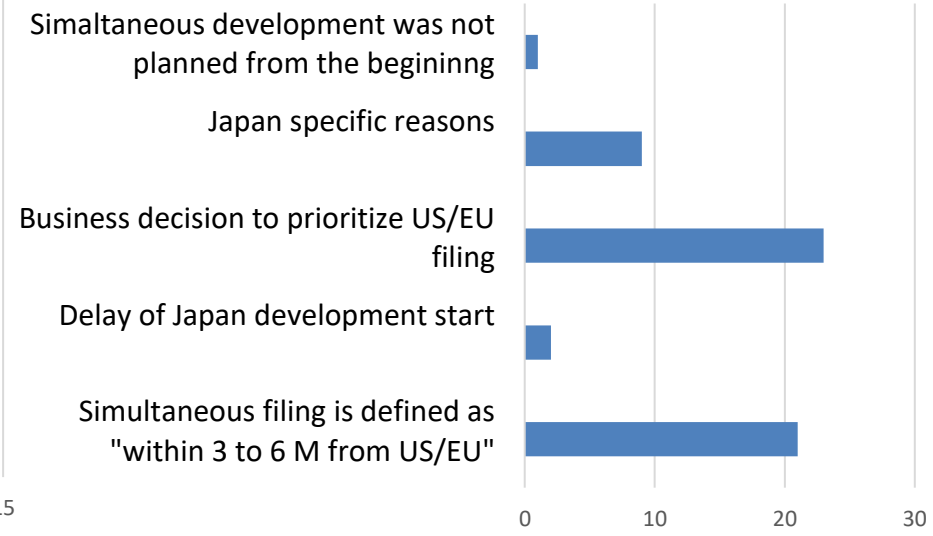
First submission in Japan or same day submission with other regions is less than 10%, but submission in Japan within 3 months is planned in around 50% projects.

Submission lag (2)

Reasons why 1st submission in Japan or same day with other regions can be done（n=19, multiple answers）



Reasons why 1st submission in Japan or same day with other regions cannot be done（n=36, multiple answers）



- Japan first or same day submission with US/EU was mainly based on business decision.
- Among the reasons why 1st submission in Japan / same day filing can be done, the proportion “Standard process” is 8/20. (2/10 in 2020)
- Major Japan specific reasons which caused delay in Japan submission were:
  - Preparation for e-data submission/consultation (2/7)
  - Lead time from data generation to pre-submission meeting (2/7)

Submission lag (3)

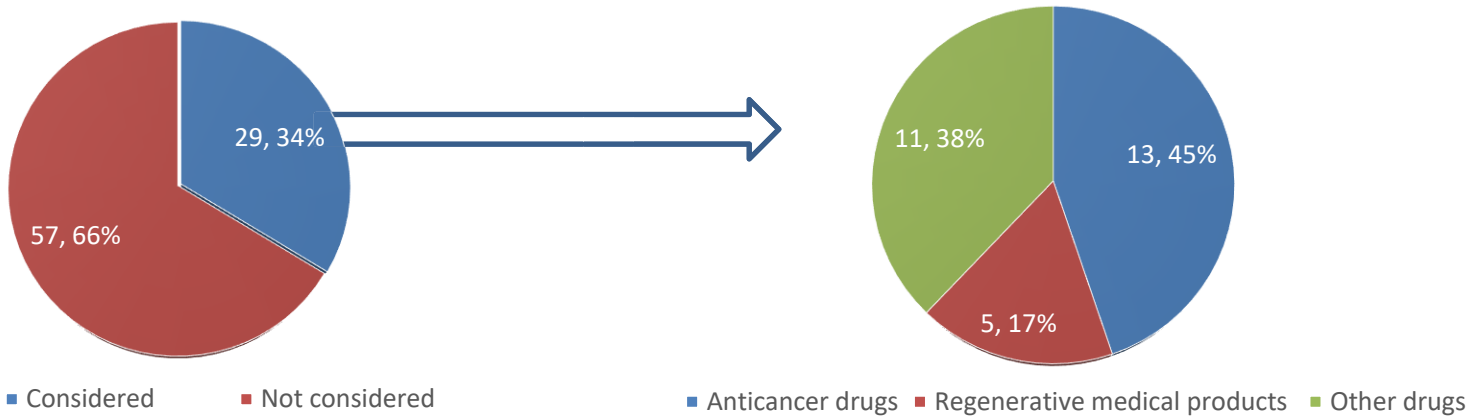
What kind of steps are implemented to minimize application submission lag?
(free description, n=27)

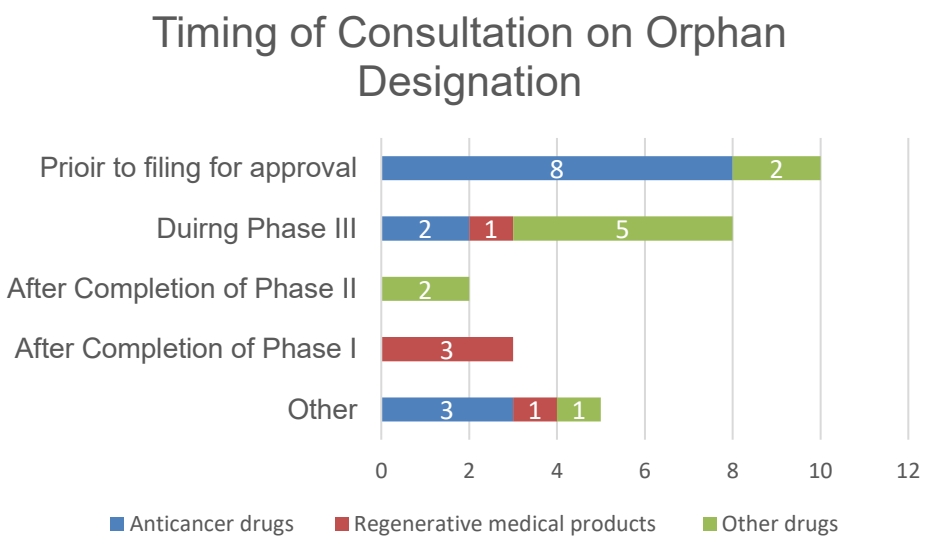
- Upfront CTD preparation / simplified review or agreement process of CTD / parallel preparation of CTD with US/EU (18/27)
- Discussion/collaboration with EU/US from early stage of development (5/27)
- Joining MRCT / minimum data package (5/27)

Are there any system or requirements which need amendment to minimize application submission lag
(free description, n=23)

- Japan specific requirements for electronic data submission (target studies and validation spec should be aligned with US FDA) (7/23)
- English CTD should be accepted (6/23)
- International harmonization of CMC (5/23)

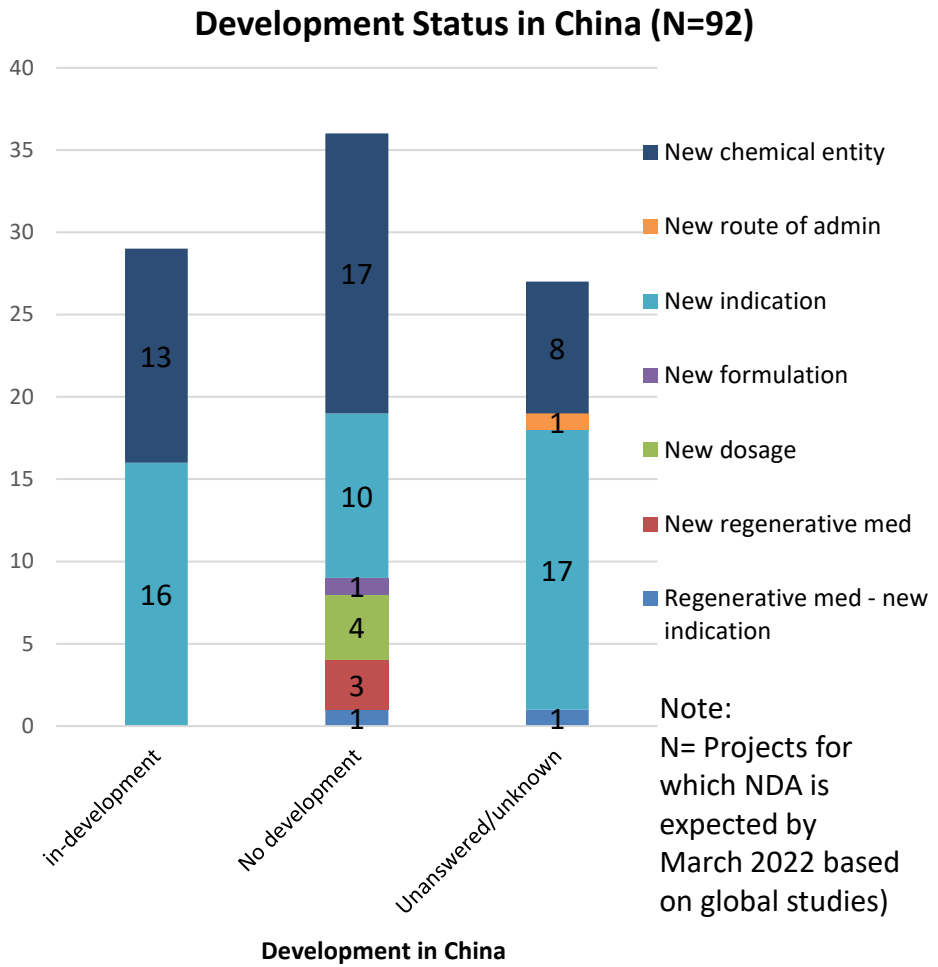
Status of Applications for Orphan Designation



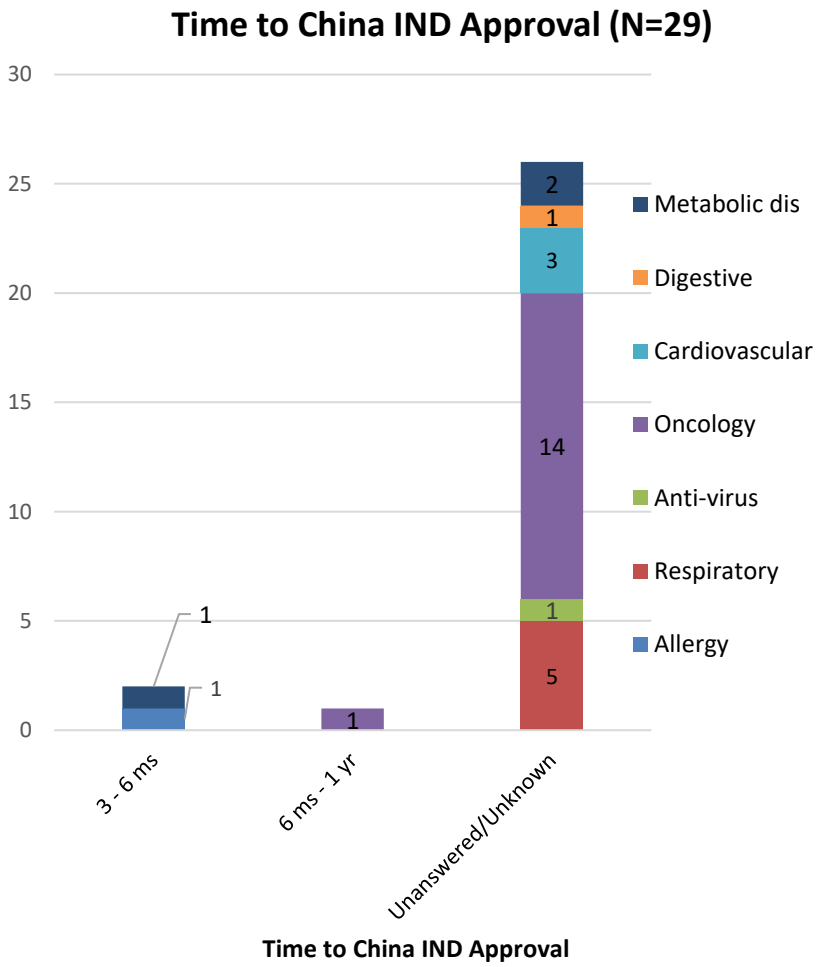


- Approximately 30% of drugs of which applications have been or are scheduled to be filed are under consideration about orphan designation
- Consultation on orphan designation is planned/submitted after completion of Phase I study in 80% (4/5) of regenerative medical products (1 project plans to submit ODD after start of Phase II study in Japanese which follows global Phase I study), while it is planned/submitted prior to filing for approval in 60% (8/13) of anticancer drugs.
- Regarding the timing of ODD, “Others” consists of:
  - after agreement on Phase III study design
  - in parallel with a bridging study.
  - under discussion
- In 2 out of 3 projects in which ODD was rejected, the reason was necessity of comparison with existing treatments

Development Status in China

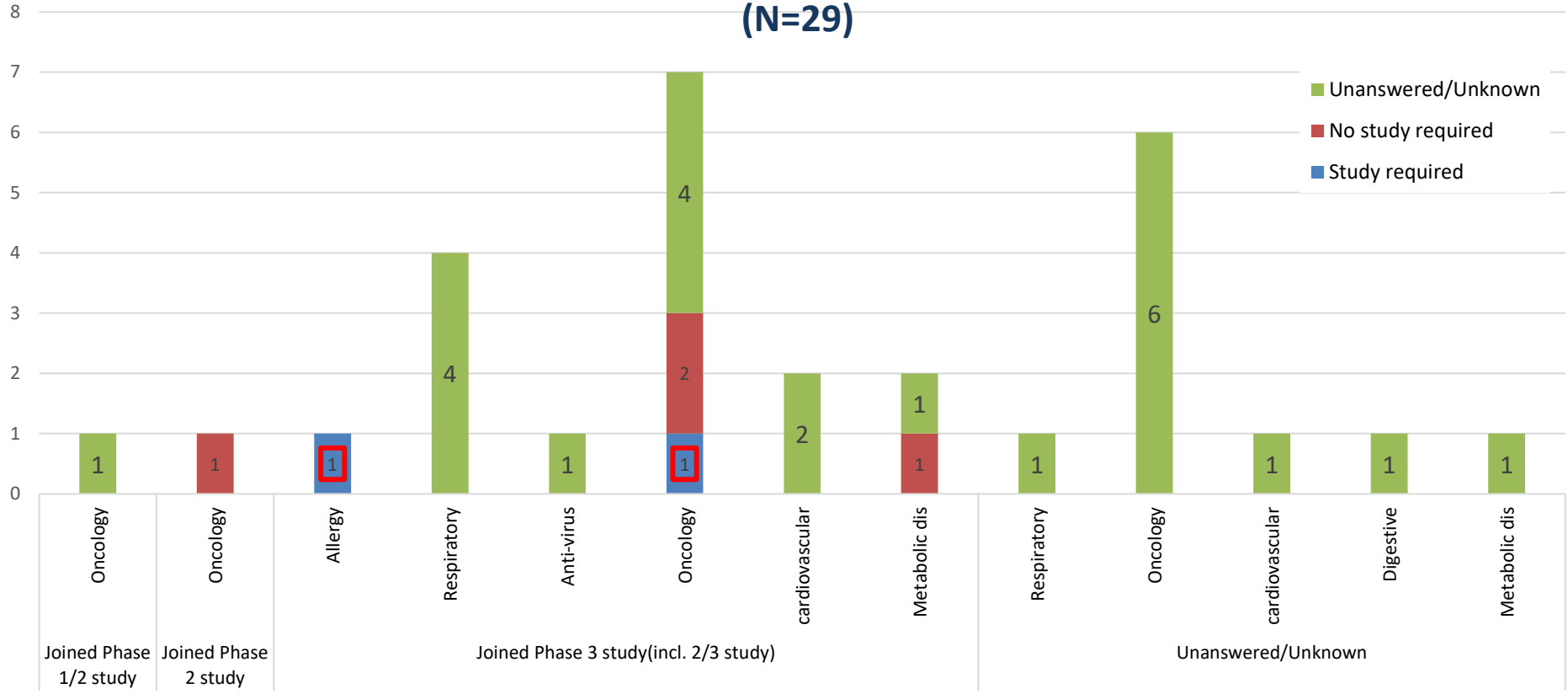


Note:
N= Projects for which NDA is expected by March 2022 based on global studies)



Among 92 projects for which Japan NDA are planned by March 2022 based on global studies, it was found out that for 29 projects, clinical development is ongoing in China. Of those, time to China IND approval were provided for 3 projects; 3-6 ms in two projects, 6 ms – 1 yr in one project.

Study Required to Conduct Prior to Involve China into Global Development (N=29)

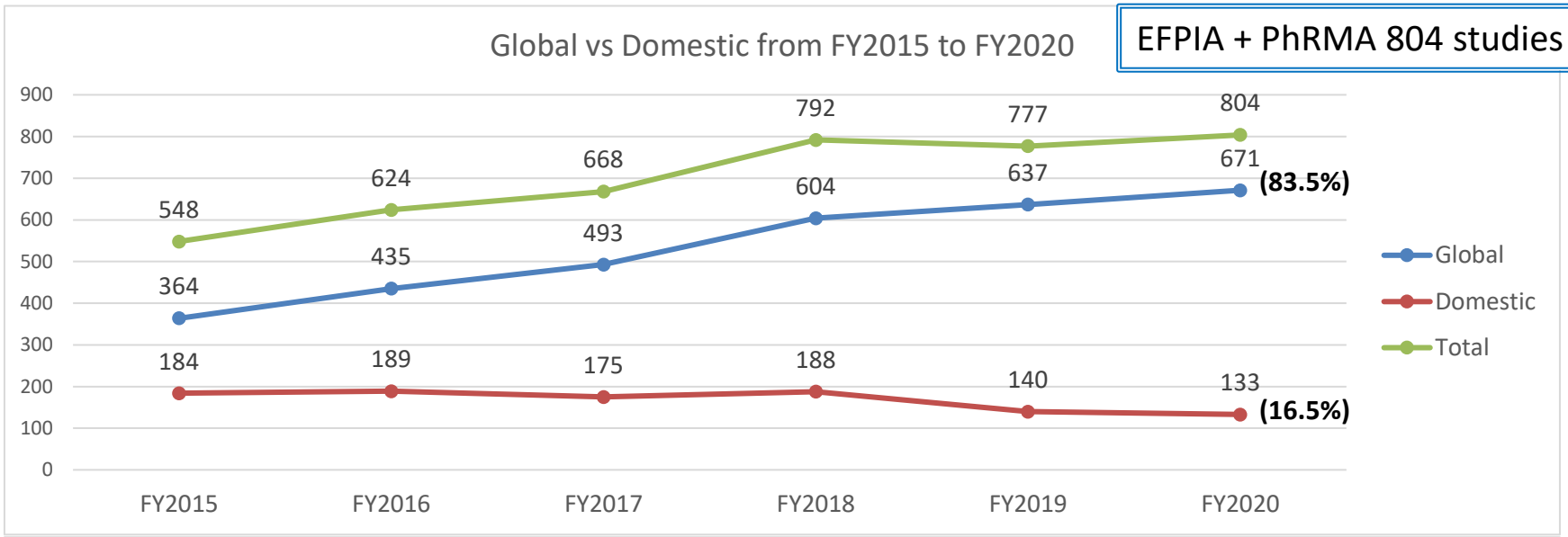


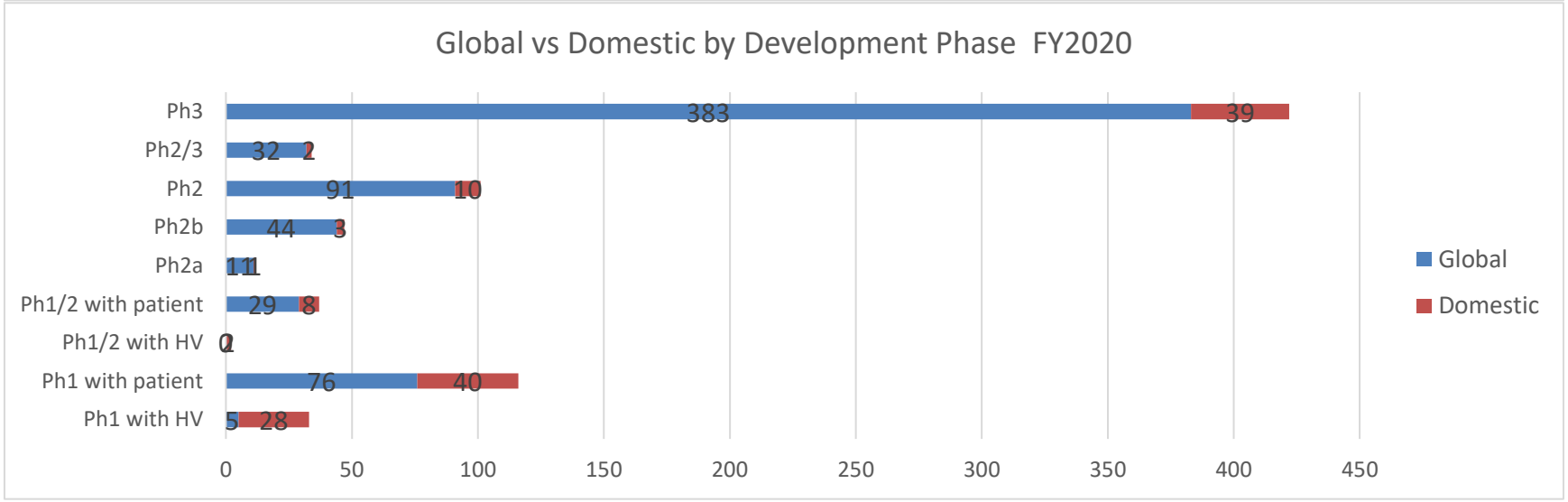
Timing of Involvement to Global Development Program

29 projects are ongoing in China, Timing of China involvement into global development program was from global phase 3 (incl. 2/3 study), except two oncology projects (from Phase1/2=1 , from Phase 2 =1). In two projects. additional study is required prior to China involvement into global development and in both cases, Chinese PK study in China was required.

Number of Clinical Studies (Global/ Domestic)

EFPIA + PhRMA 804 studies



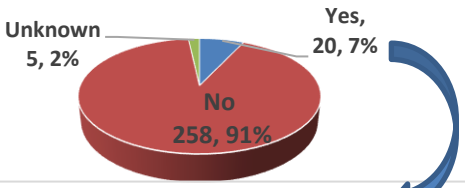


- The total number of studies was 804 and the ratio of Global studies was 83.5% in FY2020.

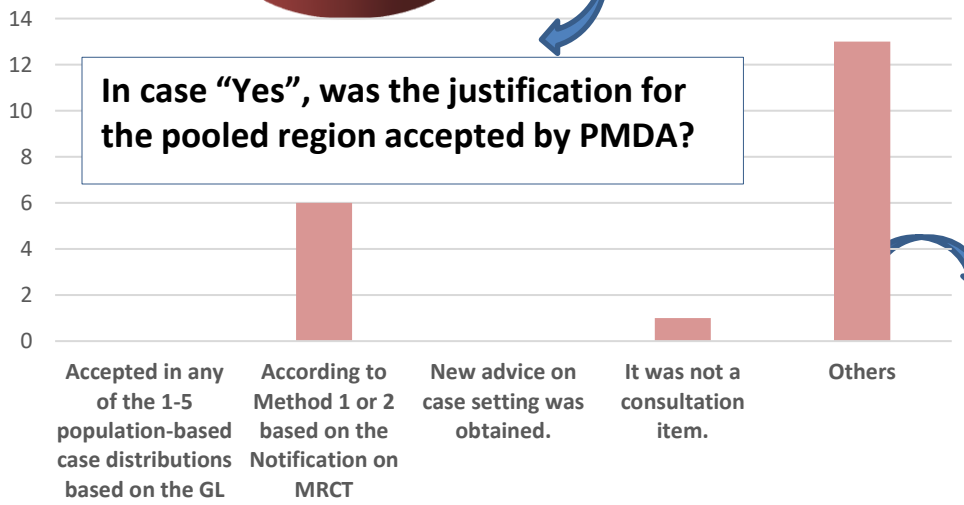
Consultation for Pooled Region acceptancy (1)

EFPIA + PhRMA: 283 studies conducted Consultation

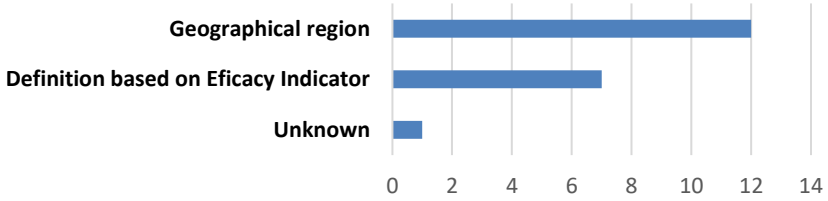
◆ **Was the pooled region question included as a consultation item ?**



In case "Yes", was the justification for the pooled region accepted by PMDA?



◆ **Category of pooled region**



Countries in the "Geographical Region" (Free text)

- China, Taiwan, South Korea (3)
- China, Taiwan, South Korea, Hong Kong (1)
- Korea (1)
- East Asia or Asia (4)
- Unknown (2)

Others (Free text)

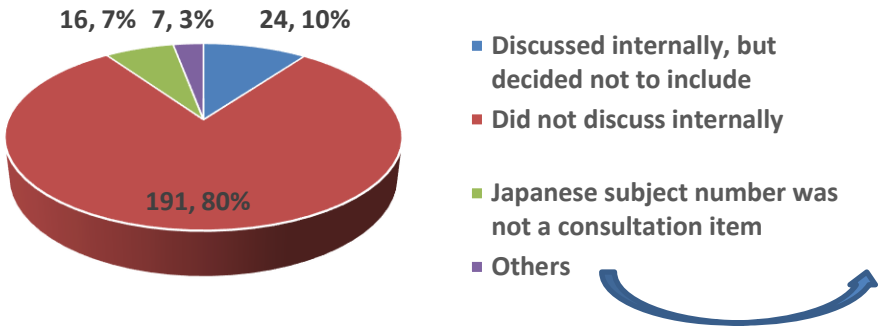
- Japanese subject was determined based on the feasibility (7)
- Requested to follow the GL of the long-term study (2)
- The strategy was not accepted nor to be discussion point (1)
- Denied the consultation due to E17 has not implemented (1)
- Did not accepted (1)

In FY2020, there were 20 cases where acceptability of Pooled Region was asked at consultation, up from 12 cases in FY 2019. The breakdown of Pooled Regions was 12 for "Geographical Region " and 7 for" Definition Based on Efficacy Indicators". "Geographical Region" included China, Taiwan, Korea, etc. . There was no case to be accepted in any of the 1-5 population-based case distributions based on the E17 GL. For 6 cases (Vaccines (1), Oncology (1), regenerative medicine products (2), cardiovascular drugs (2)) , it was suggested based on the method 1 or 2 of the notification on MRCT. For 7 cases (Immunosuppressants (2), digestive agents (2), metabolic diseases (1), urogenital organs and anal drugs (2)), Japanese subject number was based on the feasibility, and for 2 cases (allergy drugs), it was suggested basis on the GL for long-term study. There were no cases with new insight/advice on pooling regions.

Consultation for Pooled Region acceptancy (2)

EFPIA + PhRMA : 238 studies did not ask acceptability of Pooled region

◆ **Was "Pooled region question" discussed internally to include consultation items?**



Others (Free text)
- As planning to collect factors to be pooled in the future
- Not eligible for Pooled region
- It was judged to be too early to discuss the pooled region based on the experience of other drugs
- It was a consultation at the time when the concept of E17 had not bee established

◆ **What conditions will make the company to conduct or consider to ask the acceptability of pooled region in the future? (Free text)**

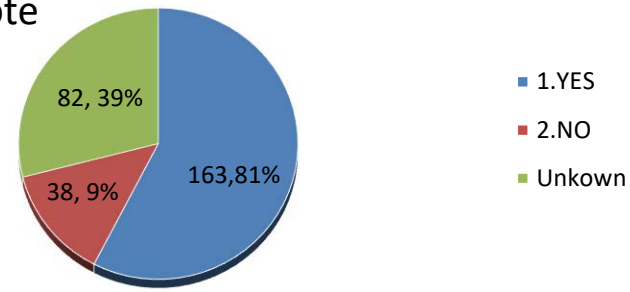
- Actual use have been accumulated, and the merits of use have been clarified.
- Clinical data in other region are accumulated and the justification become ready
- There is a significant advantage for development
- If the PMDA's stance on the number of Japanese subjects has changed
- In case there is no choice other than pooled region and there is evidence to specify a pooled region
- If E17 GL becomes widespread globally

etc.

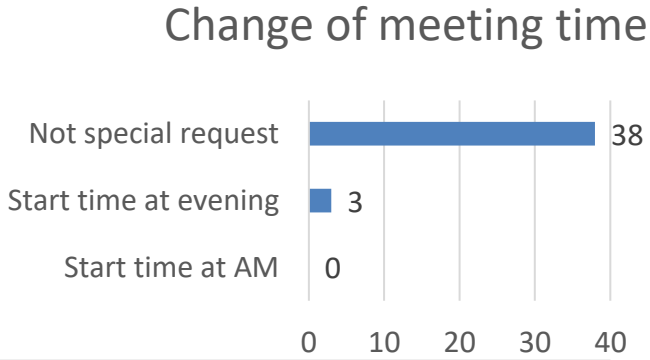
Of the 238 cases for which no consultation was made regarding pooled regions, 24 cases were considered internally but not consulted, and 191 cases were not considered internally. In the free text responses for the conditions to make the company to conduct or consider to ask, the following conditions were mentioned: When actual use have been accumulated and the merits have been clarified; when supporting data have been accumulated; when there are advantages for development; when the PMDA's stance on the number of Japanese subjects has changed; and when E17 GL becomes widespread globally.

Remote consultation

Experience of remote consultation
N=201

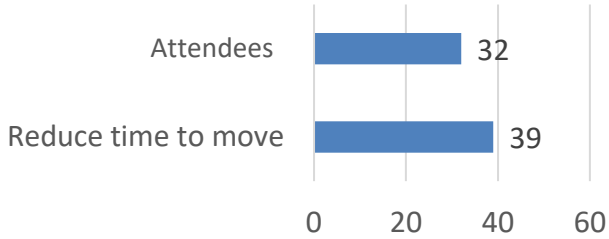


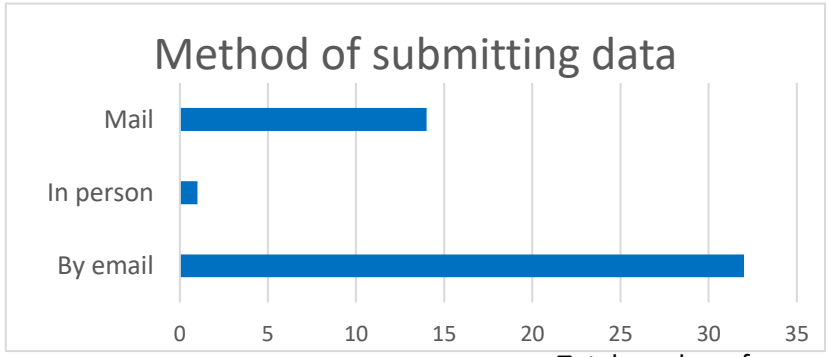
Accepted items of requests



Pros &Cons of remote consultation

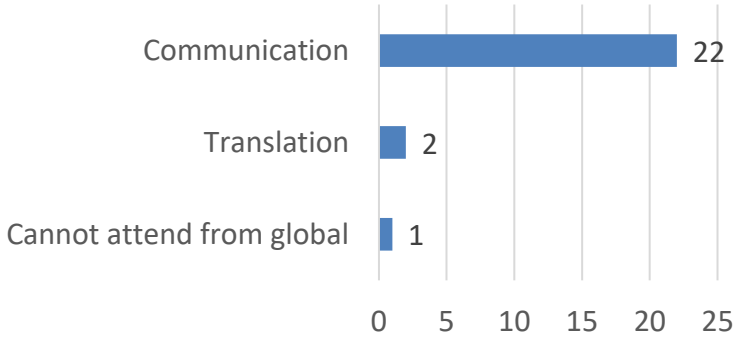
Pros





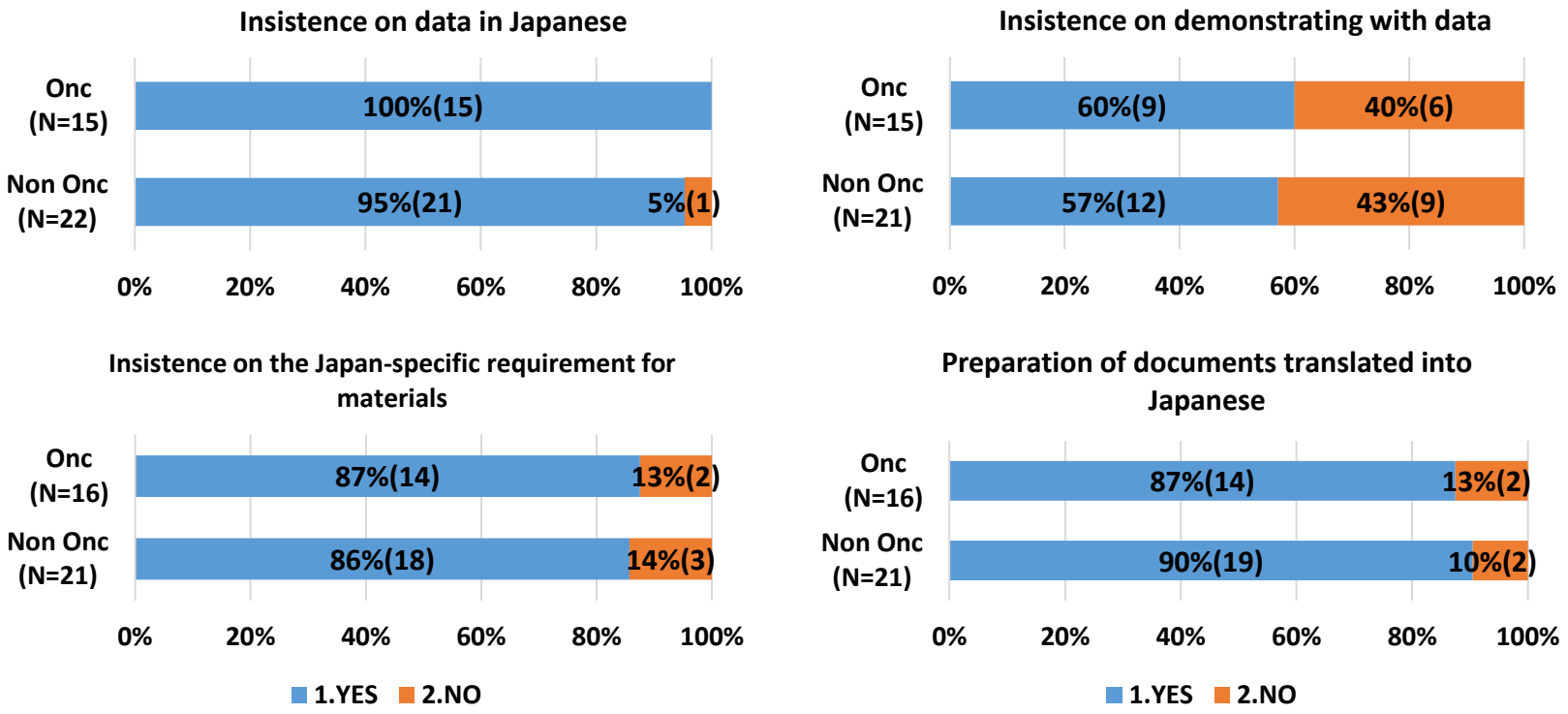
Total number of cases (multiple choices allowed)）

Cons



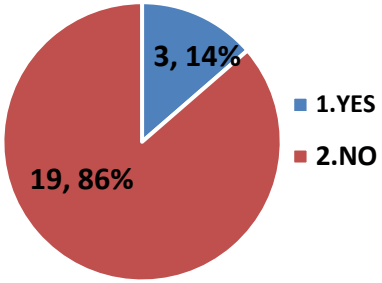
- 81% of the companies had experienced remote
- There are some challenge to adjust the participation time, but there were also merits such as reducing travel time and relaxing the limit on the number of participants.
- In addition, flexible handling of changes in the meeting time and submission materials was also accepted.
- As requests in the future, there were many requests for abolishing the Web conference confirmation sheet, and next were possibilities of using simultaneous translation application, etc. and measures to identify the speaker.

Challenges minimizing development start lag and reducing submission lag

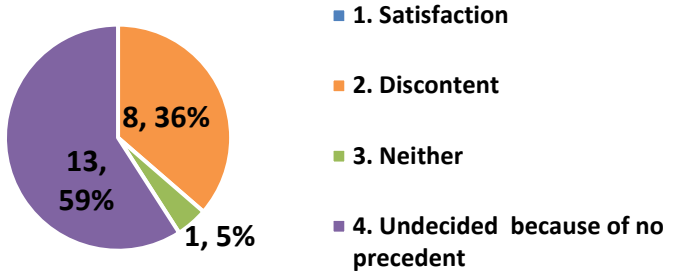


- Regarding issues for minimizing the starting development lag and reducing the submission lag, no difference was observed in trends between Onc and non Onc.
- Insistence on Japanese data is a challenge for all companies to reduce submission lag except for one company (non Onc).
- Preparation of materials unique to Japan and translation has become a challenge for many companies to reduce submission lag
- The collection of Japanese data and preparation of materials unique to Japan have become issues that affect the submission timing Japan.

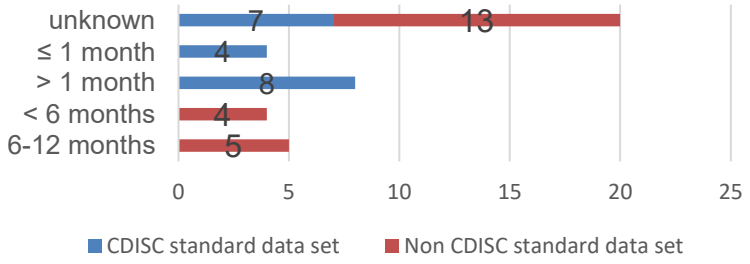
Observe CDISC is used for review



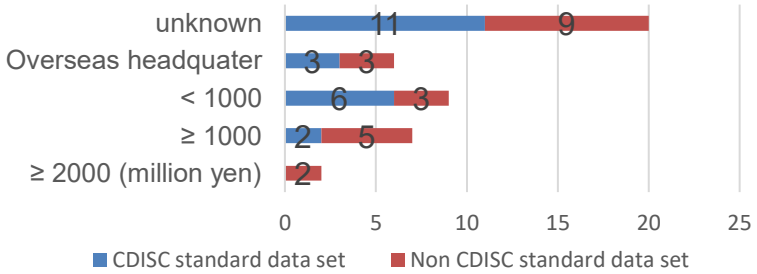
Company Satisfaction of CDISC usage by HA



Time required to create CDISC



Cost required to create CDISC



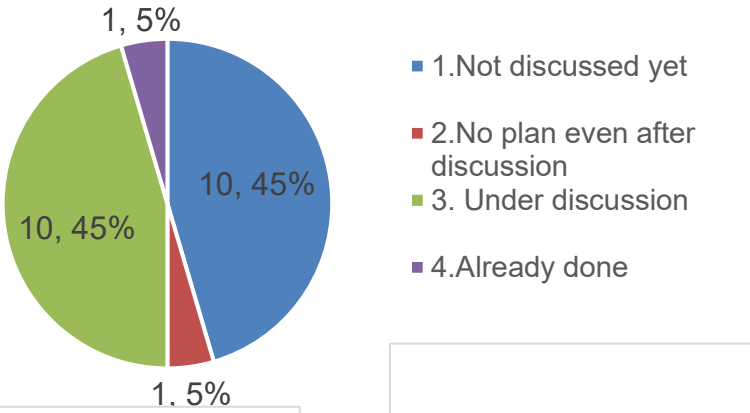
Expectation and request for improvement for use of CDISC (Free text、Response 19 /24 companies)

Expectation for using CDISC	
Promotion of utilization in NDA review（reducing # of query、reducing review period, etc）	8
Disclosure of cases of CDISC utilization such as review cases and findings contributing to future drug development by analyzing data across all drugs	7
Promotion of consideration of new utilization, such as independent evaluation by secondary use of data within PMDA, and examination of secondary use of submitted data by companies	3
Reduction of the list of cases required for the GCP inspection	1
Request for using CDISC	
Flexible handling of timing of submission and submission process	6
Harmonization of CDISC standards with other countries such as FDA	3

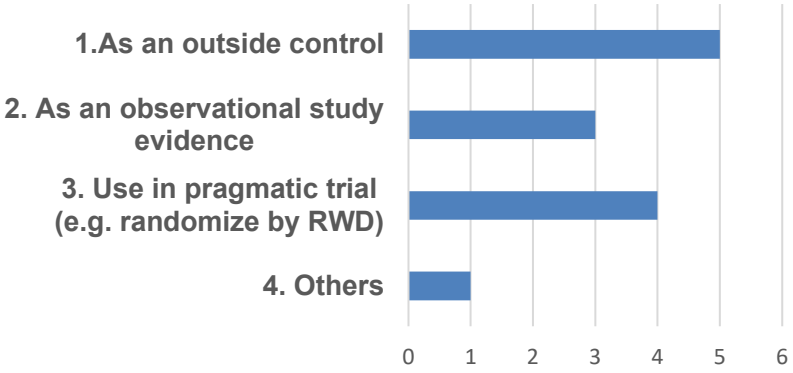
There are high expectations for CDISC, but its utilization has not been evident and recognizable at this point in time

Utilization of Real World Data（1）

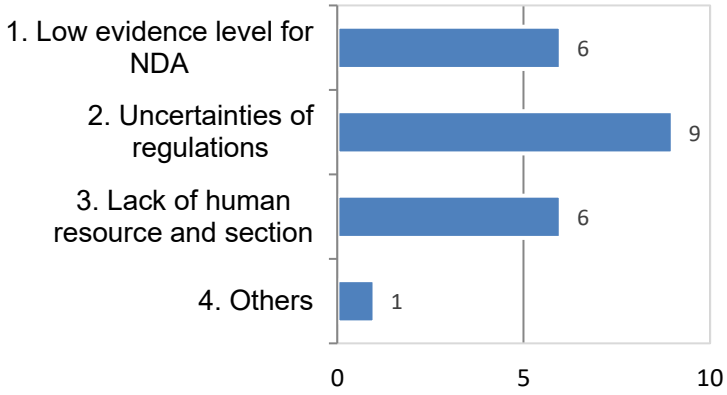
Do you have a plan to utilize RWD as a part of NDA?



Details about “Under discussion”



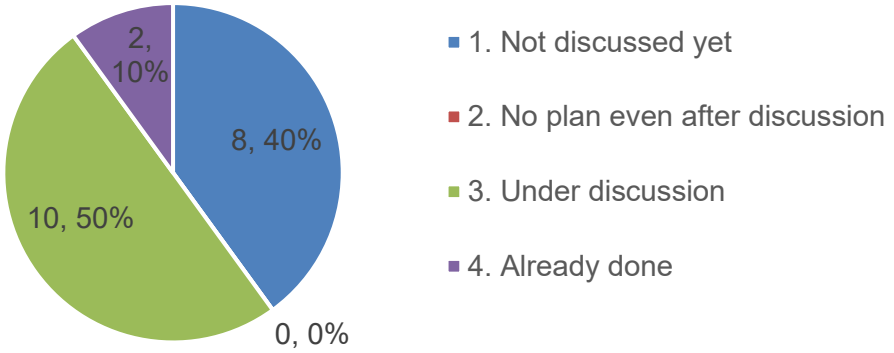
Reasons for “Not discussed yet”



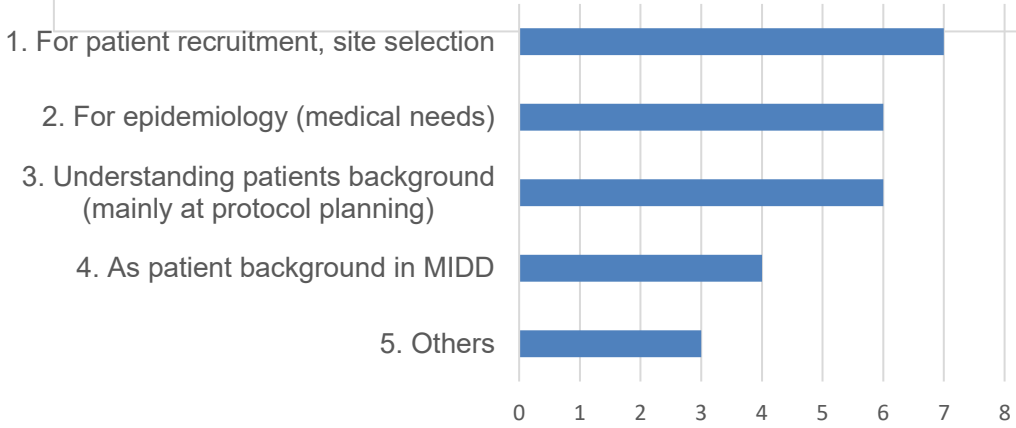
About half of the companies have not discussed RWD utilization. The reasons for this is related to uncertainties of regulations, evidence level and resource required. Remaining half of the companies are considering use as an outside control, use in pragmatic trial, etc.

Utilization of Real World Data（2）

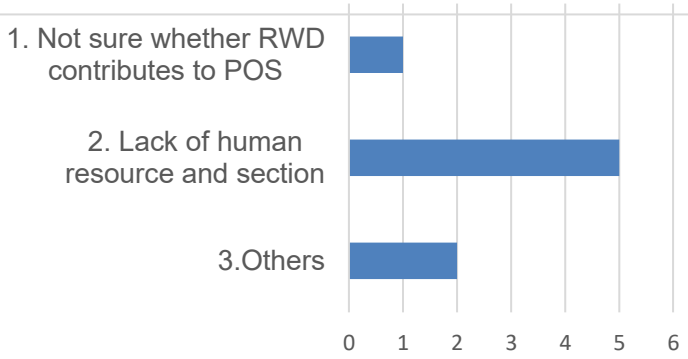
Do you have a plan to utilize RWD in order to accelerate development speed or to increase probability of success of clinical trials by patient recruitment speed-up or understanding of epidemiology and patients background?



Details about “Under discussion”



Reasons for “Not discussed yet”



About half of the companies are planning to utilize RWD for clinical trials. Details about the discussion varies but use for patient recruitment, site selection, epidemiology use, etc. are listed.