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

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PhRMA/EFPIAで実施した2017年度の合同調査結果は以下の通りであった。

審査期間と承認品目

- 2017年度（2017年4月～2018年3月）にPhRMA及びEFPIA加盟会社で承認された新医薬品は54品目で、そのうち通常審査品目は31品目であり、審査期間は80%tileで11.2カ月であった。公知申請を含む優先審査品目は23品目で、70% tileで9カ月であった。
- 審査期間のラグは解消してきているが、同時申請にはまだ改善の余地があり、早期開発戦略の検討、諸制度の活用及び国際調和による日本特有の要件の緩和があげられる。
- 日米欧での迅速制度の利用状況については、FDAで一番多く複数の制度が利用されており、制度の利用状況には品目によって当局別で差があった。

開発品目

- 2017年度に開発中のプロジェクト数は527であり、668試験が実施されていた。そのうち国際共同治験は493試験であり、74%を占めていた。また開発中のプロジェクト数のうち約半数は新有効成分であった。疾患領域として抗悪性腫瘍薬が多く、全体の49%を占めていた。また欧米と同時申請を目指しているものは全体の61%を占めており、増加傾向にあった。
- 先駆け審査指定制度は、外資系企業の指定希望の割合が依然として低く、比較して米国、欧州の早期承認制度（Breakthrough、PRIME）指定希望の割合が高かった。
- 小児開発については、全プロジェクトのうち18%程度で開発が進められており（予定を含む）、半数が成人適応承認後の後追い開発であった。
- 国際共同治験に参画する前の対面助言は約半数の47%で行われた。対面助言によりプロトコール変更の指示は48%に認められた。そのうち日本人症例数の変更指示は35%であり、その54%で指示通りに症例数を変更した。

PMS調査
- PMS調査は承認品目の81%で実施され、その半数は全例調査であった。2018年4月に施行された改正GPSP省令の影響により、データベースを用いた調査も7%実施されている。改正GPSPの浸透、更にはICT基盤法施行に伴い、今後データベース調査の更なる増加が期待される。

Introduction

PhRMA/EFPIA Performance Metrics Survey 2018

- Review Time
  - Drug approvals in FY2017
  - Background, Review time
  - Regulatory Pathways in JP, US and EU
- Global Study and Local Study
  - Number of Global and Local studies
  - Therapeutic area of Global and Local studies
  - Interaction with the Agency
- PMS
  - Baseline data of PMS in approved projects

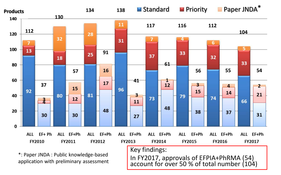
Executive Summary of the Survey

- Scope:
  Review Time
  - Drugs approved in FY2017 (April 2017 to March 2018)
  Global and Local Studies
  - Clinical studies initiated/continued/completed during FY2017
- Companies involved:
  PhRMA (11 companies)
  - Abbvie, Alexion, Amgen Astellas BioPharma, Biogen Japan, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, MSD, Mundipharma, and Pfizer

  EFPIA (17 companies)
  - Actelion, AstraZeneca, Bayer, CHUGAI, CSL Behring, Ferring, GlaxoSmithKline, Janssen, LEO, Lundbeck, Merck Serono, Boehringer Ingelheim, Novartis, Novo Nordisk, Sanofi, Shire, and UCB

Review Period

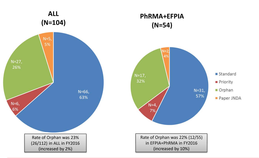
The Number of Drug Approvals in Japan



* Paper JNDA : Public knowledge-based application with preliminary assessment

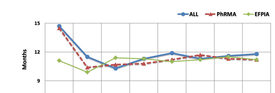
Key findings:
In FY2017, approvals of EFPIA+PhRMA (54) account for over 50 % of total number (104)

Review Category of Approvals in FY2017



Key findings : The rate of Orphan in PhRMA + EFPIA vs ALL accounts for 63% (17/27) in FY2017 and the rate of Orphan is higher than 26% in all and 32% in PhRMA+EFPIA

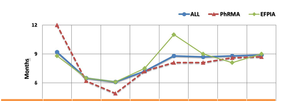
Standard Review



	FY2010	FY2011	FY2012	FY2013	FY2014	FY2015	FY2016	FY2017
	Median	Median	Median	Median	60%tile	70%tile	70%tile	80%tile
ALL	14.7	11.5	10.3	11.3	11.9	11.3	11.6	11.8
PhRMA	14.5	10.4	10.7	10.8	11.2	11.7	11.3	11.2
EFPIA	11.1	9.9	11.4	11.3	11.0	11.2	11.5	11.2

Key findings : 80% of cases for Standard Review in FY2017 were completed less than 12 months, the PMDA's targeted review time.

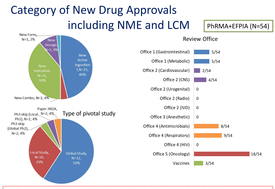
Priority Review Including Paper JNDAs



	FY2010	FY2011	FY2012	FY2013	FY2014	FY2015	FY2016	FY2017
	Median	Median	Median	Median	60%tile	60%tile	70%tile	70%tile
ALL	9.2	6.5	6.1	7.2	8.8	8.7	8.8	8.9
PhRMA	12.0	6.2	4.9	7.2	8.1	8.1	8.6	8.7
EFPIA	8.8	6.3	6.1	7.5	11.0	9.0	8.1	9.0

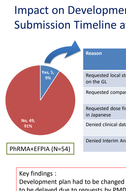
Key findings : 70% of cases for Priority Review in FY2017 were completed less than 9 months, the PMDA's targeted review time, including paper JNDAs.

Category of New Drug Approvals including NME and LCM



Key findings : Majority of new drugs were New active ingredient (46%) and new indication (39%)
Type of pivotal data consisted of global studies (59%), and local studies (29%)
33% of the drug were reviewed by office 5, Oncology. Next portion (31%) was reviewed by the office 4.

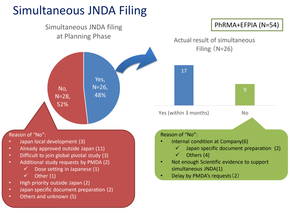
Impact on Development Plan and Submission Timeline after PMDA Consultation



Reason	Review Team	Timing of PMDA consultation	Length of the delay
Requested local study based on the GL	Office 2 Cardiovascular	Pre-JNDA	1Y or more
Requested comparator	Office 4 Anticmicrobials	EoP2	Less than 3M
Requested dose finding study in Japanese	Office 4 Anticmicrobials	Before Pre-P2	1Y or more
Denied clinical data package	Office 5 Oncology	Pre-JNDA	more than 3M and less than 1Y
Denied Interim Analysis	Office 5 Oncology	Pre-JNDA	1Y or more

Key findings :
Development plan had to be changed and Submission schedule had to be delayed due to requests by PMDA at PMDA consultation

Simultaneous JNDA Filing



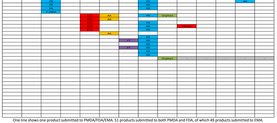
Suggestions for Improvement on the Submission Lag

By Applicant(s) :
- Prioritize product development
- Secure resources including Global
- Evaluate unmet medical needs in Japan
- Construct processes that enables determination of development at an early stage in Japan
- Make Japan development strategies at an early stage and align with global
- Get a consensus for CTD preparation scheme at an early stage
- Consider the timing of licensing-in of product from other company

To MHLW :
- Promote utilization of the current regulatory system and Strengthen PMDA organization
- Accept CTD in English and relax the Japan specific requirement for CTD preparation
- Review and revise Japan specific GL, e.g., long term clinical study for chronic disease
- Promote globalization of CMC documents and Japan pharmacopoeia
- Be flexible to accept global clinical data and joining MHCT

Key Findings:
- **NOT simultaneous submission from the beginning:**
  The delay to start development in Japan, not participation in MRCT, required additional CT and the necessity of preparing documents for JNDA requested by PMDA
- **Not achieved simultaneous submission:**
  The necessity of preparing documents for JNDA, the additional request from PMDA and one case due to clinical trial results

Utilization of Expedited Program



One line shows one product submitted to PMDA/FDA/EMA 51 products submitted to both PMDA and FDA, of which 49 products submitted to EMA

Key findings on Expedited Programs

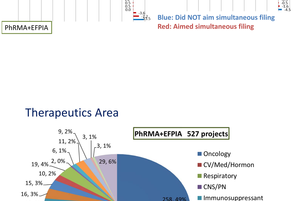
- Expedited program is widely used in the US. But the variety of program is comparable between 3 Health Authorities.
- FDA was the agency with the shortest approval time in 2017 (243days), likely due to the wide use of these pathways*.
- 16/51 projects(31%) were reviewed as standard in JP/US/EU

Facilitated Regulatory Pathways	PMDA (n=51)	FDA (n=51)	EMA (n=49)
Sakigake, Breakthrough Therapy PRIME	0	13 (25%)	3 (6%)
Conditional Early Approval Accelerated Approval Conditional Marketed Authorization	0	7 (14%)	2 (4%)
Fast track	0	8 (16%)	0
Priority Review Accelerated Assessment	22 (43%)	24 (47%)	9 (18%)
Orphan	17 (33%)	17 (33%)	14 (29%)
Projects utilizing at least 1 Pathway(s)	22 (43%)	34 (67%)	17 (34%)

51 products submitted to both PMDA and FDA, of which 49 products submitted to EMA.

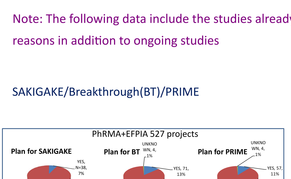
* Centre for Innovation in Regulatory Science(CIRS), May 2018, R&D Briefing

Submission Lag (months) including NME and LCM



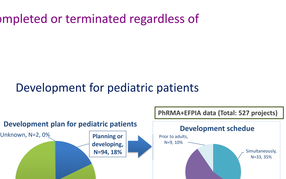
Clinical Studies and Development Plan

Total Projects in FY2017



Key findings:
- Total project number is 247 for PhRMA, and 527 for PhRMA+EFPIA are on-going. The ratio of NCE is 51%.

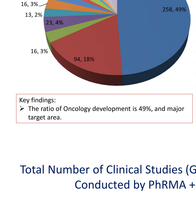
Development Status in FY2017



Key findings:
- The target products of simultaneous submission are planed 61%.

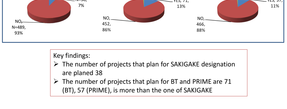
Note: The following data include the studies already completed or terminated regardless of reasons in addition to ongoing studies

Therapeutics Area



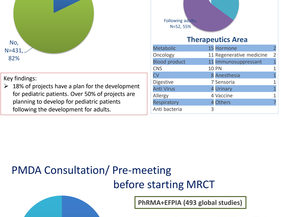
Key findings:
- The ratio of Oncology development is 49%, and major target area.

SAKIGAKE/Breakthrough(BT)/PRIME



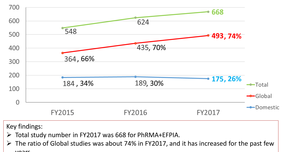
Key findings:
- The number of projects that plan for SAKIGAKE designation are planed 38
- The number of projects that plan for BT and PRIME are 71 (BT), 57 (PRIME), is more than the one of SAKIGAKE

Development for pediatric patients



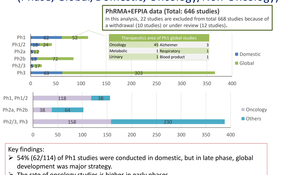
Key findings:
- 18% of projects have a plan for the development for pediatric patients. Over 50% of projects are planning to develop for pediatric patients following the development for adults.

Total Number of Clinical Studies (Global/ Domestic) Conducted by PhRMA + EFPIA



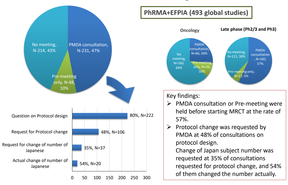
Key findings:
- Total study number in FY2017 was 668 for PhRMA+EFPIA.
- The ratio of Global studies was about 74% in FY2017, and it has increased for the past few years.

Clinical Studies in FY2017 (Phase, Global/Domestic, Oncology/Non-Oncology)



Key findings:
- 54% (62/114) of Ph1 studies were conducted in domestic, but in late phase, global development was major strategy.
- The rate of oncology studies is higher in early phases.

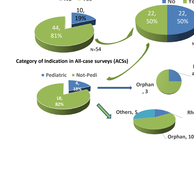
PMDA Consultation/ Pre-meeting before starting MRCT



Key findings:
- PMDA consultation or Pre-meeting were held before starting MRCT at the rate of 57%.
- Protocol change was requested by PMDA at 48% of consultations on protocol design.
  Change of Japan subject number was requested at 35% of consultations requested for protocol change, and 54% of them changed the number actually.

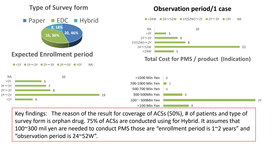
PMS Survey from approved projects in 2017

All-case surveys are 50% because ***many orphan drugs*** got approval in 2017.



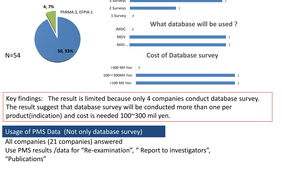
Key findings:
- ACSs are 50%
- Most of orphan drugs and Rheumatism's drug are conducted ACSs

Detail of PMS Survey N=44



Key findings: The reason of the result for coverage of ACSs (50%), # of patients and type of survey form is orphan drug. 75% of ACSs are conducted using for Hybrid. It assumes that 100~300 mil yen are needed to conduct PMS those are "enrollment period is 1~2 years" and "observation period is 24~52W".

Database survey in PMS



Key findings: The result is limited because only 4 companies conduct database survey. The result suggest that database survey will be conducted more than one per product(indication) and cost is needed 100~300 mil yen.

Usage of PMS Data: (Not only database survey)
All companies (21 companies) answered
Use PMS results /data for "Re-examination", " Report to investigators", "Publications"