資料２－７
中釜　斉様
Document2-7

Gate Opening Summit for Innovative Drug Discovery (2024. 07. 30)

Challenges and Future Prospects for Cancer Drug Development in Japan
～ Initiatives to Overcome Drug Lag and Drug Loss ～

日本のがん治療薬創開発における課題と展望
～ドラッグラグ・ドラッグロスの克服に向けた取り組み～

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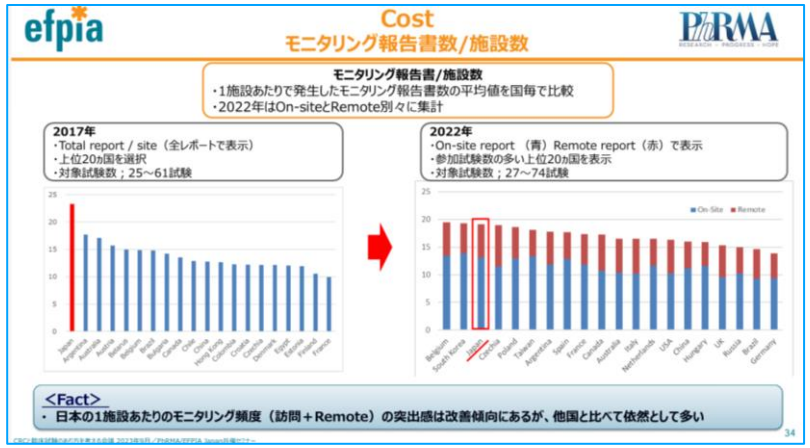
Efficiency of clinical trials in Japan still have challenges

What is clinical trial efficiency?

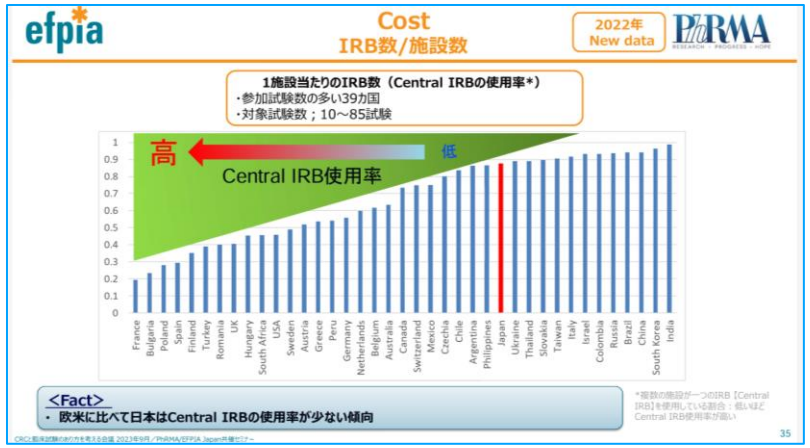
Japan performance compared to other countries

- ○ *Quality*: Compliance of Data entering, Query, deviation, etc. → ✓ Good
- ○ *Speed*: No. of patient enrolled in clinical trials per site/study, etc. → Moderate
- ○ *Cost*: No. of reports/site, Usage ratio of CRB, No. of sites/CRA, etc. → × Bad

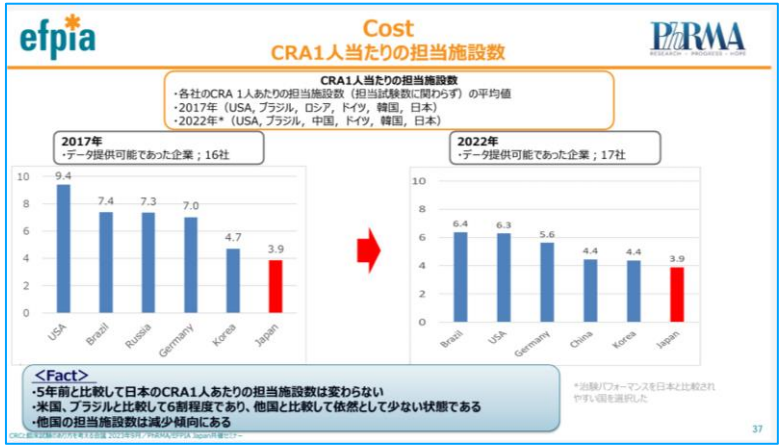
No. of reports/site



Usage ratio of CRB



No. of sites/CRA



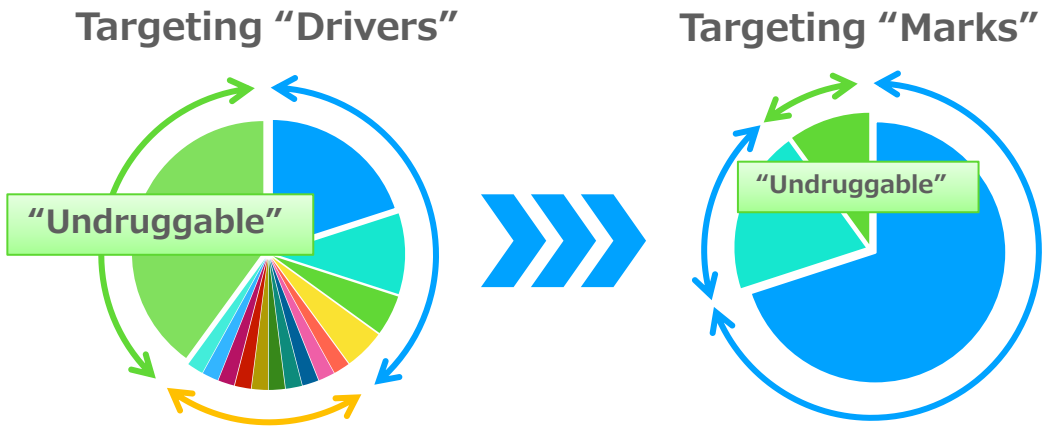
EFPIA / PhRMA's Clinical Trial Performance Survey

第23回 CRCと臨床試験のあり方を考える会議2023 in 岡山PhRMA/EFPIA Japan共催セミナー 日本がグローバル試験から排除される日 ～5年間で我々は変われたのか？最悪のシナリオを回避するための意識・行動改革～ より引用

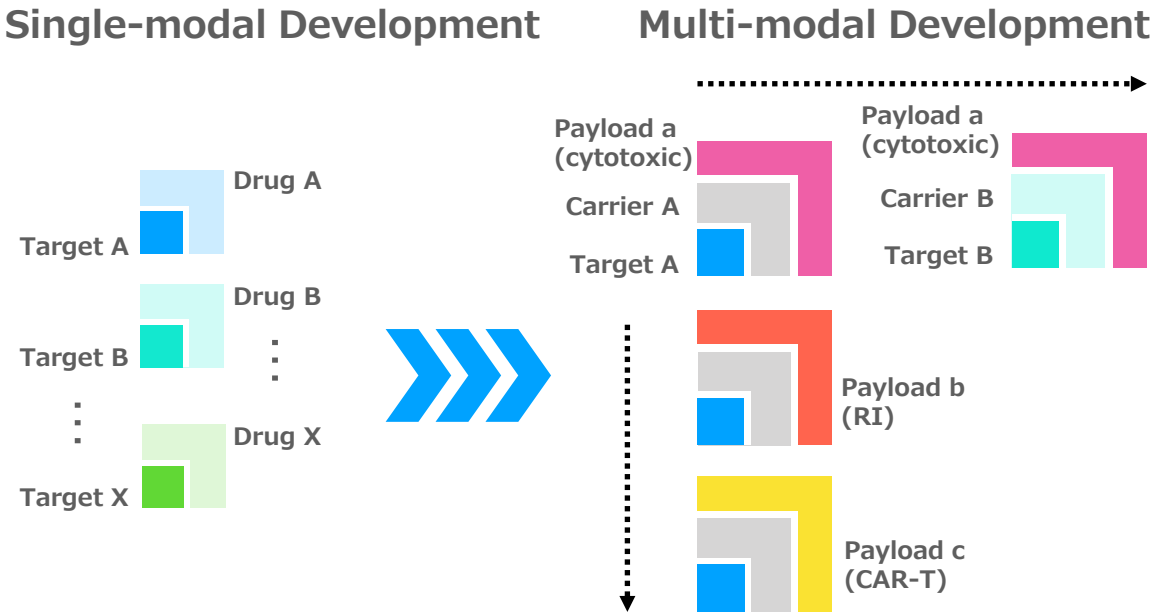
- ▸Japanese clinical trial site are still less efficient by global standards in terms of cost.
- ▸High costs are one of the barriers for EBPs in conducting clinical trials in Japan.
- ▸Some measures are required to improve these issues, especially in non-oncology area.

(*i.e.* Human resource development, Central IRB, DX in clinical trials, Regulatory reforms of IRBs, etc.)

A Drug Development Ecosystem Based on Basic Science



Mark: specifically expressed in the cancer cells, but not essential for the driver function



✓Expansion of druggable target molecules

- Targeting molecules specifically expressed and/or mutated in cancer cells as guiding markers

✓Single-modal to multi-modal drug development

- Developing specific inhibitors for each target is costly
- Acquired resistance is inevitable
- Functional unknown molecules are undruggable

- Combination of specific carriers and multiple payloads
- Selection of combinations for each cancer cells and tumor microenvironment

Concerns…

- Requiring a strategic integration of both excellent biology and engineering

i.e. **CONVERGENCE RESEARCH**

Paradigm Shift in Cancer Therapy Development

National Cancer Center Japan

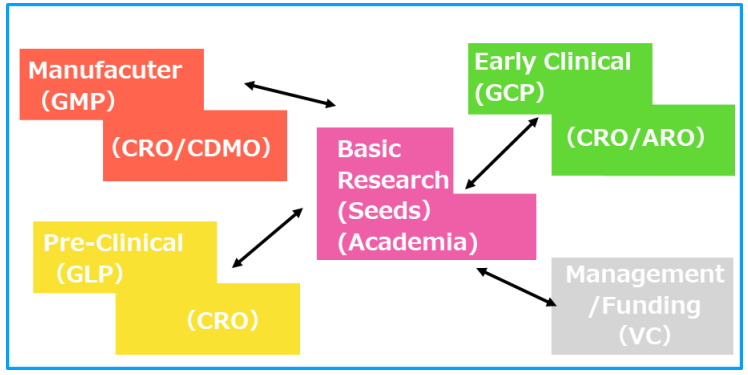
The Cancer Therapy Development system should be changed from "**Orchestra**"(Fixed Team and well-planned Procedure) to **"Jazz"** (Diverse and Agile Procedure).

"Orchestra" (ex. Pharma) model

- All functions required for development are supplied in one company.
- Effective for **"Single modality to multi-targets"** sequential development

As drug development shifts to **"Multiple modalities to a single target," (ex. P53, RAS, etc.)** the "Orchestra" model does not function well.

"Jazz" (ex. Startups Eco System) model

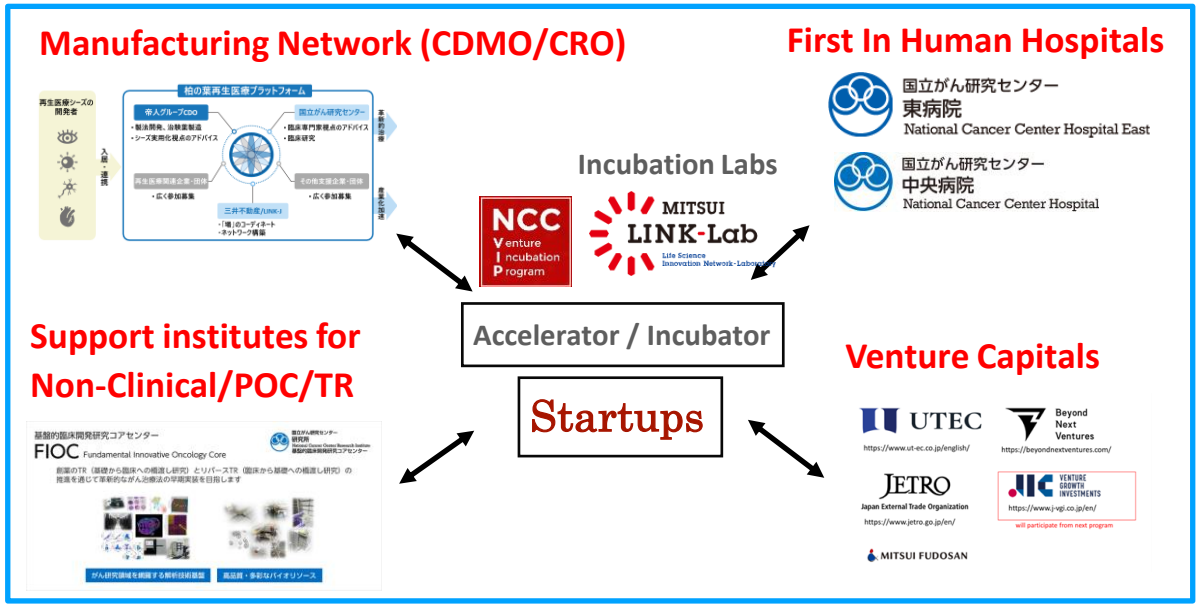


This model needs a **coordinator** to work efficiently.
Thus, ecosystems have centered around **Accelerators/Incubators.**

- Flexible and speedy development can be conducted simultaneously for various types of seeds (startups)

Horizontal and synchronized development system targeting multiple targets in diverse disease fields

Development of Ecosystem Model around Accelerators/Incubators

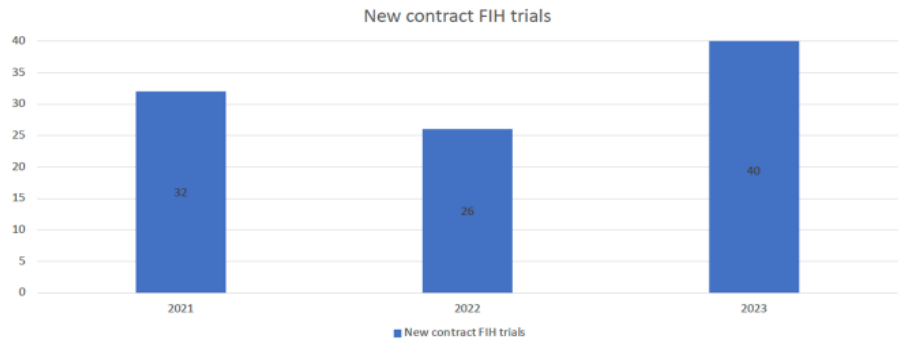


- One-stop services from Basic Science → Manufacturing → Clinical Development
- Accelerator/Incubator-centered ecosystem for Japanese-style company creation and drug development
- A global ecosystem in collaboration with overseas accelerators

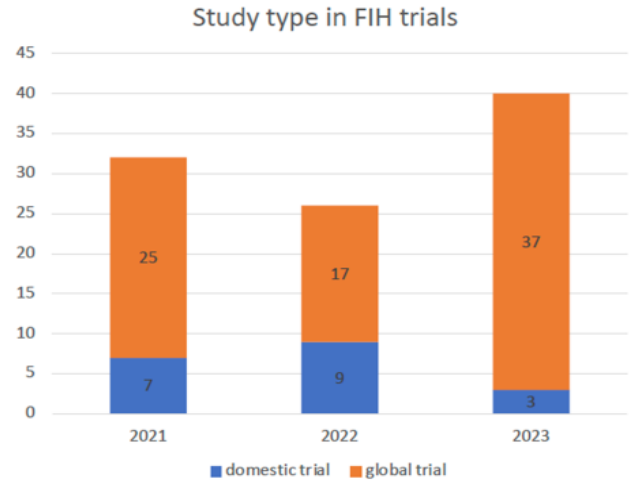
References

National Cancer Center (NCC) capability for FIH

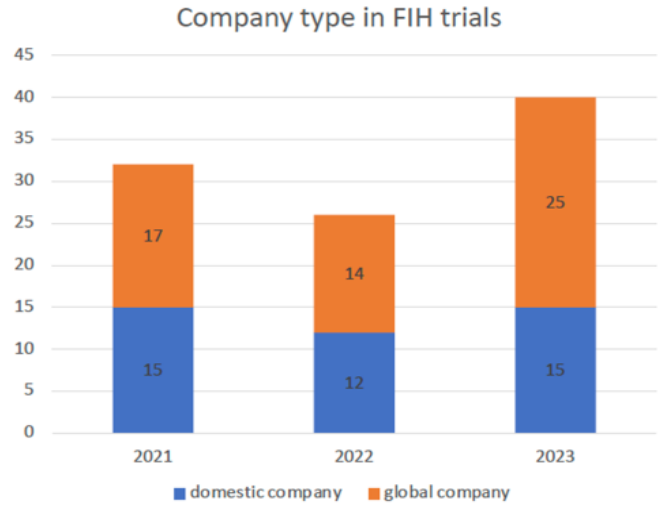
FIH trials in NCC 2021-2023 FY (new contract)



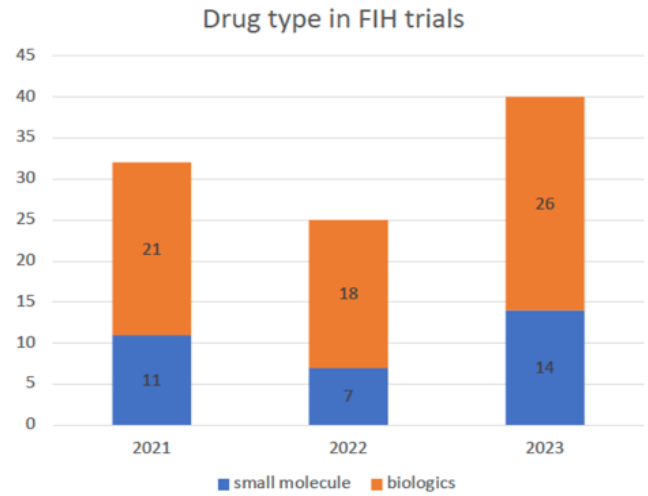
The number of FIH trials contracted is increasing, although it varies from year to year. 40 trials were conducted by the NCC in FY2023.



FIH trials have mostly participated in simultaneous global development (Global-FIH) in recent years, and FIH is rarely initiated in Japan alone.



The number of clients is about the same for foreign and domestic companies, or slightly more foreign-owned. (Considering the number of products developed, the number of foreign-owned FIHs is still low in Japan).



The novel drugs in which Japan participates are varied, but the development of small molecule is still very active. On the other hand, the development of biologics, which are highly novel, is still less active in Japan.

FIH trials are increasing, but 'Drug Lag' and 'Drug Loss' Issues are also increasing. Why?

Acceleration of drug lag and loss is due to delays in responding to development of new modalities, including non-cancer drugs ①

- As of March 2023, 86 drugs that have been approved in Europe and the U.S. have not been developed yet in Japan (60.1% (86/143) of unapproved drugs)
- Analysis of 86 products whose development in Japan has yet to initiate: high proportion of venture(emerging biopharma)-originated, orphan, and paediatrics.

Drug lag/loss status in Japan, U.S., Europe (number of items)

	approved	unapproved		
	total	total	Under-development	Not yet started
US	136	7	3	4
Europe	86	57	26	31
Japan	0	143	57	86

Break-down

Breakdown of drugs not yet developed in Japan

venture-developed	orphan drug	pediatric drug
56%	47%	37%
48*	40*	32*

*number of items

Out of the 86 drugs, 14 drugs (16%) were neither developed by venture companies nor designated as orphan or pediatric drugs.

※Source: Published information from PMDA, FDA, and EMA, prepared by the Pharmaceutical and Industrial Policy Research Institute based on tomorrow's new drugs (Technomic Co., Ltd.), and tabulated by the Ministry of Health, Labour and Welfare.
※1:Of the NMEs approved in Europe and the United States in 2016-2020, those not approved in Japan as of the end of 2022 are counted as unapproved.
※2:As of March 2023, items for which no development information was available are counted as undeveloped products in Japan.
※3:Figures are totaled for development companies with sales of less than US$500 million within 30 years of approval in Europeand the U.S.

※4:Compiled as orphans for items designated as orphan drugs by the time of approval in Europe and the U.S.
※5:2022 Calculated based on pediatric products approved for pediatric use in Europe and the U.S.

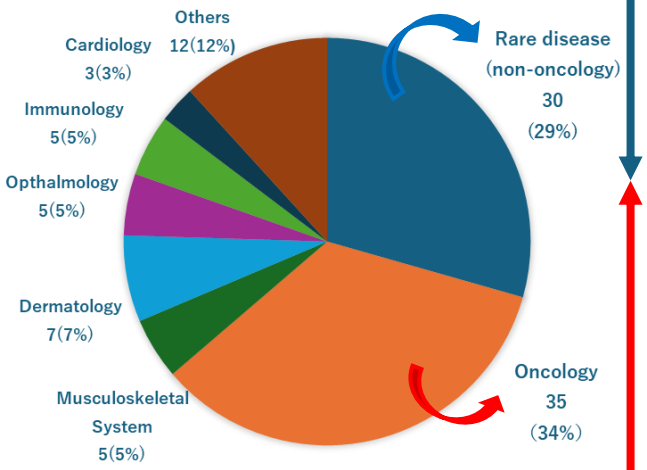
https://www.cas.go.jp/jp/seisaku/souyakuryoku/dai2/gijisidai.html

Adapted from "Reference Material 4 of the 1st Meeting of the Committee on Regulatory Measures for Strengthening Drug Discovery Capabilities and Securing Stable Supply" implemented by the Pharmaceutical and Environmental Health Bureau, MHLW

第2回 創薬力の向上により国民に最新の医薬品を迅速に届けるための構想会議資料３改変（藤原氏資料）

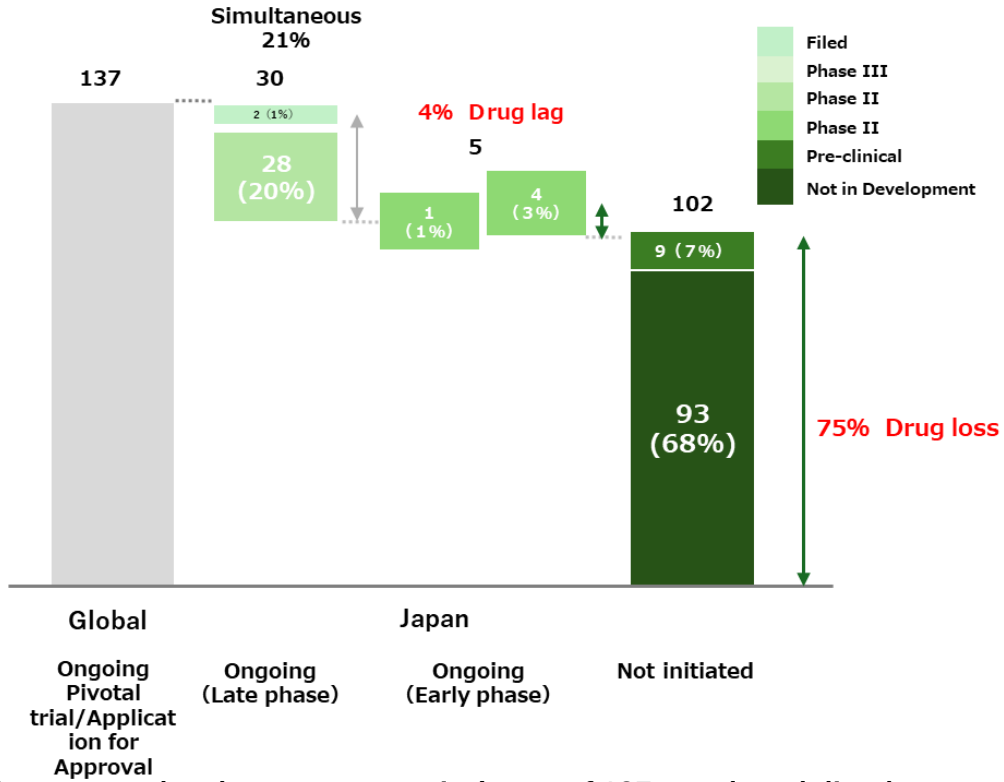
Acceleration of drug lag and loss is due to delays in responding to development of new modalities, including non-cancer drugs ②

Among late-stage new modalities, 75% have not started clinical development in Japan



Modality	Pharmaceutical company	Pipeline
Cell therapy	BrainStorm Cell Therapeutics Lonza, Capricor Therapeutics	debamestrocel XAP-1002
Nucleic acid drug	Takeda, Arrowhead Pharmaceuticals AstraZeneca, Ionis Pharmaceuticals	fazirsiran eplontersen
Gene therapy	Ultragenyx Pharmaceutical CRISPR Therapeutics, Vertex Pharmaceuticals …	pariglasgene brecaparvovec exagamglogene autotemcel …
Antibody conjugate drug	Ambrx Biopharma MacroGenics	anvatabart opadotin vobramitamab duocarmazine
Bi-specific Ab	Zymeworks, Jazz Pharmaceutical Compass Therapeutics	zanidatamab CTX-009
Cell therapy	AiVita Biomedical SOTIO, Therapeutic Solutions	AVGBM-01 stapuldencel-T
Nucleic acid therapeutics	AIM Immuno Tech Geron	rintatolimod imetelstat
Gene therapy	Candel Therapeutics Trizell	aglatimagene besadenovec nadofaragene firadenovec
Genetically engineered cell therapy	Angiocrine Bioscience Iovance Biotherapeutics	AB-205 lifileucel
Oncolytic virus	Genelux …	olvimulogene nanivacirepvec …

Categorized by disease, of a new modality with 102 pipelines that is currently in Phase 3 trials or under regulatory review in the US and Europe but has yet to initiate clinical development in Japan.



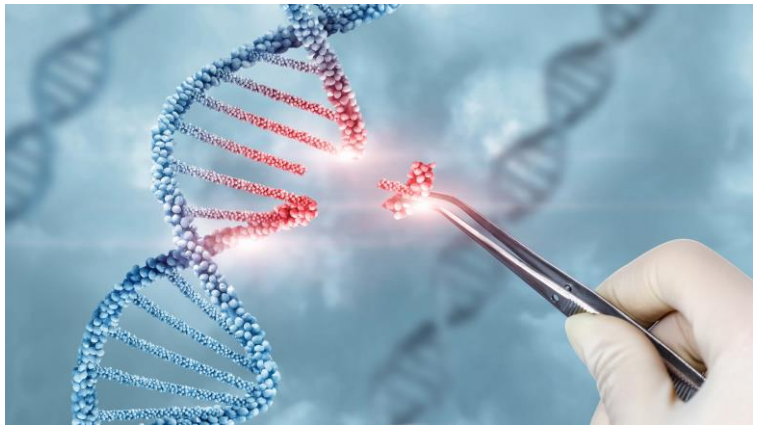
The current development status in Japan of 137 novel modality drugs that are in Phase 3 clinical trials or under regulatory review in global markets as of July 2023

第2回 創薬力の向上により国民に最新の医薬品を迅速に届けるための構想会議資料３（藤原氏資料）
https://www.cas.go.jp/jp/seisaku/souyakuryoku/dai2/gijisidai.html

Biopharmaceutical development requires a new clinical trial system under government support and guarantees

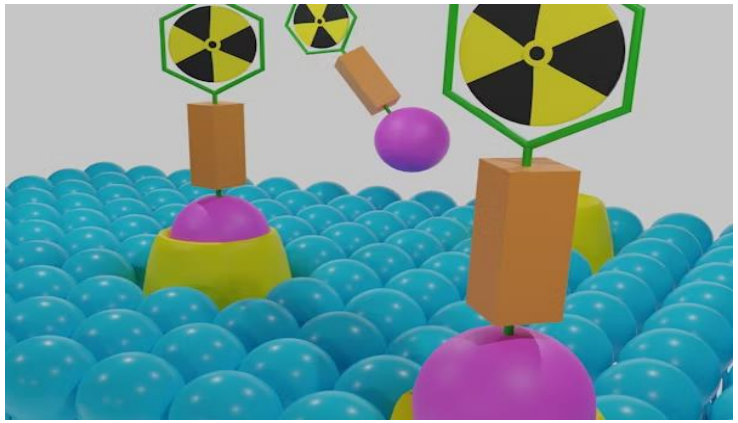
- Necessities for special facilities to comply with domestic laws and regulations that are different from conventional clinical trial regulations.
- Due to the need for coordination with multiple ministries, the clinical trial initiation process becomes complex and time-consuming.

Gene and Regenerative Medicine (Cartagena law)



- Vaccinia virus: zoonotic disease
- Vaccines and antibody for infectious diseases of livestock⇔simultaneously control
- Zika virus and Herpes virus

Radio-ligand drug (RI law)



- Supply system (engineering, physics) Production, Transportation system
- Safety Management (Materials Engineering)
- Therapeutic Optimization for theranostics (Physical/Radial/Biological/Technical)
- Radioactive waste disposal

Australia offers the essential elements for success to any Emerging Biopharma(EBP): Spe financial benefits, globally accepted quality data

Speed
of delivery with
Simple regulatory framework

Rapid start up and fast approvals.

- **CTN* scheme** (No IND* Application Required)
- Ethics submission/ approval 4-6 weeks for healthy volunteer studies
- Required documents only: IB*/Protocol/PICF*

Cost saving Significantly **cheaper** than conducting Phase I in US

- **R&D tax incentive** from the AUS government (43.5% Tax refund)
- Favorable AUD exchange rate
- Save up to 60% compared to US/EU Phase I study

Quality

Globally accepted quality data in Australia can be used to support international regulatory applications, including the US FDA* and the EMA*

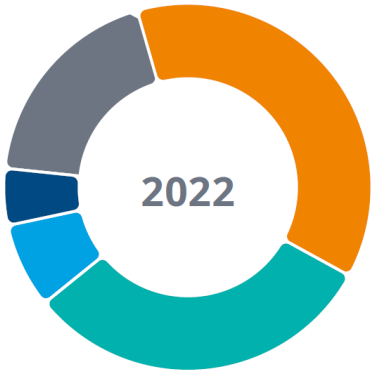
Local excellence, global thinking

World leading investigator & KOLs*

* CTN: Clinical Trial Notification, IND: Investigational New Drug, IB: Investigator Brochure, PICF: Participant Information and Consent Form, FDA: Food and Drug Administration, EMA: European Medicines Agency, KOL: Key Opinion Leader

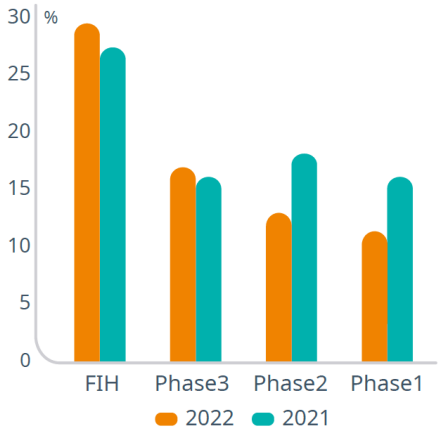
International investment in early phase trials

One-thirds of public early phase trials involved investment from **sponsors in Australia.**



Distribution of trials by phases

Data showed continued strength of Australia in **FIH* and Phase I trials.**



Source: Bellbery Clinical Trial Report 2022 Dataset; Research approved by Bellberry HRECs (2022 calendar year) and NSW Early Phase Clinical Trial (EPCT) Framework (2022 calendar year).

* FIH: First In Human

In Australia, the government is promoting clinical development as a national policy (supporting start-up companies)

Australia is a leading global destination for early phase trials

- Quality medical research infrastructure, a skilled workforce and world-class healthcare system
- An efficient regulatory pathway and compliance with high international standards for data
- Intellectual property, ranked 11th most secure in the world
- An ethnically diverse, English-speaking population and close proximity to Asia

https://www.iqvia.com/locations/australia-and-new-zealand