

The Case for The Japanese Foundation for Rare Disease Research (JFRDR)

Prepared by: Christian Elze, JFRDR

20260507

Note to the Reader

- This document focuses on the **economics of the Venture Capital model** at a **systems level**
- Thus, the “**multiples required**” to entice investors to invest their money into a VC fund are calculated based on the **overall returns of all VC funds**; in other words, a few **successful projects and funds** need to pay for the multiple **losses** incurred by all **other projects and funds**
- To drive home the main point, namely the **importance of the cost of capital**, the model is based on **highly simplified assumptions**
 - In reality, VC funds usually invest only in specific stages of drug development and usually do so in a **consortium** with other investors
 - In this way, **exit multiples** are generated for funds from **drugs that ultimately fail**, but these multiples are **other investors’ losses**
- All calculations in the presentation take into account only development cost and focus on the role of **cost of capital**
- **CMC, commercialisation** and all related costs will only be reintroduced at the end for a **like-for-like comparison with the VC-funded Biopharma model**

Executive Summary: There are four main reasons why JFRDR is needed and should be funded by the government

1. Social Contract

Rare Disease **patients** in Japan and elsewhere need drugs to **survive and live better lives**

2. Biomedical Innovation

The Japanese R&D ecosystem needs **public investment to re-establish long-lost competitiveness**, especially for **emerging modalities**

Here is an **opportunity for Japan to duplicate the success of GHIT in an emerging global collaboration to address another market failure: Ultrarare disease drug loss**

4. National Security

At a time when global supply chains and alliances are disrupted, **Japan needs a much larger degree of biopharma innovation and manufacturing capability (= lower dependence on US)** than available today

3. Business Model Innovation

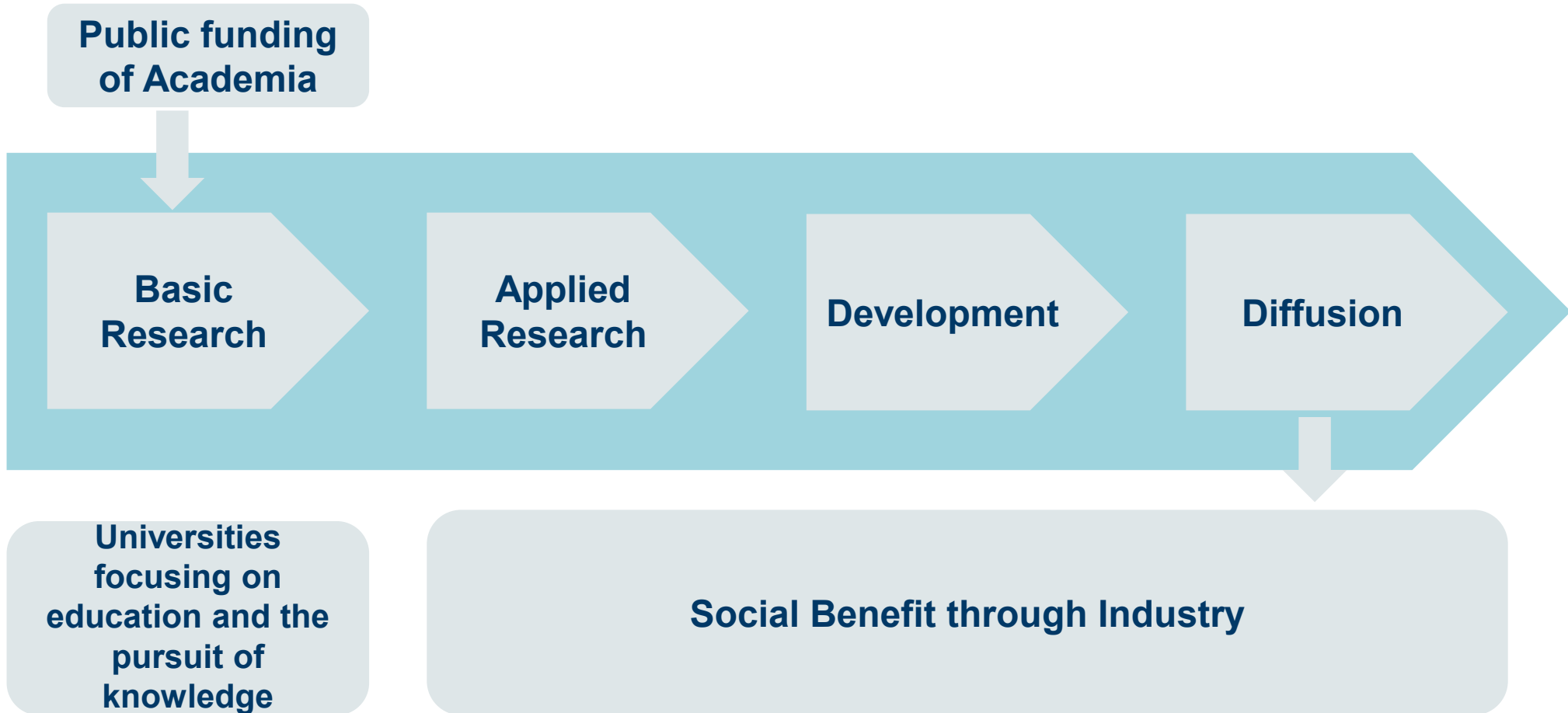
JFRDR provides the Japanese policy makers with an opportunity to **test an alternative business model for financing, developing and reimbursing biopharma innovation**, focusing on drugs for which **market mechanisms fail**

Agenda

- **The Economics of Biopharma Innovation**
- Emerging Models to Address Market Failure for Ultra-rare Diseases
- JFRDR - For Patients in Japan and Beyond
- Why You Should Support JFRDR

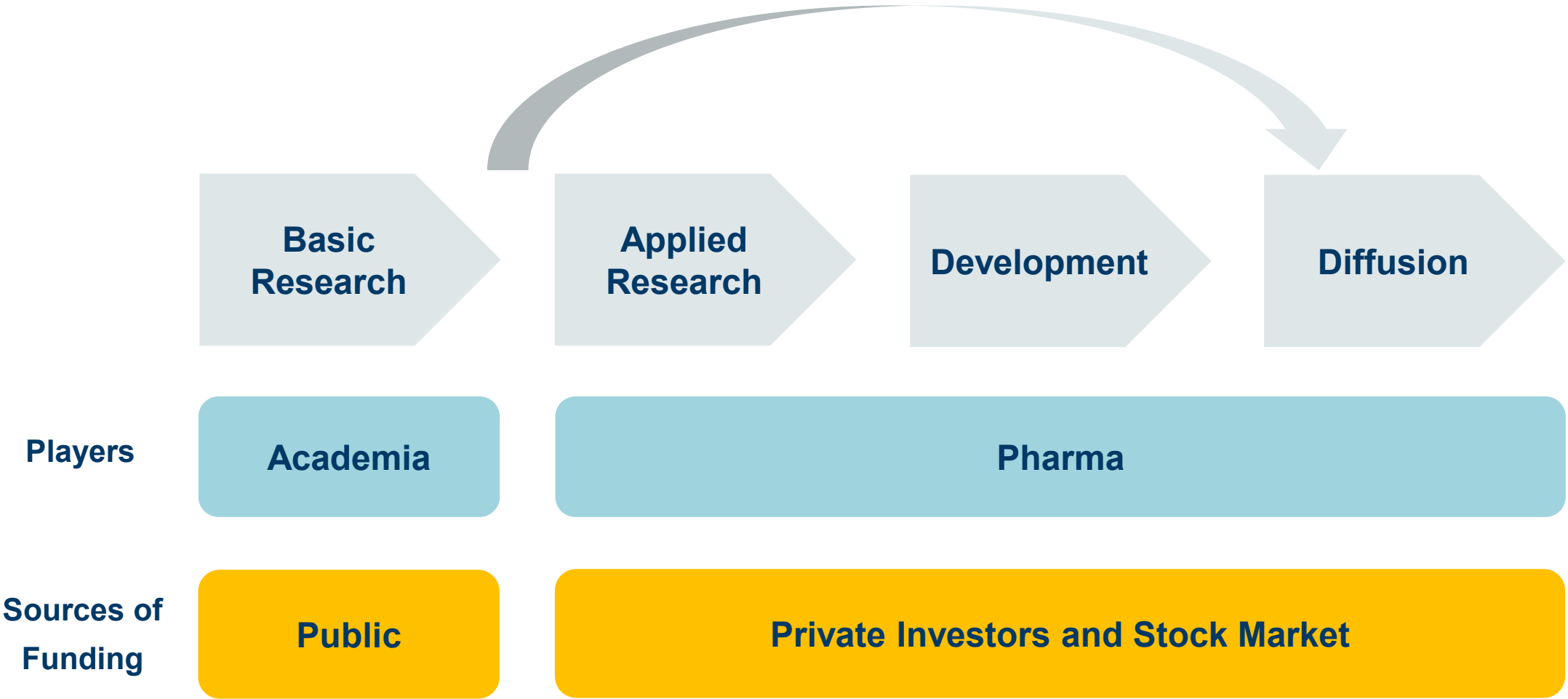


In the US, the post-WW II consensus on funding biomedical research was based on Vannevar Bush's report on „**Science – the Endless Frontier**¹“, where **public science funding would ultimately lead to social benefit**



Source: 1) https://nsf-gov-resources.nsf.gov/2023-04/EndlessFrontier75th_w.pdf

In a highly simplified view on the division of tasks, publicly-funded **Academia** focused on **Basic Research** and **for-profit Pharma** took care of **translation, development and commercialisation**



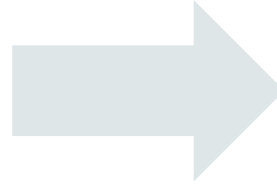
Source: JFRDR

Around 1980, the dominant **Political Economy** of Western countries radically changed, leading to **major financial and antitrust deregulation**, as well as the new model of **VC-financed biotech and focused BigPharma**, all ultimately **fuelled by rapidly rising US price levels**

Main Reform Triggers

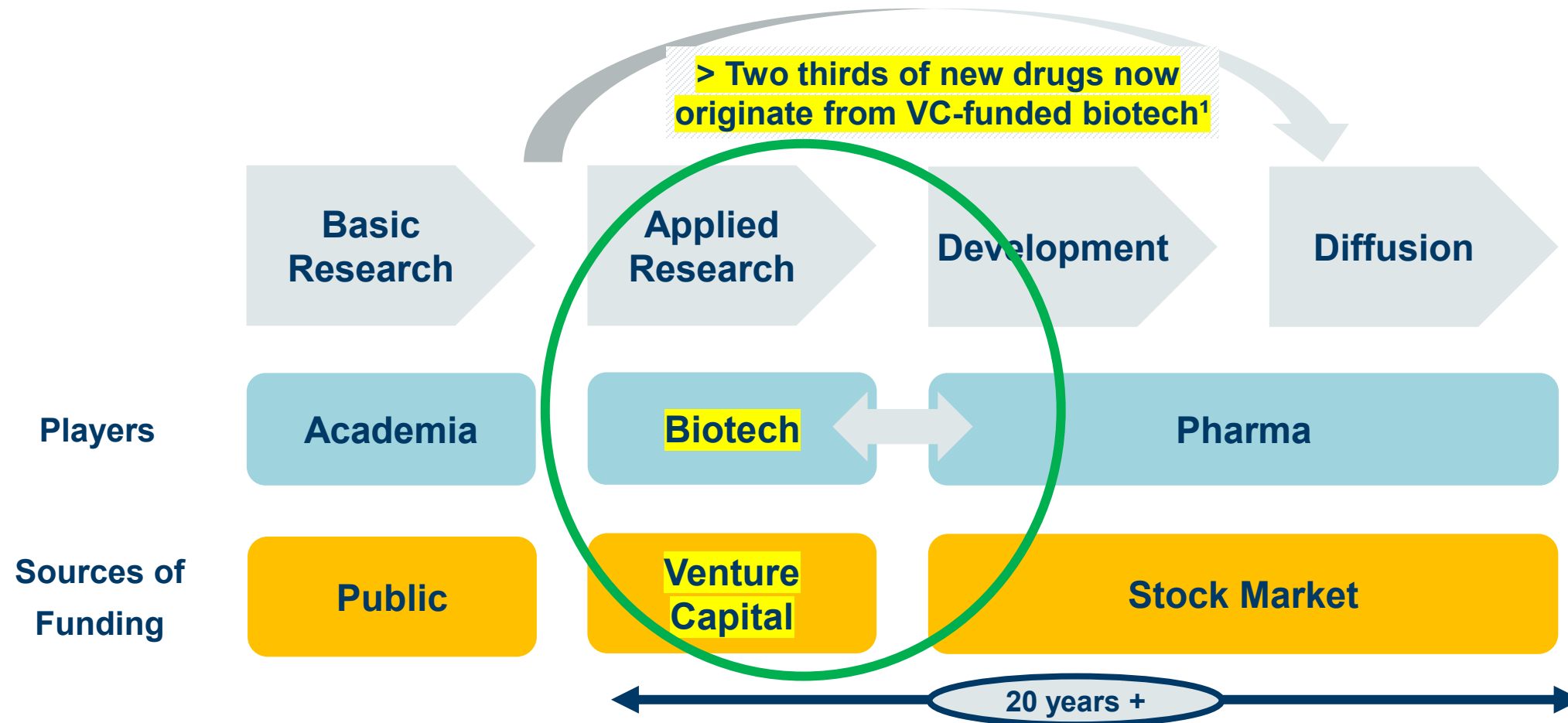
Bipartisan deregulation driven by political unhappiness with **slowing innovation at a time of reduced science funding**

- **Bayh Dole Act**
- **Diamond vs Chakrabarty**
- **Strengthening of Patent Courts**
- **Cut in top tax rate on capital gains from 49% to 28% in 1978**
- **Relaxation of the Prudent Man rule**
- **Orphan Drug Act 1983,**
- **Breakthrough Denomination 2012**
- **Lax NASDAQ listing requirements**
- A dozen more regulatory and legislative changes around 1980
- (for the larger context, cf. Kurt Anderson's "Evil Geniuses")



- **An explosion of innovation...**
- **...and of US price level for newly-launched drugs...**
- **...increasingly driven by the emergence of VC-funded biotech and focused Big Pharma**

These policy changes in the US around 1980 aimed at removing some of the key barriers to innovation and drove the emergence of the current US Biomedical Innovation System in which innovation looks like being driven by markets



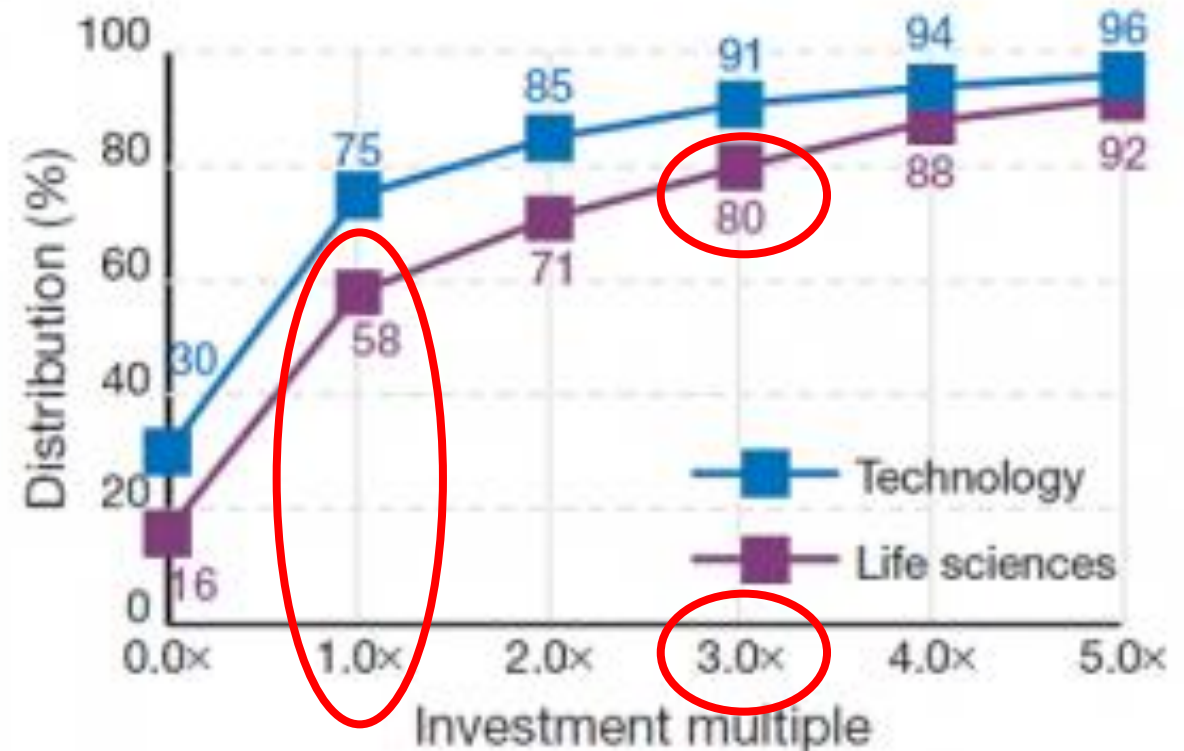
Source: 1) <https://www.fiercebiotech.com/biotech/emerging-biopharma-companies-dominate-rd-pipeline-22-iqvia-finds>

The economics of VC-funded Biotechs

Expected and actual returns of VC funds in tech and the life sciences

- As a Life Sciences investor, you stand a **58% chance** of losing part of your principal
- In combination with the **lack of liquidity**, this translates to average expectation of **investment multiples of 3x over ten years**, corresponding to a 13% compound interest pa – only **20% of funds** in the sample have delivered on this promise
- Some investors expect **5x**, corresponding to 17% compound interest pa

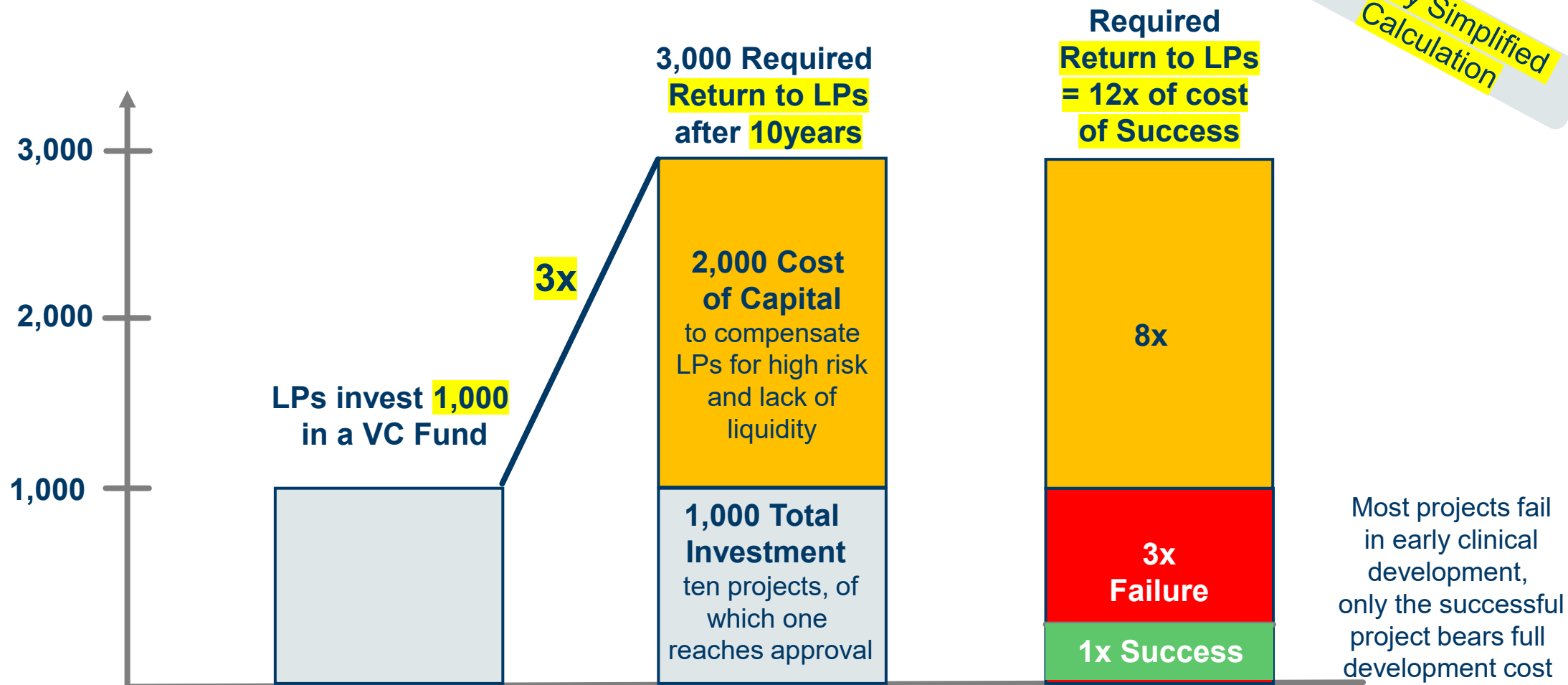
Actual Fund Returns



Source: Booth et al: <https://lifescivc.com/2011/07/life-sciences-the-rodney-dangerfield-of-venture-capital/>;

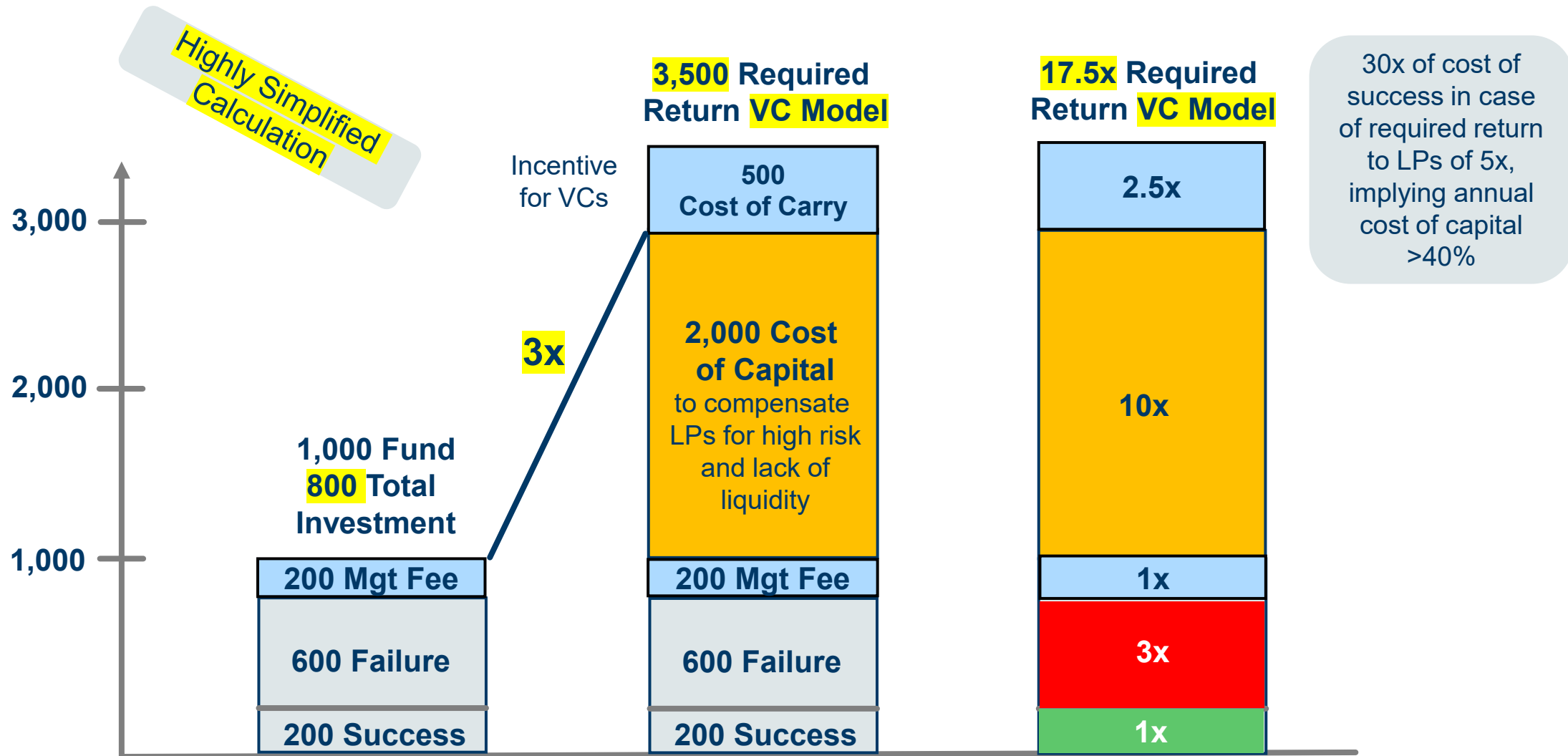
A similar distribution of returns can be found in <https://www.baybridgebio.com/blog/biotech-power-law>

At first sight, with a systems-wide **economically-reasonable** expectation of **3x return** on invested capital, **one successful project/company** needs to **return 12x** of its **development cost**



VC = Venture Capital; LP = Limited Partner, i.e. investors in the VC fund

But VCs do not work for free - multiples of “cost of success” with VC compensation (2% pa plus 20% >1x carry) rise to **17.5x**; for the **successful project/company** this implies an **annual cost of capital of above 30%**



Source: JFRDR

Two **random plausibility checks** with real life cases confirm the order of magnitude of the above analysis

Zolgensma

(onasemnogene abeparvovec-xioi)

- Sma-type 1 targeting gene therapy
- Developed by **Avexis**, total **accumulated deficit** as per March 2018 = **\$581.7mn**
- Acquired by **Novartis** in April 2018 for \$8.7bn gross (minus \$586.6mn cash holdings) = \$8.1bn net
- **\$8.1bn net exit value : \$600mn total investment = ~13.5x**

Yescarta

(axicabagene ciloleucel)

- CD-19 targeting autologous CAR-T therapy for DLBCL et al
- Developed by **Kitepharma**, total **accumulated deficit** as per Sept 2017 - estimated **~\$690mn**
- Acquired by **Gilead** in August 2017 for \$11.9bn gross (minus ~\$625mn cash holdings) = \$11.25bn net
- **\$11.25bn net exit value : \$690mn total investment = ~16x**

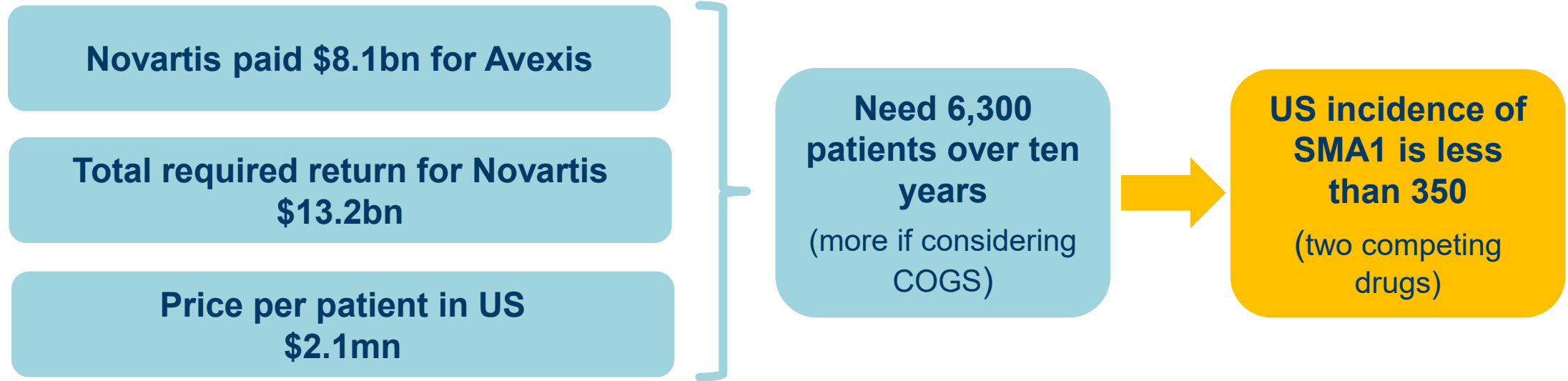
Sources: for Avexis - <https://www.sec.gov/Archives/edgar/data/1652923/000155837018004054/avxs-20180331x10q.htm>

For Kite - <https://www.bamsec.com/filing/151058017000003?cik=1510580>

https://www.sec.gov/Archives/edgar/data/1510580/000156459015001985/kite-10k_20141231.htm#Item_7_Management_Discussion

<https://www.sec.gov/Archives/edgar/data/1510580/000119312517161774/d384838dex991.htm>

So the Novartis acquisition of Avexis/Zolgensma does not look like a good investment – they paid less than the **right price**, but **there are not enough patients in the US to recoup the cost of capital**



- To make a reasonable return, Novartis needs to find many more patients in other countries at significantly lower prices
- Life cycle management has limited upside (intrathecal injection for kids >2y)
- \$5mn would have been an economically reasonable clearing price
- **This drug would no longer be developed today by VC-funded Biotech**

Sources: 1) Verhaart et al. Orphanet Journal of Rare Diseases (2017) 12:124 DOI 10.1186/s13023-017-0671-8

2) <https://database.earth/population/united-states-of-america/births>

The analysis shows that the **current biopharma innovation model** is quickly **reaching its limits**, first in the field of **rare diseases**, in particular for “**ultrarare diseases**”

There are only a few rare diseases left that are **economically viable** in this model

Rare Diseases

Prices of rare disease drugs are **so high** that even in the US these drugs are **seldom prescribed**²

Price levels are diverging more and more (**US = 3.4x** Japan for brand.name drugs)¹, leading the US government to its aggressive policy of MFN

General Pharma

Established pharma companies are **rebalancing** their portfolios towards **lower average risk**
(e.g.: Recent termination of gene therapy programs by Pfizer and exit from cell therapies by Takeda, Sanofi and others)

Sources: 1) RAND Corporation: Report on International Prescription Drug Price Comparisons, using 2022 data

2) <https://www.fiercepharma.com/special-reports/most-expensive-drugs-us-2025>

What do we mean by “Rare Disease” Drugs?

“Rare Disease” Drugs

- Drugs for diseases with **orphan status**, i.e. < 200,000 patients in the US and <50,000 patients in Japan
- Historically a **driver of the industry** growing from zero before 1983 to **>20% of biopharma revenues** in mid-2020's

“Ultrarare Disease” Drugs

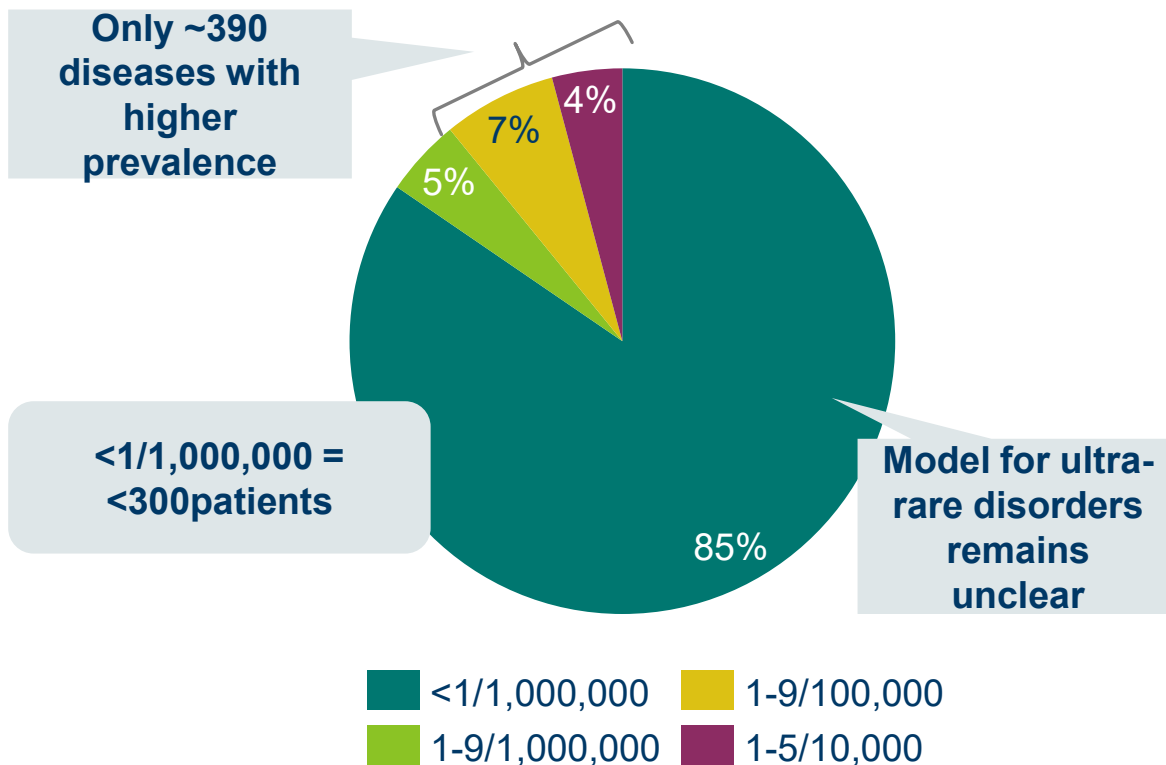
- Drugs for diseases deemed **too rare to be financially viable in the biopharma R&D and regulatory model**
- Differing definitions of **US incidence** somewhere between **low teens to up to 1,000 patients** or required **price per patient >\$500K**

“Nano-rare Disease” Therapeutics

- **N=1/n=few**
- Today mostly **antisense nucleotids** for **individual patients** or a small number of patients; (gene editing expected)
- Require **IND in US** but **no FDA approval**, in **EU** only **IRB approval**
- Essentially **hospital products** following a **different pathway**

Only about **400 rare diseases** have sufficient patient numbers to be **commercially viable**, most of these are now being addressed on the market or in clinical pipelines

Prevalence - Repartition of Rare Diseases (n = 3500)



- Many diseases **unknown incidence and prevalence**
- **N=1 is a subset** of the total, e.g.: >150 mutations causing PKU
- Often, **more patients than expected are identified** once a treatment is available
- On the other hand, **penetrance and expressivity** are variable and there are limitations for treatment, e.g.: Prior exposure to AAVs

Source: Wakap et al, European Journal of Human Genetics volume 28, pages165–173 (2020), DOI: [10.1038/s41431-019-0508-0](https://doi.org/10.1038/s41431-019-0508-0)

Agenda

- The Economics of Biopharma Innovation
- **Emerging Models to Address Market Failure for Ultra-rare Diseases**
- JFRDR - For Patients in Japan and Beyond
- Why You Should Support JFRDR



Drug Loss is a global challenge and it is getting worse – the current biopharma business model based on high cost of capital is the main culprit that needs to be addressed



Most visible and politically sensitive



Less severe than in Japan but increasing numbers



Hundreds of drugs stopped in clinical development due to commercial reasons



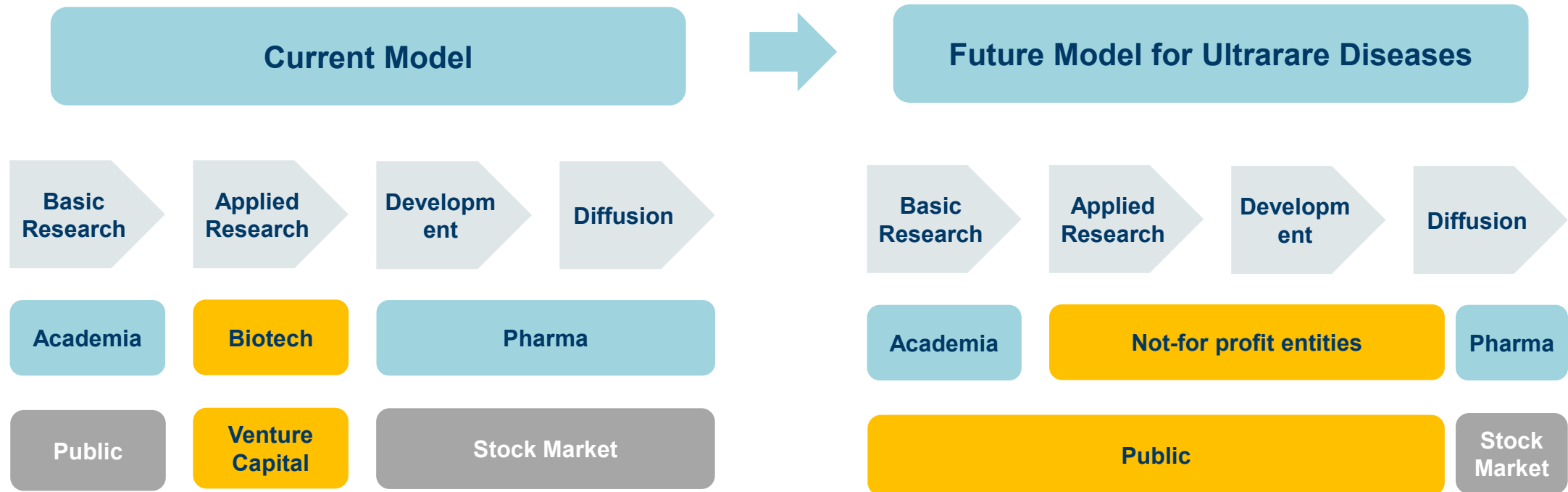
Many drugs not affordable for local healthcare systems

Challenges to be tackled

1. **Failure rates** are high – AI will help but not solve this issue
2. **Regulatory complexity** – too burdensome, too expensive, too long – needs to be adapted
3. **CMC** is too expensive – correct, limited economies of scale
4. Biopharma **valuations** are low/IPO window is closed since 2022, first signs of re-opening

The main challenge is the current VC-funded biotech business model with its high cost of capital and it is beginning to be addressed across the globe

Future innovation for thousands of ultrarare diseases will require a **different “business model”** which operates **in parallel** with the current model

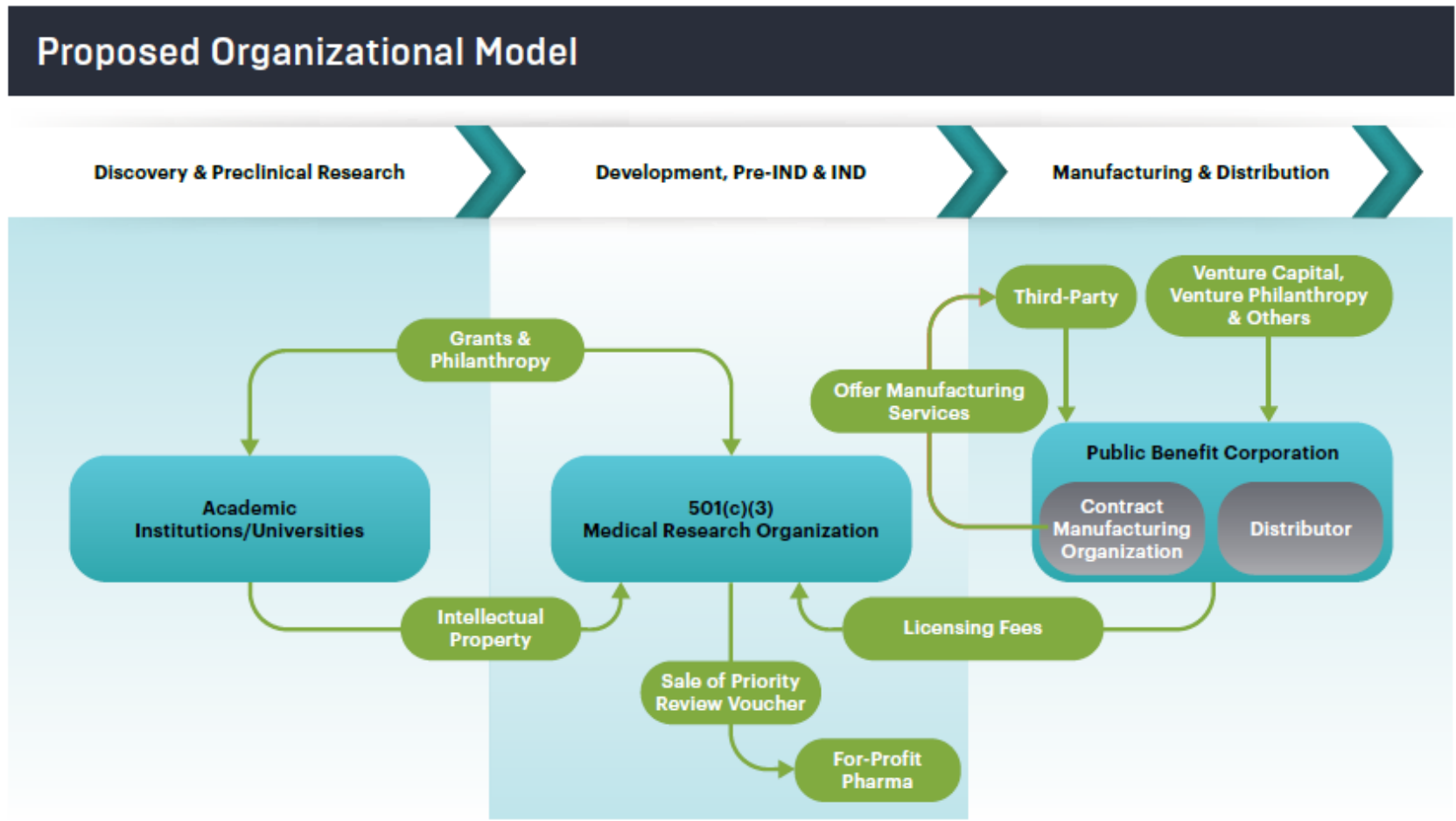


One way to look at this is to **extend the public financing of Basic Science without a direct economic return expectation to the clinical development of ultrarare diseases to tackle market failure**

Source: JFRDR

A proposed **mixed organizational model for CGT**: A non-profit conducts grant-funded R&D; an MRO further develops and translates the product through clinical trials and a public benefit corporation would manufacture and distribute the product on a financially self-sustaining basis

Not-for-profit approach advocated by Jennifer Doudna's Innovative Genomics Institute



Source: Innovative Genomics Institute: <https://innovativegenomics.org/making-genetic-therapies-affordable-and-accessible/>

Emerging models in action: **Two long-established players in Europe**

Telethon Italia

- Established in **1990**
- Funded by donations from the public and based on extensive national TV campaigns involving celebrities and patients
- Currently raise ~€50mn pa
- **Total financing since 1990 €741mn**
- Grant funding agency with in-house research labs
- Now MA holder for Strimvelis after drug was withdrawn from market by Orchard Tx
- FDA recently approved Waskyra for Wiskott-Aldrich syndrome; US rights licensed to OTXL
- <https://www.fondazionetelethon.it/en/>

AFM Téléthon and Généthon

- Established **1958** and **1990** respectively
- Funded by donations from the public and based on extensive national TV campaigns involving celebrities and patients
- 2024 Telethon raised €96,553,593
- Initial focus on muscular dystrophy, now much broader
- <https://www.genethon.com/who-are-we/our-history/>
- <https://www.afm-telethon.fr/en/our-history>

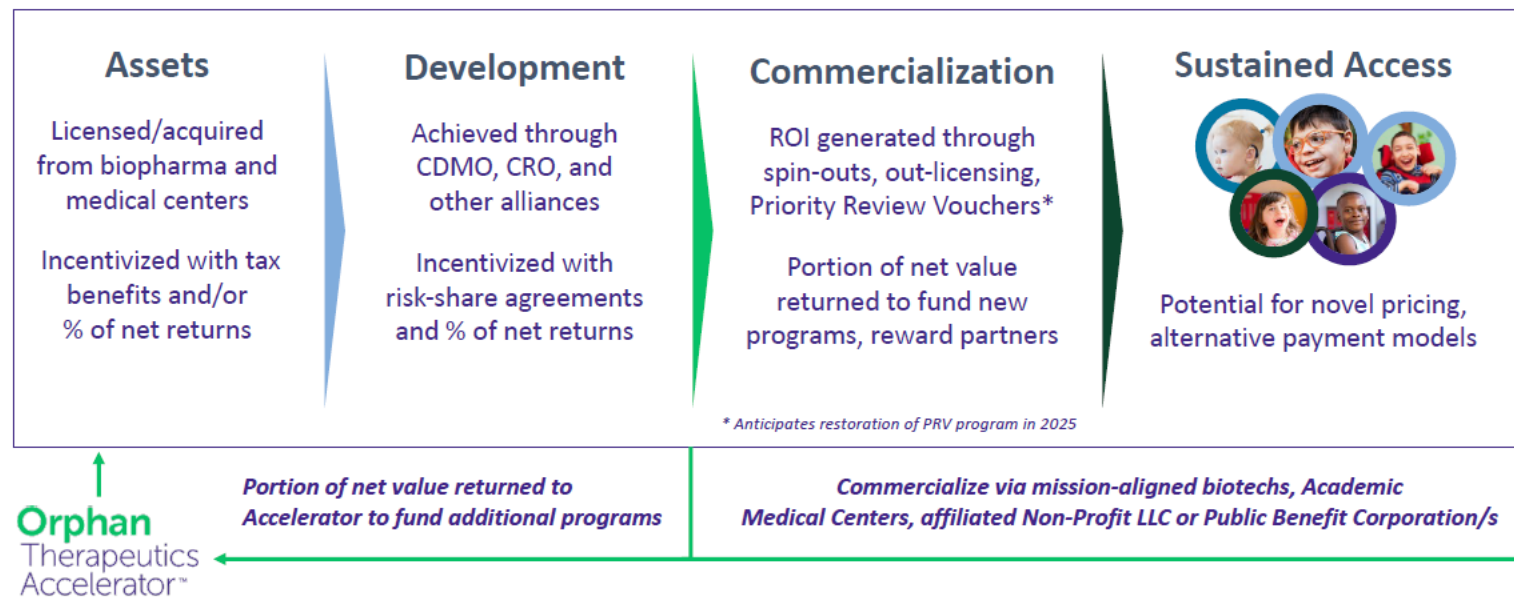
Emerging models in action: It is the mission of OTXL to “Create a viable path forward to bring promising treatments for **ultra-rare diseases** to patients”

OTXL – Orphan Therapeutics Accelerator

- Established **2024**
- Start-up funding provided by **Chiesi** and **Bial**
- Not-for profit model, funding unclear, target are patient organisations, charity, Venture Philanthropy
- Will initially focus on >100 candidates stuck in US clinical development due to lack of commercial viability
- <https://www.orphantxl.com/about-us>

Source: JFRDR

Business Model is Value-Generating | Prioritizing Access, Scale & Sustainability



Emerging models in action: focusing on different **technology platforms** highly relevant for ultra-rare diseases

Gemma Bio/Rare Tx

- Launched Oct 1, 2024 by **Jim Wilson**, a pioneer of **AAV-based gene therapy**
- Partnered with CRO **Franklin Biolabs**, specialised on gene therapy
- **VC-funded, business model to be clarified**
- <https://www.gemmabiotx.com/>
- **Tech transfer deals for gene therapy platform with Brazil**
<https://www.prnewswire.com/news-releases/gemmabio-announces-100-million-agreement-with-brazils-leading-health-research-institute-302270296.html>
- **And Abu Dhabi** <https://www.bizjournals.com/philadelphia/news/2025/07/07/gemma-bio-jim-wilson-abu-dhabi-gene-therapy.html?b=1751908897^22562564>
- Now developing three ultrarare gene therapies in partnership with the Brazilian government

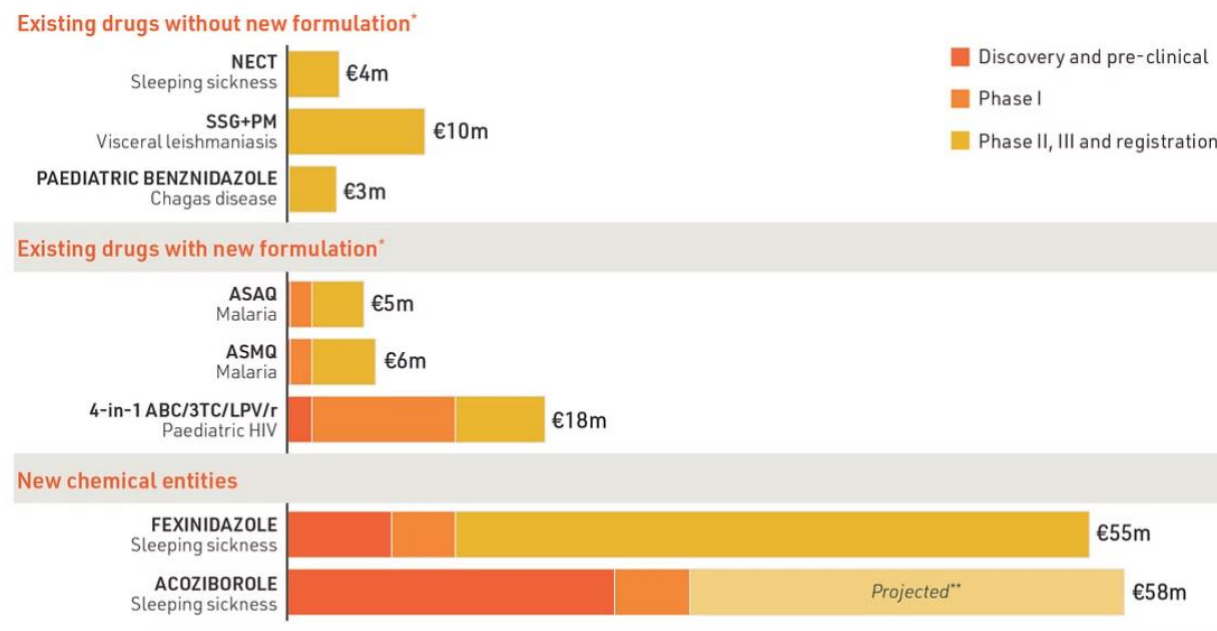
Emerging models in action: “DNDi acts as a conductor of a ‘virtual orchestra’ of over 200 partners around the world to develop treatments for patients – not profits”

DNDi – Drugs for Neglected Diseases Initiative

- **Not-for-profit** initiative to develop drugs for neglected diseases
- Set up in 1999
- Funded by **Médecins sans Frontières**, Institut Pasteur and gvt institutions of half a dozen developing countries
- **In 2024, €57mn raised for grants**
- Total raised in 20 years: **€880mn** – 62% public/38% private, ~15% from Gates Foundation
- Supported by in-kind contributions from commercial players along the value chain
- <https://dndi.org/about/who-we-are>
- <https://dndi.org/wp-content/uploads/2025/06/DNDi-FinancialReport-2024.pdf>

Source: JFRDR

DNDi R&D real life expenses at cost



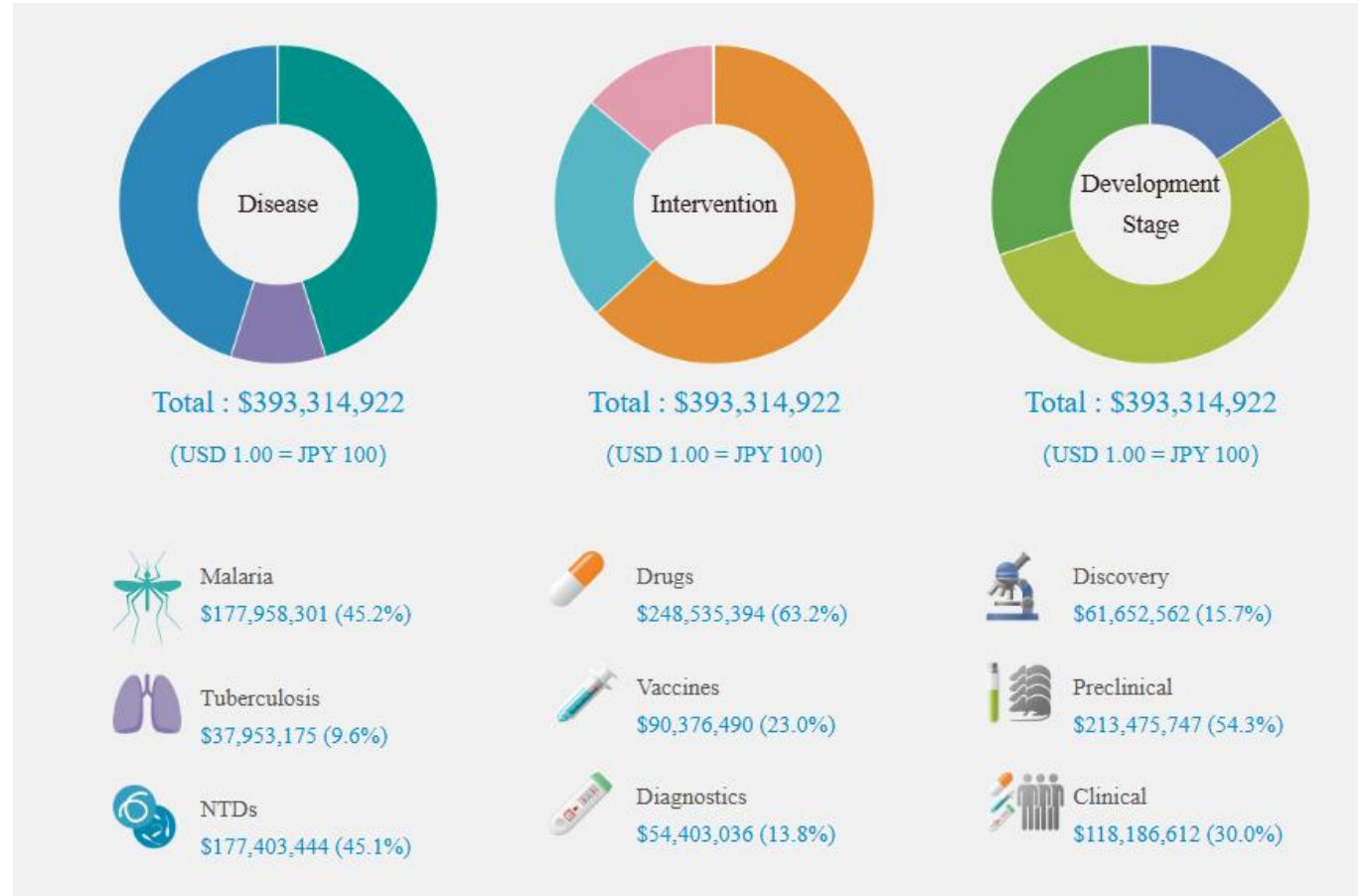
* Combinations (as loose or fixed-dose combinations) or repurposing of existing drugs
 ** Acoziborole is still under development. Late-stage costs are projections.

plus in-kind contributions by industrial partners

Emerging models in action: **GHIT** was set up in 2013 to “leverage Japanese innovation and leadership to fight against neglected infectious diseases through investing in **research and development**, and promoting **global partnerships**”

GHIT – Global Health Innovative Technology Fund

- Registered in **2013** as a general incorporated association in Japan
- Funded by the **Japanese government**, the Gates Foundation, the Wellcome Trust and **half a dozen Japanese pharmaceutical companies**
- Have allocated **\$393mn since 2013**
- **First approval** for schistosomiasis treatment in **2024**
- <https://www.ghitfund.org/> and
- <https://www.ghitfund.org/investment/overview/en>



Source: JFRDR

Agenda

- The Economics of Biopharma Innovation
- Emerging Models to Address Market Failure for Ultra-rare Diseases
- **JFRDR - For Patients in Japan and Beyond**
- Why You Should Support JFRDR



JFRDR sees four categories of drug loss

Current Drug Loss

Well-known - 86 drugs approved by FDA and EMA by 2020

Mostly not high unmet need or irrelevant or being addressed
JFRDR analysis on-going

Less known - estimated 100 rare disease drugs approved by FDA and EMA since 2020

Many addressing high unmet need
JFRDR analysis on-going

Future Drug Loss

Unknown # of drugs (active and stopped) in clinical trials without Japan involvement

Many addressing high unmet need
JFRDR analysis on-going

Translational projects in Japanese academia (AMED)

Many addressing unmet need; mostly under-funded and under-coached

Importantly, these categories have **different risk profiles and timelines** to reach Japanese patients, which will have to be taken into account by **JFRDR** as it builds its **portfolio**

Current Drug Loss

Well-known - 86 drugs approved by FDA and EMA by 2020

Low risk
Short timeline of 2-3 years

Less known - estimated 100 rare disease drugs approved by FDA and EMA since 2020

Low risk
Short timeline of 2-3 years

Future Drug Loss

Unknown # of drugs (active and stopped) in clinical trials without Japan involvement

Medium risk
Timeline of 5-7 years

Translational projects in Japanese academia (AMED)

Highest risk
Timeline of 10 – 15 years +

Due to the low number of patients in any one country, addressing the ultrarare disease challenge requires **new not-for-profit business models** and **global collaboration**

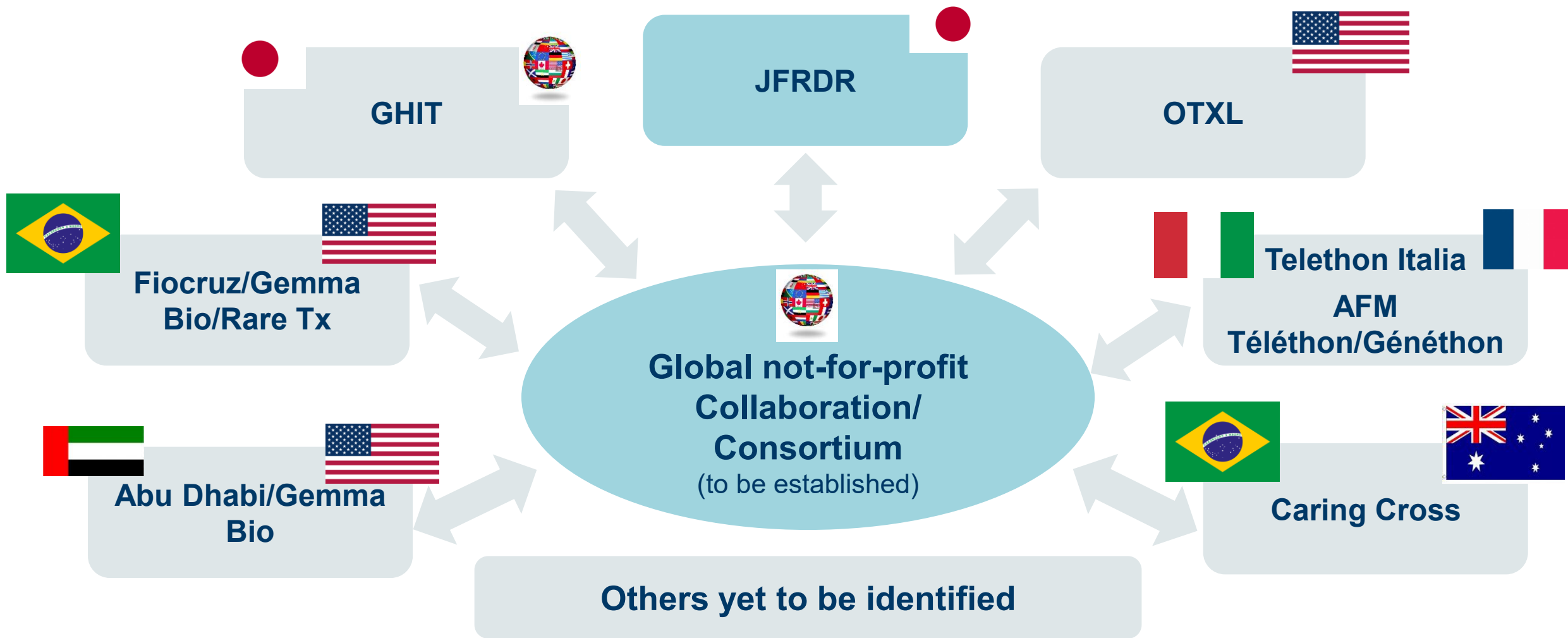
Not-for-profit Business Models

- Basic and translational research funded by governments
- **Clinical research, manufacturing and distribution** to patients delivered by **professionally managed not-for-profit organisations**
- Funded by **donations from the public, patient organisations, corporate donations and governments**

Global Collaboration

- Joint **registries, natural history studies, biomarker development and clinical studies**
- **Shared materials and services:** Oligos, vectors, LNPs, CDMOs, CROs...
- **Joint approaches to manufacturing**
- Shared models for ensuring **patient organisation & engagement**, as well as **patient access**

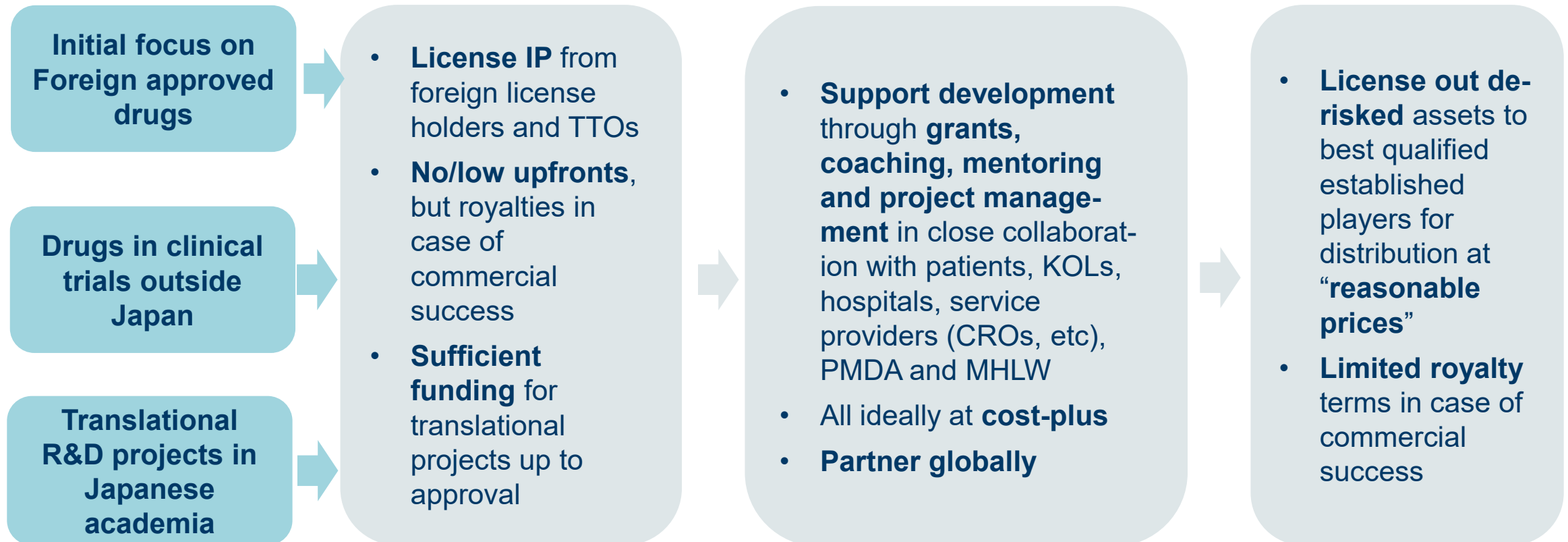
The Vision: JFRDR aims to be the key Japanese player in a global collaboration tackling drug R&D for economically infeasible ultra-rare diseases



Source: JFRDR

JFRDR's basic value proposition is to successfully **develop ultra-rare disease drugs thought to be commercially non-viable** and help making them accessible to **Japanese patients** via established commercial entities at **“reasonable prices”**

Basic Philosophy: Be complementary with market players, do not compete



Source: JFRDR

To achieve its objectives, JFRDR will implement a **new operating model in Japan** which is tied into **an emerging global ecosystem** tackling the **development of economically infeasible ultrarare disease drugs**

- Key to JFRDR's success will be
 1. A **professional management approach** to all activities, led by a small team of **seasoned executives** supported by top notch national and **global advisors** for project selection and KOL coaching
 2. The use of **low-cost capital** and **at cost-plus services** leading to drugs that can be commercialised at relatively **low reimbursement cost to the public healthcare system**
- **New models** for tackling **ultra-rare disease drug development** – many of them **not-for-profit** - are being set up in other geographies and **Japan** needs to establish an **organisation** that can **efficiently represent its interests** in the **emerging global network of similar-minded organisations**
- Together with these **peer organisations** in the US, Europe and elsewhere, **JFRDR** will strive to **adapt the not-for profit models of global virtual collaboration** for the development of **drugs for neglected and tropical diseases** (cf DNDi and GHIT) to the **specific requirements of ultra-rare diseases**

JFRDR aims to finalise initial **fund-raising by the end of 2026** and to **start operations in early 2027**

Initial Founders and Funding

- **Hiroshi Mizushima**, Research Scientist and currently President, Mizushima Institute of Medical Information
- **Norikazu Eiki**, Former Chairman, Bayer Yakuhin
- **Rob Koremans**, CEO, Recordati SpA
- **Christian Elze**, Strategy consultant and advisor to companies, academia and governments
- Start-up funding provided by **Recordati SpA**

On-going Activities

- **JFRDR** is incorporated as a “**General Incorporated Association**”, to be transformed into “Public Interest Incorporated Foundation - Koueki Shadan Hojin “ at a later stage
- **CEO with hands-on rare disease experience** has been hired: **Hiroshi Kowaki** (ex-Alnylam, Amylyx et al)
- **Prioritising drug loss projects and preparing operations**
- **Fund-raising**

Funding is a political choice: The preferred financing model is **full funding by government**; alternatively, JFRDR could **gradually** become **self-financing**; however, this would entail **higher prices** and potentially more **limited patient access**

Preferred Approach

JFRDR generates no profit and is fully funded by government

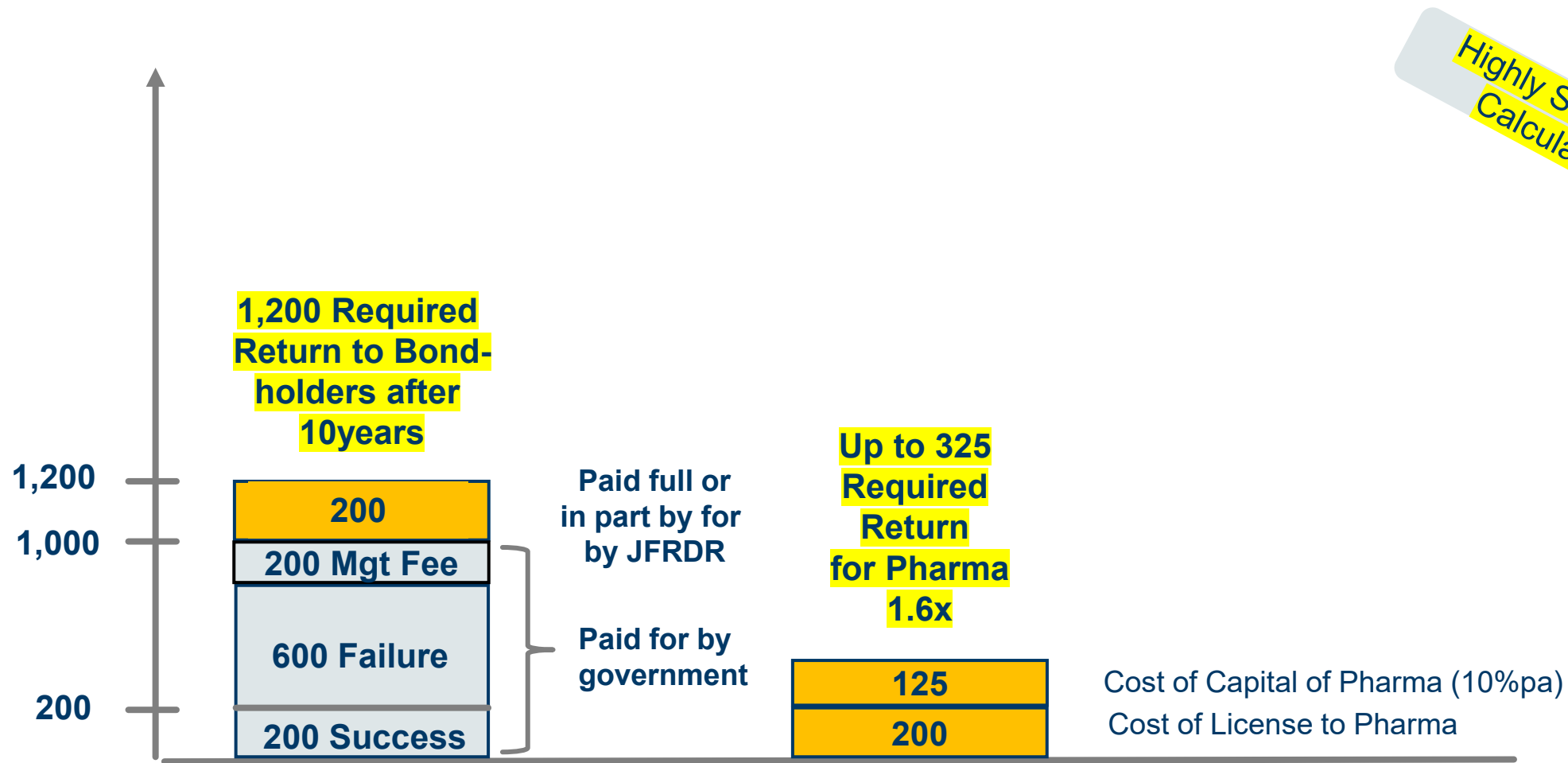
- Approach followed by **California for CIRM**
- Government pays for the full cost of JFRDR throughout its lifetime (Basic Science model) incl all or part of bond yield
- JFRDR is not sustainable on its own but contributes to the **sustainability of the healthcare system and the competitiveness of the larger innovation ecosystem**
- **Prices of drugs** developed by JFRDR will be in the range of **20% - 25%** of what is required in the VC model – **best accessibility**

Alternative Approach

JFRDR is expected to become financially sustainable over time

- **FILP** approach
- Government would fully fund JFRDR for the first five to ten years to allow for the build-up of a mature portfolio
- The maturing portfolio will **gradually allow JFRDR to reach “steady state” in which all cost can be fully covered and it becomes financially sustainable**
- **Prices of drugs** developed by JFRDR will be in the range of **50%** of what is required in the VC model, **reducing savings to the healthcare system**

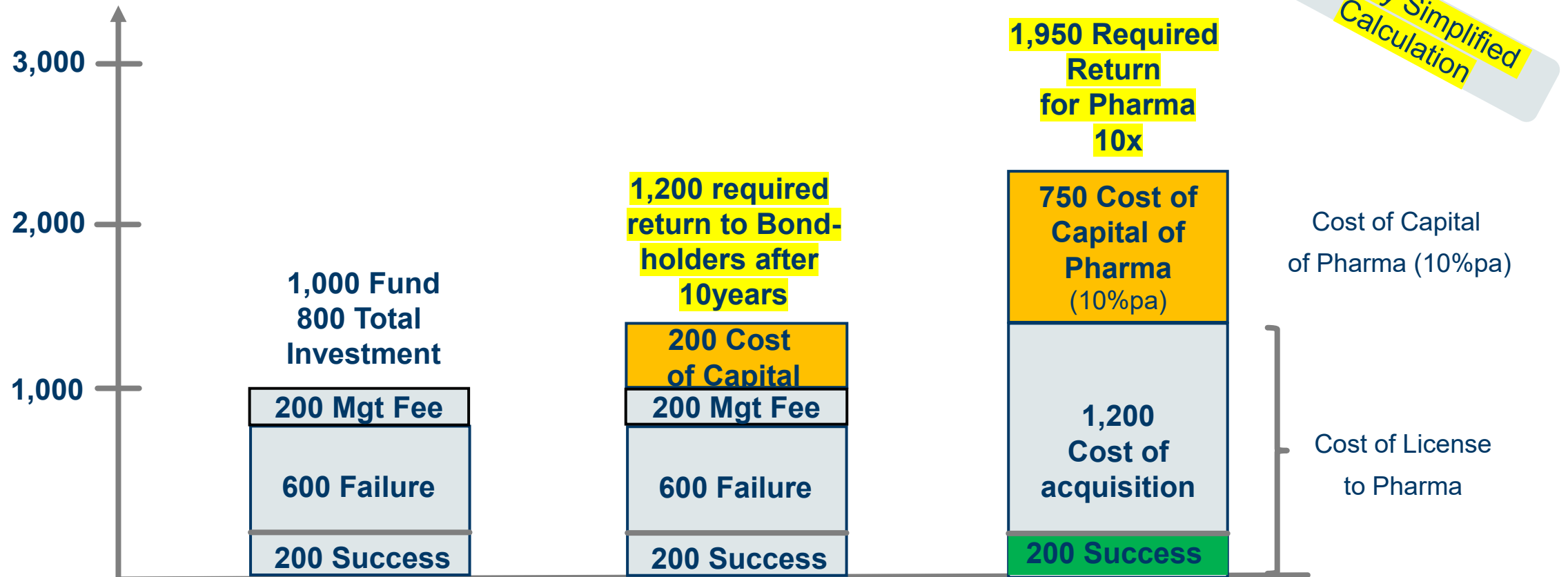
Preferred Approach: Assuming the **principal** and part of bond yield is funded by **government**, JFRDR could license the successful drug for 200 or less to pharma which would then need to generate sales of up to 325 over ten years to cover its cost of capital



Note: Current yield of ten year Japanese government bonds is closer to 2.5%

Source: JFRDR

Alternative Approach: In a self-sustaining model, there will be a management fee but no carry for management; if the drug is then licensed to Pharma for 1,200, bond principal can be paid back including the bond yield

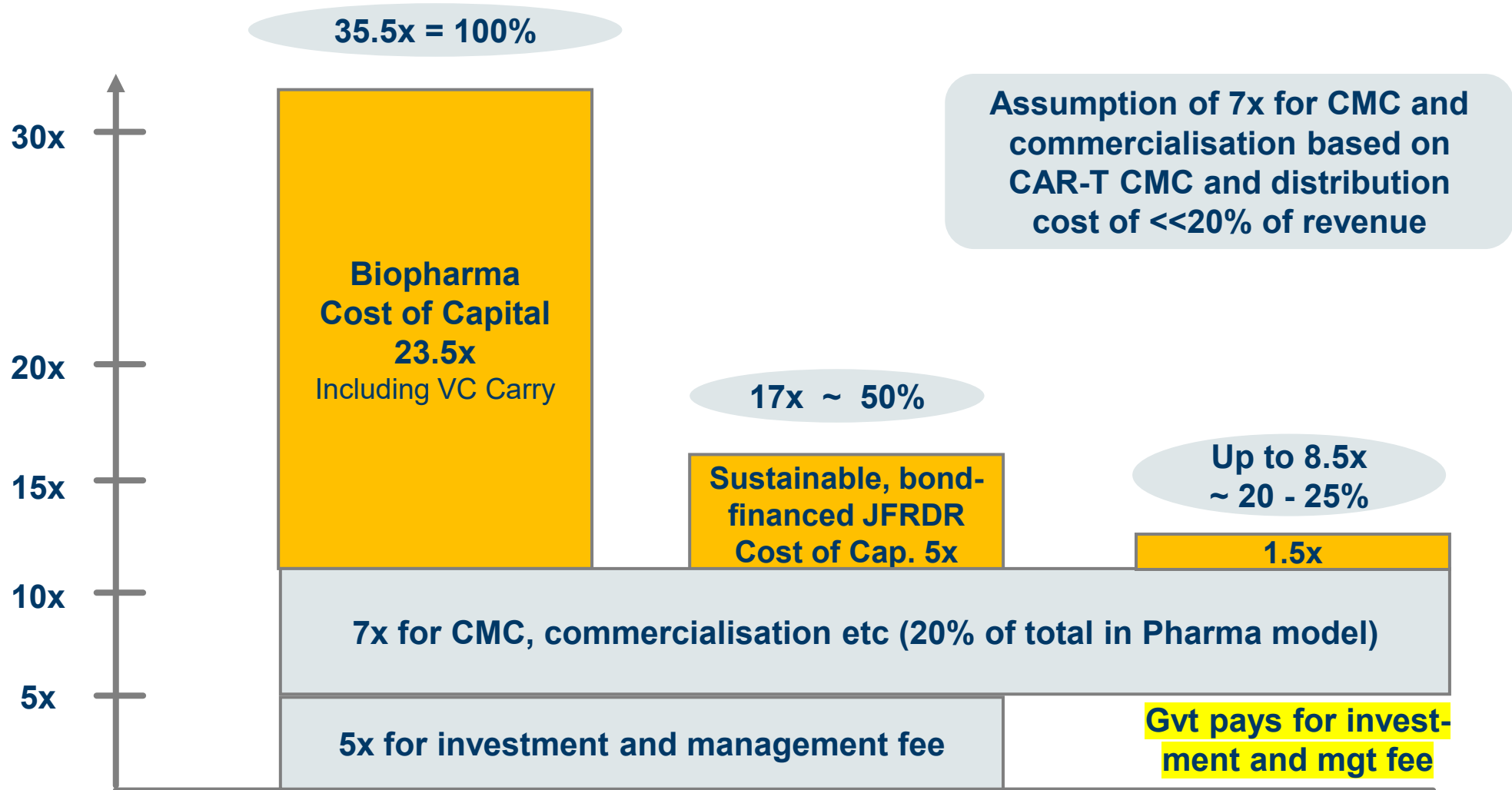


Note: This analysis assumes an acquisition (M&A); the cost of capital would be lower in case of a licensing deal made up of upfront, milestone and royalty payments

Source: JFRDR

Note: Current yield of ten year Japanese government bonds is closer to 2.5%

Finally, in a like-for-like comparison where **CMC and commercialisation cost** are equal and pharma distributes in all three scenarios based on an acquisition, **prices for JFRDR-developed drugs can be reduced to 20% to 50%** compared with the VC model



Source: JFRDR

Agenda

- The Economics of Biopharma Innovation
- Emerging Models to Address Market Failure for Ultra-rare Diseases
- JFRDR - For Patients in Japan and Beyond
- **Why You Should Support JFRDR**



So who benefits from JFRDR? **Mainly Japanese stakeholders**, but also patients and their families outside Japan

Patients and their Families

Increased and faster access to therapeutics, in part delivering disease modification and/or cure

Founding Companies

Positive effect on reputation

Academia

Capability building, increased scope for publications and treatment for patients

Industry

De-risked product supply/local infrastructure, materials, equipment and capabilities in academia, hospitals and CROs, etc

Innovation Ecosystem

Capability building in academia and hospitals beyond iPSCs, CMC infrastructure for novel modalities, higher attractiveness for foreign researchers and investors, ultimately higher value added and tax base, lower biopharma imports & higher exports, lower drug prices

Patients and their Families worldwide

Increased number of products with patient access for ultrarare disease therapeutics

