The Case for JFRDR

The Japanese Foundation for Rare Disease Research

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20260215

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 three 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

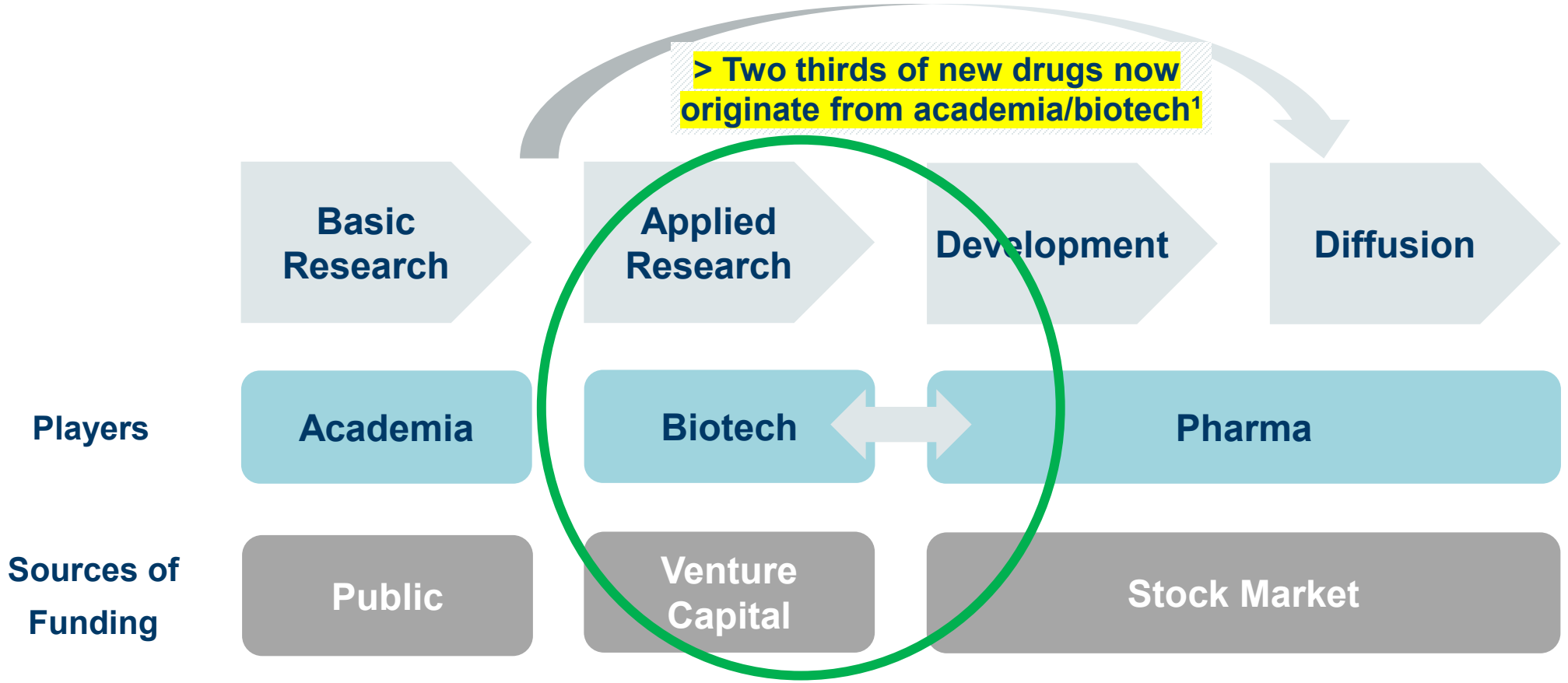
These three reasons translate into an **opportunity for Japan** to duplicate the success of GHIT in an **emerging global collaboration to address another market failure: Ultrarare disease drug loss**

3. 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 than available today

Agenda

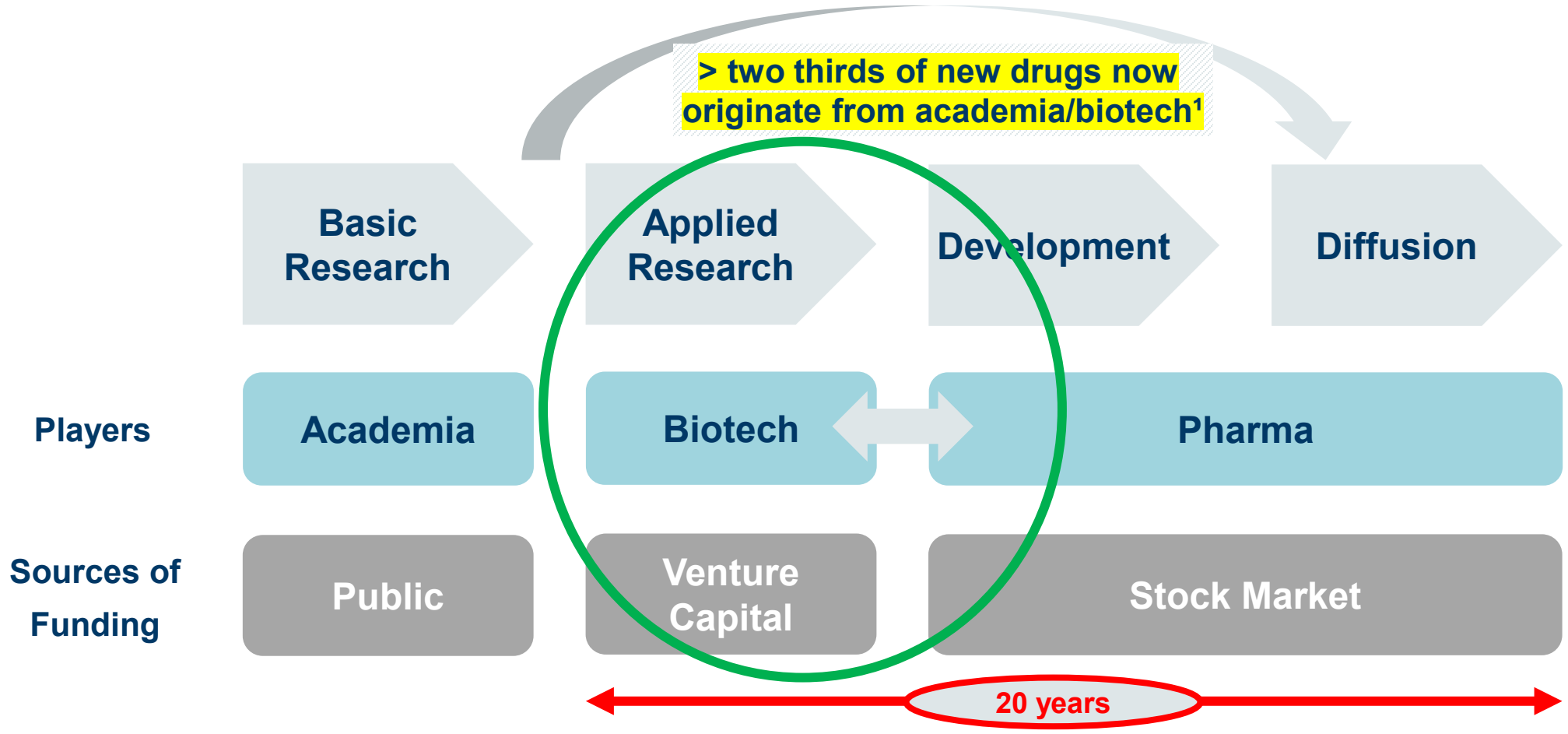
- **The Economics of Biopharma Innovation**
- Emerging Models to Address Market Failure for Ultra-rare Diseases
- JFRDR - For Patients in Japan and Beyond
- Why You Should Support JFRDR

Multiple 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** with a new division of labor between the various players



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

It takes approximately **20 years** from **translation** to **end of exclusivity** (for novel modalities significantly longer)

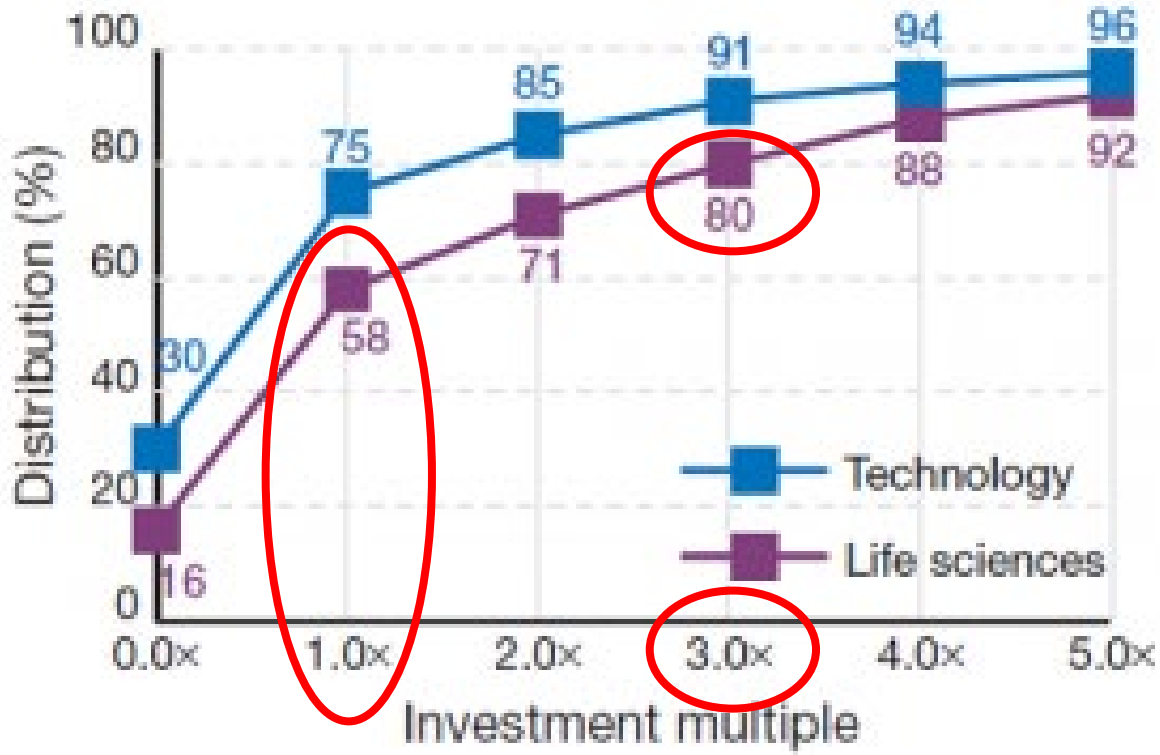


Source: 1) https://www.fiercebiotech.com/biotech/emerging-biopharma-companies-dominate-rd-pipeline-22-iqvia-finds

The **economics of market failure**
Expected and actual returns of VC funds in tech and the life sciences

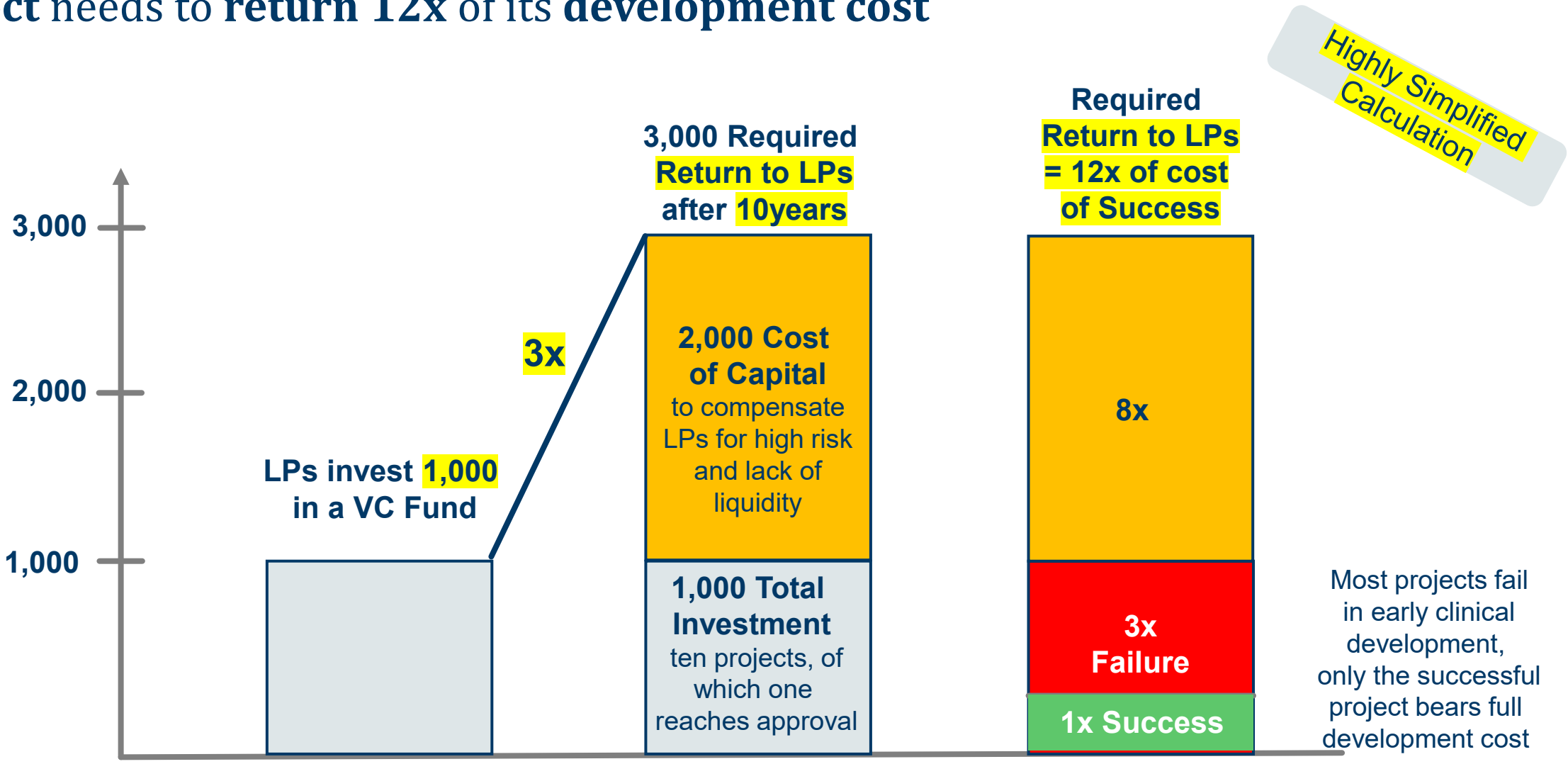
- As a Life Sciences investor, you stand a **58% chance** of losing part of your principal
- In combination with the **lack of liquidity,** this translates to average expectation of **investment multiples of 3x over ten years,** corresponding to a 13% compound interest pa – only **20% of funds** in the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

Actual Fund Returns



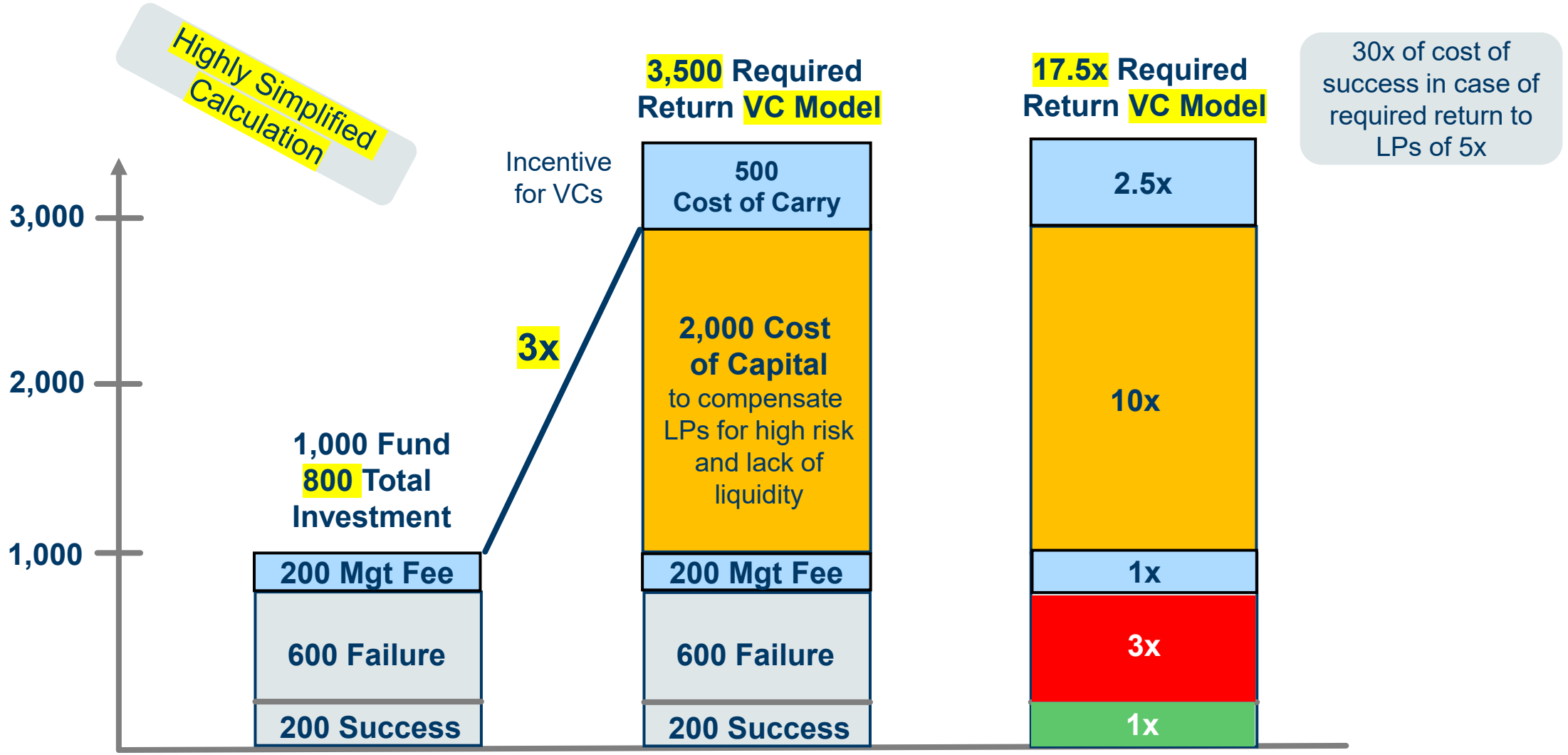
Source: Booth et al: https://lifescivc.com/2011/07/life-sciences-the-rodney-dangerfield-of-venture-capital;
A similar distribution of returns can be found in https://www.baybridgebio.com/blog/biotech-power-law

With a systems-wide expectation of **3x return** on invested capital, **one successful project** 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**



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**

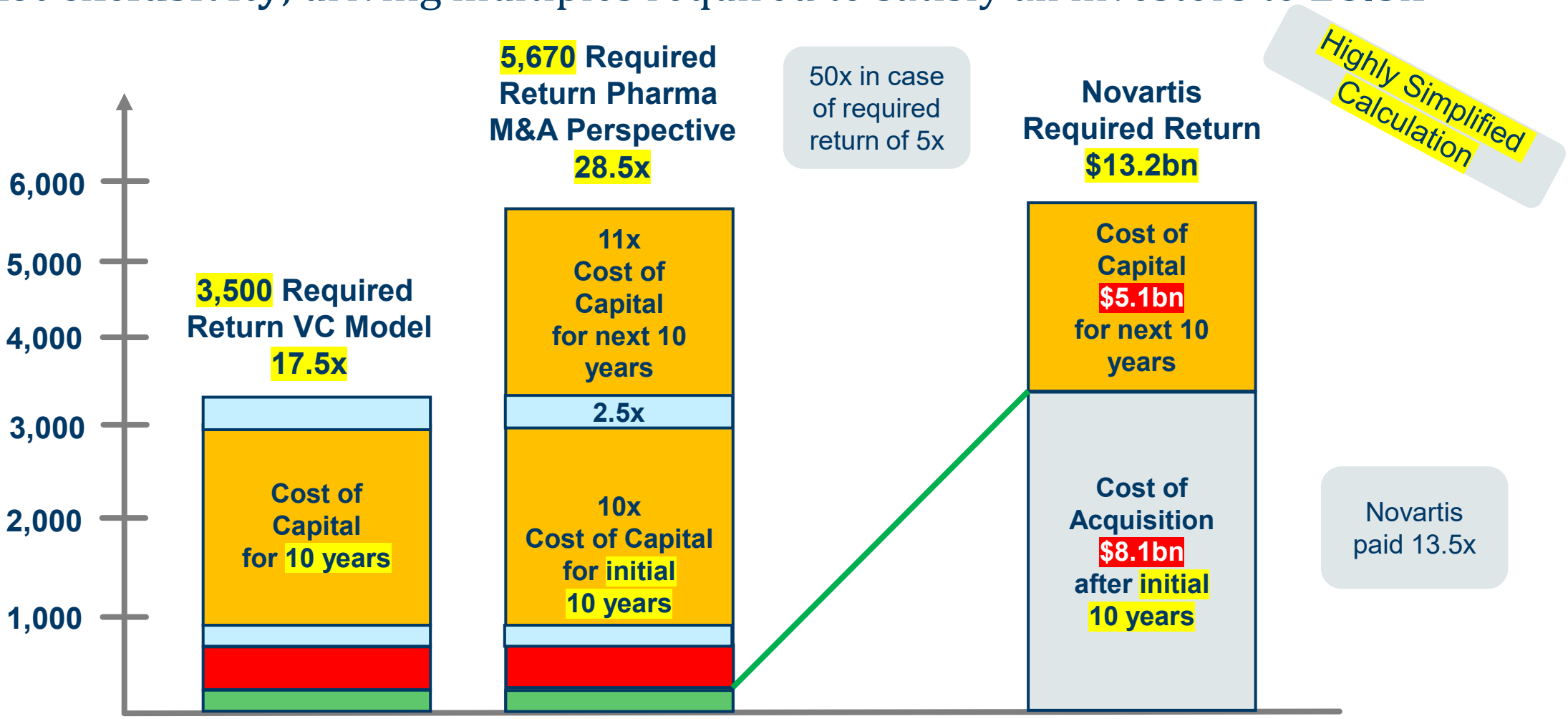
Sources: for Avexis - https://www.sec.gov/Archives/edgar/data/1652923/000155837018004054/avxs-20180331x10q.htm

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

But this is not the end of the story; once it has **acquired an approved drug, pharma** needs to recoup **its own cost of capital of 10% pa** for this transaction during **market exclusivity**, driving multiples required to satisfy all investors to **28.5x**



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

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 to recoup the cost of capital**

Total required return for Novartis $13.2bn

Price per patient in US $2.1mn

→ **Need 6,300 patients over ten years** (COGS comes on top)

→ **US incidence of SMA1 is less than 350** (two competing drugs)

→

- **To make a reasonable return, Novartis needs to find many more patients in other countries at lower prices**
- **Life cycle management has limited upside (intrathecal injection for kids >2y)**

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**

There are only a few rare diseases left that are **economically viable** in this model (cf next page)

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

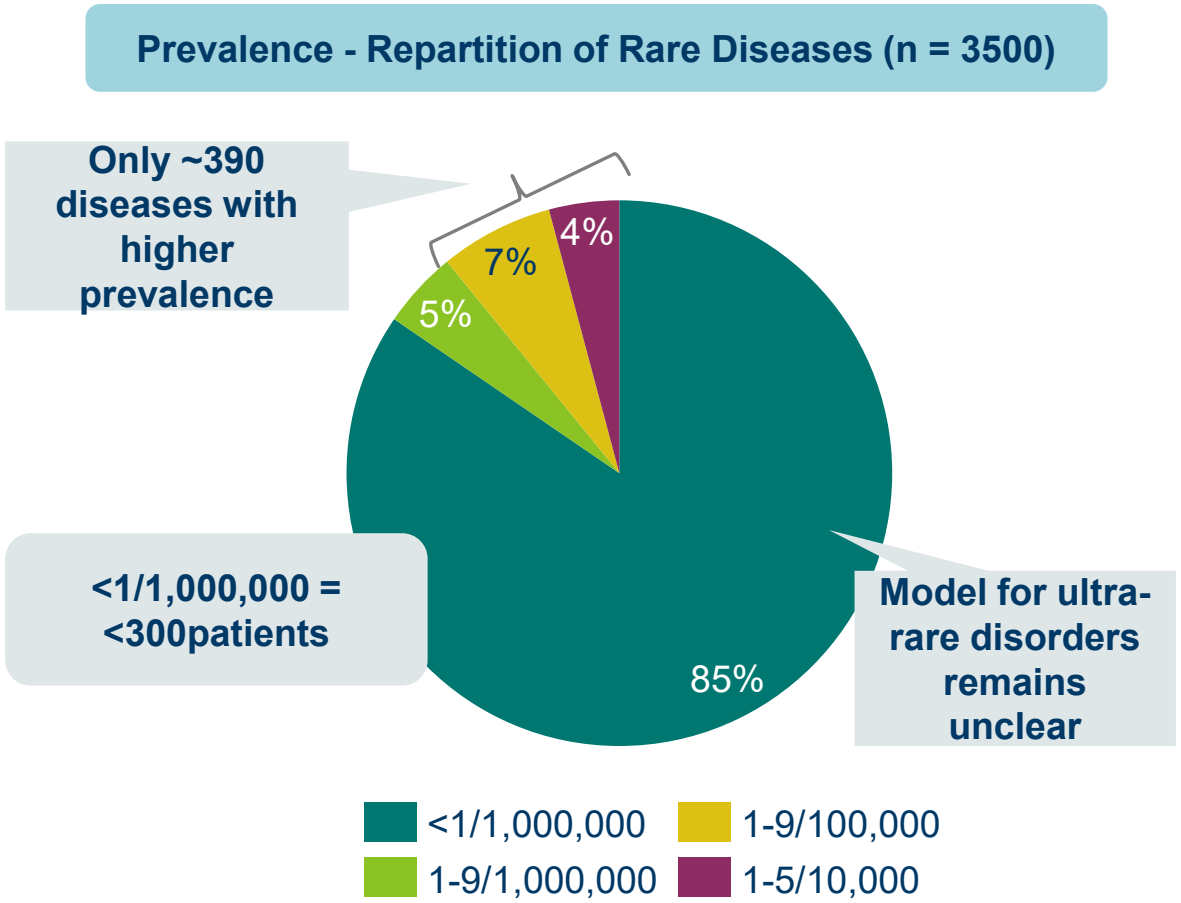
General Pharma

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

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



- Orphan Drug Act privileges and rising prices in the US (and in other markets) have facilitated the development of hundreds of rare disease drugs
- However, for thousands of **ultra-rare diseases**, **the current model does not seem to be viable**
- **FDA calls diseases/indications with US incidence <300 pa "economically infeasible"**

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

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- **Emerging Models to Address Market Failure for Ultra-rare Diseases**
- JFRDR - For Patients in Japan and Beyond
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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

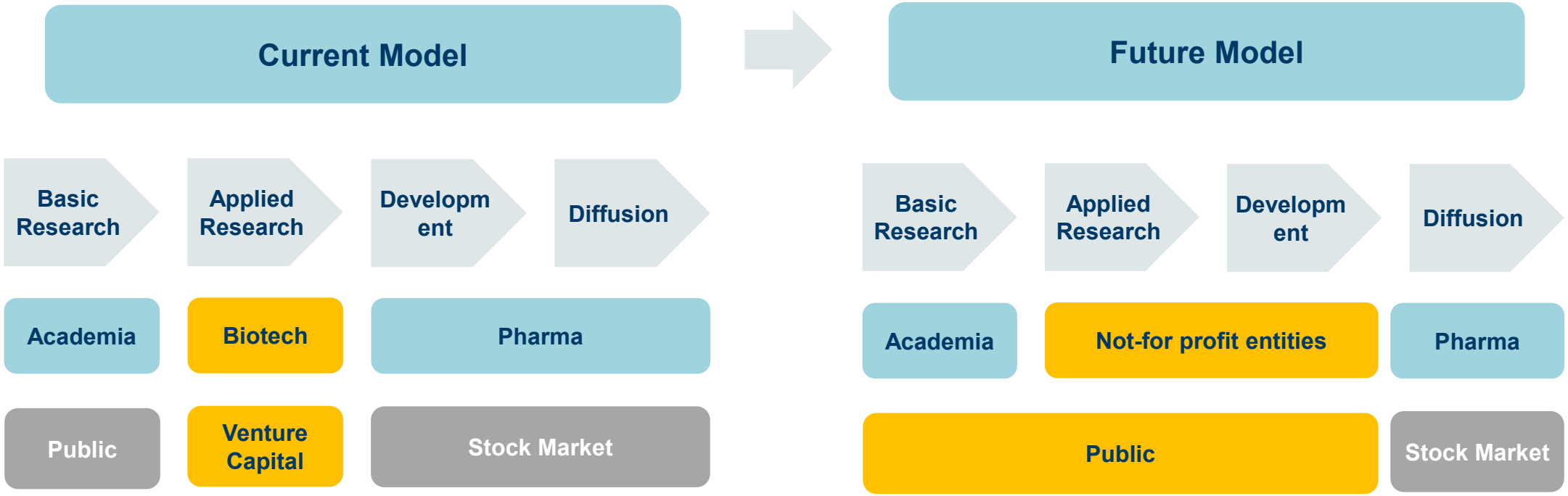
Many drugs not affordable for local healthcare systems

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

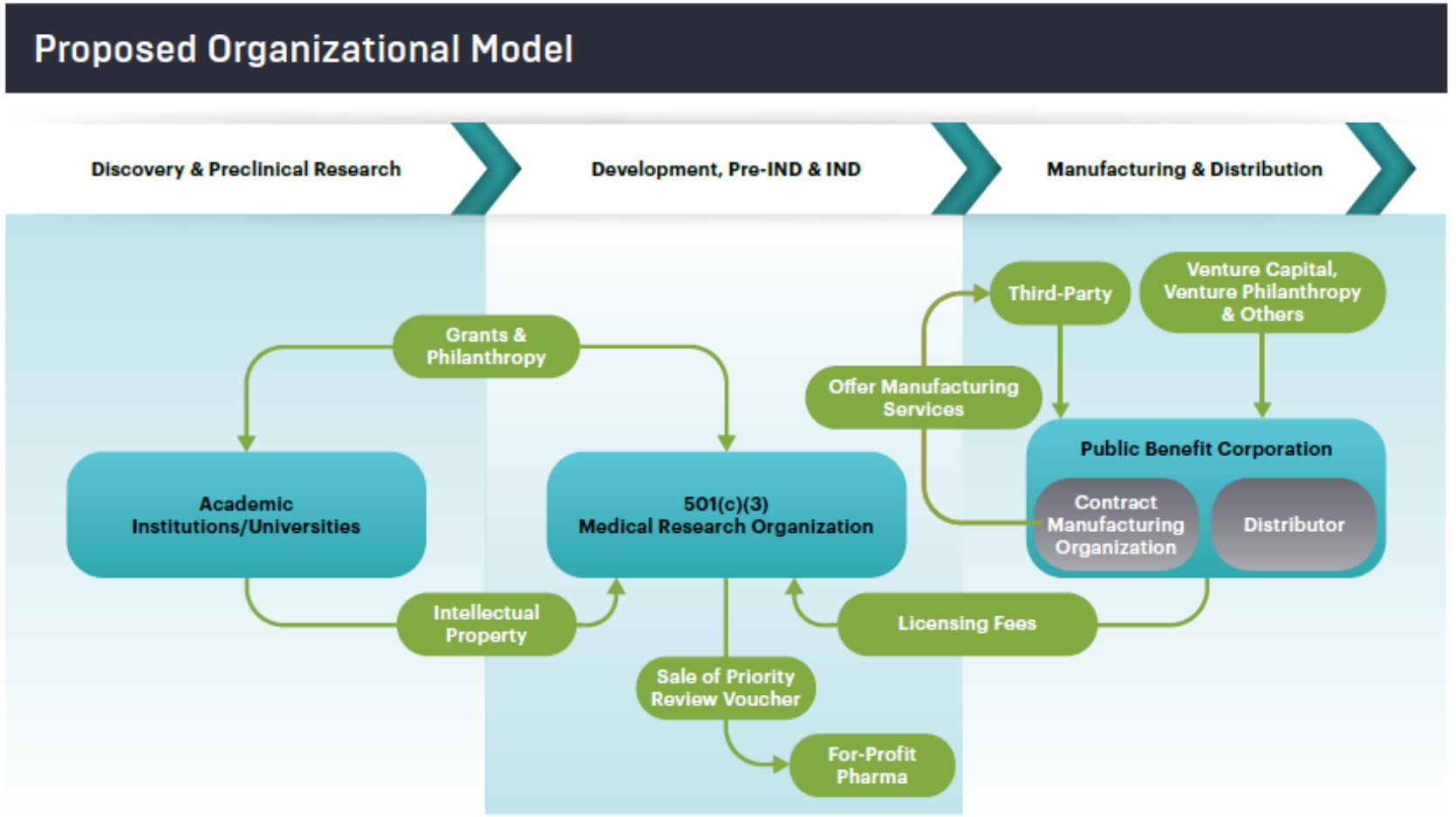
Future innovation for thousands of ultrarare diseases will require a **different "business model"** which operates **in parallel** with the current model



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**; "**ultrarare**" in this context can be defined as **incidence<300 in US** or **price per patient required in the commercial model >$500K**

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 Jenifer Doudna's Innovative Genomics Institute

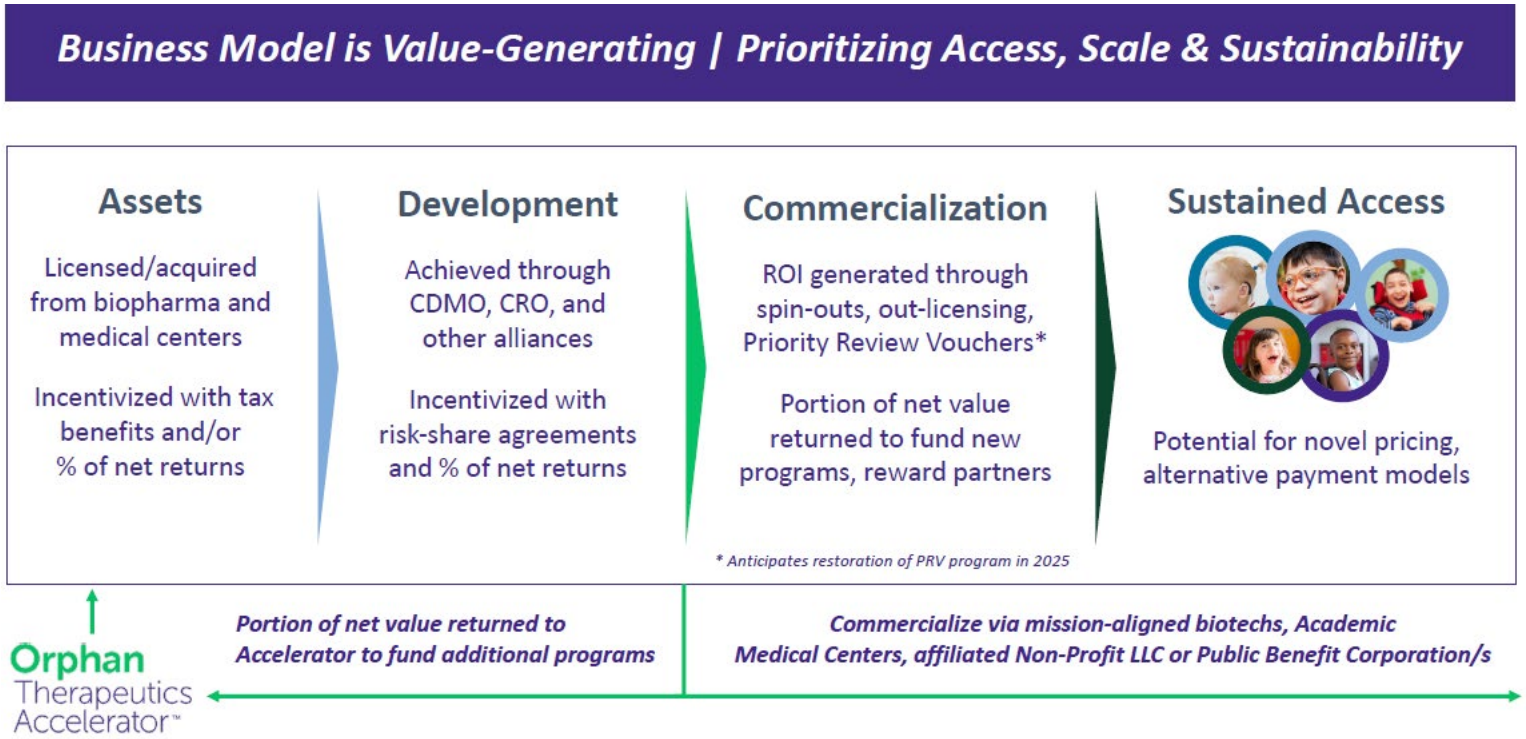


Source: Innovative Genomics Institute: https://innovativegenomics.org/making-genetic-therapies-affordable-and-accessible/

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



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

Gemma Bio

- 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

N-lorem Foundation

- Established 2019 by **ST Crooke**, founder of Ionis as a not-for-profit foundation
- **ASO platform**, focus on "**nano-rare diseases"** with <30 pts with same mutation worldwide
- Funding from **multiple corporate donors, NIH and various foundations**
- https://www.nlorem.org/our-approach/our-partners/
- Among multiple others, have entered into partnership with **Nitto Avecia**, "the world's largest oligonucleotide therapeutics manufacturer"
- https://www.nlorem.org/n-lorem-foundation-announces-partnership-with-nitto-avecia-to-strengthen-development-of-personalized-medicines-for-patients-with-ultra-rare-diseases/

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

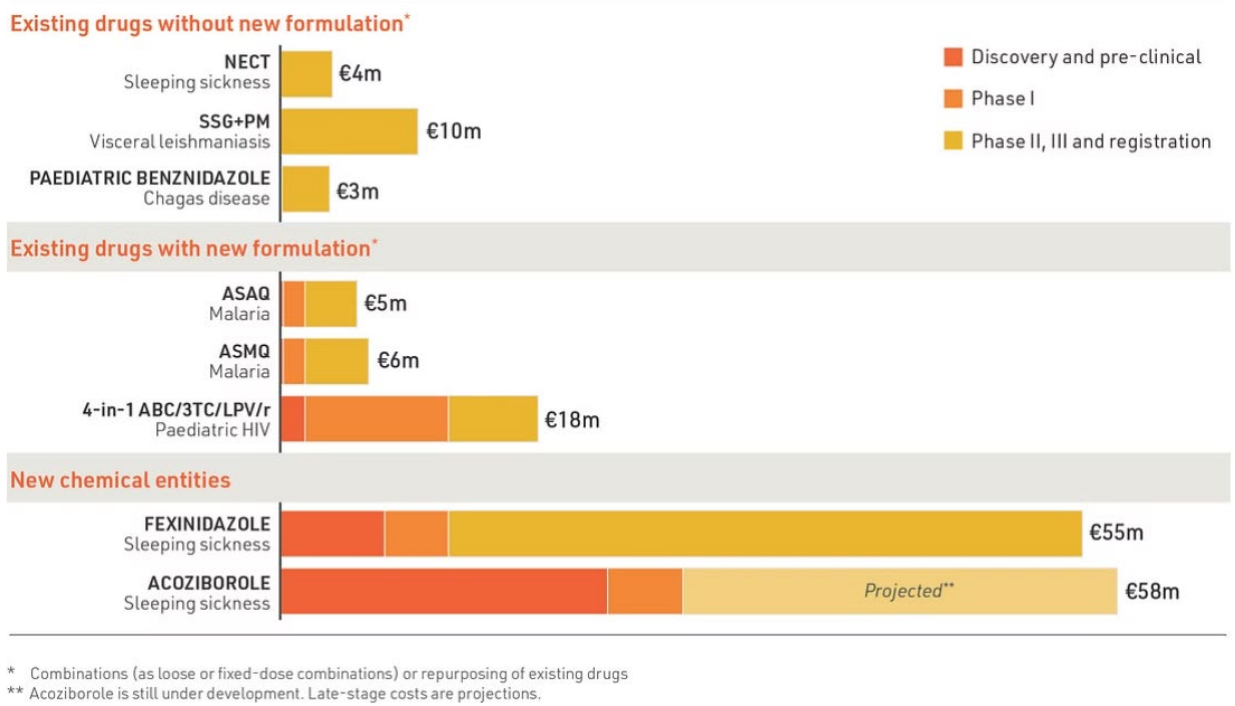
- Established **1958** and **1990** respectively
- Funded by donations from the public and based on extensive national TV campaigns involving celebrities and patients
- 2024 Telethon raised €96,553,593
- Initial focus on muscular dystrophy, now much broader
- https://www.genethon.com/who-are-we/our-history/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

Emerging models in action: "**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 a long the value chain
- https://dndi.org/about/who-we-are
- https://dndi.org/wp-content/uploads/2025/06/DNDi-FinancialReport-2024.pdf

DNDi R&D real life expenses at cost

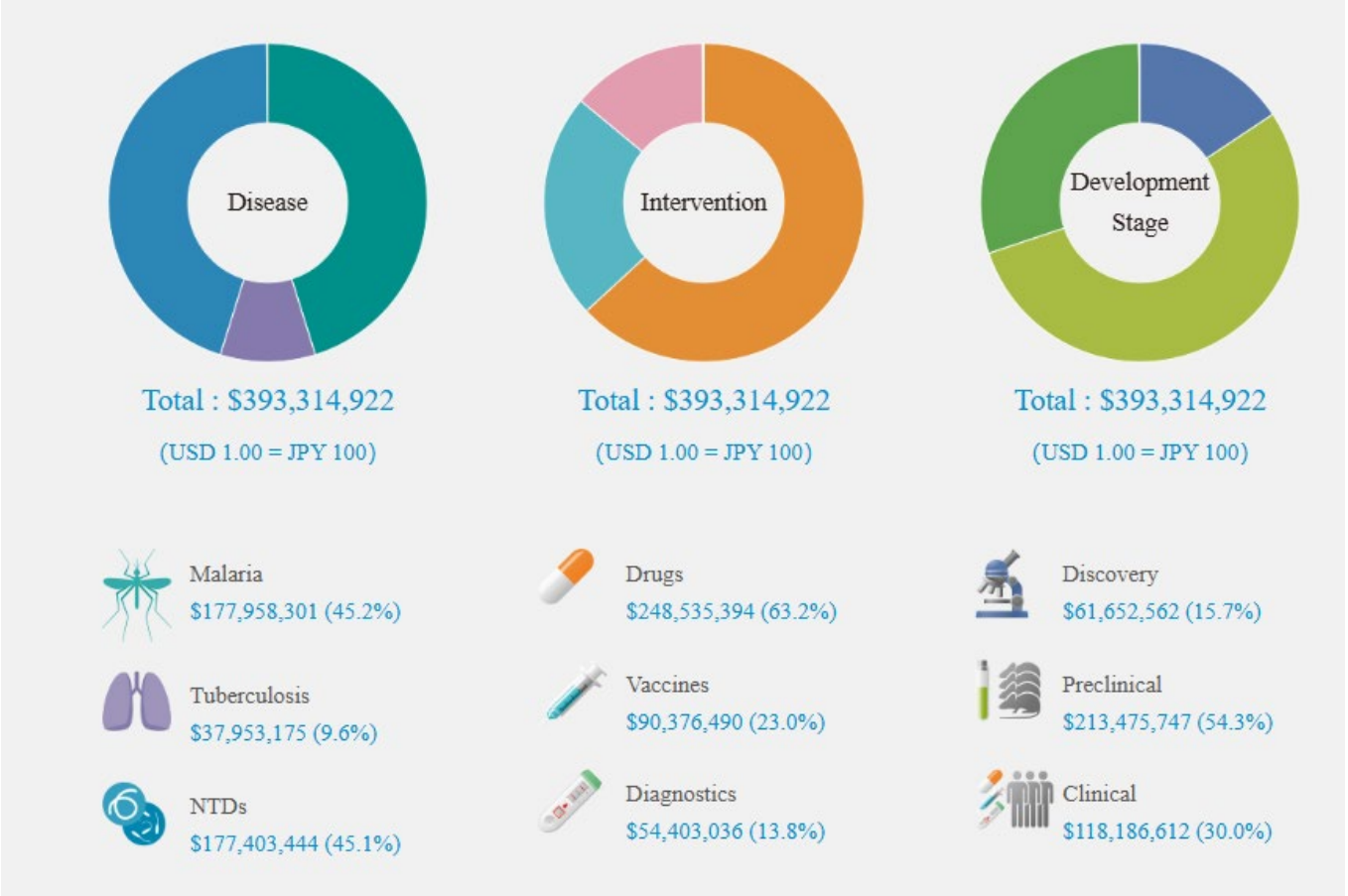


plus in-kind contributions by industrial partners

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



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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

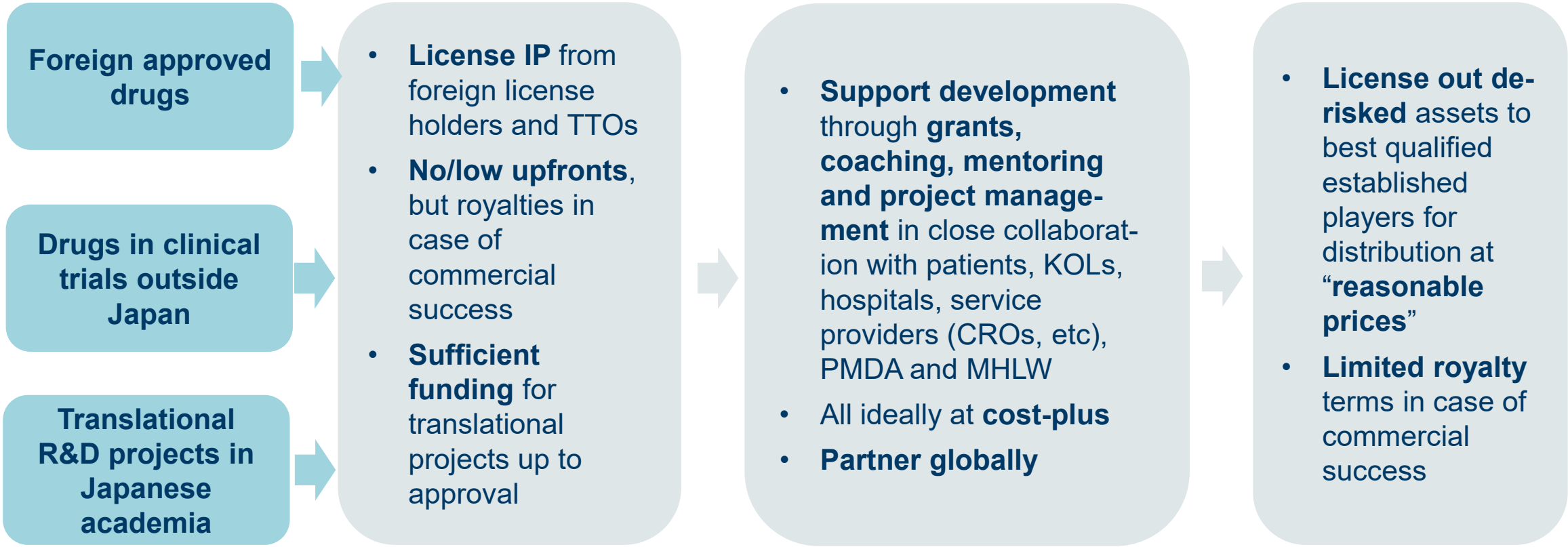
Translational projects in Japanese academia (AMED)

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

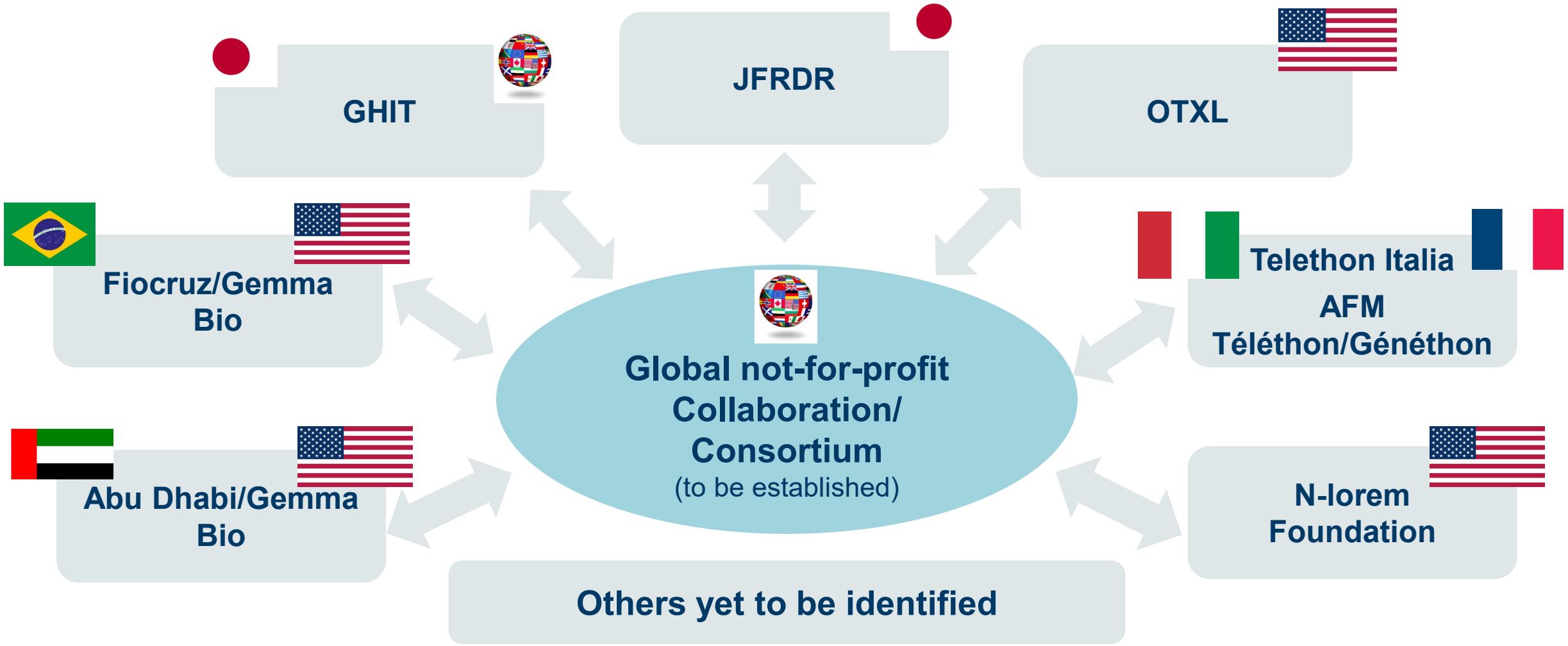
Importantly, these categories have **different risk profiles and timelines** to reach Japanese patients, which will have to be taken into account by **JFRDR** as it builds its **portfolio**

Current Drug Loss	Future Drug Loss
Well-known - 86 drugs approved by FDA and EMA by 2020 **Low risk** **Short timeline of 2-3 years**	Unknown # of drugs (active and stopped) in clinical trials without Japan involvement **Medium risk** **Timeline of 5-7 years**
Less known - estimated 100 rare disease drugs approved by FDA and EMA since 2020 **Low risk** **Short timeline of 2-3 years**	Translational projects in Japanese academia (AMED) **Highest risk** **Timeline of 10 – 15 years +**

The basic value proposition of JFRDR 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”



The Vision: JFRDR aims to be the **key Japanese player** in a **global collaboration** tackling **drug R&D** for **economically infeasible ultra-rare diseases** (1/2)



The Vision: JFRDR aims to be the **key Japanese player** in a **global consortium** tackling **drug R&D** for **commercially non-viable ultra-rare diseases** (2/2)

The Vision: A Global Not-for-Profit Consortium tackling ultra-rare diseases

- **Grant-funded translational research** for ultra-rare diseases, bringing together KOLs, patients and data from **different geographies**
- Aligned **prioritisation** and **avoidance of redundancies**
- Joint **registries**, **natural history studies**, **biomarker development** and **clinical studies**
- **In-kind support** from **biopharma** and **service providers**
- **Shared materials** and **services**: Oligos, vectors, LNPs, CDMOs, CROs…
- **Shared contractual models** for
  - Licensing rights in and out (TTOs, commercial license holders)
  - Cross-licensing
  - Paying materials and service providers and academic hospitals
- **Joint approaches** to **manufacturing** to reap (limited) economies of scale
- **Shared models** for ensuring **patient organisation & engagement,** as well as **patient access**

First step could be to clarify with PMDA whether inclusion of 3-5 Japanese patients in pivotal clinical trials initiated by ex-Japan organisations is required for conditional approval[1]

Source: 1) 000273721.pdf

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 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**

Setting up **JFRDR** as a **professionally-managed, not-for-profit catalyst** to help turn Japan into a global player in ultra-rare diseases, as part of a **future biopharmaceutical innovation strategy** for the country

Funding from Government as part of national biopharma innovation strategy

(bond financing?)

Donations from companies and the public

(tax exempt)

JFRDR
Public Interest Foundation
Requires sustainable funding over long-term

Create benefits for patients, academia, companies and the ecosystem as a whole

Licensing rights to and developing foreign-approved drugs in Japan via ISTs and including Japanese patients into global trials

Funding translational science in Japanese academia and international collaborations up to approval

Catalysing changes in the Japanese ecosystem including patient advocacy and PMDA regulations

Source: 1)https://www.nature.com/articles/d41586-025-01143-7

JFRDR - Current status and next steps

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
- **Experienced CEO has been hired: Hiroshi Kowaki** (ex-Alnylam, Amylyx et al)
- Continued activities to ask **for feedback and support** from relevant players in industry, academia, government and patient advocates
- Preparing active **fund-raising**

Targeted start of operations second half of 2026
Funding requirements are currently being reviewed and Fund-raising is being prepared

There are basically two ways to approach the funding of JFRDR

Approach 1
JFRDR generates no profit and is fully financed by government

- Approach followed by **California for CIRM**
- Government pays for the full cost of JFRDR throughout its lifetime (Basic Science model)
- 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%** of what is required in the VC model – **best accessibility**

Approach 2
JFRDR is expected to become financially sustainable over time

- Government would 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**

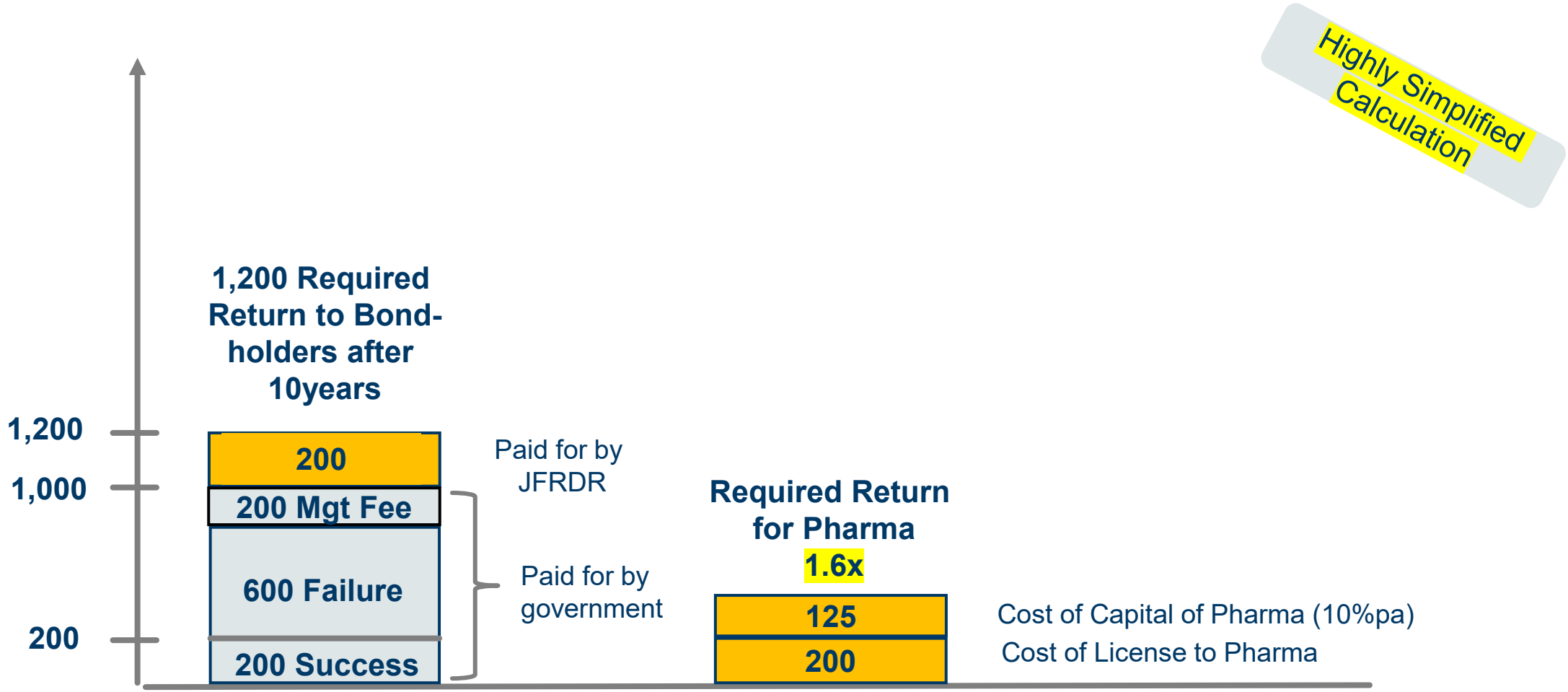
Source: For the calculation of price levels, cf pages 35 - 37

Deciding which approach is best will require a **political choice** based on a trade-off between **budget impact** on the one hand and **price levels & patient access** on the other

- In **Approach 1**, funding could come out of the **budget** or from **dedicated ten-year bond sales**; JFRDR would pay for the annual yield (currently slightly over 2%) but **government will** have to **pay back the principal**
- Following the California model for CIRM (the California Institute of Regenerative Medicine) which was initially funded for $300mn pa for ten years by the California State government, the payback could be stretched over a longer period of time (35 years for CIRM) in order to minimise annual budget impact
- **Approach 2** corresponds to the long-established **FILP-logic**, where **government-backed bond** proceeds are used to make **long-term loans** to facilitate **investments not feasible for the private sector** due to **high risk** and **long timelines**, but which are deemed to be able to **generate a profit** in the future; the recipient pays bond yields and returns the principal after a stipulated period, often decades into the future
- In the case of JFRDR, given the long **timelines required to build up a portfolio of revenue-generating projects**, full pay-back of cost incurred from the beginning will likely take 20+ years; **covering current outlays might be achieved after ten to fifteen years**

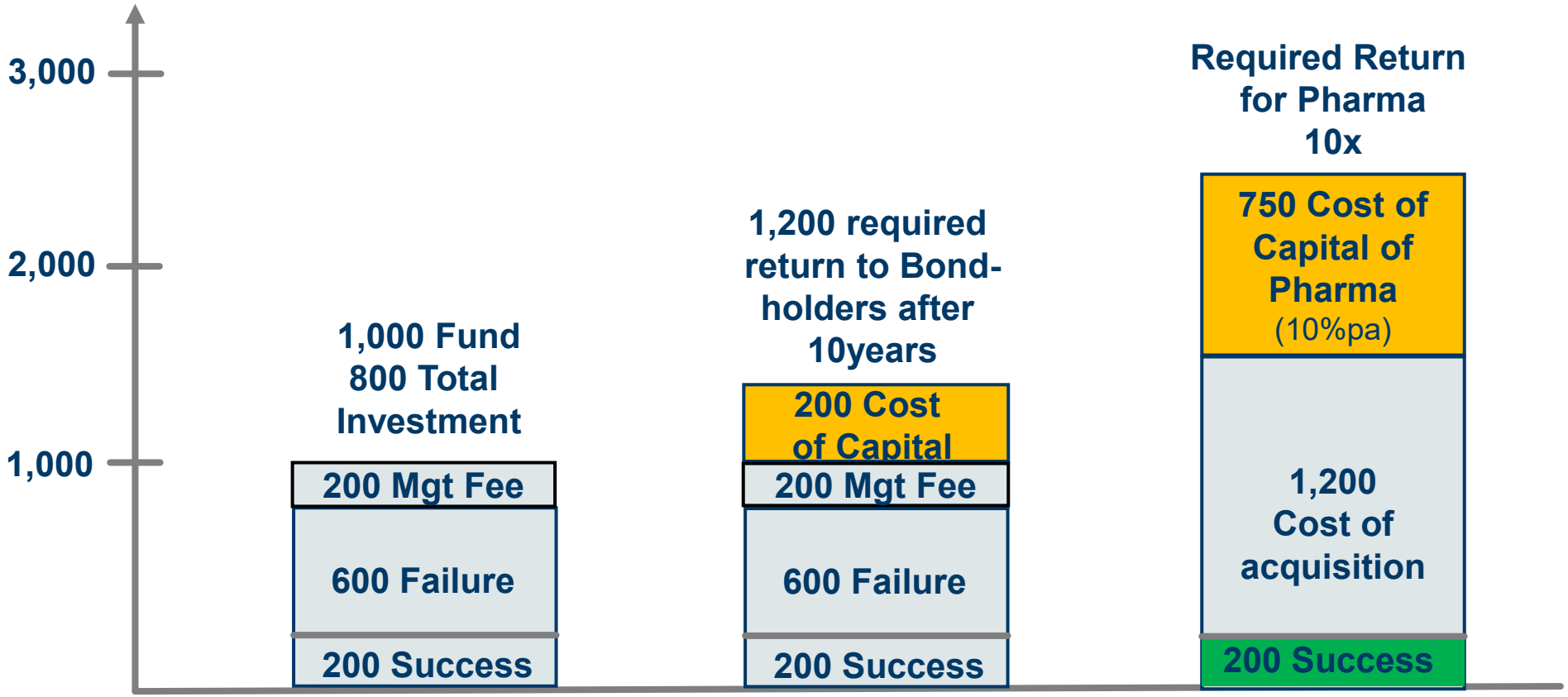
Sources: http://dx.doi.org/10.5966/ sctm.2011-0049; National Academies: The California Institute for Regenerative Medicine: Science, Governance, and the Pursuit of Cures, 2013

Approach 1: Assuming JFRDR pays bond yield but the **principal is funded by government**, JFRDR could license the successful drug for 200 to pharma which would then need to generate sales of 325 over ten years to cover its cost of capital



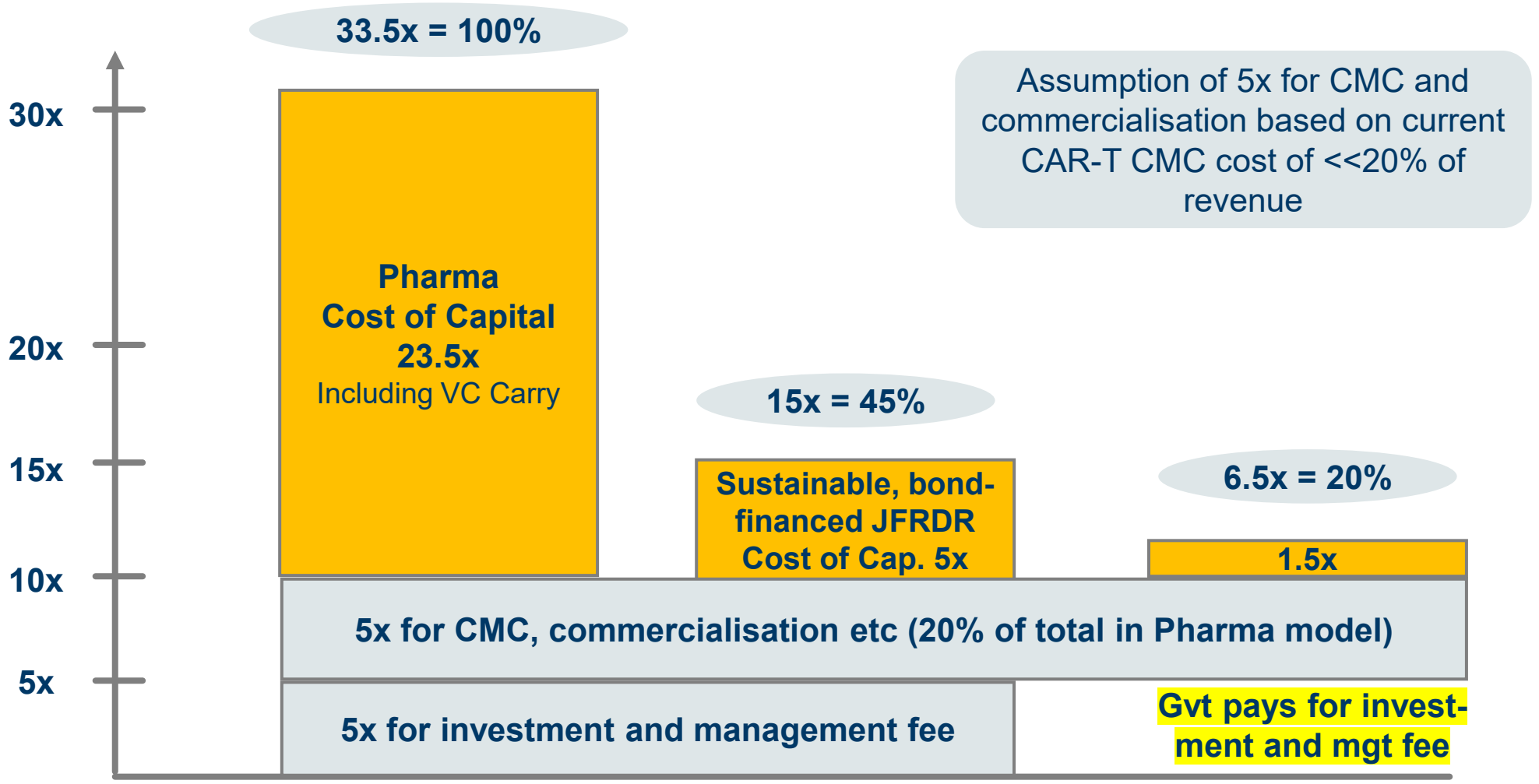
Approach 2: In a **self-sustaining model**, there will be a management fee but no carry for management; if the drug is then licensed to Pharma for 1,200, bond **prinicipal can be paid back including the bond yield**

Highly Simplified Calculation



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

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



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

Academia
Capability building, increased scope for publications and treatment for patients

Founding Companies
Positive effect on reputation

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