JFRDR - Tackling the Ultrarare Disease Drug Loss

The Case for Supporting The Japanese Foundation for Rare Disease Research

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A. Executive Summary

Drug development since the 1980's has been largely driven by **VC-funded biotechs** developing and then licensing drugs to established pharmaceutical companies for distribution; this model was and still is based on **expensive high-risk capital** provided by pension funds, life insurers and others. While successful in terms of providing **innovation**, the model has led to a rapid **increase in prices in the US**, with launch prices doubling every four years since the early 2000's. As a consequence, price levels in the US are now three times higher than in Japan.

This model is reaching its **limits,** in particular for the **9,500 or so ultrarare diseases** with an incidence of less than 300 patients in the US, as the high cost of capital now requires **price tags of several millions of US$ per patient** for investors to continue to provide funding. Consequently, innovation in the field of science and technology must be complemented by **new models of organising and financing innovation.** Novel non-profit business models for ultrarare disease therapeutics are beginning to emerge in the US, Europe and elsewhere, but so far **not in Japan**, where the "**drug loss**" has become a significant political problem.

The **Japanese Foundation for Rare Disease Research** (JFRDR) is being set up as a non-profit to tackle **current and future drug loss**. It aims to make use of low-cost capital in the form of government-backed grants and thus **provide drugs** which would otherwise not be available to Japanese patients at a cost that ensures the Japanese Social Security systems remains **financially sustainable**.

JFRDR aims to be a **key change agent** in the **Japanese biopharma ecosystem**, by aiming to vitalise and professionalise Japanese patient organisations, educating the public as to the realities of living with rare diseases and contributing through the projects it supports to building critical translational and CMC infrastructure that can also be leveraged by commercial biopharma. In addition to working for Japanese patients, JFRDR strives to become a **key player** in the **emerging global collaboration** between **similar non-profit ventures** along the **R&D value chain**; the ultimate goal will be not only to develop drugs for ultrarare diseases but to make them **available** to **patients all over the world**, wherever they may live.

The organisation has been **incorporated** as of late December 2025 and has **selected a CEO** to build a small team and commence operations once the **seed funding** provided by **Recordati SpA** has been complemented by a substantive government-backed grant for the first **five years.**

B. Biopharma Innovation in the 20th Century

In the US, the post-WW II consensus on funding biomedical research was based on Vannevar Bush's report on „**Science – the Endless Frontier**", where **public science funding** would ultimately lead to **social benefit**. In a highly simplified view of the division of tasks, publicly-funded Academia focused on Basic Research and for-profit Pharma, mostly divisions of large chemical conglomerates, took care of translation, development and commercialization.

After leading to a plethora of therapeutic innovations at comparatively low prices for three decades, by the end of the 1970's there was a sense that despite the emergence of recombinant proteins and hybridization technology to generate antibodies, the **massive investment** in basic research by the federal government did **not yield a commensurate return** in terms of novel therapeutics for patients.

As a result, **multiple policy changes around 1980** aimed at removing some of the key barriers to innovation and drove the emergence of the current US Biomedical Innovation System with the new model of **VC-funded biotech** and **focused BigPharma**. Of crucial importance, broad **deregulation of the financial system** in the US, including a drastic reduction in capital gains tax incentivised a constant flow of capital from pension funds, life insurers and other large fund holders into **high-risk VC-funded biotech companies**, which in recent years have generated **around two thirds of new drug launches** via licensing and M&A deals by BigPharma.

Together with the US, **Europe** and to a lesser extent **Japan had co-led the first wave** of biopharmaceutical innovation in the post-WWII period, but they failed (for good reason) to deregulate their financial systems sufficiently to remain competitive in the field of commercial translation; their **venture capital & start-up ecosystems never became competitive** and, despite an excellent basis in basic research, technology and clinical care, as well as multiple national strategies and initiatives, they have been falling far behind the US ever since.

Of note, **orphan drugs** have been a key growth driver of the biopharma industry since the late 1990's; enabled by the 1983 Orphan Drug Act in the US and followed in subsequent years by similar legislation in Europe and Japan, the share of orphan drugs in biopharma approvals reached over 50% and sales grew from single digits to around **20%** of total biopharma sales in the **early 2020s**. This success was possible due to a combination of various factors, among them lower than average attrition, lower clinical development and commercialization cost, extended exclusivity and **attractive pricing & reimbursement conditions**.

C. Why the Model is Reaching its Limits

Launch prices of new drugs approved by FDA have increased by an average of **20% per year** since the early 2000's, thus doubling every four years and leading to two well-known effects: **Restricted access** and **personal bankruptcy** for American patients and an **increasing gap** between net prices in the US compared to Europe and Japan; a recent RAND study shows this gap to amount to a **factor of three** when comparing prices in Japan, England, Spain and Italy on the one hand and the US on the other.

This has led to unsustainable political tension with the Trump administration proclaiming a Most Favoured Nation approach to pharma pricing and recently singling out England, forcing the country to significantly increase launch prices and reduce statutory rebates. Who will be next?

There are a number of factors contributing to this exorbitant rise in launch prices, among them constant failure rates in R&D, increased regulatory requirements and rising manufacturing cost, due to the advent of new modalities (e.g.: Cell and gene therapies, oligonucleotides and novel biologics) with complex and expensive manufacturing processes.

However, the **key cost driver** far outstripping all these factors is the **cost of capital** employed by **biotechs** in the crucial mid-stage translational development phase of novel therapeutics: When the resources invested by Limited Partners (LPs) in Venture Capital (VC) funds are **illiquid for ten years** or longer and have a **50% chance of not being fully repaid**, these LPs will need to see a substantial return on the few projects that make it to market; insiders consider a **return of 3x over ten years on financial resources employed** in biotech as acceptable, which leads to immense pricing pressure on the few successful drug candidates; rough calculations show a required return of 20x of cash outlays for each successful project for VC funds and 30x for a drug in-licensed or acquired after approval by Big Pharma.

So why is the model reaching its limits? The **economic facts** sketched above are hitting **rare disease drugs** especially **hard**, as there are relatively **few patients to recover the cost of capital** spent on their development.

Out of an estimated 10,000 rare diseases, only **5%** do have sufficient patient numbers in the US to be **economically feasible** and for most of these, drugs are now available; the remaining 95% show **incidence below 300 in the US**, requiring launch prices of **several million US$ per patient**. And with such price tags, even in the permissive US market, insurance companies overwhelmingly refuse reimbursement and/or patients cannot pay the required co-payments for these "ultrarare disease" therapeutics.

D. Ultrarare Disease Therapeutics - Challenges and Solutions

A visible consequence of this state if affairs is that it is increasingly becoming apparent that the world does not have a business model to leverage the rapid progress in science and technology to develop ultrarare disease drugs and make them available to patients.

In **Japan**, the "**drug loss**" consists mostly of such drugs and despite years of debate, no viable solution has been found to date. In the **US**, the drug loss takes a different shape as investors have begun to recognise the problem: **Since 2023**, more than a **hundred gene therapy drug candidates** targeting ultrarare diseases have been **shelved in clinical development** for commercial reasons and some have been withdrawn from the market; Reimbursement authorities in Europe and emerging markets refuse to grant prices required for the economics of the VC-funded biotech model to work.

The development of ultrarare disease therapeutics presents a set of **specific challenges** which are all ultimately due to **small, often heterogeneous patient populations**

- At the **R&D** stage, **natural history studies** are required to provide comparators for single-armed pivotal studies; in addition, novel biomarkers and diagnostic approaches must be developed;
- **CMC cost** is relatively high as there will be only **limited economies of scale** with current manufacturing approaches;
- **Regulatory requirements** designed for large patient populations come with significant hurdles in terms of cost and time - FDA have long recognised this and granted multiple alleviations, most recently announcing a new "Plausible Mechanism" pathway for gene editing;
- **Patient access** becomes close to impossible when prices amount to **millions of US$.**

Among the first to recognise the emerging problems were some of the scientists behind recent breakthroughs in gene and oligonucleotide therapies, among them Jim Wilson, Stanley Crooke and Jennifer Doudna.

In a recent report from Jennifer Doudna's **Innovative Genomics Institute** entitled "**Making Genetic Therapies Affordable and Accessible**", it is proposed to develop a **mixed organizational model** comprising

- An **academic institution** raising **grants** to finance Research;
- A **nonprofit medical research organization** raising capital at low cost;
- A **public benefit corporation** to distribute drugs at cost - plus a charge to ensure financial sustainability.

Around the world, a number of organisations are emerging which experiment with parts or all of these proposals, among them

- **Telethon Italia**, set up in the 1990's as a non-profit research foundation funded by donations form the Italian public; after years of ultimately failed collaborations with pharma, Telethon Italia have brought three ultrarare therapies to market and hold a Market authorisation for Strimvelis (ADA-SCID) in Europe and for Waskyra (Wiskott-Aldrych syndrome) in the US;
- The **Orphan Therapeutics Accelerator (OTXL)** is a not-for profit initially focusing on therapies stuck in clinical development in the US and adopting a model of developing these drugs at cost-plus;
- **N-lorem** in the US and **Sheba Hospital** in Israel are developing antisense oligonucleotids for nano-rare diseases, sometimes with just one patient, again in a non-profit approach;
- CAR-Ts have been developed in academic settings in **Spain** (Barcelona) and **Brazil** (Sao Paulo) and elsewhere to make these therapies accessible to local patient populations at significantly lower cost (approx. 20%) compared to commercial products
- **Qatar, Abu Dhabi** and **Saudi Arabia** are pouring huge financial resources into R&D for ultrarare diseases, based in part on the fact that for cultural reasons, there is a relatively high number of rare disease patients on the Arabian peninsula
- A number of emerging economies are investing in manufacturing capabilities for ultrarare disease therapies, in the case of **Brazil** in CAR-Ts, oligo-nucleotids and AAV-gene therapies.

The one unresolved issue remains **financial sustainability** of these organisations; it is tempting for them to out-license approved drugs to established companies for distribution, letting the highest bidder win and set prices at whatever level they feel is justified; the proceeds (royalties) of such licensing agreements can then be **reinvested in the R&D activities** of the non-profit organisation and its service providers, following the model of the Cystic Fibrosis foundation and its monetization of royalties due by Vertex. The obvious **drawback** of this approach is **reduced patient access**.

Encouragingly, **Telethon Italia** and **OTXL** have recently entered into a distribution agreement whereby Telethon's Waskyra will be commercialised by **Orphan Therapies**, a non-profit commercialisation subsidiary of **OTXL**; it will be interesting to see what launch price they settle on, but this collaboration is indeed encouraging because it addresses one of the specific challenges of R&D, manufacturing and distribution of ultrarare disease drugs; ultimately, success will require **scale** through **global collaboration** among the dedicated non-profit entities and academic hospitals, CROs, CMOs and other service providers.

E. JFRDR - For Patients in Japan and Beyond

Among the developed nations, **Japan sits in the worst spot of all** -it has by far the largest drug loss among developed nations in terms of drugs approved elsewhere not being available to Japanese patients; it lacks the **financial infrastructure** driving the development of drugs based on novel modalities via VC-funding and as a consequence, it is relatively weak in terms of the **translational and CMC capabilities and infrastructure** required for ultrarare disease R&D. In addition, **funding** for basic research and even more so for translational research in Japanese academia remains woefully **inadequate** to support early-stage drug development, despite recent initiatives driven by AMED and the Ministry of the Economy.

The **Japanese Foundation for Rare Disease Research (JFRDR)** is being set up as a **professionally-managed, not-for profit organisation** to remedy these issues; its primary goal is to **resolve current and future drug loss** by adopting three approaches:

- Obtaining the Japanese rights to drugs approved in the US but of **no interest to commercial players**, develop them at cost-plus in academic hospitals with the support of local CROs, CMOs and other service providers and out-license the commercial rights to established entities in the Japanese market for distribution at “reasonable prices”;
- Including a handful of **Japanese patients** in **global pivotal trials** to facilitate PMDA approval and thus avoid future drug loss;
- Supporting **selected translational projects** in Japanese academia **financially** and with **coaching and mentoring** by pharmaceutical experts to bring them to PoC and/or approval, thus readying them for licensing to commercial entities.

The key to JFRDR’s approach is to raise funds backed by government guarantees and operate on the basis of **grants with very low cost of capital**, thus enabling the development of and access to drugs which would otherwise remain unavailable in a commercial model; JFRDR thus will operate in a mode which is **complementary to that of commercial entities**, i.e. it will only spring into action on high-quality projects and drugs which are commercially infeasible.

For the first five years, JFRDR’s **strategy** is to focus on projects with relatively low-risk and short timelines: **Drug loss projects** and **projects currently in clinical development outside Japan**; rough calculations show that with a five year budget of **$60mn, five to six approvals** are a realistic goal for this period. Once the organisation has been established and has **proven its worth**, JFRDR aims to continue working on drug loss and ex-Japan clinical trial projects.

In addition it plans to extend the scope of its activities to higher risk projects with longer timelines, i.e. **translational and clinical projects in Japanese academia** which do not receive sufficient funding from other sources (mainly AMED, VC's and pharmaceutical companies); the budget requirement for years 6-10 will be significantly higher and JFRDR aims to deliver an additional 15 PMDA approvals from a maturing project portfolio until year 10.

To put this into perspective, the California Institute of Regenerative Medicine, a public funding agency funded by the California State government announced in January 2026 that they would set aside **$100mn** to support **rare disease R&D** with a focus on **gene therapies** for the **next two years.**

JFRDR will work hard to convince the **Japanese public** and Japanese corporations – Pharma, Medtech and others – to significantly contribute to funding in later years. Note that the research charity Telethon Italia raised $60mn from the public in 2024 and with its French sister organisation Généthon raising $90mn in the same year.

F. Why You Should Support JFRDR

There are many reasons to support **JFRDR and its mission to deliver therapies to ultrarare disease patients**; they partially overlap seen from the perspective of the government, pharmaceutical companies and the public.

From the **government's point of view**

- JFRDR will help solve the **current and future drug loss** challenge which is getting bigger as time progresses; not only will otherwise unavailable drugs become accessible to **Japanese patients**, but they will cost only a **fraction of what the cost** would have been had they been commercially developed;
- JFRDR thus aims to contribute to the **sustainability** of the Japanese Social Security system (and Social Contract) rather than aiming to generate profits from commercialising product licenses such that it becomes financially sustainable itself;
- To operate efficiently, JFRDR strives to become a **key player** in the **emerging global collaboration** between **similar non-profit ventures** along the **R&D value chain**; the ultimate goal will be not only to develop drugs for ultrarare diseases but to make them **available** to **patients all over the world**, wherever they may live;
- This goal ties in nicely with **Japan's significant contribution** to developing drugs for patients with neglected/tropical diseases in emerging economies, driven by **GHIT;**
- An **accessory benefit** of JFRDR's planned activities is of importance both to **the commercial biopharmaceutical sector** in the country and to **National Security**; R&D in the field of rare diseases has historically been a key driver for **de-risking & validating** novel technology platforms; as mentioned above, Japan's translational and CMC infrastructure and capabilities are far from competitive, in particular in the emerging fields of **gene therapies** and **oligo's** including antisense oligo-nucleotids and various RNA and cell therapy modalities (with the possible exception of iPSCs). Today, a country like Brazil is in a better position to face geopolitical headwinds and produce advanced therapies for its population if needed than Japan, this needs to change.
- Finally, another attractive feature of JFRDR is that it channels a **productive, non-inflationary investment** in **long-term industrial growth**, whether financed by the issuing of bonds or a loan by the Japan Development Bank that will ultimately be written off by the Central Bank. It thus should be viewed as one of the constituent pillars of **Japan's future biomedical innovation strategy**.

A number of **Japanese pharmaceutical companies** have stakes in the rare disease field, among them Kyowa Kirin, Kissei, Nippon Shinyaku, Otsuka, Astellas, Eisai, Kaken, Shionogi, Sumitomo Pharma and others, as well as some specialised players, among them JCR, Nobelpharma and Orphan Pacific; JFRDR will have to rely on their support in terms of mentoring and coaching translational projects it funds.

In return,

- JFRDR will act as an **additional source of approved products** to license for the Japanese market – and beyond - at relatively **low cost**;
- They will benefit for their commercial activities from the development of **translational and CMC infrastructure** to support projects funded by JFRDR.

And last but not least: The **public**!

- A common trope holds that the Japanese public doesn't care about its neighbors and hence, is **fundamentally averse to donating** for public causes; hence, families with incapacitated children tend to hide them;
- The founders of JFRDR hold that this may be partially true but that the **underlying attitudes can and must be changed** by a multi-year **professional public relations** campaign; what can be learned from organisations like Telethon Italia and Généthon is that a combination of **scientific education** ("genetics is not the parents' fault, it can strike anybody"), mobilisation of **celebrities** on television and in social media, as well as the **voice of patients and their families** can make a huge difference in terms of eliciting **compassion** and enhancing the willingness to provide support; generous support from the public and from corporations after the 2011 earthquake show what is possible in Japan if peoples' hearts are touched;
- Finally, such a campaign also requires a long-term effort to "catch up" with the US and Europe in terms of **creating and professionalising patient support groups**, who make their voices heard by the public and engage in **dialogue** with **academics, regulators and companies** to adapt regulations, approaches to translational research, as well as trial designs originally developed for large indications to the specific realities of ultrarare diseases.