

Challenges and facilitators in the development of orphan and paediatric medicines

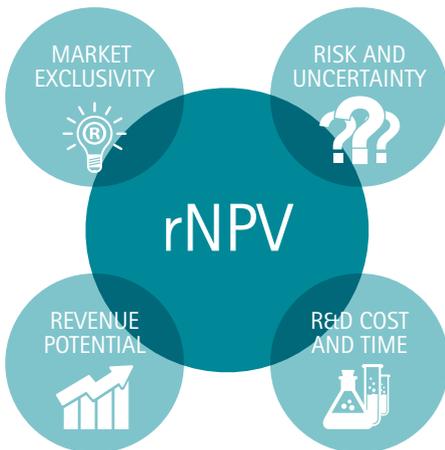
To understand how commercial potential is seen in development decisions, and to understand how new legislation or incentives may affect development around rare and/or paediatric conditions, it is useful to have a conceptual framework of development decision-making. To this end, we used two similar conceptual frameworks: one from Neez et al. of Dolon Ltd. (2020) and one from the US Congressional Budget Office (CBO) (2021). Both frameworks suggest that pharmaceutical developments are necessarily based on economic considerations. Neez et al. (2020) suggest that these considerations can be represented by four key questions:

1. How much would I be expected to invest?
2. What level of revenues can I expect if I succeed, and for how long?
3. What are the probabilities of success / risks of failure?
4. How long do I need to wait before revenues start coming in?

Neez et al. (2020) suggest that this decision-making process can best be understood in terms of **risk-adjusted net present value (rNPV)**. This concept combines information on the expected investment costs, expected revenues – including time to market, duration of the revenue stream, and the competitive landscape – and the uncertainty around these other dimensions into a single statistic that can be used to inform decision-making. The relative importance of each of these factors in the final development decision will vary by context, but each of the dimensions of rNPV will be considered to a greater or lesser degree in each decision. The dimensions of rNPV are illustrated in Figure 1.

If, taking all factors into consideration, rNPV is (sufficiently) positive, development will proceed. If rNPV is negative (i.e. the costs and risks of development outweigh expected revenue), the development will not proceed. In this view, anything that positively influences one or more of these elements improves rNPV and acts as a driver of development. Conversely, anything that negatively influences one or more of these elements worsens rNPV and acts as a barrier to development.

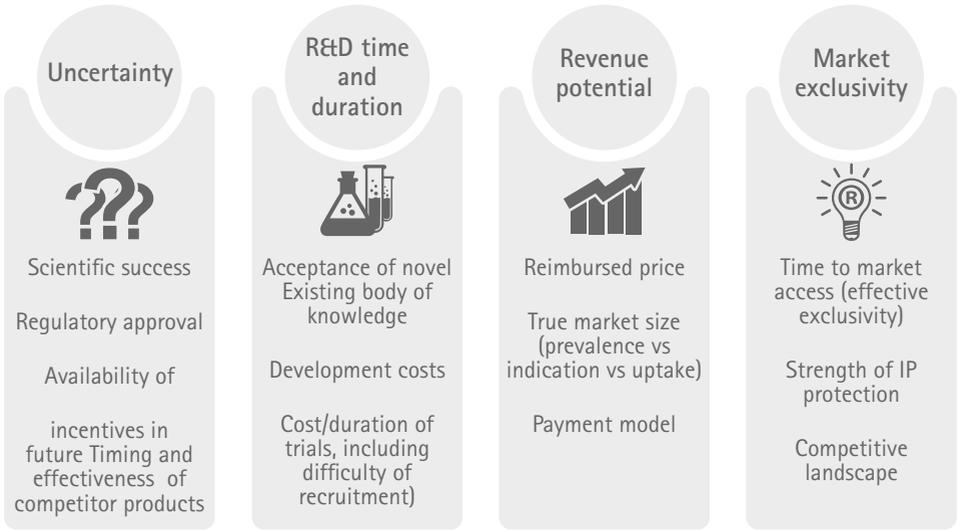
FIGURE 1: DIMENSIONS OF RISK-ADJUSTED NET PRESENT VALUE



Each dimension of rNPV can be influenced by multiple factors, and one factor may affect multiple dimensions, as illustrated in Figure 2 below.

Critically, this model suggests that although commercial potential as represented by rNPV is central to development decisions, these decisions are not made on the basis of revenue potential alone. For example, policies that ‘de-risk’ R&D, in terms of cost, duration, or likelihood of approvals, can play just as important a role as revenue potential. Likewise, revenue potential can be enhanced through appropriate protection of intellectual property or maintaining a competitive pharmaceutical landscape, not simply by higher prices.

FIGURE 2: ILLUSTRATIVE ELEMENTS OF RNPV BY DIMENSION

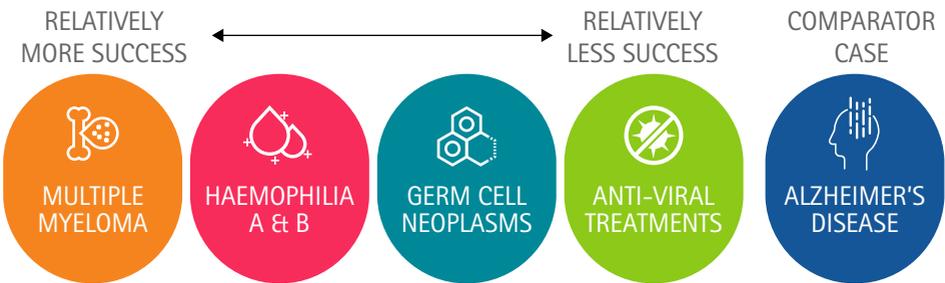


This conceptual model provides a useful framework for understanding how to best ensure sustained innovation in areas of need.

Therefore, illustrative case studies are a useful way to highlight some of the specific challenges and facilitators around developing medicines for rare and paediatric conditions.

Many of the drivers and barriers are context-specific; that is, what may be a significant driver in one disease context may be relatively unimportant in another.

Illustrative case studies



CASES STUDIES SUMMARY

| | Uncertainty | R&D cost and duration | Revenue potential / incentives | IP & exclusivity |
|---|---|---|--|---|
| MULTIPLE MYELOMA  | <ul style="list-style-type: none"> ✓ Significant improvements in understanding of the underlying science ✓ Regulatory pragmatism and flexibility | <ul style="list-style-type: none"> ✓ Acceptance of novel endpoints and trial designs ✓ Re-purposing existing medicines | <ul style="list-style-type: none"> ✗ Gene therapies challenge conventional value and budget frameworks | <ul style="list-style-type: none"> • Despite relatively crowded competitive landscape, there is a high rate of development |
| HAEMOPHILIA  | <ul style="list-style-type: none"> ✓ Progress in molecular medicine ✓ Accelerated assessment pathway led to MA in EU (Emicizumab) | <ul style="list-style-type: none"> ✗ Challenges in regulatory approval (unexpected FDA regulatory rejection a gene therapy) extending trial duration and cost. | <ul style="list-style-type: none"> ✗ Gene therapies challenge conventional value and budget frameworks | <ul style="list-style-type: none"> ✗ Existing treatments: challenge to demonstrate the value of novel products |
| GERM CELL NEOPLAS (GCN)  | <ul style="list-style-type: none"> ✗ Intrinsic complexity of disease | <ul style="list-style-type: none"> ✗ Young age of onset ✗ Low overall prevalence ✓ Multi-indication and tumour-agnostic development ✓ Increase in targeted funding | <ul style="list-style-type: none"> ✗ Payer resistance to multi-indication pricing | <ul style="list-style-type: none"> ✓ Limited competition in the area presents opportunity for first-movers |
| ANTI-VIRAL TREATMENTS  | <ul style="list-style-type: none"> ✗ Scientific barrier (continuous evolution and mutation of the virus/drug resistance) ✗ Good stewardship guidelines protect against drug resistance but make it difficult to predict utilisation ✓ Science & Technological advances (HCV) | <ul style="list-style-type: none"> ✓ Funding (HIV) ✗ Logistical barrier: need for high-security, biosafety containment facilities for R&D | <ul style="list-style-type: none"> ✗ Economic challenge (similar to those for antibiotics): conventional payment models / payers reluctant to adopt reimbursement models 'de-linked' from utilisation ✓ DAAs for HCV: cooperative pricing negotiations between payers and industry | <ul style="list-style-type: none"> • Exclusivity protections must be compatible with good stewardship guidelines than discourage use of novel products |
| ALZHEIMER'S DISEASE (AD)  | <ul style="list-style-type: none"> ✗ Science is highly complex ✗ Subjective measure of outcomes (with important variability) → uncertainty in significance and acceptability of trial endpoints | <ul style="list-style-type: none"> ✗ Historically, limited funding for AD research ✗ Challenges around patient recruitment, consent, and participation ✗ Difficulty of measurement of disease progression and clinical endpoints | <ul style="list-style-type: none"> • A truly breakthrough disease-modifying therapy in AD is likely to disrupt health system budgets | <ul style="list-style-type: none"> ✓ Limited competition in the area presents opportunity for first-movers |

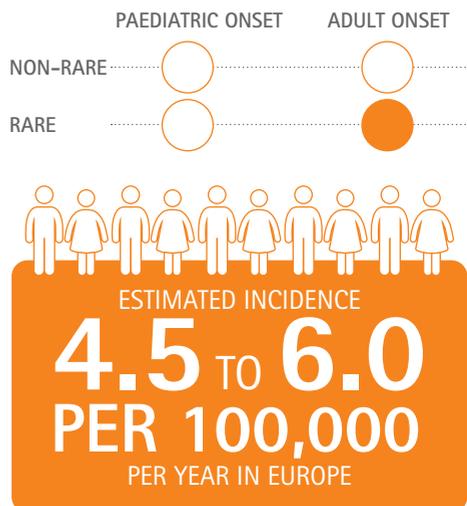
Multiple Myeloma (MM)



- Rare cancer of the bone marrow plasma cells.
- Primarily affecting elderly patients (median age at diagnosis: 72 years).
- While there is still no definitive cure, the survival of patients with multiple myeloma has increased significantly in recent years, with a large number of novel therapeutics becoming available to patients with progressive and relapsed disease.

Treatment options prior to the early 2000s were limited, but with the 're-purposing' of thalidomide as a treatment for MM in 1997, and its subsequent approval by the FDA in 2006, began an era of new drug approvals for myeloma including immunologic and other treatments. Currently available treatments include immunomodulatory drugs, proteasome inhibitors, HDAC inhibitors and monoclonal antibodies, along with regimens using a combination of therapies. Following the rapid development of treatment options in the early 2000s, the primary challenge in the treatment of MM has shifted from a limited number of treatment options to identifying optimal combinations from the many options available. A cure is not yet available, but the dramatic increase in treatment options and patient survival represent an unambiguous success.

One notable facilitator was **'re-purposed' medicines** – in this case, thalidomide – which offered a more favourable risk-reward profile than developing an entirely novel compound, given that much data on the compound's safety and efficacy were already available. Critically, though, interest in more widespread re-purposing of medicines is often limited by the lack of incentives, particularly if the product is off-patent. The potential for off-label use for cost reasons is also a clear disincentive to investing in re-purposing, as lower-priced products are often used without formal regulatory approvals for the new use that would ensure the safety and efficacy of the new use is based on scientific evidence and regulatory evaluation. There is also

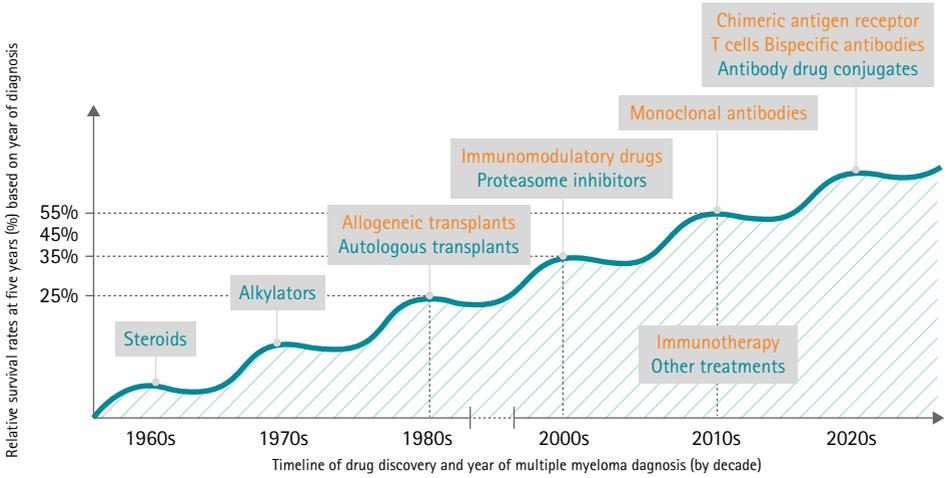


limited recognition by payers of the added value of re-purposed medicines, further discouraging investments to investigate re-purposing.

Developments in MM have also been facilitated by significant **improvements in understanding of the underlying science** such as a deeper understanding of multiple myeloma pathobiology driven by sustained support for preclinical studies which have informed drug development and clinical practice.

At the same time, the drug development around MM has benefited from **flexible regulatory processes** – including alternative regulatory pathways, acceptance of novel endpoints and innovative trial designs, and contingent approvals – which have reduced uncertainty and R&D costs for developers, particularly in terms of the duration and cost of clinical trials. Greater regulatory pragmatism and flexibility allowed FDA approvals to be granted based on evidence from smaller, single-arm studies in cases where conducting a full randomised trial would not be practical or ethical. The use of accelerated approval contingent on additional requirements

FIGURE 3: TIMELINE OF ADVANCES IN MYELOMA THERAPY



(Shah and Mailankody, 2020)

and conditional marketing authorisation allows earlier access to effective and innovative treatments in suitable patient populations. The precedent from previous approvals is potentially a strong

incentive for pharmaceutical developers to continue developing further innovative therapies, which is vital for a disease such as multiple myeloma, as patients eventually become resistant to previous treatments.

SUMMARY OF RNPV ELEMENTS FOR MULTIPLE MYELOMA

| | | | |
|---|--|--|--|
| <p>Uncertainty</p>  <p>Significant improvements in understanding of the underlying science.</p> <p>Flexible regulatory processes facilitated approvals and reduced uncertainty.</p> | <p>R&D time and duration</p>  <p>Acceptance of novel endpoints and trial designs reduced R&D costs.</p> <p>Re-purposing existing medicines also reduced R&D costs and unlocked further developments.</p> | <p>Revenue potential</p>  <p>Gene therapies on the horizon could challenge conventional value and budget frameworks.</p> | <p>Market exclusivity</p>  <p>Despite relatively crowded competitive landscape, there is a high rate of development.</p> |
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Haemophilia A & B



- Haemophilia A : prevalence of approximately 0.7 in 10,000 people, equivalent to around 36,000 people in the European Union.
 - o 60% of severe form of the disease.
 - o 15% of moderate cases.
 - o 25% of mild cases.
- Haemophilia B : prevalence of between 0.2 in 10,000 people, equivalent to around 10,000 people in the European Union.

Haemophilia A and B are hereditary haemorrhagic disorders characterised by the deficiency or dysfunction of coagulation protein factors VIII and IX, respectively. Individuals with severe haemophilia will experience recurrent, spontaneous bleeds, often in the absence of any trauma event. Approximately 90% of people with severe haemophilia experience chronic haemophilic joint disease in one or more major joints by the age of 30. As well as joint stiffness and diminished range of motion, individuals with haemophilia experience significant acute pain during bleed events and chronic pain due to arthropathy, leading to disability and impaired quality of life in more than half of cases.

Until the mid-20th century, there was no effective treatment for haemophilia or other inherited coagulation disorders. Whole blood was the only treatment approach available, and this was of such limited clinical efficacy that the life expectancy of haemophiliacs was only 10-15 years, even in the most favourable circumstances.

In the last 50 years, scientific research has advanced the treatment of haemophilia dramatically. This was primarily powered by **rapid progress in molecular medicine** that not only clarified the genetic basis of the coagulation defects but also and arguably more importantly, led to the therapeutic production in the 1990s of recombinant coagulation FVIII and IX. Since this important development, there has been relatively slow progress characterised by the refinement of recombinant factors but no major breakthroughs.

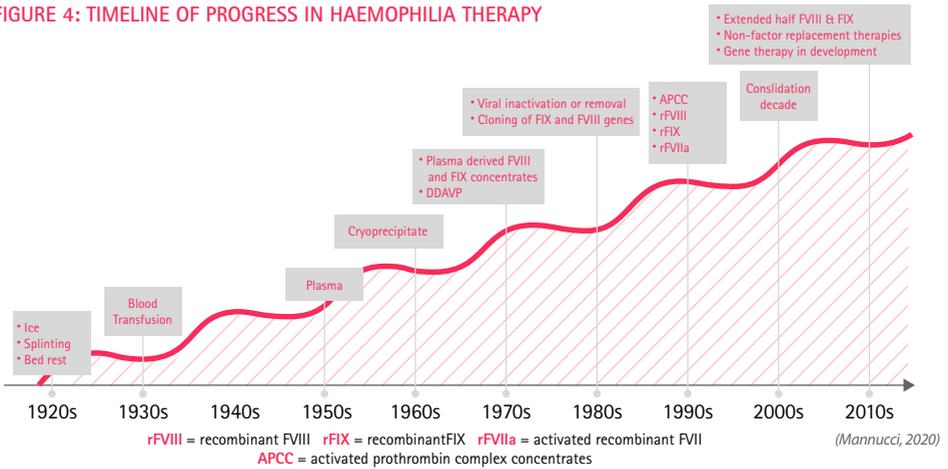


Current preventative treatment of haemophilia A involves regular injections of octocog alfa, which is an engineered version of clotting factor VIII. Injections every 48 hours are typically required. Treatment of haemophilia B is very similar, where injections of nonacog alfa (clotting factor IX) are recommended twice a week. Depending on the severity of haemophilia, these patients may be required to have additional treatment, such as immune tolerance induction, bypass therapy, or immunosuppressants.

A gene therapy for haemophilia holds promise for long-term benefit after a single treatment procedure. Strategies for gene therapy in haemophilia involve direct intravenous administration of a viral vector carrying a therapeutic gene in vivo. Several relevant virus vectors have been developed, and in the most of current clinical trials in haemophilia, adeno-associated virus (AAV) has been used to transduce FVIII or FIX genes directly into liver cells. Adeno-associated virus (AAV) vectors are the leading platform for gene delivery for the treatment of a variety of human diseases. Following the first reports on the discovery of adeno-associated virus (AAV) in 1965 and 1966, the next 15–20 years of basic biology research culminated in the cloning and sequencing of the AAV2 genome. It is acknowledged that the **early studies of the basic biology of AAV laid the foundation for vector development and therapeutic applications.**

Haemophilia is an example of a condition that is largely controlled but not cured. Developments over time have improved life expectancy from 10-15 years to something like a normal life expectancy, but it continues to impose significant burdens on patients and health systems. These indicate a need for continued development despite the availability of existing treatments.

FIGURE 4: TIMELINE OF PROGRESS IN HAEMOPHILIA THERAPY



Development in this area has been **simultaneously helped and hindered by regulatory processes**: first, with a marketing authorisation under an accelerated assessment pathway in Europe for a new therapy (Emicizumab) and second, by the unexpected rejection of clinical evidence for a haemophilia A gene therapy by the FDA on the grounds of unanticipated evidence requirements (and requirement for further data that is expected to take an additional year to collect).

The progress of clinical developments in gene therapy for haemophilia has appeared promising, however the potential of gene therapy in

haemophilia comes with the challenge of valuing “game-changing” curative therapies and attendant affordability concerns. **Despite academic enthusiasm for innovative payment models, payers remain sceptical about their necessity and usefulness.** The constraints of arbitrary budget cycles fail to account for the long-term value of truly innovative medicines. This disconnect, between short-term budget impact and long-term value, is a key disincentive to development in disease areas where it may otherwise be possible to provide substantial health benefits – outcomes that should be seen as health breakthroughs rather than threats.

SUMMARY OF RNPV ELEMENTS FOR HAEMOPHILIA

| | | | |
|--|--|---|---|
|   Unexpected regulatory rejection extended trial duration and cost. |   Developments in haemophilia largely benefitted by progress in other areas, minimising direct cost of R&D. Challenges in regulatory approval extending time and cost. |   Gene therapies challenge conventional value and budget frameworks. |   Existing treatments pose a challenge demonstrating the value of novel products and may discourage new development. |
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Germ cell neoplasms (GCN)

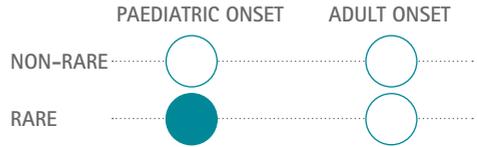


- Germ cell neoplasms (GCN), also known as germ cell tumours or gonadal germ cell tumours, are cancers that form in the ovaries or testes.
- Incidence peaks between 0 and 4 years of age, and again at age 9 in girls and age 11 in boys.

Current treatments for germ cell neoplasms include tumour removal surgeries, radiotherapy, and combination drug therapies. Germ cell neoplasms were identified in 2015 as a developmental “white spot”, with neither an effective drug treatment nor clinical development occurring in the pharmaceutical pipeline (Papaluca et al., 2015). Since its identification as a white spot in 2015, however, there has been significant pipeline activity, with between 29 and 57 ongoing trials, transforming an empty pipeline into a relatively promising source of novel treatments.

The sparse number of developments prior to 2015 and the jump in trials after 2015 are the product of a number of barriers and facilitators. A primary barrier to development related **to the very characteristics of the disease** that develops in the womb and then remains latent until after birth or during adulthood. This makes understanding the disease course difficult to research. Furthermore the clinical and biologic characteristics of GCNs differ by sex and age group, requiring different therapeutic approaches for different patient groups.

The **young age of onset** also acts as a barrier, as age eligibility cut-offs might prevent or delay the enrolment of very young patients, whilst the **low overall prevalence** limits the statistical power of trials, making it more difficult to generate gold standard evidence. Continuing development around **multi-indication and tumour-agnostic products**, which could allow recruitment of patients with different cancers into a single, sufficiently-powered trial, likely offers the greatest hope for breakthroughs in the treatment of GCN, as it would allow development costs to be spread across additional indications but would require more flexible regulatory and HTA approaches.



GERM CELL NEOPLASMS REPRESENT
2% TO 4%
OF ALL CANCERS
IN CHILDREN AND ADOLESCENTS
YOUNGER THAN 20 YEARS OLD

These multi-indication products may face barriers to market access in the form of **payer resistance to indication-based pricing**. By itself, GCN is too small a market to justify substantial investments and progress is most likely to be driven by multi-indication or even tumour-agnostic products.

In terms of drivers of development, **advances in understanding and technology** have begun to unlock developments.

Progress in the number of GCN trials has coincided with an **increase in targeted funding**, reinforcing the importance of ‘push’ incentives that support ‘upstream’ collaborative science and promotes a solid understanding of disease pathology and mechanisms of action. Greater support for R&D also mitigates the financial impact of development failures or setbacks, encouraging developers to take on otherwise riskier developments. **Orphan designation** also appears to have acted as a ‘push’ factor, as a number of multi-indication products in the pipeline have an orphan designation.



BY ITSELF, GCN IS A TOO SMALL MARKET TO JUSTIFY SUBSTANTIAL INVESTMENTS: PROGRESS IS MOST LIKELY TO BE DRIVEN BY MULTI-INDICATION OR TUMOUR-AGNOSTIC PRODUCTS.

SUMMARY OF RNPV ELEMENTS FOR GERM CELL NEOPLASM

Uncertainty



Understanding of GCN growing, improving chances of development success.

R&D time and duration



Small and very young patient population complicates trial enrolment.

Increase in targeted funding improving understanding of disease and mitigates cost of research failures.

Accelerated regulatory processes through orphan designation.

Revenue potential



Payer resistance to indication-based pricing that could encourage development of multi-indication or tumour-agnostic products with applications in GCN.

Market exclusivity

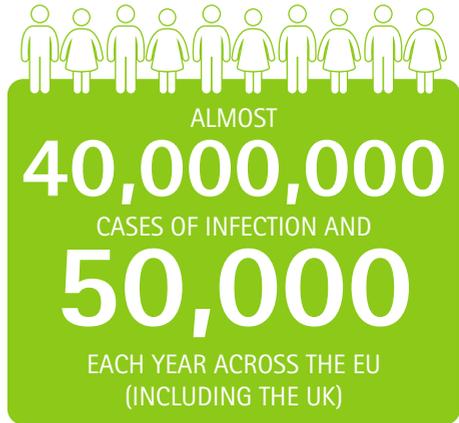
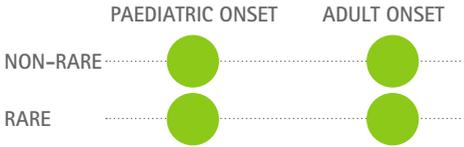


Limited competition in the area presents opportunity for first-movers.

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Anti-viral treatments



The prevalence of infectious diseases varies, from conditions that are extremely rare in the EU like rabies to more prevalent conditions like influenza, tuberculosis, and HIV/AIDS. Despite this range of prevalence, we believe that many of facilitators we observe in the development of ‘non-rare’ anti-viral treatments, including around HIV/AIDS and Hepatitis C, hold important lessons for the development of treatments for rarer viral diseases.

Despite the substantial health impact of viral infections each year (now including Covid-19), **development of anti-viral medicines has been limited.** This is similar to what has been seen in the context of the “antibiotic paradox”: an imbalance between the burden of infectious diseases and the slow (and declining) pace of innovation in this area. There are antiviral medicines available for only 10 of more than 220 viruses currently known to infect humans. Of the 90 antiviral medicines developed between 1959 and 2016, almost half are for a single disease (HIV).

The number of HIV medicines developed in a relatively short period have transformed HIV/AIDS from a terminal diagnosis to a chronic condition and demonstrates the potential of pharmaceutical science to find solutions to urgent societal health

needs, but progress in other viral diseases has been much slower. **The pace of HIV development has benefited from dedicated research funding** that quickly accelerated from nothing in the mid-1980s to US\$2.5 billion annually today. Arguably, the pace of development around HIV was driven by the extent of the epidemic and the severity the condition.

Notwithstanding the relative success of HIV antivirals, these medicines present a range of distinct challenges to developers, including **scientific, logistical, and economic.**

A key scientific barrier to all antiviral development is **drug resistance**, particularly amongst RNA viruses, due to the “error-prone” nature of RNA virus reproduction that leads to frequent mutations. Drug resistance increases the time and costs of

THERE WERE 90 ANTIVIRAL MEDICINES DEVELOPED BETWEEN 1959 AND 2016:



development and can render a medicine less effective, or even ineffective, over time.

A key logistical barrier to antiviral development is the need for **high-security, biosafety containment facilities** for research and development. Such facilities are expensive to build, commission, and maintain and require a high level of training and oversight. As a result, there are relatively few such facilities around the world, constraining opportunities to research and test compounds against live viruses. This logistical challenge represents a unique barrier to antiviral development.

Finally, these scientific and logistical challenges combine to present distinct economic challenges. Some of these are similar to those seen around

novel antibiotics. Drug resistance has significant implications for health, but it also detracts from the commercial viability of new products under conventional payment models: the continuous evolution of viruses can render successful antiviral obsolete before they ever come into widespread use, whilst novel medicines are often held in reserve under good stewardship guidelines to prevent drug resistance. Whilst holding the most innovative medicines in reserve is a sensible strategy, this limits the revenue potential of new antivirals, and to date **payers have been reluctant to adopt reimbursement models that are 'de-linked' from utilisation**. More innovative payment models are required to reward and incentivise development in this area.

SUMMARY OF RNPV ELEMENTS FOR ANTI-VIRAL TREATMENTS

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|--|---|--|--|
|  <p>Uncertainty</p>  <p>Random viral mutations can reduce drug effectiveness.</p> <p>Good stewardship guidelines protect against drug resistance but make it difficult to predict utilisation.</p> |  <p>R&D time and duration</p>  <p>Developments around HIV driven by sustained R&D funding.</p> <p>New technologies, including genetic sequencing, assist with drug targeting.</p> |  <p>Revenue potential</p>  <p>Antiviral 'cures' challenge conventional value and budget frameworks.</p> <p>Currently greater incentives for development around chronic rather than acute conditions.</p> |  <p>Market exclusivity</p>  <p>Exclusivity protections must be compatible with good stewardship guidelines than discourage use of novel products.</p> |
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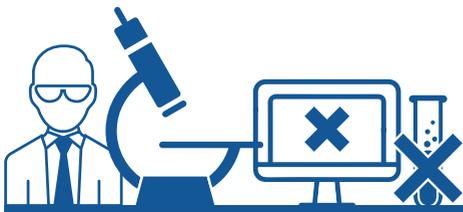
Alzheimer's Disease (AD)



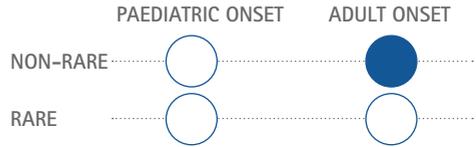
This condition is neither rare nor paediatric but illustrates the challenges of development even where commercial potential in terms of the size of the patient population and their relative affluence, and the value of preventing or reversing cognitive decline, would suggest that any successful product would quickly become a commercial 'blockbuster'. AD is presented as a contrasting case to highlight that many of the challenges observed around the development of medicines for rare or paediatric conditions are generalisable to more common conditions.

Despite intensive and ongoing efforts, development around AD has historically been characterised by failure. The reasons for the low success rate in AD are multifactorial. First, **the science of AD is highly complex**, and there are competing and unresolved hypotheses of the causes and mechanism of action in AD.

Second, the assessment of effect is complicated by the difficulty to measure disease progression and clinical endpoints. Technological advances in brain imaging and biomarkers, and a greater understanding of the causes and staging of AD may help to resolve some of these challenges.



DESPITE INTENSIVE AND ONGOING EFFORTS, DEVELOPMENT AROUND AD HAS HISTORICALLY BEEN CHARACTERISED BY FAILURE.



A REVIEW OF ALZHEIMER'S TRIALS IDENTIFIED 413 TRIALS IN THE PERIOD BETWEEN 2002 AND 2014

99.6%
OF THESE TRIALS FAILED

But currently most AD trials rely on a **subjective measure of outcomes**. This has historically led to questions over the reliability of study outcomes and delays in regulatory approvals, but the **US Food and Drug Administration (FDA) recently approved, aducanumab, through its 'Fast Track' accelerated approval pathway** based on a surrogate endpoint of reduction of amyloid beta plaque in the brain. Such pragmatism can accelerate developments.

Third, **the nature of the disease presents challenges to conventional clinical trial designs and barriers for patients and caregivers to trial participation** limiting the pool of potential participants and extend the time that trials must spend recruiting. Therefore, innovative trial designs that can produce reliable results with a smaller pool of participants, and greater support for patients and caregivers participating in trials, will be critical in generating robust clinical evidence.

Fourth, in contrast to the sustained funding available for oncology and HIV/AIDS research, **funding for AD research has been much more limited.**

SUMMARY: RNPV ELEMENTS FOR ALZHEIMER'S DISEASE

Uncertainty



Very high failure rate in AD trials.

Subjective outcome measures with important inter-rater variability leads to uncertainty in trial endpoints.

R&D time and duration



Unresolved questions over causes and mechanism of action of AD limiting development.

Difficulty recruiting participants extends duration and cost of trials.

Revenue potential



Value of disease-modifying therapy in AD likely to disrupt health system budgets.

Market exclusivity



Limited competition in the area presents opportunity for first-movers.

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Discussion and recommendations

This conceptual framework of development decision-making elucidates some of the key elements of pharmaceutical development decision-making and can help to inform the development of effective legislation and incentives. Broadly speaking, this framework shows that reducing the uncertainty and cost of development, and ensuring appropriate incentives and compensation for break-throughs, are the primary means to promote development in areas of need.

The individual case studies highlight some additional lessons. First, as illustrated by the Alzheimer's case, **commercial potential in itself is not sufficient to guarantee success**. The science of Alzheimer's disease is difficult, and this fundamental obstacle has been exacerbated by challenges around measuring endpoints and recruiting participants for clinical trials. Similar challenges were observed around germ cell neoplasms, which develop whilst 'patients' are still in the womb. The recent accelerated approval of aducanumab, though, demonstrates how regulators can promote ongoing development through pragmatic consideration of novel endpoints. Technological developments in brain imaging and biomarkers may help to address subjective endpoints in AD, **but regulatory flexibility around trial design, including greater acceptance of surrogate endpoints, real-world evidence, and 'synthetic' control arms, can help reduce the cost and duration of trials, promoting R&D efforts**.

The potential value of developments in AD, haemophilia, and direct-acting antivirals, as well as many other rare and paediatric conditions, pose a challenge to existing value frameworks. Many payers prioritise budgets over patient value in reimbursing these breakthrough medicines. This is a critical disincentive in the context of rNPV and, perversely, discourages development in areas of the greatest health burdens and potential value. Different reimbursement challenges are associated with other anti-viral treatments, where good stewardship guidelines and the risk of drug resistant mutations increase uncertainty around expected revenues. **Overcoming resistance to**

reimbursement models that are 'de-linked' from utilisation will be essential to resolving this barrier. **Innovative reimbursements models, particularly indication-based pricing**, could be useful in incentivising development of multi-indication or tumour-agnostic products for rare and ultra-rare conditions, where a single indication may not provide sufficient economic incentives to undertake development.

As seen in the case of multiple myeloma, **re-purposing existing on-patent or off-patent products can also be an effective means of addressing orphan and paediatric health needs**.

Finally, a consistent theme across all the cases was the **importance of flexible and pragmatic regulatory processes**. This can reduce the time to market access, the costs of clinical trials, and the uncertainty around the likelihood of approval at different stages of development. Given the large financial sums associated with the development of new products, a series of small regulatory changes that improve and accelerate the likelihood of approval at different points along the development pathway can have an impact on rNPV-based development decisions.

We note that development in almost all the cases was driven to a greater or lesser degree by scientific or technological developments in unrelated areas, including gene sequencing, brain scanning, and even advances in blood transfusion during World War 2. This emphasises the complexity and multiple dependencies of the development process: **pharmaceutical innovation does not occur in isolation**.

We suggest that many of the barriers identified in this report – especially a lack of flexibility and pragmatism in regulatory and reimbursement policies – could be reduced through **closer and earlier collaboration between industry and regulators/payers**. Such collaboration could reduce uncertainty, time, and costs in the development process and encourage greater developments in the most urgent areas of unmet need.