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Rare innovation: How it happens, when it doesn't, and what can be done to sustain it

A white paper exploring through case studies the scientific, economic, and policy factors that drive drug development

Prepared by Dolon Ltd for
Alexion, AstraZeneca Rare Disease

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Abbreviations

AMR	Antimicrobial resistance
BARDA	Biomedical Advanced Research and Development Authority
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DNA	Deoxyribonucleic acid
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FDA	US Food & Drug Administration
GAIN	Generating Antibiotic Incentives Now
IP	Intellectual property
NORD	National Organization for Rare Disorders
ODA	US Orphan Drug Act
OMP	Orphan medicinal product
P&R	Pricing and reimbursement
PDUFA	Prescription Drug User Fee Act
PhRMA	Pharmaceutical Research and Manufacturers of America
PRIME	Priority medicines
PRV	Priority review voucher
R&D	Research and development
RC20	Ring chromosome 20
RCT	Randomised controlled trial
RNA	Ribonucleic acid
rNPV	Risk-adjusted net present value
ROI	Return on investment
UK	United Kingdom
US	United States
WHO	World Health Organization
WTP	Willingness to pay

Introduction

The US Orphan Drug Act (ODA), introduced 40 years ago, offers incentives to bolster research and development for the treatment of rare diseases (Food & Drug Administration 2018). Similar regulations were implemented nearly two decades later in Europe (European Commission 2000). In the wake of these initiatives, tremendous advances in drug development for rare diseases have been achieved, resulting in transformative – and in some cases, potentially curative – therapies to address pressing unmet medical needs (IQVIA 2020).

Yet rare diseases remain a global health concern: an estimated 400 million people suffer from one of approximately 10,000 known rare diseases, 95% of which still lack an approved treatment (Fermaglich and Miller 2023). Often chronic and severe, rare diseases are highly burdensome for patients, families, and society – 50% of people living with a rare disease are children, 30% of whom will not live beyond five years of age (The Lancet 2019).

In recent years, orphan regulations in the US and Europe have become subject to review, driven by a perception that existing incentives are in need of recalibration (Dolon for EFPIA 2020) (IQVIA 2020). This increased scrutiny has emerged out of criticism from some stakeholders about the price and availability of orphan drugs and whether incentives continue to be necessary to encourage biopharmaceutical innovation for diseases that affect small populations.

Against this backdrop, this paper aims to explore the question: *Which drugs get developed and why, and how does policy affect this?* It examines through case studies the necessary conditions for drug development, and how these are influenced – for better or worse – by incentives and policy frameworks that seek to meet societal health goals.

Two case studies are considered: antibiotics and orphan drugs. These were selected because both areas have seen dramatic changes in rates of new drug discovery over time and both are associated with specific policy interventions. The case studies were developed through desk research, examining historic trends in the rate of new drug discovery alongside key scientific, economic, and policy events that may have impacted those trends. These findings were then tested with five experts in biopharmaceutical policy, clinical development, and investment strategy who had firsthand experience of the case areas.

Insights from this analysis have been used to identify the conditions necessary for biopharmaceutical innovation. This paper summarises the findings of this work and is organised into the following sections:

- Overview of the biopharmaceutical innovation model
- Learnings from case studies
- Policy implications for rare diseases

The purpose of this paper is to facilitate an informed dialogue with policymakers concerning the interplay between science, economics, and policy and how this dynamic can affect the availability of new medicines for people living with a rare disease.

1. The biopharmaceutical innovation model

1.1 Defining 'innovation' and the 'innovation model'

'Innovation' is one of the most important – and overused – terms in the biopharmaceutical industry. Hence, it is important to establish a working definition.

The defining feature of innovation is novelty. In the context of drug development, it could refer to anything from the breakthrough discoveries that lay the foundation for drug development to the drugs themselves.

In this paper, 'innovation' refers specifically to *biopharmaceutical innovation* (i.e., tested clinical product with regulatory approval for human use) rather than *basic science innovations* (i.e., breakthrough with no immediate clinical application).

The 'innovation model' is the whole process by which new biopharmaceuticals are discovered, developed, and commercialised to address a particular unmet medical need. The dynamics and necessary conditions for this process are described in (1.2). The role policy can play in directing this process is described in (1.3).

1.2 Necessary conditions: When is innovation possible?

Drug development occurs at the centre of two landscapes: the scientific and the commercial.

Within the **scientific landscape**, the factors that drive which drugs get developed relates to the relative degree of disease knowledge and treatment ability in that indication. Across all the areas of unmet need requiring innovation, only a small subset of disease areas are 'clinically viable'. ***Clinical viability*** is informed by the current *scientific understanding* of the disease pathophysiology and burden, as well as the existing *technological capability* to diagnose and treat safely and effectively. Contributors to clinical viability include disease awareness, presence of natural history data, awareness of pathophysiology, and disease targets.

The **commercial landscape** represents the cumulative economic factors that propel investments. In addition to clinical viability, ***economic viability*** is the other pre-requisite to innovation where only a small sub-set of areas requiring innovation qualify. Economic viability effectively accounts for a drug company's *willingness to invest* in investigating and commercialising a product to address a specific unmet need due to there being sufficient economic incentive. See Figure 1.

Figure 1. Clinical and economic viability for innovation

Industry investment decisions are multifactorial and extremely complex. That said, business economics nearly always plays a part, and is typically evaluated alongside clinical results at key 'go / no-go' decision points in the development process (e.g., the decision to progress from a phase I to a phase II trial). Risk-adjusted net present value (rNPV) modelling is a common industry tool used to determine if an asset is likely to provide sufficient return on investment (ROI) to satisfy investors and sustain development pipelines. The model essentially aggregates several factors to determine if an asset is likely to provide sufficient ROI to pay back investors and sustain their development pipeline:

The first factor in the equation is the **total financial investment required**, which includes the costs associated with *acquiring the asset*, conducting the necessary *research and development* (R&D) to produce the evidence required for market authorisation and launch, and then finally *commercialising* the product.

The second factor is the **time** it takes from the point of investment to yield a return accounting for the duration of Intellectual Property (IP). Indeed, the longer it takes to develop and commercialise a product, the shorter the IP period remains to realise returns.

The third factor accounted for is the **potential return on investment**, which is determined by the *price potential* (i.e., what the company may be able to charge for such a product in a specific indication based on unmet need and existing standard of care, ability to demonstrate added benefit and payers' willingness to pay) multiplied by the *patient potential* (i.e., total volume of sales the company is likely to make based on disease prevalence and market uptake, accounting for reimbursement decisions).

The final factor is **risk**, which is frequently the complicating factor and includes anticipated probability of clinical success (i.e., trial shows safety and efficacy) as well as commercial success (i.e., that the company reaches the market before their competitors, payers are willing to reimburse, etc.). The sub-elements which make up the key clinical and economic factors affecting whether an innovation is viable for development are detailed in Table 1.

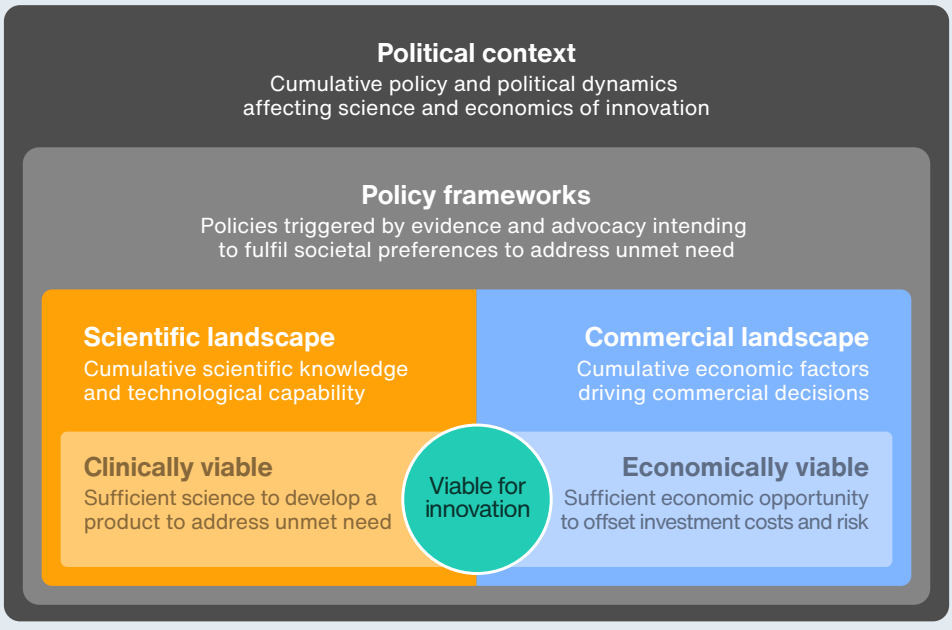
Table 1. Factors driving the innovation model

Factors	Sub-elements	Description
Clinical	Scientific understanding	Knowledge of disease burden, natural history, clinical targets, and (sub)populations
	Technological capability	Ability to diagnose and treat patients
Economic	Patient potential	Number of patients given disease prevalence, expected reimbursement status, uptake, and market share
	Price potential	Determined by unmet need, added clinical benefit, competitive landscape, patent protection, and cost offsets
	Financial investment	Cost of investment in R&D, acquisition fees, royalties to academic institutions, manufacturing, and distribution
	Time from investment to return	Duration of R&D, manufacturing, and launch accounting for duration of IP
	Risk of failure	Probability of clinical and commercial success

1.3 The role of policy in influencing where innovation is most likely to occur

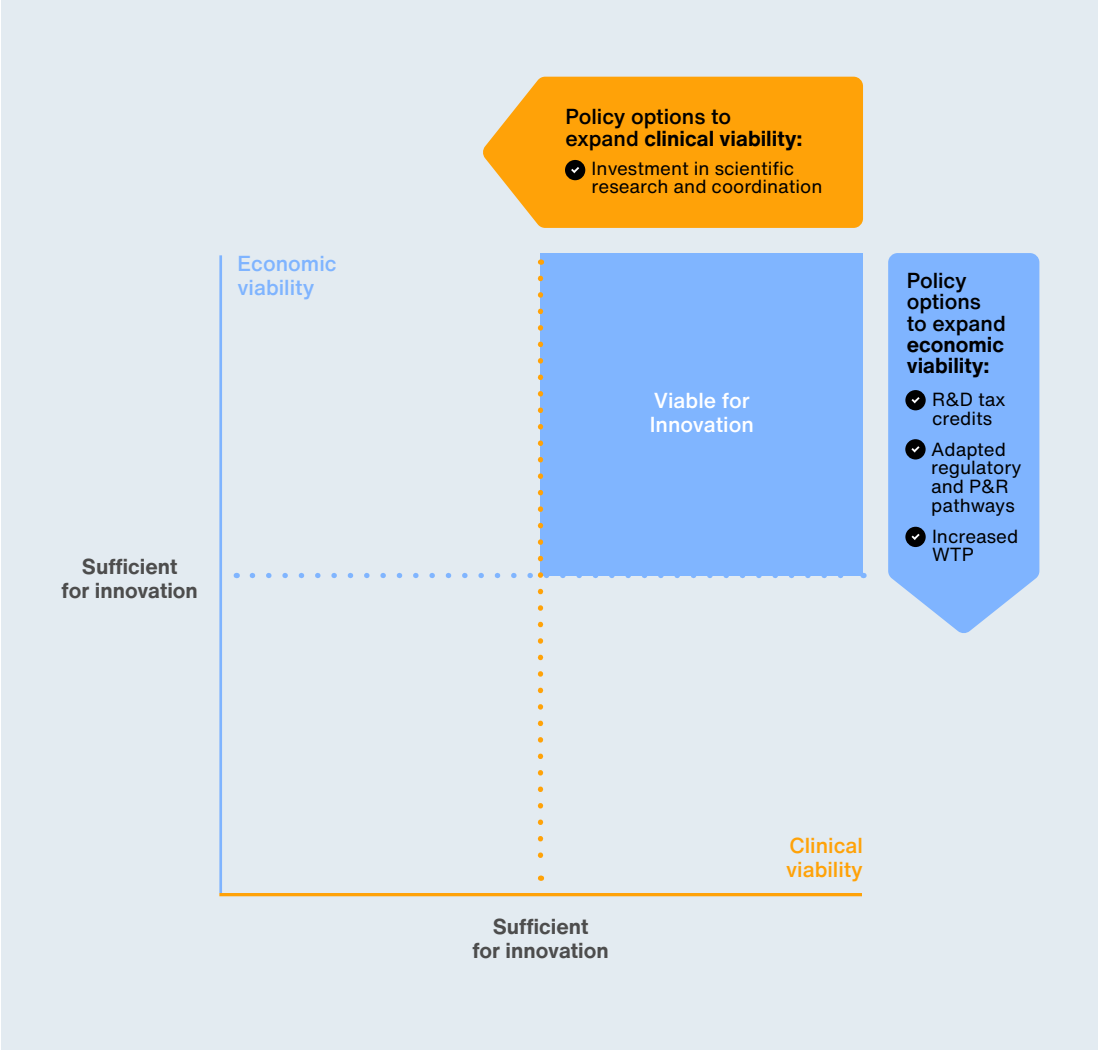
The clinical and economic conditions for biopharmaceutical innovation are impacted by the political context and can be modulated more or less favourably by the policy frameworks implemented. These as a result can shape and direct opportunities for biopharmaceutical innovation. See Figure 2.

Figure 2. Role of policy in the innovation ecosystem



Innovation occurs in an evolving political context. This refers to the cumulative public policy and political dynamics that shape the clinical and economic landscapes driving innovation. Indeed, from the earliest stages of R&D, industry decisions are governed by regulations and incentives set by policymakers, often driven by political sentiments of the moment. Changes in policy frameworks are usually triggered by the recognition of societal needs brought about by emergences in evidence and advocacy. Such changes impact the viability for innovation in a disease area by improving or hampering the clinical and economic conditions. See Figure 3.

Figure 3. Policy options to expand clinical and economic viability for innovation



Policy can encourage innovation by signalling priorities through mandates, incentives, and funding which enhance scientific and commercial opportunity in particular areas. For instance, public investment in basic and translational science can help improve the clinical viability of drug development. Financial incentives can improve price potential (e.g., through higher willingness to pay or value-based assessments) as well as reduce the cost of development (e.g., via R&D tax subsidies and vouchers). Regulatory reforms can also help to reduce commercial risk and time to market (e.g., market exclusivity, adapted evidence requirements, protocol advice and accelerated pathways).

Yet policy can also hamper innovation through frameworks that reduce scientific and commercial opportunities or otherwise erode industry confidence in investing. Reversing incentives, for example, serves as a signal to industry that innovation in a particular area is less of a priority, as does the failure to adjust frameworks in areas where innovation is inherently more challenging. Examples of this include anchoring price potential of an innovative drug to low-value comparators, strict and insufficient willingness to pay thresholds, or stringent evidence requirements that fail to account for unique specificities or what is feasible. Altogether, such frameworks risk reducing industry's appetite to invest in new and risky areas of development.

The next section examines how policy has influenced the pace of new medicine development in the case of antibiotics and rare diseases by impacting the scientific and economic conditions for innovation.

2. Innovation in practice

2.1 Antibiotics: Boom then bust

In May 2015 at the World Health Assembly, the World Health Organization (WHO) endorsed the global action plan on antimicrobial resistance. Counted among its key strategic objectives is to ensure sustainable investment in the R&D of new antibiotics (World Health Organization 2020). This was overdue: the last novel antibiotic class that has been successfully introduced in clinical practice was discovered over 35 years ago in 1987 (Hutchings et al. 2019). This dearth of development stands in contrast with the rate of discovery throughout the 1950s and 1960s, when nearly one new class of antibiotics was approved each year. What led to the rapid decline in antimicrobial innovation, and what was the role of scientific, economic and policy factors over the past 100 years?

In the pre-antibiotic era, the burden from bacterial infection was extremely high. Pneumonia and tuberculosis, both highly treatable today thanks to antibiotics, were the leading causes of death in the US in 1900, due to poor sanitation (Centers for Disease Control and Prevention 1999). The famed discovery of penicillin by Alexander Fleming occurred in 1929. However, technical limitations at the time prevented Fleming from isolating his 'mould juice' into a sufficiently pure form for clinical application. This changed in 1940 with the Oxford Penicillin Purification Protocol. Around the same time, advances in manufacturing capabilities, coupled with war-time demand for infection-fighting drugs, catalysed the necessary scientific and economic conditions that launched the Golden Era of antibiotic discovery (Hutchings et al. 2019) (Aminov 2010).

'Wonder drug' enthusiasm reigned throughout the 1950s and 1960s, driving antibiotic R&D and sales. However, as scientific, economic, and regulatory conditions changed, cracks in the innovation model began to show.

First, the science became more challenging. Antibiotics are traditionally sourced from natural environments, and after two decades new discoveries had become increasingly difficult to procure. Second, growing awareness of antimicrobial resistance (AMR) during the '60s and '70s reduced the public and industry's confidence in antibiotics. Stewardship policies, seeking to limit AMR by restricting antibiotic use, came into effect, slowing the uptake of new drugs and negatively impacting their economic viability (Podolsky 2018).

These clinical and economic challenges were amplified by incoming regulatory policy that further diminished the market for new antibiotics. In 1962, the Kefauver-Harris Amendment introduced efficacy requirements for all drugs marketed in the US. This policy was a landmark for ensuring that marketed drugs were clinically effective in practice, but also fundamentally changed the economics of drug development. Facing higher costs and risks, industry was forced to be more selective with investment opportunities (Greene and Podolsky 2012).

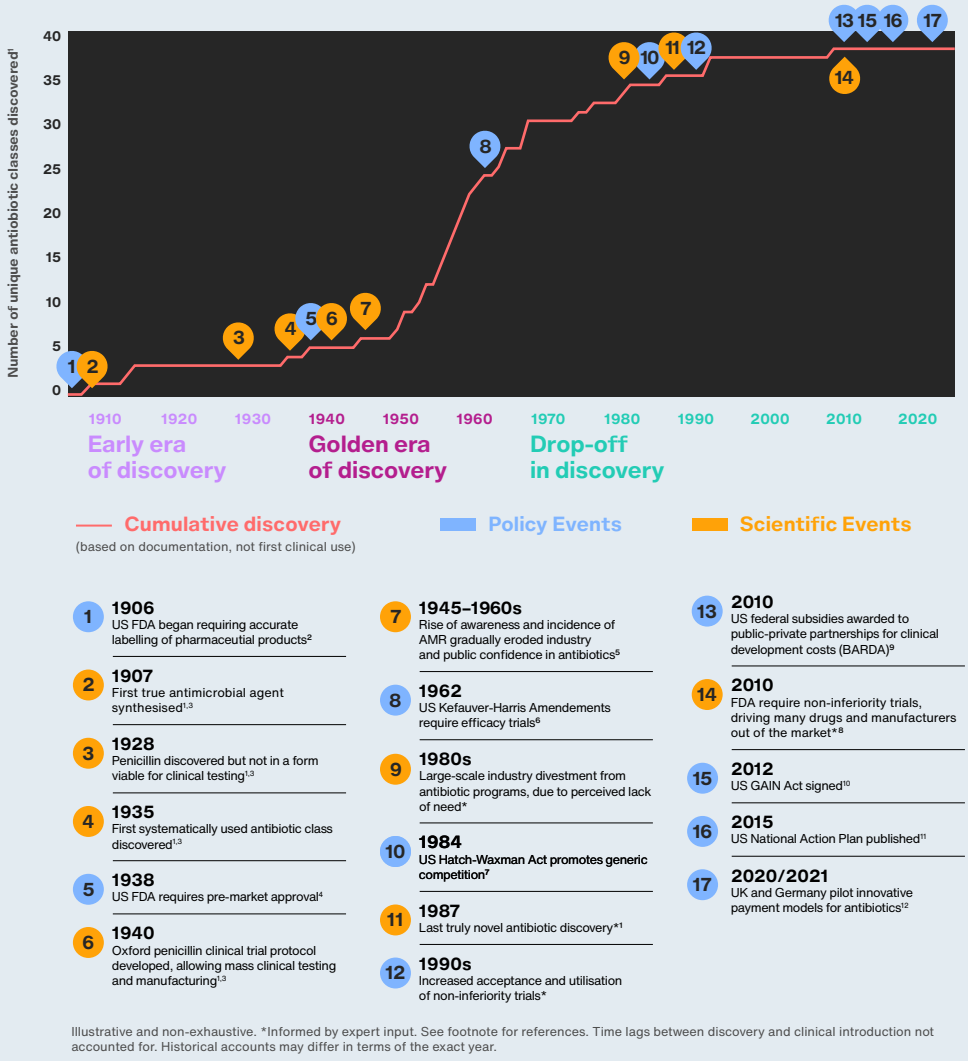
Meanwhile, antibiotics were becoming less profitable versus other potential areas of investment. The 1984 Hatch-Waxman Act expanded drug patent protections, while also seeking to encourage generic competition. The policy succeeded in making certain drugs more affordable, but also eroded the price of new antibiotics because there is no clinically relevant way to show superiority from one antibiotic to the next. This characteristic precludes new antibiotics from commanding price premiums (Venkatesh et al. 2011). Therefore, the economic viability of antibiotics is not only negatively influenced through restricted volumes by stewardship policies, but the price is also tethered to existing low-cost generics.

Today, antibiotics are not considered a viable economic investment. Small biotechs on the frontline of antibiotic development are folding before they reach the market. Even if they succeed in reaching the market, outcomes can be just as bleak. Achaogen was founded in 2002 to develop a new hospital antibiotic and even received $700m in 'push' funding as an incentive to get their asset into clinical trials. When they launched their first product, Plazomycin, in 2018 the WHO included it in its list of essential medicines. Despite this, the firm declared bankruptcy one year later after making less than $1m in its first year (Wellcome Trust 2020).

The abstract nature of the unmet need and lack of centralised patient advocacy have historically precluded the radical policy solutions needed to incentivise and sustain innovation in antibiotics, although recent reports estimating the human and economic burden of AMR have helped to expand awareness and understanding of this public health threat (World Health Organization 2023).

Policy interventions have emerged in recent years with the aim of offering financial incentives to stimulate needed innovation in antibiotics. One strategy is to 'push' antibiotic innovation by financially supporting early stage developments to the clinical trial stage (Wasan et al. 2023). Another approach has been to offer tangible financial rewards for successful development. In Europe this has come in the form of guaranteed reimbursement models for new antibiotics (Mahase 2020) and transferable data exclusivity vouchers for successful development of priority antimicrobials (European Commission 2023). Time will tell if these are sufficient to bolster the waning antibiotics market. See Figure 4.

Figure 4. Case analysis of historic trends in antibiotic innovation and influencing policies[a]



Illustrative and non-exhaustive. *Informed by expert input. See footnote for references. Time lags between discovery and clinical introduction not accounted for. Historical accounts may differ in terms of the exact year.

Case reflections

Studying the history of antibiotic innovation in the context of those clinical and economic factors which drive drug development (i.e., the 'biopharmaceutical innovation model') can aid in identifying the issues that policy should target to improve conditions for antibiotic innovation.

First, it is observed that economic viability (and not clinical viability) is the limiting factor to antibiotic innovation. It may be that there are fewer 'low-hanging fruit' antibiotic discoveries today than there were in the 1950s, but scientific understanding and technological capability are not the factors preventing innovation.

[a]1. (Hutchings et al. 2019) 2. (Food & Drug Administration n.d.) 3. (Aminov et al. 2010) 4. (Food & Drug Administration n.d.) 5. (Podolsky 2018) 6. (Greene and Podolsky 2012) 7. (Venkatesh et al. 2011) 8. (Plakett 2020) 9. (Eichberg 2015) 10. (Darrow and Kesselheim 2020) 11. (The Open Government Partnership 2015) 12. (Mahase 2020)

Indeed, the ultimate failure of the antibiotics market is that they are life-saving drugs that would, ideally, never be used. From a business economics perspective, the potential returns *(patient potential x price potential)* do not warrant the necessary investment (*financial* and *time*) and risk required to discover, develop, and commercialise a new antibiotic drug. See Table 2.

Table 2. Challenges facing antibiotic innovation today

Factors	Challenges
Clinical	New discovery approaches are needed due to so much of the 'low hanging fruit' having already been discovered
Economic	Patient potential limited by volume restrictions as a result of stewardship policies to avoid AMR
	Price potential limited by ill-adapted reimbursement models that fail to account for the total nominal burden of AMR
	Price potential anchored to low-cost generics due to inability to demonstrate clinical superiority in head-to-head trial

Finally, the antibiotic case highlights that the innovation ecosystem is dynamic and thus sustained output over time is not guaranteed. Clinical and economic conditions are evolving, and further influenced by the changing political landscape of regulation and incentives. Hence, there is a need for policy frameworks to be adapted over time and to account for specific characteristics of diseases to maintain innovation in areas of unmet need.

2.2 Rare diseases: Unfinished business

Policy has and continues to play a significant role in the trajectory of orphan drug innovation. Historically, the rare disease patient population had been underserved by the pharmaceutical industry, owing to the greater degree of risk associated with securing a return on investment in a small patient population suffering with diseases of limited or fragmented medical research compared to more common diseases.

This challenge came to light after the 1962 Kefauver-Harris Amendment fundamentally changed the economics of drug development by introducing the requirement that all pharmaceutical products marketed in the US undergo efficacy trials, including retrospectively for existing products (Mikami 2017). Importantly, the regulation helped to ensure that marketed drugs, including generics, were effective in clinical practice. However, as observed with antibiotics, the increased R&D cost and commercial risk had negative implications for drug development for small populations. This ultimately drove industry to abandon, or 'orphan', drugs deemed insufficiently profitable due to the small size of their markets relative to the significant upfront investment in efficacy trials.

In reaction to this event, rare disease patient advocacy and public awareness grew throughout the 1970s, eventually culminating in the 1983 Orphan Drug Act (ODA) (Swann 2018). The aim of the ODA is to offer financial and regulatory incentives that can help offset the costs and risk of developing and commercialising a drug for a rare indication. It also serves as a signal to encourage industry to pursue drug development in traditionally underserved diseases. Major advancements in genetic research were achieved in the decades following the Act, driving further innovation and discovery in genetic disorders (Claussnitzer et al. 2020), the significance of which cannot be overstated, with an estimated 70%–80% or more of rare diseases having a genetic origin (Wakap et al. 2019) (Rare-X 2022). In 2000, Europe established its own incentive framework in the form of the EU Orphan Medicinal Products (OMP) Regulation and later supplemented by the Paediatric Regulation (European Commission 2000) (European Commission 2006).

This combination of transformative scientific progress alongside policy incentives has revolutionised drug development for rare disease: pre-ODA there were fewer than 40 drugs approved for orphan indications in the US, versus over 600 today (National Organization for Rare Disorders and Avalere 2021).

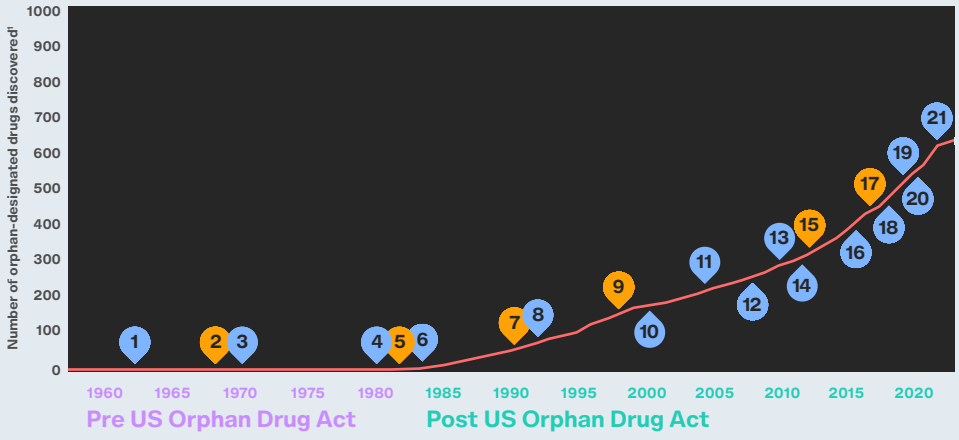
Yet, in the face of the success of these orphan incentives, substantial unmet need in rare diseases remains: 95% of approximately 10,000 rare diseases still lack any approved treatment (Fermaglich and Miller 2023). Further, innovation appears to be concentrated such that a few rare diseases have numerous approved products while the vast majority have none, reflecting the significant clinical risk associated with conducting clinical research in the many rare diseases for which little to no substantial medical literature exists. This, alongside more general access and affordability challenges, has prompted some US and EU policy stakeholders to question the effectiveness of existing incentive structures (European Commission 2020) (Institute for Clinical and Economic Review 2022).

In the US, a reduction of the Orphan Drug Tax Credit by 50% in 2017 served as a negative signal to orphan drug manufacturers that ODA incentives are vulnerable to policy change (National Organization for Rare Disorders 2021). In Europe, the EU Orphan and Paediatric Regulations have been under review since 2020 and in April 2023 the European Commission put forward a proposal for a 'modulated system of incentives' with strict criteria aimed at rewarding innovations that fulfil specific public health objectives (European Parliament 2023).

This erosion of orphan incentives is happening at a time when launching orphan drugs is becoming increasingly challenging due to downward price pressure from payers. European payers have grown stricter on value assessments and more frugal in their willingness to pay since the 2008 financial crisis (Dolon 2021). Meanwhile, the US Inflation Reduction Act of 2022 excludes only single-indication orphan drugs from the Medicare Drug Price Negotiation Program (Cubanski et al. 2023), effectively discouraging indication expansion and limiting the total number of patients that may benefit from innovation in the future (Chambers et al. 2023).

These policy changes collectively risk undermining future investment in rare diseases. For example, an rNPV modelling analysis has estimated that the provisions relevant to orphan medicines proposed by the European Commission in April 2023 would hamper the development of 45 products in Europe between 2020 and 2035 – a projected 12% decrease in innovation (Dolon for EFPIA 2023). See Figure 5.

Figure 5. Case analysis of historic trends in orphan innovation and influencing policies[b]



1 1962
When US Kefauver-Harris Act requires retrospective efficacy trials, unprofitable products go untested and unmet need in rare diseases is revealed[2]

2 1968
Clinical discovery of virus-mediated gene transfer[3]

3 1970s
US FDA recognise "orphan" status and public awareness grows[4]

4 1980s
Patient group coalition (later to become NORD) lobbies for legislative change to incentivise development in orphan diseases[6]

5 1982
Discovery of T-cell antigen receptor, scientific basis for immunotherapy[5]

6 1983
US Orphan Drug Act established the "orphan" designation and financial incentives for development[6]

7 1990–2003
Human Genome Project expands basic understanding around disease mechanisms and new opportunities for treatment[7]

8 1992
US PDUFA passed, providing more timely access for new drugs*[8]

9 1998
Discover of RNA interference and of first human embryonic stem cell line[9]

10 2000
EU OMP regulation established designation and financial incentives in the EU[10]

11 2004
Central authorization for OMPs in EU[10]

12 2006
EU Regulation incentivises paediatric OMP trials[10]

13 2010s
Acceleration of national P&R provisions and earmarked fund to support OMP access in the EU[11]

14 2012
FDA extend PRV to rare paediatric diseases incentivising R&D*[13]

15 2012
CRISPR-Cas9 technology discovered allowing DNA editing[12]

16 2016
EMA PRIME Scheme introduced*[14]

17 2017
First FDA-approved gene therapies enter US market*

18 2017
Orphan tax credit reduced[15]

19 2018
FDA approves first 'N of 1' trial 1 year after development*[16]

20 2020
Review of existing EU OMP Regulation[17]

21 2023–27
PDUFA VII acknowledging clinical endpoints are barriers and importance of patient*[8]

Illustrative and non-exhaustive. *Informed by expert input. See footnote for references.

[b]1. (Food & Drug Administration n.d.) 2. (Greene and Podolsky 2012) 3. (Novartis n.d.) 4. (Huyard 2012) 5. (Eno 2017) 6. (Mikami 2017) 7. (Posey 2019) 8. (PhRMA n.d.) 9. (Fire et al. 1998) 10. (European Medicines Agency n.d.) 11. (Zamora et al. 2019) 12. (Britannica n.d.) 13. (Food & Drug Administration n.d.) 14. (European Medicines Agency n.d.) 15. (National Organization of Rare Disorders 2021) 16. (Kim et al. 2019) 17. (European Commission 2020)

Case reflections

Rare diseases inherently face unique **scientific challenges** that constrain their viability for innovation. Scientific knowledge in terms of *disease understanding* is hampered by several factors: limitations to patient identification due to the scarcity of patients (National Organization for Rare Disorders 2020); conditions which are often are more complex and difficult to study owing to high levels of heterogeneity exacerbated by a lack of understanding of disease natural history (Kempf et al. 2018); and the fact that many diseases affect children, making it difficult to distinguish disease progression from natural development (Nicod et al. 2023). In terms of identifying and testing treatment options, scientific knowledge is further confined by the fact that randomised controlled trials (RCTs) may not be feasible or ethical in cases where diseases are severe and there is a lack of alternative treatments (Mallerio 2022) (orphan trials are 2x as likely to be single arm versus non-orphan (Bell and Smith 2014)). There is also a greater reliance on surrogate, multiple, or even individual endpoints where diseases are heterogenous and/or affect multiple organ systems (Cox 2018).

Rarity also presents **commercial challenges**, even with existing incentive frameworks in place. Per drug spending on R&D is hugely variable, and while the total R&D expenditure is typically lower in rare diseases due to smaller trials, *per patient development costs* are estimated to be significantly higher in rare diseases (Jayasundara et al. 2019). Evidence suggests that risk of *clinical failure* is also higher: one study finds that only 6.2% of orphan drug development projects reach the market versus 13.8% probability of success for all drugs (Wong et al. 2019). Because of these development challenges, alongside low patient volumes, *price* can be an essential lever for achieving the necessary returns required to stimulate investment. Even within rare diseases, drug prices need to be proportional to rarity: adjusting for population size, it has been estimated that achieving a similar ROI in rare as in non-rare requires 2x to 47x the willingness to pay of non-rare disease medicines (Berdud et al. 2020). See Table 3.

Table 3. Global challenges facing orphan innovation today

Factors	Challenges versus non-rare
Clinical	Generally poorer disease knowledge
	More challenging to run confirmatory trials due to population characteristics (i.e., patients are scarce and often geographically dispersed, frequency of heterogenous, paediatric, and/or cognitively impaired populations, etc.)
Economic	Higher risk of R&D failure
	Fewer patients eligible and thus reduced volumes to recoup investment
	Ill-adapted pricing and reimbursement models that fail to recognise the unique evidence challenges and/or need for higher prices in rare diseases to achieve economic viability

Contrast the following two rare disease cases: Haemophilia and Ring chromosome 20 syndrome (RC20). The former is an innovation success story, where orphan incentives combined with historically high disease knowledge and awareness to propel continued development through the 1990s and 2000s approaching a possible cure (Orphanet n.d.) (National Bleeding Disorders Foundation n.d.). RC20, on the other hand, has had access to the same orphan incentives, but the lack of established diagnostic capability and outstanding questions about disease pathology has yet precluded any promising drug candidates for these patients (Orphanet n.d.) (Peron et al. 2020).

Reflecting on the clinical and economic factors within the innovation model may help to explain how a baseline level of incentives can support *economic viability* for some rare disease drugs (e.g., as in Haemophilia), but incentives alone cannot bring innovation to many of the extremely rare diseases which are not yet *clinically viable* because the science simply has not been established yet (e.g., as in RC20). Policies supporting basic science research remain foundational for future innovation, but without the necessary clinical *and* economic opportunity, there is little chance of industry investment.

3. Policy implications

Advances in genetic medicine have resulted in an explosion of clinical viability over the last 20 years, driving transformative technologies from cell and gene therapy to precision medicine and beyond. Rare diseases are at the forefront of this wave of innovation, offering a 'testing ground' for new and revolutionary treatments with immense future potential. The fact that more than 50% of first in class FDA drug approvals between 2011 and 2020 were for orphan products (Gu et al. 2022) is a testament to the scale of innovativeness and success of existing policy to support and encourage development.

Nevertheless, there is a risk that erosion of long-standing orphan regulations will cut short this era of unprecedented orphan innovation, leaving behind future rare disease patients who could one day benefit from today's burgeoning discoveries. Indeed, the antibiotics case study highlights how neglecting incentives today can be a detriment to future innovation. In this case, changing science and clinical practice eroded the commercial landscape over several decades to the present point where new policies to support antibiotics innovation are in dire and urgent need. To ensure that the trajectory of orphan drug development does not follow a similar path, nurturing a *positive and enduring policy environment* will be critical for sustaining investment in rare diseases and hope for future generations.

Achieving this requires first and foremost *maintaining existing orphan incentives* which have proven to be effective in catalysing drug development. Indeed, existing orphan regulations have been key drivers of innovation in rare diseases by broadly enhancing clinical and economic viability and thus expanding opportunities for industry to take viable options over the line. Altering long-standing incentives exacerbates uncertainty for manufacturers with rare disease treatments in their pipelines, heightening the economic risk in an already risky process. The impact of policy decisions taken today will not be known until far into the future. If orphan innovation is to continue to be a priority, it will not serve to curb incentives now.

Second, but equally important, the next wave of innovation may require *new or adapted policy approaches* to encourage continued investment into novel treatment modalities and paradigms. Looking towards the future, cell and gene therapies are an example of true breakthroughs in science, but where economic viability is by no means assured. To enable access to these transformative therapies for more patients who can benefit demands new policies to address the economic side of the equation. These could include regulatory reforms and adapted appraisal methodologies to reduce the cost of development or payment reforms with a more flexible approach to price.

Sustainable innovation in rare disease means *ensuring policy frameworks are sufficiently flexible to evolve with scientific progress*, accounting for the iterative and uncertain nature of drug discovery. Because it is not known where the next breakthrough will occur, incentives and policy frameworks need to keep pace with scientific advancements so that once the science is established, there exists a pathway for economic viability to enable industry investment. Now more than ever, there is a need for policymakers and industry partners to work together to understand and address the clinical and economic hurdles to innovation for the benefit of people living with a rare disease.

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