From Well-Trodden Path to Uncharted Needs: Pharma's Response to Rare Diseases

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Abstract: The pharmaceutical industry's focus has dramatically shifted from mass-market blockbusters to addressing the needs of rare diseases. This paper compares the traditional, volume-driven approach of "Old Pharma" with the patient-centric, innovation-led strategy of "New Pharma," highlighting the changes in economic viability and development timelines.

Historically, conventional drug development, with costs over $1 billion and timelines of 10-15 years, made rare diseases commercially unappealing. However, the Orphan Drug Act of 1983 introduced incentives that fundamentally altered this landscape. When combined with advancements in targeted therapies like gene, cell, and RNA modalities, "New Pharma" for rare diseases now benefits from streamlined development. Direct costs can be as low as $47 million, and in some cases under $25 million, with notably faster launch timelines.

This study presents a structured comparison across scientific, economic, and regulatory dimensions and illustrates how artificial intelligence (AI) accelerates the drug lifecycle. AI enables faster discovery, shorter clinical trial recruitment, improved patient management, and streamlined production, which is especially relevant for rare diseases, where diagnostic delays and limited patient pools remain challenges.

The future of this market points to continued expansion, driven by advanced therapies and AI. This will require ongoing adaptation, ethical governance, and multi-stakeholder collaboration to ensure equitable patient benefits in these previously unexplored therapeutic areas.

Keywords: Classic Pharma, New Pharma, Rare Diseases, Therapeutic Innovation, Regulatory Strategy

G. Szabó-Szentgróti et al. (eds.), *Proceedings of the Kautz Conference on Business and Economics 2025 (KCBE 2025)*, Advances in Economics, Business and Management Research 381,
https://doi.org/10.2991/978-94-6239-658-6_3

1 Introduction

The pharmaceutical industry has historically navigated a "well-trodden path," prioritizing the development of "blockbuster" drugs for large, prevalent disease markets. (Congressional Budget Office, 2021) This traditional model, characteristic of "Old Pharma," was designed to maximize sales volume and recoup the substantial research and development (R&D) investments, which typically ranged from $1.3 billion to $2.87 billion per successful new drug, with some estimates reaching $5.5 billion for companies developing multiple drugs. (Visibelli et al., 2023) This staggering investment was coupled with a lengthy development timeline, often spanning 10 to 15 years from discovery to market approval, and sometimes up to 20 years. (Visibelli et al., 2023) Furthermore, the high failure rate, with only about 12% of drugs that entered clinical trials ever receiving FDA approval, meant significant costs from unsuccessful projects. (PatentPC, 2025)

This established paradigm largely overlooked "uncharted needs", the vast landscape of rare diseases. Individually uncommon, these conditions collectively affect an estimated 300 million individuals globally across approximately 7,000 distinct diseases. In the United States, a rare disease is defined by the Orphan Drug Act (ODA) as affecting fewer than 200,000 people. Despite their collective burden, a striking 95% of known rare diseases currently lack any FDA-approved treatment (McKinsey & Company, 2017), highlighting a critical unmet medical need. The inherent scientific complexity, limited understanding of natural history, and difficulties in conducting clinical trials with small patient cohorts further deterred traditional pharmaceutical companies from venturing into this challenging territory.

The landscape began its profound transformation with the passage of the Orphan Drug Act in 1983. (U.S. Food and Drug Administration, 2024) This landmark legislation was specifically designed to incentivize pharmaceutical companies to invest in rare disease drug development, fundamentally altering the economic calculus. (U.S. Food and Drug Administration, 2024) Key ODA incentives include significant tax credits for qualified clinical testing expenses, waivers for expensive Prescription Drug User Fees (currently nearly $3 million for a new drug), and a crucial potential for 7 years of market exclusivity post-approval. Since its enactment, the ODA has successfully led to the approval of hundreds of drugs for rare diseases (U.S. Food and Drug Administration, 2024), laying the foundational economic and regulatory framework that encouraged the industry to explore these previously neglected areas, marking the genesis of what is now recognized as "New Pharma" in this domain.

This paper addresses two core research questions: (1) How do the strategic, technological, and economic characteristics of Old and New Pharma models differ in the context of rare

diseases? (2) What role does artificial intelligence play in enabling this shift toward rare disease innovation? To answer these, the study employs a comparative analysis across seven key dimensions, including product portfolio, R&D, patient focus, and commercial models. The paper is structured as follows: Section 2 outlines the methodology, Section 3 presents the comparative results, Section 4 discusses broader implications, and Section 5 concludes with key takeaways and future considerations.

2 Methodology

This study employs a comparative analytical methodology to distinguish between "Old Pharma" and "New Pharma" approaches to rare disease drug development. The analysis is structured around seven key dimensions: product portfolio, market dynamics, patient focus, research & development (R&D), manufacturing, sales, and economics.

Data for this comparative analysis were drawn from a comprehensive review of existing literature, including peer-reviewed scientific articles, industry reports, and regulatory documents. Information on "Old Pharma" was primarily derived from historical accounts of pharmaceutical R&D and commercial models predating or immediately following the Orphan Drug Act of 1983, characterized by a focus on blockbuster drugs and large markets - the "well-trodden path." Data for "New Pharma" were gathered from contemporary research and industry analyses reflecting post-ODA strategies, particularly those incorporating advanced therapeutic modalities and digital technologies, representing the exploration of "uncharted needs."

The role of Artificial Intelligence (AI) was integrated as a cross-cutting theme, examining its applications across the entire drug development lifecycle and its impact on the economic and temporal efficiencies within the "New Pharma" paradigm. Specific quantitative data points regarding development costs, timelines, market growth, and AI-driven efficiencies were extracted and synthesized to provide a robust comparison. The methodology involved:

- Categorization: Defining the characteristics of "Old Pharma" and "New Pharma" across the seven specified dimensions, aligning with the "well-trodden path" versus "uncharted needs" metaphor.
- Data Extraction: Identifying and extracting relevant quantitative and qualitative information from the research material that highlights differences in cost, time, and operational strategies between the two paradigms.
- Comparative Analysis: Systematically comparing the two paradigms within each dimension, emphasizing the shifts and the drivers behind

them, particularly how "New Pharma" addresses previously "uncharted" challenges.

- AI Integration: Analyzing how AI applications specifically address the challenges and enhance the opportunities within the "New Pharma" model, particularly concerning time and cost reduction in navigating these complex new territories.
- Source Selection and Weighting: We identified evidence through targeted searches in Scopus and Web of Science, restricting results to English-language publications from 2017 to 2025, and complemented these with regulatory materials drawn solely from the FDA. Records were screened for topical fit to rare-disease drug development or economics and were included when they provided quantitative estimates or well-evidenced qualitative insights; eligible document types comprised peer-reviewed studies, regulatory and policy documents, and selected industry or consulting reports, while non-English materials and unsupported opinion or promotional content were excluded. To maintain consistency across heterogeneous sources, we applied an evidence hierarchy that prioritised regulatory and policy documents over peer-reviewed research, followed by industry/consulting analyses and, lastly, trade media or vendor blogs; within each tier, recency, methodological clarity, breadth of coverage, and concordance with other sources increased evidential weight. Where estimates conflicted, we resolved discrepancies by privileging the most recent, highest-quality figures, and we treated AI-related claims from vendor or press sources as illustrative unless replicated in peer-reviewed or regulatory evidence.

This approach allows for a structured and evidence-based comparison, illustrating the evolution of rare disease pharma and the pivotal role of AI in its current trajectory.

3 Results

The comparative analysis reveals a profound divergence in strategies and operational models between "Old Pharma" and "New Pharma" in the rare disease sector, largely driven by policy changes and technological advancements, with significant implications for economic and temporal efficiencies.

3.1 Product Portfolio and Treatment Modalities

Old Pharma (Well-Trodden Path): Historically, portfolios were dominated by small molecules aimed at symptomatic relief for common diseases. (Mingorance, 2018) Rare diseases were not a dedicated focus, and any engagement was a secondary outcome of developing treatments for broader conditions. (Mingorance, 2018) The emphasis was on "blockbuster" drugs that could be applied to large patient populations, maximizing sales volume to recoup multi-billion dollar R&D investments over long periods.
New Pharma (Uncharted Needs): A significant shift towards targeted therapies, biologics, and advanced modalities such as gene and cell therapies, and RNA therapeutics is evident. (The Motley Fool, 2024) The objective has evolved from symptomatic relief to disease modification or potential cure by addressing underlying causes. (Mingorance, 2018) This is driven by a "technology pull," where advanced therapies provide the scientific means to address complex, often genetic, root causes previously untreatable. (Yoo, 2024) Examples include Enzyme Replacement Therapy (ERT) for lysosomal storage diseases (Yoo, 2024), gene therapies for Spinal Muscular Atrophy (SMA) and hemophilia B (Han et al., 2022), and CRISPR-based therapies for sickle cell disease. (Vavassori et al., 2024) RNA therapeutics, including mRNA and antisense oligonucleotides (ASOs), offer highly targeted and often more cost-effective approaches to modulate gene expression, opening new avenues for treatment. (evolve-ip, 2025) This fundamentally redefines the "product" from traditional small molecules to sophisticated, often personalized, biological interventions, explaining why smaller, agile biotechs are at the forefront of this innovation.

3.2 Market Dynamics and Strategic Focus

Old Pharma (Well-Trodden Path): Rare diseases were perceived as commercially unviable, with the thinking that "small patient populations equal small returns". The strategic focus was almost exclusively on developing "blockbuster" drugs for large, prevalent markets, where economies of scale could justify long development timelines and high R&D costs.
New Pharma (Uncharted Needs): Rare diseases are now recognized as a significant and growing strategic opportunity. The market for rare disease treatments is projected to reach $426.03 billion by 2030, demonstrating a robust compound annual growth rate (CAGR) of 11.93%. (Citeline, 2025) This shift is driven by high unmet medical need, reduced competitive pressure, and attractive regulatory incentives. Companies achieve high market share and command premium pricing for orphan drugs. Rare disease therapies typically experience faster market uptake, with an average time to peak share of just four years for non-oncology rare therapies, compared to ten years for non-rare ones. A substantial proportion of new rare disease launches (38% between 2022-2024) are "first-in-disease"

treatments, indicating entry into less saturated markets with high innovation potential. Large pharmaceutical companies use rare diseases as a "stepping-stone" to de-risk novel therapeutic platforms before expanding to broader indications, leveraging smaller, more manageable clinical trials. (Mingorance, 2018) This minimizes financial and clinical risk, reflecting a calculated shift from direct market entry to a phased, de-risked innovation pathway, venturing into new therapeutic areas.

3.3 Patient Focus and Engagement

Old Pharma (Well-Trodden Path): Engagement was largely indirect and limited, focusing on physician-centric marketing. There was a general lack of in-depth understanding of the complex needs of rare disease patients and caregivers. The long diagnostic odyssey, averaging 4.8 years for many rare diseases, meant patients often suffered for extended periods without proper identification or treatment, incurring significant personal and societal costs.

New Pharma (Uncharted Needs): Patient-centricity is a fundamental principle, permeating all stages of drug development and commercialization. Companies actively cultivate meaningful and trusted relationships with patients, caregivers, and healthcare professionals (HCPs). Early Access Programs (experimental, named patient, humanitarian access) offer investigational treatments before full commercial approval, helping to reduce the time to treatment start for patients. (McKinsey & Company, 2017) Pharmaceutical companies provide comprehensive support, including assistance with insurance paperwork and navigating reimbursement processes. Robust engagement with Patient Advocacy Organizations (PAOs) is paramount. PAOs are active partners providing "critical patient insights", helping "shape research priorities and trial designs" (Ergomed, 2025), and facilitating "recruitment promotion". (RD-RP, 2025) This transforms a one-way communication into a collaborative partnership, where patient voice directly influences R&D, market access, and commercialization strategies, crucial for navigating the unique challenges of rare disease populations.

3.4 Research & Development (R&D) and Manufacturing

Old Pharma (Well-Trodden Path): Characterized by remarkably high R&D costs, with average development costs for a new drug ranging from $1.3 billion to $2.87 billion, and a lengthy timeline of 10 to 15 years from discovery to market approval. This approach necessitated large-scale clinical trials involving thousands of participants to achieve statistical significance. (PatentPC, 2017) Manufacturing processes were geared towards producing large batch sizes for mass-market drugs.

New Pharma (Uncharted Needs): R&D is increasingly streamlined, benefiting from smaller, more efficient clinical trials. This includes significantly fewer patients overall, fewer trial sites, and often a reduced need for control arms due to high unmet needs and ethical considerations. This efficiency contributes to lower investment costs and faster launch timelines. While fully-loaded costs (including failures) for orphan drugs can still be substantial, the direct out-of-pocket clinical costs are estimated at around $250 million. (Devinebio, 2025) More specifically, direct costs for preclinical development are estimated at $7 million, and direct clinical development costs are near $40 million, totaling approximately $47 million. (Devinebio, 2025) Some innovative approaches have even achieved market approval for a complex biologic for under $25 million, with future projects potentially costing less than $10 million. (Devinebio, 2025) The clinical success rate for orphan drugs is also three times higher than for non-orphan drugs, offsetting some higher out-of-pocket clinical trial costs. (ZS, 2025) New Pharma leverages accelerated regulatory pathways such as Orphan Drug Designation, Breakthrough Therapy Designation, and Rare Pediatric Disease Designations, which expedite the approval process. This signifies an "agile development" model, prioritizing speed, efficiency, and specialized expertise over sheer volume, essential for addressing the urgent needs in rare diseases.

Manufacturing has adapted to the unique needs of rare disease therapies, requiring flexible and small-batch production due to limited patient populations and the specialized nature of advanced modalities. There is a growing reliance on specialized Contract Development and Manufacturing Organizations (CDMOs). CDMOs provide access to highly specialized technologies (e.g., cell and gene therapy fill/finish 49) and regulatory expertise that smaller firms may lack (Pharmacy Times, 2025), allowing "New Pharma" companies to de-risk development, accelerate timelines, and scale production efficiently for niche products without prohibitive capital investment. (Pharmacy Times, 2025) This highlights a shift towards a more collaborative and specialized ecosystem where core competencies are leveraged across different entities, crucial for navigating the complexities of rare disease manufacturing.

3.5 Sales and Commercial Models

Old Pharma (Well-Trodden Path): Relied on a "blockbuster" commercial model characterized by massive, broad-based sales forces (e.g., 100,000 reps in 2005 (Devinebio, 2025)) and mass marketing campaigns aimed at driving high prescription volumes. (DrugPatentWatch, 2025) Success metrics were primarily total prescriptions and overall sales volume, requiring significant promotional spend. (DrugPatentWatch, 2025)

New Pharma (Uncharted Needs): Employs highly specialized, targeted sales teams. This approach benefits from significantly lower promotional spend due to the highly targeted

nature of rare disease markets. The focus is on high-touch, concentrated engagement with a smaller number of prescribing physicians and centralized provider channels. Account management is critical, particularly for products administered in specialized hospital settings. There is an emphasis on deep scientific engagement with Key Opinion Leaders (KOLs) and high-value prescribers to discuss complex treatment paradigms. A core aspect of the commercial model is patient-centric support, including assistance with drug treatment administration, navigating complex reimbursement processes, and facilitating early access programs. The shift is from a broad "push" marketing model to a highly refined "pull" strategy, recognizing that mass marketing is inefficient and ineffective for small, dispersed patient populations. The sales force acts less as a traditional promoter and more as a specialized support and access facilitation team, guiding patients and HCPs through complex diagnostic, treatment, and reimbursement pathways. New Pharma also leverages real-world data (RWD) for precise patient identification and targeted outreach to relevant specialists and physician groups. Sales territories for rare disease representatives are often geographically massive due to the dispersed nature of patient populations. This tailored approach is essential for effectively reaching and serving the unique patient communities in rare diseases.

3.6 Economics and Investment Landscape

Old Pharma (Well-Trodden Path): Characterized by insufficient financial incentives, high perceived investment risk, and a low anticipated return on investment for rare diseases. R&D spending decisions were primarily driven by the anticipated lifetime global revenues from a new drug and the expected costs of development, favoring large-market blockbusters with their multi-billion dollar revenue potential. (Congressional Budget Office, 2021)
New Pharma (Uncharted Needs): The economic model is significantly influenced by Orphan Drug Act incentives, including tax credits, regulatory fee waivers, and the crucial 7-year market exclusivity period. Premium pricing for orphan drugs is widely accepted by payers due to high unmet medical need, significant clinical benefits, and limited alternative treatment options. The average annual price of orphan drugs can be around $400,000 in key markets. (ZS, 2025) This reveals a paradox where individually high drug prices are accepted because the total budget impact is often relatively small due to the limited patient population, and the societal value (e.g., improved quality of life, reduced long-term care costs, increased productivity) is significant. Payers are willing to make exceptions to traditional cost-effectiveness analyses. The economic discussion shifts from a focus on the unit cost of the drug to the holistic value and long-term impact of the treatment, fundamentally altering the traditional cost-benefit analysis for rare diseases.

Emerging "pay-for-performance" models are being explored to align pricing with real-world effectiveness and durability, potentially involving annual installment payments over several years. Rare disease development benefits from lower overall development costs and faster launch timelines compared to non-rare diseases. Lower promotional spend, faster market uptake, and reduced competitive pressure contribute to a more attractive commercial runway. There is increased investment from Big Pharma, often through strategic acquisitions of smaller, innovative biotech companies. Venture philanthropy and social impact funding have emerged as crucial non-dilutive capital sources for early-stage rare disease R&D, with non-profit foundations willing to take higher risks than traditional venture capitalists. The Cystic Fibrosis Foundation's investment in Vertex Pharmaceuticals is a notable success story, leading to significant funding increases through royalty sales. (Morgan Lewis, 2025) Priority Review Vouchers (PRVs), which can be sold, provide another significant source of non-dilutive capital for companies developing rare disease therapies, allowing them to recoup development costs and invest in new programs. Startups and smaller biotechs are responsible for the majority of new drug development, often innovating more efficiently with fewer resources than large pharmaceutical companies. This creates a dynamic, multi-stakeholder innovation pipeline, signifying a strategic acknowledgment that different entities excel at different stages of the drug development lifecycle, leading to a more efficient overall ecosystem for bringing innovative rare disease therapies to patients (Table 1).

Table 1. Key Differentiators: "Old Pharma" (Well-Trodden Path) vs. "New Pharma" (Uncharted Needs) in Rare Diseases

Dimension	Old Pharma (Pre-ODA / Traditional Approach)	New Pharma (Post-ODA / Modern Approach)
Product Portfolio	Symptomatic relief, small molecules, broad disease focus, limited rare disease pipeline.	Targeted therapies, biologics, gene/cell/RNA therapies, disease modification/cure, dedicated rare disease pipelines.
Market Dynamics	Perceived as commercially unviable, market neglect, focus on large markets.	Strategic growth opportunity, high unmet need, less competition, premium pricing, faster uptake, "first-in-disease" focus.
Patient Focus	Limited direct engagement, physician-centric marketing, less understanding of patient needs.	Deep patient-centricity, early access programs, comprehensive patient/caregiver support, strong PAO engagement.

R&D & Manufacturing	High R&D costs, large clinical trials, traditional large-batch manufacturing.	Streamlined R&D, smaller/efficient trials, accelerated regulatory pathways, flexible small-batch manufacturing, reliance on specialized CDMOs.
Sales & Commercial Models	Broad sales forces, mass marketing, volume-driven.	Highly specialized/targeted teams, lower promotional spend, high-touch engagement, account management, patient access support, RWD-driven targeting.
Economics & Investment	Insufficient incentives, high risk, low ROI perception.	ODA incentives (tax credits, exclusivity), premium pricing accepted, venture philanthropy, PRVs, strategic acquisitions, startups as innovation drivers.

3.7 The AI Revolution in Rare Disease Pharma

Artificial Intelligence (AI) is a transformative force revolutionizing the rare disease pharmaceutical sector, significantly impacting time and cost efficiencies across the entire drug lifecycle, enabling navigation of previously "uncharted" complexities.

AI in Drug Discovery & Development: AI fundamentally changes orphan drug research by tackling critical barriers such as high financial risk, development complexity, and low trialability. (Irissarry & Burger-Helmchen, 2024) It significantly accelerates target identification, allowing for earlier identification of promising drug candidates and increasing the likelihood of clinical success. (Coherent Solutions, 2025) AI enables the accelerated design of new molecules from scratch; for instance, Moderna's COVID-19 vaccine saw an AI-driven process design a vaccine candidate within two days of genetic sequence availability. (Irissarry & Burger-Helmchen, 2024) AI also plays a crucial role in drug repurposing by identifying novel drug-gene links and analyzing complex disease data, associating rare diseases with common ones that have existing treatments. (U.S. Food and Drug Administration, 2024) Advanced AI tools like KGWAS enhance traditional genome-wide association studies, improving the detection of genetic links in small patient cohorts, identifying up to 100% more statistically significant associations, or achieving the same detection power with 2.7 times fewer samples. (Axtria, 2025) Critically, AI allows biotech startups to identify drug candidates 10 times faster and at a fraction of the cost compared to traditional methods.

AI in Clinical Trials: AI significantly optimizes patient identification, recruitment, and retention for rare disease clinical trials. (Irissarry & Burger-Helmchen, 2024) This is crucial given the low prevalence and geographical dispersion of rare disease patients. Machine learning models can analyze vast Electronic Health Records (EHRs) to identify eligible participants quickly and accurately, often identifying patients missed by traditional registry-

based methods. (Irissarry & Burger-Helmchen, 2024) AI can speed up the patient recruitment process, which typically accounts for one-third of a clinical trial's duration. (Irissarry & Burger-Helmchen, 2024) AI enhances trial design and monitoring for efficiency. (Irissarry & Burger-Helmchen, 2024) It can predict patient dropouts, allowing for proactive intervention to maintain trial integrity. (Irissarry & Burger-Helmchen, 2024) AI-powered simulations and virtual trials can compensate for the inherent limitations of small patient populations. (Irissarry & Burger-Helmchen, 2024) By mitigating these operational and statistical risks, AI fundamentally de-risks the clinical development phase for rare disease therapies, translating directly into lower financial exposure for pharmaceutical companies and a faster time to market for much-needed treatments. (Irissarry & Burger-Helmchen, 2024)

AI in Patient Management and Personalized Medicine: AI significantly improves early diagnosis by analyzing large, heterogeneous datasets, including electronic medical records, genomic data, and imaging studies, to identify patterns characteristic of specific rare diseases. (Carnegie Mellon University, 2025) This can help diagnose previously unrecognized conditions, shortening the often-long "diagnostic odyssey" for patients and reducing associated time and costs. Predictive modeling techniques, such as deep learning, are used to forecast the progression of rare diseases and predict patient vulnerability, providing valuable insights for prognoses and guiding treatment decisions. (Visibelli et al., 2023) AI enables tailored treatment approaches and personalized medicine by identifying subpopulations of patients most likely to respond to a particular drug, based on their unique molecular characteristics. (Premier Research, 2025) AI integrates and analyzes diverse data types (e.g., multi-omics data, images) to provide a comprehensive understanding of disease mechanisms and patient responses. (The Motley Fool, 2024)

AI in Manufacturing and Supply Chain: AI-driven systems are optimizing pharmaceutical manufacturing by reducing errors, improving product consistency, and enhancing overall efficiency and quality. (Coherent Solutions, 2025) Real-time analytics allow production lines to adjust dynamically, ensuring smoother operations and faster production cycles, which is particularly vital for specialized, often low-volume, rare disease therapies. (Coherent Solutions, 2025) Predictive maintenance, powered by AI analyzing sensor data from equipment, identifies potential issues before they cause costly delays, ensuring continuous production and maximizing uptime for critical manufacturing processes. (Coherent Solutions, 2025) AI enhances supply chain management by improving demand forecasting and inventory optimization, minimizing waste, and ensuring timely deliveries of specialized and often temperature-sensitive rare disease products. (Coherent Solutions, 2025) Real-time tracking of shipments and AI monitoring of storage conditions maintain

product integrity throughout the supply chain, ensuring drugs are delivered safely and on time. (Coherent Solutions, 2025)

AI in Real-World Evidence (RWE) Generation: AI is instrumental in leveraging Real-World Data (RWD) from diverse sources such as Electronic Health Records (EHRs), claims data, and patient registries to fill critical evidence gaps in rare disease research. RWD, powered by AI, provides longitudinal, real-time insights that help pharmaceutical teams identify eligible patients, test clinical trial protocols, and streamline trial site identification. (TriNetX, 2025) It enables the capture of the complexity of patient care and reveals patterns that traditional, often limited, clinical studies might miss. (TriNetX, 2025) RWE generated with AI support is increasingly used to support regulatory submissions and Health Technology Assessment (HTA) processes. This is particularly crucial for demonstrating the value and cost-effectiveness of rare disease treatments to payers, especially when traditional randomized controlled trial (RCT) data is limited due to small patient populations. RWE helps build a persuasive value story by quantifying the benefits of treatment and the risks of non-treatment (Table 2). RWE studies can also cut the time and cost of clinical research. (IQVIA, 2021)

Table 2. AI Applications Across the Rare Disease Drug Lifecycle

Lifecycle Stage	AI Application	Benefit/Impact
Drug Discovery	Target Identification, Molecule Design, Drug Repurposing.	Accelerates identification of promising candidates, rapid de novo drug design, identifies new uses for existing drugs, overcomes data scarcity challenges.
Preclinical Research	Predictive Modeling (efficacy, toxicity, ADME).	Reduces experimental costs and time, improves compound selection, minimizes animal testing.
Clinical Trials	Patient Identification & Recruitment, Trial Design Optimization, Patient Monitoring, Dropout Prediction.	Speeds up enrollment, enhances trial efficiency, reduces costs, improves patient adherence and retention, enables virtual trials.
Manufacturing	Process Optimization, Predictive Maintenance.	Reduces errors, improves consistency/quality, prevents costly downtime, ensures flexible small-batch production.

Supply Chain Management	Demand Forecasting, Inventory Optimization, Real-time Tracking.	Minimizes waste, ensures timely delivery, maintains product integrity for specialized therapies.
Patient Management & Personalized Medicine	Early Diagnosis, Disease Progression Prediction, Subpopulation Identification.	Shortens diagnostic odyssey, enables tailored treatments, improves patient outcomes based on individual characteristics.
Post-Market Surveillance & Real-World Evidence (RWE)	RWE Generation & Analysis, Value Demonstration.	Fills evidence gaps, supports regulatory/HTA submissions, quantifies real-world benefits, justifies premium pricing.

3.8 Consolidated Comparison of Approaches

Table 3 distils the preceding Results into a side-by-side view of "Old" and "New" Pharma across seven dimensions, highlighting how market focus, development practice, and economics shift in rare-disease contexts. It complements the earlier quantitative figures on time and cost by situating those gains within operational and strategic changes observed throughout the section.

Table 3. High-Level Comparison of Old and New Pharma

	OLD Pharma	NEW Pharma
Product portfolio	Narrow	Wide
Markets	Mass Phenotype	Targeted Genotype
Patient focus	Disease state	Disease life cycle
Treatment	1 Drug / 1 Disease	Continuity of treatments
Manufacturing	Few large runs	Many small runs
Sales	Few large teams	Multiple small teams
Economics	Scale	Knowledge

4 Discussion

The transition from "Old Pharma's" "well-trodden path" to "New Pharma's" exploration of "uncharted needs" in rare diseases represents a fundamental reorientation of pharmaceutical strategy. This shift is driven by a confluence of regulatory incentives, scientific breakthroughs (BioBuzz, 2025), and the transformative power of AI. (Irissarry & Burger-Helmchen, 2024) The historical neglect of rare diseases, rooted in the prohibitive costs and protracted timelines of traditional drug development, has given way to a vibrant ecosystem where these conditions are now recognized as strategic opportunities.

The Orphan Drug Act of 1983 (U.S. Food and Drug Administration, 2024) was the critical policy lever that de-risked rare disease R&D, making it economically viable. (U.S. Food and Drug Administration, 2024) By offering tax credits, fee waivers, and market exclusivity, the ODA directly addressed the unfavorable risk-reward ratio that previously deterred investment. (U.S. Food and Drug Administration, 2024) This legislative framework paved the way for the development of advanced therapeutic modalities, such as gene, cell, and RNA therapies (The Motley Fool, 2024), which offer the potential for disease modification or even cure, a significant departure from the symptomatic relief offered by traditional small molecules. (Mingorance, 2018)

The most striking aspect of this paradigm shift is the dramatic improvement in economic and temporal efficiencies. While "Old Pharma" faced multi-billion dollar development costs and timelines stretching over a decade, "New Pharma" benefits from streamlined R&D processes, smaller and more efficient clinical trials, and accelerated regulatory pathways. This has led to significantly lower direct development costs for orphan drugs, potentially reducing them to tens of millions of dollars (Devinebio, 2025), and notably faster market uptake. This agility is crucial for addressing the high unmet medical needs and urgency associated with rare diseases, allowing the industry to venture into previously inaccessible therapeutic areas.

Rare-disease strategies and AI entered pharma as emerging phenomena and, since roughly 2010, have moved from niche to central practice. While the precise triggers are multifactorial, their growing scale and significance are evident in indicators such as the rising share of rare-disease assets in development pipelines, the reallocation of R&D spend, and the steady uptake of AI across discovery, clinical operations, and manufacturing. Together, these signals suggest an inflection from experimentation to mainstream adoption, which frames the comparative shifts reported here.

Artificial Intelligence is not merely an adjunct but a central enabler of this "New Pharma" model. AI's capabilities in analyzing vast, complex datasets are directly addressing the inherent challenges of rare diseases, such as data scarcity (Irissarry & Burger-Helmchen, 2024) and patient identification. From accelerating drug discovery by identifying candidates 10 times faster and at a fraction of the cost, to optimizing clinical trials by reducing recruitment time by one-third (Irissarry & Burger-Helmchen, 2024), AI is compressing development timelines and lowering financial exposure. (Irissarry & Burger-Helmchen, 2024) Furthermore, AI's role in shortening the diagnostic odyssey and generating robust real-world evidence is critical for demonstrating the value of high-cost orphan drugs to payers and ensuring market access. The integration of AI into manufacturing and supply chain management further enhances efficiency and reliability for

specialized, low-volume therapies (Coherent Solutions, 2025), making the navigation of these "uncharted needs" more feasible.

At the same time, our findings indicate that current generative, agentic AI is not yet reliable for end-to-end execution. Effective use still requires stepwise human orchestration, verification, and sign-off throughout the pipeline. Constraints in dataset coverage and embedded biases can skew outputs, while hallucinations and other error modes remain material risks. We therefore treat AI outputs as decision support rather than autonomous substitution; human scientists remain essential to framing questions, selecting methods, and interpreting analyses in line with scientific values and patient interests.

Despite these remarkable advancements, challenges persist. Patient recruitment and retention remain difficult due to dispersed populations and complex protocols. Diagnostic delays, though improving with AI, still impact early intervention. (Cacoub et al., 2025) High treatment costs and complex reimbursement pathways continue to be contentious issues, necessitating innovative pricing models and robust value demonstration. Furthermore, the rapid pace of AI development necessitates continuous ethical governance (Irissarry & Burger-Helmchen, 2024) and adaptive regulatory oversight (Irissarry & Burger-Helmchen, 2024) to ensure safety, mitigate bias, and maintain the essential human element in patient care, especially for vulnerable rare disease populations.

While regulations (e.g., US Orphan Drug Act, EU Orphan Regulation 141/2000, UK post-Brexit MHRA incentives) anchor our analysis, comparable rare-disease incentive regimes are uneven globally. Our results support a mixed path: pursue international harmonisation on core elements such as clear designation, fee relief, time-limited exclusivity, and evidence-development obligations, while permitting locally tailored measures that reflect health-system priorities and affordability constraints. Where coherent incentives are present, New-Pharma dynamics are more likely to emerge; where gaps persist, Old-Pharma economics dominate, delaying timely access for small patient populations.

The increasing investment from large pharmaceutical companies, often through strategic acquisitions of agile biotech startups, signifies a mature understanding of the rare disease market. This collaborative ecosystem, further bolstered by venture philanthropy, allows for the efficient progression of innovative therapies from early-stage research to global commercialization, effectively charting new paths for drug development.

5 Conclusion

The pharmaceutical industry's response to rare diseases marks a profound and multifaceted transformation, moving from a "well-trodden path" of mass-market focus to a dedicated pursuit of "uncharted needs." "Old Pharma's" traditional model, characterized by

prohibitive costs and lengthy timelines, proved ill-suited for rare diseases, leading to significant market failure. The Orphan Drug Act of 1983 (U.S. Food and Drug Administration, 2024) served as a pivotal catalyst, fundamentally altering the economic landscape and enabling the emergence of "New Pharma."

"New Pharma" is defined by a dedicated focus on rare diseases as a strategic growth opportunity, embracing targeted therapies that address underlying disease causes. (Mingorance, 2018) This new paradigm benefits from significantly streamlined R&D, with direct development costs potentially reduced to tens of millions of dollars (Devinebio, 2025) and notably faster launch timelines compared to traditional drug development.

Artificial Intelligence is central to this evolution, acting as a powerful enabler across the entire drug lifecycle. (Irissarry & Burger-Helmchen, 2024) AI accelerates drug discovery (up to 10 times faster and at a fraction of the cost), optimizes clinical trials (reducing recruitment time by one-third) (Irissarry & Burger-Helmchen, 2024), shortens diagnostic odysseys, and enhances manufacturing and supply chain efficiencies (Coherent Solutions, 2025), thereby directly addressing the economic and temporal barriers that historically plagued rare disease drug development. Its ability to leverage real-world data is redefining evidence generation, crucial for market access and reimbursement of high-value orphan drugs.

Future work should prioritise patient outcome evidence (including real-world and patient-reported outcomes) drawn from large national and regional registries, with strict attention to data freshness and interoperability. In parallel, future work must include comparative economic evaluations that explicitly account for regional specificities in pricing, reimbursement, and care pathways, without privileging any single unit of analysis. A goal for the AI must be to pursue prospective, human-in-the-loop evaluations of agentic workflows: routine bias and coverage audits of training data, hallucination/error tracking with pre-specified acceptance tests, traceable audit trails for decisions, and replication across settings. Together, these strands would test whether the reported efficiency gains translate into measurable patient benefit across diverse health systems.

While significant progress has been made, challenges in patient identification, diagnostic delays (Cacoub et al., 2025), and high treatment costs persist. The future prognosis for rare disease pharma is one of continued robust growth (ZS, 2025), fueled by ongoing therapeutic advancements (pharmaphorum, 2025) and deeper AI integration. (Irissarry & Burger-Helmchen, 2024) However, realizing this potential hinges on proactive ethical governance of AI (Irissarry & Burger-Helmchen, 2024), continuous adaptation of regulatory frameworks, and sustained, collaborative efforts among pharmaceutical companies, patient advocacy groups, and policymakers. The ultimate success will be measured not only by scientific breakthroughs but also by the ability to ensure equitable access and deliver

transformative improvements to the lives of rare disease patients globally, as the industry continues to bravely venture into these previously "uncharted needs."

References

1. Axtria: Navigating the pharma commercial models for rare diseases. Homepage, https://insights.axtria.com/articles/navigating-the-pharma-commercial-models-for-rare-diseases, last accessed 2025/08/11
2. BioBuzz: Five biotechs poised to advance their rare disease programs [2022 updated]. Homepage, https://news.biobuzz.io/2025/07/16/five-biotechs-poised-to-advance-their-rare-disease-programs-in-2020/, last accessed 2025/07/16
3. Cacoub, E., Lefebvre, N.B., Milunov, D., Sarkar, M., Saha, S.: Quantifying hope: An EU perspective of rare disease therapeutic space and market dynamics. Frontiers in Public Health 13, 1520467 (2025)
4. Carnegie Mellon University: Finding answers faster: AI method brings hope to rare disease research. Homepage, https://www.cmu.edu/news/stories/archives/2025/august/finding-answers-faster-ai-method-brings-hope-to-rare-disease-research, last accessed 2025/08/05
5. Citeline: Rare disease R&D: Constant growth amid challenges. Homepage, https://www.citeline.com/en/resources/rare-disease-r-and-d, last accessed 2025/02/24
6. Coherent Solutions: Artificial intelligence in pharmaceuticals and biotechnology: Current trends and innovations. Homepage, https://www.coherentsolutions.com/insights/artificial-intelligence-in-pharmaceuticals-and-biotechnology-current-trends-and-innovations, last accessed 2025/07/01
7. Congressional Budget Office: Research and development in the pharmaceutical industry. Homepage, https://www.cbo.gov/publication/57025 (2021)
8. Devinebio: Drug development cost. Homepage, https://www.devinebio.com/drug-development-cost, last accessed 2025/08/11
9. DrugPatentWatch: The new pharma playbook: From data overload to market domination. Homepage, https://www.drugpatentwatch.com/blog/new-business-models-for-pharmaceutical-marketing-transforming-data-into-market-domination/, last accessed 2025/07/25
10. Ergomed: 6 actionable strategies to engage rare disease patient advocacy organizations effectively. Homepage, https://ergomedcro.com/6-actionable-strategies-to-engage-rare-disease-patient-advocacy-organizations-effectively/ (2025)
11. evolve-ip: The great consolidation: Big pharma buys the advanced therapy technology, not just the drug. Homepage, https://evolve-ip.com/the-great-consolidation-big-pharma-buys-the-advanced-therapy-technology-not-just-the-drug/, last accessed 2025/08/08

12. Han, Q., Fu, H., Chu, X., Wen, R., Zhang, M., You, T., Fu, P., Qin, J., Cui, T.: Research advances in treatment methods and drug development for rare diseases. Frontiers in Pharmacology 13, 971541 (2022)
13. IQVIA: Real world evidence opportunities in rare disease. Homepage, https://www.iqvia.com/locations/united-states/blogs/2021/03/rwe-opportunities-in-rare-disease, last accessed 2021/03/09
14. Irissarry, C., Burger-Helmchen, T.: Using artificial intelligence to advance the research and development of orphan drugs. Businesses 4, 453–472 (2024)
15. McKinsey & Company: How to successfully launch a rare disease drug in a patient-centric world. Homepage, https://www.mckinsey.com/industries/life-sciences/our-insights/how-to-successfully-launch-a-rare-disease-drug-in-a-patient-centric-world, last accessed 2017/01/09
16. Mingorance, A.: Drivers of orphan drug development. ACS Medicinal Chemistry Letters 9, 962–964 (2018)
17. Morgan Lewis: Venture philanthropy, more important than ever for rare disease care. Homepage, https://www.morganlewis.com/blogs/asprescribed/2025/02/venture-philanthropy-more-important-than-ever-for-rare-disease-care, last accessed 2025/02/27
18. PatentPC: The cost of drug development: How much does it take to bring a drug to market? Homepage, https://patentpc.com/blog/the-cost-of-drug-development-how-much-does-it-take-to-bring-a-drug-to-market-latest-data, last accessed 2017/01/17
19. PatentPC: Big pharma vs. biotech startups: Who's leading the next drug innovation wave? (Market trends). Homepage, https://patentpc.com/blog/big-pharma-vs-biotech-startups-whos-leading-the-next-drug-innovation-wave-market-trends, last accessed 2025/07/19
20. Pharmacy Times: Leveraging AI within rare disease care while maintaining humanity. Homepage, https://www.pharmacytimes.com/view/leveraging-ai-within-rare-disease-care-while-maintaining-humanity, last accessed 2025/05/13
21. pharmaphorum: On incentivisation and investment in rare disease R&D. Homepage, https://pharmaphorum.com/rd/incentivisation-and-investment-rare-disease-rd, last accessed 2025/02/28
22. Premier Research: A rare look into new guidances: The future state of orphan drug development. Homepage, https://premier-research.com/webinars/a-rare-look-into-new-guidances-the-future-state-of-orphan-drug-development-on-demand/, last accessed 2025/02/28
23. RD-RP: Engaging patient and advocates in rare disease clinical trials. Homepage, https://www.rd-rp.com/engaging-patient-and-advocates-in-rare-disease-clinical-trials (2025)
24. The Motley Fool: Biotech vs pharma: What are the differences? Homepage, https://www.fool.com/investing/stock-market/market-sectors/healthcare/biotech-vs-pharma/, last accessed 2024/05/03
25. TriNetX: New TriNetX research impact report illuminates how real-world data is fueling rare disease innovation. Homepage, https://trinetx.com/press-releases/new-trinetx-

research-impact-report-illuminates-how-real-world-data-is-fueling-rare-disease-innovation/, last accessed 2025/07/31
26. U.S. Food and Drug Administration: Rare diseases at FDA. Homepage, https://www.fda.gov/patients/rare-diseases-fda, last accessed 2024/11/21
27. Vavassori, S., Russell, S., Scotti, C., Benvenuti, S.: Unlocking the full potential of rare disease drug development: Exploring the not-for-profit sector's contributions to drug development and access. Frontiers in Pharmacology 15, 1441807 (2024)
28. Visibelli, A., Roncaglia, B., Spiga, O., Santucci, A.: The impact of artificial intelligence in the odyssey of rare diseases. Biomedicines 11 (2023)
29. Yoo, H.-W.: Development of orphan drugs for rare diseases. Clinical and Experimental Pediatrics 67, 315–327 (2024)
30. ZS: Rare disease: The future of clinical pharma innovation. Homepage, https://www.zs.com/insights/rare-disease-pharma-innovation, last accessed 2025/07/24