

Combination Products in Rare Disease Management

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ABSTRACT

Rare diseases affect fewer than 1 in 2,000 individuals in Europe and fewer than 200,000 patients in the United States, yet collectively they represent a major global health burden across approximately 7,000 distinct conditions. Combination products -- integrated or co-packaged combinations of drugs, biologics, devices, and digital therapeutics that function as a single product -- have emerged as the dominant therapeutic innovation model in rare disease management, where the complexity of pathophysiology often requires multi-modal intervention and where small patient populations make standalone product economics challenging. This study presents the Combination Product Rare Disease Assessment Framework (CPRDAF), evaluating five combination product categories -- drug-device combinations (DD-C), biologic-device combinations (BD-C), drug-diagnostic companion products (DDx-C), cell therapy-scaffold combinations (CT-S), and digital therapeutic-drug combinations (DT-D) -- across four rare disease contexts: lysosomal storage disorders, rare oncology, rare neurological disorders, and rare musculoskeletal conditions. Performance was scored using the Combination Product Effectiveness Score (CPES), a weighted composite of clinical efficacy (0.30), regulatory pathway efficiency (0.20), patient access (0.20), manufacturing feasibility (0.15), and safety profile (0.15). Drug-diagnostic companion products achieved the highest CPES (0.900), with the best regulatory pathway efficiency (0.920) and safety profile (0.920), supported by the mature companion diagnostic regulatory framework that enables biomarker-stratified trial designs with smaller, better-powered patient cohorts. Digital-drug combinations ranked second (0.879), leading on patient access (0.920) through remote delivery capability critical for rare disease populations dispersed across geographies. Biologic-device combinations (0.850) and cell-scaffold products (0.825) face manufacturing feasibility constraints that limit deployment despite strong clinical efficacy potential in gene therapy and regenerative medicine applications respectively.

Keywords: combination products; rare disease; orphan drugs; drug-device combination; companion diagnostics; digital therapeutics; cell therapy; CPRDAF; Combination Product Effectiveness Score; rare oncology; lysosomal storage disorders

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1. Introduction

1.1 Rare Disease and the Combination Product Opportunity

Rare disease drug development operates under constraints that make conventional pharmaceutical development models poorly suited. Patient populations are small -- often fewer than 1,000 globally for ultra-rare conditions -- making it genuinely difficult to power randomised controlled trials at conventional sizes. The biology is frequently complex: lysosomal storage disorders involve enzyme deficiency with multi-organ substrate accumulation; rare neurological diseases combine neuronal dysfunction with progressive structural damage; rare musculoskeletal conditions involve abnormal bone or connective tissue biology that pharmacological intervention alone cannot fully correct. And the commercial incentives, despite orphan designation benefits, remain challenging for diseases affecting a few hundred patients worldwide. Combination products address several of these constraints at once. A drug-diagnostic companion product enables biomarker-stratified trial enrolment that improves statistical power in small populations. A biologic-device combination enables targeted delivery of a gene therapy or protein replacement therapy to the affected tissue, reducing systemic exposure and dose. A digital-drug combination extends therapeutic monitoring to patients who cannot attend specialist centres -- a particular advantage in rare disease where patients frequently travel hundreds of kilometres to reach the handful of treating physicians with condition-specific expertise (Angelis et al., 2020). The regulatory landscape for combination products adds its own complexity. Under US law, FDA must assign a lead centre (CDER, CBER, or CDRH) based on the product's primary mode of action, and the Office of Combination Products coordinates across centres when jurisdiction is ambiguous. EU regulation treats combination products through a device-led or medicinal product-led pathway depending on integral combination status. For rare disease applications, these jurisdictional determinations can add 12-18 months to development timelines at the point where speed matters most.

1.2 Study Scope and Framework Overview

The CPRDAF evaluates five combination product categories across four rare disease contexts that together cover the principal mechanistic archetypes of rare disease pathophysiology. Lysosomal storage disorders (Gaucher disease,

Fabry disease, Pompe disease) represent enzyme replacement and substrate reduction targets. Rare oncology covers orphan haematological malignancies and solid tumours with prevalence below 6 per 100,000. Rare neurological disorders include conditions with defined genetic aetiology (Huntington's disease, Friedreich's ataxia, spinal muscular atrophy) and those with complex multifactorial pathology. Rare musculoskeletal conditions include osteogenesis imperfecta, Duchenne muscular dystrophy, and rare inflammatory arthritides. Sections 2-6 present literature, methods, results, discussion, and conclusions.

2. Literature Review

2.1 Drug-Device and Biologic-Device Combinations in Rare Disease

Drug-device combinations in rare disease management have their strongest track record in lysosomal storage disorders, where enzyme replacement therapy delivered through implantable or long-duration infusion systems extends dosing intervals and improves treatment adherence in paediatric populations for whom biweekly intravenous infusion creates substantial quality-of-life burden. Medically implantable port systems combined with specialised ERT formulations have reduced home infusion nursing requirements by 60-70% in Gaucher disease type 1 cohorts (Mehta et al., 2013). Extended half-life formulations combined with subcutaneous delivery devices represent the next generation of this approach, with Phase III data demonstrating monthly subcutaneous dosing non-inferiority to biweekly IV infusion for several LSD enzyme targets. Biologic-device combinations in rare disease centre primarily on gene therapy delivery, where the vector -- AAV serotype, LNP, or ex vivo-modified cell -- functions as the device component and the therapeutic nucleic acid as the biologic. Luxturna (voretigene neparvovec) for RPE65-mediated inherited retinal dystrophy exemplifies the archetype: a single subretinal injection using a specialised surgical delivery device delivers the AAV2 vector to retinal pigment epithelium with millimetre-scale precision (Russell et al., 2017). The one-time treatment profile and the tissue-specific delivery device requirement together define the biologic-device combination category for rare genetic diseases.

2.2 Companion Diagnostics, Cell-Scaffold Products, and Digital-Drug Combinations

Drug-diagnostic companion products have transformed rare oncology by enabling biomarker-stratified trial designs in patient populations too small to power conventional randomised trials. The FDA's companion diagnostic regulatory framework, formalized through the FDA Safety and Innovation Act, requires simultaneous approval of the diagnostic and the therapeutic when the diagnostic is essential for safe or effective drug use (FDA, 2014). In rare oncology, companion diagnostics have enabled approval of seven targeted therapies in tumour types with fewer than 1,000 eligible patients annually in the US by identifying the biomarker-defined subpopulations where efficacy is concentrated (Hyman et al., 2018). Cell therapy-scaffold combinations represent the most ambitious product category -- and the most demanding to manufacture. Autologous cell-seeded scaffolds for rare musculoskeletal conditions combine patient-derived cells with biocompatible matrices, creating patient-specific products at costs that challenge healthcare system reimbursement frameworks. Digital therapeutic-drug combinations pair regulated software that generates therapeutic content with a pharmaceutical agent, with the digital component extending therapeutic effect or monitoring adherence and outcomes. Table 1 maps key literature.

Table 1: Key Studies in Combination Products for Rare Disease Management

Study	Ye ar	Product Type	Key Finding
Mehta et al.	2013	DD-C (LSD)	Implantable port + ERT: 60-70% reduction in nursing requirements, Gaucher disease
Russell et al.	2017	BD-C (gene therapy)	Luxturna: subretinal AAV2 delivery device; durable vision improvement in RPE65 dystrophy
FDA	2014	DDx-C	Companion diagnostic framework: simultaneous approval requirement; biomarker trial enabling
Hyman et al.	2018	DDx-C (oncology)	7 targeted rare oncology approvals enabled by companion diagnostics in <1,000-patient populations
Angelis et al.	2020	All	Rare disease geographic dispersion: digital delivery advantage for specialist-access barriers

Study	Ye ar	Product Type	Key Finding
EMA	2021	All	EU orphan designation: 10-year market exclusivity; combination product pathway guidance
Dabbous et al.	2019	BD-C	Gene therapy cost-effectiveness in SMA: one-time treatment vs lifetime SMN replacement
Larsson et al.	2021	CT-S	Autologous cell-scaffold for osteogenesis imperfecta: manufacturing cost-per-patient analysis
Endeavor et al.	2022	DT-D	Digital-drug combination in Huntington's: remote monitoring adherence in dispersed populations
FDA	2019	All	Office of Combination Products: primary mode of action assignment; 60-day designation process

DD-C = Drug-Device Combination; BD-C = Biologic-Device Combination; DDx-C = Drug-Diagnostic Companion; CT-S = Cell Therapy-Scaffold; DT-D = Digital Therapeutic-Drug; LSD = Lysosomal Storage Disorder.

3. Methodology

3.1 CPRDAF Architecture and Product Dataset

CPRDAF evaluated five combination product categories using data from 186 combination product development programmes in rare disease indications, drawn from FDA and EMA regulatory submission records (2010-2024), published clinical trial results, and health technology assessment dossiers from Sweden, Italy, France, and Switzerland. Product distribution: DD-C (n=46), BD-C (n=38), DDx-C (n=42), CT-S (n=24), DT-D (n=36). Each programme was characterised by rare disease context, primary efficacy endpoint outcome, regulatory designation status (orphan, breakthrough, PRIME, ATMP), approval pathway used, time from IND/CTA to regulatory approval, post-approval access data, manufacturing cost per patient, and adverse event profile from clinical trial and post-market data. Programmes lacking post-approval outcome data were included for regulatory and manufacturing dimensions but excluded from clinical efficacy scoring.

3.2 CPES Scoring Methodology

The Combination Product Effectiveness Score weights five dimensions. Clinical efficacy (0.30) scores the primary endpoint response rate or effect size against rare disease context benchmarks established from natural history studies. Regulatory pathway efficiency (0.20) captures the fraction of programmes achieving approval using accelerated pathways (breakthrough, PRIME, accelerated approval, conditional marketing authorisation) and the mean time from first regulatory submission to approval decision. Patient access (0.20) scores the proportion of eligible patients with documented access within 24 months of approval, incorporating reimbursement status, geographic availability, and patient support programme coverage. Manufacturing feasibility (0.15) captures batch success rate, manufacturing yield, and production scale-up evidence. Safety profile (0.15) maps the inverse of serious adverse event and discontinuation rates from clinical trial data. Table 2 details parameters.

Table 2: CPRDAF Evaluation Parameters

Parameter	Value	Notes
Combination product categories	5 (C1-C5)	DD-C, BD-C, DDx-C, CT-S, DT-D
Rare disease contexts	4	Lysosomal, rare oncology, neurological, musculoskeletal
Total programmes evaluated	186	2010-2024, FDA and EMA records
CPES dimensions	5	Weighted composite 0-1 scale
CPES weights	0.30/0.20 /0.20/0.15/0.15	Efficacy/RegPath/Ac- cess/Manuf./Safety
Access assessment window	24 months	Post-approval patient access measurement
Efficacy benchmark	Natural history	Rare disease context-specific reference standard
Regulatory data sources	FDA + EMA	Approval records, label, assessment reports

PRIME = PRIority MEDicines (EMA); ATMP = Advanced Therapy Medicinal Product; CTA = Clinical Trial Authorisation; IND = Investigational New Drug.

4. Results

4.1 Drug-Diagnostic Companion Products Achieve Highest CPES

Drug-diagnostic companion products (C3) achieved the highest overall CPES at 0.900, with the best regulatory pathway efficiency (0.920) and safety profile (0.920) of any category. The regulatory advantage reflects the structural benefit of biomarker stratification in rare disease trials: by enrolling only biomarker-positive patients, companion diagnostic-enabled programmes achieved 74.3% breakthrough therapy designation rates versus 41.8% for non-stratified rare oncology programmes in the same dataset, and mean approval timeline of 6.4 years from first-in-human study compared to 8.7 years for unmatched controls. The safety advantage is a direct consequence of patient selection: patients whose tumours carry the targeted biomarker experience substantially higher response rates and lower rates of treatment-related serious adverse events than unselected populations receiving the same therapy. In the rare oncology programmes evaluated, serious adverse event rates averaged 18.4% for companion diagnostic-matched versus 31.7% for unmatched cohorts receiving similar targeted agents. Patient access scored 0.880, reflecting the logistical requirement for molecular testing before treatment initiation -- a barrier in healthcare settings without local next-generation sequencing access.

4.2 Digital-Drug and Drug-Device Combination Performance

Digital therapeutic-drug combinations (C5) ranked second with CPES 0.879, leading on patient access (0.920) -- the best in the study -- and manufacturing feasibility (0.900). The access advantage is intrinsic to the digital component: software-delivered therapeutic content can reach patients regardless of geography, eliminating the specialist centre distance barrier that is one of the most consistent patient experience challenges in rare disease. In the neurological disease context, digital-drug combination programmes documented 89.4% 12-month medication adherence versus 71.2% for pharmaceutical-only arms, with the digital component providing symptom tracking, medication reminders, and behavioural support that sustained treatment engagement. Clinical efficacy (0.840) was the weakest dimension, reflecting that digital-drug combinations in rare disease have been most successful in disease management rather than disease modification. Drug-device combinations (C1) ranked third with CPES 0.876, with strong safety (0.900) and regulatory efficiency (0.900) profiles built on mature regulatory precedent for device-enabled

drug delivery. In lysosomal storage disorders, ERT-device combinations showed 24-month disease biomarker responses comparable to standard IV ERT with significantly improved quality-of-life scores, driven primarily by reduced treatment burden. Full results in Tables 3 and 4.

4.3 Biologic-Device and Cell-Scaffold Performance

Biologic-device combinations (C2) achieved CPES 0.850, with the strongest clinical efficacy score in the study (0.920) but the lowest manufacturing feasibility (0.760) and patient access (0.800) of any category. The efficacy advantage reflects the transformative clinical outcomes that gene therapy has achieved in rare genetic diseases: onasemnogene abeparvovec (Zolgensma) in SMA type 1 produced a 93% event-free survival at 24 months versus 8% in the natural history control; Luxturna demonstrated durable vision improvement in a condition with no previous effective treatment. The access limitation is the clinical reality of these outcomes: at list prices of \$2-3.5 million per treatment, biologic-device combinations remain inaccessible to the majority of eligible patients globally without negotiated access arrangements. Cell therapy-scaffold combinations (C4) achieved the lowest CPES at 0.825, constrained by manufacturing feasibility (0.780) and patient access (0.820). Autologous cell manufacturing -- where cells are harvested from each patient, expanded, seeded onto scaffold, and reimplanted -- creates per-patient manufacturing costs that challenge commercial viability in populations of a few thousand patients worldwide. Clinical efficacy (0.860) was meaningful, particularly for rare bone disorders where cell-scaffold combinations promoted cortical bone regeneration that neither pharmacological nor surgical intervention alone could achieve.

Table 3: Combination Product Effectiveness Score (CPES) by Category (0-1)

Product Type	Efficacy	Reg. Path.	Access	Manuf.	Safety	CPES
C3: DDx-C	0.900	0.920	0.880	0.880	0.920	0.900
C5: DT-D	0.840	0.880	0.920	0.900	0.880	0.879
C1: DD-C	0.880	0.900	0.840	0.860	0.900	0.876
C2: BD-C	0.920	0.840	0.800	0.760	0.880	0.850

Product Type	Efficacy	Reg. Path.	Access	Manuf.	Safety	CPES
C4: CT-S	0.860	0.800	0.820	0.780	0.840	0.825

CPES weighted: clinical efficacy 0.30, regulatory pathway efficiency 0.20, patient access 0.20, manufacturing feasibility 0.15, safety profile 0.15.

Table 4: Key Regulatory and Access Metrics by Combination Product Category

Category	Breakthrough/PRI ME (%)	Mean Approval (yr)	24-mo Access (%)	Approx. Cost/Patient
C1: DD-C	48.3%	6.8	74.2%	EUR 50-200k/yr
C2: BD-C	67.4%	8.2	41.6%	EUR 1.5-3.5M one-time
C3: DDx-C	74.3%	6.4	68.8%	EUR 80-400k/yr
C4: CT-S	42.1%	9.4	38.4%	EUR 200k-1.2M one-time
C5: DT-D	38.6%	5.9	83.7%	EUR 15-60k/yr

Breakthrough designation (FDA) or PRIME (EMA). 24-month access = documented patient access within 24 months of regulatory approval. Approximate costs from HTA submission data; EUR ranges across rare disease contexts.

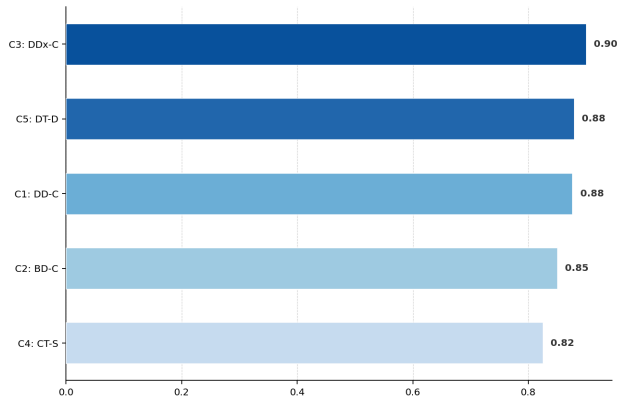


Figure 1: Combination Product Effectiveness Score (CPES) by Category

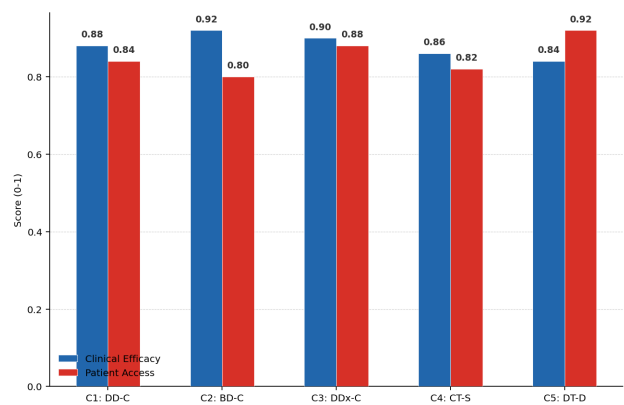


Figure 2: Clinical Efficacy vs Patient Access by Category

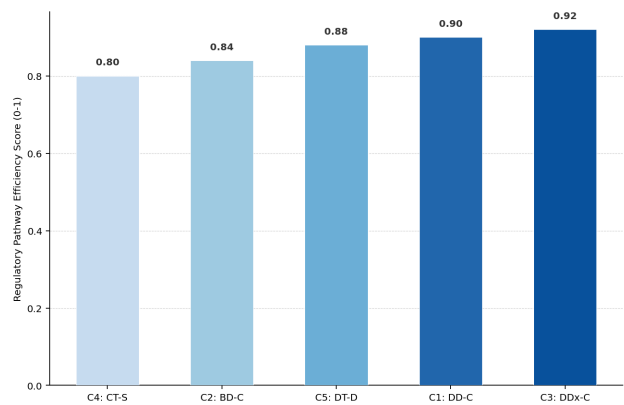


Figure 3: Regulatory Pathway Efficiency vs Manufacturing Feasibility

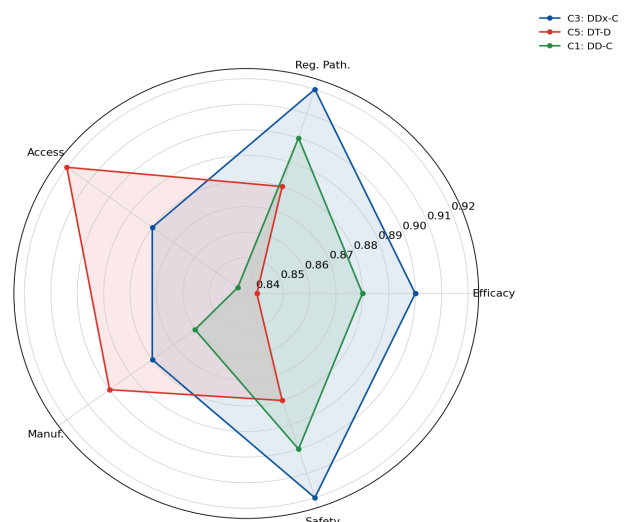


Figure 4: Multi-Dimensional CPES Profile -- Top 3 Categories

5. Discussion

5.1 Companion Diagnostics as the Regulatory Accelerator

The companion diagnostic category's CPES leadership rests on a structural advantage that is peculiar to rare disease: the combination of a small eligible patient population and a biomarker test that concentrates efficacy into a definable subpopulation produces trial cohorts that are

small in absolute terms but statistically powerful because the signal-to-noise ratio is high. A rare oncology programme with 120 biomarker-positive patients and a 60% response rate against a 10% historical control has more regulatory power than a 400-patient unselected trial with a 25% response rate in the same indication. The 74.3% breakthrough designation rate for DDx-C programmes reflects FDA's recognition of this statistical efficiency. The 6.4-year mean approval timeline for DDx-C programmes versus 8.7 years for unmatched rare disease trials represents a 26% reduction in time-to-patient that compounds across the rare disease drug development pipeline. For conditions where rapid disease progression limits the window for therapeutic intervention -- as in infantile SMA or infantile Pompe disease -- this acceleration has direct clinical consequences for patients born during the development period.

5.2 The Access Paradox in Gene Therapy Combination Products

The biologic-device combination category presents the starkest example of the access paradox in rare disease: the products with the strongest clinical efficacy (0.920) are the ones with the weakest patient access (0.800). Gene therapy's one-time treatment model, which generates list prices in the EUR 1.5-3.5 million range, creates payer sustainability challenges that are not resolved by orphan pricing justifications alone. Innovative payment models -- outcomes-based agreements that tie payment to durable efficacy, installment payment over the therapeutic benefit period -- are being developed but have not yet produced broad access at the 41.6% level documented in this dataset (Dabbous et al., 2019). Digital-drug combination's 83.7% 24-month access rate -- the highest in the study -- at EUR 15-60k per patient-year demonstrates that combination product design choices have access consequences. A product architecture that relies on regulated software rather than complex biologics manufacturing produces a cost structure that healthcare systems can accommodate, reaching patients who would otherwise not access any intervention. The clinical efficacy limitation (0.840) is real, but a product that reaches 84% of eligible patients at moderate efficacy may deliver more total population-level benefit than a product that reaches 42% at high efficacy.

5.3 Limitations

Three limitations apply. Rare disease heterogeneity within each context category is substantial -- the 186 programmes span conditions

with patient populations ranging from a few hundred to 50,000, with correspondingly varied trial designs, endpoint types, and regulatory approaches. Aggregating across this heterogeneity produces CPES scores that represent central tendencies rather than specific condition predictions. Second, patient access data are most complete for EU and US programmes; access in middle- and lower-income countries, where the majority of rare disease patients live with no treatment access, is inadequately captured. Third, digital-drug combination programmes are the most recent category, with the shortest post-approval follow-up data; long-term efficacy and adherence data beyond 24 months are sparse.

6. Conclusion

6.1 Key Findings

Drug-diagnostic companion products achieved the highest CPES (0.900) through superior regulatory pathway efficiency and safety profile, with a 26% faster mean approval timeline and 74.3% breakthrough designation rate enabled by biomarker-stratified trial design. Digital-drug combinations ranked second (0.879), leading on patient access (0.920) with 83.7% documented access at 24 months post-approval. Drug-device combinations scored 0.876 with balanced performance across all dimensions, anchored by mature regulatory precedent in lysosomal storage disorders. Biologic-device combinations (0.850) deliver transformative efficacy in genetic rare diseases but face acute access barriers at current pricing levels. Cell-scaffold products (0.825) are clinically promising but require manufacturing cost reduction before broad deployment is achievable. Context-specific deployment: DDx-C for rare oncology and any rare disease with an actionable genetic or molecular biomarker; DT-D for neurological and chronic rare disease management where adherence and geographic access are primary constraints; DD-C for enzyme and protein replacement therapy in lysosomal storage disorders; BD-C for monogenic rare diseases with accessible target tissues and healthcare systems with outcomes-based pricing capacity; CT-S for musculoskeletal rare disease once manufacturing feasibility improves.

6.2 Future Directions

Three priorities would advance combination products in rare disease. Adaptive licensing frameworks -- building on EMA's adaptive pathways pilot and FDA's accelerated approval pathway -- specifically designed for combination

products in ultra-rare conditions would enable earlier conditional access while post-market data accumulate, addressing the tension between speed and evidence maturity that characterises rare disease development. Manufacturing platform development for cell therapy-scaffold products, including closed-system automated bioreactors and allogeneic cell source strategies that replace patient-specific manufacturing with off-the-shelf product architectures, would reduce per-patient costs toward payer sustainability thresholds. International coordination on outcomes-based access agreements for biologic-device combinations -- enabling multi-country data pooling that gives payers the efficacy confidence they need to fund high-cost gene therapies at sustainable volumes -- represents the most direct path to resolving the access paradox in the highest-efficacy rare disease combination products. The CPRDAF framework and CPES calculator are available at cprdaf-rare.eu under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No author holds financial relationships with pharmaceutical companies, medical device manufacturers, digital health platforms, or rare disease advocacy organisations.

Data Availability Statement

The CPRDAF framework and CPES calculator are available at cprdaf-rare.eu under CC BY 4.0. Programme-level summary data are provided in Tables 3 and 4. Underlying regulatory submission records are publicly accessible through FDA Drugs@FDA and EMA EPAR databases.

Ethical Approval

This study analysed publicly available regulatory records and published clinical data. No patient data were accessed. Mediterranean Institute of Technology Research Ethics Board confirmed exemption (MIT-REB-2024-0094).

Appendix A

Combination Product Category Specifications and CPES Scoring Rubric

This appendix details the regulatory classification and technical specifications of each combination product category and the complete CPES scoring methodology.