How the Definition of "Rare Disease" Shapes Competition Under the Orphan Drug Act

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The Orphan Drug Act (ODA) provides manufacturers with seven years of market exclusivity to encourage the development of therapies for rare diseases. However, an unresolved policy question is whether exclusivity should attach to the approved indication or to the broader rare disease designation. These alternative definitions create opposing incentives. Disease-level exclusivity may limit competition by preventing follow-on sponsors from obtaining approval for different patient subpopulations, whereas indication-level exclusivity permits competition across subpopulations but may encourage manufacturers to sequentially subdivide diseases to obtain multiple exclusivity periods. Despite the centrality of this debate, little empirical evidence exists regarding the relative importance of these competing effects.

We evaluate both mechanisms using all FDA-approved orphan drugs from 1983 through April 2025. First, we examine how often a disease-level definition, as adopted by the Eleventh Circuit in *Catalyst Pharmaceuticals v. FDA*, would have prevented or delayed competing approvals involving different manufacturers. Second, we quantify the prevalence and magnitude of within-firm orphan exclusivity stacking arising from multiple orphan designations and FDA-approved indications. We combine FDA orphan designation and approval data with exclusivity records and commercial revenue data to characterize both competitive effects and economic significance.

Disease-level exclusivity would have affected only five drug pairs among 791 orphan drug approvals (approximately 1%), delaying competing approvals by eight months to seven years depending on the product. Thus, redefining rare disease at the disease level would have had relatively little effect on inter-firm competition.

By contrast, orphan exclusivity stacking is common. Twenty-nine percent of orphan drugs received multiple orphan designations, multiple approved indications, or both. Drugs with both multiple designations and indications accumulated an average of 15.1 years of orphan exclusivity and were disproportionately blockbuster products, with more than half generating annual revenues exceeding $1 billion. These findings suggest that the dominant competitive consequence of the current framework is not reduced entry by rival firms but prolonged market protection for incumbent manufacturers through sequential exclusivity awards.

Our results demonstrate that the definition of "rare disease" creates asymmetric effects on pharmaceutical competition. The costs of disease-level exclusivity appear limited because relatively few competing products would be excluded, whereas indication-level exclusivity enables extensive within-firm extensions of market protection through indication fragmentation. These findings suggest that reforms focused on limiting cumulative exclusivity or tying additional exclusivity to clinically meaningful innovation could better balance incentives for orphan drug development with competition and affordability. More broadly, the study illustrates how subtle regulatory definitions can substantially influence market structure, firm strategy, and the allocation of innovation incentives in pharmaceutical markets.