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The End of the Global Pharma Model: Why Geographic Spin-offs Are Inevitable

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Executive Summary

The pharmaceutical industry's unitary global business model—discover once, launch globally, but with the U.S. market driving the majority of revenues—is facing unprecedented pressure from the implementation of "Most-Favored-Nation" (MFN) reference pricing in the U.S. Simultaneously, the Inflation Reduction Act's (IRA) "Pill Penalty" and the "Orphan Loophole" introduced with the One Big Beautiful Bill Act (OBBBA) are triggering a radical review of R&D pipelines.

While the industry is still exploring tactical defenses, this analysis argues that these pressures ultimately lead to one unavoidable conclusion: **Geographic Spin-offs**. Just as the industry previously separated innovative pharma from generics and consumer health, the next wave of value creation will require separating high-value U.S. assets from price-controlled international portfolios.

1. The Fracture of the Global Profit Pool

For decades, the U.S. market served as the global industry's "profit pool," driving the majority of shareholder return on innovation while the rest of the world controlled drug prices in their healthcare systems. The convergence of the OBBBA, the executive implementation of "Most-Favored-Nation 2.0" via the **"Regulatory Trinity" (GENEROUS, GLOBE, and GUARD models)**, and major pharma companies committing to offer new drugs on the **TrumpRx** platform at MFN prices has put this business model in question. The U.S. is no longer a safe harbor; it is a reference-priced market where U.S. revenues are increasingly tethered to the lowest common denominator of other developed markets.[1]

2. The New R&D Reality: Orphan Biologics

Even without MFN pricing, the regulations of the OBBBA force pharma leaders to fundamentally reassess their R&D pipelines and future strategy.

A. The “Pill Penalty” Favors Biologics

The OBBBA did not fix the IRA's core distortion: the "Pill Penalty." Under Section 1192(e) of the Social Security Act (as added by the Inflation Reduction Act), FDA-approved "drug products" (typically small molecules) face **negotiation eligibility at 7 years** (price effective Year 9), while "biological products" (licensed under a BLA) are **eligible at 11 years** (price effective Year 13).[3]

This 4-year disparity can translate into **a >30% erosion in Net Present Value (NPV)** for a potential blockbuster program, creating a permanent capital allocation bias. Small molecule programs for mass-market diseases become financially unattractive or even unviable compared to biological products. Consequently, R&D pipelines will aggressively pivot toward biologics, antibody-drug conjugates (ADCs), and cell therapies to secure the longer exclusivity runway.

B. The “Orphan Loophole” Dictates R&D Strategy

The OBBBA’s expansion of the **Orphan Drug Exclusion** creates a powerful incentive for "Orphan First" or “Orphan Only” development. Companies will **micro-segment patient populations** (e.g., using biomarkers) to secure initial approval in a niche, exempt orphan indication. They will then **stack additional orphan indications** to maximize the exempt revenue pool. Since the negotiation clock (7 or 11 years) now **resets** upon the approval of the first **non-orphan** indication, any mass-market indication will be **delayed** toward the end of the patent life to trigger the clock reset as late as possible.[4]

3. The Failure of Tactical Defenses

Strategists debate several potential plays to reduce the risk of international reference prices triggering price cuts in the U.S. markets. Especially since it appears increasingly likely that the prices offered to Medicare, Medicaid, and out-of-pocket paying patients through TrumpRx will also spill over into the commercial insurance market. However, **a stress test of these tactics reveals them to be temporary stopgaps at best rather than sound strategy.**

A. Confidential Global Pricing: The Transparency Trap

- **The Strategy:** Maintain high visible international list prices to satisfy U.S. reference checks while granting **significant, confidential rebates or clawbacks** to national payers. Alternatively, use complex outcomes-based agreements to obscure net prices.
- **The Counter-Argument:** The U.S. government has anticipated this. The GENEROUS and GLOBE models explicitly mandate the reporting of "Manufacturer-Reported Net Prices," effectively piercing the veil of international confidentiality.[5] Similarly, CMS has signaled it will use a "blended average" methodology to convert complex deals into a standardized unit price.

  Furthermore, for companies listed on U.S. stock exchanges, the disparity between gross and net revenues is auditable. Relying on the secrecy of international net prices is a fragile strategy in an era of **algorithmic enforcement**.

B. Outlicensing International Rights

- **The Strategy:** Legal experts propose an outlicensing agreement with strict price floors, combined with confidential rebates managed by the partner, to insulate the U.S. company from price reporting obligations.
- **The Counter-Argument:** Any outlicensing agreement will require a significant transfer of value to the licensing partner, **eroding the global margin**. Additionally, U.S. regulators are likely to apply **"Look-Through" provisions** for related parties or exclusive licenses, treating the licensee's price as the reference price. It remains questionable how long it would take the U.S. government to enforce pricing transparency if strategic outlicensing became common practice.

C. Extending Launch Sequences

- **The Strategy:** Optimizing launch sequences to factor in IRP risk is standard practice. Pricing teams assess the price-volume trade-offs of **delaying or cancelling launches** in reference markets to maintain higher prices in the U.S. Launching *only* in the U.S. could optimize the equation for smaller biopharma companies.
- **The Counter-Argument:** This "America First" launch strategy faces a new threat: **EU Regulatory Conditionality.** The revised **EU Pharmaceutical Legislation** threatens to **shorten data exclusivity periods** if a product is not put onto the market in all 27 member states within two years.[6] Thus, delaying an EU launch to protect U.S. pricing may result in the forfeiture of European IP rights. Furthermore, excluding international affiliates from future launches creates stranded costs and unbalanced infrastructure in global companies.

D. Molecular Decoupling: The "Gaming" Risk

- **The Strategy:** The most technically sophisticated defense is **Molecular Decoupling**: creating **Distinct Molecular Entities (DMEs)** for the U.S. market (e.g., via deuteration) supported by a clinical study program to break the "sameness" link with international reference products.
- **The Counter-Argument:** While legally sound, this strategy carries high political risk. The U.S. administration and CMS are likely to view this as **"sham innovation"** designed solely to evade pricing laws. The **"Line Extension" rule** in Medicaid already penalizes reformulations.[7] It is highly probable that future rulemaking would grant CMS the authority to treat "functionally similar" assets of one company as the same for MFN purposes, creating significant **retroactive rebate liabilities**.

4. The Inevitable Conclusion: Corporate Spin-offs

If tactical decoupling is risky R&D pipelines must be bifurcated to minimize MFN reference pricing risk, leverage the “orphan loophole” and avoid the “pill penalty”. This puts the integrated global business model under pressure. **"Valuation drag"** occurs when high-value U.S. assets are shackled to price- and

volume-controlled European markets. Investors will push for boards to unlock the full value of their companies by separating the undervalued U.S. business from the international activities.

The industry has successfully used spin-offs to unlock value in two previous waves. The current crisis demands a third.

Wave 1: Risk Separation (Patented vs. Generics)

In the 2010s, the industry recognized that high-risk/high-value innovation and low-margin volume businesses required different operating models.

- **Abbott / AbbVie (2013):** Abbott spun off its proprietary pharma business (AbbVie) to separate it from its diversified medical products. This allowed AbbVie to trade as a pure-play innovation growth stock.[8]
- **Pfizer / Viatris (2020):** Pfizer spun off its Upjohn division (off-patent brands) to combine with Mylan, forming Viatris. This purified Pfizer's portfolio, allowing it to re-rate as an innovation engine.[9]

Wave 2: Focus Separation (Pharma vs. Consumer)

More recently, the industry shed consumer health assets to focus capital on high-margin R&D.

- **Pfizer / Zoetis (2013):** The separation of Animal Health proved that distinct end-markets deserve distinct equity stories.[10]
- **The Consumer Exits:** The spin-offs of Haleon (GSK, 2022), Kenvue (J&J, 2023), and the separation of Opella (Sanofi, 2025) demonstrated that capital markets reward "pure-play" focus over conglomerate scale.[11, 12, 13]

Wave 3: Geographic Separation (The 2026 Imperative)

Just as investors pushed for the separation of consumer health, they will soon demand the liberation of U.S. growth assets from European regulatory drag.

- **Rationale:** U.S. operations require high R&D reinvestment into specific therapeutic modalities (Biologics/Orphans) to avoid penalties and command high P/E multiples. European operations are becoming "utility-like" cash generators with capped upside. Keeping them together depresses the valuation of the company.
- **Feasibility:** Many companies historically run their U.S. operations with a high degree of independence. More recently, they committed significant investments in **domestic R&D and manufacturing** (e.g., Roche's $50B U.S. pledge, Novartis's $23B plan)[14, 15] in exchange for tariff exemptions, **completing the operational foundation for a standalone U.S. entity.**

Conclusion

The era of the global pharmaceutical conglomerate is ending. Tactical maneuvers like molecular decoupling may buy time, but they cannot solve the structural conflict between a price-controlled world and a value-based U.S. market. The "Pill Penalty" and "Orphan Loophole" have already begun to reshape *what* the industry builds. The final step is reshaping *how* the industry is owned. Following the playbook of Abbott, Pfizer, J&J and GSK, the **creation of standalone US-centric biopharma companies** is not just a defensive necessity—it is the **ultimate value-unlocking strategy for the MFN era**.

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