If I were launching an orphan drug ex-US today, here's how I'd navigate MFN

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Most of the MFN commentary I read is written from a Big Pharma seat: a diversified portfolio, the option to defer a launch, deep legal benches modelling "what-ifs." That's not the company most orphan drugs actually belong to. The typical rare-disease asset sits inside a smaller, often single-asset developer for whom one launch is a make-or-break event — and for whom the ex-US question is existential, not incremental.

So let me flip the seat. If I were responsible for taking a first orphan asset outside the US while the Most-Favored-Nation (MFN) pricing models take shape, this is how I'd think about it.

First, a calibration that changes everything

MFN drag is a function of the gap between your US price and your reference-country price, because the models rebate the excess of the US price over an international benchmark. And here's the part that gets lost in the noise: that gap is far narrower for orphan drugs than for primary care.

The most-cited industry analysis puts US prices at roughly **4.8x** ex-US for cardiovascular but only about **1.1–1.2x** for orphan and haematology assets. A note on that number: it's a US-versus-ex-US figure across a broad basket, not a European-specific one. If you look specifically at Europe, the independent academic work lands in a similar place — US orphan prices average roughly **1.6–1.7x** the European average, and that ratio is widest at launch and for the most recently approved products. Either way, the direction is the same: the orphan price differential is compressed (typically under 2x), where high-volume primary-care categories run well above 4x.

That single fact reframes the whole strategy. The orphan game is **not** about absorbing a large rebate — it's structurally modest for this class. It's about protecting a narrow corridor, because when the gap is small, one badly sequenced launch or one low reference-country net price can compress it disproportionately. Precision on a handful of prices beats blunt, portfolio-wide caution.

Which is why my base case would almost never be "delay ex-US for clarity." The MFN downside is bounded; the cost of delayed access — revenue *and* patients waiting — is real and immediate.

One more calibration worth stating plainly: for orphan drugs the US is roughly **45–50% of global value**, not the ~70% you often hear quoted for the industry as a whole. Ex-US is close to half the prize. That cuts both ways — it means the ex-US decision genuinely matters to the asset's value, and it means you can't treat Europe, Japan and Canada as an afterthought you sacrifice to protect the US price.

The key thing to watch: it's a lookback, not a launch date

The most common planning error I see is treating the MFN "start date" as the moment to act. It isn't. The benchmark is captured on a lookback of foreign price data, so the price that counts is the one on the day the benchmark is struck — not your intention today.

That means the real planning horizon is the **pre-implementation window we're in right now**, before the mandatory models' benchmarks lock. The dates to hold in your head:

- **GENEROUS** (Medicaid, voluntary) — applications and agreements run through mid-2026, pricing retroactive to Jan 1, 2026.
- **GLOBE** (Medicare Part B, mandatory) — proposed start Oct 1, 2026.
- **GUARD** (Medicare Part D, mandatory) — proposed start Jan 1, 2027.

The window between now and those dates is when ex-US prices can still be positioned. Treat it as the asset, not the deadline.

How I'd actually progress — four steps

Step 1 — Quantify, then find the countries that matter. Build an asset-level exposure model across all three mechanisms. For an orphan asset the likely output is a modest rebate — and that finding is itself the permission to launch ex-US rather than withhold. Then identify the *marginal binding reference markets*: the specific countries whose net price would actually set your benchmark. Concentrate effort there rather than everywhere.

Step 2 — Protect the corridor; don't prune the map. The instinct to simply not launch in low-price markets is usually the wrong one for orphan drugs, where access and equity optics are acute. The better lever is net-price confidentiality. Raise the visible list price and offset with a confidential rebate so the *referenceable* price stays high while access is preserved. Launch first and confidently into markets whose net prices aren't publicly visible — Germany's confidential-price regime, and the managed-entry-agreement markets (Belgium, Netherlands, Sweden, Italy, Spain) where the real net price never reaches a public source. Set a global floor price so no single outlier drags the benchmark.

Step 3 — Sequence deliberately. US first, then the rest of the world ordered by *confidentiality strength, not market size*. Protected, high-price markets go early; transparent low-price markets go later, with confidential terms secured before launch.

Step 4 — Fix your governance and your deals. Every ex-US price decision now carries a US consequence, so pricing can no longer live in a regional silo. That has real implications for how you contract and how you organise.

The licensing caveat (and the NewCo alternative)

Here's the trap. The traditional orphan playbook — out-license ex-US rights to a regional partner for non-dilutive cash — now contains a hidden cost: a partner pricing independently abroad can damage *your* US benchmark. With the US at roughly half of global value and ex-US the other half, handing a third party the pricing pen on that ex-US half puts a benchmark lever outside your hands.

The obvious fix — "just keep control of the partner's price" — is at risk of running straight into competition law. Vertical price coordination is regulated in the EU and elsewhere; a tribunal may refuse to enforce a clause that may read as resale-price maintenance, and in some jurisdictions you can't contract around those rules at all. So the honest answer is more nuanced than "retain control."

The cleanest protection isn't a clause — it's structure. Options, in rough order of protection:

- **Keep ex-US rights in-house, or commercialise through a NewCo you oversee.** If pricing authority stays within a structure you have genuine oversight of, much of the problem dissolves. For a small developer without international infrastructure, a purpose-built commercial NewCo — or a co-build with a partner who *doesn't* take independent pricing control — is increasingly the way to get ex-US reach without importing MFN risk. This is a large part of why the NewCo model is having a moment for MFN-exposed orphan assets.
- **Be specific about geography when you narrow territory.** Carving the reference markets out of a licence is a real lever, but be careful: it's not just the named basket countries that matter. Markets sit inside blocs that reference *each other* — a low price in one EU member state can propagate through European external-reference-pricing networks well beyond the formal MFN basket. So think in terms of coherent

geographies you protect as a whole — the EU, the UK, Japan, Canada — rather than assuming a country is "safe" simply because it isn't on the MFN list.
- **If you must license a sensitive market, convert control into consequence.** Since you can't safely dictate the partner's price, allocate the *economic outcome* instead: MFN indemnities / make-whole provisions, royalty adjusters that flex if referencing is triggered, and a contractual net-price floor framed as protecting your royalty base rather than commanding the partner's absolute price. Pair these with a confidentiality-first pricing obligation and launch-sequencing consent rights.

Governance, revision and exit provisions I'd insist on

Whatever the structure, I'd build in the ability to react as the policy moves:

- **A "Pricing Policy Change" trigger opening a revision window.** Define the event — a final GLOBE/GUARD rule, a codifying statute, a new tariff proclamation — that opens a mandatory good-faith *revision* window, with defined parameters and a backstop if the parties don't agree. Framing it as a revision (a structured reopener on defined terms) rather than an open-ended renegotiation keeps it disciplined.
- **A pre-agreed buy-back / rights-reversion option.** Negotiate the mechanism and the formula to reacquire ex-US rights *up front*. A buy-back after the asset has de-risked commands a steep premium; agreeing the price of the exit before you need it is far cheaper.
- **A joint pricing governance body** with a mandate over global price-corridor policy — but structured with information barriers so it respects competition-law limits on your involvement in a partner's actual price decisions (aggregated data, not transaction-level).
- **An antitrust savings / severability clause** so that if a pricing provision is struck down in one jurisdiction, the rest of the protection survives and falls back to the damages mechanics rather than collapsing.

The watch-items that would change my plan

I'd hold the strategy loosely, because a few things could shift it materially:

1. **A final-rule orphan carve-out.** The rare-disease community's single biggest ask of CMS was an orphan exclusion from the mandatory models. If the final rules grant it, most of this exposure disappears and the confidentiality effort can be dialled back. Worth remembering: orphan drugs are already protected from IRA *negotiation* by the ORPHAN Cures Act — but that protection does **not** currently extend to GLOBE/GUARD. That asymmetry is the crux.
2. **The first preliminary-injunction ruling.** The mandatory models rest on contested legal authority, and the 2020 MFN rule was enjoined. An injunction delaying GLOBE/GUARD would *extend* the pre-implementation window — more time to reposition.
3. **A US–EU trade settlement** that softens the reference-country dynamic.

The bottom line

For an orphan-drug first launcher, MFN isn't a reason to hide from ex-US markets — the price gap is too narrow for the drag to be existential, and with ex-US at roughly half the asset's value, the cost of waiting is too high. It's a reason to be deliberate: launch, but protect the corridor; prefer structure over clauses; keep pricing authority within a structure you oversee where you can; be precise about the geographies you protect; and build the triggers, buy-backs and governance that let you adapt as a genuinely unsettled policy settles.

The companies that will do best here aren't the ones betting on whether MFN survives. They're the ones who've made that question matter less.

This reflects my own read of a fast-moving, pre-final-rule situation and isn't legal or investment advice — the deal mechanics in particular need qualified antitrust counsel in each market. Curious how others are approaching the ex-US question for orphan assets right now.

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