May 6, 2025

Mr. Eric Longnecker
Deputy Assistant Secretary for Technology Security
Bureau of Industry and Security
Office of Strategic Industries and Economic Security
U.S. Department of Commerce
1401 Constitution Ave., NW
Washington, DC 20230
Submitted Electronically

BIS-2025-0022
XRIN 0694–XC120

Re: Request for Exclusion of Orphan Drugs and Components

Dear Mr. Longnecker,

On behalf of BioMarin Pharmaceutical Inc., we respectfully request that orphan drugs and their components be excluded from any tariffs or other import restrictions recommended in the ongoing Section 232 investigation of pharmaceuticals imports under the Trade Expansion Act of 1962.[1] Such an exclusion is justified based on not only the scope of a section 232 investigation, but also the practicalities of the orphan drug market:

- Orphan drug imports do not present a national security risk;
- Orphan drugs serve global populations, but the volume is too small to require multiple source manufacturing or otherwise increase domestic production; and
- The supply chain for orphan drugs is sufficient to meet limited patient demand in the United States.

BioMarin is a San Rafael, California-based biopharmaceutical company dedicated to developing and commercializing transformative therapies for individuals with rare genetic disorders that typically present with serious and life-threatening symptoms in childhood. In most cases, the patients we serve have no alternative treatment options. Orphan drugs, by definition, treat diseases affecting fewer than 200,000 patients in the United States.[2] Historically, their "limited commercial value"[3] made them unattractive investments until the bipartisan enactment of the

[1] *See* 90 Fed. Reg. 15951(April 16, 2025).

[2] See 21 U.S.C.S. § 360bb(a)(2) (LexisNexis 2025).

[3] *See, e.g.*, *Drug Regulation Reform – Oversight: Orphan Drugs: Hearing Before the Subcomm. on Health & the Environment, H. Comm. on Interstate & Foreign Commerce*, 96th Cong. 15-20 (1980) (statement of Abbey Meyers, Vice President, Tourette Syndrome Assoc.) (providing policy rationale for Congress to take action to solve the problem of orphan drugs by highlighting the devastation for children suffering from Tourette who are unable to obtain a safe and effective therapy in the U.S.). *See also* 127 CONG. REC. 31,610—31,611 (1981)

Orphan Drug Act created incentives for companies like BioMarin to bring hope and treatments to underserved patients.[4]

Due to the longstanding U.S. commitment to fostering biomedical innovation for treating rare disorders and their unique role in the biopharmaceutical ecosystem, a range of policies – including trade policy – have recognized the need to protect incentives for orphan drugs.[5] This precedent from both Congress and agencies is notable. Any action resulting from the section 232 investigation should preserve that principle. In other words, the national security interest in reshoring the biopharmaceutical supply chain should not undermine the Orphan Drug Act.

While BioMarin shares the goal of strengthening domestic manufacturing and improving supply chain resilience, ***we urge the Department to expressly exclude orphan drugs and their ingredients,*** including finished drug products, medical countermeasures, critical inputs such as active pharmaceutical ingredients ("APIs"), key starting materials, and derivative products of those

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(statement of Rep. Waxman) (introducing the ODA in the House and describing its intent); 128 Cong. Rec. 2,126 (1982) (statement of Sen. Kassebaum) (introducing the ODA in the Senate and describing its intent).

[4] *See* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C.S. §§ 360aa-360ee (LexisNexis 2025); 26 U.S.C.S. § 45C (LexisNexis 2025)).

[5] *See, e.g.,* 162 CONG. REC. S1384-S1385 (Mar. 9, 2016) (statement of Sen. Hatch) (stating that it is the intent of Congress that all trade policies support incentives for orphan drug development); *see also* 21 U.S.C.S. § 379h(a)(1)(F) (LexisNexis 2025) (excluding orphan designated drugs from certain fees required under the Prescription Drug User Fee Act); 21 U.S.C.S. § 355c(k) (LexisNexis 2025) (excluding orphan designated drugs from submitting an initial pediatric study plan under the Pediatric Research Equity Act); Medicare Program; Competitive Acquisition of Outpatient Drugs and Biologicals Under Part B, 70 Fed. Reg. 39022, 39028-39029 (Jul. 6, 2005) (illustrating CMS recognition of the need to protect certain rare disease populations from "severe access issues" by exercising its discretion to explicitly exclude from CAP several lifesaving rare disease therapies, including IVIG, alglucerase, alpha$_1$-proteinase inhibitor, blood clotting factors, daclizumab, imiglucerase, and oprelvekin); Patient Protection and Affordable Care Act § 9008(e)(3), 124 Stat. 119, 860 2010 (codified at 26 U.S.C.S. § 4001 note prec. (LexisNexis 2025)) (excluding from the calculation of a manufacturer's annual branded pharmaceutical fee the sales of orphan designated drugs that successfully claimed the orphan drug credit); *id*. § 2501(a), 124 Stat. at 306-307 (codified at 42 U.S.C.S. § 1396r-8(c)(1)(B)(iii)(II)(aa) (LexisNexis 2025)) (significantly limiting the Medicaid outpatient drug minimum rebate percentage increase under the ACA for blood clotting factors); *id*. § 6301(a), 124 Stat. at 730-731 (codified at 42 U.S.C.S. § 1320e(d)(2)(B)(ii)(III); § 1320e(d)(4)(A)(iii) (LexisNexis 2025)) (requiring the Patient Centered Outcomes Research Institute to convene disease-specific advisory panels each instance a rare disease is considered by the Institute or proposed in a grant application for a comparative effectiveness research study); Health Care and Education Reconciliation Act of 2010 § 2302, 124 Stat. 1029, 1082–1083, *amended by* Medicare and Medicaid Extenders Act of 2010 § 204, Pub. L. No. 111-309, 124 Stat. 3285, 3289 – 3290 (codified at 42 U.S.C.S. § 256b(e) (LexisNexis 2025)) (excluding orphan designated drugs from being sold at the 340B discount to the new categories of hospitals eligible for the 340B Drug Pricing Program); Food and Drug Administration Safety and Innovation Act § 908, Pub. L. No. 112-144, 126 Stat. 993, 1094-1098 (2012) (codified as amended at 21 U.S.C.S. § 360ff (LexisNexis 2025)) (establishing the Rare Pediatric Disease Priority Review Voucher Program); Inflation Reduction Act of 2022 § 11001, Pub. L. No. 117-169, 136 Stat. 1818, 1840 (2022) (codified at SSA § 1192(e)(3)(A), 42 U.S.C.S. § 1320f–1(e)(3)(A)) (LexisNexis 2025) (excluding from the IRA Medicare price setting policy orphan drugs designated for only one rare disease or condition and solely approved for an indication or indications for the same disease or condition).

items, ***from any new tariff measures***. Such a policy could be ***implemented by collaborating with the U.S. Customs and Border Protection and the Food and Drug Administration ("FDA") to establish a dedicated Harmonized Tariff Schedule of the United States classification for drugs that FDA has designated as "orphan" pursuant to 21 U.S.C. § 360bb(a) (codified at 21 C.F.R. § 316.24(b))***. Such action would ensure consistent tariff treatment.

Tariffs on these finished products and critical inputs would have an immediate and disproportionate effect on the availability and affordability of orphan drugs. Increased costs and supply disruptions could delay treatment development, constrain manufacturing capacity, and threaten timely access to life-saving medicines for patients who have no therapeutic alternatives.

1. **Orphan drug imports do not present a national security risk**

Under section 232 of the Trade Expansion Act of 1962, the Department of Commerce must determine whether the good under investigation is being imported ***"in such quantities or under such circumstances as to threaten to impair the national security."***[6] This assessment explicitly requires whether domestic industry has sufficient capacity to satisfy the need of national defense.

From a national security perspective, the Department of Commerce should prioritize reshoring drugs that FDA has identified as "Essential Medicines, Medical Countermeasures, and Critical Inputs." This list, which the first Trump Administration called for in 2020,[7] comprises anti-infective and anti-viral agents, cardiovascular therapies, paralytic and reversal agents, and pain medicines, among others, due to their critical role in emergency preparedness, defense readiness, and the public health.[8] Ensuring a resilient supply chain for these vital, high-volume drugs that are not only broadly used, but also most at risk for shortages, is fundamental to our national security.[9]

Orphan drugs, by contrast, are developed for extremely small, targeted patient populations and are produced in very limited quantities. These therapies are not relevant to defense preparedness and pose no risk to the national supply chain given their low volume and limited use. Therefore, imposing tariffs or other trade restrictions on orphan designated drugs would fall outside the scope and intent of the statute.

2. **Orphan drugs serve global populations, but the volume is too small to require multiple source manufacturing or otherwise increase domestic production.**

BioMarin is committed to U.S.-based manufacturing and research and development. ***Over the last decade, we have invested nearly $8 billion in U.S. R&D infrastructure***. BioMarin currently operates two manufacturing sites – our flagship facility in Novato, California and our Shanbally,

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[6] 19 U.S.C. § 1862(b)(3)(A) (emphasis added).

[7] *See* Exec. Order 13944, 85 Fed. Reg. 49929, 49932 (Aug. 14, 2020).

[8] *See* FOOD & DRUG ADMIN., DRUG AND BIOLOGIC ESSENTIAL MEDICINES, MEDICAL COUNTERMEASURES, AND CRITICAL INPUTS FOR THE LIST DESCRIBED IN SECTION 3(C) OF THE EXECUTIVE ORDER 13944 (OCT. 2020), https://www.fda.gov/media/143406/download.

[9] *See* U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-25-107110, DRUG SHORTAGES, HHS SHOULD IMPLEMENT A MECHANISM TO COORDINATE ITS ACTIVITIES (April 2025), https://www.gao.gov/assets/gao-25-107110.pdf.

Ireland site. ***Since 2015, BioMarin has invested nearly $1 billion in its U.S. operations infrastructure (inclusive of manufacturing sites and R&D laboratories)***, including the first commercial-scale gene therapy production facility in the United States. The International Society for Pharmaceutical Engineering recognized this portion of the Novato site as the 2018 Facility of the Year for Project Execution.[10] In Novato, BioMarin manufactures API for Aldurazyme, Naglazyme, Palynziq, Voxzogo, and Roctavian. The Shanbally site produces API for Brineura and Vimizim. ***In 2024, BioMarin's U.S. produced therapies accounted for approximately 60% of its global revenue. In fact, we are currently a net exporter of our medicines from the U.S. at approximately [redacted].***

Although our therapies serve patients around the world, orphan drugs treat extremely small populations. Across our seven marketed orphan drugs, BioMarin treats just a few thousand patients in the U.S., with individual product populations ranging from [redacted]. Our medicines are indicated for rare diseases that are characterized by rapid progression, life threatening episodes, and narrow treatment windows, including CLN2 Batten disease, MPS diseases, hemophilia A, and achondroplasia, respectively. For these patients, even temporary barriers to access can have irreversible, debilitating, or fatal consequences.

To meet this global need efficiently and safely, BioMarin has designed our manufacturing network around the realities of orphan drug productions: low volume, small batch sizes, highly specialized processes, and a limited number of manufacturing runs each year.[11] For instance, Brineura, our treatment for CLN2 Batten disease, is produced ***just once every two years*** in Shanbally. This commercial scale is sufficient to meet global demand, including the needs of U.S. patients. The prevalence of CLN2 Batten disease in the United States is less than 500 patients[12] and many less than that are eligible for this medicine.

Establishing a ***redundant*** U.S. manufacturing site for the scant U.S. supply is not commercially viable. Nor is it economically rational to reshore the entire production of Brineura for its ***biennial production runs***. Expanding U.S. capacity to manufacture Brineura – whether in whole or in part – would require substantial capital investment and years of regulatory work. Bringing a new biopharmaceutical facility online, including construction, technology transfer, qualification, and

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[10] *See* Press Release: BioMarin's Gene Therapy Manufacturing Facility Recognized with Industry Award (March 21, 2018), https://www.biomarin.com/news/press-releases/biomarins-gene-therapy-manufacturing-facility-recognized-with-industry-award/.

[11] *See, e.g.*, Cornell Stamoran et al, *The Complexities of Manufacturing Orphan Drugs in Product Development*, EUROPEAN PHARMACEUTICAL MANUFACTURER (Dec. 9, 2023, 1:50 PM), https://pharmaceuticalmanufacturer.media/pharmaceutical-industry-insights/latest-pharmaceutical-manufacturing-industry-insights/the-complexities-of-manufacturing-orphan-drugs-in-product-de/.

[12] *See, e.g.*, Ryan D. Geraets et al., *Moving Towards Effective Therapeutic Strategies for Neuronal Ceroid Lipofuscinosis*, 11 ORPHANET J. OF RARE DISEASES 40 (Apr. 2016), https://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0414-2.

process validation is quite complex.[13] Such investments can exceed $2 billion and require between 5 and 10 years to complete.[14] For a drug whose annual net product revenue in 2024 was only $169 million, such an undertaking is economically unjustifiable. It is unreasonable to compel BioMarin to choose between the commercial inefficiency of reshoring Brineura's highly limited production or incurring tariffs on importing a product that already reaches American patients safely and reliably.

Moreover, establishing redundant manufacturing with very low production volumes could inadvertently elevate the risk of product shortages due to infrequent production cycles. Complex manufacturing processes demand precise reproducibility and extensive training. Skilled and experienced personnel are crucial to achieving this reproducibility. For instance, in the case of Brineura, implementing redundant manufacturing would result in each facility conducting the manufacturing process only once approximately every four years. This infrequency would make it nearly impossible to retain a significant number of operators with sufficient experience with the Brineura process, thereby increasing the likelihood of failed production runs and potential product shortages.

3. **The supply chain for orphan drugs is sufficient to meet limited patient demand in the United States.**

While BioMarin supports broader efforts to strengthen domestic manufacturing capacity, increasing U.S.-based production of orphan drugs and their ingredients is not necessary to meet current or projected demand in the U.S. and would be cost-prohibitive. Because most rare diseases are genetic and diagnosed early in life, the number of patients eligible for a given orphan drug are generally well-defined and stable over time. As a result, orphan drugs rarely experience the kind of unexpected large-scale surges in demand seen with treatments for infectious disease or chronic conditions.

U.S. patient demand for orphan drugs is well supported by a highly specialized and proven global supply chain network. Unlike high-volume treatments – such as cholesterol and weight loss drugs – orphan drug therapies face higher development and production costs but generate comparatively lower revenues due to the small patient populations they serve. Accordingly, orphan drugs require a more deliberate and cost-conscious approach to commercialization. Mandating U.S.-based production through tariff policy could disrupt patient access, negatively affect patient outcomes, increase out-of-pocket costs, and divert resources from orphan drug research and development without making a meaningful difference in supply chain resiliency.

As is common among biopharmaceutical companies dedicated exclusively to rare diseases, BioMarin has limited operating margins. For efficiency, we rely on specialized third-party partners—including those located in Europe—for final dosage form and packaging (including infusion kits,

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[13] *See* FDA, GUIDANCE FOR INDUSTRY: PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES (2011), https://www.fda.gov/files/drugs/published/Process-Validation--General-Principles-and-Practices.pdf.

[14] *See Biopharmaceutical Manufacturing*, Pharmaceutical Research and Manufacturers of America, https://phrma.org/policy-issues/research-development/manufacturing-supply-chain (last visited May 1, 2025).

needles, and syringes). While we are always exploring opportunities to enhance our U.S. manufacturing footprint, further expanding our domestic capabilities at this time is neither practical, nor economically feasible given the limited U.S. patient demand for these orphan drugs.

The greatest risk posed by tariffs is to the future of rare disease innovation. Orphan drug developers are already facing significant financial headwinds, including expiration of the Rare Pediatric Disease Priority Review Voucher Program[15] and the 50 percent reduction of the orphan drug credit in the Internal Revenue Code.[16] Tariffs will exacerbate downward pressure on this unique segment of the biopharmaceutical industry. By further eroding net product revenues, reinvestment of those revenues into R&D for new orphan drugs, which already have "limited commercial value,"[17] will be much more difficult to justify to investors. Simply put, if orphan drug developers are forced to reshore or pay tariffs, the result is the same: fewer resources for companies like BioMarin to bring future transformative rare disease therapies to patients.

4. <u>Targeted incentives are preferable to tariffs.</u>

If the section 232 investigation recommends the application of tariffs on imported biopharmaceuticals and their inputs, tariffs are not appropriate or necessary for orphan drugs. Excluding imports of orphan designated drugs from section 232 tariffs would protect patient access to life-saving therapies for rare diseases without compromising national security. Again, these products typically serve small, targeted populations and pose minimal risk to the domestic industrial base or supply chain resilience. U.S. rare disease patients are well served by the current supply chain, so it must not be disrupted. Alternatively, targeted domestic incentives are a more effective and sustainable solution than tariffs considering the unique market conditions facing orphan drugs.

BioMarin and other orphan drug manufacturers should not be faced with choosing between two economically unsustainable solutions – reshore or pay tariffs – for addressing national security issues related to the biopharmaceutical supply chain. The United States has historically excluded imported biopharmaceuticals and their inputs from tariffs.[18] Mandating the reshoring of orphan designated drugs through tariffs would significantly disrupt rare disease innovation by introducing untenable manufacturing burdens that fail to reflect the unique economics of these therapies – all without improving our national security.

Given the small patient populations and high development costs, companies need predictable and meaningful incentives to invest in U.S.-based production. Policymakers should consider streamlining regulatory inspections, relaxing Environmental Protection Agency permitting

[15] See 21 U.S.C.S. § 360ff(b)(5).

[16] *See* Tax Cuts and Jobs Act § 13401, Pub. L. No. 115-97 (2017).

[17] *See* Kassebaum statement, *supra* note 3.

[18] *See, e.g.*, 1994 Agreement on Trade in Pharmaceutical Products, Mar. 25, 1994, GATT L/7430 [hereinafter Pharma Agreement]., https://docs.wto.org/gattdocs/q/GG/L7599/7430.PDF (eliminating tariffs and other duties and charges on pharmaceutical products and the substances used to produce them).

requirements and Occupational Safety and Health Administration construction rules, expanding tax credits for U.S.-based manufacturing, extending market exclusivity for domestically produced orphan drugs, and exempting such products from federal price controls under the Inflation Reduction Act, foreign reference pricing frameworks, Medicaid rebate obligations, and the 340B Drug Pricing Program.

BioMarin became GAAP profitable only recently, despite more than two decades of sustained investment and multiple FDA-approved orphan drugs. During this time, we took significant risk by reinvesting the majority of our net product revenues back into research and development. For example, between 2014 and 2023, BioMarin annually invested an ***average of 55% percent*** of its net product revenues into R&D programs. Many early-stage rare disease companies operate under similar financial models—prioritizing innovation over short-term profit.[19]

The Orphan Drug Act has encouraged and enabled BioMarin and other rare disease companies to take this risk. With 95% of the more than 10,000 known rare diseases still lacking an FDA-approved therapy,[20] it is in the interest of the public health to preserve incentives that sustain this innovation ecosystem for rare diseases. Notably, the late Senator Orrin Hatch (R-UT), co-author of the Orphan Drug Act, stated in 2016 that it was the intent of Congress that all trade policies support incentives for orphan drug development.[21]

Conclusion

In conclusion, we urge the Department of Commerce to preserve patient access and uphold the bipartisan legacy of the Orphan Drug Act by expressly excluding orphan drugs and their components from any Section 232-related tariff actions. We welcome the opportunity to engage with you and your staff further on this issue.

Sincerely,

/s/ G. Eric Davis

G. Eric Davis
Executive Vice President, Chief Legal Officer
BioMarin Pharmaceutical Inc.

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[19] *See* RARE DISEASE COMPANY COALITION, 2024 OUTLOOK (May 2024), https://www.rarecoalition.com/2024/05/22/rdcc-presents-2024-outlook/.

[20] *See* GOV'T ACCOUNTABILITY OFFICE, RARE DISEASE DRUGS, FDA HAS STEPS UNDERWAY TO STRENGTHEN COORDINATION OF ACTIVITIES SUPPORTING DRUG DEVELOPMENT, GAO-25-106774 at 1 (Nov. 18, 2024), https://www.gao.gov/assets/gao-25-106774.pdf.

[21] *See* Hatch statement, *supra* note 5.