Subject: Response to Notice of Request for Public Comments on Section 232 National Security Investigation of Imports of Pharmaceuticals and Pharmaceutical Ingredients

ID: BIS-2025-0022-0001

XRIN 0694-XC120 Pharmaceuticals 232 Notice

Background on Manus

We would like to first express our appreciation for the opportunity to provide input on opportunities for stabilizing access to pharmaceuticals and pharmaceutical ingredients. Manus has developed fully integrated capabilities for the development, scale-up, manufacturing, and commercialization of innovative bioproducts with a myriad of applications, including food ingredients, agricultural chemicals, and pharmaceutical products. This has allowed us to gain unique insight into the necessary technology and infrastructure investments for securing domestic production of critical chemicals and material accessible through biotechnology, including essential medicines and pharmaceutical ingredients.

Briefly, Manus is a leading next-generation industrial biotechnology company that has developed a fully-scaled commercial platform for producing complex natural products through biomanufacturing. Over the last 13 years, we have (1) developed a highly efficient and data-driven cell factory engineering platform for bio-based products, (2) refurbished and expanded a once-idle 44-acre large-scale biomanufacturing facility and created more than 150 jobs in rural Georgia, and (3) successfully scaled up multiple products to multi-ton scale production. We are proud to be one of only a few next-generation industrial biotechnology companies that has successfully navigated the path from lab to scale-up and commercialization *and the only one that has done so by building out full capabilities within the U.S.*

Please find our response to selected questions from the "**Notice of Request for Public Comments"** below. We remain at your immediate disposal in case additional information or clarification is needed.

This investigation is being undertaken in accordance with part 705 of the National Security Industrial Base Regulations (15 CFR parts 700 through 709) ("NSIBR"). Interested parties are invited to submit written comments, data, analyses, or information pertinent to this investigation to BIS's Office of Strategic Industries and Economic Security no later than May 7, 2025. The Department is particularly interested in comments and information directed at the

criteria listed in § 705.4 of the regulations as they affect national security, including the following:

(ii) the extent to which domestic production of pharmaceuticals and pharmaceutical ingredients can meet domestic demand

Next-generation production methods for pharmaceuticals and pharmaceutical ingredients present a timely and strategic opportunity for targeted investment to strengthen U.S.-based manufacturing of critical medicines. In particular, biotechnology-enabled production – wherein pharmaceutical compounds are synthesized using genetically modified organisms – offers a compelling alternative to traditional manufacturing methods that rely on harsh chemical processes or extraction from plant materials. Biotechnological approaches not only reduce environmental and supply chain risks but also create scalable pathways to reshore the production of essential medicines currently sourced from foreign regions. Many of these medicines depend on raw materials or production processes that are either impractical to implement domestically under existing methods or require access to specific plants that grow only in limited global regions. By investing in and supporting the development and deployment of these innovative biomanufacturing technologies, the U.S. can significantly reduce its dependence on foreign supply chains, enhance national health security, and ensure a more resilient pharmaceutical infrastructure.

Manus has developed a scalable, validated platform for engineering microbial cell factories to produce a broad spectrum of natural products, including terpenoids, phenylpropanoids, and flavonoids. These complex molecules serve critical roles in pharmaceutical manufacturing of natural-product based drugs, functioning either as active pharmaceutical ingredients (APIs) or as key starting materials (KSMs). Over the past 14 years, Manus has built core capabilities in the rapid development of these microbial systems, their scale-up to commercial production, and their deployment in industrial-scale manufacturing. This work is anchored at our fully integrated, 44-acre biomanufacturing facility in Augusta, Georgia, which we own and operate.

Manus has applied its proprietary biomanufacturing platform to the production of artemisinin, a key starting material (KSM) for artesunate, a critical antimalarial drug designated by the U.S. Food and Drug Administration (FDA) as an essential medicine and listed under drug shortage status since 2021. As part of Project BioMaP-24-02-KSM-API-007 administered by the Biopharmaceutical Manufacturing Preparedness (BioMaP) Consortium, Manus is partnering with

ArtemiFlow to deploy an integrated manufacturing infrastructure that combines advanced biomanufacturing with continuous flow chemistry to enable the domestic production of artemisinin at scale.

This same technology and infrastructure can be leveraged to manufacture a broader range of essential medicines. As part of this initiative, Manus conducted a landscape assessment to identify additional essential medicines accessible through the combined biotechnology and flow chemistry platform. The assessment identified more than 50 essential medicines that could be produced using this approach, all through domestically deployable technologies. We believe this represents only a portion of the total opportunity, with many more pharmaceutical ingredients potentially accessible through these methods – highlighting the promise of a resilient, flexible, and scalable domestic supply chain for critical medicines.

(iii) the role of foreign supply chains, particularly of major exporters, in meeting United States demand for pharmaceuticals and pharmaceutical ingredients

Foreign supply chains continue to play a dominant role in meeting U.S. demand for pharmaceuticals – particularly for natural products that are essential in treating a wide range of medical conditions. Among these, natural products remain of growing interest due to their unique, evolutionarily-honed molecular structures and biological activities. Despite their therapeutic potential, these compounds are frequently found in trace amounts within specific plants, which often grow exclusively in limited non-domestic regions. This geographic constraint introduces multiple supply chain vulnerabilities. Production is highly susceptible to environmental disruptions – such as adverse weather events that can devastate crops – as well as geopolitical tensions that may interrupt access to foreign sources. Furthermore, the low natural abundance of these bioactive compounds contributes to high costs and technical challenges in purifying them to pharmaceutical-grade standards. These limitations present a compelling opportunity for biotechnology to enable resilient, domestic production pathways. Manus' platform is particularly well-suited to address this challenge, offering a scalable solution for the synthesis of complex natural products using engineered microbial systems.

Project BioMaP-24-02-KSM-API-007 exemplifies this approach. Artemisinin, a key starting material (KSM) for the antimalarial drug artesunate, is traditionally derived from the plant *Artemisia annua*, which is native to China and grows primarily in temperate and subtropical climates. As such, the artemisinin supply chain is exposed to both environmental and geopolitical risks. Through the

combined application of Manus' biomanufacturing platform and ArtemiFlow's continuous flow chemistry capabilities, this project enables scalable, domestic production of artemisinin at population scale. This not only reduces reliance on foreign sources but also enhances the robustness and flexibility of the U.S. pharmaceutical supply chain.

(vii) the potential for export restrictions by foreign nations, including the ability of foreign nations to weaponize their control over pharmaceuticals supplies

Natural products derived from agriculture in specific global regions pose a distinct vulnerability to U.S. pharmaceutical supply chains. Many of these critical compounds are sourced from plants that grow only in particular climates – often in countries such as China or other regions where geopolitical tensions could result in export restrictions or supply disruptions. Artemisinin, derived from *Artemisia annua*, is one such example, highlighting the strategic risk of relying on foreign-controlled agricultural production for key starting materials. The concentrated geographic origin of these natural products makes them particularly susceptible to being weaponized through export controls or trade barriers. In the absence of diversified or domestic alternatives, the U.S. remains exposed to foreign leverage over essential medicines.

To mitigate this risk, it is imperative to develop alternative sourcing strategies that reduce dependence on vulnerable foreign supply chains. Biotechnology presents a robust and scalable solution. By leveraging engineered microbial production platforms, critical natural products can be synthesized domestically, eliminating reliance on geographically constrained agriculture and enhancing the resilience and security of the U.S. pharmaceutical supply base.

(viii) the feasibility of increasing domestic capacity for pharmaceuticals and pharmaceutical ingredients to reduce import reliance

The BioMaP-24-02-KSM-API-007 project exemplifies a feasible and forward-looking approach to expanding domestic pharmaceutical manufacturing capacity. This initiative leverages modular technology platforms – specifically, biomanufacturing/biotechnology and continuous flow chemistry – to build flexible, reconfigurable infrastructure for the production of pharmaceutical ingredients. The core strength of this approach lies in the versatility of the equipment and infrastructure. Fermentation lines, downstream processing units, and continuous flow chemistry reactors can be adapted to produce a variety of key starting materials or APIs. This modularity enables manufacturers to maintain baseline production of high-demand or high-value products

under normal conditions while retaining the ability to rapidly pivot and scale production of other critical inputs in response to supply chain disruptions or national emergencies.

For instance, a facility may routinely manufacture a commercially dominant product to maintain economic stability and operational sustainability, while retaining the capability to produce additional pharmaceutical ingredients using the same core infrastructure. In the event of a supply chain disruption, whether due to a natural disaster, geopolitical conflict, or export restriction, the facility can be rapidly reconfigured to support surge production of other critical materials.

This model effectively balances efficiency with resilience, allowing the U.S. to benefit from global supply chains during periods of stability while ensuring a robust, domestically controlled rapid-response capacity in times of crisis. Additionally, it offers a more capital- and operationally-efficient alternative to constructing dedicated production lines for each compound, all while preserving the strategic capability to manufacture essential pharmaceutical ingredients onshore when needed.

(ix) the impact of current trade policies on domestic production of pharmaceuticals and pharmaceutical ingredients, and whether additional measures, including tariffs or quotas, are necessary to protect national security

Current trade policies present significant challenges to the economic viability of domestic pharmaceutical and pharmaceutical ingredient production. Many critical inputs to the U.S. pharmaceutical industry are currently sourced from abroad, where lower labor costs and substantial government subsidies enable foreign producers to operate at significantly reduced costs. As a result, U.S.-based manufacturers face structural disadvantages that make it difficult to compete on price, threatening the long-term sustainability of domestic production capacity.

To ensure that future investments in U.S. pharmaceutical manufacturing infrastructure are viable and resilient, there must be mechanisms in place to support profitability, particularly when producing low-margin or intermittently needed products. This is where a modular and flexible production model, as described in the previous response, becomes particularly impactful. Under this model, a facility can remain economically viable by focusing on high-demand, commercially competitive products during normal conditions, while maintaining the validated capability to pivot toward the production of less profitable but strategically important ingredients during times of supply chain disruption.

In this framework, temporary economic support – whether through procurement guarantees, targeted incentives, or other flexible measures – could be deployed to activate production of these critical materials only when needed. Once the disruption subsides, the facility can revert to more profitable operations, preserving both business sustainability and national security.

This approach minimizes the need for permanent, broad-based interventions such as tariffs or quotas, instead favoring targeted, responsive support mechanisms that promote self-sufficiency while preserving market-driven efficiency. In doing so, it enables a reactive, cost-effective domestic pharmaceutical manufacturing base that mitigates strategic risk without placing undue or ongoing burdens on federal resources.