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Passion for Innovation.
Compassion for Patients.™

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May 6, 2025

VIA REGULATIONS.GOV

The Honorable Howard Lutnick
Secretary of Commerce
Attention: Bureau of Industry and Security,
Office of Strategic Industries and Economic Security
U.S. Department of Commerce
14th Street and Constitution Avenue, N.W.
Washington, DC 20230

Re: Comments Regarding the Section 232 National Security Investigation of Imports of Pharmaceuticals and Pharmaceutical Ingredients (BIS-2025-0022; XRIN 0694-XC120)

Dear Secretary Lutnick:

Daiichi Sankyo respectfully submits these comments regarding the U.S. Department of Commerce's ("Commerce") investigation under Section 232 of the Trade Expansion Act of 1962 ("Section 232")[1] to determine the effects on the national security of imports of pharmaceuticals and pharmaceutical ingredients.[2]

Daiichi Sankyo is an innovative global healthcare company with more than 125 years of experience that leverages its world-class science and technology to create innovative medicines for people with cancer, cardiovascular, and other diseases with high unmet medical need. As explained further below, the company has made and is making significant, half a billion dollar investments in U.S. manufacturing, and they drive significant contributions to U.S. employment, labor income, GDP, and government tax revenues.

[1] 19 U.S.C. § 1862.

[2] *Notice of Request for Public Comments on Section 232 National Security Investigation of Imports of Pharmaceuticals and Pharmaceutical Ingredients*, 90 Fed. Reg. 15951 (Apr. 16, 2025).

Daiichi Sankyo appreciates the efforts of President Trump and his Administration to promote U.S. national security in relation to imports of pharmaceutical drugs and ingredients. These comments concern the need to ensure that any actions recommended by the Secretary of Commerce, or taken by the President, account for key facts and are effective in promoting America's national security and economic prosperity.

I. Key Facts That Should Be Considered in this Investigation and in Formulating Any Subsequent Action: The Story of Daiichi Sankyo

A. Background on Daiichi Sankyo's Presence in the U.S.

With a 125-year history of innovation and world-class science, the Daiichi Sankyo Group, headquartered in Japan, has over 19,750 employees globally and a footprint in over 32 countries and regions, including more than 4,000 employees in the U.S.

The Daiichi Sankyo Group has 13 worldwide manufacturing sites, with 4 located in the U.S. in Hilliard, Ohio; New Albany, Ohio; Shirley, New York; and Brea, California. Daiichi Sankyo, Inc., a member of the Daiichi Sankyo Group, is headquartered in Basking Ridge, New Jersey, and is focused on the development and delivery of oncology and specialty medicines. American Regent, Inc., another member of the Daiichi Sankyo Group headquartered in Shirley, NY, provides industry-leading, U.S.-manufactured sterile injectables.

Daiichi Sankyo's medicines approved in the U.S. treat a range of cancers and other diseases, including breast, lung and gastric cancer, tenosynovial giant cell tumor, thrombosis, acute myeloid leukemia and iron deficiency anemia.

B. The Cancer Drug ENHERTU® Is Reshaping the Treatment Landscape for American Patients

Daiichi Sankyo's flagship oncology treatment in the U.S., ENHERTU, embodies the next frontier in cancer therapy and provides a case study in the company's commitment to patients. ENHERTU is a type of drug known as an "antibody drug conjugate" or "ADC," a biopharmaceutical that links a monoclonal antibody (a protein that targets specific cells) with a cytotoxic drug (to eliminate the cells). In other words, ADCs help expand the therapeutic window for cancer by merging the power of chemotherapy with the precision of antibodies to target cancer cells, while minimizing damage to normal cells. With this improved targeting of cancer cells, use of ADCs like ENHERTU has grown considerably in the past five years.

In 2024, ENHERTU was awarded the Prix Galien USA Award for "Best Biotechnology Product" for innovation in health and medicine—essentially, the pharmaceutical industry's equivalent to a Nobel Prize. ENHERTU was selected from among 21 nominees approved by the FDA in the last five years, each of which "demonstrate tremendous potential to improve human

health." Indeed, ENHERTU is extending the lives of tens of thousands of cancer patients in the U.S. whose disease has progressed to a point where they have few, if any, other options.

ENHERTU is FDA-approved to treat cancers that test positive for a protein called the human epidermal growth factor receptor 2 (HER2). HER2-positive cancers tend to be more aggressive than other types because the HER2 protein promotes growth of cancer cells. ENHERTU is extending the lives of patients who have certain types of HER2-positive tumors that cannot be surgically removed or that have spread to other parts of the body, including patients that have already been treated with another therapy and had their cancer reoccur or progress. ENHERTU is approved for adult patients with **breast cancer, stomach cancer, lung cancer, and other solid tumors.** Specifically, ENHERTU is approved for:[3]

- Unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy;
- Unresectable or metastatic:
    - Hormone receptor-positive, HER2-low, or HER2-ultralow breast cancer that has progressed on prior endocrine therapies in the metastatic setting;
    - HER2-low breast cancer and who received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy;
- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma [a type of stomach cancer] who have received a prior trastuzumab-based regimen;
- Unresectable or metastatic non-small cell lung cancer whose tumors have activating HER2 mutations and who have received a prior systemic therapy; and
- Unresectable or metastatic HER2-positive solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

ENHERTU's approval for certain types of metastatic breast cancer (for HER2-low and HER2-ultralow indications) **is a groundbreaking paradigm shift**. Data supporting ENHERTU's approval for these indications redefined the classification of metastatic breast cancer to identify and, for the first time, bring targeted cancer therapy to these patient segments. These indications mean ENHERTU could be a treatment option for up to 90% of people with metastatic breast cancer. In addition, ENHERTU is the first ADC approved with a "tumor agnostic" indication,

[3] *See* "Highlights of Prescribing Information: Indications and Usage," available at: https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true. ENHERTU's indications for unresectable or metastatic non-small cell lung cancer and other solid tumors are approved under FDA's accelerated approval pathway.

meaning any unresectable or metastatic HER2-positive solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options regardless of the tumor location.

ENHERTU's treatment potential does not stop there. In recent clinical trials, ENHERTU demonstrated efficacy as a "first-line" treatment for HER2-positive breast cancer (in patients who had not previously been treated with chemotherapy), providing patients with a statistically significant and clinically meaningful improvement in progression-free survival (the length of time patients survive without their cancer getting worse). For stomach cancer, studies of ENHERTU as a second-line therapy demonstrated efficacy in patients' overall survival. For certain types of non-small cell lung cancer, ENHERTU is likewise being studied as an alternative to the existing, first-line standard of care. And, building on the success of ENHERTU's tumor agnostic indication, Daiichi Sankyo is in the process of studying or preparing studies of ENHERTU for biliary tract cancer and ovarian cancer.

Cancer is a chronic disease, and patients need new treatments. Between 2017 and 2021, in the U.S., 8,722,295 new cases of cancer were reported.[4] In 2021 alone, the latest year for which incidence data are currently available, the U.S. saw 1,777,566 new cases.[5] Breast cancer, specifically, represents a considerable portion of those cases. In 2025, over 300,000 women will be diagnosed with invasive breast cancer, reflecting more than 15% of the estimated new cancer cases.[6] One in eight women will develop invasive breast cancer at some point in their life.[7]

In total, between January 2020 and March 2025, ENHERTU has been used to treat more than 67,000 cancer patients in the U.S., with the top ten states by number of patients treated being California, New York, Florida, Texas, Illinois, Pennsylvania, Georgia, Ohio, North Carolina, and Michigan.

ENHERTU is **only one** of Daiichi Sankyo's flagship oncology products. DATROWAY®, a TROP2-directed ADC, was approved in the U.S. in January 2025 for the treatment of adult patients with unresectable or metastatic hormone receptor-positive, HER2-negative breast cancer who have received prior endocrine-based therapy and chemotherapy. By 2030, Daiichi Sankyo aims to become a global top 10 company in oncology, bringing treatments for more than 30 indications to hundreds of thousands of cancer patients.

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[4] U.S. Centers for Disease Control and Prevention, *United States Cancer Statistics: Data Visualizations*, available at https://www.cdc.gov/united-states-cancer-statistics/index.html.

[5] *Id*.

[6] NIH, *National Cancer Institute, Surveillance, Epidemiology, and End Results Program, Cancer Stat Facts: Female Breast Cancer*, available at https://seer.cancer.gov/.

[7] *Id.*

C. Manufacturing Biological Products like ENHERTU® Requires an Extraordinarily Complex Series of Processes

Large molecule drugs like ADCs are far more difficult to manufacture than small molecule drugs typically dispensed in pill or capsule form. Manufacturing ENHERTU is a time-intensive, complicated, and expensive process that depends on a complex supply chain of inputs, coupled with highly technical equipment and skilled labor. Production of ENHERTU involves essentially three steps: (i) preparation of the antibody, the linker, and the small molecule cytotoxin, (ii) the conjugation reaction, and (iii) purification and fill. Because of the complexity of the drug's design, there is significant potential for batch-to-batch variation in the manufactured products and other quality issues. As a result, the manufacturing process for ENHERTU has been carefully developed, characterized, validated, and controlled. In addition, because the finished product is in the form of a powder—which health care providers then reconstitute with sterile water for intravenous infusion—the manufacturing process and facilities must conform to extensive Good Manufacturing Practices (cGMP) for production of sterile products to prevent contamination.

ENHERTU's production depends on a complex global chain, involving manufacturing facilities in the U.S., Japan, and Europe, followed by packaging in Ohio with warehousing and distribution from Tennessee. Moving the overseas manufacturing steps to the U.S. would require significant overhaul of the company's operations and substantial financial costs. As discussed below, the company has plans underway to on-shore additional production steps in the coming years. However, production of the conjugated product—the second step—is performed overseas and would be subject to tariffs if they are imposed. The application of tariffs to ENHERTU and Daiichi Sankyo's other medicines risks real consequences on the company's ability to meet its goals for significant investment in the future of new treatments for patients and planned manufacturing capacity in the U.S.

II. Daiichi Sankyo is Committed to Increasing U.S. Manufacturing of its Drugs

Daiichi Sankyo appreciates the Administration's focus on ensuring a more robust supply chain for pharmaceuticals, including the critical need to guard against shortages of life-saving and life-sustaining pharmaceuticals. This is nowhere more important than with oncology drugs. Daiichi Sankyo has undertaken substantial efforts to further these goals within the U.S. and intends to do more in the future.

This includes a $350 million investment in one of the Daiichi Sankyo Group's manufacturing sites in Ohio—a significant portion of which will be used for part of the third step in the manufacturing process of Daiichi Sankyo's ADCs, including ENHERTU. The expansion will also feature a new laboratory and warehouse space. Construction is underway and the

expansion is due to be operational by March 2028. Daiichi Sankyo Group estimates adding around 900 jobs in the U.S. over the next three years.

In addition, Daiichi Sankyo currently contracts with six contract development and manufacturing organizations (CDMOs) in the U.S. to manufacture complex large molecule drug ingredients that are used to produce the ADCs. Although CDMOs in the U.S. are capable of manufacturing ADCs, there is a scarcity of CDMOs capable of large scale manufacturing of highly potent compounds utilizing proper containment equipment, which has caused Daiichi Sankyo to take a diversified approach to ensure consistent and resilient production of ADC drugs in the U.S., through substantial investments in multiple manufacturing sites.

But Daiichi Sankyo is not stopping with its current investments. The company is considering scaling up additional manufacturing investments in the U.S. These efforts will take time. To establish additional manufacturing capabilities at existing sites, it takes at least two years to ensure an appropriate design and transfer of technology such that production can happen on a consistent, high-quality basis, and an additional 10-15 months to complete the regulatory procedures and approvals.

Similarly for installation of new manufacturing facilities, the total timeline is five years or more. That includes: (i) approximately five years to design the appropriate facility, construct it, source, procure and install pharmaceutical equipment, and ensure the necessary high-level quality controls are in place to produce high quality drugs; and (ii) an additional 10-15 months to complete the necessary regulatory procedures for a manufacturing site change, including FDA's review of the "post approval change" regulatory submission and completion of a facility inspection. The time and cost associated with the regulatory compliance for bringing a new manufacturing facility online, including the potential setbacks and delays of approval, are not insignificant and can take several years.

III. Broad Tariffs Will Stifle Our Ability to Make Those Investments

Broad tariffs on pharmaceutical drugs will undermine Daiichi Sankyo's ability to scale these U.S. investments and will also undermine Daiichi Sankyo's ability to innovate new oncology treatments. Tariffs will increase price pressure on our pharmaceutical products, with an expected impact on patient costs through higher cost-sharing and health insurance premiums.[8] Tariffs also will lead to strained supply chains and increase the risk of shortages. Ultimately, the

[8] Choi, Joseph and Weixel, Nathaniel, *Why Trump's pharma tariffs are a political minefield*, The Hill, ("A 20-percentage point increase in the effective tariff rate on drugs would be something like a 2.4 percent increase in overall health insurance costs," said Josh Bivens, chief economist at the Economic Policy Institute.)

strain of tariffs jeopardizes American patients' continued access to a stable and predictable supply of our current and future medicines.

As we believe our comments demonstrate, Daiichi Sankyo is committed to manufacturing in the U.S., and it has already created jobs for many Americans. Moreover, Daiichi Sankyo has already been actively planning and making the investments to move significantly more drug manufacturing and jobs to the U.S. by 2028. Because of the complexity and regulatory compliance burden of manufacturing ADC drugs like ENHERTU for cancer, however, there are limitations on the speed at which any company can relocate those manufacturing operations. We respectfully request the Administration take these considerations into account as it evaluates restrictions on trade and incentives for domestic production of pharmaceuticals.

We thank you for your attention to these comments.

Sincerely,

Ken Keller

President and Chief Executive Officer of Daiichi Sankyo, Inc.
Global Head of the Daiichi Sankyo Oncology Business