May 6, 2025

Department of Commerce
Bureau of Industry and Security
1401 Constitution Ave NW
Washington, D.C. 20230

Re: Notice of Request for Public Comments on Section 232 National Security Investigation of Imports of Pharmaceuticals and Pharmaceutical Ingredients (BIS-2025-0022)

Submitted electronically

Dear Sir/Madam:

Tega Therapeutics appreciates the opportunity to offer comments on the national security investigation of imports of pharmaceuticals and pharmaceutical ingredients (XRIN 0694-XC120 Pharmaceuticals 232 Notice)[1].

Tega Therapeutics is a biotechnology company founded in 2014. The Company manufactures a bioengineered heparin, also described as recombinant heparin or Tega rHeparin, an anti-coagulant that is one of the world's most critical drugs. Currently, 80% of the U.S. supply of heparin comes from China. This represents one of the biggest medical threats to the U.S. population.

Tega Therapeutics shares the Department of Commerce's interest in protecting our country's national security and ensuring that our pharmaceutical supply chain remains strong and stable. We support efforts to incentivize domestic manufacturing, especially those that represent a national security risk. 80% of the U.S. supply of heparin comes from China. Tega has a solution to reshore heparin manufacturing. We appreciate the opportunity to provide comments on the Section 232 investigation, and we offer the following responses:

Maintaining a Robust U.S. Drug Supply Chain

Biosynthetic Heparin Can Reduce Drug Shortages and End Reliance on Chinese Pig Heparin

Issue — Heparin is a blood thinner dosed more than 300,000 times each day in the United States. However, the current U.S. heparin supply is stressed because of its reliance on the Chinese pig population for production. Widespread swine disease outbreaks have and will continue to cause heparin shortages, which may force clinicians to limit heparin to only patients who need it most. TEGA Therapeutics has developed biosynthetic heparin which has anticoagulant activity equal to pharmaceutical heparin but does not rely on the pig supply, thereby reducing shortage risks and ending our reliance on China for this critical drug.

Addressing U.S. Dependency on Chinese Heparin

[1] Federal Register, 90 FR 15951, pp. 15951-15952, April 16, 2025.

Problem — Heparin is a critical drug used in a wide range of applications including deep vein thrombosis (DVT), open-heart surgeries and kidney dialysis. It is on the World Health Organization's Model List of Essential Medicines.[2] Heparin is a drug produced primarily from pig intestines. Although it can also be derived from cow sources, for more than 20 years the United States and many other countries have adhered exclusively to porcine origin because of concerns over mad cow disease. Given the porcine requirement for heparin, the United States is largely dependent on China for its heparin because more than half of the global pig supply is in China.[3]

Nearly 80% of the world's supply of crude heparin is made in China. Pharmaceutical researchers are raising concerns that an ongoing outbreak of African swine fever in China, which at one point had reduced the pig population by one-third, will cause an unprecedented shortage of heparin's raw material.[4] China has been struggling to contain the highly contagious virus since August 2018 and African swine fever is surging again in China, renewing questions about the dependability of the country's swine herd. Today's situation is hardly unique. Reduced heparin supply and the resulting heparin contamination crisis in early 2008 are attributed to an outbreak of the Blue Ear Virus in China.[5] Attached are letters from Energy and Commerce Committee to the FDA emanding action.

Already, the heparin supply is stressed. The American Society of Health System Pharmacists (ASHP) currently lists heparin on their drug shortage list.[6] Experts are now suggesting clinicians start prioritizing heparin for certain patients and situations where the need is greatest. If the heparin shortage were to progress to a critical status, physicians may have to prioritize heparin for only urgent or emergent cardiac surgeries.[7] But with 12 million patients using heparin each year and more uses for heparin being discovered, it is critical we find an alternative source for heparin.

Solution — TEGA Therapeutics has created a recombinant source of heparin that eliminates dependence on any animal population, thereby dramatically reducing the associated risks of shortage and contamination. Cells have been genetically engineered to produce heparin in bioreactors using completely animal-free materials. Such production could be performed in U.S. manufacturing facilities rather than depending on a supply of Chinese crude heparin. TEGA bioengineered heparin has anticoagulant potency equivalent to pig derived heparin. TEGA's production methods will improve the quality of heparin, potentially eliminating heparin's side effects and extend the use of heparin for other non-anticoagulant uses. TEGA published this data in January 2022, Metabolic Engineering 70 (2022) 155–165.

Like 7 of 10 of the largest selling drugs, TEGA Therapeutics produces biosynthetic heparin from cells grown in stainless steel bioprocessors instead of from animal tissues. This is a completely controlled process that doesn't depend on pig intestine or Chinese pig farms. TEGA recombinant heparin is of higher quality produced in more consistent batches with reduced risks of contamination. This also removes the

[2] World Health Organization: https://list.essentialmeds.org
[3] Food and Agriculture Organization of the United Nations: http://www.fao.org/3/i3166e/i3166e00.pdf
[4] European Pharmaceutical Review: https://www.europeanpharmaceuticalreview.com/news/95829/swine-fever-in-china-raises-concern-over-heparin-supply-for-us/
[5] Food and Drug Law Journal: https://pubmed.ncbi.nlm.nih.gov/24479237/
[6] ASHP Drug Shortage List: https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortages-List?page=CurrentShortages&loginreturnUrl=SSOCheckOnly
[7] Cardiovascular Business: https://www.cardiovascularbusiness.com/topics/vascular-endovascular/6-things-know-about-potential-heparin-shortage ; Metabolic Engineering 70 (2022) 155–165

vulnerability to shortages caused by diseases in animal populations allowing the United States to free itself from a source of heparin controlled by the Chinese.

We have support from Congress for bioengineered heparin specifically called out in 4 locations of the 2023 Omnibus budget approved by Congress (see below). We also have an initial $2 million from U.S. agency BioMADE in order to re-shore heparin production. For $10 million we can get into human clinical trials, and for another $40 million we can bring the program to commercial.

Request — Collaborate with TEGA Therapeutics to increase development of biosynthetic heparin as an alternative to pig-derived heparin sourced from China. Please fund the TEGA rHeparin program as described in the 2023 Omnibus budget from Congress.

Contacts —
Tim Scott, TEGA Therapeutics, (619) 838-8579, tscott@tegatherapeutics.com

Current Situation: BioMADE Grant and Omnibus 2023 Funding

In October 2024, we secured $2,058,498 from BioMADE, a government agency focused on U.S. manufacturing objectives. This funding supports scale up of our recombinant heparin program. Our original request was for $10M to take the program to a clinical trial. BioMADE was not able to provide all the funding requested but they did also fund a group called BioFAB that will help us work through the regulatory process, which is not trivial. We hope to show good progress over the next year that will justify additional funding.

The BioMADE grant is a nice validation of our case for a new source of heparin, one that is higher quality, doesn't come from an animal source and is not reliant on a foreign government for 80% of our heparin supply. However, the funding does not cover all of our expenses. So, we will continue looking for investors that believe in the vision of recombinant heparin and HS.

Further validation of TEGA rHeparin comes from a recent scientific review paper in publication by Sultana et al, "Bioengineered Heparin: Advances in Production Technology." The paper reviews all current methods of engineered heparin and devotes an entire section (4.3 Multiplex Genome Editing) describing TEGA's technology, concluding:

> Therefore, this study using multiplex genome engineering represents a significant advance in the synthesis of recombinant HS from genetically engineered mammalian cells. The resulting HS exhibits anticoagulant efficacy comparable to or superior to that of pharmaceutical heparin, highlighting the potential role of synthetic biology in replacing animal-derived heparin.

2023 Omnibus calls for the U.S. Congress to Pursue Bioengineered Heparin

We held calls with the following offices to brief them on TEGA and our request for appropriations in the 2023 budget. For each of the offices with which we spoke, we submitted an appropriations request form for the corresponding request.

o Rep. Andy Harris (R-MD-01)
o Rep. Jaime Herrera Beutler (R-WA-03)
o Rep. Katherine Clark (D-MA-05)
o Rep. Mark Pocan (D-WI-02)
o Rep. Betty McColllum (D-MN-04)
o Rep. Chuck Fleischmann (R-TN-03)
o Rep. Pat Fallon (R-TX-04)
o Rep. Andy Kim (D-NJ-03)
o Rep. Tom Cole (R-OK-04)
o Rep Marilyn Strickland (D-WA-10)
o Rep. Lisa McClain (R-MI-10)
o Rep. Chrissy Houlahan (D-PA-06)
o Rep. Lucille Roy-Allard (D-CA-40)
o Rep. Ben Cline (R-VA-06)
o Rep. Stephanie Bice (D-OK-05)
o Rep. Marc Veasey (D-TX-33)
o Rep. Mike Gallagher (R-WI-08)
o Rep. John R. Moolenaar (R-MI-04)
o Rep. Robert Aderholt (R-AL-04)
o Rep. Barbara Lee (D-CA-13)
o Rep. Matt Cartwright (D-PA-08)
o Sen. Jerry Moran (R-KS)
o Rep. Dutch Ruppersberger (D-MD-02)
o Sen. Thom Tillis (R-NC)
o Rep. Mike Levin (D-CA-49)
o Sen. Elizabeth Warren (D-MA)

We submitted a total of 80 appropriations forms to the House and Senate for the 4 following requests:

o **Labor, Health, and Human Services.** $50M appropriation for Health and Human Services Assistant Secretary for Preparedness and Response to shift to sourcing heparin domestically and manufacturing biosynthetically and report language.

o **Agriculture, Rural Development, and Food and Drug Administration.** language to direct the FDA to provide guidance on shifting to sourcing heparin domestically and manufacturing biosynthetically.

o **Commerce, Science, Justice.** $10M appropriation for the National Institute of Standard and Technology (NIST) for projects to scale the manufacturing of biosynthetic heparin and report language.

o **National Defense Authorization Act (NDAA)**. language asking the Department of Defense to invest in the development of heparin sourced in the United States and independent of animal sources and to provide a report within 180 days of enactment on how execute this directive.

2023 Omnibus Budget Language: Approved Language for Biosynthetic Heparin

Through our efforts with the various congressional offices, we were successful in getting the following language in various areas of the Omnibus budget. This budget was approved at the end of December 2022. Below is the language that can be found in the 2023 Omnibus budget:

House Labor, Health, and Human Services:
Active Pharmaceutical Ingredients and Manufacturing of Essential Drugs—

> "The Committee continues to be concerned with the risk of increased reliance on foreign-based sources of active pharmaceutical ingredients (APIs), their chemical components, and off- shore drug production. The Committee recognizes the importance of domestic drug manufacturing and onshore production of medicine and medical countermeasures, and the successful work of BARDA in addressing these public health vulnerabilities, including APIs, such as those included in Heparin, and to collaborate within ASPR to support domestic manufacturing surge capacity. The Committee requests an updated report within 180 days of the date of enactment of this Act, including efforts to ensure robust domestic drug manufacturing and stockpiling and mitigation of supply chain vulnerabilities to enable continuous manufacturing capabilities of APIs from procurement to finished drug formulations."

House NDAA:
Heparin Supply Chain —

> "The committee recognizes the importance of heparin for military service members as an essential blood product used in the field, at other operational locations, and at hospitals. The committee is concerned about the overreliance on pigs from foreign sources. As prolonged field care and other operational settings continues to increase, the Department of Defense must ensure heparin remains available and invest in the development of heparin sourced in the United States and independent of animal sources. The committee directs the Secretary of Defense to provide a briefing to the House Committee on Armed Services by March 1, 2023, on opportunities to expand the heparin supply chain for the Department and how investments in research of artificially made heparin can assist military readiness."

House Ag/FDA:
Heparin—

> "The Committee is concerned about the over-reliance on foreign sourcing and manufacturing of pharmaceutical drugs that cause supply chain problems that can harm patients, including Heparin. The Committee encourages the FDA to work with stake- holders on sourcing heparin domestically and manufacturing bio- synthetically."

House Commerce, Science, Justice:
Biosynthetic Heparin—

> "The Committee recommends that NIST thoroughly consider projects to scale the manufacturing of biosynthetic heparin to allow for domestically made heparin in order to reduce the reliance on China, prevent shortages, and provide patients the care they need. Even though heparin is on the

> World Health Organization's list of essential drugs, shortages from adulteration due to African swine fever and Blue Ear Virus have threatened supply."

The 2023 Omnibus Budget report and briefing requirements mean both HHS and DOD must study the heparin shortage problem and come up with a plan to address it, and TEGA can be the one to help them do this. We are prepared to work directly with these agencies in order to reshore heparin production, move away from an animal source and reduce our reliance on Chinese pig heparin. We encourage Congress to support the above appropriations with funding of $50 million in order to secure an alternative heparin source that can be made in the United States.

Sustained Competitiveness in U.S. Biotechnology Innovation, R&D, and National Defense

Biomedical research plays a major role in fueling innovation in the U.S. by generating life-saving products and economic gains that benefit local communities, individual states, and the entire country. The U.S. stands as the global leader in biomedical R&D investment, with U.S.-based life science companies responsible for nearly twice as much R&D investment as all their European counterparts combined[8]. In 2019, the United States performed 27% or $656 billion of global R&D[9].

Not acting on the heparin crisis risks further strengthening of China and a weakening U.S. leadership in biomedical innovation. **Lack of U.S. based heparin manufacturing would place the U.S. at a strategic disadvantage if a tariff or other escalating crisis occurs. Lack of U.S. production of heparin would encourage international customers to continue to work with foreign suppliers, such as China.** This unintended consequence would significantly weaken the U.S. in the global market, reduce competitiveness, and negatively affect our position as a leader in the global economy.

Furthermore, heparin could play a significant role in China's ability to threaten U.S. defense applications, including treatments for battlefield injuries and rapid-response biological countermeasures. **Leveraging existing initiatives such as the Industrial Base Expansion (IBx) program for heparin production in the U.S. can reduce our dependence on Chinese heparin and maintain the U.S.'s global leadership position**.

Conclusion

Thousands of American patients could die if China were to decide to reduce or stop providing crude heparin to U.S. suppliers. Chinese heparin makes up 80% of the U.S. heparin supply. We urge the Federal Government to consider investing in alternative measures to Chinese heparin that would strengthen U.S. pharmaceutical resilience, support patients, and maintain the U.S.'s position as a global leader in API manufacturing.

We appreciate the opportunity to provide feedback on behalf of our members and thank you for your time and diligence in examining our comments. Please contact Tega Therapeutics Chairman, Tim Scott. for additional information or questions. We look forward to continuing to work with you on this matter.

[8] Powaleny, New research: American biopharmaceutical investment in R&D drives transformational innovation 2024
[9] The state of U.S. Science and Engineering 2022 | NSF - National Science Foundation 2022