Centrient Pharmaceuticals (1): Global Leader in Biomanufacturing Fermentation-Based Antibiotics and Essential Medicines

COMMENTS ON SECTION 232 INVESTIGATIONS BY US DEPARTMENT OF COMMERCE RELATED TO PHARMACEUTICAL IMPORTS

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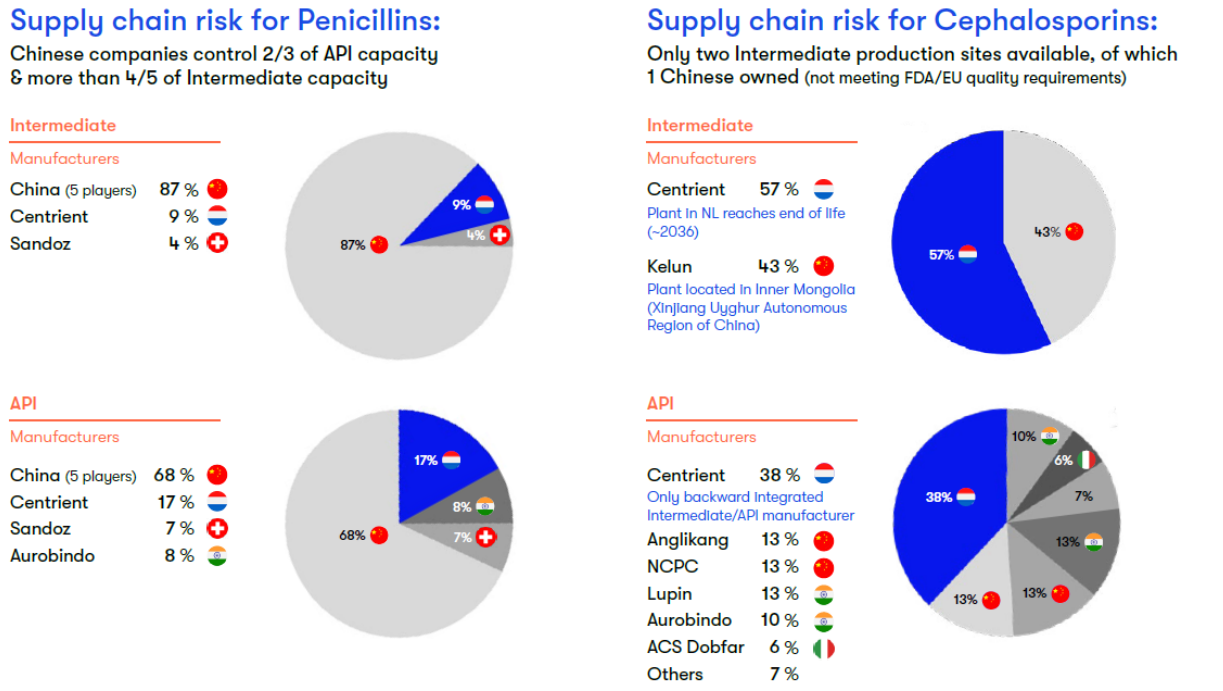
I. EXECUTIVE SUMMARY

Antibiotics are the cornerstone of modern healthcare, that also holds true for the US. However, currently the antibiotics supply chain at the API and intermediary steps is concentrated in a limited number of suppliers. These suppliers and their production capacity for penicillin and cephalosporin API and intermediary product is primarily located in China. There is no domestic Intermediate or API manufacturer for antibiotics in the US. This leaves the US in a very vulnerable position and also requires sensitive consideration when evaluating tariffs on this molecule group. If China were to decide tomorrow to stop the exports of the crucial intermediate 6APA on which the antibiotics supply chain relies, this would have detrimental consequences on the US.

This stresses the importance of the U.S. government efforts to diversify supply chains and move reliance away from China. However, because of the unique capital costs, low returns, and critical importance of antibiotics to U.S. and global healthcare, the U.S. government should carefully consider any steps taken to address its reliance on Asia.



Source: Centrient management information, based on public data and company information

While tariffs and other border measures may be sufficient to reorient other supply chains, it is our expectation that increased costs imposed on importers will not be sufficient to onshore supply chains for generic antibiotics, for 2 reasons: Onshoring antibiotics manufacturing takes a long time, requires significant capital and the expected returns are very low, making it unattractive for anyone to even consider this.

Onshoring Intermediate and API manufacturing capabilities for antibiotics is capital intense and takes time. To bring a greenfield site into production takes at least 4-5 years. Even if tariffs increase the pressure, they would not be able to speed up the timelines. This issue is particularly acute as there are no available, idle facilities in the United States, instead production would need to be started from scratch.

While tariffs might increase the pressure on players to consider onshoring to the US, due to the long timelines, high capital requirements and low expected returns, there might not be a lot of enthusiasm for this. Unless the United States considers providing financial incentives.

On the other hand, imposing tariffs on antibiotics - while having limited upside - comes with a range of risks:

The risks of imposing tariffs on essential medicines such as antibiotics, are multiple:

- **Threat to national security & public health:** Antibiotics are crucial for hospitals, military readiness and emergency preparedness. Tariffs might cause higher costs and delays in delivery, leading to a weaker response to future pandemics, wars or even basic infections.
- **Risk of supply shortages followed by price increases:** if the height of the tariff is higher than the margins the manufacturers make on this product group, they might decide not to supply the US with these fundamental medicines. This would lead to shortages in the short term, and a price increase in the long term to incentivize them to supply after all. Both are not intended effects.
- **Risk of negative publicity:** Should too high tariffs lead to a situation of supply disruption of these fundamental medicines, there is a risk that patients in need cannot receive accurate treatment. As antibiotics are fundamental for the healthcare system – they are required in the most basic operations – there is a very real risk that patients might suffer or even die if they are not available.

- **U.S. farmers will be impacted:** American livestock producers rely heavily on imported antibiotics to keep animals healthy and maintain productivity. A significant share of the nation's penicillin imports goes to the meat industry. Tariffs on these imports would drive up production costs, likely raising meat prices across the board—impacting both farmers' bottom lines and American families at the grocery store.
- **Antibiotic Resistance:** If doctors or patients switch to less effective or inappropriate alternatives due to cost, this can worsen antimicrobial resistance.

Our clear recommendation is to exempt these foundational, generic medicines from tariffs on the grounds that imposing tariffs would not lead to a positive change but comes with a range of risks.

Recognizing it is a national priority to become independent of China for crucial medicines, we would urge the United States to consider a more holistic approach including providing domestic incentives and financial support for the set-up of domestic manufacturing facilities. With proper resourcing, we expect this could be done in 4-5 years. In the meantime, continued duty-free imports of generics will be necessary. This is done as an effort to gain independence and being able to supply the most crucial medicines of the healthcare system from within the US. By the American people, for the American people.

Centrient Pharmaceuticals (**Centrient** or the **Company**) is a global business-to-business leader in biomanufacturing of semi-synthetic penicillins (**SSPs**), first- and second-generation semi-synthetic cephalosporins (**SSCs**) as well as the relevant key intermediates, antifungals, and next-generation statins based in the Netherlands. Centrient Pharmaceuticals manufactures the critical active pharmaceutical ingredient (**API**) for several of the medicines currently stored in the Strategic National Stockpile and on the FDA's Essential Medicines list.

Being the world leader in antibiotic production, we are open for a dialogue with the USG on how to create a stronger supply chain for the US.

II. EXISTING INFRASTRUCTURE RELATED TO BIOMANUFACTURING OF FERMENTATION-BASED ANTIBIOTICS, KEY INTERMEDIATES AND OTHER ESSENTIAL MEDICINES

A. Centrient's Global Antibiotic Production

Centrient Pharmaceuticals has been a global technology leader in fermentation-based manufacturing of antibiotics for over 70 years and continues to lead the field in efficiency, quality, and environmental protection in the fight against antimicrobial resistant bacteria (**AMR**) by combining its enzymatic synthesis technology with proprietary zero predicted effect concentration wastewater treatment technology.

Centrient's global operations currently include manufacturing facilities on three continents and employs over 1,800 employees. Centrient manufactures and sells key intermediates and APIs as well as finished-dosage-form products (**FDFs**) manufactured at facilities in the Netherlands, Spain, Mexico, India, and China. The Company's customers include the world's major pharmaceutical companies as well as leading regional pharmaceutical companies on all continents.

Centrient's intermediates and APIs accounting for about half of the beta-lactam antibiotics on FDA's essential medicines list and provides nearly 60% of Americans with an essential medicine each year. Centrient Pharmaceuticals manufactures the API for about 40% of the amoxicillin in the U.S. market, 60% of the cefalexin and 100% of penicillin G in the U.S. human market. Its

APIs treat over 1.5 billion people around the world each year. Centrient's API production sites can produce over 9,000Mt of SSP APIs, over 3,500Mt of SSC APIs and over 200Mt of other APIs. In total the intermediate sites can produce roughly 6,000Mt of key intermediates for the use in SSP & SSC APIs. Additionally, Centrient produces all the enzymes used in these production processes in-house.

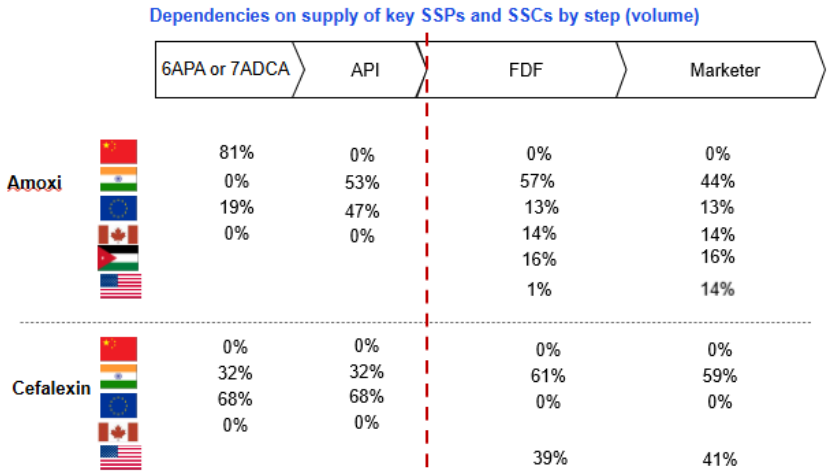
Centrient Pharmaceuticals Current Global Manufacturing Operations

Centrient Pharmaceuticals Netherlands B.V. Delft, The Netherlands	Centrient Pharmaceuticals Co. Ltd. Shandong Province, China
Centrient Pharmaceuticals Spain S.A. Barcelona, Spain	Centrient Biochem Intermediate Limited Corporation Changchun, Jilin Province, China
Centrient Pharmaceuticals (Fersinsa GB S.A de C.V.) Ramos Arizpe, Mexico	Centrient Pharmaceuticals India Private Limited Punjab, India

B. Asia Dependency Challenges Secure Supply of Antibiotics in U.S.

While broad spectrum antibiotics like Amoxicillin, and first and second generation Cephalosporins form the backbone of every healthcare system, they are not produced in the United States. Today, there is not a single entity in the United States producing APIs used to make generic antibiotics, making the United States fully dependent on imports. This fact is not immediately visible, if you simply look at the ANDA's registered or the marketers, but requires detailed investigation into the supply chains.

As an example, Amoxicillin, and first and second generation Cephalosporins reliant on China and to a lesser extent, India. As illustrated below, for Amoxicillin, the United States is 100% dependent on API imports and 99% dependent on imports for FDF. For Cefalexin, the supply chain is slightly more diverse with API sourced from India and the EU, with one U.S. producer of FDF (Teva).



Source: Centrient management information, based on IQVIA data and import/export information

Consolidation and concentration in the generic antibiotic industry has been driven both by the economic reality of the antibiotic industry and by reliance on government subsidies to build up this infrastructure.

If the U.S. wants to secure its supply chains for these essential medicines, it must compete with China and India and will have to invest in underwriting the capital-intense infrastructure required to biomanufacture these medicines at a commercially viable scale in the U.S.

III. A CASE FOR SUPPORTING ROBUST ANTIBIOTICS SUPPLY IN THE U.S. BY STRENGTHENING GLOBAL SUPPLY CHAINS

Generic antibiotics are a low-cost, low-margin product but require extensive and expensive facilities to manufacture at a commercially viable scale. As a preliminary matter, antibiotic fermentation requires extensive capital expenditure to build out massive (and dedicated, since it concerns beta lactam antibiotics production) plants necessary to achieve the economical viable scale. Moreover, generic antibiotics are some of the most affordable, low-cost prescription drugs available. Given the low prices/low margin for generic antibiotics, the investment in infrastructure—without government support—is extremely difficult. As a reference, the margins for antibiotics like Amoxicillin are limited: $10 - $12 per kilogram average gross profits (sales price – cost of goods but excluding fixed costs like capital expenditure) are usual. The U.S. market for Amoxicillin API is about 2,000,000 kilograms (1 kilogram equals 2.205 lb) each year, so total gross profits across the entire market is approximately $15 million - $21 million. It is not possible to repay the capital expenditure on a $800 million investment over a reasonable timeframe with these margins.

However, China has recognized this issue and strategically invested in pharmaceutical production – even when not commercially viable. China used this strategy to capture much of this supply chain twenty years ago, and China is actively working to invest in keeping this manufacturing in China. The United States will remain reliant on foreign pharmaceutical supply for its essential antibiotics unless it makes a commensurate investment bringing production facilities to the United States.

IV. STRATEGIES FOR ONSHORING PRODUCTION OF ANTIBIOTICS

A. Tariffs are an ineffective tool for reshoring antibiotic production

Derisking and onshoring these supply chains is - rightfully - identified as a national security issue, across the government, including by the Department of Defense.[1] Recent global events have highlighted that risk. Demand spiked in the U.S. for pediatric amoxicillin at the same moment that there were supply chain disruptions in China and Europe, leaving the U.S. with a shortage of pediatric amoxicillin since the 28th of October 2022, as reported by the FDA.[2] The vulnerability of the anti-infectives supply chain was also identified in a recent white paper published by HHS, with the support of ASPR.[3]

[1] Inspector General, U.S. Dept. of Defense, *Evaluation of the Department of Defense's Mitigation of Foreign Suppliers in the Pharmaceutical Supply Chain (DODIG-2021-126)* (Sept. 22, 2021) https://www.dodig.mil/reports.html/Article/2784301/evaluation-of-the-department-of-defenses-mitigation-of-foreign-suppliers-in-the/

[2] FDA reported drug shortages – Amoxicillin Powder for oral suspension: https://dps.fda.gov/drugshortages/activeingredient/amoxicillin-powder-for-suspension

[3] US department of Health and Human Services, *White paper: Policy Considerations to Prevent Drug Shortages and Mitigate Supply Chain Vulnerabilities in the United States* (Jan. 26, 2024): https://aspe.hhs.gov/sites/default/files/documents/3a9df8acf50e7fda2e443f025d51d038/HHS-White-Paper-Preventing-Shortages-Supply-Chain-Vulnerabilities.pdf

Recognizing the need to expediently shift supply chains, it is Centrient's view that tariffs may not be well suited to this objective in the antibiotic sector. Two unique features make tariffs potentially a less effective tool in achieving the goal:

- First, onshoring Intermediate and API manufacturing capabilities is capital intense and takes time. To bring a greenfield site into production of the first volumes that can be sold to the US market takes at least 4-5 years. Even if tariffs increase the pressure, they would not be able to speed up the timelines. This issue is particularly acute as there are no available, idle facilities in the United States, instead production would need to be started from scratch.

Second, the molecules in scope (Amoxicillin, Cefalexin) are low margin generics. The current manufacturers most likely don't have the funds it takes to undergo such a substantial investment, with extremely long payback times. Moreover, requiring substantial tariff payments, even if shared between exporter and import, would further diminish available capital. This dynamic is different for originator companies, but the incentive for generic players to invest is simply not there. Additionally, the risks of imposing tariffs on essential medicines (as explained above are a result of the U.S. almost complete dependence on imports of these drugs) such as antibiotics, are multiple:

- **Threat to national security & public health:** Antibiotics are crucial for hospitals, military readiness and emergency preparedness. Tariffs might cause higher costs and delays in delivery, leading to a weaker response to future pandemics, wars or even basic infections.

- **Risk of supply shortages followed by price increases:** if the height of the tariff is higher than the margins the manufacturers make on this product group, they might decide not to supply the US with these fundamental medicines. This would lead to shortages in the short term, and a price increase in the long term to incentivize them to supply after all. Both are not intended effects.
- **Risk of negative publicity:** Should too high tariffs lead to a situation of supply disruption of these fundamental medicines, there is a risk that patients in need cannot receive accurate treatment. As antibiotics are fundamental for the healthcare system – they are required in the most basic operations – there is a very real risk that patients might suffer or even die if they are not available.
- **U.S. farmers will be impacted:** American livestock producers rely heavily on imported antibiotics to keep animals healthy and maintain productivity. A significant share of the nation's penicillin imports goes to the meat industry. Tariffs on these imports would drive up production costs, likely raising meat prices across the board—impacting both farmers' bottom lines and American families at the grocery store.
- **Antibiotic Resistance:** If doctors or patients switch to less effective or inappropriate alternatives due to cost, this can worsen antimicrobial resistance.

Our clear recommendation is to exempt these foundational, generic medicines from tariffs on the grounds that imposing tariffs would not lead to a positive change (long timelines to set up manufacturing sites and unfavorable economics to do so in the first place) and comes with a range of risks.

Instead, we suggest the Trump administration make it a national priority to become independent of China for crucial medicines by financially supporting the set up of domestic manufacturing facilities. This is done as an effort to gain independence and develop the ability to supply the most crucial medicines of the healthcare system from within the US. By the American people, for the American people.

B. The Administration Should Consider a Holistic Approach Centered on Increased U.S. Investment

An alternative to imposing tariffs on essential medicine imports would be to incentivize domestic manufacturing of these drugs. Use of tax credits, grants/subsidies, private-public partnerships, fast-track FDA approvals and "Buy American" procurement rules could all help build supply chains within the United States. These efforts could be compounded by partnering with allies or free trade agreement partners.

Fermentation-based pharmaceutical manufacturing sites for antibiotics are some of the most expensive production sites in the world. Centrient has engaged their internal engineering team as well as a global engineering firm to provide cost estimates for the CapEx requirements to build-out in the United States, and that current estimate is between $1.4 - $1.6 billion for a comprehensive campus, comprised of up to 7 separate production units, capable of producing key intermediaries, API, and sterile FDF for beta-lactam SSPs (amoxicillin, penicillins, etc.) and SSCs (e.g. cefalexin, cefadroxil). With the recent innovation in genetic bioengineering and strain development, Centrient's current technology for an integrated production set-up could make a U.S. manufacturing facility cost-competitive with China and self-sustaining (requiring no ongoing government support) for the foreseeable future. However, with a low-margin product

subject to significant continued downward pressure on costs, building a new site in the United States to accomplish this is commercially infeasible without significant support to fund the capital expenditure. Centrient urges the U.S. government to consider options for grants, tax incentives or public-private partnerships that will facilitate access to increased capital.

The estimated time to get the core intermediate and API manufacturing sites operational would be approximately 4-5 years (from engineering and construction up until commercial operations), while getting sterile manufacturing sites operational would take approximately 3-4 years.

With sufficient access to capital, in the next five years, the United States could onshore the entire supply chain for 100% of the beta lactam antibiotics (like amoxicillin and penicillin G) in Centrient's portfolio, end-to-end from U.S. sourced inputs, manufacturing of key intermediate, API, and sterile finished dose formulation, securing U.S. supply and making the U.S. a net exporter and supplier to the world.

V. CONCLUSION

As describe above, given the unique economics of generic antibiotics, the United States is entirely reliant on foreign supply chains for its access to semi-synthetic penicillins and semi-synthetic cephalosporins—and those supply chains almost entirely rely upon China. There is no key intermediate or API manufacturing of these medicines in the United States, little or no sterilization capacity in the United States, and limited fill and finish capabilities.

However, imposition of significant tariffs would likely exacerbate this situation doing little to improve the security of U.S. access to antibiotics. Specifically, the low margins and high capital

expenditures in this sector would likely result in tariff excluding significant volumes of antibiotics from the market rather than encouraging U.S. production.

Instead, securing these supply chains will require a broader government plan to facilitate U.S. investment in commercial-scale fermentation-based infrastructure including changes in regulatory policy, government support for capital expenditure commensurate with those of China and India, and other efforts to level the playing field.

However, if the U.S. invests in the current leading enzymatic fermentation-based manufacturing technology, these end-to-end supply chains can be onshored with current technology that would make it commercially cost-competitive with API from China and would not require any ongoing government support.

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