

The US Active Pharmaceutical Ingredient Infrastructure: The current state and considerations to increase US Healthcare Security

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“Keeping the Nation’s drug supply chain secure, robust, and resilient is essential for the national security and economic prosperity of the United States¹.”

I. Summary

Active Pharmaceutical Ingredients, APIs, are the essential components of a medicine that provide the therapy needed for the patient. These chemical and biological compounds are formulated and manufactured into finished dosage forms - tablets, solutions, creams - for administration. The challenge in securing enough API to meet the nation’s needs has been highlighted in the June 2021 White House report of Supply Chain Resiliency² which referenced the epidemic of national drug shortages before COVID and the pandemic itself. The focus of this examination is to provide a deeper view into the US manufacturing infrastructure associated with API production.

Our analysis shows that:

- Greater than 80% of APIs for essential medicines and across key therapeutic areas have no US manufacturing source
- Less than 5% of large-scale API sites, globally, are located in the US – the majority of large scale manufacturing sites are in India and China
- The causes for US weakness in API manufacturing are the ‘race to the bottom’ on pricing against global players with structural advantages for ex-US manufacturers in greater government subsidies, lower input costs, and lesser regulatory burdens.
- Solutions to protect US Healthcare security must address the risk to US Healthcare Security by creating (1) a critical mass of domestic manufacturing infrastructure to protect domestic interests, (2) a level playing field for global competition and (3) sustainable domestic markets for American manufacturers.

II. Background: Active Pharmaceutical Ingredients are the essential component of medicines, and the fragility of their supply was highlighted before and through the COVID-19 pandemic

“The active pharmaceutical ingredient (API) is the part of any drug that produces the intended effects³.”

¹ “Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth” June 2021, White House Report; <https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf>

² IBID

³ “Very Well Health”; <https://www.verywellhealth.com/api-active-pharmaceutical-ingredient-2663020>; Accessed: Feb 22, 2021

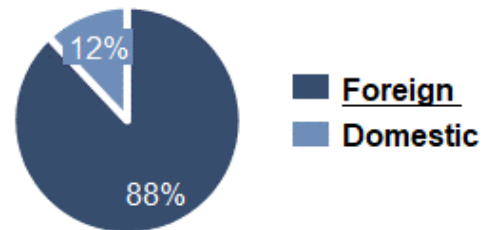
The API is the active component of any medicine. As such, if there are shortages of APIs, then there is no way to manufacture the medicine or to obtain the therapeutic benefit of the medicine. National drug shortages peaked in 2011, with 267 medicines in a national shortage – notably many chemotherapy medicines that directly threatened the safety of patients⁴. Following this crisis, the FDA took action to study and seek remedies for the challenges of maintaining the nation’s supply of needed medicines.

The FDA’s analysis of Drug Shortages, published in 2019 and updated in 2020, highlights three root causes: low profitability, low value for quality, and complex, global supply chains⁵. All three causes are prevalent in commoditized essential medicine production. Notably, the drugs most likely to be in shortage were 35 years on-market,⁶ meaning those with the greatest exposure to competition were also those at greatest risk. Due to the intense competitive pressure, many of these medicines were manufactured overseas, where costs are lower. A contributing factor cited by the FDA was the length and complexity of most pharmaceutical supply chains – with 88% of APIs overseas⁷.

The COVID-19 crisis highlighted the reliance on long and complex supply chains. Multiple drug shortages made national headlines in the early stages of the crisis. An April 4th, 2020 headline in CNBC stated, “There’s a shortage of everything” based on the demands in New York City as the virus surged⁸. Most initial shortages were demand driven – too much need. But there were concurrent supply-driven shortages, as 40+ Chinese manufacturers were locked down under national restrictions⁹ and the government of India briefly ceased the export of 26 medicines (including acetaminophen and many antibiotics) by rule¹⁰.

This demand and supply driven shortages are compounded by the structure of the US generic pharmaceutical supply chain. For valid safety reasons, changing API sources is a lengthy process requiring finished dose manufacturers to test the new API and confirm that it is safe and compliant for their processes. Typically introducing a new API supplier takes 12-15 months, including time for regulatory approval. It is also a costly process, and as a result most price-sensitive generic medicines had only 1 to 2 qualified API sources. If an API manufacturer needs to develop a new API, then that process can take 4+ years, a challenging market burden when many foreign sources of API are ready today, and shortages rarely last multiple years. The system assures safety but does not provide for flexibility in the time of crises.

LOCATION OF API MANUFACTURING SITES SERVING US MARKET



**“Drug Shortages: Root Causes and Potential Solutions”
FDA, 2019, Page 28, Figure 3**

⁴ “Drug Shortages: A complex Health Care Crisis” Mayo Clinic, 2014 [https://www.mayoclinicproceedings.org/article/S0025-6196\(13\)01043-4/pdf](https://www.mayoclinicproceedings.org/article/S0025-6196(13)01043-4/pdf)

⁵ “Drug Shortages” page 21

⁶ “Drug Shortages” page 24

⁷ “Drug Shortages: Root Causes and Potential Solutions” FDA Oct 2019, <https://www.fda.gov/media/131130/download> page 28

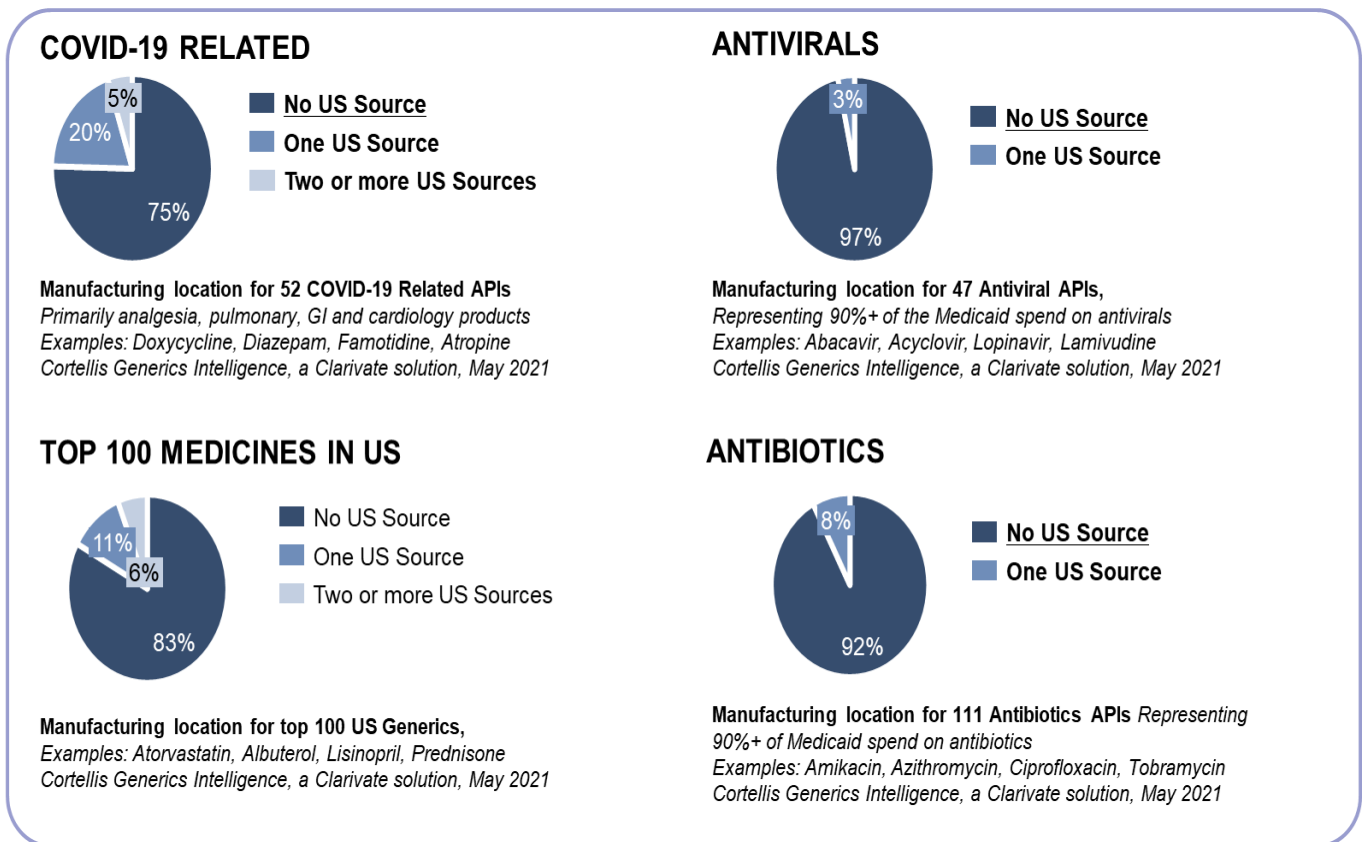
⁸ [Coronavirus: Pharmacies in NYC struggle to meet demand amid supply shortages \(cnbc.com\)](https://www.cnn.com/2020/04/04/health/coronavirus-pharmacies-nyc-shortage/index.html)

⁹ “New Opportunities for Global API Market” European Pharmaceutical Review, <https://www.europeanpharmaceuticalreview.com/article/136976/new-opportunities-for-the-global-api-market/>

¹⁰ <https://www.theguardian.com/world/2020/mar/04/india-limits-medicine-exports-coronavirus-paracetamol-antibiotics>

III. State of Supply: The US is reliant on foreign production for 80%+ of nation’s active pharmaceutical ingredient (API) needs

Getting a clear picture of the API supply landscape is challenging, as supply sources are protected as confidential information for finished dose manufacturers, and there is not a transparent market place. Clarivate, a leading data and benchmarking company in the Healthcare industry has developed a data set, Cortellis Generics Intelligence, which provides insights across the sector. Utilizing Clarivate’s Cortellis Generics Intelligence dataset, our analysis of FDA approved, commercial API suppliers reveals a significant reliance on foreign manufacturers.



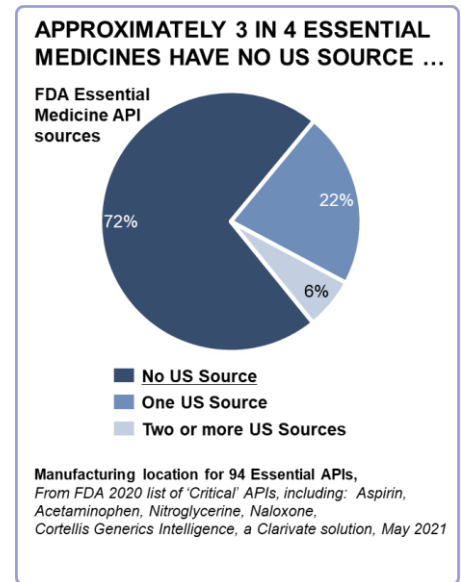
¹¹ Sources of COVID-19, Antivirals, Antibiotics and Top 100 Medicines in the United States. Cortellis Generics Intelligence, formerly known as Newport. Copyright Clarivate 2021

An assessment of 52 COVID-related medicines showed that 75% had no US source of API. An assessment of the top 100 generic medicines consumed in the US revealed that 83% had no US source of API. Both of these data sets included medicines that are controlled substances, which by policy, are required to be manufactured within the US and face strong import/export controls. When looking at segments without those protections, the figures are starker. 97% of the 47 most prescribed antivirals have no US source of API and 92% of the 111 most commonly prescribed antibiotics have no US API source.

¹¹ Sources of COVID-19, Antivirals, Antibiotics and Top 100 Medicines in the United States. Cortellis Generics Intelligence, formerly known as Newport. Copyright Clarivate 2021

The FDA published an essential medicines list in 2020, with a set of APIs identified as ‘critical’. Of 94 APIs (excluding saline, surfactants, basic salts, etc.), 72% have no US source. Those with a US source are predominantly either controlled substances manufactured at large scale or niche APIs that smaller scale US manufacturers can compete in at smaller scale. Of those with no US source, the total US market value for 34 (31%) of the critical APIs is estimated to be below \$2M each¹². Given the cost to develop an API in the US is typically \$1-2M, this creates an economic challenge to reshoring that is difficult to overcome.

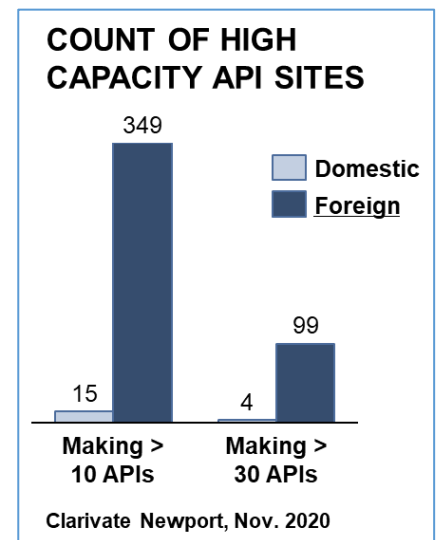
Even over-the-counter products rely heavily on overseas manufacturing. For instance, 80% of the global supply of PAP, a precursor material for acetaminophen, comes from China.¹³ The Chinese government shutdown of a leading PAP producing factory for environmental reasons, led to global shortages in early 2021 and contributed to price spikes within the global markets¹⁴.



IV. Manufacturing base: US API Manufacturing Infrastructure is below critical mass, and unable to protect US Healthcare Security

Manufacturing of APIs requires the chemical conversion of key starting materials into refined, and highly controlled chemical outputs. Large scale manufacturing sites capable of manufacturing ten or more different APIs provide the infrastructure required to deliver the APIs cost competitively. Truly large scale sites can manufacture thirty or more APIs for the global market.

The majority of APIs provided to the US market are from overseas factories – only a very limited US manufacturing base exists for APIs. Of the 103 sites worldwide that manufacture and sell over 30 API products, only four are in the US¹⁵ and only 15 sites in the US make more than ten API products versus nearly 350 outside the US.¹⁶ In comparison, India has 60+ API sites with 30 APIs and China has 10+ such sites. These foreign sites enjoy both a scale advantage and a factor cost advantage over their US competitors.



Many US investments have been made towards advanced manufacturing but results to date have not proven able to compete against large-scale, low cost overseas factories. Cost reductions in API manufacturing can be achieved through advanced technology, and continuous manufacturing of APIs, in particular, has shown tremendous promise

¹² Estimated by using market pricing and annual US market consumption data

¹³ “Market Research Report on Global and Chinese p-Aminophenol Industry 2009-2019” Prof Research; market analysis

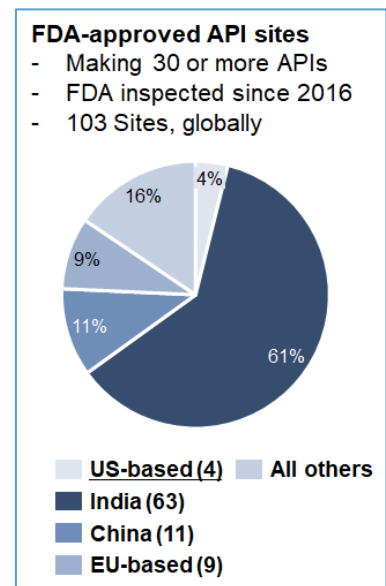
¹⁴ [See high paracetamol prices to be a blip over a quarter or two: Granules Pharma - cnbctv18.com](https://www.cnbc.com/2021/05/11/paracetamol-prices-to-be-a-blip-over-a-quarter-or-two-granules-pharma-cnbctv18.com)

¹⁵ APIs defined as FDA approved sites and commercially available Drug Master Files (DMFs)

¹⁶ Analysis of Clarivate Newport API manufacturing database, 2020

and received FDA support¹⁷. Estimates as high as a 30-50% reduction in COGS¹⁸ seem possible, in a far smaller footprint with less labor – nullifying many advantages ex-US manufacturers enjoy. Industry 4.0 proponents believe that automation of traditional manufacturing processes can make these gains even greater¹⁹, when the right technologies extend across the supply chain. But, these promises are not yet able to address the challenge at hand. Disruptive innovators in the US lack access to commercial scale, FDA-approved cGMP facilities and the commercial, quality, regulatory and physical infrastructure required to bring products to the commercial market. Further, the leaders in chemistry may not have access to leaders in control systems or equipment engineering or training programs for these new technologies. There is a substantial gap between bench scale proof-of-concept and commercial scale cGMP production that has not yet been bridged.

While advanced manufacturing technologies hold the promise of enhancing the security of US healthcare through US based manufacturing, language discrepancies between the Trade Agreements Act of 1979 (“TAA”) and the Buy American Act (BAA), which were further complicated by the recent Acetris ruling represent a significant obstacle for US based API manufacturing. On February 10, 2020, the Federal Circuit Court of Appeals rejected the longstanding U.S. government position that the country of origin of pharmaceuticals in the context of U.S. government procurement is determined by where the API is made (Acetris Health, LLC v. United States, 2018-2399)²⁰. Under the BAA, to be compliant, a threshold of 55% of all component parts must also be mined, produced, or manufactured in the United States. The court’s decision creates a challenge in that it allows US manufactured finished dosage pharmaceuticals to be deemed compliant under the TAA and the BAA, as ‘Made in America’ though 100% of the API could be sourced outside of the USA.



V. The causes for US API manufacturing weakness are the ‘race to the bottom’ on pricing and structural advantages held by foreign manufacturers

Market forces drive a ‘race to the bottom’: As medicines, particularly high-volume essential medicines, become generic, competition increases, market pricing falls dramatically, and production shifts to the lowest-cost sites globally. Absent a change in US governmental influence or policy, the basic laws of economics result in the manufacturing of many critical medicines moving from the US to low-cost countries. Essential medicines become low-margin commodities and victims of lowest-cost site production issues – vulnerable to shortages and susceptible to under-investment and quality control issues. Crystallizing the “race-to-the-bottom” forces impacting essential medicines, the FDA succinctly and correctly judged that, “[t]he market does not foster a reliable supply of generic drugs.”²¹

¹⁷ FDA MOU 225-21-006 in support of “Advanced Manufacturing Technologies in Commercial Manufacturing” <https://www.fda.gov/about-fda/domestic-mous/mou-225-21-006>

¹⁸ ‘The Benefits of Continuous Manufacturing’, Dec 2016, [Pharmaceutical Processing World](#) ([link](#))

¹⁹ “Digital Manufacturing is (Finally) Coming to Pharma” Bain consulting ([link](#))

²⁰ ‘Federal Circuit Revolutionizes Country of Origin Analysis for Pharmaceuticals.’ [The National Law Review](#). February 12, 2020

²¹ “Drug Shortages” page 41

Structural advantages: Winning the ‘race to the bottom’ is aided by the structural advantages that ex-US manufacturers enjoy. Manufacturers in China and India are able to secure good manufacturing and laboratory talent far below US wages – estimated to be 33% lower than western counterparts²². Manufacturers in these countries also enjoy advantages on utility costs, tax rates, land acquisition costs, and services.

Government actors: The market influence of government actors far outweighs any individual company’s impact. Rosemary Gibson, in Senate testimony in early 2020, highlighted the role of China in driving industrial policy supporting its pharmaceutical industry as a key risk²³. “The United States faces, and existential threat posed by China’s control over the global supply of ingredients in thousands of generic medicines.” She highlighted the risk posed by adding that, “Chinese cartels and Chinese government subsidies ... are driving US and other western generic companies out of the business of generic manufacturing.” One example of the leverage gained by China, “resulted in a price increase of up to 50 percent for a few molecules”, not directly to the US market, but through the Indian Pharmaceutical market where many US generics are made²⁴. Partially in response to the dual challenges of COVID and over-reliance on China, the government of India invested \$1.3bn in 2020 to expand its domestic capabilities for key starting materials in support of their API businesses²⁵.

²² Indian Pharmaceutical Alliance, “The Indian Pharmaceutical Industry – the way forward” page 16. <https://www.ipa-india.org/wp-content/uploads/2020/10/indian-pharmaceutical-industry-way-forward.pdf>

²³ Testimony of Rosemary Gibson before the Senate Committee on Small Business and Entrepreneurship, March 12, 2020 ([link](#))

²⁴ Indian Pharmaceutical Alliance, “The Indian Pharmaceutical Industry – the way forward” page 18.

²⁵ “India to spend \$1.3bn to Boost Pharmaceutical Production” Bloomberg, March 2020 ([link](#))


VI. Solutions must build a critical mass of US manufacturing, address areas of asymmetry and assure sustainability

Full repatriation of API manufacturing is unrealistic given the infrastructure limitations, and as such an objective of achieving a minimum level of self-sustainability for the US-based API industry is more realistic and attainable.

Below are three areas of consideration to facilitate US Healthcare Security by fostering US-based production.

- I. Initiate efforts to protect existing API manufacturing base and capabilities currently within the US. Such efforts can include:
 - Infrastructure investments
 - Support innovators of advanced manufacturing technologies and research collaborations
 - Define ‘Made in America’ and harmonize language in the Trade Agreement Act (TAA) and Buy American Act (BAA)
- II. Address areas of asymmetry in the global marketplace
 - Inspections of foreign and domestic API manufacturers
 - Government investment support in domestic infrastructure
 - Environmental and labor compliance
- III. Create sustainable domestic markets
 - Leverage US Government purchasing for those medicines made with US API
 - Account for quality and sustainability in selecting suppliers
 - Address Acetris ruling and federal regulations defining threshold of US-sourced API

Rebuilding US manufacturing of APIs to drive healthcare security will take time. In the meantime, our reliance on foreign manufacturers will continue and a rapid shift is neither possible nor advisable. Instead, a deliberate plan is required that aligns public and private enterprise with direct infrastructure investment and supportive policies favoring US sources of essential APIs.

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Cortellis Generics Intelligence, a Clarivate solution and formerly known as Newport, provides access to validated and comprehensive API manufacturing insights and is comprised of data spanning more than 64,000 small molecules and biologics, 72,000 manufacturers and marketers, 1.1 million worldwide patents, 62,000 regulatory documents and more.