

# A BOLD GOAL: RESHORING 25% OF SMALL MOLECULE API TO THE U.S. IN 5 YEARS

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**A Bold Goal: Reshoring 25% of Small Molecule API to the U.S. in 5 Years**

# EXECUTIVE SUMMARY

Our nation's overreliance on China and India for most of our active pharmaceutical ingredients (APIs) poses a significant threat to quality and availability of essential medications in the U.S. As a result, our [national health security](#) is compromised. The National Economic Council (NEC) Director and the National Security Advisor (NSA) called for a "[new approach](#)" aimed at guaranteeing Americans reliable access to essential medications. The Office of Science and Technology Policy (OSTP) laid the foundation for this strategy in their plan, [Bold Goals for U.S. Biotechnology and Biomanufacturing R&D](#). Their initiative aims to deploy advanced synthetic biology and biomanufacturing in the U.S. within 5 years to produce 25% of all APIs for small molecule drugs.

To achieve this goal, this white paper proposes API manufacturers adopt advanced manufacturing technologies provisioned through public incentives. Industry should leverage existing technologies while furthering research and development of innovative and disruptive technologies, in partnership with academia and government. A single public entity should coordinate the public-private partnerships established as part of this national strategy. Identifying a subset of APIs for initial deployment would yield invaluable insights that further propel the nation towards achieving the 25% goal. These conclusions were formulated by a panel of 15 subject matter experts from within the drug supply chain ecosystem. The panel convened a plenary event titled Pathway to Build Supply Chain Resilience for Critical Drugs in November 2023 at the API Innovation Center in St. Louis, Missouri, to explore:

- Current U.S. capacity and technologies to support small molecule API production, including the impact of key starting material availability on U.S. API production.
- Criteria for selection of essential medicine small molecule APIs for manufacture.
- Barriers to reshoring small molecule API manufacturing.
- Ways to build a resilient drug supply chain.

To mitigate the risk of relying on China and India for small-molecule APIs, the panel determined advanced manufacturing biotechnologies and biomanufacturing processes must be implemented. Advancements in synthetic chemistry realized through advanced technology can improve small molecule API manufacturing. The cost of implementing these technologies must be addressed. Price erosion and consolidation have had a major impact on the U.S. generic pharmaceutical industry, which in part has resulted in lower profit-margins. A public-private modernization model that establishes federally committed contracts and encourages private sector committed contracts is essential. These contracts should prioritize purchasing drugs produced using advanced manufacturing technologies and reliable supply chains. This public-private partnership could be administered through the new U.S. Health and Human Services' Supply Chain Resilience and Shortage Coordinator. Regulatory barriers to implementation should also be addressed and additional "Made in America" incentives could help to enhance market competitiveness.

The significance of prioritizing a list of small molecules for production cannot be overstated. Identifying the most essential APIs will drive alignment with current manufacturing technologies and capacities and support initial research and development for disruptive technologies. Innovations can be made in both realms. Criteria should include past, present and predicted essential medicine shortages, APIs with single manufacturing sites and those that have experienced site quality issues (including U.S. Food and Drug Administration warning letters). Key starting material sourcing, geographical risks, medical need, and therapeutic alternatives should also be considered.

The coordinating entity should drive policy and programs that support a pharmaceutical supply chain transparent to all stakeholders. This will allow stakeholders to evaluate the potential risks of supply disruptions and make well-informed decisions regarding contracting, purchasing, and inventory management. Stakeholders should see a drug's origin, and the origin of associated key starting materials and APIs. Incorporating quality and reliability scores is essential in leveraging this information to mitigate risks. This endeavor is well-positioned for digital transformation, harnessing technologies like artificial intelligence and machine learning to enhance the efficiency and transparency of the U.S. pharmaceutical supply chain.

Rebuilding and sustaining the U.S. generic pharmaceutical supply chain must bring the greatest benefit to the single most important stakeholder: the patient. The patient absorbs 100% of the clinical care risk; they are the most vulnerable to the impact of supply disruptions and the least able to do anything about it. Improving our national health security requires significant mitigation of risk by creating a diversified manufacturing base and distributed buffer inventories that will guarantee Americans reliable access to essential medications.



## ABOUT THE API INNOVATION CENTER

The API Innovation Center (APIIC) is a 501(c)(3) non-profit, public benefit organization dedicated to enabling the delivery of a market-competitive commercial supply of U.S.-made APIs to address national health security. To de-risk advanced manufacturing, APIIC is forming a consortium of partners to invest in the development of domestic API through advanced technology and repurposing idle manufacturing capacity. APIIC is supported by the State of Missouri through a grant awarded by the Department of Economic Development and the Missouri Technology Corporation.

## PANELISTS

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## A Bold Goal: Reshoring 25% of Small Molecule API to the U.S. in 5 Years

*“There is little value in new drugs that patients cannot afford—and there is no value in drugs that do not exist. Thus, there is a fundamental tension between ensuring the availability of new drugs in the future and ensuring the affordability of those drugs that exist today.”*

# INTRODUCTION

The over-reliance on foreign manufacturing of essential medicines has exposed vulnerabilities in the U.S. pharmaceutical supply chain. These vulnerabilities have created threats to national health security, as revealed in Tony Sardella’s study, [U.S. Generic Pharmaceutical Industry Economic Instability](#). Sardella serves as the Chair of the API Innovation Center in St. Louis, Missouri, a consortium dedicated to delivering a market-competitive commercial supply of U.S.-made active pharmaceutical ingredients (APIs) to address these threats. According to Sardella, 83% of the top 100 generic medicines prescribed in the U.S. have no U.S.-based source of API. Over 90% of the most frequently prescribed antivirals and antibiotics have no U.S. API manufacturing source.

The lack of U.S. sources of API is a problem of such magnitude that it cannot be disregarded, and as a result, the U.S. government has developed an initial strategy and established a goal equal in scope.

The White House Office of Science and Technology Policy laid the foundation for this strategy in their plan, [Bold Goals for U.S. Biotechnology and Biomanufacturing R&D](#). Their initiative aims to deploy advanced synthetic biology and biomanufacturing to produce 25% of all APIs for small molecule drugs in the U.S. within 5 years.

To explore this goal, the API Innovation Center formed a working group from industry, academia, and government to identify topics of concern. Over several months, the working group narrowed the topics and identified a panel of 15 subject matter experts to provide their knowledge and insights to further develop a plan for U.S. production of small molecule APIs. The panelists convened an event titled Pathway to Build Supply Chain Resilience for Critical Drugs, in November 2023, at the API Innovation Center. Their discussions are the essence of this white paper, centered on these topics:

**Most APIs provided to the U.S. market are from overseas factories.** These foreign sites enjoy both a scale and cost advantage over their U.S. competitors. As other countries have made significant investments in API facilities in the last decade, the U.S. has fallen further behind. There is little incentive to build new U.S. API facilities or adopt advanced manufacturing technologies as the profit margins on APIs used in generic drugs are, in part, too low to create a return on investment. Nearshoring presents is a noteworthy option to address critical medicine needs but must be coupled with addressing the U.S.’ need for long-term investments in its domestic manufacturing infrastructure.

**Implementing advanced manufacturing technologies must be the cornerstone of efforts to rebuild the foundations of a U.S.-based pharmaceutical industry.** Disruptive and innovative technologies will reduce labor and production costs to increase profit margins and more importantly, the quality of the product produced. Increasing quality will benefit patients and hospitals seeking reliable sources of essential medicines. It will also create positive impacts for U.S. competitors in the generic pharmaceutical market.



**Excess U.S. manufacturing capacity must be leveraged in our first steps towards reshoring small molecule API to the U.S.** Underutilization of manufacturing capacity equates to an astonishing 30 billion doses of medicines that could be made here, by existing manufacturers in existing facilities. It is both critical and efficient to mobilize this capacity to propel the U.S. towards manufacturing 25% of all small molecule APIs here, within 5 years.

**Upskilling and reskilling the workforce for the pharmaceutical manufacturing sector is necessary and feasible.** Industry should engage both universities and professional training institutions to develop a workforce with the specific set of knowledge and skills necessary for advanced manufacturing. There is a well-worn path between industry and academia that can transfer the knowledge and skills necessary to drive an advanced manufacturing era in the U.S.

**Identifying the most essential small molecules requires a designated entity to oversee ongoing research on drug supply, quality, and market conditions to create a predictive and transparent drug supply forecast for all stakeholders.** U.S. generic medicine stakeholders should be publicly provisioned and incentivized to produce and maintain buffer inventories of these identified essential medicines.

**The greatest barrier to reshoring small molecule APIs is the lack of a customer and a committed contract for U.S. manufacturers.** While there are many barriers to reshoring small molecule APIs, industry and academia agree that government must provision the implementation of advanced manufacturing technologies and incentivize production through federal committed contracts and federal support for private sector committed contracts.

**Public-Private partnerships, led by a single public entity, are the drivers of progress in reshoring small molecule API to the U.S.** Rebuilding and sustaining the U.S.-based pharmaceutical supply chain will require both regional and national partnerships among industry, academia, and government. A single entity with oversight and coordinating authorities is one option to build this network, develop policy and provide resources.

This white paper captures the knowledge of subject matter experts in direct quotes to highlight, without filter, the critical insights necessary to understand the impact of reshoring API to the U.S. These experts represent manufacturers who are currently using advanced manufacturing technologies and understand how they must be implemented. They represent former U.S. API manufacturers who were driven out of the market by international competition. And they represent advocates for actual patients who desperately searched for drugs that doctors prescribed but were not available.



# The Current State of U.S. API Production

**What is API?** The medicines taken to cure or mitigate disease are composed of both active and inactive ingredients. The most critical component is the active pharmaceutical ingredient (API). The API is the chemically or biologically active agent in the human body that create the desired therapeutic effect that eases pain, prevents disease progression, or eliminates disease altogether. Inactive ingredients, sometimes referred to as excipients, play a role in the dispersion of the API within the body or enhance attributes such as flavor and color. APIs can be grouped into two broad categories: biologics and synthetics. Biologics are extracted from living organisms and synthetics are derived through chemical synthesis. The size of the molecule used in production is also aligned with these two categories. Large molecules are typically used in APIs produced through biologics, while small molecules are commonly used in APIs produced through chemical synthesis. Nearly all generic drugs are made with small molecule APIs and generic drugs make up [91% of all prescriptions](#) in the U.S. The finished forms of drugs made with small molecule APIs are most often oral doses. However, critical API molecules may be used in sterile injectables, inhalers, eye drops, ointments and cream drugs, and other finished projects.

**“Continuous manufacturing, as a technological paradigm, is the only possibility the U.S. has to maintain competitiveness and reach the goal.”**

Andrea Adamo, Ph.D.- Founder and CEO,  
Zaiput Flow Technologies



# Comparing U.S. and Foreign API Manufacturing Sites

Research from [The U.S. Active Pharmaceutical Ingredient Infrastructure: The Current State and Considerations to Increase U.S. Healthcare Security](#) indicates the majority of APIs provided to the U.S. market are from overseas factories – only a few U.S. manufacturing bases remain for APIs. Of the 103 sites worldwide that manufacture and sell over 30 API products, just four are in the U.S. and only 15 sites in the U.S. make more than ten API products versus nearly 350 outside the U.S. In comparison, India has more than 60 API sites capable of producing 30 or more APIs and China has more than 10 such sites. These foreign sites enjoy both a scale and cost advantage and a factor cost advantage over their U.S. competitors.

Stephen Schondelmeyer, PharmD, Ph.D., a professor with the College of Pharmacy at the University of Minnesota stated, “When I looked at the number of new API-facility locations built to make API molecules in the world in the past decade, Taiwan had the largest percentage growth with 326% (189 new API-facilities). India was second with 254% growth (3,676 API-facilities). Israel was third with 131% growth (142 new API-facilities).



China was fourth, having grown by 55% (531 API-facilities). Think about just these four countries with the largest percentage growth in new API-facilities: Taiwan, China, India, Israel. Do you see any geopolitical risks there? In the past decade, the number of U.S. API-facility locations has decreased by 61% (1,951 API-facilities).” Said differently, as other countries have made investments in API facilities and developments, the U.S. is falling further behind. Most notably, these countries present geopolitical uncertainties and concerns, leaving the U.S. vulnerable if we are dependent on their API production for our domestic pharmaceutical needs. “We have been moving in the wrong direction. We should see the U.S. on the list of countries with growth in new API-facility locations. That is what we are all about here. That is what the API Innovation Center is all about,” shares Schondelmeyer.



# Key Starting Material Availability

A [key starting material](#) can be defined as a raw mineral or a more basic chemical compound, that is used in the production of a drug substance and incorporated into the structure. The terms key starting materials, starting materials and raw materials are often used interchangeably. “Key starting materials inputs are typically compounds that are pulled out of the petroleum industry and turned into advanced intermediates. The API is not made from just one reaction but rather, from several chemical compounds – the intermediates,” said Matt Hancock, Director of Business Management API at Thermo Fisher Scientific. “The irony of that situation is twofold. A lot of those petroleum-based chemicals that are used as the key starting material inputs to intermediates come from the U.S. Even more ironic is the fact that those key starting materials almost exclusively use flow chemistry for their manufacture. We have the technology here and we do it well and efficiently, but the infrastructure we had to produce key starting materials in the U.S. 50-60 years ago has been abandoned. Even if we focus on making APIs in the U.S., for the vast majority, it is only those last three to five steps that would be done here. The problem is the key starting materials, and the intermediates are still coming from outside the U.S. We really have even less momentum to produce key starting materials than reshoring APIs.”

## Current Pharmaceutical Manufacturing Technologies

### | Batch Processing

The batch manufacturing process for small molecule APIs includes the performance of a series of chemical transformations, in sequence, to convert key starting materials into a complex API chemical compound in a single reactor system.

Hancock explains, “each individual transformation includes multiple unit operations or subtasks like reaction, workup, crystallization, filtration, and drying. These subtasks often take multiple days in the same reactor. Before the subsequent transformations take place, the reactor is stopped, and offline analysis is conducted. Offline testing is still commonplace in pharmaceutical manufacturing, with material being held or stored at intermediate steps until the testing is completed. The finished product is also subjected to a full array of final tests to ensure it meets specifications. Methodologies for achieving efficiencies in batch manufacturing are typically focused on increasing scale – larger reactors, more efficient isolation equipment, increasing the number of batches, etc. This approach is also how typical lab scale development is still performed today.”

The stops and starts in batch processing take time and can be extremely costly. “Ironically, they are also a point of vulnerability, where human error or contamination can be introduced,” said Bayan Takizawa, M.D., co-founder and Chief Business Officer, CONTINUUS Pharmaceuticals. “They also lead to a phenomenon called batch-to-batch variability, as not all environmental conditions can be controlled from one batch run, or campaign, to the next. Batch manufacturing also requires large facilities and large equipment that may be idle for parts of the year. The two largest subsections for batch manufacturing are the upstream manufacturing of API, and the downstream manufacturing of the drug product – the actual dosage that patients take, such as tablets. These two processes are performed separately.”

The challenge for API manufacturers using batch processing is the need for in-process checks to determine the purity of each reaction. “The question is, did you make what you intended to make?” said William Foley, a subject matter expert in process analytical technologies in pharmaceutical manufacturing.

“Pharmaceutical manufacturers have been using the same batch processes for a century, with very few fundamental changes. In other industries, there has been a need to optimize manufacturing methods to reduce costs. Many of these industries have adopted continuous manufacturing,” said Takizawa.

## I Advanced Manufacturing

The FDA asserts, “[advanced manufacturing technologies](#) have the potential to improve the reliability and robustness of the manufacturing process and supply chain and increase timely access to quality medicines for the American public.” Advanced manufacturing includes continuous manufacturing (also known as continuous processing or flow chemistry), which is an alternative to batch processing. Continuous manufacturing employs a flow reactor that uses dosing pumps and tubes that move reactant fluids in a continuously flowing stream until the complete API volume is achieved. This process is in contrast to the multiple starts and stops of batch processing.

“Continuous manufacturing has emerged as an approach that offers cost reduction, ease of scale up, and a more robust process, leading to higher product quality. A comparison can be drawn between this and the assembly line, a continuous manufacturing scheme designed by Henry Ford for automobile production,” said Andrea Adamo, Founder and CEO of Zaiput Flow Technologies. “Chemical transformations involve dangerous, toxic, or explosive materials. Continuous processing protects workers and surrounding communities, as this approach is typically safer to operate. In China, continuous manufacturing is mandated by law for the more dangerous chemical transformations; batch is not an option. Generally speaking, continuous manufacturing will provide improvements by process intensification.”

[Process intensification](#) is defined as “a set of innovative principles applied in process and equipment design, which can bring significant benefits in terms of process and chain efficiency, lower capital and operating expenses, fewer wastes, improved process safety and higher quality of products.”

“For the U.S. API manufacturing industry to adopt new technologies associated with advanced manufacturing, the cost must be addressed. This is not something we will achieve in the next six months, but it is something for which we can aim. True technology applied in a specific way to reduce effort and reduce costs - there is a hope of becoming competitive again,” said Adamo.

Adam Fisher, Ph.D., and Director of Science Staff at the Office of Pharmaceutical Quality, Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA) explained that CDER has established a [Framework for Regulatory Advanced Manufacturing Evaluation \(FRAME\)](#) initiative to prepare a regulatory framework to support the adoption of advanced manufacturing technologies.

“Flow chemistry must be a cornerstone of how we do this, along with process analytical technologies (PAT). There are several PAT tools like spectrometry or chromatography that are very deployable in flow chemistry,” said Foley.

## I Disruptive and Innovative Opportunities in API Production

“The other way I view this is an opportunity to recreate some of the pathways to make the API can provide higher yields and reduce byproduct formation. We have new tools to make the target and some of these may require a different set of key starting materials that can be bio-renewably sourced.



There are multiple technical challenges, but I view them as opportunities for pushing towards greener production by use of either biologic expression, directed evolution to create an enzyme that you need to make a key starting material, or by reducing CO2 emissions through continuous manufacturing. These innovations, combined with the proven capabilities of flow chemistry, can lead to safer and more efficient API production in the U.S.," said David Thompson, Ph.D., Co-Founder and Chief Technology Officer, Continuity Pharma.

Implementing new forms of API production can also address the cost-prohibitive nature of developing an API and create efficiencies not previously realized. "Looking at both new chemistry and perhaps known chemistries like flow technology, might make that route now economically feasible, where it wasn't 30 years ago," added Dennis Hall, Vice President of Advanced Manufacturing Technologies at U.S. Pharmacopeia. "The layering in of an advanced technology opens doors for traditional batch key starting materials that might have presented a roadblock. Processed with new technology, the roadblock is removed."

"With enzymatic reactions, you can do a specific oxidation or reduction without having to protect the rest of the molecule. By doing that, not only is it potentially more efficient than chemical transformation traditionally, but it is also more route efficient. And so, you are going from seven steps to four steps or those kinds of applications. That is an area where there is a lot of promise. It is still developing," said Hancock.

While there is an opportunity to improve current small molecule manufacturing through synthetic biology, Bayan Takizawa, M.D., co-founder and Chief Business Officer, CONTINUUS Pharmaceuticals, believes the effort should be focused on those "solutions that can get us to our objective faster and cheaper. Continuous manufacturing is one of them. There is much less time-consuming and costly research and development required to implement continuous manufacturing, and the benefits have been clearly demonstrated."



# Current Capacity in the U.S. API Manufacturing Base

Evaluating the current state of the U.S. API manufacturing base is a complex task as finished dose manufacturers treat supply sources as confidential information. The marketplace has limited transparency. Tony Sardella, the Chair of the API Innovation Center (APIIC) in St. Louis, Missouri, together with Washington University, conducted a [study](#) that identified U.S. production capacity and utilization rates. These studies also reveal the number of U.S. API producers in four categories of medicines: COVID-19 relate, antivirals, antibiotics and the top 100 medicines in the U.S.

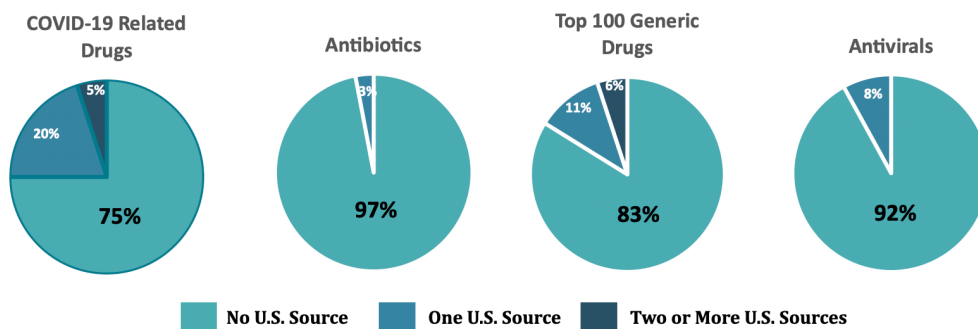
**“The establishment and maintenance of a baseline of existing U.S. drug manufacturing capacity, together with the expansion of domestic production, provides an opportunity to create a more resilient and stable U.S. pharmaceutical supply chain.”**

Tony Sardella, Chair of the API Innovation Center

## The U.S. Drug Supply Chain Is Vulnerable

### We are over-reliant on foreign-sourced drug API

*Our dependence on foreign countries for pharmaceuticals and API has created both a public health and national security risk.*



Source: Sardella, A., "The US Active Pharmaceutical Ingredient Infrastructure: The Current State and Consideration to Increase US Healthcare Security." Olin Business School, Center for Analytics and Business Insights, Washington University, August 2021.

API = Active Pharmaceutical Ingredients



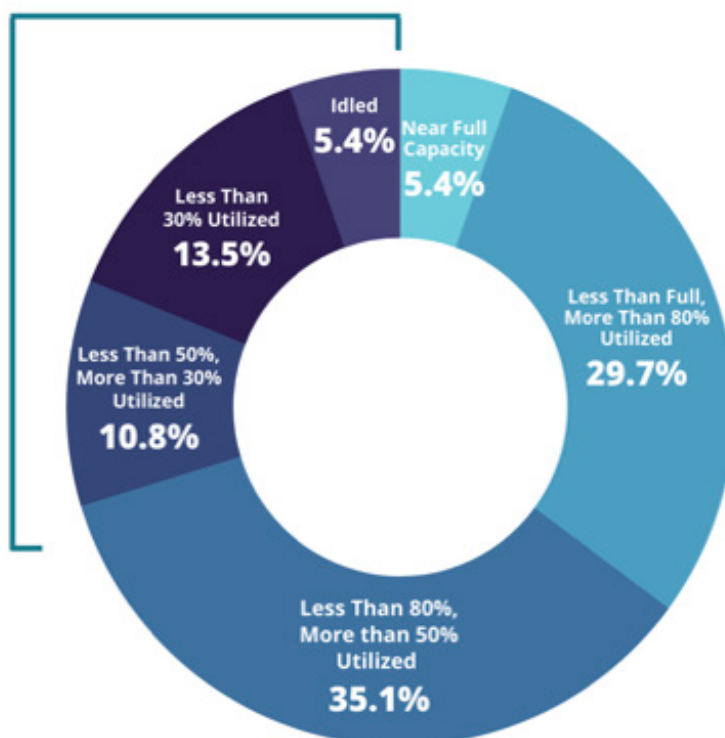
<sup>10</sup> Sources of COVID-19, Antivirals, Antibiotics and Top 100 Medicines in the United States. Cortellis Generics Intelligence, formerly known as Newport. Copyright Clarivate 2021

While this picture highlights the scarcity of API sources in the United States, there are specific regions where capacity is concentrated and, in numerous cases, there is excess capacity.

# Leveraging Excess Manufacturing Capacity

This research included the study of 37 generic manufacturing sites in the U.S. (25% of the generic drug manufacturing infrastructure). Only two of the 37 manufacturing sites are producing at full capacity. And while 70% of the sites are producing above 50% capacity, 30% are less than 50% utilized. Over 13% of the sites are less than 30% utilized.

**30% of the U.S. Pharmaceutical Manufacturing Sites are at or less than 50% Utilization**

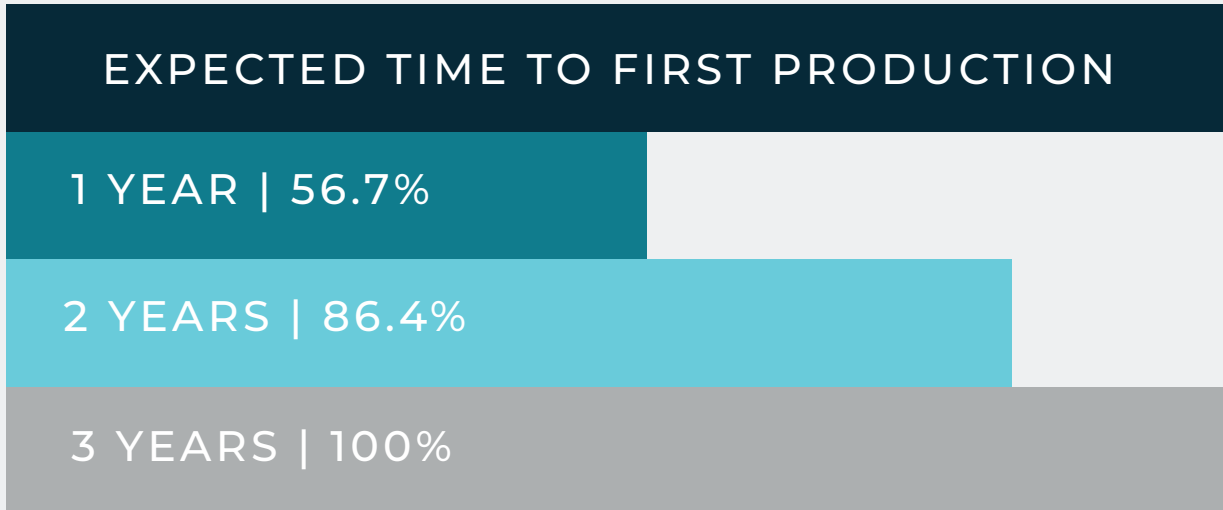


Nearly 60% of the generic pharmaceutical manufacturers surveyed are already producing FDA identified essential medicines. The excess manufacturing capacity of these same manufacturers can be quickly repurposed within one to two years to expand manufacturing allowing the FDA to meet most, if not all of their essential and critical medicine needs.

As part of the deliverables of the White House 100-day pharmaceutical supply chain report, the National Forum to Secure America's Supply Chain for Essential Medicines prioritized 86 medicines as most critically needed for acute patient care. Over 87% of the prioritized medicines are either injectable or oral solid dose, both readily produced by the generic manufacturers which participated in this research study. Respondents indicated idle capacity could be immediately repurposed to begin manufacturing critical and essential medicines. Once manufacturing lines are repurposed, manufacturers indicated 57% of the generic pharmaceutical sites could be at full production within one year, and 86% within two years.



**57% of the U.S. pharmaceutical manufacturing sites could be at full production within 1 year; 86% at full production within 2 years.**



## Leveraging CDER's Quality Management Maturity Program

Part of ensuring a resilient supply chain is to prioritize sustained manufacturing quality over time, as shortages have often been caused by poor quality management practices. For example, when a quality control issue is detected, a manufacturer may need to temporarily shut down and remediate a manufacturing line, leading to a drug shortage.

The FDA CDER's Quality Management Maturity program is designed to identify manufacturing sites investing in a strong quality culture and quality management practices. "The assumption underlying this program is that medical products manufactured in highly compliant facilities with mature quality systems, which receive high ratings from FDA based on predetermined quality metrics, will be able to justify higher prices, thus averting a race to the bottom with respect to quality driven by pricing pressures," said Margaux Hall, Greg Levine, Beth Weinman, and Jenna McCarthy, in Bloomberg Law's blog Corporate Compliance, Professional Perspective – Potential Costs of Reshoring Pharmaceutical Manufacturing.

Investments in advanced manufacturing technologies can improve quality control at drug manufacturing sites, which is a critical step towards ensuring that quality products can be reliably produced over time. QMM, once implemented, will assess the level of commitment to quality demonstrated by manufacturing sites. When coupled with federal and private sector support, QMM can incentivize manufacturers to adopt advanced manufacturing technologies and implement strong quality management practices. This can enable a more reliable drug supply and ultimately benefit public health.

# The U.S. API Manufacturing Workforce

## I A Shrinking Workforce

The workforce available to U.S. small molecule API manufacturers, batch or advanced, has been shrinking. “To become a great chemist and make new drugs or be a process chemist and scale them up to tremendous quantities, does not have the luster that it did 50 years ago. This is because there are new technologies that are incredibly exciting and have the potential for incredible health outcomes for patients. The focus has shifted. Some of the brightest minds are now focused on those new modalities. They are not focused on the advanced innovations we need in small molecules,” said Matt Hancock, Director of Business Management API at Thermo Fisher Scientific.

Andrea Adamo, Founder and CEO of Zaiput Flow Technologies believes universities must change curricula. “If you look at how many students graduate from U.S. universities knowing what advanced manufacturing or flow chemistry is, you find that number small, even close to zero. There are few programs where these processes are taught, and it is not in the standard curriculum. The American Chemical Society does not list flow-based technologies as part of the core curriculum. In China, the effort is impressive. It is at warp speed. In Europe they are much further ahead of the U.S. in education. If you want to implement a new process, you need a workforce that does not have to figure things from zero.”

Identifying resources that can support U.S. API manufacturers is important to the sector’s successful transition to advanced manufacturing. “The availability of talent, be it technicians, operators, quality assurance people, or regulatory people, will be challenging as there is not a wide talent pool to draw from. That is a big hurdle for pharmaceutical companies who will have to put a tremendous amount of investment into training and education,” said Karthik Raghavan, founder and Chief Executive Officer at Sentio Biosciences.

## Prioritizing Small Molecule Selection for U.S. API Production

The U.S. Department of Health and Human Services (HHS) and the National Academies of Sciences, Engineering, and Medicine (the National Academies) collaborated on a comprehensive study in 2022 titled “[Building Resilience into the Nation’s Medical Product Supply Chains](#).”

This study involved the establishment of an ad hoc committee dedicated to examining the security and resilience of U.S. medical product supply chains. The committee directed their efforts towards identifying measures that will yield the highest impact on public health and safety relative to the invested funds. To assist in the process of identifying medical products that require attention, they utilized the definition of

essential drugs and devices provided by the FDA: those that are deemed “medically necessary to have available at all times.” However, this definition fell short. A product that falls within the definition of medical essentiality, and already possesses a reliable supply chain, would not be a suitable candidate for resilience investments. The committee established the term “supply chain critical medical products” to encompass items that are both medically essential and susceptible to shortages.

**“Just give us a list. Pick one of the 12. We will start. You know, it is the idea that we have capabilities. We just need some momentum.”**

Dennis Hall, Vice President of Advanced Manufacturing Technologies at U.S. Pharmacopeia



In prioritizing small molecule APIs for production in the U.S., APIs required in medications necessary to create essential medicines that are in short supply should be selected. However, the list of essential medicines a doctor in a hospital would create differs from the list the Centers for Disease Control (CDC) would create. What is essential is relative to the life being saved today.

The panel determined that a list could be created, but it must be flexible and respond to current shortages or predicted events. And while this list would co-exist with many other fit-for-purpose lists, it should be a specific list that determines which small molecule APIs are prioritized for U.S. manufacture.

## | How Do We Define “Critical” Small Molecules?

Kyle Hoelting is the Senior Clinical Manager for Drug Information and Shortages at Vizient Center for Pharmacy Practice Excellence. He explains critical small molecules are used for life-sustaining therapies deemed necessary or essential for patient care.

“The way that we’ve defined essential medications are those medications that, if not available, would prove the greatest threat to a hospital’s ability to provide immediate and high-quality patient care,” said Hoelting. [Vizient further categorizes critical medicines in these subsets:](#)

- **Acute treatment drugs with no alternatives** – Medicines used in acute and critical circumstances to sustain life and for which there are no current alternatives.
- **Chronic treatment drugs with no alternatives** – Products used in chronic disease states or conditions where no alternatives are available (e.g., nutritional deficiencies).
- **High impact drugs** – Medicines for which alternatives are available but may be less clinically desirable and/or are more operationally difficult to use. Also reflects drugs where the absence of one medication can affect therapeutically related drugs.
- **Pediatric impact** – These medications, if supply is disrupted, would have a disproportionate effect on the pediatric population due to preferred formulation and/or concentrations and limited treatment options.
- **Antibiotic resistance** – Includes identification of antimicrobials necessary to treat organisms listed in the CDC’s Antibiotic Resistance Threats in the U.S.
- **Antidotes** – Medications used to counteract or neutralize the effect of another drug or poison.
- **Oncology** – Traditional chemotherapy and targeted medication for life-saving cancer treatment and supportive care agents.

“The [FDA](#) and the World Health Organization (WHO) also have essential medications lists. Across those three reference points, we have a great starting point to identify what is critical, what is essential, and what are these molecules or medications of highest importance,” said Hoelting.

## | Many Lists and Terms: “Critical meds by any other name are critical.”

Stephen Schondelmeyer, PharmD, Ph.D., a professor with the College of Pharmacy at the University of Minnesota, emphasized the importance of standardizing a critical medicines list, saying “the term essential medicines list was being used by WHO for national formularies, as far back as the 1970s. But in this current context of drug supply chain issues, we have seen a new round of lists that are not meant to be just a formulary with all of the drugs we would cover, but rather lists with the most critical ones, the ones that would affect the population’s health or survival or ability to improve their health condition on a short-term basis.”

Schondelmeyer emphasized his point by calling attention to the many lists currently used to define an essential medicine:

- **FDA** – List of Essential Medicines, Medical Countermeasures, and Critical Inputs
- **Biomedical Advanced Research and Development Authority (BARDA)** – API Solicitation for Strategic National Stockpile

- **Administration for Strategic Preparedness and Response (ASPR)** – Essential Medications Needed for Acute Patient Care
- **University of Minnesota** – Resilient Drug Supply Project's List of Critical Acute Medicines
- **USP, Angels for Change, and Vizient** – Project Protect List of Pediatric Oncology Drugs
- **Vizient** – List of Essential Medications

“By my count, there are at least 11 or 12 lists. It is probably still growing. These lists are not frozen in time. They need to be dynamic. Most of these lists do report drug molecules, while some report drug products and specific dosage forms. Sometimes pointing us toward the product that’s going to be used is important too, because you may need to make the API differently to be used in a sterile injectable than you do to be used in a tablet or capsule or in an inhaled product,” said Schondelmeyer. “We use the term ‘essential;’ we use the term ‘critical;’ we use the term ‘acute.’ Some lists include drugs that are ‘critical chronic’ medications. Who could argue that insulin isn’t critical? Critical meds by any other name are critical.”

## Identifying the Most Essential Small Molecules for API Production

Schondelmeyer advocates casting a broad net to start. “Then we focus in on concentric circles that become tighter and tighter. Within the broad net, there may be about 2000 - 2500 small molecules on the market that are important.” The list can be informed, and the circles tightened with the following data on small molecules and drugs:

### ALL SMALL MOLECULE DRUGS

- Consider the more than 2,000 generic API molecules in the U.S. market to determine annual utilization, cost, FDA application holders, and types of marketed dosage forms.
- Products with a higher number of daily doses should generally be given priority.

### WIDELY RECOGNIZED CRITICAL DRUGS

- Examine widely-recognized lists of critical and essential drugs to identify the most frequently mentioned drug molecules.
- Drug molecules on multiple critical drug lists should get greater consideration.

### EXPERIENCED QUALITY ISSUES AND SHORTAGES

- Assess the quality experience of API molecules such as FDA 483 inspections, product recalls, import alerts, and other quality indicators.
- Identify API molecules that have had shortages in the past 5 years (either FDA or ASHP).
- API molecules with quality issues or drug shortage history should be given priority.

### PRODUCTION LOCATION & REDUNDANCY

- Inventory the more than 11,000 API facilities to determine the country of origin and consider the number, concentration, and diversity of countries making an API molecule.
- Rate and consider geopolitical risk of the dominant country of origin for API molecules.
- Give preference to production of API molecules with concentrated geographic production and/or with the greatest geopolitical risk.

### LIMITED OR NO THERAPEUTIC ALTERNATIVES

- Assess how important each API is to the treatment of medical conditions and determine which APIs (& related drug products) have limited or no therapeutic alternatives.
- Assess whether there are APIs in the pipeline that will reduce the need for this API.
- Critical acute molecules with no therapeutic alternative should be given greater priority.

### **PUBLIC GOOD DRUGS NEED INCENTIVES**

- Identify “public good” APIs based on factors such as limited patient population, high therapeutic value, very small market size (less than \$50 million revenue per year or even \$100 million), and limited suppliers (e.g., 0, 1 or 2 producers).
- Provide incentives to keep “public good” products on the market despite what appears to be low economic demand.
- Give preference and incentives to encourage production of public good API molecules.

## **SMALL MOLECULE SELECTION ANALYSIS**

- 1 ALL SMALL MOLECULE DRUGS**
- 2 WIDELY RECOGNIZED CRITICAL DRUGS**
- 3 EXPERIENCED QUALITY ISSUES AND SHORTAGES**
- 4 PRODUCTION LOCATION & REDUNDANCY**
- 5 LIMITED OR NO THERAPEUTIC ALTERNATIVES**
- 6 PUBLIC GOOD DRUGS NEED INCENTIVES**
- 7 PRIORITY DRUGS FOR API PRODUCTION**

*Stephen Schondelmeyer, PharmD, Ph.D., University of Minnesota*

Schondelmeyer recommends conducting ongoing research on the drug supply and market conditions to: (1) identify other factors that may predict drug shortages; and (2) determine the relative weight of the various risk factors in predicting the likelihood of a drug shortage for a given API and/or its related drug products.

Hoelting adds it would be helpful to look at supply constraints and drug shortages in the past to help identify the greatest need. “Multiple organizations have been following drug shortages for years like the FDA or the American Society of Health-System Pharmacists. We have a repository of data to focus on moving forward into the future.”

“I think those essential medications, those older essential medications, are going to continue to become more and more essential.” He emphasized we need to think “through what those critical molecules are along with their dosage forms and the critical components needed to prevent any supply constraints.”

## | Factoring Key Starting Materials Availability

“Having the key starting material analysis of not just what’s available, but also then layering the various chemistries and engineering that are necessary to make those key starting materials. And whether that is economically viable is also a key aspect of this analysis. We have the information that we need to analyze key starting materials. “There is significant trade data you can look at and get down to actual molecules,” said Dennis Hall, Vice President of Advanced Manufacturing Technologies at U.S. Pharmacopeia. “The U.S. has specific information about what molecules we’re bringing in, and what molecules were exporting. Using some digital tools, like machine learning to understand all the potential routes of synthesis that may have been published in literature or in other sources, you can start to understand where there are opportunities. Eventually you need a synthetic chemist to sit down and determine what will work. Then bring in the synthetic chemists that know flow technology.”

## | Making the Patient the Priority

As manufacturers contemplate the molecules, they should focus on developing and weighing costs against revenue, the panelists highlighted the importance of giving priority to the patient as the primary customer. Shifting towards a patient-centered, value-oriented approach and addressing necessary changes in the supply chain should also be considered.

“There is no other supply chain that holds that kind of risk to our citizens. And why? It’s because the patient really has no power. They do not know what they need when they need it. They do not know what choice they would make because they have no medical knowledge. There is no risk in a hospital not supplying a drug. There is no risk in a manufacturer not making a drug. There is no risk of a purchaser not buying a drug. The only risk associated with non-supply is to the patient. The patient either gets treatment or they do not. How can any rational decision be made when life and death may be at the end and the supply chain holds no risk in non-supply?” said Laura Bray, Chief Change Maker at Angels for Change.

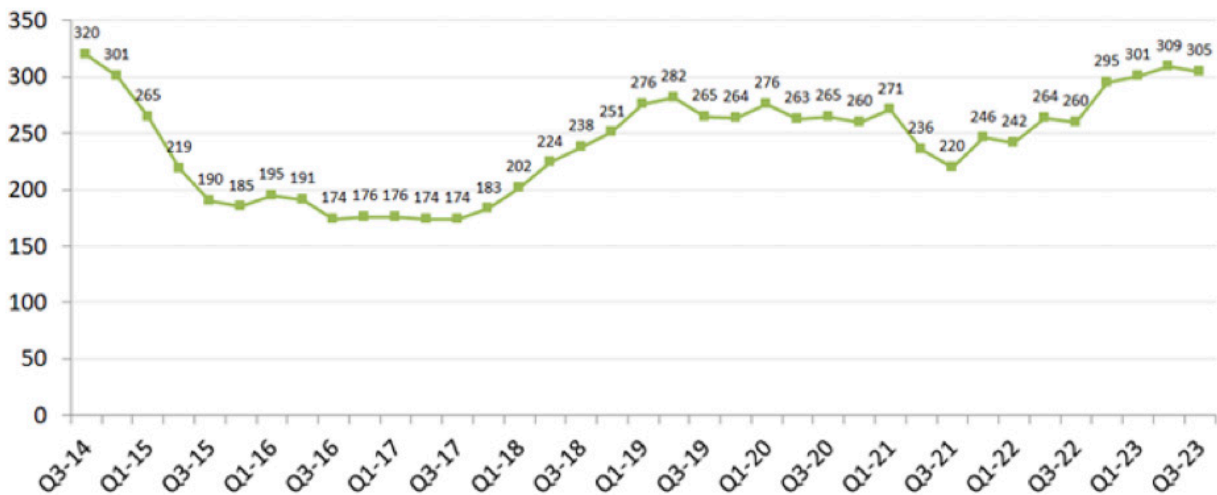
“What customer are we trying to serve?” asked Matt Hancock, Director of Business Management API at Thermo Fisher Scientific. “The patient. I am a patient myself. When I look at the pill I’m going to take in the morning, I just see a pill.” He adds patients might think about how much the pill costs or wonder where it came from. They might question if the pill is what they believe it to be. These considerations are secondary for the patient who just wants to get well. Hancock believes there must be more the industry must consider, beyond financial incentives. The question to ask is not what customer the industry is trying to serve, but which patients are they going to save?

## | When Patients and Hospitals Struggle to Obtain Essential Medicines

The [American Society of Health Systems Pharmacists \(ASHP\)](#) stated, “The U.S. healthcare system currently is experiencing the most drug shortages since 2014. Shortages of local anesthetics and basic hospital drugs albuterol solution common oral and ophthalmologic products an attention deficit hyperactivity disorder treatments are affecting large numbers of hospitals and health systems and patients. Chemotherapy drugs often without alternatives are increasingly in short supply and have returned to the list of top five drug classes affected by shortage.”

# National Drug Shortages

## Active Shortages by Quarter – 10 Year Trend



**Note:** Each point represents the number of active shortages at the end of each quarter.

### University of Utah Drug Information Service

Kyle Hoelting, Senior Clinical Manager for Drug Information and Shortages at Vizient Center for Pharmacy Practice Excellence stated that essential drug shortages have reached a critical point. “It ranges from 40 to 50% of essential medications required for life saving care that are on shortage. At the end of this quarter (Q3, 2023), there were 305 active shortages in the U.S. on the ASHP list. The record is 320. We were at 309 (Q2, 2023) in the previous quarter, so we are truly on the cusp of what hospitals and health systems can handle day-to-day.”

Beyond the impact to patient care, there are often less noticeable implications because of a drug shortage, but still just as costly:

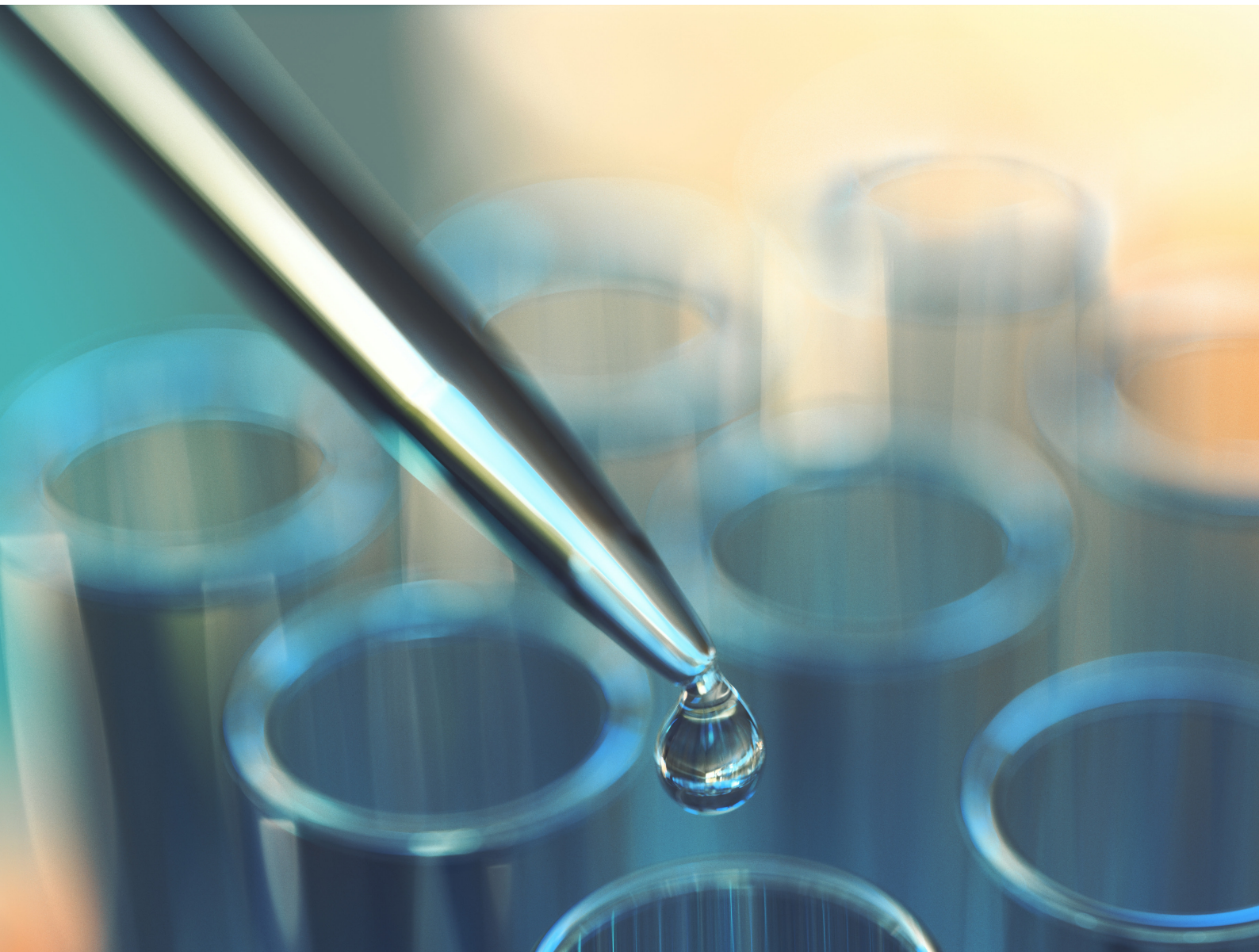
- **Labor.** Managing drug shortages is both resource and time intensive. Additional staff and resources are often required to mitigate shortages. For example, if hospitals and health systems have been purchasing a pre-made bag that is no longer available due to a shortage, to mitigate the shortage, the medication may be compounded in-house. This will pull staff from other responsibilities to account for the added work.
- **Inventory.** To manage and mitigate shortages, hospitals and health systems will often protective purchase, or purchase more (ie, more than the average daily usage) of a product on shortage, or expected to be, in order to ensure patients can be treated with the affected product. Thus, shortages can increase the pharmacy’s budget, and can lead to purchasing off-contract items, ensuring availability for patients, but at an added expense to the hospital or health system.
- **Stress/Burnout for Frontline Staff.** Shortages introduce added variables and stress to already complex frontline care. Pharmacy, with other stakeholders, do their best to prevent, manage, and mitigate the ever-changing shortage landscape. Physician prescribing and nursing practices can regularly be adjusted or impacted, leading to frustration and potential medication safety events when prescribing and administering alternative therapies with less familiarity.
- **Patient Safety.** Patient safety events linked directly to shortages have been reported. The Institute for Safe Medication Practices released the results of a survey in September 2023 which reported nearly 25% of the institutions responding could point to a medication safety error directly linked to a shortage 6 months prior to the survey.



# The Impact of Generic Sterile Injectable (GSI) Shortages

In the Brookings Institute Report, Federal Policies to Address Persistent Generic Drug Shortages, Marta Wosinska and Richard Frank note: “Nearly every hospital patient in the U.S. is treated with generic sterile injectable drugs (GSIs). Any shortage can have substantial adverse impacts through treatment delays, the use of inferior alternative products, and increased risks of medication errors. GSI shortages are disproportionately triggered not by exogenous factor, such as demand shocks or natural disaster, but rather by market-driven manufacturing problems.” Hospitals have limited, standardized information other than price when making purchasing decisions for competing GSI products, as they cannot directly assess drug quality and there is no standardized approach to assessing drug quality. Further, manufacturers’ dedication to adhering to good manufacturing practices can vary substantially despite quality-related requirements.

“It is important to recognize that these medicines are notoriously complex, challenging, and expensive to manufacture. Yet, despite the challenge and investment required to reliably supply these important products, they are often sold at a relatively low price. And according to [new IQVIA research](#), shortages are more common in drugs with very low list prices. Low margins coupled with the volatile demand created by constant shortages in the market creates a domino effect that further disincentivizes manufacturers that remain in the market from reinvesting and building excess capacity, which further perpetuates the drug shortage crisis over time.” said Marcus Lumpuy, U.S. Vice President for Hospital Business Unit at Pfizer Biopharmaceuticals.



# Barriers to Reshoring Small Molecule API Manufacturing

Lowering barriers to U.S. production of small molecule API begins with adequate funding. While addressing these impediments is a top priority, manufacturers also expressed their concerns over the unfavorable impact of the current drug supply chain on the sector. Overwhelmingly, however, the manufacturers who participated in the panel cite financial incentives as an imperative step towards returning API manufacturing to the U.S. The panel sees clear direction, capital investments for technology and facility upgrades, contract commitments, and tax incentives as necessary initiatives.

**“Looking ahead in terms of commitment as an API manufacturer, it’s hard to jump in and say, I’m going to start looking at this molecule that’s on this list because it’s critical, or if it’s a national security issue, whatever it is, and fund it and drive it to a drug master file. There is little private equity appetite for this kind of stuff. Very few players will take that kind of risk unless they are well funded.”**

Karthik Raghavan, Founder and Chief Executive Officer, Sentio Biosciences

## I Low Profit Margins – High Production Costs

One of the largest impediments to manufacturers investing in the generic drug market is the limited financial return weighed against production costs. “The average API and finished dosage manufacturer get about \$0.06 to \$0.08 cents of every dollar that gets spent, and the other 90 plus cents per dollar goes to the wholesalers, distributors, the pharmacy benefit managers, and the pharmacies,” said Ed Price, former CEO at PCI Synthesis.

Low profits do not support a strategy for API manufacturers to expand operations beyond existing lines and the expected return on investment for new lines in generic API manufacturing simply falls short. Andrew Gonce, MBA, Vice President of Commercial & Strategy at Mallinckrodt Pharmaceuticals said, “We conducted an analysis on all the small molecule APIs listed in the FDA Essential Medicine List.

The procurement of a year’s worth of supply for each non-U.S. manufactured API would incur an average cost [or value to suppliers] of around \$4 million dollars. The cost of developing, producing, and manufacturing means you would be entering a market underwater for no less than five, maybe ten years, if you could find a customer. It is an economic problem.

“The value assigned to active pharmaceutical ingredients has degraded over time. Right or wrong, everybody is looking to make money,” said Karthik Raghavan, founder and Chief Executive Officer, Sentio Biosciences.

## Consolidation and Distribution Structures Lower Profits

Other factors also contribute to lower return on investments. “The pricing profile in the last six years for a 30 pack of pills has gone down 50% because of the consolidation of the buying groups. The market is unattractive to everybody. To come in as an American manufacturer trying to do the right thing at a price point that is higher... it is awfully tough,” said Gonce.

“We have a very convoluted system,” said Ed Price, former CEO at PCI Synthesis. “We distribute drugs through wholesalers and distributors and pharmacy benefit managers and pharmacies. There are several models throughout the world of how drugs can be distributed. The layered structure we employ extracts billions of dollars out of the system. The question is, does Congress and the Administration have the political will to change the system to extract some of the existing value and give it to the manufacturers so that we can make this a more viable and sustainable industry?”

## Scaling Up is Challenging

As is typical when developing any novel technologies or processes, there are inherent challenges. In the case of advanced technology like flow chemistry, after a successful research and development process to determine the route of synthesis, the next step is to scale the process. Using existing technology, most notably batch processing, can be difficult as it requires developing larger scale instrumentation and equipment. Using new technology can increase the complexity of the traditional scaling process given the added variable.

“When these APIs are first developed, they are developed in a lab at medical chemistry scale, in a small reactor using traditional chemical transformations and tools. To shift to a new technology and make a much larger batch – there’s a much bigger gap,” said David Thompson, Ph.D., Co-Founder and Chief Technology Officer, Continuity Pharma. “One way to address this issue is to deploy a network of smaller scale production units that would require lower capital investments and provide both greater resiliency and agility in response to changing market needs.”

However, the relative challenges are marginal in the context of continuous manufacturing technology’s advantages. “Technology transfer and scale up can really be a hurdle,” said Adam Fisher, Ph.D. Director of Science Staff, Office of Pharmaceutical Quality, CDER, FDA but adds other benefits of continuous manufacturing should be considered. “The FDA conducted a study where we looked at the approved applications that had used batch technology for drug product manufacturing, and compared them to applications that used continuous manufacturing technology. The amount of time between the approval and when that product hit the market was zero months.” Expressed differently, continuous manufacturing not only provides a safer, environmentally friendly, and more efficient process, but also has reaped the benefits of FDA approval in the same timeframe as the length batch processing.

## Incentives are Needed: A Customer and a Committed Contract

Ed Price, former CEO at PCI Synthesis, described a manufacturer’s first order of business: there must be a customer. The cost of bringing a product to the market is an investment worth millions of dollars. It takes four to six years. Market fluctuations can be dramatic and there is no guarantee a market will exist six years into the future.

“If the Department of Defense and the Department of Veterans Affairs and Medicare and the Strategic National Stockpile all got together and combined their buying power of pharmaceuticals, that is a pretty sizable market. And then said these are the first 50 strategic drugs that we want developed and manufactured here in the U.S.” Price believes that those commitments, plus a firm-fixed-priced contract could work.

“The government can take on committed contracts as they are one of the biggest purchasers of generics. They also receive the largest rebates from generics. They have the power to decide not to take rebates for generics and opt for committed contracts,” adds Laura Bray, MBA, Chief Change Maker, Angels for Change.

“When implementing incentives for a more reliable supply chain, the missing piece is often demand-side incentives. One type of demand-side incentive is a committed or advance contract, where both the supplier and the purchaser face meaningful financial penalties if their commitments are not met. Some examples of committed contracts include Civica Rx’s model and programs through the hospital GPOs. There are multiple other demand-side incentive options available as well, and we are working on recommendations to progress those options through the [Duke-Margolis ReVAMP Drug Supply Chain Consortium](#),” said Stephen Colvill, MBA, Assistant Research Director, Duke-Margolis Center for Health Policy. The Duke-Margolis consortium is comprised of drug supply chain stakeholders working towards developing policy that promotes reliable drug supply using advanced manufacturing.

## Additional Incentives for U.S. API Manufacturers

“Incentives are the primary driver,” said Kurt Karst of Hyman, Phelps & McNamara, Co-Founder of the [FDA Law Blog](#). “Whether we’re talking about periods of marketing exclusivity or vouchers for priority reviews or some other tax incentive, these are the incentives that will motivate manufacturers.” Tax incentives could include credits for upgrading technology and facilities that support production of API, much like tax credits proposed for the semiconductor industry under the [CHIPS and Science Act](#), or reduced taxes on income generated from production of those medicines.

According to the U.S. Generic Pharmaceutical Industry Economic Instability report, the federal government bears the largest share of total health spending in the United States at 34%. However, unlike Germany, Brazil, India, and China, the U.S. does not have sourcing policies that favor or incentivize domestic manufacturing or manufacturers with stronger compliance records. To address this, the federal government can consider implementing policies such as improving provider reimbursements for U.S.-made generic products and realigning preferred drug lists/formularies for Medicaid/Medicare to incentivize U.S.-based manufacturing. State governments can also make similar adjustments for Medicaid with federal approval.

To reduce incentive costs, the report also suggests leveraging existing idle manufacturing bases to expedite stabilizing drug supply chains and save millions in spending. Funds can be directed towards research and development into novel advanced manufacturing technologies that reduce production costs, improve product quality, worker safety, and environmental footprint. APIIC conducted a study where an incumbent manufacturer estimated a 60% savings in capital and a two-to-three-year acceleration if existing facilities are used to support domestic production efforts versus starting from a greenfield plot.



Providing increased funding support from government agencies to industry coalitions that present the fastest and most efficient solutions to generic supply chain challenges can increase the probability of success by aligning incentives to bring these products to market prior to industry investments on development. This can prove to be a cost-effective approach that utilizes existing structures rather than creating new, and potentially costly infrastructure.

## | Industry Focus is on New Medicines

Matt Hancock, Director of Business Management API at Thermo Fisher Scientific, describes an industry enamored with new medicines, detracting from the necessary focus for small molecule API and further emphasizing the need for incentives and supply chain adjustments to recapture the allure in this vital industry. “There have been tremendous applications of biologics, monoclonal antibodies, proteins, ADCs, cell, and gene therapy. These new modalities are incredibly exciting and do incredible things for patients. The unintended consequence is that the focus on innovation and knowledge is no longer on small molecules. Some of the brightest minds are now focused on those new modalities. To become a process chemist and scale [small molecules] up to tremendous quantities does not have the luster that it did 50 years ago.”

Foley explains the way the industry deploys capital and investment on product lines is also centered on new products. “There is no planned investment to squeeze more out of existing lines. The fact is the profits have been wrung out from current products on the market. We have got very solid equipment that we think can impact process, analytical and real time feedback and the way that that’s chosen to be deployed in many cases is on new products,” said Foley.

While the development of new medicines is important for securing the future of healthcare in the U.S., it is equally vital to maintain focus and determine innovative approaches to continue providing the known small molecule API needs.

“I’m optimistic about the opportunity that we have as an industry,” said Hancock. “The industry, in terms of new drugs, is certainly shifting in their profile. The blockbuster drug is going away. The new drugs are more focused on smaller patient populations, with smaller quantities of doses. Correspondingly, smaller amounts of API will be needed. Our infrastructure is built more towards blockbusters. As the industry shifts towards these smaller niche type of drugs, there will be a shift in the way infrastructure is built. There is an opportunity to leverage that shift in a way that lends itself to advanced manufacturing.”

## | Some Critical Drugs are Public Goods Needing Market Support

Stephen Schondelmeyer, PharmD, Ph.D., a professor with the College of Pharmacy at the University of Minnesota noted that, “There may be some APIs needed in critical drug products that are essential to health care, but which have such a low volume that they will never be profitable in the market without some form of cost sharing support. These ‘Public Good’ drug products should be designated based on carefully designed criteria and then should be produced through a public-private partnership that is funded by the government, much like we may for fire departments and national defense.” These ‘public good’ products should be made when possible, using advanced manufacturing methods.





# Regulatory Barriers to Reshoring API Manufacturing

The API manufacturing industry faces regulatory constraints that have an impact on both the cost of development and the speed at which products can enter the market. Implementing risk reduction measures in this area could serve as a motivation for API manufacturers to adopt innovative technologies. During the pandemic, regulators and industry were able to successfully collaborate and agree on the importance of [speeding market entry for vaccines and treatments](#). This cooperation helped to reduce obstacles and facilitate the adoption of pharmaceutical innovations. However, outside the context of a crisis like a pandemic, the dynamics between regulators and industry become more difficult once again.

## Regulatory Impediments to Using New Routes of Synthesis

A collaborative approach between the industry and the FDA is necessary to overcome the challenges that impede the utilization of new technologies. An API made from a different route of synthesis could generate new impurities that require further study. If there is a long-established history of that molecule, a phased review process that leads to faster approval should be considered. “Would a U.S. manufacturer receive a priority review of their submission compared to an overseas applicant?” asked Karthik Raghavan, founder and Chief Executive Officer at Sentio Biosciences. “Would a domestic priority create eligibility for a reduced fee schedule?”

In the [FDA Law Blog](#), Kurt Karst discusses the process for Suitability Petitions, which allow for the submission of an Abbreviated New Drug Application (ANDA) that differs from a previously approved listed drug. This can include changes in strength, dosage form, route of administration, or active ingredient in a combination drug. However, an ANDA cannot be submitted until the FDA approves the Suitability Petition. While the statute sets a 90-day deadline for FDA to approve or reject the petition, it is rare for the agency to meet this timeframe.

The FDA's [commitment letter for Generic Drug User Fee Amendments \(GDUFA\) III](#) indicates there are plans to clear the backlog in the coming year and give priority to petitions that can mitigate drug shortages. Prioritization of these petitions is critical to support the adoption of new technologies that would change routes of synthesis.

According to Matt Hancock, Director of Business Management API at Thermo Fisher Scientific, the FDA exhibits a proactive approach in evaluating new technologies, although there is room for improvement to publicize collaborations with companies that have implemented such technologies to aid manufacturers considering commercialization of a single molecule without needing to deliver the final product to patients. “That is a significant leap. Especially when there is not a well-worn path of how to do that and what the regulatory impacts might be.”

Because of commercial confidentiality, the FDA is not always able to share that information until the manufacturer publicly announces the use of a new technology. Adam Fisher, Ph.D. Director of Science Staff, Office of Pharmaceutical Quality, CDER, FDA, said it is an area the FDA could explore further.

Similarly, the FDA could disclose that a new technology had been reviewed and summarize the regulatory implications of using that type of technology. Andrea Adamo, Founder and CEO of Zaiput Flow Technologies believes that would inform the customer and reduce the perception of risk.

Finally, the FDA could prioritize the updating of [cGMP](#) regulations to keep pace with processes associated with new technologies.

Fisher shared that both the [CDER's Emerging Technology Program](#) and the advanced technologies team in the [Center for Biologics Evaluation and Research \(CBER\)](#) conduct early engagements with stakeholders developing new technologies. "Some people have interpreted it to mean that one must be a drug product manufacturer to engage with that program. That is not the case."

The panelists also shared support about the way the FDA has helped modernize the pharmaceutical industry: "I want to make one point of fact here. The only reason the pharmaceutical industry, in my 30 years in it, has modernized anything is because the FDA took a stance very clearly where they say we need to improve the way we make things. Credit to them," said Fernando Muzzio, Ph.D., Professor of Chemical Engineering at Rutgers University. "They want a solution to this problem and so do we."

## I USP Drug Product Monographs Could Help

The term intellectual property refers to rights obtained by businesses for the purpose of advancing their business interests. Patent rights are considered intellectual property. Besides patents, there are three other main categories of IP: trademarks, trade secrets, and copyrights. USP works with the manufacturer's trade secrets when building monographs, a point emphasized by Dennis Hall, Vice President of Advanced Manufacturing Technologies at U.S. Pharmacopeia, "We have to push up into understanding what that manufacturing process is and help build standards around quality at the manufacturing process level."

A [USP monograph](#) becomes publicly available after a medicine's patent protection expires and following completion of a transparent process that includes multiple opportunities for input from stakeholders. "That is an area where I think USP can do some additional work to unlock that potential of what that process IP looks like. A product-specific monograph could be used as an end-product test. That would be the test for the lifecycle of the product until release," said Hall. On average, drugs with [USP drug product monographs](#) had approximately fifty percent more generic manufacturers in the U.S. than their counterparts after accounting for factors such as market volume, age, route of administration and vintage.

## I How the ACETRIS Ruling Devalues API

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 U.S.-based API manufacturing. Tony Sardella explains in his [research](#) that 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), No. 2018-2399, slip. op. (Fed. Cir. Feb. 10, 2020). 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 U.S. 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.

"You can have an American-made product if you simply compress a tablet in the U.S. The therapeutically active component of that medicine could be made overseas but if you wrap it in starch and cellulose here, it becomes American made. That fundamentally devalues API and leads to a whole set of actions around off shoring supply and pushing it to the lowest cost locations," said Andrew Gonce, MBA, VP, Commercial & Strategy, at Mallinckrodt Pharmaceuticals.

To establish the proper incentives in Federal procurement that support onshoring efforts in the pharmaceuticals industry, closing the "Acetris loophole" is a necessary initial step. As previously described, companies have transferred API manufacture overseas mainly for economic reasons, which should also be addressed. By requiring a substantial transformation of an API to qualify a product with a non-U.S.-made API, manufacturers that want their products to be eligible for all U.S. procurements will have to move API manufacturing to the U.S.

Developing API manufacturing capabilities in the U.S. will lead to an increase in manufacturing, management, regulatory, and a host of other jobs in the U.S. This will also increase U.S. oversight capacity to ensure quality pharmaceuticals are produced. Acting to revise the U.S.-made end product definition (to clarify that “manufacture” requires meeting the “substantial transformation” standard), will encourage the industry to work toward manufacturing API and other critical components in the U.S., and/or procuring these components from other U.S. manufacturers.

# Building a Resilient Drug Supply Chain - A Public-Private Partnership

## I A Clear Purpose

“The first step is clarity of mind,” said Fernando Muzzio, Ph.D., Professor of Chemical Engineering, Rutgers University. “What exactly are we trying to do? What problem are we trying to solve and by what criteria?” Muzzio recently participated in [research](#) that identified six possibilities:

- Reshoring of pharmaceutical manufacturing as a national security issue
- Promoting economic development and creation of high paying manufacturing jobs
- Addressing drug shortages
- Preparing the country for future medical emergencies
- The protection of patients from fake and diverted products.
- The production of high-quality medications

“I appreciate the nobility in the goal but I’m not sure it’s helpful to say 25% in five years. Even before we get promises that there is going to be money, we need to define the problem and come up with a reasonable strategy for achieving a solution and then commit the resources needed,” said Muzzio.

## I Incremental Steps

That strategy requires incremental steps. “If we started today and took X drug in the market that is in short supply, you might develop all the things you need in a year. And if you were ready to file in a year, you would still then have an approval process to go through. Even if we said that you could do all of that in two years, we would be halfway through our goal timeline. The five years is beyond ambitious, to be honest. But in five years we can make strides,” said Matt Hancock, Director of Business Management API at Thermo Fisher Scientific. “Select a subset of that 25% to advance quickly and get feedback on how to model it, how to understand what the consequences are, how to make it achievable. That would be a practical next step.”

“You must first establish the credibility of advanced manufacturing of those agents. And why not set the bar at a level that you can actually achieve and build that experience that you can leverage into more complex molecules, more challenging molecules?” added David Thompson, Ph.D., Co-Founder and Chief Technology Officer, Continuity Pharma.

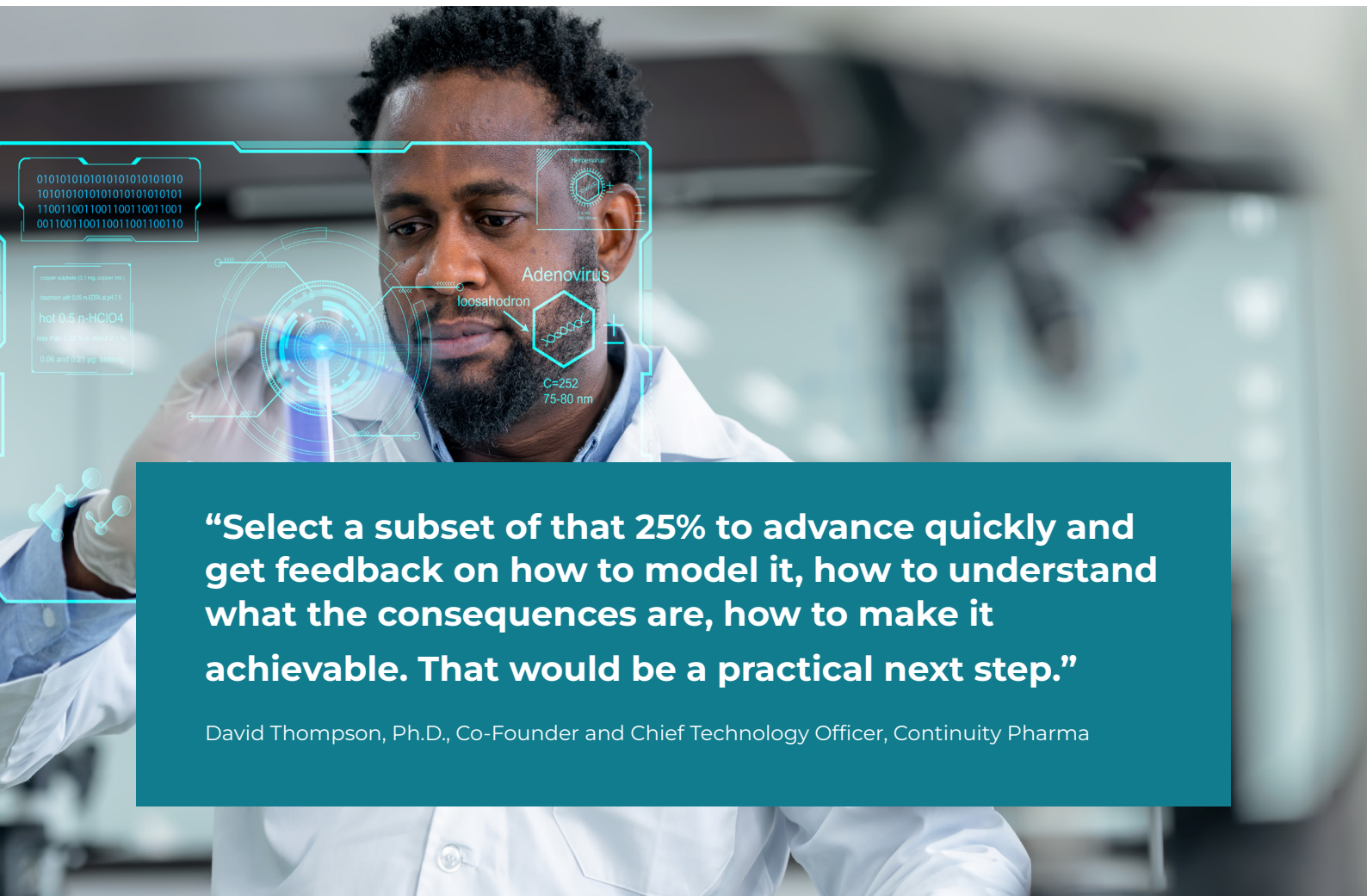
William Foley, a subject matter expert in process analytical technologies, also believes establishing an initial subset of tasks and working through that to determine challenges is a worthy first step. “There are consequences with everything. If you said today that the government’s funding 25% repatriation of the API supply chain, there are consequences to the other 75% of that as well. We need to understand it thoroughly.”

## I A Coordinating Entity

There have been coordinating efforts by government entities, but to date, none of them have been institutionalized. “It feels like starting from scratch every time the issue becomes more pressing. Having an entity that builds institutional knowledge over time would be helpful,” said Stephen Colvill, MBA, Assistant Research Director, Duke-Margolis Center for Health Policy. There are several ongoing efforts that require a coordinating entity to connect their efforts. The FDA’s CDER’s [Quality Management Maturity program](#), CDER’s FRAME Initiative, and ASPR’s Industrial Base Management and Supply Chain (IBMSC) Office are a few examples, and these programs are relevant to other areas, such as a potential payment program that incentivizes actions promoting reliability. A payment program may be triggered by levers in other programs. “Establishing a coordinating entity will pave the way towards sustainability, and such coordination can be done with minimal funding, but there is also a significant private sector component.”

A coordinating entity can connect innovators with commercial scale resources, FDA-approved cGMP facilities and the commercial, quality, regulatory and physical infrastructure required to bring products to market. Efforts by entities such as APIIC help innovators work together with existing manufacturers to de-risk commercialization, increasing the potential for successful production. Further, the leaders in chemistry may not have access to leaders in control systems or equipment engineering or training programs for these new technologies. [Research](#) reveals there is a substantial gap between bench scale proof-of-concept and commercial scale cGMP production that requires bridging through public-private partnerships.

Shortly after the APIIC plenary, the Biden administration [announced](#) New Actions to Strengthen America’s Supply Chains, which includes the establishment of a HHS Supply Chain Resilience and Shortage Coordinator, a position that could lead such a coordinating entity and administer a public-private partnership.



**“Select a subset of that 25% to advance quickly and get feedback on how to model it, how to understand what the consequences are, how to make it achievable. That would be a practical next step.”**

David Thompson, Ph.D., Co-Founder and Chief Technology Officer, Continuity Pharma



## | A Public-Private Partnership

“A public-private partnership involving various federal agencies should be established. A model like the [National Institute for Innovation in Manufacturing Biopharmaceuticals \(NIMBL\)](#) should be considered, which involves both government and private sector funding. This group here today and the End Drug Shortage Alliance should think about how this model could work. The institution could set clear goals with a long-term perspective, develop tools that help to measure supply chain reliability, and include private sector engagement,” said Colvill.

There are other public-private partnerships which emulate model practices and are expanding their reach to incorporate perspectives all the way to the patient level. For example, in addition to REVAMP, Duke-Margolis has established two other consortiums which involve significant engagement from payers, and as a next step, also plans to involve payers in supply chain discussions.

In terms of financial investments, APIIC’s partnership with the State of Missouri exemplifies such a public-private partnership. In 2023, the Missouri Department of Economic Development and the Missouri Technology Corporation awarded APIIC ~\$10 million to further its efforts to develop an ecosystem of stakeholder partnerships and networks for supply chain coordination from R&D to FDA-approved cGMP. This partnership between public entities and private enterprises is the most effective way to de-risk the challenges of strengthening domestic manufacturing and delivering timely and sustainable solutions to U.S. healthcare security.

The ecosystem includes key pharma technology equipment companies, cGMP manufacturers and supply chain partners, innovators, researchers, and economic development practitioners, all of whom share a vision of building a robust, scalable, and inclusive regional innovation ecosystem to protect U.S. security interests and ensure a safe, reliable supply of pharmaceutical ingredients necessary for producing drugs essential to U.S. public health.

## | Prioritize the Patient

To make the supply chain more resilient and reliable, Laura Bray, MBA, Chief Change Maker, Angels for Change says it is crucial to reconnect and collaborate. “It was called a chain on purpose because the supply chain must be connected for the customer to receive supply,” said Bray. “One tool that is not being used to create collaboration and purposefully connect is patient advocacy – inserting the patient-experience throughout the supply chain gives all members true purpose and urgency. This is the supply chain that fills the hands that save our people. If the patient is not at the center of design and innovation we will spend a lot of time, money, and effort and still not save our people.”





# I Create Transparency in Supply and Quality

“Despite our collective efforts, there are still opaque areas that create real barriers to transparency in this marketplace, including competition, intellectual property, regulations, contracts, and legal issues. These barriers make it difficult for us to understand the situation. Without a clear understanding of the situation, it becomes challenging to create a viable plan,” said Laura Bray, MBA, Chief Change Maker, Angels for Change.

“If there is a public-private partnership influencing incentive development, a data sharing infrastructure could be a big component of that partnership, which would help to provide insights into how to target supply chain incentives. Many innovative data sharing models exist, for example IQVIA where wholesalers and manufacturers voluntarily report sales data through a trusted framework. We can use similar models to provide insights to those making critical supply chain decisions, whether it is the federal government or purchasers/providers,” said Colvill.

## Where is Drug Supply Coming From and Where is it Needed?

“We need transparency,” said Stephen Schondelmeyer, PharmD, Ph.D., a professor with the College of Pharmacy at the University of Minnesota. “If I go to the grocery store and buy avocados, I know where they came from. We do not know that for drugs. The FDA might, but they get information that is proprietary and confidential. I think we should require country of origin disclosure for finished dosage form for API, and maybe even for key starting materials.”

“We don’t have a master drug supply map,” said Schondelmeyer. “The USP has a start on it. We have developed one at the University of Minnesota. We need to bring these efforts together to create a national drug supply map, so we know where drug supply is needed, where it is coming from and what we need to be doing to have the right facilities out there. Our health is too critical not to have that map.”

## A Quality Scorecard

The largest share of total health spending in the United States is borne by the federal government (34%), according to research from the [U.S. Generic Pharmaceutical Industry Economic Instability](#) report. However, the U.S. is unique in not having sourcing policies that favor and incentivize domestic manufacturing or manufacturers with stronger compliance records – a practice already employed in Germany, Brazil, India, and China. For example, improving provider reimbursements for U.S. made generic products and realigning preferred drug lists/formularies for Medicaid/Medicare is a policy change that can be undertaken by the federal government to enable an incentive for U.S.-based manufacturing.

“It is documented in multiple reports that at least 62% of shortages are attributable to quality. If we want to address that, it is also recognized that the key issue is the immaturity of the quality control systems. What kind of quality scorecard can we create so that quality can be recognized and paid for?” asked Fernando Muzzio, Ph.D., Professor of Chemical Engineering at Rutgers University.

Hoelting suggests purchasers may be open to a slightly elevated price given a quality product with a robust supply. “I have heard from hospitals and health systems that they will pay slightly more for a drug with high quality that they know is resilient to supply constraints. Not all of that burden should fall onto the hospitals and health systems. It needs to be discussed how that would work itself out.”

“Transparency of quality and reliability information is critical if we want and expect buyers (i.e., hospitals, chains, insurers, health plans, and patients) to pay more for quality,” according to Schondelmeyer. “With quality information that is company and product-specific, buyers would be open to paying more for better quality products, but without this information buyers are not likely to pay more just because some unspecified product made by some undisclosed company might be better quality.”

## | Leverage Manufacturing Capacity

The United States holds existing available infrastructure that can be utilized to strengthen the pharmaceutical supply-chain as revealed in research on [U.S. Generic Pharmaceutical Manufacturer Available Capacity Research Survey](#). Repurposing currently idle capacity can enable U.S.-based manufacturing of critical and essential medicines to address shortages, enable supply chain resiliency and allow for supply within a 24–36-month timeframe. Capacity is readily available.

Sardella further determined that funding of advanced manufacturing technologies, such as continuous flow and on-demand manufacturing capabilities in idled manufacturing sites offers the ability to reduce production cost, create new work force development opportunities, and increase the economic sustainability of U.S. drug manufacturing. Advanced manufacturing lowers costs by condensing processes that used to take months of expensive work into a few days. [It also promotes the use of automation and robotics to shrink labor costs while improving quality controls to minimize waste.](#) In addition to being less expensive, continuous manufacturing can expedite regulatory checks without compromising oversight, improves manufacturing agility, and utilizes a smaller environmental footprint.

## | Build Talent: Upskill and Reskill

The [National Strategy for Advanced Manufacturing](#) acknowledged that advanced manufacturing relies on a strong STEM workforce and education system. However, advanced manufacturing technology and career awareness are not given much importance as objectives in popular STEM programs and competitions. Investing in industry-recognized credentials and certifications for emerging manufacturing technologies and fostering collaborations between educators and industry presents a significant opportunity to enhance these programs.

“We can train people. The U.S. universities transitioned from being about 10% online to being 100% online in two weeks at the beginning of Covid-19. There is no question that we can implement training programs, and not just at universities. There are trade groups and organizations, as well as professional trade schools. We could train people,” said Fernando Muzzio, Ph.D., Professor of Chemical Engineering at Rutgers University.

## | Build a Buffer Inventory

Vizient operates a contingency inventory program that may provide insight into how a national model might work. This program, called [Novaplus Enhanced Supply](#), contracts with suppliers to hold up to six months of drug inventory to guarantee support health systems access to product. The Essential Medications List and a demand prediction model are used in determining which drugs are held in contingency. “We started with 11 molecules. We are up to 120 – 130 molecules,” said Kyle Hoelting, Senior Clinical Manager for Drug Information and Shortages at Vizient Center for Pharmacy Practice Excellence.

“To motivate manufacturers to produce more than the market demands, incentives are necessary. A safety net should be in place to prevent manufacturers from incurring losses and wasting products,” said Marcus Lumpuy, U.S. Vice President, Hospital Business Unit, Pfizer Biopharmaceuticals.

## I Diversify Manufacturing Sources

“We should encourage near-shoring, not only production in the U.S.,” said Stephen Schondelmeyer, PharmD, Ph.D., a professor with the College of Pharmacy at the University of Minnesota. “We could increase production in Mexico and Canada, in Chile, Argentina, Brazil, or places like the Dominican Republic or even go back to our own U.S. territory of Puerto Rico. We worry about concentration and need to encourage diversity of production locations. We need to have our drug supply made in multiple places, and we need redundancy. Not just one place, but two or three or four alternatives.”

“A narrow focus on ensuring a primarily domestic pharmaceutical supply chain risks interfering with and damaging existing supply chains, contracts, and relationships thus jeopardizing supply chain capacity and redundancy. Globalization of supply chains can have a protective function. The U.S. is not immune from natural disasters or other problems that can shut down production and cause serious supply chain shocks,” warned Margaux Hall, Greg Levine, Beth Weinman, and Jenna McCarthy, in Bloomberg Law’s blog [Corporate Compliance, Professional Perspective – Potential Costs of Reshoring Pharmaceutical Manufacturing](#).



# Conclusion and Recommendations

In their report, [Innovations in Pharmaceutical Manufacturing on the Horizon](#), the National Academies of Science, Engineering and Medicine acknowledged, “the challenge of modernizing technology is particularly acute for manufacturers of generic and biosimilar drugs.”

The Pathway to Build Supply Chain Resilience for Critical Drugs panel discussions explored these challenges and what technologies could help make possible the Administration’s Bold Goals for U.S. Biotechnology and Biomanufacturing vision to **“produce at least 25% of all APIs for small molecule drugs” in the U.S. within five years.**

To mitigate the risk of relying on China and India for small-molecule APIs, the panel determined advanced manufacturing biotechnologies and biomanufacturing processes must be implemented. Advancements in synthetic biology realized through advanced technology can improve small molecule API manufacturing. The cost to implement these technologies must be addressed. Price erosion and consolidation have had a major impact on the U.S. generic pharmaceutical industry resulting in low profit-margins. A public-private modernization model and leveraging the purchasing power of the federal government through committed contracts, along with federal support for private sector committed contracts, will accelerate the implementation of advanced manufacturing technologies and other aspects of reliable supply chains. Regulatory barriers to implementation should also be addressed and “Made in America” incentives should be applied to enhance market competitiveness.

“I am biased towards technology, but I think some of the answers will lie in there,” said Andrea Adamo, Founder and CEO of Zaiput Flow Technologies. “If you look at the semiconductor industry, for instance, and you look at the rate of progress, you know, it was driven by demand. There were financial drivers that were from the market. But the type of innovation that has been generated in the last 70 years is extraordinarily large. I do not see why some shifts of paradigm in the pharmaceutical industry cannot happen now.”

“My optimism comes from the opportunity that we have as an industry,” said Matt Hancock, Director of Business Management API at Thermo Fisher Scientific. “It has been discussed for quite a while now that the industry as a whole, in terms of new drugs, are certainly shifting in their profile. The blockbuster drug is going away. The new drugs are more focused on smaller patient populations. They are smaller quantities of doses. Correspondingly smaller amounts of API will be needed. Our infrastructure is built more towards blockbusters. As the industry shifts towards these smaller niche type of drugs, there will be a shift in the way infrastructure is built. There is an opportunity to leverage that shift in a way that lends itself to advanced manufacturing.”

The significance of prioritizing small molecules for production cannot be understated. Identifying the most essential APIs will drive alignment with current manufacturing technologies and capacities as well as initial research and development supporting disruptive technologies. Innovations can be made in both realms. Criterion should include past, present and predicted essential medicine shortages, APIs with singular manufacturing sites and those that have experienced site quality issues (including FDA warning letters). Key starting material sourcing, geographical risks, and therapeutic alternatives should also be considered.



The coordinating entity should drive policy and programs that support a pharmaceutical supply chain transparent to all stakeholders. This will allow stakeholders to evaluate the potential risks of supply disruptions and make well-informed decisions regarding contracting, purchasing, and inventory management. Stakeholders should see a drug's origin, and the origin of associated key starting materials and APIs. Furthermore, the incorporation of quality and reliability scores is essential in leveraging this information to mitigate risks. This endeavor is well-positioned for digital transformation, harnessing disruptive technologies like artificial intelligence and machine learning to enhance the efficiency and transparency of the U.S. pharmaceutical supply chain.

Rebuilding and sustaining the U.S. generic pharmaceutical supply chain must bring the greatest benefit to the single most important stakeholder, the patient. The patient absorbs 100% of the risk; they are the most vulnerable to the impact of supply disruptions and the least able to do anything about it.

## I Recommendations

- Public incentives must be established to encourage API manufacturers to adopt advanced manufacturing technologies.
- Industry should leverage existing technologies while furthering research and development of innovative and disruptive technologies, in partnership with academia and government.
- A single public entity should coordinate the public-private partnerships established as part of a national strategy.
- The coordinating entity should direct prioritization of small molecules for production. Identifying the most essential APIs will drive alignment with current manufacturing technologies and capacities as well as initial research and development supporting disruptive technologies.
- The coordinating entity should drive policy and programs that support a pharmaceutical supply chain transparent to all stakeholders.
- Identifying a subset of APIs for initial deployment would yield invaluable insights that further propel the nation towards achieving the 25% goal.

**“We have the ability to do this. We can solve this through innovation and through new tools.”**

William Foley, MBA, Process Analytics, Subject Matter Expert

## I Next Steps

### **Immediate Actions:**

A clear and incremental strategy needs to be established to achieve the Bold Goal of reshoring 25% of APIs in 5 years and address the domestic production of APIs. The U.S. must take tangible steps that the various parties that comprise the drug supply chain can agree on to drive the country toward its goal. A strategic approach that the U.S. could consider is convening an entity or agency to determine a specific number of APIs and their key starting materials to reshore and establish grants and funding mechanisms to achieve this objective. Other specific considerations include:

- Designate a coordinating entity or agency to develop a national strategy to secure the U.S. drug supply chain, specifically focused on critical and essential drugs. The newly announced HHS Supply [Chain Resilience and Shortage Coordinator](#) could potentially lead this entity or agency.
- Consider incorporating a public-private partnership as part of the entity or agency to ensure that the voice of government, industry, and patients are represented in strategy development.
- The Administration and Congress should designate a funding stream for the entity or agency, focused on key objectives, including developing a national strategy, providing transparent oversight of the full pharmaceutical supply chain, developing incentives for manufacturing essential and critical pharmaceuticals, and reviewing current statutes, agreements, and regulations that may hinder reshoring efforts and consider new actions that will encourage reshoring activities.

### **Short-Term Actions:**

Immediate actions to address reshoring efforts will inform and assist in establishing “incremental” steps leading to short-term actions. During this time, consolidation of resources, implementation of new recommended investments, and long-term strategic preparedness activities can take effect, including:

- Building a flexible U.S. critical drug list informed by public-private drug supply stakeholders and maintained by the coordinating entity or agency. The list should consider access to generic drugs in shortage or high risk of shortage, funding for data sharing technology upgrades, development of federal policy to authorize data sharing, and multi-stakeholder consensus on a critical drug priority list.
- Building a government-funded critical drug buffer inventory that includes pharmaceuticals that would be detrimental to the U.S. if in shortage. The inventory should have dedicated fund management and distribution of inventory systems.
- Building U.S. API manufacturing capacity through selective incentives that consider granular visibility of U.S. API manufacturers' current capacity, selecting APIs for batch or continuous processing, and funding short-term manufacturing technology upgrades.

### **Long-Term Actions:**

The immediate and short-term actions set the stage for a long-term strategy to secure the U.S. drug supply chain in subsequent years. The following actions can be taken to implement these strategies:

- Select manufacturers for API continuous processing technology upgrades to maintain the latest innovations in advanced manufacturing.
- Design a sustainable, long-term drug supply chain management plan that utilizes a holistic approach to the pharmaceutical supply chain, including diversification plans for key starting materials and API to prevent over-dependence on a single source.

A comprehensive approach of the U.S. government, including the appointment of a coordinating entity, establishment of new funding lines, and rigorous review of regulatory authorities and policies, is imperative in implementing the incremental steps mentioned above. Improving our national health security requires significant mitigation of risk by creating a diversified manufacturing base and distributed buffer inventories that will help ensure Americans reliable access to essential medications.

# Biosketches

## | API INNOVATION CENTER

**Tony Sardella, MBA.** Chair, API Innovation Center. Mr. Sardella oversees the Center's commitment to strengthen the U.S. domestic drug supply chain and global competitiveness while reducing manufacturing costs. In addition, he is an Adjunct Professor at the Olin Business School at Washington University in St. Louis and Senior Advisor to the University's Center for Analytics and Business Insights. Mr. Sardella is a toxicologist by training and has authored or co-authored over 25 papers in human health and environmental risk assessment prepared on behalf of government agencies and non-governmental scientific bodies. He also serves as Vice Chair of evolve24, a St. Louis data science firm he founded in 2004. He earned his MBA at Northwestern University.

**Kevin Webb, MBA.** Chief Operating Officer, API Innovation Center. Mr. Webb leads efforts at a national level to strengthen domestic pharmaceutical manufacturing in the United States. Mr. Webb is a highly respected and trusted representative of the pharmaceutical industry. A thirty-year veteran of the healthcare community, he has broad, cross-functional technical expertise in government affairs, communications, manufacturing, operations, sales, and brand management. Prior to the API Innovation Center, he held leadership roles at Mallinckrodt Pharmaceuticals, Sanofi Pasteur Vaccines and Memorial Medical Center, a tertiary health center in Central Illinois. He holds an MBA from the University of Illinois and a Bachelor of Science from St. Louis University.

## | MODERATORS

**Adam Fisher, Ph.D.** Director, Science Staff, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA). Dr. Fisher specializes in advancing pharmaceutical manufacturing technologies at the FDA. In his capacity, he has served as a primary and secondary reviewer of Abbreviated New Drug Applications (generics) and Drug Master Files, team lead, and subject matter expert and other areas instrumental in FDA operations. His background includes co-founding a biotech startup and holding a Ph.D. in chemical and biomolecular engineering from Cornell University. He brings significant expertise to FDA initiatives.

**Kurt Karst, J.D.** Hyman, Phelps & McNamara, Co-founder of the FDA Law Blog. Mr. Karst provides regulatory counsel to pharmaceutical manufacturers, specializing in Hatch-Waxman patent and exclusivity, drug development, and pediatric testing. He aids clients in product lifecycle management, approval strategies, post-marketing issues, and exclusivity periods. He is a prolific writer and legal expert, offering insights into FDA precedents and regulations and timely updates on enforcement actions and proposed rules as co-founder of the FDA Law Blog. He received a Fulbright Scholarship for post-graduate studies in Germany and has co-authored textbooks.

## I PANELISTS

**Dr. Andrea Adamo, Ph.D.** Founder and CEO, Zaiput Flow Technologies. Dr. Adamo is the developer of core technologies at Zaiput Flow Technologies and serves as an Innovation Advisor at Snapdragon Chemistry. With a background in engineering, he has excelled in continuous flow chemistry and microfluidic system design and manufacturing. His expertise also lies in developing groundbreaking engineering solutions.

**Stephen Colvill, MBA.** Assistant Research Director, Duke-Margolis Center for Health Policy. Mr. Colvill leads the launch of the Duke-Margolis ReVAMP Drug Supply Chain Consortium. He also serves as the Executive Director of RISCS, a nonprofit drug supply chain rating and certification organization dedicated to preventing drug shortages. With previous experience at Pfizer and Hospira in supply chain, manufacturing, finance, marketing, portfolio management, and business analytics, he brings extensive expertise to address pharmaceutical supply chain and drug shortage issues.

**Laura Bray, MBA.** Chief Change Maker, Angels for Change. Ms. Bray leads a global, volunteer-driven nonprofit founded in 2019 with a mission to combat drug shortages. Inspired by her daughter's pediatric cancer journey, she champions a resilient supply chain to ensure patients don't face life-saving drug shortages. Her advocacy has connected patients and facilities during crises, increased supply access, and fostered multi-stakeholder engagement. She initiated the SummitONE supply chain conference, co-launched the End Drug Shortage Alliance, participated in the NASEM drug shortages report, and testified before Congress as an expert witness.

**William Foley, MBA.** Process Analytics, Waters Corporation. Mr. Foley, with over 35 years in the technology industries, leads cross-functional projects for new technology adoption. His recent work focuses on introducing process analytical technologies in biopharma and pharma development. He has successfully led projects conducting technology assessments for acquisitions and bringing real-time liquid chromatography into manufacturing for specialty measurement applications.

**Andrew Gonce, MBA.** Vice President, Commercial and Strategy, Mallinckrodt Pharmaceuticals. Mr. Gonce heads commercial, business development, and strategy for Mallinckrodt Specialty Generics, a leading U.S. producer of essential medicines with the largest API plant in the nation. Before joining Mallinckrodt in 2019, he spent a decade at McKinsey & Co., driving operational, supply chain, and quality improvements in global pharma factories.

**Dennis Hall, MBA.** Vice President, Advanced Manufacturing Technologies, U.S. Pharmacopeia. Mr. Hall leads a team focused on identifying and deploying advanced manufacturing and analytical technologies in the biopharmaceutical industry. His work encompasses standards, R&D, consulting, and government-sponsored supply chain solutions. With a key leadership role at USP since 2001, he has been instrumental in strategy, marketing, and global expansion for product development.

**Dr. Matt Hancock, Ph.D.** -Director, Business Management API, Thermo Fisher Scientific. Dr. Hancock, an industry veteran with over 20 years of experience in pharmaceutical development and manufacturing, currently serves as the Business Management Director for API at Thermo Fisher Scientific. His specialization lies in small molecule API manufacturing, amorphous spray drying, and sterile fill-finish processes.

**Kyle Hoelting, PharmD, BCPS.** Senior Clinical Manager, Drug Information and Shortages, Vizient Center for Pharmacy Practice Excellence. Dr. Hoelting's primary focus areas include management of drug shortages, the essential medications report, and clinical support for the Novaplus Enhanced Supply program and sourcing opportunities. Dr. Hoelting leads various Vizient initiatives related to drug shortages, including shortage mitigation strategies, the Member Drug Shortage Mitigation Group, and the Shortage Surveillance & Readiness Team.



**Marcus Lumpuy.** U.S. Vice President, Hospital Business Unit, Pfizer Biopharmaceuticals. Mr. Lumpuy oversees and manages GPO, Hospital, Specialty Pharmacy, and Trade Distribution contracts. With over three decades of experience at Pfizer, he held diverse leadership roles in sales, contracting, operations, and training, including a significant tenure leading the U.S. Sales Organization for the Hospital Business Unit.

**Fernando Muzzio, Ph.D.** Professor of Chemical Engineering, Rutgers University. Dr. Muzzio has dedicated the last two decades to pharmaceutical product and process design. His research spans various areas, including continuous manufacturing, powder handling, and capsule filling. Dr. Muzzio, with over 260 research papers, contributes to FDA events and serves as a voting member on the FDA committee for Pharmaceutical Sciences and Clinical Pharmacology. He also serves as the director of the National Science Foundation Engineering Research Center.

**Ed Price.** Former CEO, PCI Synthesis. Mr. Price served as the CEO of PCI Synthesis, a leading Pharmaceutical CDMO, which was the largest small molecule drug substance manufacturer in New England. With 25 years of CDMO experience, he now serves as a Small Molecule Life Science Consultant, aiding private equity firms and emerging pharma companies in CDMO engagement, project evaluation, and organizational development.

**Karthik Raghavan.** Founder and Chief Executive Officer, Sentio Biosciences. Karthik Raghavan is the founder and CEO of Sentio Biosciences LLC, a St. Louis-based pharmaceutical development and manufacturing company specializing in API and drug product development. With two registered drugs in the market and an active pipeline, he operates an innovative API manufacturing model, with focus areas that include antiparasitics, osteoarthritis, anti-inflammation, and oncology.

**Stephen Schondelmeyer, PharmD, Ph.D.** Professor, University of Minnesota, College of Pharmacy. Dr. Schondelmeyer serves as Co-Director of the Resilient Drug Supply Project (RDSP) which has demonstrated proof-of-concept for an upstream drug supply map and its application in addressing drug supply issues, drug shortages, and national security implications. He is an expert in pharmaceutical policy and economic analysis, particularly in areas like prescription drug reimbursement under various government and commercial programs. He was appointed to the Prescription Drug Payment Review Commission and has conducted research projects for entities such as CMS, GAO, and FDA. With a unique background spanning pharmacy practice, reimbursement, pricing, and more, his expertise influences the evolving pharmaceutical landscape.

**David Thompson, Ph.D.** Co-Founder and Chief Technology Officer, Continuity Pharma. Dr. Thompson is a Professor of Chemistry at Purdue University, where he led the Organic Chemistry Division and Center for Cancer Research- Medicinal Chemistry group. He has spearheaded research in high-throughput experimentation and continuous synthesis of API using flow chemistry methods. Dr. Thompson has authored over 170 peer-reviewed publications, 10 patents, and is the co-founder of Continuity Pharma.

**Dr. Bayan Takizawa, M.D.** Co-Founder and Chief Business Officer, CONTINUUS Pharmaceuticals. Dr. Takizawa is instrumental in CONTINUUS Pharmaceuticals' business development and strategy. His achievements include securing substantial contracts and raising substantial funds for the development of Integrated Continuous Manufacturing (ICM) facilities, and most recently securing a multi-million-dollar contract from the U.S. Department of Defense to establish an Integrated Continuous Manufacturing facility in the U.S.

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