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# Overcoming Global Risk to the Pharmaceutical Supply Chain for the United States: Achieving Pharmaceutical Independence by Reshoring Manufacturing Capacity and Capability

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## Executive Summary

During the past three decades, entire manufacturing sectors have largely moved overseas. This is particularly prevalent in the manufacturing of Active Pharmaceutical Ingredients (APIs) and also, to a considerable degree, finished pharmaceutical products. By recent estimates, more than 80% of all APIs consumed in the US are currently manufactured overseas, predominantly in China. There is a rapidly growing national consensus that such dependence on imports of critical medical materials places the population of the United States at risk[1].

This document outlines a strategy for mitigating the risk to the US pharmaceutical supply chain, based on four interconnected priorities:

- Priority 1: Create a consensus process to identify and prioritize the fifty (50) most critical drug products that are affected by supply chain risk.
- Priority 2: Use of automated retrosynthetic procedures, in conjunction with models of the medicines supply chain, to identify new synthesis pathways based on domestically sourced chemical building blocks.
- Priority 3: Implement, demonstrate, scale up, register, and transfer to the commercial manufacturing environment new processes for US-based manufacture of each API in Priority 1 in a compliant environment.
- Priority 4: Develop new product formulations and manufacturing processes for each of the drug substances (APIs) on the critical list. These processes will be demonstrated, scaled up, registered, and transferred to commercial manufacturing.

[1] Senate Majority Report: Short Supply - The Health and National Security Risks of Drug Shortages, March 2023.

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## The Problem: The Pharmaceutical Supply Chain is Highly Vulnerable

It is common knowledge that, during the past 30 years, entire US manufacturing sectors largely moved overseas. One area where this is prevalent is in the manufacturing of Active Pharmaceutical Ingredients APIs) or "drug substances" -- and also, to a considerable degree, finished pharmaceutical products. Drug substances are the therapeutic components of drug products. By some recent estimates, more than 80% of all APIs consumed in the US are currently manufactured overseas, predominantly in China or, to a lesser extent, in India[2].

It's difficult to imagine or quantify the impact on the health of the US population if a major disruption of international commerce were to disrupt the United States' ability to import APIs and finished pharmaceutical products. Since the Pharmaceutical industry only keeps about 75 days of inventory at hand[3], the domestic supply of many life-saving drugs would be exhausted in a matter of weeks, grinding the pharmaceutical industry to a standstill. Such an event could cause massive loss of life, as millions of US citizens would lack access to drugs required to keep them alive, including hundreds of substances that are critical to maintaining the lives of many of our citizens afflicted by heart disease, metabolic conditions, HIV, cancer, infectious diseases, and many other potentially fatal conditions.

Importantly, at present, we not only lack much of the industrial capacity to replace API imports, but we also have lost much of the know-how needed to make these substances. Recreating this capacity from scratch would require several years of sustained efforts, a process that would be further delayed by our current lack of an implementation and prioritization plan.

## A Strategy for Mitigating the Risk to the US Pharmaceutical Supply Chain

Overcoming the current situation requires meaningful action in the following directions:

- The obvious starting point is to reach a consensus regarding priorities. The current list of approved medicines comprises more than one thousand APIs. This list needs to be prioritized to enable efforts to be focused on creating reliable sources of the most critical drug substances and finished drug products.
- A similar analysis is needed for pharmaceutical excipients (e.g., non-active ingredients). All effective medicines involve a combination of drug substances and excipients structured into products with the required performance attributes. Most modern excipients are entirely or partially synthetic and could also be in shortage; ensuring the availability of critical excipients required to formulate and manufacture medicines is as critical as ensuring the supply of drug substances.
- For both API and excipients, we need to determine new synthetic pathways (the sequence of reaction steps involved in transforming raw materials into a target molecule) that enable us to source these materials using chemical building blocks that are manufactured in the US or closely allied countries. In evaluating alternative pathways to manufacture essential APIs and excipients, we can also build efficiency and environmental and economic sustainability into these updated, advanced manufacturing processes.
- Once such synthetic pathways are determined, they need to be implemented, characterized, scaled up, and optimized to enable suppliers to implement these processes at scales sufficient

[2] Socal, M. P., Ahn, K., Greene, J. A. & Anderson, G. F. Competition and Vulnerabilities in The Global Supply Chain for US Generic Active Pharmaceutical Ingredients. Health Aff. 42, 407–415 (2023).
[3] T. Foster, P. Patel, and K. Skiba, Four Ways Pharma Companies Can Make Their Supply Chains More Resilient, McKinsey report, September 2021, https://www.mckinsey.com/industries/life-sciences/our-insights/four-ways-pharma-companies-can-make-their-supply-chains-more-resilient

to source the US and its allies. The APIs and excipients produced by these methodologies need to be registered with the FDA to enable their utilization in manufacturing medicines.

- The APIs need to be formulated into drug products (i.e., therapeutically effective medicines). Manufacturing processes for such finished products need to be implemented, characterized, scaled up, and approved by the FDA so that they can be used by pharmaceutical manufacturers to produce medicines that can be dispensed to US patients.

These activities can be structured as a portfolio of four synergistic priorities, described below:

**Priority 1: Creating a Prioritized List of Critical APIs and Excipients**

Medicine is produced using active pharmaceutical ingredients (API) in a manufacturing process that begins with Regulatory Starting Materials (RSM). The United States has outsourced a significant portion of the pharmaceutical supply chain, including RSMs. As of 2021, India and China were top API manufacturers, producing 62.1% and 22.0% respectively of all generic medications.[4] Additionally, the US is susceptible to upstream supply chain disruptions to API manufacturing, particularly in the case of RSM and other intermediate chemicals. For example, nearly 80% of the RSM required for API synthesis in India is imported from China, thus further compounding the potential risks associated with the supply of necessary medications.[5]

As of March 2023, the FDA National Drug Code (NDC) Drug Directory contains 106,241 Unique Drug Products across all categories of drug classifications, including new drug applications (NDA), abbreviated NDA (ANDA), and over-the-counter (OTC) monographs. Associated with these drug products are 8,733 unique APIs. There are 44,157 generic drug products (ANDA and NDA Authorized Generic) for which there are 1,188 APIs. By leveraging public and private information, data science, and automation, it is possible to identify the commercial synthetic routes and regulatory starting materials for any given portfolio of drug substances, such as the FDA Drug Shortages List[6], the Top 500 Drugs[7] by prescription volume (2020), the WHO Essential Medicine List[8] - or the entire collection of all API registered for use in the United States.

This Priority will:

1. Build a consensus regarding a prioritized list of critical and live-saving medicines that must be supplied from new, predominantly domestic sources, considering the availability of alternative treatments, the severity of impact on both the patient and health care system for going off treatment, the size of the patient population, and the impact of untreated populations on disease transmission.
2. Map the supply chain of these APIs and the associated RSMs.
3. Create a risk score that contemplates manufacturing location and materials sourcing.
4. Assess supply shocks associated with geopolitical instability or other supply distresses.

Many tools are available to perform this work. Multiple entities, including the FDA and the AMA, have already created "critical medicine" lists. Multiple organizations, including Virginia Commonwealth University, the University of Minnesota, and USP, have developed tools for supply

[4]Socal, M. P., Ahn, K., Greene, J. A. & Anderson, G. F. Competition and Vulnerabilities in The Global Supply Chain for US Generic Active Pharmaceutical Ingredients. Health Aff. 42, 407–415 (2023).
[5] U.S.-China Economic and Security Review Commission. Section 3: Growing U.S. Reliance on China's Biotech and Pharmaceutical Products. 248–282 (2019).
[6] https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm
[7] Kane SP. The Top 300 of 2020, ClinCalc. Drug Stats Database, Version 2022.08. ClinCalc: https://clincalc.com/DrugStats/Top300Drugs.aspx. Updated August 24, 2022. Accessed April 27, 2023.
[8] World Health Organization. (2021). World Health Organization model list of essential medicines: 22nd list (2021). World Health Organization. https://apps.who.int/iris/handle/10665/345533. License: CC BY-NC-SA 3.0 IGO

chain analysis. All of this work will provide valuable data in assessing and prioritizing the list of critical medicines to reduce dependencies outside of the US.

*Priority 1 will establish a consensus list of critical APIs and excipients needed to source the US market with its most important medicines and a realistic analysis of supply chain risks and alternatives for each of them.*

**Priority 2: Retrosynthetic Analysis to Determine Feasible Alternative Pathways to Critical APIs and Excipients Using Domestically Sourced Key Starting Materials**

The transformation sequence from raw materials to a target molecule is called the synthetic route. Manufacturing of a chemical target relies on a supply of raw materials (resources), knowledge of the reaction (transformation) conditions, the facilities (capital asset collections) to enable production, and the ability to analyze accurately and release the manufactured intermediates and API for utilization. A chemical target may have many possible synthetic routes with different sets of raw materials. The possible synthetic routes for creating a target molecule can be obtained through automation-assisted retrosynthetic analysis. In the analysis, precursor chemicals are identified that can be transformed into the target according to plausible reaction selection rules. When the precursors are available in the free market, these can be purchased. When they are unavailable for purchase, the precursors can be further decomposed into simpler chemical building blocks, transformation by transformation. When all plausible precursors are traced recursively back to building blocks, a tree of all synthetic routes can be constructed.

Creating a portfolio synthetic plan requires selecting a synthetic path for each target. A retrosynthetic analysis will generate the full trees of possible synthetic paths for each of the targets in a manufacturing portfolio. Each target molecule may have hundreds of synthetic paths available, resulting in a combinatorial explosion of manufacturing options when considering a portfolio of targets jointly. Since many paths are possible, other considerations can be included to optimize for portfolio-wide objectives. The search for the optimized synthetic plan is carried out through in-depth analysis and pruning of sub-optimal synthetic paths, algorithmic targeted sampling of the combination space, and evaluation of portfolio metrics.

It is possible to identify the collection of synthetic routes for the portfolio that simultaneously:

1) Maximizes the use of domestically available raw materials,
2) Minimizes the breadth of inventory required to manufacture the portfolio, and
3) Optimizes the total route (e.g., cost, sustainability, and other metrics.)

Additionally, it is also advantageous to identify the key chemical transformation that enables the largest improvements to the objectives above.

Priority 2 will focus on the assessment of the domestic manufacturability of high-risk API and excipients. Manufacturability can be assessed by comparing the manufacturing requirements of a target molecule (e.g., RSM) with domestic asset availability. Manufacturing requirements are derived from synthetic chemistry and separations/workup procedures. Synthetic chemistry procedures can be generated by AI tools based on molecular features of the target molecules in a chemical reaction. To explore the manufacturability of each RSM, databases, and tools such as Reaxys, ASKCOS, and

custom automation[9,10,11] will utilize AI-assisted retrosynthetic analysis and reaction databases to create a large number of potential routes to each RSM. Despite progress in AI-assisted retrosynthetic analysis, there are no tools that have been developed to predict or infer separation/workup procedures from a prospective organic reaction. Occam (or other available tools) will be expanded to leverage the procedures in the reaction databases, create templates of the molecules to be separated, and use these templates with the reported separation procedures to create an AI-assisted framework to infer or predict a separation procedure for an unknown reaction, considering also the potential of a different synthetic route to generate new impurities that must be detected, quantitated, and separated from the desired product. When all manufacturing requirements for a manufacturing route are established, real-time bulk costs for Key Starting Materials (KSM) and other necessary materials such as solvents and catalysts will be obtained from integration to customs and import data services. Using automation, potential routes will be assessed and ranked by manufacturability (e.g., process conditions and hazards), environmental sustainability, and cost. Domestic availability of capital equipment assets can be assessed by synergistic automation developed in other efforts.

*Priority 2 will establish a set of alternative synthetic routes for every API in the target list and for the key excipients required to compound them into finished pharmaceutical products.*

## Priority 3: Demonstrate, Scale Up, and Transfer to Industry the Synthetic Pathways Developed in Priority 2

Legacy API processes are frequently carried forward into the product lifecycle post-patent expiration, impacting the cost structure of many generic drugs. In many cases, the API cost represents 65 to 75% of the total drug product cost.[12,13] As a result, sub-optimal synthetic routes can have a major impact on the availability of these medicines. In the case of the domestic healthcare supply, the resulting manufacturing costs often cause drug shortages, in particular by reducing the project margins of generic manufacturers and contributing to the ensuing difficulty in modernizing manufacturing facilities.

We and others have demonstrated that new approaches using state-of-the-art chemical methods and novel reactor platforms can yield significant improvements in API production costs and efficiency. Based on these observations, we have established a set of core principles for API process development, which are derived from fundamental elements of process intensification that are commonly known but often neglected. These principles include (a) implementation of innovative chemical methodologies and new manufacturing platforms, (b) consolidation of high-yielding reactions into a minimal number of unit operations with common solvents and limited intermediate isolations, and (c) vertical integration of advanced starting materials prepared from commodity chemicals.

In this initiative, these principles will be used to demonstrate and scale up the alternative synthetic manufacturing processes identified in Priority 2 in a compliant environment, and to transfer them to

[9] Ishida, S.; Terayama, K.; Kojima, R.; Takasu, K.; and Okuno, Y.; Journal of Chemical Information and Modeling 2022 62 (6), 1357-1367. DOI: 10.1021/acs.jcim.1c01074, AIChE Journal, May 2023 https://doi.org/10.1002/aic.18114

[10] Coley, C. W.; Green, W. H.; Jensen, K. F. Machine Learning in Computer-Aided Synthesis Planning. Acc. Chem. Res. 2018, 51, 1281–1289, DOI: 10.1021/acs.accounts.8b00087, Reaxys. https://www.reaxys.com/, 2020 (accessed 2020-12-16).

[11] Le, Q .; Feingold, J .; Glandorf, W .; Kent, J .; Sherman, R .; Ferri, J.K.; Model-based systems engineering approaches to chemicals and materials manufacturing.

[12] Teoh, S. K.; Rathi, C.; Sharratt, P. Practical assessment methodology for converting fine chemicals processes from batch to continuous. Org. Process Res. Dev. 2016, 20 (2), 414– 431, DOI: 10.1021/acs.oprd.5b00001

[13] Bana, P.; Örkényi, R.; Lövei, K.; Lakó, Á.; Túrós, G. I.; Éles, J.; Faigl, F.; Greiner, I. The route from problem to solution in multistep continuous flow synthesis of pharmaceutical compounds. Bioorg. Med. Chem. 2017, 25 (23), 6180– 6189, DOI: 10.1016/j.bmc.2016.12.046

industry for commercial operations. Critically, new analytical tests are often required for new routes, in particular, to detect and quantify new (and often unknown) impurities, and the reliability and performance of analytical testing can often be as challenging as the scale-up of the manufacturing process. Replacing an API route requires verification that the impurity profile is equivalent or superior to the purity profiles used in clinical trials. Implementing a new, more efficient API route requires proving the equivalent safety of the API generated at scale.

A key strategic consideration essential to accomplish the implementation of alternative commercial manufacturing routes is to promote technology alignment among the development laboratory and pilot plant and the commercial manufacturing facility. The more closely aligned these systems are in terms of design and operating principles, the faster and easier it is to scale up the process and transfer it from development to manufacturing. In fact, if sufficient information is collected at the development scale regarding the chemical reactions and separation processes required to make the product, the scale-up and technology transfer procedures can be greatly facilitated by the extensive use of process modeling software. Lastly, a focused effort to use and develop official USP quality standards and best practice guidelines in parallel with developing alternative commercial manufacturing routes will result in reduced time to scale up and– as much as 19% reduction in total product development time[14] – and facilitate FDA approval.

This approach will leverage the existing infrastructure at US-based organizations. Resources will be needed to fill gaps and to upgrade existing hardware to equip it with sensors, model-based control systems, and a sufficient level of automation to ensure its ability to perform competitively in the future.

This initiative will proceed based on the following tasks:

1) Inventory domestic capabilities available in the specialty and fine chemicals and pharmaceuticals manufacturing facilities. Inventory commercial equipment configurations at API manufacturing firms that can be used to implement API and excipient manufacturing processes.
2) Implement a highly flexible, advanced pharmaceutical manufacturing pilot facility able to accommodate any of the equipment configurations available in the industry.
3) For each API and synthetic excipient of interest, implement an appropriate bench-top synthesis and separation process, and develop this process for commercial manufacturing. If necessary, modify the alternative synthetic pathway. Once a feasible pathway is determined, optimize the solvent selection, reaction conditions, and other parameters. Determine all physical and chemical information required to scale up the process.
4) For each API and synthetic excipient of interest, once a feasible pathway is demonstrated at the bench scale, use advanced simulation to establish an appropriate pilot scale process.
5) For each API and synthetic excipient of interest, assemble the pilot-scale laboratory and perform tests required to validate model predictions. Identify and minimize impurities generated by the process. Utilize the validated model to determine the conditions required to implement the process at the commercial scale.
6) Develop suitable Technology Transfer protocols to support implementation in commercial equipment. Support the implementation of new equipment, instrumentation, and automation, as required by each process. Support technical work required at the commercial manufacturing site to ensure compliance of the process with impurity profile requirements. Support

[14] Warthin, IK; Berik, J; Podolsky, D; Raghavendran, V.; Reddy, R.; Chang, J.; Porter, N.; Garito, N. Commentary on the Benefits of US Pharmacopeial Standards: A Generic Pharmaceutical Industry Survey. J Pharm Sci. 2020 Feb;109(2):944-949. doi: 10.1016/j.xphs.2019.10.008. Epub 2019 Oct 10. PMID: 31606539.

compilation of Drug Master File documentation to enable filing with regulatory authorities and subsequent commercialization.

*Priority 3 will establish a set of manufacturing processes for every API and excipient in the critical list, entirely based on domestically sourced starting materials.*

**Priority 4: Create a Platform for Rapid Development, Scale Up, Manufacturing, and Technology Transfer.**

Drug substances must be compounded into finished products with the desired functionality to become medicines that can be dispensed to people. This compounding process, when performed at scale, is required to generate a large number of product units with the desired quality attributes. For solid dose products, this typically required blending the drug substance with multiple ingredients, processing in wet or dry form, often with the goal of modifying attributes of the blend of drug material and excipients, and then compressing the final blend into tablets or filling it into capsules. This situation describes the great majority of small molecule products at risk of supply chain shocks.

Fortunately, there is a large amount of manufacturing capacity that can be used to perform this second stage of the manufacturing process. However, because drug substances generated as a result of Priority 3 may have different physical properties than the materials currently used, and because many excipients will need to be replaced by other materials, it will be necessary to *reformulate* each of these products; to create new manufacturing processes for each of them, and to obtain regulatory approval for their commercial manufacture and distribution.

As in Priority 3, we propose to work closely with commercial manufacturers to ensure technology alignment and rapid technology transfer. We plan to leverage the very rapid product and process development capabilities of continuous manufacturing systems to enable rapid product reformulation. Whenever possible, we also propose to upgrade commercial manufacturing systems to enable them to perform 100% real-time quality assurance of finished products. We believe implementing highly capable quality control systems should facilitate and expedite regulatory approval, avoiding delays in implementing the alternative product sources described here. As with Priority 3, the use of existing official USP standards and the development of new platform-specific USP standards and best practice guidelines for quality control for these new formulations can reduce the overall time required to scale finished dosage manufacturing. Specifically for the development and approval of finished formulations, this reduction in time can be as much as 26%[14].

To implement new manufacturing processes at the commercial scale, this initiative will focus on the following sequence of tasks:

1. Survey the capabilities available in the industry. Inventory commercial equipment configurations available for finished product manufacturing at contract manufacturing firms that can be used to implement API and excipient manufacturing processes.
2. Implement a highly flexible continuous manufacturing line to enable very rapid development of product formulation and manufacturing processes.
3. Implement a highly flexible pilot plant facility able to enact any of the equipment configurations available in the industry (e.g., at CMOs) for the processes required to manufacture each product.
4. For each API of interest, use the continuous line to create a new formulation capable of achieving the critical quality attributes of the product. Use the continuous line also to create an analytical methodology able to monitor in real-time as many critical quality attributes as possible. Emphasize quality control methods based on the final compounding step (i.e., tablet compression or capsule filling) as these process components are the same in continuous and batch manufacturing and therefore enable migration of the process analytical methodology.

5. For each API of interest, once a new formulation, manufacturing process, and analytical methodology have been determined in the continuous system, translate the process to a batch manufacturing system operating at the pilot scale. Migrate the quality system developed in the continuous line to the batch process. As necessary, adjust the manufacturing process and/or the analytical method to enable real-time quality control of the product stream.
6. For each API of interest, develop suitable Technology Transfer protocols to support implementation in commercial equipment (e.g., at a CMO). Support the implementation of new equipment, instrumentation, and automation, as required by each process. Support technical work required at the commercial manufacturing site to ensure compliance with the process quality control requirements. Support compilation of regulatory documentation (ANDA, PAS, etc.) to enable filing with regulatory authorities and subsequent commercialization.

For each API and excipient in the target list, we estimate that the work required to develop, scale up, and transfer each new formulation will require approximately six months. However, bioequivalence studies and stability testing can add a substantial amount of time to this timeline. Since most of the products considered here are likely to be generic drugs with well-known safety profiles, a waiver of in-vivo BE and long-term stability studies (or alternative, allowing to perform these studies concurrently) would be a major factor in reducing the overall timeline.

*Priority 4 will establish a set of manufacturing processes for sourcing the US market at the commercial scale for every finished product in the critical list, entirely based on domestically sourced starting materials and excipients.*

**Overall Organization and Management of the Proposed Program**

The complexity and breadth of the overall effort required to develop domestic sources of materials and to formulate and manufacture finished products for a meaningful number (>50) of critical medicines will necessitate a governance structure capable of involving many key contributors. We propose to create a non-profit corporation (NPC) that will be the main program management entity. The NPC will recruit personnel with ample industrial experience managing contract development and contract manufacturing activities. The NPC will be responsible for the development of a detailed project plan inclusive of a realistic cost- and time estimation of each activity required by the proposed initiatives. The NPC will contract activities with Universities and Companies capable of performing the required work. The NPC will report to the government and a board designated by the government and the main participating organizations. The time for action is now.

**About NIPTE**

The National Institute for Pharmaceutical Technology and Education (NIPTE) is a non-profit academic organization of 17 US universities that collaborate with industry, academia, and government to improve the way medicines are designed, developed, and manufactured to meet the needs of patients. The current membership includes Duquesne University, Illinois Institute of Technology, Long Island University, Purdue University, Rutgers University, Texas A&M University, University of Connecticut, University of Kansas, University of Massachusetts, University of Maryland, University of Michigan, University of Minnesota, University of Mississippi, University of Puerto Rico, University of Rochester, University of Texas at Austin, and Virginia Commonwealth University. For more information see http://nipte.org.

**Biographical Sketches**

Dr. Fernando Muzzio is a Distinguished Professor of Chemical and Biochemical Engineering at Rutgers University, and the Director of C-SOPS, a National Science Foundation Engineering Research Center focused on pharmaceutical product and process design.

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Dr. James Ferri is Associate Chair and Professor in CLSE at VCU. His research leverages multi-discipline methods and tooling ranging from information architecture (IA) and model-based systems engineering (MBSE) to expert artificial intelligence (AI) for product and process lifecycle including design, development, and manufacturing operations.

Dr. Vadim J. Gurvich is the Executive Director of the National Institute for Pharmaceutical Technology and Manufacturing (NIPTE), Associate Director of the Institute for Therapeutics Discovery and Development, Director of Therapeutic Process Development, and Research Associate Professor of Medicinal Chemistry at the University of Minnesota.