Increasing Domestic Resiliency in the Supply of Essential Active Pharmaceutical Ingredients

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Introduction: Increasing domestic resiliency in the supply of essential active pharmaceutical ingredients

Small molecule Active Pharmaceutical Ingredients (APIs) are the therapeutic active ingredients in drugs that are formulated into tablets, capsules, injections and so on. Over decades, API production has become a truly international endeavor: about 54% of the world's manufacturing facilities are in the U.S. or E.U., with another 18% in India and 13% in China. Over the past several years, drug shortages in many regions have led to significant supply disruptions, and during the Covid-19 crisis, border closures and other logistical challenges revealed supply chain vulnerabilities that could threaten the availability of APIs, interrupt pharmaceutical manufacturing and put patients at risk. Gaps in API supplies and a spike in demand during the pandemic led to shortfalls of hydrocortisone, for example.

The International Society for Pharmaceutical Engineering (ISPE), in keeping with its vision and mission and to provide solutions to complex pharmaceutical industry challenges and enhance efforts to develop, manufacture and reliably deliver quality medicines to patients, has produced this report in response to a request from a U.S. federal agency. The report lays out technical, regulatory and workforce changes that stakeholders in any country or region could consider to reduce the risks of API shortages to meet demands for essential medicines at any time, but particularly in pandemics and other emergencies.

Building a more resilient API supply chain in any country could include a combination of steps, such as enhancing existing manufacturing and building new capacity, improving logistics, stockpiling specific APIs and strengthening communication channels with API manufacturers and other trusted trade partners. Because each API has unique properties and manufacturing requirements, industry and regulators would likely need to agree on a unique strategy for each essential API.

In the regulatory framework in any market, quality and compliance are prime considerations. Indeed, quality deficiencies have been major factors in shortages of medicines, especially APIs sourced in areas of the world with less-developed health authority oversight, fewer personnel experienced in good manufacturing practices (GMP), and less robust pharmaceutical quality systems. Ensuring quality is therefore a key in setting up API manufacturing operations anywhere. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), and long-established GMP standards, define quality API expectations from end-to-end manufacturing through storage and distribution, with specific filing requirements. Companies can manufacture APIs under these globally harmonized GMP standards nearly anywhere in the world. (For more on the ICH and its evolving role, please see the Appendix.)

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The analysis and opportunities identified in this report by ISPE are based on the insights of a 14-person task force of subject-matter experts with years of experience in the technical, regulatory and supply chain aspects of API manufacturing. The report is intended for a global audience, reflecting ISPE's commitment to provide guidance on the supply of medicines to the people of every nation. (To learn more about the backgrounds of task force members, please see the Appendix.)

The report focuses on the manufacture of small molecule APIs, only one link in a long and complex logistical supply chain that ends with the manufacture and distribution of Final Dosage Forms (FDFs). The scope of the report is deliberately narrow to address specific threats to API supplies highlighted in the coronavirus pandemic. Among pharmaceutical ingredients, APIs typically have the longest lead time to manufacture, and most generic APIs are made in India and China, whose borders closed during the recent crisis.

The report does not attempt to address every challenge in the pharmaceutical supply chain, which includes a multitude of raw materials, suppliers, factories, distributors, storage systems and volume forecasts (before and during emergencies), as shown in the simplified chart in Exhibit 1. More work will be required to assess all of the interdependencies, risks and requirements that arise as stakeholders make changes in that supply chain. In the recent pandemic, for example, some manufacturers have had more trouble obtaining excipients—critical but non-active ingredients in medications—than APIs.

The World Health Organization adds dozens of pharmaceutical APIs to its list of essential medicines every two years, and national health agencies create their own lists. The U.S. FDA, for example, released its revised list of more than 200 "Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs" on October 30, 2020. The Covid-19 pandemic has demonstrated just how difficult it can be to predict which drugs may suddenly be in short supply in an emergency. The small molecule API known as remdesivir, for example, was manufactured in small quantities as a potential treatment for Ebola before Covid-19 emerged. After the drug was identified as a potential treatment to fight the coronavirus, the manufacturer had to do significant work to find partner suppliers and scale up production to meet the sudden rise in demand. Indeed, the company is still struggling to meet demand at the time of this writing, six months later.

The remdesivir case, and acute shortages of many older generic drugs used in intensive care settings, illustrate many of the challenges associated with spikes in API demand and volume with respect to raw materials, supply chains, suppliers, and contract manufacturers, etc. Companies across the pharmaceutical industry, ISPE and other stakeholders are committed to working together to respond quickly to the world's changing needs, but any list of essential medicines is a first step and only as good as demand forecasts and knowledge of disease and treatments—all of which can change in a matter of weeks.

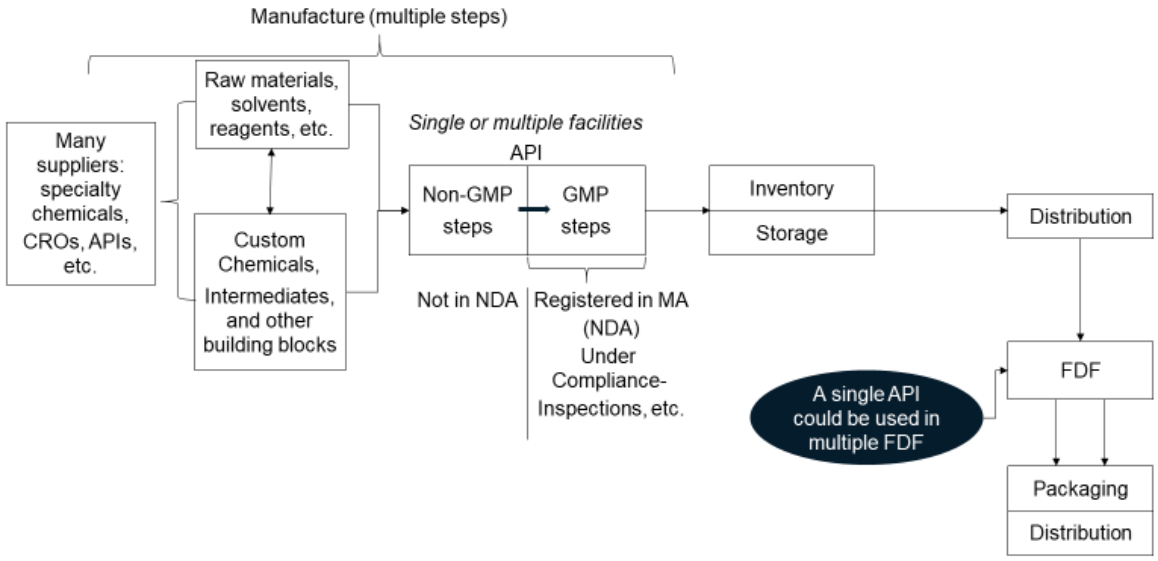
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This report focuses on APIs because the manufacturing process typically requires more time than other steps in the supply chain, including FDF manufacturing, packaging and so on. Once the API bottleneck is addressed, governments and industry can work together to improve the overall resilience of FDF production and supply. While recommendations to policymakers are beyond the scope of this effort, the report concludes with a list of possible next steps and collaborations.

Exhibit 1: Simplified View of the Pharmaceutical Value Chain



Overcoming challenges in ramping up domestic API manufacturing

As noted, small molecule APIs are manufactured around the world, including in Europe and the U.S. Business decisions about API manufacturing locations have been shifting for decades as manufacturers seek tax advantages, lower-cost labor and raw materials, and simpler, less-restrictive regulations. Some manufacturers also choose locations based on their proximity to larger customer demand, especially in Asia. Companies wishing to sell their products in China, Russia and some other countries can be required to manufacture products there. (For details on the share of APIs in the U.S. that come from abroad, refer to reports from the U.S. Government Accountability Office.)

Given the global nature of the pharmaceutical industry, creating a considerably more robust API ecosystem would require significant international cooperation. No country could bring every element of API manufacturing within its borders, since the raw materials, solvents, intermediates and reagents, etc. used to produce just one API are typically sourced from markets around the world. Regardless of where companies build API manufacturing facilities, they supply these products to global markets—serving just one market would not make business sense or meet ethical responsibilities to serve patients. Every major pharmaceutical supply chain is built to serve the world, not one country or region.

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Companies wishing to relocate the manufacturing sites of some older APIs could be required by regulatory agencies to update syntheses and other manufacturing processes and standards. Making even a minor change in a manufacturing process requires regulatory notification, which can trigger expensive regulatory burdens and delay production for months. Likewise, a dosage technology change or reformulation might require an API manufacturer to identify new physical properties, such as a salt or particle size change or polymorph. Approval for even a minor change can take two to six years—a disincentive for manufacturers considering process optimization and other innovations.

Global API manufacturers and regulatory agencies work together under ICH, providing guidelines for global uniform standards and expectations in manufacturing and other practices. These guidelines apply to products registered and approved in new drug applications and other marketing applications (MAs), including those covered under a Drug Master File,[1] which are typically manufactured by third parties and purchased by pharmaceutical marketing authorization holders.

> "Using traditional pharmaceutical manufacturing technology, a U.S.-based company could never offset the labor and other cost advantages that China enjoys simply by achieving higher productivity. However, FDA believes that advanced manufacturing technologies could enable U.S.-based pharmaceutical manufacturing to regain its competitiveness with China and other foreign countries, and potentially ensure a stable supply of drugs critical to the health of U.S. patients."
> —Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the FDA, in testimony to Congress, October 30, 2019

While there is no technical or logistical reason why an API can't be manufactured in any country or region, much of the manufacturing of generic APIs has moved to India, China and other regions where labor costs are relatively low. This is especially true for older products with narrow profit margins. Some APIs might be made by multiple manufacturers, reducing supply risks and helping secure global capacity and volume needs.

Countries around the world typically have the academics, chemists, engineers and quality and regulatory specialists to produce APIs, but talent may be needed in other parts of the supply chain to scale up manufacturing. Manufacturers of APIs and intermediates, for example, rely on manufacturing capacity in Europe or Asia for lined pipe, glass-lined vessels, filter dryers and so on. Extensive training might be required to fill some front-line factory jobs, especially if a country wished to greatly expand API manufacturing capacity.

The API industry, including its talent and technology, will remain global: manufacturers will not need to change locations to harness any technology, nor will they gain advantages by becoming market-centric. That said, the U.S. might play major role in attracting new

[1] A Drug Master File (DMF), a submission to the U.S. Food and Drug Administration, typically provides detailed, confidential information about facilities, processes or articles used in manufacturing, processing, packaging and storing one or more drugs.

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technologies in manufacturing and creating a global strategy to secure supplies of each essential API, collaborating with allied nations. International collaboration from a regulatory standpoint has precedent, including the 2018 Report on the International API inspection program. This international collaboration allowed for several European Union national authorities (France, Denmark, Ireland, Italy, and the United Kingdom), the U.S. FDA, Australia's Therapeutic Goods Administration (TGA), Health Canada, the Japanese Ministry of Health, Labour and Welfare (MHLW), and the World Health Organization (WHO) to share information on GMP inspections of manufacturers of APIs that are located outside the participating countries.

Expanding domestic API manufacturing could offer important benefits

In addition to strengthening the value chain to protect patients at all times, including during pandemics, expanding domestic API manufacturing could provide other important benefits for any country. Manufacturers building production facilities from the ground up could more easily adopt the latest innovations and update old techniques, for example, gaining significant advantages over foreign manufacturers who continue to rely on antiquated tools and approaches.

Newer chemistries and technology, such as organometallic chemistry, biocatalysis and continuous flow, might improve manufacturing processes for some older API candidates, boosting efficiency while reducing costs and environmental impacts. Some APIs, such as penicillin, require unique standalone facilities, but others that rely on similar processes, equipment, handling, volume and expertise might be manufactured in multipurpose facilities. This could help maximize capacity and boost the resilience of supplies without the need to create duplicate facilities.

As noted, ICH has played a crucial role in shaping the industry's ability to respond to the challenges implicit in this journey. The U.S. FDA published the vitally important pharmaceutical quality systems guidance known as ICH Q10 in 2009, establishing several of the fundamental principles now associated with the industry's "quality journey."

The ICH's harmonization guidelines ICH Q7 (Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients) and ICH Q10 (Pharmaceutical Quality System) are widely recognized as quality standards facilitating manufacture in regions throughout the world. They provide the foundations for the adoption of ICH Q12, by having "Established Conditions" based on a sound quality risk management program and minimizing regulatory burdens for changing manufacturing locations and subsequent post-approval changes. The guidelines in Q7 provide systematic direction for good manufacturing practices to ensure "that APIs meet the quality and purity characteristics that they purport, or are represented, to possess." Building on Q7 and Q9, ICH Q10 introduced a "comprehensive model for an effective pharmaceutical quality system that is based on International Organization for Standardization quality concepts." ICH Q10 offers a quality system that can be implemented throughout a product lifecycle to facilitate innovation and strengthen the link between pharmaceutical development and manufacturing activities.

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Novel or more flexible regulatory approaches could lower costs and make manufacturers more willing to pursue continual improvements. Using a performance-based approach, for example, as outlined in the ICH's harmonized guidelines (ICH Q9: Quality Risk Management and ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management), only the final product attributes and the most critical process parameters would be part of the regulatory dossier, easing post-approval change filing burdens. Processes developed following ICH Q11 principles may represent a greater level of understanding and require less regulatory oversight to transfer. Applying ICH Q 9 to quality risk management is also useful in determining the need for technology transfer studies and the level of regulatory oversight required.

Stakeholders would rely on GMP and the pharmaceutical quality system (PQS) for risk assessment and change control with responsibility taken by the industry and subject to inspection. For example, the rigidity of regulatory frameworks around the introduction of alternative analytical methods can be cumbersome, but ICH Q12 could allow for more efficient post-approval improvements.

For APIs that present more risk or with less extensive manufacturing experience, regulators could encourage manufacturers to use a performance-based "established conditions" (EC) approach, as outlined in ICH Q12. The established conditions would include product specifications and minimal additional critical process parameters necessary to ensure quality only if direct linkage to a critical quality attribute, such as implementation of process analytical technologies (PAT). For example, those linked to purging genotoxic impurities that are not measured under release testing could be controlled under GMP and the PQS under a validated process and validated cleaning procedures. Simplifying the established conditions for API manufacturing could help manufacturers improve their processes. To illustrate quality-by-design concepts, regulators could publish "mock DMFs" similar to mock abbreviated new drug applications (ANDAs).

To greatly simplify post-approval changes and better support continual improvements in the production of older, well-characterized drug APIs, regulators could consider adopting the U.S. FDA's "monograph" approach. The impurity and stability profiles of many of these APIs are well understood through years of historical data and process knowledge, and their risks are similar to those of older non-application monograph products. Eliminating the need for DMFs for these APIs could incentivize continual improvement, since API manufacturers would no longer need to notify every ANDA holder of a change and wait for approval.

As in non-application products, API manufacturers would still be subject to regulatory inspections, but unlike non-application products, ANDAs for the drug products would still be filed. Advancing such an approach in the U.S. would require revamping ANDA regulations and guidance but likely would not require changes in the FD&C Act. Policymakers might limit the monograph approach to APIs with good stability profiles and

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