Securing the Supply of Critical Drugs by Restoring Manufacture of Critical Drug Ingredients to the USA

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The recent pandemic caused by SARS-CoV-2virus and the related COVID-19 illness has ignited a federal initiative regarding the security of supply of critical drugs needed in the United States. "The pandemic has revealed a troubling truth: Global supply chains operated by stateless multinational corporations simply aren't reliable. Americans are learning this in real-time as they see imports from China cut off, particularly for critical medicines and pharmaceuticals. That has put millions of lives at risk since 90 percent of the generic medications that Americans use each day are imported. Even worse, 90 percent of the ingredients for generic drugs used to treat coronavirus infections are sourced from China."[1]

In response, the US Government has launched a federal initiative to restore manufacturing of critical drug products to the USA.[2] The central theme in this initiative has been focused primarily on one key part of the final drug product: the Active Pharmaceutical Ingredient (API). The API is the essential element of the drug that provides a unique therapeutic effect. Other elements of the drug serve as functional ingredients to stabilize, support, or enhance the effect of the API. Still other elements of the final drug product involve binders and coatings and the means of introduction of the drug into the human body, be that orally, infusion, injection, inhalation, or transdermal (permeation through the skin).[3]

All elements of the final drug product are essential for the proper functioning of the drug and many of these elements, along with other pharmaceutical grade chemicals needed to make the final drug product are at risk.[4] Ensuring the security of only one element at risk in the final drug product while not considering the risks of all elements will not result in complete security of supply for that finished drug product. Many of the necessary chemicals to manufacture the final drug product, as well as those chemicals to be included as ingredients in the final drug product, are currently manufactured only in countries with quality issues and concerns with security of supply. Simply put, for a drug product to be truly secure, all elements and components of the drug need to be secure. What makes a drug component "at risk", is when the supply of that component comes from areas of the world that lack the quality and regulatory controls required to meet US standards.[5]

Many essential ingredients are only manufactured in countries that lack quality and regulatory controls needed to meet US standards[6] and many more chemicals required to manufacture US drugs are only

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[1] Stumo, Michael. "The Fight To Reshore US Pharmaceuticals." The Daily Caller. The Daily Caller, May 25, 2020. https://dailycaller.com/2020/05/25/michael-stumo-reshore-pharmaceuticals/.

[2] Blankenship, Kyle. "U.S. Seeks to 'Onshore' Drug Production in Response to COVID-19. Is Pharma Even Interested?" FiercePharma, June 4, 2020. https://www.fiercepharma.com/manufacturing/pharma-pushes-back-u-s-legislation-to-bring-drug-manufacturing-stateside.

[3] Inactive Ingredients in Approved Drug Products Search: Frequently Asked Questions §. Accessed August 7, 2020. https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-approved-drug-products-search-frequently-asked-questions.

[4] Stumo, "The Fight to Reshore."

[5] Newton, Paul N., Michael D. Green, and Facundo M. Fernández. "Impact of Poor-Quality Medicines in the 'Developing'World."-Trends-in-Pharmacological-Sciences31,no.3,(February-1,2010):99–101. https://doi.org/10.1016/j.tips.2009.11.005.

[6] Stumo, "The Fight to Reshore."

produced today in countries at risk.[7] Most, if not all of these chemicals could be reshored back to the US by restoring the manufacturing base in the US. This is possible as they are all synthetic in origin (synthesized and not naturally grown only in specific regions of the world).[8]

The effort to reshore whole supply chains for critical drugs can only be accomplished with "sustained political will and financial support for coordinated action"[9] including federal Initiatives and a change in federal policy, combined with State and Local Government support in partnership with the Private Sector.

To truly secure the quality, safety, and supply of finished drugs deemed critical to the US, the US must also secure the entire supply chain of ingredients including many starting, base chemicals from which they come.[10] These "starting" base-chemicals, are used in the process to make the drug or further purified to be included as a key ingredient in the final drug product. As with the final drug product, these too are at risk in countries that lack the desire or resources for appropriate environmental controls, quality systems, or regulatory oversight thus putting those supply chains at risk.[11]

Why the Exodus Overseas?

Offshoring was the result of several enduring factors including fear, costs, distraction and the impact of unintended consequences of certain Federal Policies in regard to the regulation of the Pharmaceutical Industry and the chemicals needed to sustain drug manufacturing in this country.

The exodus occurred because of the need to reduce the perceived environmental impact of chemical manufacturing in the USA and the associated fear of living near these facilities. Americans wanted the end-product but not the waste and pollution. As long as those problems were "over there", the concern was greatly reduced. Even with the rise in public awareness of the environmental problems in India and China, the connection is not always made between the increased levels of pollution in China and India caused in part, by the increase in exported chemicals manufactured in those countries. Regardless of where chemicals are made, they should be produced in a way that is sustainable for the planet.[12]

The exodus occurred as the perceived cost of doing business rose dramatically in the US. To some degree the exodus of APIs and generic drug manufacturing went under the radar as the US continued to experience spectacular success with new therapies and blockbuster drugs.[13] This contributed to the

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[7] Lupkin, Sydney. "What Would It Take To Bring More Pharmaceutical Manufacturing Back To The U.S.?" NPR.,NPR,April,24,2020.https://www.npr.org/sections/health-shots/2020/04/24/843379899/pandemic-underscores-u-s-dependence-on-overseas-factories-for-medicines.

[8] Stumo, "The Fight to Reshore."

[9] Newton, Green, and Fernández, "Impact of Poor-Quality Medicines."

[10] Stumo, "The Fight to Reshore."

[11] "Pharmaceuticals Companies in China - Spending on Healthcare Counts for Over 5% of GDP & Expected to Grow Over the Next Decade - ResearchAndMarkets.com." Business Wire: A Berkshire Hathaway Company. ResearchAndMarkets.com,January24,2020.https://www.businesswire.com/news/home/20200124005197/en/Pharmaceuticals-Companies-China---Spending-Healthcare-Counts.

[12] Albert, Eleanor, and Beina Xu. "China's Environmental Crisis." Council on Foreign Relations. Council on Foreign Relations, January 18, 2016. https://www.cfr.org/backgrounder/chinas-environmental-crisis.

[13] Floether, "Offshoring of Chemical."

overall expansion of the US economy with annual GDP now estimated at twenty two trillion dollars per year.[14]

Without sensing the immediate ramifications, the exodus of "dirty" chemicals was welcomed. The need to engage government and private business to create strategies to reduce environmental impacts of chemical operations in the US was decreased. Many chemical companies either went out of business or followed the path of minimal economic resistance overseas. "Chinese firms… face fewer environmental regulations regarding buying, handling and disposing of toxic chemicals, leading to lower direct costs for these firms."[15]

The pharmaceutical sector became only one of several core industries that was impacted as a result of this exodus. China became the global leader in low cost manufacturing for tens of thousands of other products.[16] The result was lower cost goods and a massive trade imbalance.[17] The dominance in world trade obtained after WWII has been lost and what is worse, it was lost to non-strategic countries and potential enemies[18]-[19]

Another key factor accelerating the offshoring of critical drug and drug ingredient manufacturing was loss of profit as hundreds and then thousands of drugs came off protective patents and went "generic",[20] where foreign countries like India and China were able to offer lower cost generic drugs but often, lower quality versions as well. This has led to other troubling, unintended consequences. For instance, India is not only a leader in the supply of generic drugs throughout the world, but also the leading source of counterfeit drugs.[21]

The Hatch-Waxman Act of 1984 was written to control spiraling drug costs in this country and it achieved that goal. There were, however, unintended consequences with the exodus of generic drug manufacturing from the US overseas.[22] Once the final drug product was exported, key components followed. Ultimately the loss of volume production here in the US drove up prices on key chemicals and other raw materials making it impossible to compete with lower-cost imports.

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[14] Silver, Caleb. "The Top 20 Economies in the World." Investopedia. Investopedia, March 18, 2020. https://www.investopedia.com/insights/worlds-top-economies/.

[15] "Safeguarding Pharmaceutical Supply Chains in a Global Economy," 2019.

[16] Bajpai, Prableen. "Why China Is 'The World's Factory.'" Investopedia. Investopedia, February 13, 2020. https://www.investopedia.com/articles/investing/102214/why-china-worlds-factory.asp.

[17] Newton, Green and Fernández, "Impact of Poor-Quality Medicines,"

[18] Office of the United States Trade Representative, U.S.-India Bilateral Trade and Investment § (2019). https://ustr.gov/countries-regions/south-central-asia/india.

[19] Office of the United States Trade Representative, The People's Republic of China. https://ustr.gov/countries-regions/china-mongolia-taiwan/peoples-republic-china#:~:text=The%20U.S.%20goods%20and%20services,was%20%24378.6%20billion%20in%202018.&text=Goods%20exports%20totaled%20%24120.3%20billion,estimated%20%2477.3%20billion%20in%202018.

[20] "Project: Pharmaceutical Product Lost Profits." Intensity Website, March 16, 2019. https://intensity.com/resources/pharmaceutical-product-lost-profits.

[21] Bate, Roger, Richard Tren, Lorraine Mooney, Kimberly Hess, Barun Mitra, Bibek Debroy, and Amir Attaran. "Pilot Study of Essential Drug Quality in Two Major Cities in India." PLoS ONE 4, no. 6 (June 23, 2009). https://doi.org/10.1371/journal.pone.0006003.

[22] "Hatch-Waxman Letters." U.S. Food and Drug Administration. FDA. Accessed August 7, 2020. https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/hatch-waxman-letters.

The result was the lack of a "level playing field" as the "deck" became stacked against US domestic manufacturers. Key contributors to an "unleveled" field are:

a. Lack of environmental control overseas
b. Lower labor and processing costs due to various reasons
c. Lack of enforcement of equivalent regulatory protocols by foreign governments
d. Manufacturing systems built for lower grade products
e. Subsidized costs for energy and raw materials
f. Subsidized, or lack of, costs dealing with waste

Combined, these factors allowed both China and India to reduce and maintain lower prices for many generic drugs.[23] During this same period, healthcare costs in the US rose sharply and the cry for lower cost drugs became much louder. The US continues to dominate the world stage in terms of new drug development, but it has long since lost its place as a leader in drug manufacturing.[24] In the meantime the US Government continues to find answers to the high costs of new biological drugs compared to new synthetic drugs and generics. [25]

In fact, the entire issue of drug costs has been clouded by rise in these biological base drugs. Bio-based drugs function much more specifically and act in very different ways in terms of their therapeutic approach than traditional synthetic (manmade) drugs but cost a great deal more to make.[26] In the mind of the average American, drug prices have soared even as massive advances in drug therapy were made. This was due in part to the confusion over the cost of generic synthetic drugs versus new, biological drugs. To the consumer, it was all the same thing. due to the continued advancement of biological therapeutics, however, the general population is finally beginning to understand the difference between synthetic pharmaceuticals and those of biological origin.[27]

Finally, the rise in regulatory requirements by the FDA with their uneven enforcement on US companies compared to level of compliance overseas, opened the door wide for the exodus of US manufacturing overseas. While the same level of compliance will likely never be achieved, the full extent of the gap cannot be understood until the US FDA conducts routine, firsthand inspections of these manufacturing sites. This has led to another unforeseen situation: the exodus of drug manufacturing in the US has put an undue burden on the FDA with thousands of manufacturing sites now located outside of the US. The demand for rigorous inspection, especially for sites outside of the US, is one that is difficult to sustain both in terms of budget and human resources. The result has been the rise in dependence on third-part audits

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[23] Mehta, Rik. "China's Dominance of the Pharma Supply Chain Is Highly Dangerous to the US." Washington Examiner, March 17, 2020. https://www.washingtonexaminer.com/opinion/op-eds/chinas-dominance-of-the-pharma-supply-chain-is-highly-dangerous-to-the-us.

[24] Floether, "Offshoring of Chemical."

[25] "Trump Administration Drives Down Drug Costs for Seniors." CMS, July 30, 2019. Centers for Medicare & Medicaid Services. https://www.cms.gov/newsroom/press-releases/trump-administration-drives-down-drug-costs-seniors.

[26]Andrick, Pharm.D, Ben, and Sam Anderegg, Pharm.D. "New 'Biosimilars' May Help Reduce Medication Costs." Pharmacist's Journal. Accessed August 7, 2020. http://safemedication.com/safemed/PharmacistsJournal/New-Biosimilars-May-Help-Reduce-Medication-Costs#:~:text=That's%20why%20biologics%20can%20be,way%20the%20product%20is%20made.

[27] "How Do Drugs and Biologics Differ?" BIO. Accessed August 7, 2020. https://archive.bio.org/articles/how-do-drugs-and-biologics-differ (emphasis added).

that has created the opportunity for foreign manufacturers to not always follow strict cGMP practices. There exists today an imbalance in the level of auditing rigor experienced by foreign manufacturers as opposed to their US counterparts. This imbalance has also served to catalyze the exodus of drug manufacturing from the US.

This increase in the overseas manufacturing of generic drugs was accelerated as the focus for blockbuster drugs increased by US pharmaceutical companies. This should not be surprising when 89% of all prescriptions dispensed in the US were filled with a generic drug yet those sales only accounted for 26% of the revenue.[28] Lack of holistic federal policies, laws and controls only served to perpetuate the imbalance. Appropriate manufacturing standards and regulations applied only to US manufacturers as opposed to their counterparts overseas serves as a good example. The combination of environmental concerns, the drive to recover lost profits, unintended consequences of government action, as well as a cost and labor structure in China and India, as well as the rise of block-buster drugs, all helped to shape the global Pharmaceutical Industry we see today.

While Americans have become the recipient of effective but expensive new, biological drug therapies, the result was the opposite for generic drugs manufactured overseas: they sank both in quality and price. "The low cost of generic drugs makes them essential to global public health. But if those bargain drugs are of low quality, they do more harm than good. For years, politicians, regulators and aid workers have focused on ensuring access to these drugs. Going forward, they must place equal value on quality and efficacy, through an exacting program of unannounced, legitimate and documented inspections, routine testing of drugs already on the market and strict legal enforcement against companies manufacturing subpar medicine." [29]

All these factors, federal policy, pharmaceutical industrial trends, uneven standards in regulations and quality, were not the only factors involved. The massive consolidation of the chemical industry and chemical supply chain of these products that support the Global Pharmaceutical Industry became another major factor accelerating the exodus of the manufacture of core chemistry and core chemicals out of the US. Over the last 20 years, wave after wave of consolidation of both manufacturing and distribution companies have occurred in the USA by public conglomerates and Venture Capital.[30]

As the size and frequency of consolidations accelerated to keep up with global M&A trends, the need for strict regulatory compliance and quality became overshadowed by the demand for financial performance. Massive multi-national companies have a different set of priorities than the concerns of the average American or even the US Federal Government. Today, there a very few US companies that focus on or have a concern for the origin of chemical raw materials. Rather, most deem the chemicals as appropriate as long as they meet the basic "standards" set by current regulatory environment.

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[28] Schwartz, Rachel. "The Generic Drug Supply Chain." Web log. Association for Accessible Medicines (blog). Accessed August 7, 2020. https://accessiblemeds.org/resources/blog/generic-drug-supply-chain.

[29] Eban, Katherine. "How Some Generic Drugs Could Do More Harm Than Good." Time. Time, May 17, 2019. https://time.com/5590602/generic-drugs-quality-risk/.

[30] Gocke, Andreas, Hubert Schönberger, Pranshu Rohatgi, and Philipp Jostarndt. "Consolidation Remakes Chemicals." BCG. United States - EN, August 16, 2018. https://www.bcg.com/en-us/publications/2018/consolidation-remakes-chemicals;

Over the same period, the deregulation of chemical manufacturing of process chemicals and excipients by the FDA coupled with consolidation of companies that constitute the supply chain further accelerated these offshore trends. Over the last twenty years, the FDA has struggled to keep up with expansion and globalization of the Pharmaceutical Industry. As a result, the FDA had to depend on third-party audits. The result was a shift in focus solely on the API and the final drug product. This shift away from other chemicals and ingredients used in the manufacturing process was placed upon Pharmaceutical industry themselves[31].

Most resellers of chemicals needed for the manufacture of drug products followed suit. They increasingly purchase chemicals manufactured overseas for other intended purposes and rather than purify them in the US in order to make them suitable for use in a drug product, they apply "*test and repack"* principles[32] The deregulation of whole sectors of the ingredient industry created a gigantic void that was exploited by many companies as "there are relatively few regulations related to chemicals exported from China."[33] To be fair, China or India themselves did not seek to exploit the situation but found themselves the primary beneficiary of increasing market share stemming from the effect of these powerful trends.

This means that a company can purchase lower grade industrial chemicals that were not manufactured with the proper controls or quality levels for their intended use in drugs. Then, rather than purify those chemicals in order to make them suitable, they simply test them against minimum standards and *declare* them as safe for use for drug manufacturing and in the drug themselves.[34] Since these companies no longer come under the regulatory authority of the US FDA, there is no recourse to these false declarations. The regulations in this regard are holistic but not often followed. Products that are declared as suitable for us must have additional levels of purification and consistent manufacturing that are not stated in the product specification and compendial monograph. There are additional "current Good Manufacturing Practices" (cGMPs) that are found in the United States Pharmacopeia (USP) as well as in the Code of Federal Regulations (CFR) Chapters 21. These manufacturing obligations are not followed by producers of industrial grade chemicals for the systematic removal of impurities that are not specified, nor can they ensure the consistent manufacture of the chemical within tolerance ranges of impurities. These requirements stand in difference to "spot testing" of chemicals made by non GMP systems. The result is higher contamination levels in final drug products.

This was further complicated by the fact that not all chemicals used in the pharmaceutical manufacturing process have standards and controls set up by the FDA. Those that do not appear in the United States Pharmacopeia (USP), must come under the "general compliance rules" found in CFR chapter 21. Deregulation allowed many of these chemicals to "all through the cracks" and drop from compliance altogether. Others were tested to meet specific requirements, but those specifications and requirements

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[31] Ahuja, Satinder, and Stephen Scypinski, eds. "Modern Pharmaceutical Analysis: An Overview." Essay. In Handbook of Modern Pharmaceutical Analysis3, 3:1–22. San Diego, CA: Academic Press, 2001. https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/drug-quality emphasis added).

[32] Schieving, Aaron. "The Seven Most Common Grades for Chemicals and Reagents." Lab Manager, November 12, 2017. https://www.labmanager.com/business-management/the-seven-most-common-grades-for-chemicals-and-reagents-2655 (emphasis added).

[33] Rep. Potential Health & Safety Impacts from Pharmaceuticals and Supplements Containing Chinese-Sourced Raw Ingredients. NSD Bio Group, LLC , 2010.

[34] Ahuja, Scypinski, eds. "Modern Pharmaceutical Analysis."

assumed GMP processes that no longer existed (as none of these chemicals are made under appropriate cGMP principles overseas). This allows for unspecified contaminants to remain in these products and find their way into the final drug products consumed by millions of Americans every day.[35]

In many cases, the chemical manufacturer chose not to adhere to more strict compliance and quality standards as the market share for that purpose was minor compared to other intended uses. This often put the pharmaceutical industry itself in precarious situations as it could not obtain the chemicals it needed at the appropriate levels of quality and compliance. This put an even greater burden on pharmaceutical companies to remain in compliance but still be able to viably manufacture the final drug product. The result was that the pharmaceutical industry were forced to set up their own, inconsistent standards and then defend them during audits.

Theoretically every chemical used in the drug manufacturing process has to comply with the USP monograph (if there is one) and/or US cGMP regulations found in the Federal Registrar title 21.[36] The situation stated previously forced many companies to bypass unenforced regulations to satisfy demand. Deregulation accelerated the use of many chemicals that were not re-purified or manufactured with the intent for use in a drug product. With little or no repercussions from the FDA, the trend seemed to be legitimized. The result was a de-facto version of cGMP requirements for many raw materials and drug ingredients. Even though current laws do not allow for such practices, justification is provided in the fear that reversing the trend would result in higher drug prices.[37]

The loss of so much volume to overseas companies only exacerbated the situation for US manufacturers who found it increasingly difficult to compete. Loss of scale volumes forced many companies in the US to give up and go out of business further impacting supply chain security as well as the US economy.[38]

To minimize costs and the impact of lost profits, big pharma looked for savings in raw material supply chain to sustain the risings costs in development of new drugs. This too, only served to accelerate offshoring trends. The reality is that while it does cost enormous sums of money to develop a novel drug it is not the same for the continued manufacturing.[39] Federal action could impact this situation by creating an environment where it does not cost, on average, $1.3 Billion dollars and ten years of time to approval of a new drug. If other countries such as China do not insist on the same levels of regulations, then surely, we will only force ourselves to buy it from them.[40]

Path to Secure Supply Chains through Reshoring

It was a combination of all these factors that has led to the offshoring of so many of our drugs and drug ingredients. The advent of the recent pandemic caused a “wake up call” that many critical drugs are no

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[35] Schieving, “The Seven Most Common.”

[36] FDA § (2018). Code of Federal Regulations - Title 21 - Food and Drugs.

[37] FDA § (2020). https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database.

[38] Prableen, “Why China Is.”

[39] “Cost of Drug Development.” Wikipedia. Wikimedia Foundation. Accessed August 7, 2020. https://en.wikipedia.org/wiki/Cost_of_drug_development.

[40] https://www.biospectra.us/images/whitepapers/Biopharmaceutical-Notes-rev_1-6-8-14-2020-cg-pd.pdf

longer secure. The trend can be reversed, but it will require sustained federal initiatives combined with State and Local Government support in partnership with private business.

1. Similar to what is happening under the "Warp Speed" initiative, the steps for approval of new drugs could be reduced with the goal of significantly reducing the time and cost of development of a new drug here in the USA.[41]
2. We can reshore critical base chemical manufacturing under appropriate environmental controls as long as we have economy of scale (volume manufacturing), tariffs or government subsidies that level the playing field for the same chemicals produced overseas and, long term contracts with the users of those chemicals.[42]
3. Companies who manufacture these chemicals and those who resell them, must be held fully accountable for their intended use and their adherence to the appropriate levels of compliance and quality through the manufacturing process.
4. The current regulation that an API cannot be repurified (especially those made overseas) should be revisited. This will resolve short term quality and supply issues and support the long-term objective of reshoring API manufacturing to the USA. The current law compels drug formulators to use APIs from countries where quality issues exist, "as is," without the ability to repurify them.[43]
5. Pharmaceutical companies can embrace the holistic view of total operational costs through the entire supply chain and not just the cost of raw materials. This can be accomplished by injecting the mindset with new methodologies, operational excellence, more focused KPI's and leaner organizations, to cut cost, improve margins, and ultimately lower the cost of drugs."[44] It can also be accomplished with support of federal iInitiatives in review of current FDA policies.[45]

It remains difficult to compete with similar (though lower) quality products coming from China and India due to a lack of a level playing field.[46] The export of so many drugs, drug ingredients and chemical raw materials needed to make those incredients has led to the current crisis. Many of these chemicals are manufactured with other intended uses without consistent quality levels for appropriate use in a drug product. The lack of availability of any alternatives means results in their inappropriate use in the US, in the manufacture of a finished drug product consumed by millions of Americans.[47]-[48]-[49] Unfortunately this

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[41] FDA § (2020). https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database.

[42] Stumo, "The Fight to Reshore."

[43] ICH Q11 Development of a Drug Substance - https://www.fda.gov/media/80909/download

[44] Fioravanti, Paul. "The Contract Pharma Market: Why CDMO's Must Transition with Long-Term Sustainability in Mind." Pharmaceutical Outsourcing, December 6, 2019. https://www.pharmoutsourcing.com/Featured-Articles/558562-The-Contract-Pharma-Market-Why-CDMO-s-Must-Transition-with-Long-Term-Sustainability-in-Mind/.

[45] FDA § (2019). Trump Administration takes historic steps to lower U.S. prescription drug prices. https://www.fda.gov/news-events/press-announcements/trump-administration-takes-historic-steps-lower-us-prescription-drug-prices.

[46] Prableen, "Why China Is."

[47] Schwartz, "The Generic Drug."

[48] Eban, "How Some Generic Drugs."

[49] Schieving, "The Seven Most Common."

has also lead to an environmental crisis for China.[50] While the US does not have the manufacturing capacity to make all the chemicals needed today, we do have the ability to purify every chemical purchased overseas. The US Government can lead the way in prioritizing which ones are needed most.

The pressure on US pharmaceutical manufacturers to use these materials without appropriate purification can and needs to be relieved. This can be accomplished with federal initiatives toward national security interests. In addition, the US FDA should put an end to the growing practice of risk avoidance plans that allow third party auditors to make claims of suitability where often, none exist. The FDA must be funded to allow direct control of critical supply chains. Often, raw materials are imported into the USA and labeled properly as a lower (industrial grade) chemical, only to be tested and repacked for a small set of specification (rather than other impurities) under quality system that do not truly comply with Federal Standards. They are then resold as grades suitable for the use in Drugs and Drug manufacturing. This occurs because these companies are no longer inspected by the FDA.

One way to level the playing field is by making all companies truly responsible for the ingredients they make, resell and use. The only way to do this is by making all parts of the supply chain subject to FDA inspection and authority. "Companies must have appropriate written procedures. This includes standard operating procedures (SOP's) for manufacturing and quality control analysis. written procedures for manufacturing, packaging, and quality control analysis allow reproducibility, continuity, accuracy and process control." [51]

The path to regain security of supply for critical drugs and their associated ingredients will also require:

1. Reestablish core chemistry and core chemical manufacturing back to the US.
2. Make sure all key ingredients used in drug manufacturing are repurified under a validated regulated manufacturing system.
3. Make sure all the APIs are manufactured in the USA for critical drug products and/or allow for their purification by regulated US companies in the meantime or if they cannot be made here.

To truly secure the US supply of critical drugs requires the transition of all critical drug components back to the USA. The benefits far outweight the challenges such as safer, more consistent drugs, and the expansion of our economy with growth in high-tech jobs. Some estimate the reshoring could create up to eight hundred thousand direct and indirect jobs.[52] Every drug ingredient manufactured in the US requires raw materials, logistics, packaging, laboratory support, manufacturing, equiptment, utilities, staff, compliance specialists and a world of support services that can be expanded in the US in support of our economy and the peopole who serve in those roles. Thus, reshoring will result in an overal increase in the US cconomy as well as much needed economic growth on the state level. The need for

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[50] Albert, Eleanor, and Beina Xu. "China's Environmental Crisis." Council on Foreign Relations. Council on Foreign Relations, January 18, 2016. https://www.cfr.org/backgrounder/chinas-environmental-crisis.

[51] Jimenez, Luis. "Analysis of FDA Enforcement Reports (2012-2019) to Determine the Microbial Diversity in Contaminated Non-Sterile and Sterile Drugs." American Pharmaceutical Review 22, no. 6 (2018): 48–72. https://www.americanpharmaceuticalreview.com/1505-Issue-Archives/.

[52] Byers, PhD, Steve L, and Jeff Ferry. "Reshoring US Pharmaceutical Production Would Create 800K Jobs." CPA, March 17, 2020. https://www.prosperousamerica.org/reshoring_us_pharmaceutical_production_would_create_800k_jobs.

more high-paying, technical jobs will in turn will place further demands for growth on the educational system needed to support this growth.[53]

If the US Federal Government seeks to have a secure supply of critical drugs then it will require much more than simply asking private business to do it. Rapid expansion of US Manufacturing for these chemicals can be supported through:

a) Federal and State money for pollution controls.
b) Guaranteed loans for Investment in infrastructure.
c) Contracts from the Federal Government to US pharmaceutical companies requiring the use of US based manufacturers.
d) Offering incentive to the State Government to "clear the way" for the rapid development of the new manufacturing sites.
e) Improving public relations with local populations.

Many companies across the US experience State and local opposition to expanding core chemical industries. [54] The result can be overwhelming and cost millions of dollars in unnessesary delays and legal issues.[55] In order to accelerate reshoring, the industry will need the help of state and local agencies in more ways than prioritized and expedited zoning approvals and building permits but also in regard to public relations. The pharmaceutical Ingredient industry is vital to the public good and should be presented that way to the public.

Finally, the federal government can continue the current trend toward the roll back of policies and programs that often punich US manfucturing for its very existance. This had become symptomatic with agencies such as the EPA and OSHA under the previous administrations.[56]

This does not necessarily require massive new industrial sites. Rather, "pocket size, GMP manufacturing plantscan be build in order to satisfy whole areas of needs for drug manufacturing such as biological buffers, carbohydrates, amino acids as well as APIs. [57]

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[53] Floether, Dr. Frank U. "Offshoring of Chemical & Pharmaceutical R&D to Asia." Pharmaceutical Outsourcing, November 27, 2012. https://www.pharmoutsourcing.com/Featured-Articles/125941-Offshoring-of-Chemical-Pharmaceutical-R-D-to-Asia/.

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