Threats to Pharmaceutical Supply Chains

The Public-Private Analytic Exchange Program

Research Findings

July 2018

From Top Left Clockwise:
Aerial Imagery of Pharmaceutical Manufacturing Facility outside Guayama, September 2017; Aerial Imagery of Pharmaceutical Manufacturing Facility outside Humacao, Puerto Rico, September 2017; US Government Personnel Plan Distribution of Aid and Water, Undated Photos; Aerial Imagery of Pharmaceutical Manufacturing Facility outside Gurabo, Puerto Rico, September 2017; US Military Helicopter Delivering Personnel, Aid to Remote Areas of Puerto Rico Post-Hurricane-Maria, Undated Photo; Aerial Imagery of Pharmaceutical Manufacturing Facility outside Caguas, Puerto Rico, September 2017; Downed Electrical Utility Lines in San Juan, Puerto Rico, November 2017; CENTER: Satellite Imagery of Hurricane Maria, post-landfall over Puerto Rico, 20 September 2017 (Aerial Imagery taken by Civil Air Patrol, available at disasters.geoplatforms.gov/ ; Satellite Imagery courtesy NASA Earth Observatory; Other photographs provided by AEP team members A. Kilianski and N. Loehr)

Vulnerabilities within the United States' Pharmaceutical Supply Chain:
Lessons Learned About Pharmaceutical Supply Chain Security in Puerto Rico
July 2018

Table of Contents:

Executive Summary 3
Acknowledgements 3
Hurricane Maria and the Impact on the US Pharmaceutical Supply Chain: A Case Study . 4
How Hurricane Maria Affected Pharmaceutical Manufacturing in Puerto Rico . 4
Bad to Worse: Hurricane Maria and the US Flu Outbreak 5
Explaining Why Hurricane Maria Had Such an Impact 6
Beyond Our Case Study: Examining Risks and Hypothetical Scenarios . . . 7
How Did We Get Here? Examining the Risks 7
Risk-based Hypothetical Scenarios 10
Observations and Recommendations 11
Goal: Expedite and Reinforce Manufacturer Disclosure of Drug Shortages to the FDA 12
Goal: Prioritize Disruptions to the Supply Chain or Manufacturing of Critical Drugs 12
Goal: Improving Incentives for Manufacturers to Maintain Supply . . 13
Goal: Prioritizing the Pharmaceutical Industry Supply Chain as National Security Assets 13
Concluding Remarks 14
Citations 15

Executive Summary:

In September 2017, Hurricane Maria caused severe devastation to the U.S. territory of Puerto Rico, which manufacturers nearly 10 percent of all drugs consumed by Americans. Given the large concentration of pharmaceutical manufacturing based in Puerto Rico, the destruction wrought by a Category 4 hurricane created shortages for specific medical products, which affected the standard of health care in the United States during an influenza epidemic throughout late 2017 and early 2018. The Analytic Exchange Program's (AEP's) team examining "Threats to Pharmaceutical Supply Chains" examines this event as a case study for the risks and implications of pharmaceutical supply chain disruption. What happened after Hurricane Maria could shed light on other supply chain vulnerabilities, including the effect of cyber-attacks against manufacturing infrastructure, geopolitical disputes affecting drug supply chain components, and the growing reliance on third party drug manufacturing and logistics suppliers.

Awareness of vulnerabilities is the first step toward protecting the pharmaceutical supply chain as a component of critical infrastructure vital to U.S. national security interests. Our team recommends mitigating future supply chain disruption by increasing private sector and government coordination. This AEP team proposes several specific solutions policymakers and corporate executives should consider, including providing incentives for greater cooperation, prioritizing the U.S. pharmaceutical industry as a unique critical infrastructure component and national security asset, creating an industry-wide list of medications deemed "critical", and streamlining the approval process for backup medications and alternative sources of temporary production.

Acknowledgements

This report, "Threats to Pharmaceutical Supply Chains" was prepared by team participants from in the 2018 Public-Private Analytic Exchange Program (AEP). As the team champion, I would like to acknowledge the team members for their dedication and professionalism in investigating, researching and writing the report:

Andrew Alvarado-Seig, Thomson Reuters
Hubert B., Department of Homeland Security/CS&C/NCCIC
Jenifer Clark, Costco Wholesale
Michelle Danks, Amazon
George Guttman, U.S. Government Accountability Office
Dr. Andrew K., Department of Defense
Nathan L., Federal Bureau of Investigation
Dr. Monique Mansoura, MITRE
Dr. Kay M., Department of Homeland Security/Intelligence & Analysis (DHS/I&A)
Thomas Proctor, Security Industry Specialists
Clifford Riggs, National Cyber Forensics and Training Alliance
Milen Zerabruk, Capgemini Government Solutions

The report contents do not reflect the views or the opinions of the affiliated members' company or specific government agency. The views and conclusions in this report are those of the authors and not necessarily those of private sectors or government agencies.

Kay M., Ph.D.
DHS/I&A 2018 AEP Team Champion

Hurricane Maria and the Observed Impact on the US Pharmaceutical Supply Chain: A Case Study

How Hurricane Maria Affected Pharmaceutical Manufacturing in Puerto Rico

On September 20th, 2017, Hurricane Maria made landfall on the island of Puerto Rico, causing millions of dollars in damage and causing the deaths of hundreds, if not thousands of American citizens throughout late 2017 and early 2018. In addition to the human toll and economic impact of the hurricane, the pharmaceutical and medical device manufacturing industry, a fundamental component of the United States health care critical infrastructure sector, was also hard hit. Ten percent of the United States pharmaceutical product manufacturing is based in Puerto Rico. Maria severely disrupted the supply chain for both the manufacture and delivery of pharmaceuticals and medical products throughout the United States. This disruption led to critical shortages of pharmaceutical and health products during a nationwide outbreak of a particularly-strong strain of influenza in late 2017, and highlighted several other vulnerabilities in the U.S. supply chain for pharmaceuticals and medical products in the months following this natural disaster.

- Hurricane Maria had a disproportionately large impact on the U.S. pharmaceutical manufacturers, who established in Puerto Rico in the 1970s to take advantage of federal tax incentives.[1] As of 2016, there were at least 49 U.S. Food and Drug Administration (FDA)-approved pharmaceutical plants in Puerto Rico; the Government of Puerto Rico also noted that there were over 70 medical device manufacturing facilities on the island.[2] [3] [4] According to the FDA, Puerto Rico produces 40 billion dollars-worth of pharmaceutical products yearly, more than any other US state or foreign country, by value.[5] Over 10 percent of drugs consumed by Americans are created on the island, including 13 of the top-selling patented drugs.[6] [7]

- Hurricane Maria disrupted components of Puerto Rico's pharmaceutical manufacturing sector in a number of ways, including:

  - **Electricity** – According to one estimate, Hurricane Maria led to the loss of 3.4 billion customer-hours of electricity service, making it the largest storm-related blackout in American history and the second-largest globally.[8] Many pharmaceutical manufacturers on the island maintain industrial-scale off-grid generators that allow partial operations to continue. However, frequent outages on the island's electrical grid and fuel shortages have led to operational disruptions.[9]

  - **Transportation** – Damage to airports, seaports, roadways, traffic management systems, and the island's aviation radar system led to delays importing and exporting goods from the island.[10][11] In addition, mudslides, downed vegetation, acute fuel shortages, and the strain on existing logistics services caused by competing road-access, heavy equipment, and cargo-space needs for disaster relief and recovery efforts, made transportation between shipping and manufacturing facilities difficult for the pharmaceutical industry.[12]

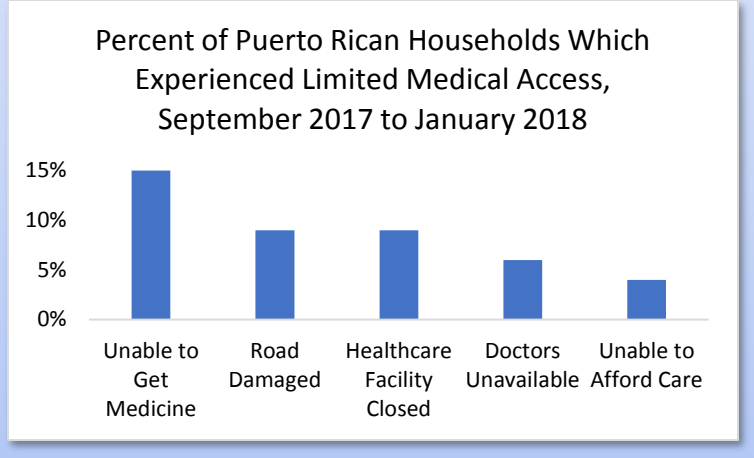
  - **Labor** – workers often dealt with significant personal injuries and significant residential property damage. Combined with a massive exodus of Puerto Rican families to other parts of the United States, injuries, frequent days without power and water, and deteriorating road conditions, many factories struggled to keep enough staff to operate.[13]

The U.S. Food and Drug Administration (FDA) reported in November 2017 that it was monitoring 90 medical products for potential hurricane-related shortages.[14] Interviews with supply chain officials at affected pharmaceutical companies indicated that most factories were able to restart at least some operations quickly after the storm. However, officials at all companies noted that damage to roads and the fuel supply made it difficult for employees to travel to work. Damage to sea and airports also reportedly made it difficult to transport needed goods on and off the island, delaying the recovery.[15] [16] FDA Commissioner Dr. Scott Gottlieb noted in an October 2017 interview that many pharmaceutical companies on the island were "manufacturing well short of [full capacity]" after the storm.[17]

Hurricane Maria: The Human Toll

Hurricane Maria, the tenth-strongest hurricane on record in the Atlantic Ocean, made landfall on Puerto Rico's southwestern coast on September 20th, 2017.[1] Preliminary official reports indicate that the hurricane killed dozens and wounded thousands of people; a May 2018 survey indicated Maria's death toll likely ranged between several hundred to over 4,600 casualties in Puerto Rico as a result of the storm. [18] Hurricane Maria caused extensive infrastructure damage throughout the island, particularly to the delivery and reliability of basic utilities like electricity, water, and mobile phone services.

In May 2018, Harvard researchers published the results of a household survey, which went door-to-door in urban and rural households throughout Puerto Rico, in order to observe possible changes in the mortality rate and availability of basic services in Puerto Rico. This survey estimated that across Puerto Rico, 15 percent of households responded that they had at least one day in the months following Hurricane Maria when they could not access their medication.[19]



Bad to Worse: Hurricane Maria's Supply Chain Disruption Likely Impacts Response to Flu Outbreak

Saline and other medications administered through the use of intravenous (IV) bags are crucial to managing severe cases of many viral infections. Unfortunately, disruptions in the pharmaceutical supply chain caused by Hurricane Maria meant that an already-low supply of IV bags became even scarcer throughout late 2017. These shortages forced health care providers to change their procedures for dealing with a highly contagious disease—influenza—in the middle of a severe outbreak.

- The Centers for Disease Control and Prevention (CDC) declared the influenza outbreak in late 2017 and early 2018 to be of "high severity," based on mortality and hospitalizations, among other factors. At its peak in early February 2018, influenza and pneumonia caused one out of every ten deaths per week in the United States, killing over four thousand people in one week

alone. The CDC estimated that over 30 thousand people required hospitalization due to the influenza outbreak in the United States between October 2017 and April 2018. [20] [21]

- Prior to Hurricane Maria, Puerto Rico manufactured 43 percent of the saline used in the U.S.[22] According to FDA Commissioner Dr. Scott Gottlieb, already existing shortages of saline were exacerbated by the damage to Puerto Rico's manufacturing infrastructure.[23]
- Alternative solutions to IV bag shortages, like using larger saline bags or manually pushing IV medications into patients, significantly impact the cost of healthcare for influenza patients and potentially impact patient safety, according to public health experts. Not only is additional training on new approaches costly, but the quality of care can decrease when shortages disrupt existing optimal procedures for administering health care.[24]

Many of the items critical to addressing a flu outbreak—such as IV solutions or antibiotics[25]—are manufactured in Puerto Rico, among other locations worldwide. It is difficult to estimate what specific pharmaceutical products were affected by Hurricane Maria, given that many companies protect information about product lines for specific facilities as a trade-secret. Despite this confidentiality, a team of researchers identified at least 101 brand-name drugs which were produced in Puerto Rico between 2011 to October 2017.[26] 21 of these drugs were listed by the World Health Organization as "Essential Medicines" in August 2017, which were used for a wide range of health problems, such as bacterial or fungal infections, diabetes, HIV, Hepatitis C, depression, or schizophrenia.[27]

Pharmaceutical Manufacturing and Medical Supply Critical to National Security

Pharmaceutical industries are part of the U.S. government's Critical Infrastructure Plan within the Healthcare and Public Health Sector, as established by Presidential Policy Directive 21. The Department of Homeland Security defines Critical Infrastructure Sectors as key components of U.S. public and private infrastructure that contributes to national security. According to DHS:

The Healthcare and Public Health Sector protects all sectors of the economy from hazards such as terrorism, infectious disease outbreaks, and natural disasters. Because the vast majority of the sector's assets are privately owned and operated, collaboration and information sharing between the public and private sectors is essential to increasing resilience of the nation's Healthcare and Public Health critical infrastructure. Operating in all U.S. states, territories, and tribal areas, the sector plays a significant role in response and recovery across all other sectors in the event of a natural or manmade disaster.[28]

Explaining Why Hurricane Maria Had Such an Impact: Broader Concerns about Supply Chain Security

Many factors contributed to the Hurricane Maria's impact on U.S. public health. Well before the storm swept through Puerto Rico, decades of U.S. government policies encouraged a significant proportion of U.S. pharmaceutical manufacturing—a core component the Healthcare and Public Health Critical Infrastructure Sector—to concentrate in one geographically-confined area. Man-made crises meant that just one extreme event could have far-reaching and long-lasting consequences.

- **Overburdened Disaster Relief and Recovery Resources** — In the weeks prior to Hurricane Maria's landfall, Florida and the U.S. Gulf Coast were hard-hit by Hurricanes Harvey and Irma. All throughout mid-2017 to late-2017, over 9 thousand wildfires tore through over 1.3 million acres in California, destroying over 9 thousand structures and killing 43 people. These natural disasters reportedly led to shortages of resources necessary for rebuilding the Puerto Rico's infrastructure, such as electrical wire, transformers, and utility poles.[29]

- **Poor Existing Infrastructure** — Well before the 2017 hurricane season, Puerto Rico's municipal debt crisis and financial austerity measures had starved much of the island's basic utilities, regulatory agencies, and transportation authorities of much-needed spending on preventative maintenance and upgrades.[30] [1]

- **Debt and Recession** — Between 1976 and 2006, federal tax policies under Operation Bootstrap encouraged manufacturers to relocate to U.S. overseas territories, by allowing manufacturers to avoid paying corporate income taxes on profits made in U.S. territories. Under this policy, a large number of U.S. and international pharmaceutical companies established a manufacturing presence in Puerto Rico. While this policy helped grow wages and employment in Puerto Rico, when the tax incentives were fully phased out in 2006, many companies closed their Puerto Rico branches and relocated to other parts of the United States, causing a spike in unemployment, a decrease in overall wages, and an incentive for municipal governments to issue more bonds to pay outstanding debt.[31]

- **Business Continuity** — Our research team interviewed several representatives of pharmaceutical manufacturers who maintained operations in Puerto Rico. Despite the decade-long economic recession, and the likelihood that another hurricane might hit the island again, none of these manufacturers indicated a desire to relocate.

Beyond Our Case Study: Examining Risks and Hypothetical Scenarios

The case study on Puerto Rico and Hurricane Maria focuses on geographic concentration in a natural disaster area as a risk factor for supply chain disruption, but this isn't the only risk to U.S. pharmaceutical industry. We should take a moment to examine:

1. What incentives exist that shape the way drugs are made and delivered?
2. What are (other) realistic scenarios which could cause a disruption with severe consequence?
3. What are potential solutions?

How Did We Get Here?

Over the past several decades, the U.S. pharmaceutical industry has been shaped by a number of major developments. A stable, relatively conflict-free international trade regime has enabled U.S. pharmaceutical manufacturing to take advantage of human capital, wider market access, and favorable regulatory regimes to augment productivity, minimize costs, and maintain competitiveness.[32] Advances

[1] In an odd turn of fate, it is possible the lack of reliable power, water, and other basic services may have forced pharmaceutical manufacturers to invest in off-grid infrastructure well before Hurricane Maria, thereby allowing many manufacturing facilities to quickly return to production.

in information technology allow drug makers to research, design, manufacture, market, and distribute their products from all corners of the globe. Remote IT support, cloud computing and the "Internet of Things"[2] improve manufacturing systems and processes, reduce costs, and ease maintenance.[33]

As a result, major pharmaceutical companies have built distributed and complex supply chains. Open trade, limited patent lifespans, and competition with foreign drug makers have driven U.S. manufacturers to focus mostly on what they do best—development and market new drugs.[34] Major pharmaceutical companies today rely on networks of contractors and suppliers for other key functions in drug production and distribution, particularly making active pharmaceutical ingredients. (APIs)[35]

The downside to these developments are plentiful. Long, complex supply chains can expose U.S. drug makers to increasing levels of risk. Geo-political tensions could upend global drug production. Extreme natural disasters are occurring more frequently, in areas crucial to the foreign production of U.S. drugs and drug components. While cloud computing, outsourcing, and the lowering overall costs to global trade have been a boon to drug-makers, they also expose these companies to a wide range of risks.

So how do these risks manifest themselves?

Third Party Risks

The pharmaceutical industry today relies on a vast network of subcontractors for the production of drugs. The average global pharmaceutical company today works with around 100 to 200 contract manufacturing organizations.[36] The production of API, packaging, and several other manufacturing functions now take place in subcontractors located overseas.[37] Just as critical, however, are power and water, waste disposal for hazardous materials, network administrators, and other third party vendors or utilities.[38] Manufacturing biologic products requires cell substrates derived from various animal sources, such as pig intestines, the prices for which can vary wildly.[39] A hiccup in any one of these subcontractors or suppliers can cause delays or shortages.

Pharmaceutical manufacturers cannot easily pivot from an unreliable third-party to another because it takes a long time for drug makers to develop new relationships and manufacturing capacity, typically between 18 and 30 months, according to our interviews with pharmaceutical industry representatives.[40] [41] Any new relationship must also meet FDA facility/supplier certifications. Building new drug pharmaceutical manufacturing capacity is also not cheap, and many large pharmaceutical companies have little cash on hand to invest in new hardware.[42]

Drug makers are also under regulatory scrutiny to guarantee the quality and safety of their products, as well as to comply with environmental protections, labor laws, tax codes, and a number of other matters. These requirements can make it challenging for companies to quickly adapt to supply chain disruptions.

Counterfeit Risks

[2] The Internet of Things (IoT) refers to computer networks that enable a range of devices—from household appliances to vehicles to heavy machinery—to track information about their functions digitally, typically through sensors, and to share that data over the internet and with other devices. Among other benefits, the IoT allows businesses and consumers to monitor trends with how these devices are used and make adjustments accordingly.

Fake drugs (including diverted, adulterated and mislabeled drugs) pose a number of risks to the pharmaceutical supply chain. It is astonishingly quick and easy for consumers to find and buy fake drugs online. Sophisticated transnational criminal networks maintain thousands of internet domains like "www.buyeasycheapdrugs-usa.com," claiming to source legitimate drugs from Canada, and will ship products in small parcels through international mail from China, India, or other source economies for fake and diverted drugs.

When shortages and other disruptions occur in the legitimate supply chain, consumers may look to the internet to find drugs they need. [43] Fake drugs pose an immediate risk to consumers; these products are not handled and stored properly, or are adulterated with hazardous substances.[44] Insulin, for example, must be stored at a specific temperature or it will not function properly.[45] Fake and diverted drugs also pose a more serious public health risk by failing to work as intended, or worse, increasing a disease's drug resistance. Fake and diverted drugs can also erode consumer confidence in a particular brand or the safety of a particular class of products.

Environmental Risks

Business executives often claim that weather is a leading cause of supply chain disruptions.[46] As extreme weather events, such as droughts, storms, fires, and floods, become more common, supply chain disruptions will become more frequent.[47] In Puerto Rico, one industry representative we interviewed explained that to sustain production, their company shipped in medicines and generators to keep their facility operational.[48] If roads or ports are inaccessible, production can grind to a halt.

Environmental risks are global. While cheap labor and raw resources and regulatory incentives draw U.S. pharmaceutical manufacturing to off-shore a large share of pharmaceutical manufacturing to Bangladesh, India, and Sri Lanka,[49] [50] these countries, are exposed to greater risks of flooding and more intense tropical cyclones.[51]

Cyber Risks

In the digital age, drug makers have never been more exposed to cyber threats, from a wide range of actors pursuing very different motivations. These threats can have unpredictable consequences for the reliability and integrity of the pharmaceutical supply chain. A 2017 study on unplanned information technology outages and cyber incidents are the leading causes of supply chain disruption. [52]

Pharmaceutical companies spend billions of dollars-worth in developing and testing new drugs. The U.S. drug industry's intellectual property is a lucrative target for investors to try to obtain material, non-public information to conduct insider trading, for cyber criminals hoping to hold this information for ransom, and foreign-government-sponsored threat actors to benefit foreign industries to attempt to out-compete US drug makers by beating them to markets with their own product.

Despite repeated targeting of this proprietary information, the U.S. pharmaceutical industry has also become increasingly reliant on managing production through IoT equipment, large-scale data analysis on new products and testing, and a greater focus on gathering patient-specific data to develop tailored products. These factors mean that IP isn't the only high-value information that motivates cyber threats—foreign investors or competitors may try to shutter manufacturing remotely, for instance, in a bid to de-value a specific drug maker.

Cyber threats do not have to target drug makers directly; a recent wargame by the Atlantic Council highlighted how malware affecting one entity can degrade equipment and systems functions using the same software.[53] The NotPetya ransomware campaign in mid-2017 was not specifically interested in affecting the pharmaceutical industry, but nevertheless disrupted Merck's HPV vaccine production line.[54] Merck lost 310 million dollars in revenue subsequent quarter, as a result of lost productivity and a halt in production for almost a week.[55]

Geopolitical Risks

Decades of trade agreements and low tariffs have allowed U.S. manufacturers to move manufacturing, packaging, and other parts of the pharmaceutical supply chain abroad. If countries begin to issue more protectionist trade policies, or erect other non-tariff-barriers to trade, this might have short- and long-term consequences for the ability to make and distribute drugs, or the viability of the U.S. pharmaceutical industry. (Should China, for instance, decide to engage in illegal dumping practices to drive US manufacturers of biologics out of business) Diplomatic or military confrontations and actions, such as embargos, blockades, sanctions, or capital controls and foreign investment bans, can have an impact. Humanitarian crises can also put a strain on manufacturing and supply chain matters

Scenarios

The following hypothetical future scenarios illustrate how some of these risks could manifest themselves and some of the ramifications for the pharmaceutical supply chain.

2020 – Floods in Mumbai, Fraud in Miami

In late summer 2020, a monsoon drops record rainfall in Maharashtra, exceeding the previous record set in 2017. The subsequent floods devastate several parts of Mumbai, a city that faces severe flooding each monsoon season.[56] Over the past few decades, India has developed a large and robust pharmaceutical sector, and Mumbai is one of the sector's principal hubs.

Most drug manufacturing facilities are spared, but the flooding causes extensive damage to ground transportation and housing around Mumbai. With much of their workforce unable to travel to work, pharmaceutical production grinds to a halt, including the manufacture of a generic version of Tamiflu, a drug used to prevent and treat influenza.[57]

A few months later, public health officials worldwide begin to notice a spike in hospitalizations and deaths attributed to a particularly dominant strain of influenza. The preceding flu seasons have been particularly severe, and demand for antiviral medication has outstripped supply.[58] Online networks trafficking fake drugs sense an opportunity, as the price for both legitimate and generic Tamiflu skyrockets. In November, Customs agents in South Florida, which has been particularly hard-hit by flu-related deaths, notice a surge in incoming Tamiflu shipments with strange and expired packaging, as well as an uptick in cargo theft targeting shipments of the antiviral medication.

> *Much like what happened last year in Puerto Rico, this scenario highlights several of the trends mentioned above and how they can work together. Drug makers and their workers relied on the consistent delivery of basic services, in a region that was prone to severe flooding. Subsequent shortages allowed opportunists to compromise the delivery of the drugs through fraud.*

2022 – A Different Type of Infection

Jup1ter was not supposed to target pharmaceutical manufacturing, and technically speaking it did not. Jup1ter's creator had never even heard of the mid-sized US drug manufacturer that Jup1ter ultimately infected via a malicious email attachment opened mid-April 2022. Jup1ter was designed to encrypt the memory on any device still running the Microsoft Windows 7 operating system, and to search for other victims within the same corporate network. So while the drug assembly line, which was largely operated by Unix-based IoT devices, remained untouched by Jup1ter, the ransomware spread through the company's human resource, accounting, and sales departments. As the ransomware encrypted hard drives for every one of the company's executives, the CEO came to the realization that even though the manufacturing lines remained active, order fulfilment would be delayed.

2023 – The Hamster Hustle

Bevacizumab is a biologic substance produced in mammalian cells used to treat numerous cancers.[59] China is a key player in providing the API for Bevacizumab, owing to the large number of hamster farms cultivated for producing the drug. Since 2020, however, a viral outbreak has decimated the Chinese hamster population, sending the cost of hamsters soaring. With the cost of the API rising, one Chinese API supplier substitutes this substance with an untested synthetic chemical which appears to bind to other ingredients of Bevacizumab similarly to the API. Though the U.S. FDA and Chinese State Food and Drug Agency have increased the number of inspections of drug manufacturing facilities in China, ongoing staffing shortages meant that some audits were not very thorough.

Given the difficulty of conducting in-depth audits of all upstream suppliers involved in the drug production, a tainted batch of Bevacizumab was made and shipped to pharmacists nationwide. The drug producer ultimately recalled the product after several cancer patients exhibited adverse reactions.

> *This story is not far-fetched; a similar case happened with a batch of tainted Heparin in 2008.[60] Although the FDA has taken steps to improve its overseas inspections, this oversight function is still hindered by staffing issues.*
>
> *The reliance on animal tissues creates opportunities for unscrupulous third-parties to cut corners during shortages. Investigators found that tainted Heparin was a result of an unapproved adulterant being used after Chinese swine herds were decimated by an epidemic. Like extreme weather events, the frequency and intensity of animal disease outbreaks is also increasing.[61] If animal stocks dwindle or perish, some suppliers might try to insert tainted tissue or other adulterants into the supply chain.*

Observations and Recommendations

Few of the aforementioned risks exist in a vacuum, as each of these scenarios highlight. As in our case study, drug makers and governments grappling with one of risk area should be prepared to manage

others. We propose a number of goals and solutions that policy-makers could consider to begin to address pharmaceutical supply chain threats; these recommendations, much like the risks we identified, are not exhaustive, but are meant to start guide the discussion of what can be done better, the next time disaster strikes.

Goal: Expedite and Reinforce Manufacturer Disclosure of Drug Shortages to the FDA

Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA) currently requires manufacturers to notify the FDA six months in advance of an impending drug shortage, or no later than five business days after experiencing a drug shortage, a rule that most companies generally follow.[62] This early warning system for supply chain issues allows the FDA to approve new suppliers' abbreviated new drug applications (ANDA), facilitate the production of alternative products, and import stockpiles prior to an impending shortage. However, the agency does not currently require manufacturers to disclose what caused a shortage, its expected duration, or an estimated timeline for resolution. Between 2001 and 2014, 46 percent of all emergency medicine shortages occurred for reasons manufacturers declined to specify.[63] This information could help the FDA devise a comprehensive response plan, especially if manufacturing of a critical drug is interrupted for a significant amount of time, which may require measures more drastic such as controlled importation of foreign drugs. [64] Without knowing the true reason behind a disruption, it is nearly impossible to use US government resources to address the root issue.

Recommendations:

- Encouraging more transparency from manufacturers, requiring them to disclose the reason behind a supply chain or manufacturing disruption, and their expected timeline for resolution.
- Providing accessible education for manufacturers on their responsibilities to report disruptions to the FDA and the importance of complete and accurate information linked to the shortage.
- Changing the requirement for manufacturers to notify the FDA five-business days after experiencing an interruption in manufacturing to immediate notification upon discovery of a disruption, especially if the drug affected is "critical" or "life-saving" in nature.

Goal: Prioritize Disruptions to the Supply Chain or Manufacturing of Critical Drugs

At this time, the FDA does not prioritize certain medications over others experiencing potential shortages. The agency requires manufacturers to notify them of possible disruptions to the production of drugs that are "life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition." [65] However, a list of high-priority drugs that would meet this definition does not exist, leading to inconsistent responses within the industry. During the AEP Pharmaceutical team's Roundtable in April 2017, representatives of one of the world's largest pharmaceutical companies provided similar feedback, stating every manufacturer develops their own unique list of what they deem "live-saving." However, this list can change frequently depending on market conditions and turnover rates, and manufacturers do not typically share this data externally. The participating company also stated that they define "life-saving" as any product that is not manufactured by anyone else, and many companies manufacture some of these products at a loss.[66]

Recommendations:

- Developing a list or more specific criteria defining what the FDA considers "life-saving" drugs, as a first step in determining whether adequate emergency stockpiles should be maintained.

Goal: Improving Incentives for Manufacturers to Maintain Supply

In the event of drug shortage, the FDA often relies on other companies, including foreign entities, to fulfil the production gap. For example, during the shortage of IV bags produced by Baxter International following Hurricane Maria, the FDA approved a Spanish and German company, Fresenius Kabi and Laboratorios Grifols, to supply saline and Baxter's Mexican branch to import IV bags to the US market.[67] However, market dynamics often deter companies from fulfilling production gaps, as there is often a lack of financial incentives to do so. During the AEP Roundtable, one company stated that it would be helpful if there were guaranteed orders (contracts that lock in a specific number of orders annually) for low supply products, to ensure their product continues to sell even after the competitor's product reenters the market.[68] A 2017 study also found that eight out of ten pharmaceutical companies interviewed would be more willing to invest in backup facilities or new manufacturing lines to prevent shortages if they had guaranteed-utilization orders and/or long-term contracts in place.[69]

The time to get an ANDA approved to develop a replacement drug often deters companies from entering the market to prevent a shortage. Although the FDA currently prioritizes ANDA submission that could "help mitigate or resolve a drug shortage and prevent future shortages", the median approval time for a prioritized review of ANDA is still over a year.[70] [71]

Recommendations:

- Incentivizing manufacturers to produce "life-saving critical" drugs facing an impending shortage or disruption by requiring Group Purchasing Organizations to retain exclusive contracts or guaranteed-volume contracts.
- Prioritizing and streamlining ANDA approvals and technology transfers for manufacturers of drugs that the FDA deems to be lifesaving and critical to patient care. The effectiveness of this solution would increase if manufacturers notified the FDA of potential shortages as early as possible, and did not wait until five-business days after disruption to production has already occurred.

Goal: Prioritizing the Pharmaceutical Industry and Supply Chain Components as National Security Assets

Despite the significant impact that threats to pharmaceutical supply chains have on the American public's well-being and the overall economy, our team found the government does not place the same priority on the pharmaceutical industry as it does other strategic national security assets, like energy security and aviation safety. This could keep drug manufacturers from disclosing vital information to the public sector, as they are not covered under the Protected Critical Infrastructure Information Program (PCII) that prevents public disclosure of information under the Freedom of Information Act (FOIA).[72][73] Designating the industry as a specific high-priority critical infrastructure sector allows the government to coordinate efforts during times of crisis or catastrophes affecting the industry. Pharmaceutical representatives interviewed at the AEP Roundtable revealed that they chartered flights to deliver

medicines and generators for their employees and production facilities in Puerto Rico following Hurricane Maria, which is an initiative the government could help coordinate on behalf of the dozens of US pharmaceutical companies clustered on the island. Finally, Congress has previously adopted policies and offered incentives to counteract market influences driving geographic vulnerabilities of highly concentrated critical infrastructure.[74]

Recommendations:

- Fostering further public-private partnerships and information sharing under the PCII Program, which protects information related to critical infrastructure,
- Allocating resources into departments or third-party organizations dedicated to assessing the threats and vulnerabilities facing the industry, in a similar fashion to how the FAA designates airline safety teams that analyze risks that the industry faces as a whole.
- Issue guidance and incentives for pharmaceutical supply chain entities to conduct self-audits and regular reporting regarding the state of business/manufacturing continuity preparedness.
- Establish a standard for new pharmaceutical manufacturing and storage site selections, taking into account necessary infrastructure, the redundancy of such infrastructure, or alternative sources.

Concluding Remarks:

Based on our team's research, there are many risks that threaten the pharmaceutical supply chain, and some of the best solutions to mitigate these risks require the government and private sector to come together further, beyond the scope of the Analytic Exchange Program. These are merely recommendations for policy-makers in government and corporate leadership in the private sector to consider, but we ask that our readers also consider this: at the time of writing, Puerto Rico is again in the middle of the 2018 hurricane season. Many of the issues regarding the effect of Maria on U.S. public health still remain unresolved.

Disclaimer Statement:

This document is provided for educational and informational purposes only. The views and opinions expressed in this document do not necessarily state or reflect those of the U.S. Government or the Public-Private Analytic Exchange Program participants, and they may not be used for advertising or product endorsement purposes. All judgments and assessments are solely based on unclassified sources and are the product of joint public and USG efforts.

Citations

---

[1] Government Report. U.S. General Accounting Office. Briefing Report to U.S. Senate Special Committee on Aging. "PHARMACEUTICAL INDUSTRY: Tax Benefits of Operating in Puerto Rico." May 1992. Last Accessed 18 June 2018 from https://www.gao.gov/assets/80/78407.pdf

[2] Online Website. Government of Puerto Rico, Department of Economic Development and Commerce. "MEDICAL DEVICES." (No date available). Last Accessed 18 June 2018 from http://www.pridco.com/industries/Pages/Medical-Devices.aspx

[3] Online Website. Government of Puerto Rico, Department of Economic Development and Commerce. "PHARMACEUTICAL." (No date available). Last Accessed 18 June 2018 from http://www.pridco.com/industries/Pages/Pharmaceutical.aspx

[4] Online Website. Government of Puerto Rico, Department of Economic Development and Commerce. "BIOTECHNOLOGY." (No date available). Last Accessed 18 June 2018 from http://www.pridco.com/industries/Pages/Biotecnology.aspx

[5] Press Release. U.S. Food and Drug Administration. "FDA In Brief: FDA analysis reinforces the important role of medical product manufacturing to Puerto Rico's economic vitality and the island's jobs recovery." 6 November 2017. Last Accessed 18 June 2018 from https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm584019.htm

[6] Press Release. U.S. Food and Drug Administration. "Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA's continued assistance following the natural disaster in Puerto Rico." 6 October 2017. Last Accessed 18 June 2018 from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm579493.htm

[7] Online Article. Pharma Boardroom, *Healthcare and Life Sciences Review*. "Puerto Rico by the Numbers." January 2016. Last Accessed 18 June 2018 from https://pharmaboardroom.com/wp-content/files_mf/1454427075PuertoRicoHCLSReviewJanuary2016Pharmaboardroom.pdf

[8] Online Article. The Rhodium Group. "The World's Second Largest Blackout." 12 April 2018. Last Accessed 18 June 2018 from https://rhg.com/research/puerto-rico-hurricane-maria-worlds-second-largest-blackout/

[9] Online Article. Pasquines.es. "Ripple effects of Hurricane Maria cause pharma shortages." 11 January 2018. Last Accessed 18 June 2018 from https://pasquines.us/2018/01/11/ripple-effects-hurricane-maria-cause-pharma-shortages/

[10] News Article. *The Miami Herald.* "San Juan airport remains crippled by Hurricane Maria damage." 25 September 2017. Last Accessed 18 June 2018 from http://www.miamiherald.com/news/weather/hurricane/article175356006.html

[11] News Article. *National Public Radio.* "In Puerto Rico, Containers Full Of Goods Sit Undistributed At Ports." 28 September 2017. Last Accessed 18 June 2018 from https://www.npr.org/sections/thetwo-way/2017/09/28/554297787/puerto-rico-relief-goods-sit-undistributed-at-ports

[12] News Article. *Washington* Post. "Puerto Rico's roadways alone are a disaster, and it will cost at least $240 million to fix them." 29 September 2017. Last Accessed 18 June 2018 from https://www.washingtonpost.com/news/dr-gridlock/wp/2017/09/29/puerto-ricos-roadways-alone-are-a-disaster-and-it-will-cost-at-least-240-million-to-fix-them/

[13] News Article. *Wall Street Journal.* "Inside Puerto Rico's Struggle to Recover a Month After Hurricane." 20 October 2017. (2017, October 20). Last Accessed 18 June 2018 from https://www.wsj.com/articles/inside-puerto-ricos-struggle-to-recover-a-month-after-hurricane-1508491811

[14] Press Release. U.S. Food and Drug Administration. "Statement by FDA Commissioner Scott Gottlieb, M.D., on efforts to address impact of IV fluid shortages following hurricane destruction and resolve manufacturing shortfalls." 17 November 2017. Last Accessed 18 June 2018 from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585720.htm

[15] Online Article. *American Shipper.* "Ports closed, cargo delayed as Hurricane Maria causes widespread destruction in Puerto Rico." 22 September 2017. Last Accessed 18 June 2018 from https://www.americanshipper.com/main/news/ports-closed-cargo-delayed-as-hurricane-maria-caus-69107.aspx

[16] News Article. *Washington Post.* "Getting relief supplies to Puerto Rico ports is only half the problem." 28 September 2017. Last Accessed 18 June 2018 from https://www.washingtonpost.com/business/economy/getting-relief-supplies-to-puerto-rico-ports-is-only-half-the-problem/2017/09/28/9ff558a6-a460-11e7-8cfe-d5b912fabc99_story.html
[17] News Article. *Reuters.* "Pharma's Puerto Rico problems could mean drug shortages: FDA chief." 10 October 2017. Last Accessed 18 June 2018 from https://www.reuters.com/article/us-usa-healthcare-gottlieb-puertorico/pharmas-puerto-rico-problems-could-mean-drug-shortages-fda-chief-idUSKBN1CF2RJ
[18] Academic Journal Special Article. Kishore, Nishant et. al. *New England Journal of Medicine.* "Mortality in Puerto Rico After Hurricane Maria." 29 May 2018. DOI: 10.1056/NEJMsa1803972
[19] Academic Journal Special Article. Kishore, Nishant et. al. *New England Journal of Medicine.* "Mortality in Puerto Rico After Hurricane Maria." 29 May 2018. DOI: 10.1056/NEJMsa1803972
[20] Online Article. U.S. Centers for Disease Control and Prevention. "Weekly U.S. Influenza Surveillance Report." 8 June 2018. Last Accessed 18 June 2018 from https://www.cdc.gov/flu/weekly/
[21] Online Article. U.S. Centers for Disease Control and Prevention. "Update: Influenza Activity in the United States During the 2017–18 Season and Composition of the 2018–19 Influenza Vaccine." 8 June 2018. Last Accessed 18 June 2018 from https://www.cdc.gov/mmwr/volumes/67/wr/mm6722a4.htm?s_cid=mm6722a4_w
[22] News Article. *CBS News.* "Hospitals struggle to battle peak flu season amid widespread IV bag shortage." 9 January 2018. Last Accessed 18 June 2018 from https://www.cbsnews.com/news/flu-season-straining-resources-iv-bag-shortage-hurricane-maria-puerto-rico/
[23] Press Release. U.S. Food and Drug Administration. "Statement by FDA Commissioner Scott Gottlieb, M.D., on efforts to address impact of IV fluid shortages following hurricane destruction and resolve manufacturing shortfalls." 17 November 2017. Last Accessed 18 June 2018 from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585720.htm
[24] Online Article. *Smithsonian Magazine.* "A Saline Shortage This Flu Season Exposes a Flaw in Our Medical Supply Chain." 22 January 2018. Last Accessed 18 June 2018 from https://www.smithsonianmag.com/innovation/saline-shortage-this-flu-season-exposes-flaw-in-our-medical-supply-chain-180967879/
[25] Journal Article. *Emerging Infectious Diseases.* Radonovich, Lewis et. al. "Stockpiling Supplies for the Next Influenza Pandemic" June 2009. Last Accessed 18 June 2018. DOI: 10.3201/eid1506.081196
[26] Online Article. *Insight-US.* "Some of These 101 Prescription Drugs – Made in Puerto Rico Before Hurricane Maria – May Soon Be Unavailable." 26 October 2017. Last Accessed 18 June 2018 from http://insight-us.org/puerto_rico_drugs.html
[27] Online Publication. World Health Organization. "Essential Medicines List." August 2017. Last Accessed 18 June 2018 from http://www.who.int/medicines/publications/essentialmedicines/en/
[28] Online Publication. U.S. Department of Homeland Security. "Healthcare and Public Health Sector." 11 July 2017; Last Accessed 18 June 2018 from https://www.dhs.gov/healthcare-public-health-sector
[29] Online Article. *E&E News.* "How Puerto Rico Became the Worst Grid Disaster." 18 April 2018. Last Accessed 18 June 2018 from https://www.eenews.net/stories/1060079499
[30] News Article. *National Public Radio.* "How Puerto Rico's Debt Created A Perfect Storm Before the Storm." 2 May 2018. Last Accessed 18 June 2018 from https://www.npr.org/2018/05/02/607032585/how-puerto-ricos-debt-created-a-perfect-storm-before-the-storm
[31] News Article. *CNBC.* "Here's How an Obscure Tax Change Sank Puerto Rico's Economy." 26 September 2017. Last Accessed 18 June 2018 from https://www.cnbc.com/2017/09/26/heres-how-an-obscure-tax-change-sank-puerto-ricos-economy.html
[32] Online Publication. United Nations Conference on Trade and Development. *Police Issues in International Trade and Commodities Study Series No. 55.* "Global Supply Chains: Trade and Economic Policies for Developing Countries." 2013. Last Accessed 18 June 2018 from http://unctad.org/en/PublicationsLibrary/itcdtab56_en.pdf
[33] Online Article. B-Scada. "What is the Internet of Things?" (No date available). Last Accessed 18 June 2018 from http://scada.com/verticals/internetofthings/
[34] Online Article. *Contract Pharma.* "The importance of Supplier Management." 23 August 2005. Last Accessed 18 June 2018 from https://www.contractpharma.com/issues/2004-12/view_features/the-importance-of-supplier-management

[35] AEP Team Interview with U.S. Pharmaceutical Industry Representative, April 2018.
[36] Online Publication. McKinsey & Company. "Outlook on Pharma Operations." 2010. Last Accessed 18 June 2018 from https://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/operations/pdfs/outlook_on_pharma_operations.ashx
[37] News Article. *USA Today.* "As Drug Making Goes Global, Oversight Found Lacking." 21 October 2012. Last Accessed 18 June 2018 from https://www.usatoday.com/story/news/2012/10/21/global-drug-manufacturing-oversight/1646487/
[38] Online Publication. Airmic Technical. "Supply Chain Failures." 2013. Last Accessed 18 June 2018 from https://www.riskmethods.net/resources/research/supply_chain_failures_2013_final_web.pdf
[39] Online Website. World Health Organization. "Biologicals/Cell Substrates." 27 September 2016. Last Accessed 18 June 2018 from http://www.who.int/biologicals/vaccines/cell_substrates/en/
[40] AEP Team Interview with U.S. Pharmaceutical Industry Representative, April 2018.
[41] Online Article. Pharmatech.com. "Will Pharma Manufacturing Move Back to the US?" 2 March 2017. Last Accessed 18 June 2018 from http://www.pharmtech.com/will-pharma-manufacturing-move-back-us-0
[42] Online Article. Pharmatech.com. "Will Pharma Manufacturing Move Back to the US?" 2 March 2017. Last Accessed 18 June 2018 from http://www.pharmtech.com/will-pharma-manufacturing-move-back-us-0
[43] News Article. *National Public Radio.* "Fake Drugs Are A Major Global Health Problem, WHO Reports." 29 November 2017. Last Accessed 18 June 2018 from https://www.npr.org/sections/goatsandsoda/2017/11/29/567229552/bad-drugs-are-a-major-global-problem-who-reports
[44] AEP Team Interview with U.S. Pharmaceutical Industry Representative, April 2018.
[45] News Article. *CBS News.* "Black Market Insulin: What You Need to Know." 20 June 2017. Last Accessed 18 June 2018 from https://www.cbsnews.com/news/black-market-insulin-what-you-need-to-know/
[46] Online Publication. Airmic Technical. "Supply Chain Failures." 2013. Last Accessed 18 June 2018 from https://www.riskmethods.net/resources/research/supply_chain_failures_2013_final_web.pdf
[47] News Article. *New York Times.* "From Heat Waves to Hurricanes: What We Know About Extreme Weather and Climate Change." 15 September 2017. Last Accessed 18 June 2018 from https://www.nytimes.com/interactive/2017/09/15/climate/does-climate-change-cause-hurricanes-drought.html
[48] AEP Team Interview with U.S. Pharmaceutical Industry Representative, April 2018.
[49] News Article. *Financial Times.* "Supply Chains: Look For the Single Point of Failure." 1 May 2011. Last Accessed 18 June 2018 from https://www.ft.com/content/12427fe4-7216-11e0-9adf-00144feabdc0
[50]Online Publication. McKinsey & Company. "Outlook on Pharma Operations." 2010. Last Accessed 18 June 2018 from https://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/operations/pdfs/outlook_on_pharma_operations.ashx
[51] Online Article. *Scientific American.* "The Unfolding Tragedy of Climate Change in Bangladesh." 21 April 2017. Last Accessed 18 June 2018 from https://blogs.scientificamerican.com/guest-blog/the-unfolding-tragedy-of-climate-change-in-bangladesh/
[52] Online Publication. Business Continuity Institute. "BCI Supply Chain Resilience Report 2017." 2017. Last Accessed 18 June 2018 from https://www.riskmethods.net/resources/research/BCI-Resilience-Report-2017.pdf
[53] Online Article. The Atlantic Council. "2017 US Cyber 9/12 Student Challenge." 17 April 2017. Last Accessed 18 June 2018 from http://www.atlanticcouncil.org/events/past-events/2017-us-cyber-9-12-student-challenge
[54] News Article. *Wired.* "The White House Blames Russia for NotPetya, the 'Most Costly Cyberattack in History.'" 14 February 2018. Last Accessed 18 June 2018 from https://www.wired.com/story/white-house-russia-notpetya-attribution/
[55] News Article. *Cyberscoop.* "NotPetya Ransomware Cost Merk More than $310 Million." 27 October 2017. Last Accessed 18 June 2018 from https://www.cyberscoop.com/notpetya-ransomware-cost-merck-310-million/
[56] News Article. *The Guardian.* "'Not a Single Thing Was Dry': Mumbai's Residents Count the Cost of Floods." 1 September 2017. Last Accessed 18 June 2018 from https://www.theguardian.com/world/2017/sep/01/mumbai-residents-count-cost-rain-floods

[57] Press Release. U.S. Food and Drug Administration. "The FDA Approves First Generic Version of Widely Used Influenza Drug, Tamiflu." 3 August 2016; Accessed 18 June 2018 https://fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm514854.htm
[58] Online Article. *HealthLine.* "Why Are We Having Shortages of Tamiflu and Other Medications?" 20 February 2018. Accessed 18 June 2018 https://www.healthline.com/health-news/shortages-of-tamiflu-and-other-meds#1
[59] Online Website. RxList. "Avastin." (No date available). Last Accessed 18 June 2018 from https://www.rxlist.com/avastin-drug.htm
[60] Online Article. The Pew Charitable Trusts. "Heparin: A Wake-Up Call on Risks to the U.S. Drug Supply." 16 May 2012. Last Accessed 18 June 2018 from http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2012/05/16/heparin-a-wakeup-call-on-risks-to-the-us-drug-supply
[61] Online Article. DW. "Animal Diseases Intensified by Climate Changes." 25 November 2014. Last Accessed 18 June 2018 from http://www.dw.com/en/animal-diseases-intensified-by-climate-change/a-18084762
[62] Meeting Notes. *American Society of Health-System Pharmacists.* "Drug Shortages Roundtable: Minimizing Impact on Patient Care." 6 November 2017. Last Accessed 18 June 2018 from https://www.ashp.org/-/media/assets/drug-shortages/docs/drug-shortages-nov-2017-shortage-meeting-report.ashx
[63] Journal Article. Hawley, Kristy et. al. *Journal of the Society for Academic Emergency Medicine.* "Longitudinal Trends in U.S. Drug Shortages for Medications Used in Emergency Departments (2001–2014)." 30 December 2015. DOI:10.1111/acem.12838
[64] Meeting Notes. *American Society of Health-System Pharmacists.* "Drug Shortages Roundtable: Minimizing Impact on Patient Care." 6 November 2017. Last Accessed 18 June 2018 from https://www.ashp.org/-/media/assets/drug-shortages/docs/drug-shortages-nov-2017-shortage-meeting-report.ashx
[65] Journal Article. Barlas, Stephen. *Pharmacy and Therapeutics.* "Manufacturers and Hospitals Spar Over Drug Shortage Reporting FDA Proposal Seeks to Improve Early Warning System." 4 March 2014. Last Accessed 18 June 2018 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005123/
[66] AEP Team Interview with U.S. Pharmaceutical Industry Representative, April 2018.
[67] News Article. *Reuters.* "Baxter to import IV saline bags from Mexico to ease U.S. shortage." 25 January 2018. Last Accessed 18 June 2018 from https://www.reuters.com/article/us-baxter-intl-saline/baxter-to-import-iv-saline-bags-from-mexico-to-ease-u-s-shortage-idUSKBN1FD36W
[68] AEP Team Interview with U.S. Pharmaceutical Industry Representative, April 2018.
[69] Online Publication. The Pew Charitable Trusts. "Drug Shortages An exploration of the relationship between U.S. market forces and sterile injectable pharmaceutical products: Interviews with 10 pharmaceutical companies." January 2017. Last Accessed 18 June 2018 from http://www.pewtrusts.org/~/media/assets/2017/01/drug_shortages.pdf
[70] Government Publication. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *Manual of Policies and Procedures.* "Prioritization of the Review of Original ANDAs, Amendments, and Supplements." 2017. Last Accessed 18 June 2018, from https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf
[71] Online Publication. The Pew Charitable Trusts. "Drug Shortages An exploration of the relationship between U.S. market forces and sterile injectable pharmaceutical products: Interviews with 10 pharmaceutical companies." January 2017. Last Accessed 18 June 2018 from http://www.pewtrusts.org/~/media/assets/2017/01/drug_shortages.pdf
[72] Government Publication. U.S. Department of Homeland Security. "Protected Critical Infrastructure Information Program." January 2017. Last Accessed 18 June 2018 from https://www.dhs.gov/sites/default/files/publications/pcii-fact-sheet-2017-508.pdf
[73] Meeting Notes. *American Society of Health-System Pharmacists.* "Drug Shortages Roundtable: Minimizing Impact on Patient Care." 6 November 2017. Last Accessed 18 June 2018 from https://www.ashp.org/-/media/assets/drug-shortages/docs/drug-shortages-nov-2017-shortage-meeting-report.ashx
[74] Government Report. U.S. Congressional Research Service. Parfomak, Paul. "Vulnerability of Concentrated Critical Infrastructure: Background and Policy Options." 12 September 2008. Last Accessed 18 June 2018 from https://fas.org/sgp/crs/homesec/RL33206.pdf