



COVID-19: Pharmaceutical Supply Chain Vulnerabilities

March 31, 2020



Executive Summary & Key Takeaways

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Threats to the drug supply chain have emerged and are worsening. Action must be taken now to stabilize the drug supply chain.



Drug shortages will first appear as regional shortages as COVID-19 progresses throughout the country in hot spots.



Many of the drugs being used to treat COVID-19 patients are already on the FDA drug shortage list and therefore have supply chain constraints. The current supply chain for these drugs is unlikely to meet the surge demand.



Since there is no single cause of drug shortages, solutions must be multifactorial.



The drug supply chain is not resilient and the time to recover for shortages is prolonged and can take upwards of 3-5 years based upon historic drug shortage recovery times.



Immediate action is needed now to mitigate current shortages and prevent additional shortages to ensure drugs with the potential to treat COVID-19 are available for patient care. FDA should immediately leverage its new authority under the CARES Act to quantify the reliance on foreign manufacturing and impact on the drug supply chain.



Premier Pharmaceutical Supply Chain Vulnerabilities Survey Results

- Fielded from March 20 – 25, 2020
- Respondent Demographics

Acute

- 377 unique hospitals and health systems
- 31% have a COVID-19 patient
- 35% do NOT have a COVID-19 patient
- 34% did not respond
- 42 states

Non-Acute

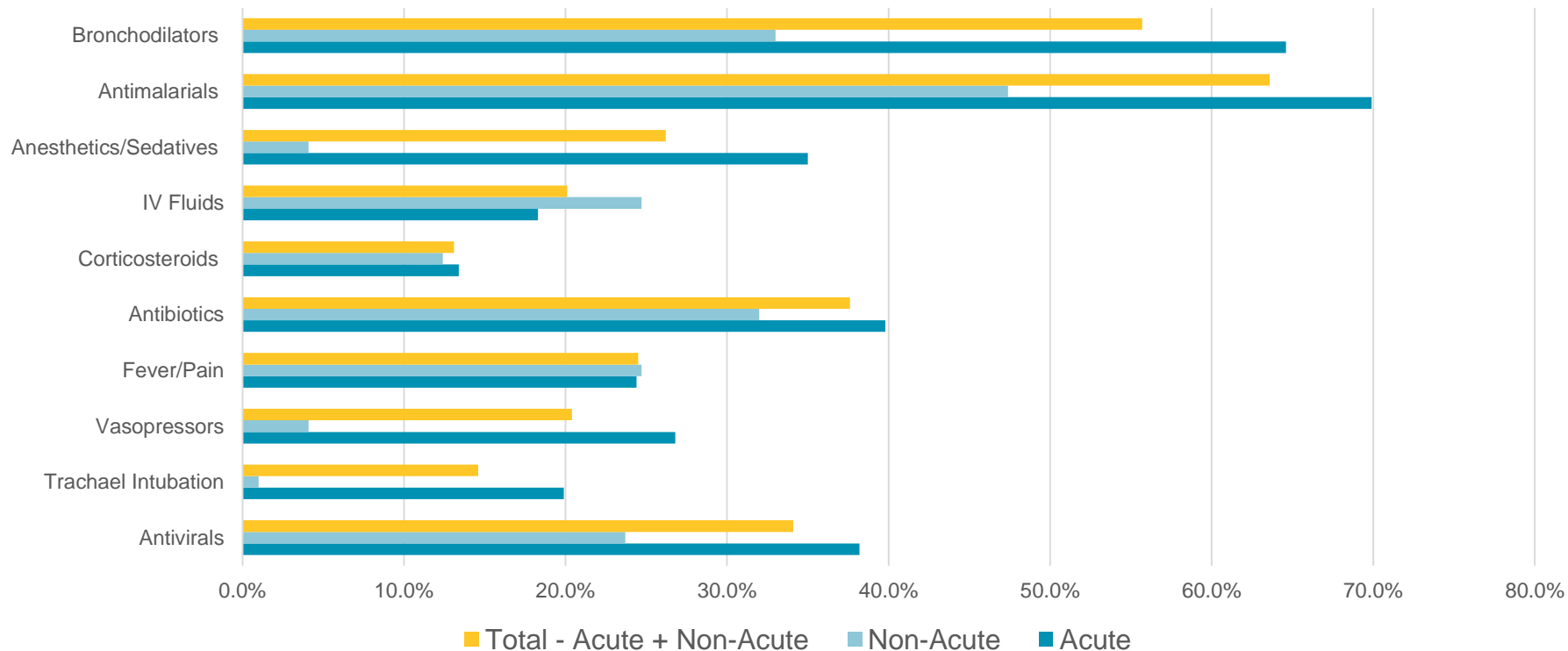
- 102 unique long-term care, home infusion, and retail pharmacies
- 16% have a COVID-19 patient
- 63% do NOT have a COVID-19 patient
- 21% did not respond
- 38 states

Drug Classes Surveyed

- **Antivirals** – lopinavir/ritonavir, ribavirin, acyclovir, oseltamivir, zanamivir
- **Tracheal intubation** – cisatracurium, vecuronium, rocuronium
- **Vasopressors for septic shock** – norepinephrine, dopamine, epinephrine, phenylephrine, vasopressin, dobutamine
- **Fever/pain** – acetaminophen, ibuprofen, aspirin, diclofenac
- **Antibiotics** - vancomycin, piperacillin/tazobactam, cefazolin, doxycycline, sulfamethoxazole/trimethoprim, azithromycin
- **Corticosteroids** – hydrocortisone, prednisone, methylprednisolone, hydrocortisone
- **IV fluids & electrolytes** - normal saline, 3% hypertonic saline, potassium chloride, calcium chloride, calcium gluconate, sodium bicarbonate, sterile water, sodium phosphate, potassium phosphate
- **Anesthetics/sedatives** – propofol, midazolam, fentanyl, hydromorphone, morphine, dexmedetomidine
- **Antimalarials** – chloroquine, hydroxychloroquine
- **Bronchodilators** – albuterol, salbutamol, ipratropium, theophylline

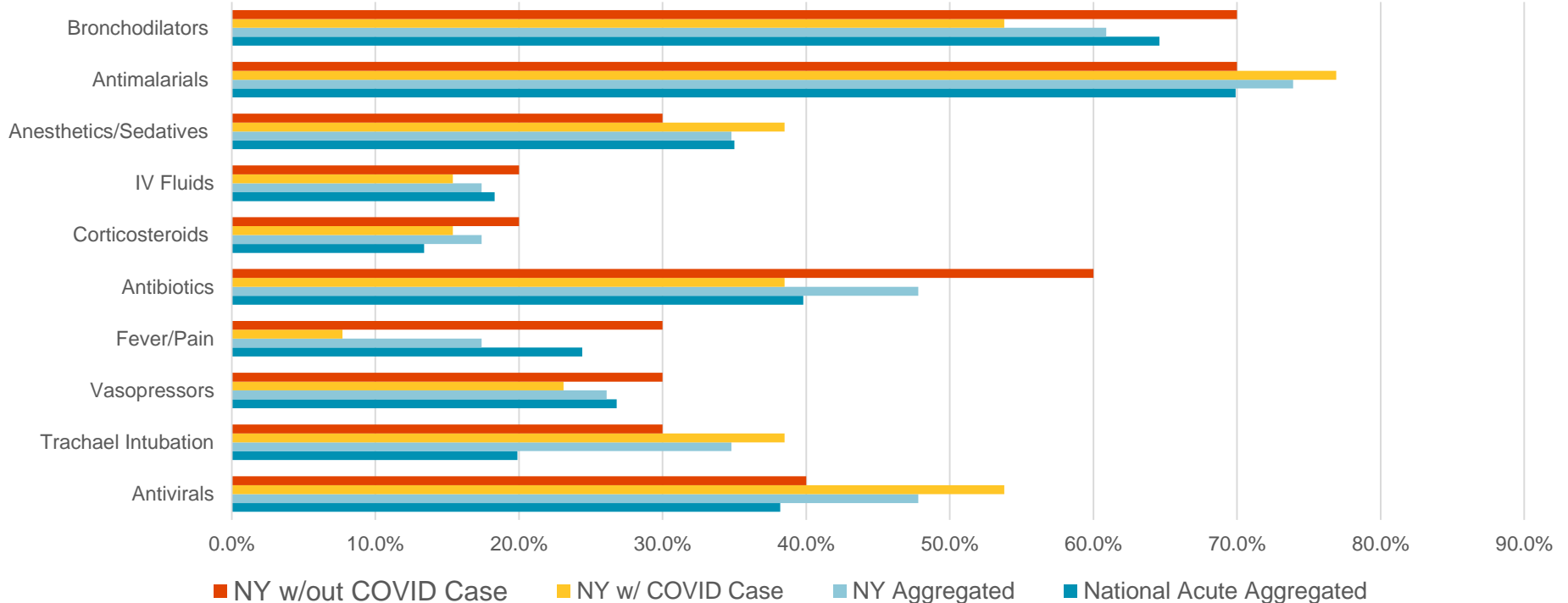
Current Shortages: Acute vs Non-Acute vs Aggregated

The primary concern for drug shortages is currently in the acute space. Therefore, the immediate focus should be on the acute setting, although more pervasive shortages in the non-acute setting are likely not far behind.



Current Shortages: New York

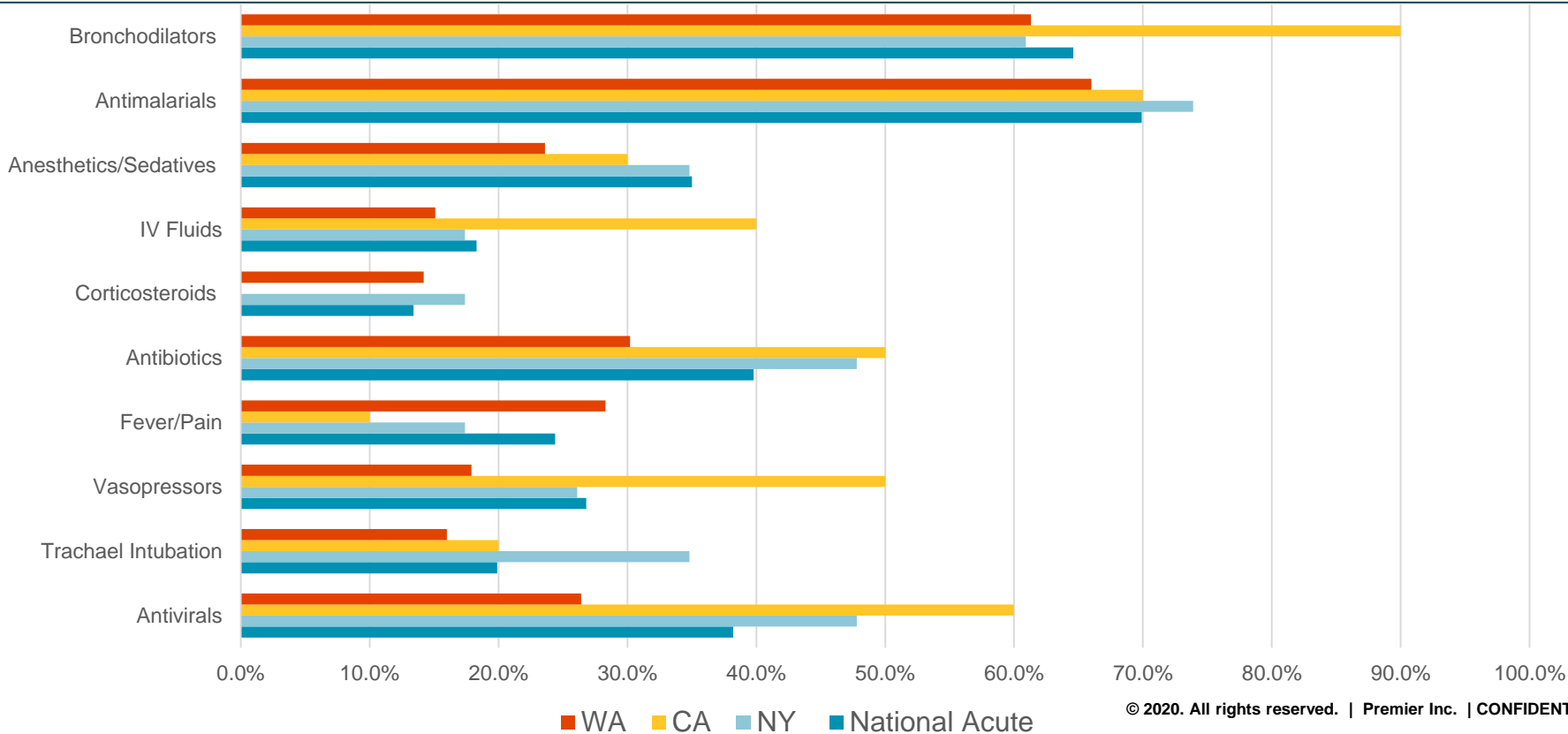
Reported drug shortages in New York are higher than the national average. Shortages for antivirals, tracheal intubation, anesthetics, and antimalarials are higher for hospitals w/ COVID patients indicating wide usage of the “COVID cocktail.” However, shortages for all other classes are higher for hospitals w/out COVID patients.





Current Shortages: New York vs California vs Washington

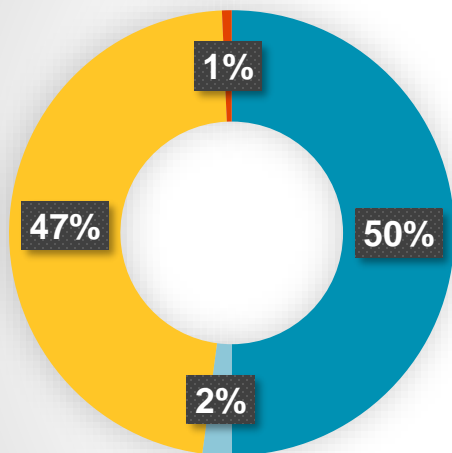
CA appears to have more substantial drug shortages compared to NY and WA. WA appears to have less shortages than the national average.



PPE Availability Impact on Pharmacy Practice

Approximately half of respondents have adjusted their pharmacy practices as a result of PPE shortages. USP guidance on PPE use and state-based USP waivers have helped with this adjustment.

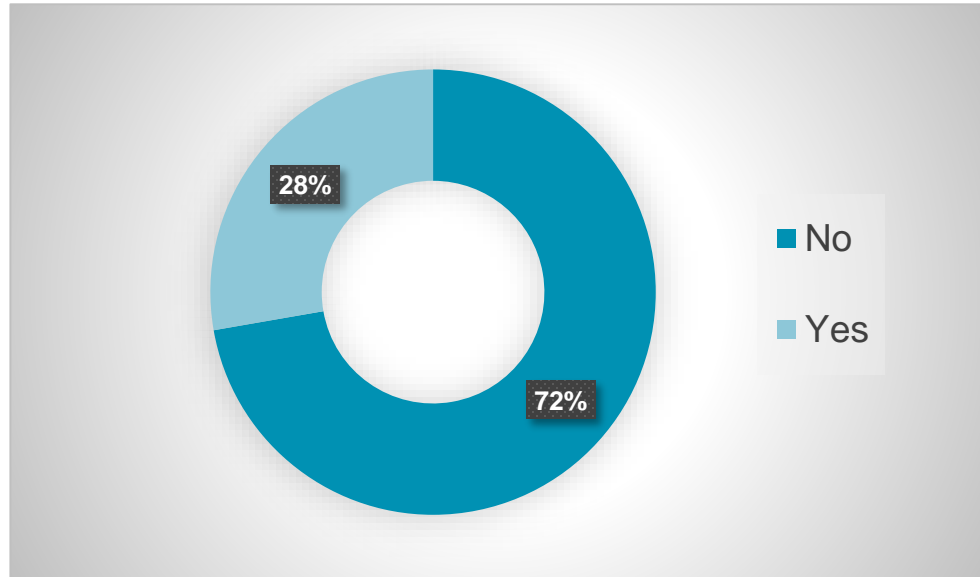
Have shortages of personal protective equipment (PPE) impacted your sterile compounding capabilities?



- No
- Yes, we have implemented a state waiver to temporarily cease garbing during compounding
- Yes, we have implemented the USP 797 PPE conservation guidance
- Yes, we have started to compound at the bedside

28% of respondents have already received a gray market solicitation for drugs used to treat COVID-19. It is likely that this number will increase as drug shortages increase throughout the country.

Have you received solicitations for gray market purchases of drugs specific to COVID-19?





Critical Drugs at Risk of Shortage

Supply vs Demand for COVID-19 Drugs

According to Premier data, several drugs used to treat COVID-19 are currently depleted in the supply chain, or are at risk of being depleted soon, based upon increases in ordering and decreases in fill rate.

Drug	Typical Orders/Month	% Increase in March	% Current Fill Rate
Azithromycin	1 million units	170%	60%
Chloroquine	149 units	3000%	19%
Hydroxychloroquine	8,800 units	260%	35%
Fentanyl	1.3 million units	100%	61%
Albuterol	3.51 million units	53%	80%
Cisatracurium	62,000 units	253%	51%
Propofol	1.3 million units	60%	82.3%
Midazolam	518,000 units	70%	79%

Supply vs Demand for COVID-19 Drugs

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Drug	Typical Orders/Month	% Increase in March	% Current Fill Rate
Norepinephrine	206,000 units	50%	67%
Rocuronium	470,000 units	84%	80%
Cefazolin	553,000 units	0%	86%
Cefepime	440,000 units	75%	83%
Ribavirin	31,000 units	200%	50%
Acyclovir	24,000 units	100%	86%
Valacyclovir	1.8 million units	20%	87%

New York: Supply vs Demand for COVID-19 Drugs

According to Premier data, increase in demand for drugs used to treat COVID-19 patients is exponentially higher in hot spots such as New York.

Drug	% Increase in March - Nationally	% Increase in March – New York
Azithromycin	170%	263%
Fentanyl	100%	533%
Albuterol	53%	1870%
Cisatracurium	253%	786%
Propofol	60%	123%
Midazolam	70%	4100%
Norepinephrine	50%	53%

Additional Risk Factors for Upcoming Shortages

Safety stock is not unlimited

- Manufacturers typically have 2-3 months of safety stock on hand.
- With increased utilization of several drugs for COVID patients, safety stock will be depleted at an expedited rate.

Drug manufacturing is not resilient

- Unlike other industries, drug manufacturing is highly regulated and not resilient. Ancillary manufacturers cannot be converted to drug manufacturers easily.
- Sterile injectable drug manufacturing is less resilient than solid oral dosage form drug manufacturing. Sterile drugs require a minimum of a 14-day sterility test prior to distribution.
- Must consider the lead time and availability of all raw materials needed for drug manufacture.
- Ramping up domestic manufacturing is contingent upon 1) available capacity; 2) API availability; and 3) expedited FDA approval process.

DEA quotas are limited for injectable CII

- Fentanyl is a key drug needed for patients requiring sedation for ventilator use.
- DEA reduced quota for fentanyl in 2020 by 31%.
- Ramping up production of fentanyl is contingent upon DEA first allocating additional quota to able manufacturers.
- Release of additional quota is dependent upon a manufacturer falling below 20% of quota inventory on hand.

Additional Risk Factors for Upcoming Shortages

Additional manufacturing restraints and export bans globally are likely

- As the disease progresses globally, manufacturing shutdown and port closures are likely to expand. For example:
 - Export bans in India may expand to additional drugs and export bans from other countries may follow.
 - Manufacturing shutdowns in Italy are also concerning as Italy is the #3 manufacturer of API globally.
 - Disease progression in Europe is concerning as the EU manufacturers approximately ~ 36% of API.
- **Drugs of greatest concern:**
 - Drugs already on the FDA drug shortage list
 - Chloroquine – all API manufacturers are located in India
 - Cephalosporin antibiotics – up to 80% of API is manufactured in Italy
 - Drugs with < 3 geographically diverse API suppliers
 - Drugs with < 3 geographically diverse finished dose form manufacturers
- The downstream impact could result in widespread drug shortages across all dosage forms, therapeutic areas, and classes of trade resulting in a very strained health care system.

Shortages will be regional

- As evidenced by the survey findings, shortages will initially be regional based upon disease progression to hot spots.
- FDA is not set-up to monitor for regional shortages, but ASHP is.



Recommendations

Threats to the drug supply chain are have emerged and are worsening. Action must be taken now to stabilize the drug supply chain. The drug supply chain is not resilient and immediate action is needed to prevent widespread drug shortages in the United States and ensure drugs with the potential to treat COVID-19 are available for patient care.

Area of Concern	Potential Solutions
<p>One-Mile Radius Rule for Sterile Compounding: With limited staff and PPE constraints, many hospitals would like to consolidate pharmacy services to a single hub. A rate-limiting step to doing so is FDA's guidance that dictates the one-mile radius rule.</p>	<p>FDA should temporarily waive the one-mile radius rule to permit hospitals to consolidate pharmacy services to a single hub. Doing so will help preserve PPE and maximize the use of available pharmacy staff.</p>
<p>Capital Constraints: Manufacturers and wholesalers may be reluctant to increase inventory levels beyond the traditional 2-3 weeks of just in time inventory due to monetary constraints.</p>	<p>The government should consider a 0% interest loan to manufacturers and wholesale distributors to increase on-hand inventory to account for surge demand.</p>

Area of Concern	Potential Solutions
<p>Allocation: Current allocation processes are based upon prior historic purchasing and do not account for surge demand.</p>	<p>Working alongside private sector partners, <i>create a dynamic allocation process</i> that accounts for surge demand. The allocation process should also balance drugs going to the retail setting to accommodate patients on chronic therapy with surge demand in acute settings.</p>
<p>Accessing the Strategic National Stockpile: The current process for accessing the SNS is extremely cumbersome and state-specific. This will become an increasing problem as donations for drugs with the potential to treat COVID-19 are being donated to the SNS and not traditional distribution channels.</p>	<p>Working alongside private sector partners, <i>create a streamlined and efficient process for accessing drugs from the SNS.</i></p>
<p>DEA Quotas: Ramping up production for controlled substances is contingent upon DEA allocating additional quota. Currently, release of quota is not triggered until a manufacturer falls below 20% of quota inventory on hand.</p>	<p>DEA should <i>temporarily increase the threshold for allocating quota to at least 50% of quota inventory on hand</i> to permit manufacturers to remain nimble and flexible to address shortages.</p>

Area of Concern	Potential Solutions
<p>Transportation: API or finished drug manufactured globally may be delayed in arriving in the US due to port closures or delays in shipping.</p>	<p>The government should leverage air transport to expedite the availability of API or drugs in shortage or at-risk of shortage to the US.</p>
<p>Transfer of Drugs: Transfer of drugs to a non-affiliated hospital or pharmacy is typically capped at 5% before an entity must register as a wholesale distributor. Additional limitations exist for the transfer of controlled substances. This may create a bottleneck for hospitals to transfer inventory to neighboring hospitals with COVID-19 patients or to hot spots.</p>	<p>FDA should temporarily waive the 5% distribution rule to permit hospitals to share inventory with hospitals with COVID-19 patients or to redirect inventory to hot spots.</p>
<p>Safety Stock: The current inventory levels and available safety stock for critical medications is unknown.</p>	<p>Working alongside private sector partners, create a centralized data repository quantifying the current inventory of critical medications. This information should be used to prioritize drugs at-risk of shortage.</p>

Recommendations

Area of Concern	Potential Solutions
<p>Domestic Capacity: To ramp up domestic manufacturing, identifying available existing capacity is critical as standing up new capacity cannot occur quickly.</p>	<p>FDA should <i>leverage line and tech transfers to expeditiously increase domestic manufacturing</i> of critical drugs at US-based pharmaceutical manufacturers.</p> <p>The President can expedite production capacity by <i>invoking the Defense Production Act</i>.</p>
<p>Regional Shortages and 503B: Shortages during COVID-19 will initially present regionally as disease progresses throughout the country. The FDA is not currently able to monitor for regional shortages, although ASHP is. 503B outsourcing facilities can only compound drugs on the FDA drug shortage list.</p>	<p>FDA should <i>collaborate with ASHP to identify and action any regional shortages</i>. In addition, FDA should <i>temporarily expand the ability of 503B outsourcing facilities to compound drugs on the ASHP list</i> to account for regional shortages.</p>
<p>Price Gouging: Prices for drugs in shortage typically double.</p>	<p>The President should <i>expand the Executive Order on price gouging to include drugs</i>.</p>

Area of Concern	Potential Solutions
<p>Gray Market: During drug shortages, shortage drugs are often sold by unauthorized vendors. The gray market creates patient safety concerns as the products may be adulterated, mishandled, mislabeled, or counterfeit.</p>	<p>FDA should <i>create a clearing house to validate and authenticate gray market offers.</i></p> <p>FDA should collaborate with the DOJ to <i>clamp down on black market scams.</i></p>
<p>Manufacturer Incentives: Manufacturers may be hesitant to enter the marketplace for shortage drugs due to the expense and uncertainty that their drug products will be purchased.</p>	<p>FDA should <i>collaborate with private sector partners, such as ProvideGx, to incentivize manufacturers to enter the marketplace</i> for shortage drugs through committed volume and/or co-investment.</p>
<p>API Supply Disruptions: API manufacturers currently do not report supply disruptions. This makes it difficult to assess downstream impact to drug shortages.</p>	<p>FDA should <i>leverage the new authority granted under Section 3112 of the CARES Act (HR 748)</i> to require API manufacturers to begin reporting supply disruptions immediately. This information will help predict impact to downstream drug shortages and prioritize API needs.</p>

Area of Concern	Potential Solutions
<p>Transparency: A lack of transparency in the drug supply chain regarding source of raw materials, active pharmaceutical ingredients (API), and finished dose forms (FDF) makes it difficult to assess the downstream risk to drug shortages.</p>	<p>FDA should <i>leverage the new authority granted under Section 3112 of the CARES Act (HR 748)</i> to require manufacturers to submit a one-time report to FDA with their exact API source and location of finished dosage form. This information will provide clarity regarding the foreign reliance on manufacturing and help prioritize drugs for domestic manufacturing.</p>
<p>Prioritization: The FDA is not required to prioritize applications and inspections for shortage drugs.</p>	<p>FDA should <i>leverage the new authority granted under Section 3111 of the CARES Act (HR 748)</i> to prioritize applications and inspections for shortage drugs. This will help expedite the availability of shortage drugs in the marketplace.</p>