•Drug Shortage and Supply Chain Issues

- *PDA Israel*
- *June 8th 2020*

- *Gil Zomber*
- *Gil Pharma*

Instructor

- Dr. Gil Zomber, freelance quality consultant and Senior Associate in the Compliance Practice at Lachman Consultants.
- Quality Systems, Internal and external audits and mock inspections, GMP audits of CMO's and supplier audits, support in preparation for and during FDA inspections.
- Lecturer at the MSc. BioMed MBA Program, The Hebrew University of Jerusalem
- Member of the Executive Committee Members of the Israel Chapter of PDA.
- In the past:

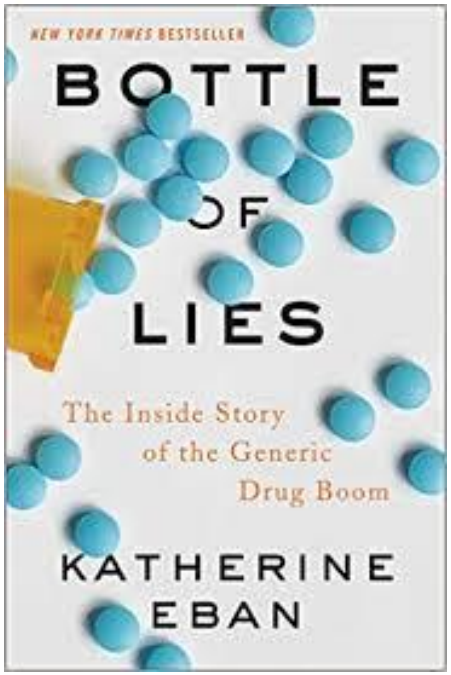
Vice President, Quality – Ayana pharma

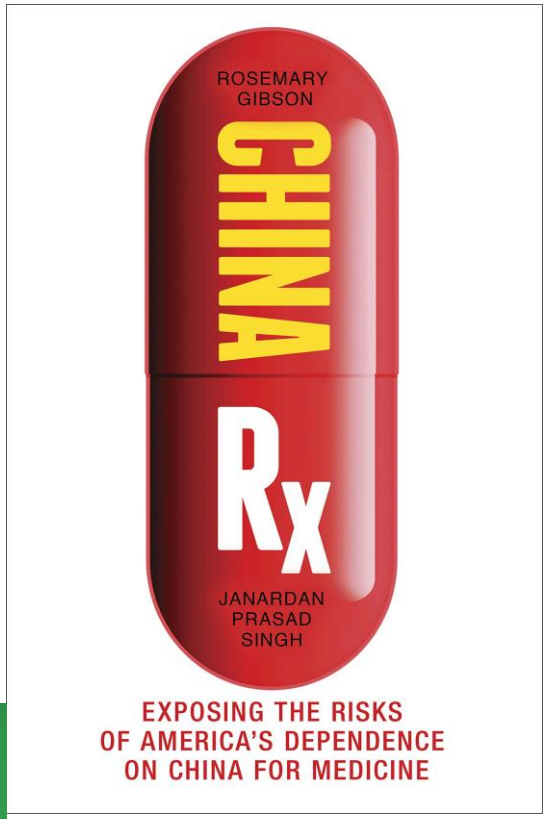
Teva, Senior Director, Quality Assurance, R&D Biologics

Israel Institute for Biological Research (Israel)

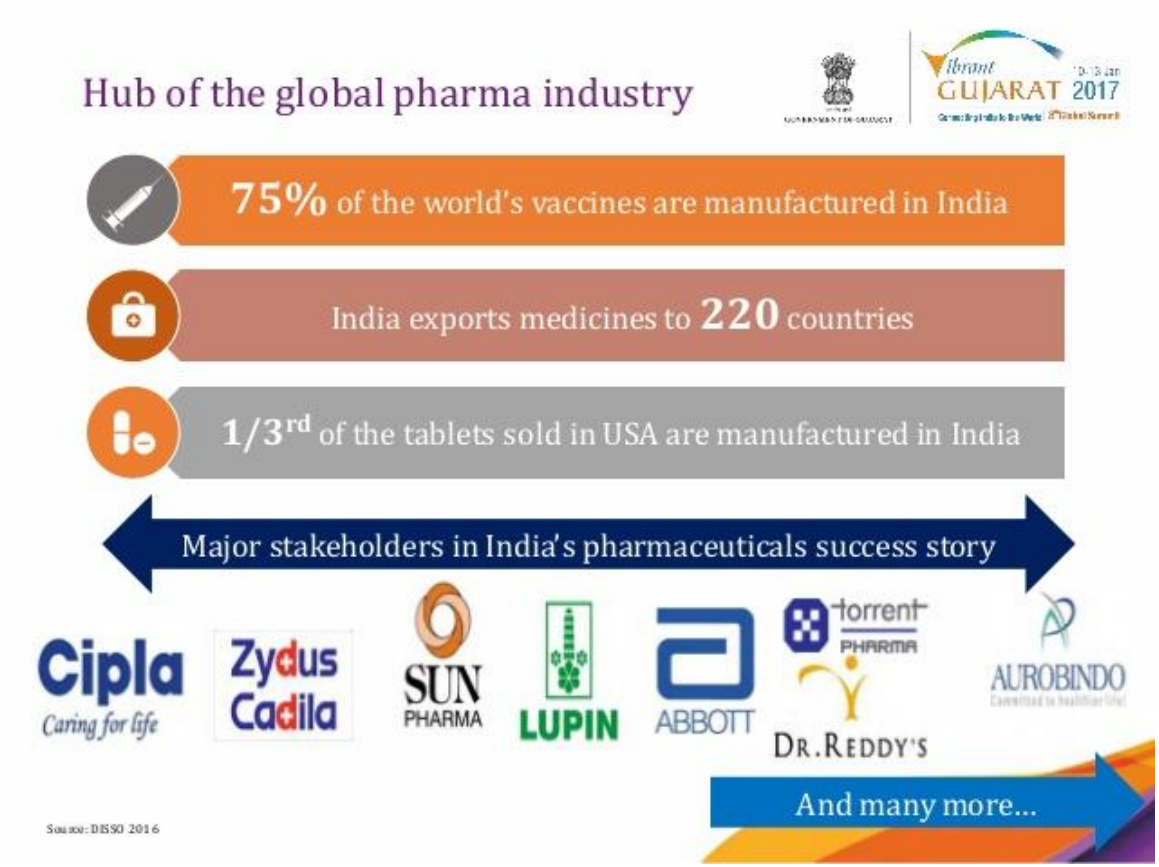
Presentation Overview

- Bottle of lies and China-RX
- Doxil Shortage
- Regulatory agencies perspective
- Reasons for shortage and prevention plan
- Coronavirus (COVID-19)


NEW YORK TIMES BESTSELLER
BOTTLE
OF
LIES
The Inside Story
of the Generic
Drug Boom
KATHERINE
EBAN


ROSEMARY
GIBSON
CHINA
Rx
JANARDAN
PRASAD
SINGH
EXPOSING THE RISKS
OF AMERICA'S DEPENDENCE
ON CHINA FOR MEDICINE

In the United States, imports from India now make up 40 percent of all generics used, and 80 percent of the active ingredients used in both generic and brand-name medications come from India and China.

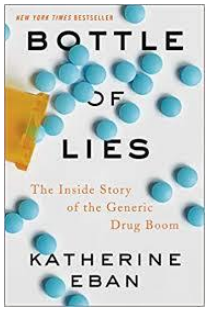


India Leads in Generic Drugs Exports

India imports about 65% of the total APIs from China

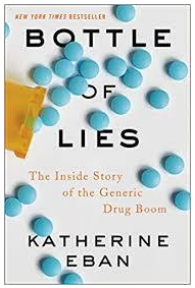
The Indian Generic industry

- **In the 1980s, when the United States began allowing the import of generics.**
- **Cipla and other generic makers became heroes to critics of Big Pharma.**
- **This admiration grew when Cipla revealed in the early 2000s that it would provide an H.I.V. drug that cost roughly a dollar a day — about 4 percent of Big Pharma's price — to tens of millions of Africans who would otherwise go untreated..**



Ranbaxy massive data fraud

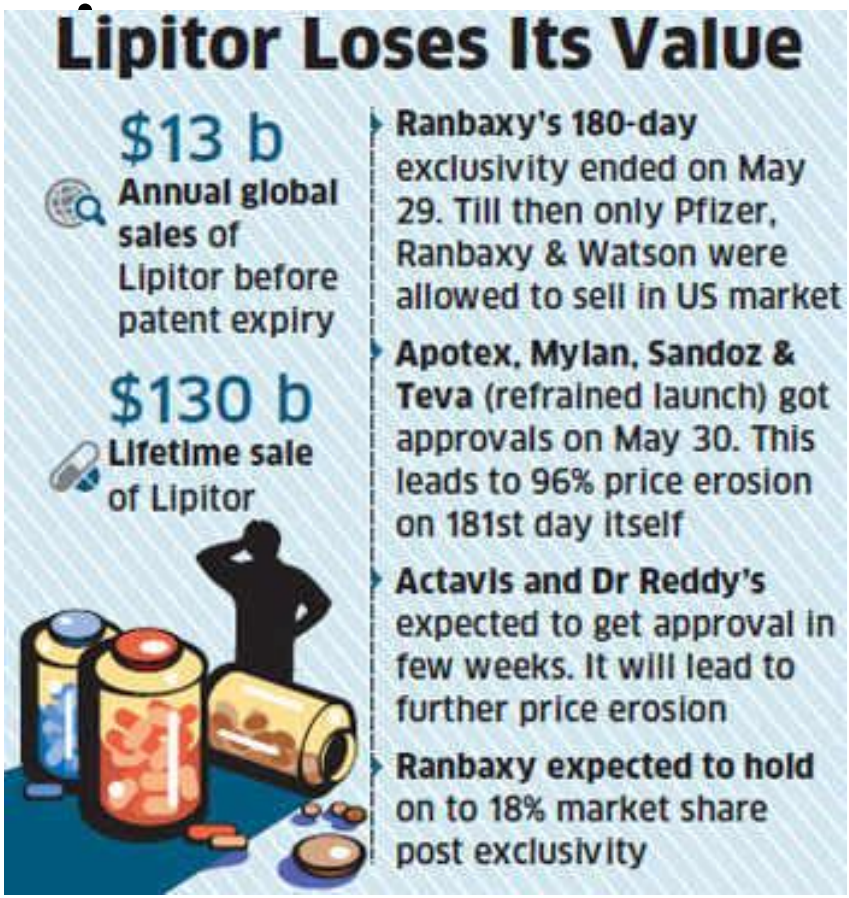
- At Ranbaxy, as Dinesh Thakur begins to learn about the company's massive data fraud, his colleague Arun Kumar asks him, "What is wrong with you guys who go to the U.S. for a few years and think you have become the moral police of the world? Do you think U.S. pharma companies never do such things
- Bottle of Lies describes the FDA's painstaking approval process surrounding the world's biggest generic drug launch—for Ranbaxy's generic Lipitor.
- The agency knew the company was saturated in fraud. Yet, facing political pressure for a low-cost generic version and concerned that Ranbaxy would "park" its exclusive right to manufacture (denying competitors an opportunity to launch), the FDA approved the drug.



זיוף תוצאות של ניסויים קליניים- רמות בדם של התרופה
זיוף תוצאות של בדיקות יציבות
מצג שווא של מתקני ייצור ומעבדות בזמן מבדקים
נסיון להשמיד מסמכים בזמן מבדק

RANBAXY
Trusted medicines.Healthier lives

Lipitor



RANBAXY
Trusted medicines.Healthier lives

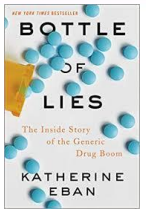
December 1, 2011 – Ranbaxy Pharmaceuticals Inc today announced that it has received final approval from the U.S. Food and Drug Administration to manufacture and market Atorvastatin and has launched the product in the U.S. market. Atorvastatin is a cholesterol-reducing medicine, the generic equivalent of the brand Lipitor®,

Ranbaxy

- **In May 2013, Ranbaxy pleaded guilty to felony charges relating to the manufacture and distribution of certain adulterated drugs made at two of Ranbaxy's manufacturing facilities in India and misrepresenting clinical generic drug data. Ranbaxy pleaded guilty to three felony FDCA counts, and four felony counts of knowingly making materially false statements to the FDA. Included in the adulterated products were antiretroviral (ARV) drugs destined for treatment of HIV/AIDS in Africa.**

- **Ownership of Ranbaxy changed twice over the course of its history. In 2008, Japanese pharmaceutical company Daiichi Sankyo acquired a controlling share in Ranbaxy and in 2014, Sun Pharma acquired 100% of Ranbaxy in an all-stock deal. The Sun Pharma acquisition brought all new management to Ranbaxy, which had been laden with controversy. Sun is the world's fifth largest specialty generic pharmaceutical company**

FDA foreign inspections

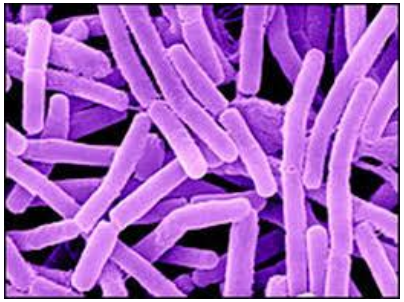


- Especially early on, inspections of foreign factories were rare — as few as 100 a year in the 1990s, which worked out to a rate of one inspection per plant every 11 years.
- These inspections were seldom surprises, because the State Department, valuing good relations over good drugs, asked the F.D.A. to give plants several weeks' notice.
- Indian origin inspectors
- Meanwhile, as more aggressive inspectors eventually learned, a second set of corporate officers would be in back rooms and production areas destroying failed quality test results and fabricating documents showing successful tests.
- Some plants even built, just for these inspections, fake production and testing areas that were kept pristine while the drugs were made in substandard conditions elsewhere.
- The plants use advanced notice of inspections to fabricate data, remove secret equipment and clean up insect and bird infestations.

China Rx: Exposing the Risks of America's Dependence on China for Medicine

- Loss of production capabilities in the U.S. for penicillin, aspirin and Vitamin C

- China controlled half of the world's supply of the active ingredient for heparin. FDA officials admitted during congressional testimony that they didn't ban all Chinese-made heparin because of fear of a shortage.
- In a worst-case scenario, experts warn, China could withhold supply of medicines like important antibiotics, or degrade the quality of our medicines -- even put lethal contaminants in them.
- Even when it comes to treating anthrax, China is the largest exporter of the building block to make ciprofloxacin, an anthrax antidote.



Doxil Shortage

The Ben Venue lab was the sole manufacturer of Doxil in the nation. It voluntarily shut down in November 2011.

A May 2011 FDA inspection found a string of problems, including inadequate oversight and metallic particle shards in some of the drugs produced on site.

A November 2011 FDA inspection found additional problems, including finding a 10-gallon can in a storage area that contained urine.

The regulator previously implemented measures to address the issue, including a “temporary, limited arrangement” in February 2012 for **Sun Pharma** to export its version of Doxil, which it markets as Lipodox, despite the fact it was yet to be approved by the agency.

In February 2013, the agency approved a generic version of Doxil. Officials from local hospitals said they still use the brand-name drug, but they also use the generic form, which should help them navigate the latest Doxil shortage

Doxil Shortage

The root of Doxil's shortages is a "voluntary shutdown" of an Ohio facility run by Ben Venue Laboratories, a contract manufacturer working for J&J, after a November 2011 inspection by FDA and EMA found "ongoing quality and manufacturing issues," reported RAPS. The Doxil shortage left as many as 2,700 patients on a waiting list for the drug last year, though J&J has since squeezed out enough supply to clear the waiting list.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

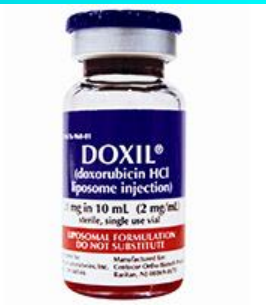
DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6751 Steger Drive Cincinnati, OH 45237 513-679-2700 Industry Information: www.fda.gov/oc/industry	11/7/11 - 12/2/11
	FEI NUMBER 1519257

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: George P. Doyle, III, President and Chief Executive Officer Executive Office

FIRM NAME	STREET ADDRESS
Ben Venue Laboratories, Inc.	300 Northfield Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Bedford, OH 44146	Pharmaceutical Manufacturer

FDA says approval of generic Doxil will ease cancer drug shortage



- *Allows Sun Pharma to manufacture its own version of the medicine*
- **US regulators have taken the unusual step of fast-tracking approval of a generic version of Johnson & Johnson's cancer drug Doxil in order to try and alleviate nationwide shortages of the medicine that stem back to June 2011.**
- At the time, J&J's subsidiary Janssen placed the blame on delays at its third-party contract manufacturer Ben Venue Laboratories, but these problems were later compounded when Ben Venue issued a temporary suspension of manufacturing and distribution of drug products due to a series of violations in standards.
- The FDA has now approved India-based Sun Pharma's generic version of Doxil (doxorubicin hydrochloride liposome injection), which is protected by orphan drug marketing exclusivity until May 2014, but only in a multiple myeloma indication. Generic patent protection for its other indications expired in 2009.

Warning letter-Altaire Pharmaceuticals, Inc. — MARCH 12, 2020

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, and the Center for Veterinary Medicine (CVM) at AskCVM@fda.hhs.gov so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your product

Drug shortages – FDA

- FDA takes great efforts, within its legal authority, to address and prevent drug shortages, which can occur for many reasons, including manufacturing and quality problems, delays, and discontinuations. The agency works closely with manufacturers of drugs in short supply to communicate the issue and to help restore availability. FDA also works with other firms who manufacturer the same drug, asking them to increase production, if possible, in order to prevent or reduce the impact of a shortage.

When to Notify the FDA: Manufacturers must inform the FDA at least 6 months in advance of a permanent discontinuance, or an interruption in manufacturing that is likely to lead to "meaningful disruption" in supply of a product. If 6-months' notice is not possible due to unforeseen circumstances, the notification must be submitted as soon as practicable, and no later than 5 business days after the discontinuance or manufacturing interruption.

Section 506C FD&C Act Guidance for Industry

Section 506C of the FD&C Act requires a manufacturer of a drug product that is " life -supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition" to notify the Food and Drug Administration {FDA or the Agency) of: {1) a permanent discontinuance in the manufacture of the drug; or {2) an interruption of the manufacture of the drug that is likely to lead to a meaningful disruption1 in the supply of that drug in the United States; and {3) the reason(s) for such discontinuance or interruption of manufacturing (FD&C Act§ 506C(a)) . The notification must be submitted at least 6 months prior to the date of the discontinuance or interruption of manufacturing, or as soon as practicable (FD&C Act§ 506C{b)). Compliance with t his notification requirement is essential to facilitating the mitigation and/ or prevention of a shortage or potential shortage, and ultimately may ensure availability of critical drugs for patients.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2013
EMA/531390/2012
Patient Health Protection

Communication by the European Medicines Agency on supply shortages of medicinal products

Discussed by CHMP	June 2013
Adopted by CHMP	September 2013

complementary/additional national communications/advice may be issued.

The following table is proposed (see annex for mock-up):

	Medicine (INN) **Strength(s) and formulation(s)**
Indication	
Reason for shortage	< Information issued previously by the EMA on the supply situation for X can be found here>
Member States affected* * This information may change. For accurate information about the status of a medicine shortage in a particular Member State the national competent authority should be contacted.	
Information to HCPs (based on core DHPC)	***High level (to allow for differences in Member States)*** ***As appropriate include the following statement: 'additional advice may be available from the national competent authority'***
Information to patients (based on core DHPC).	***As above***
Status (potential/ongoing/ resolved)	***Include information on duration of shortage or expected date of resolution if available***
Date of last update	**Optional**

Information to healthcare professionals

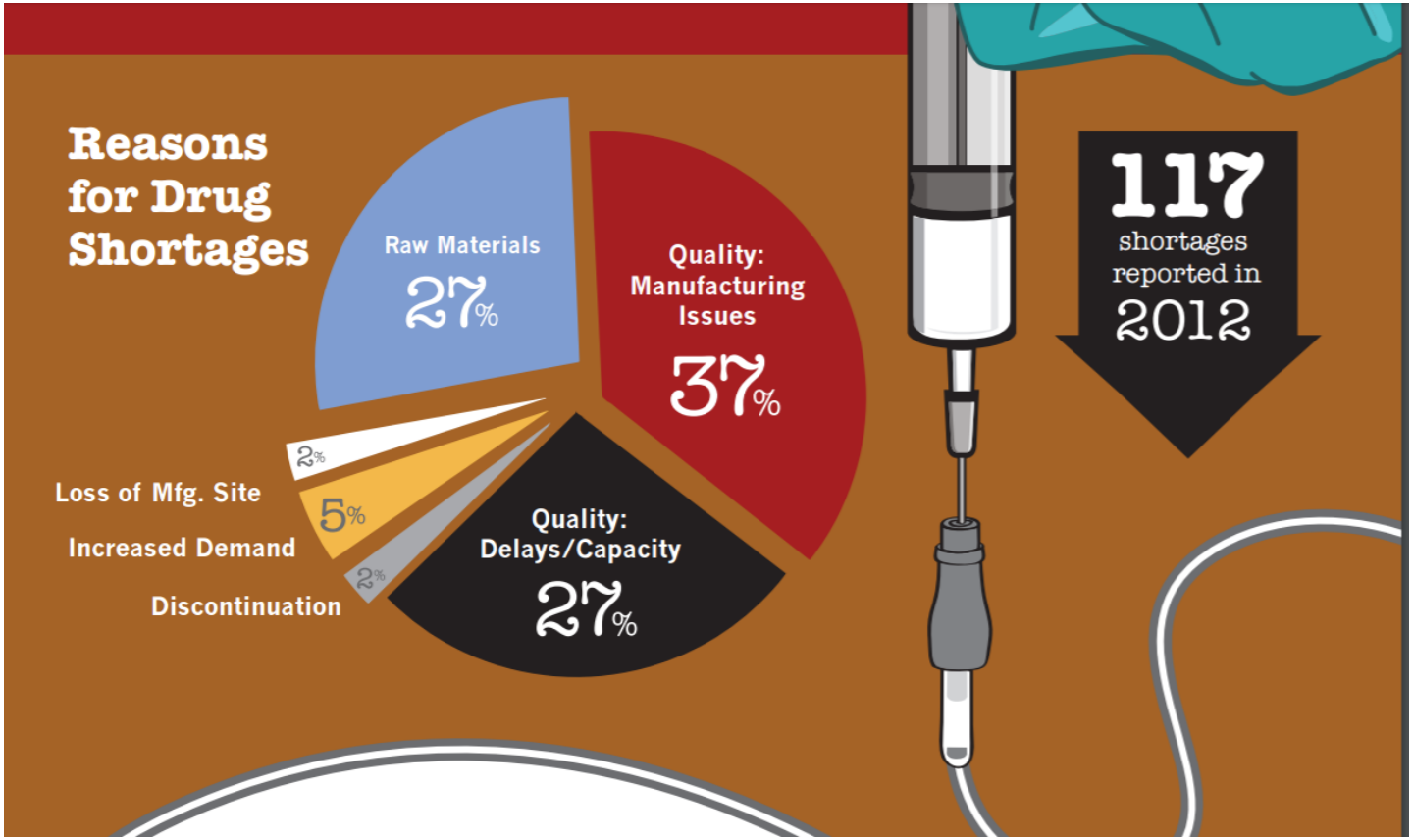
Direct healthcare professional communication

הודעות על הפסקת שיווק תרופות

בהתאם לנוהל, חובת ההודעה חלה על בעל הרישום בנוגע לכל הפסקת שיווק או מחסור זמני של התכשיר בשוק, גם אם המחסור אינו קשור לכוונה שלא לחדש או לבטל רישום.

תקנה 9(ה) לתקנות הרוקחים (תכשירים), התשמ"ו- 1986, קובעת תקנה לתקנות את חובת בעל הרישום לתת למנהל הודעה על כוונתו שלא לחדש רישום בפנקס ולציין במסגרת הודעה זו את הסיבה לאי החידוש של הרישום ולהפסקת השיווק של התכשיר. בהתאם להוראות אלו על בעל רישום להודיע על כוונתו להפסיק שיווק או לא לחדש רישום 6 חודשים טרם הפסקת השיווק. נוהל "דיווח על כוונה להפסיק שיווק / כוונה שלא לחדש רישום תכשיר רפואי מסמך pdf" מפרט ומסדיר את אופן הדיווח על הפסקת שיווק או מחסור צפוי של התכשיר בשוק למחלקה לניהול סיכונים ומידע תרופתי.

Drug shortages- Reasons



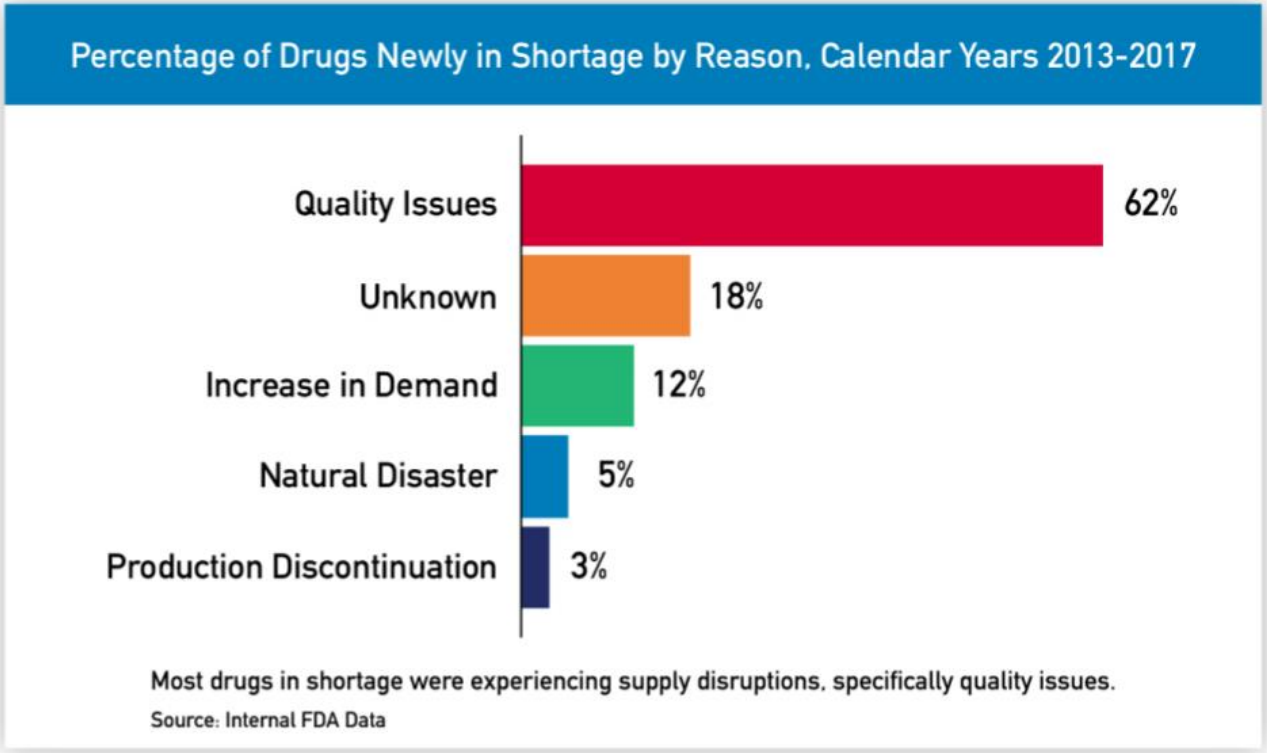
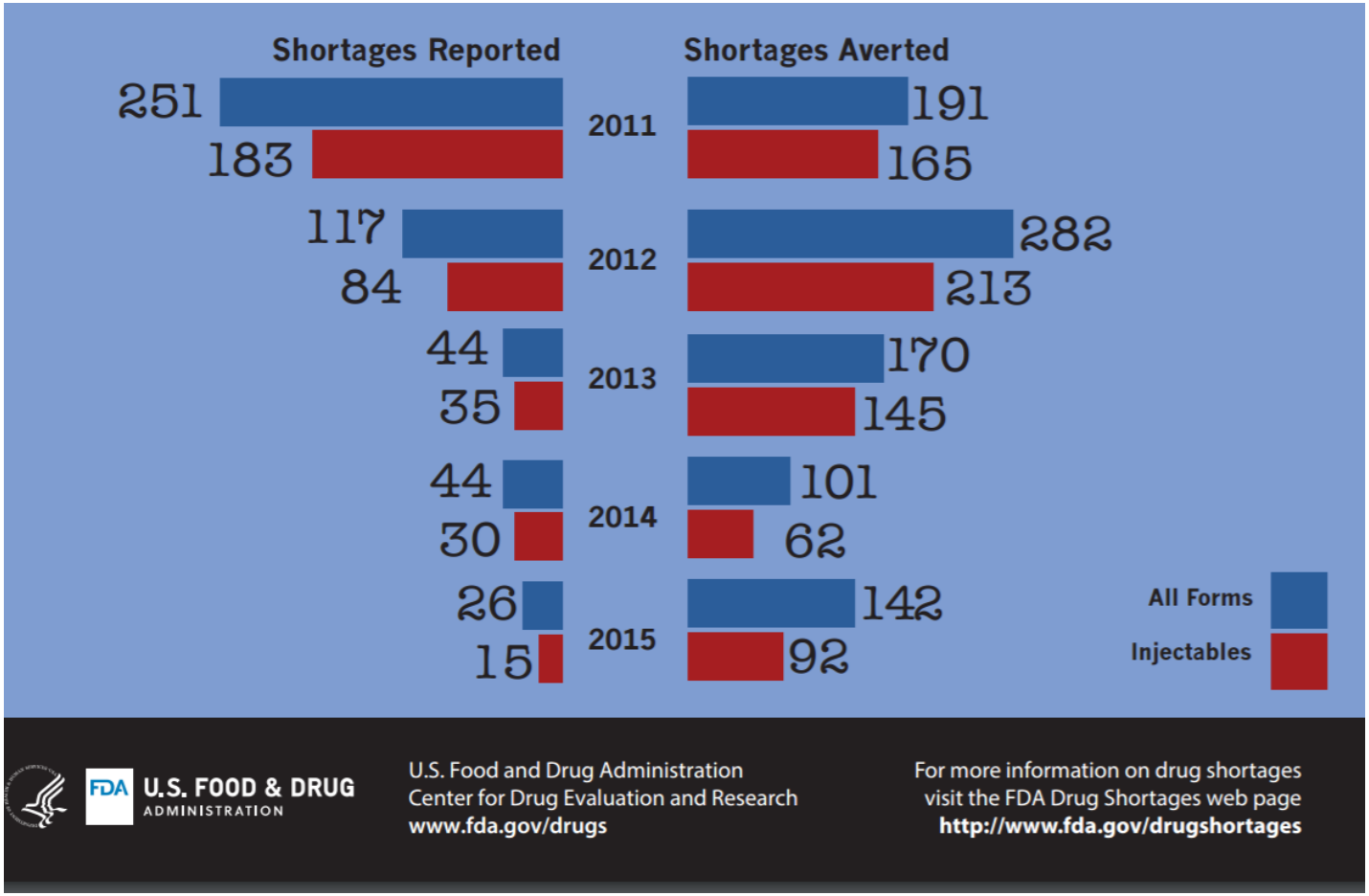


Figure 6. Of 163 drugs that went into shortage between 2013 and 2017, 62 percent went into shortage after supply disruptions occurred that were associated with manufacturing or product quality problems.

Shortages

Drug shortages - Numbers



PDA Parenteral Drug Association

FDA U.S. FOOD & DRUG ADMINISTRATION

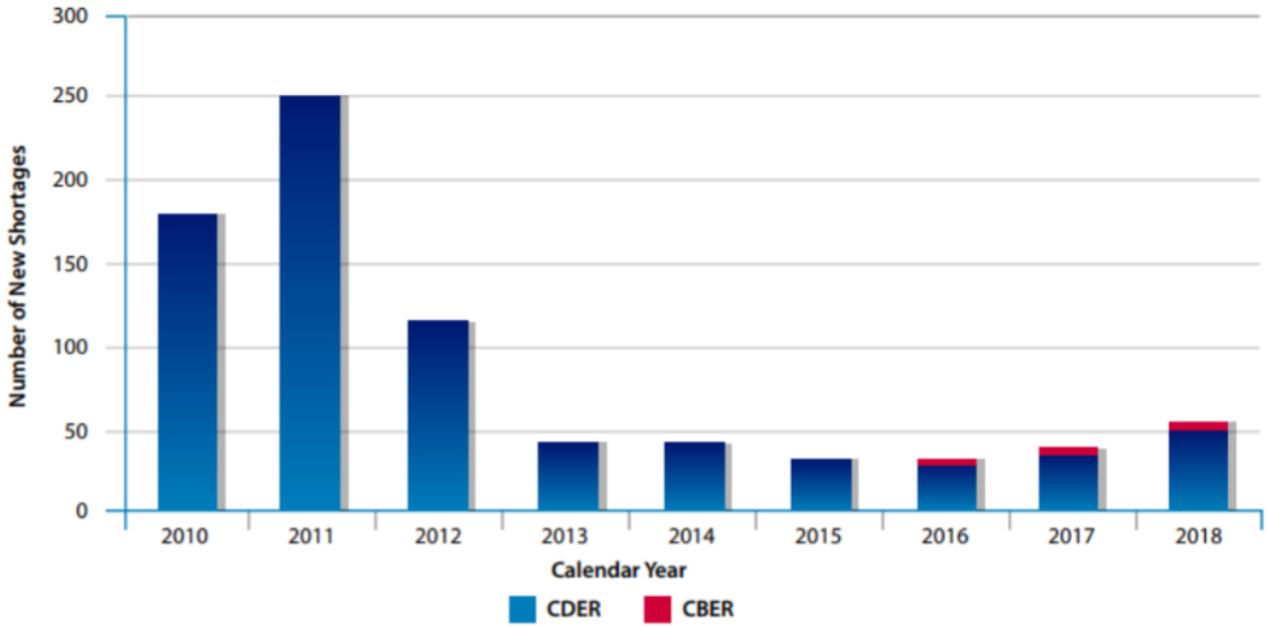
Report on Drug Shortages for Calendar Year 2018

Required by

Section 506C-1 of the Federal Food, Drug, and Cosmetic Act

Number of New Drug Shortage 2010-2018

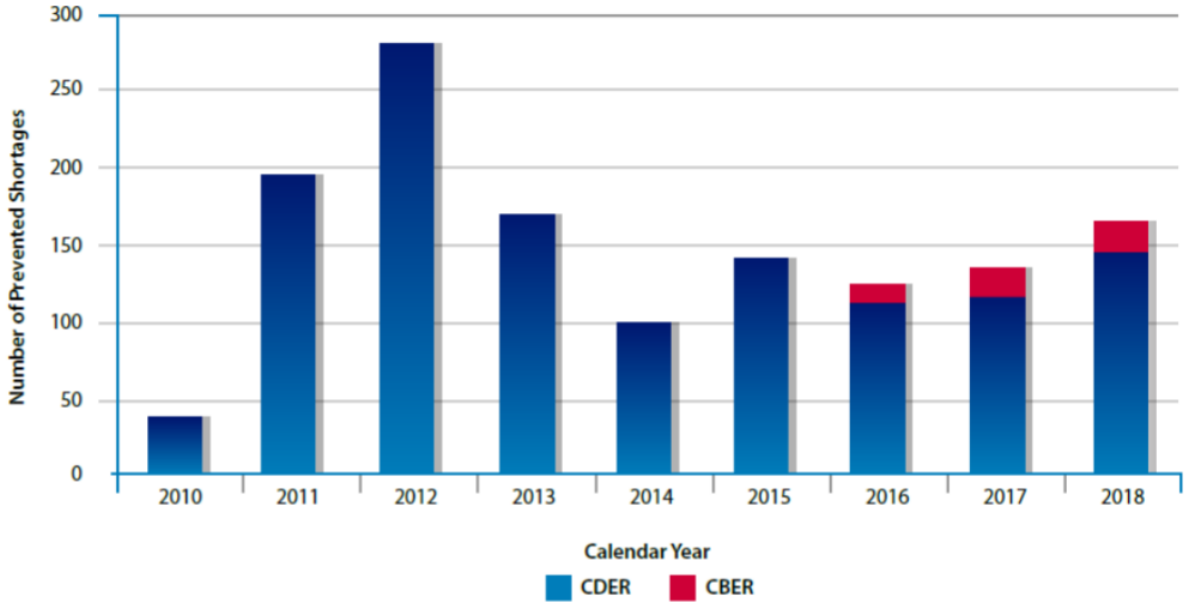
Figure 1. Number of New Drug Shortages Per Year, 2010 - 2018[4]



Although the number of new drug shortages has declined since 2011 as a result of work by many groups including FDA, shortages continue to pose a real challenge to public health. This is especially the case when a shortage involves a critical drug to treat cancer, to provide parenteral nutrition, or to address another serious medical condition, such as the shortage of intravenous saline solution. While there has been a steady decrease in

Number of Prevented Drug Shortage 2010-2018

Figure 2. Number of Prevented Drug Shortages Per Year, 2010 - 2018[6]



Many actions have been taken that are helping FDA address drug shortages.

1. **Executive Order 13588 – Reducing Prescription Drug Shortages**

The Report was updated on 2/21/20 to include revised economic analysis about production increases and supply restoration after a shortage. See the FDA Archive for the original Report.

Drug Shortages:

Root Causes and Potential Solutions

2019

U.S. Food and Drug Administration

Lack of Incentives to Produce Less Profitable Drugs

- .

Lack of Incentives to Produce Less Profitable Drugs. When market conditions limit manufacturers' profitability, they reduce a firm's motivation to maintain a presence in, or enter the market for older prescription drugs, and to invest in manufacturing quality and redundant capacity

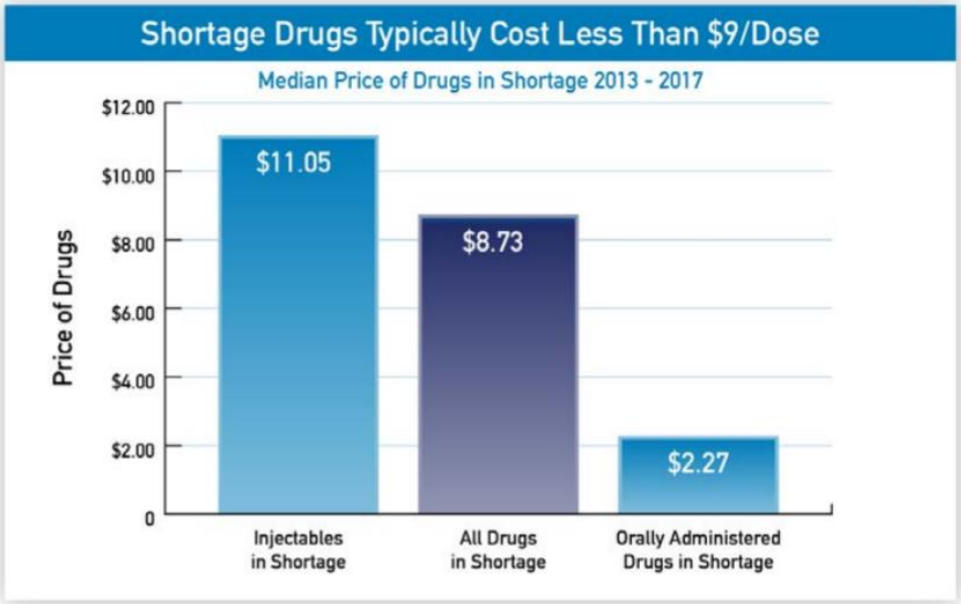


Figure 1. Median price of drugs in shortage from 2013 – 2017 was less than $9 per dose.

FDA analysis shows that the majority of drugs that went into shortage had these characteristics:

- Steeply declining revenues
- Declining prices
- Very limited contributions to a company's total revenues

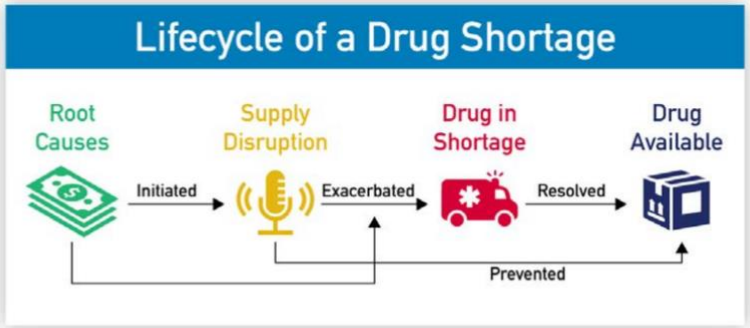


Figure 5. Root causes lead to a supply disruption. When exacerbated, this disruption becomes a shortage that may be resolved when production increases or demand decreases.

Location od manufacturing site

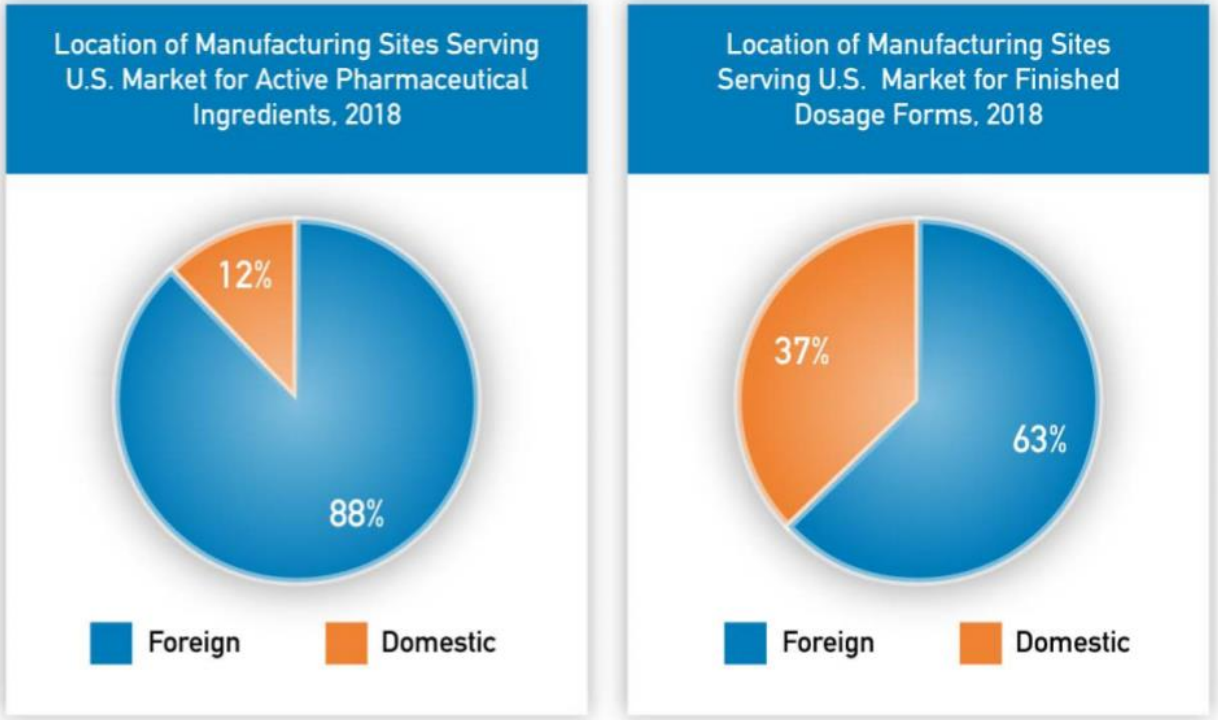
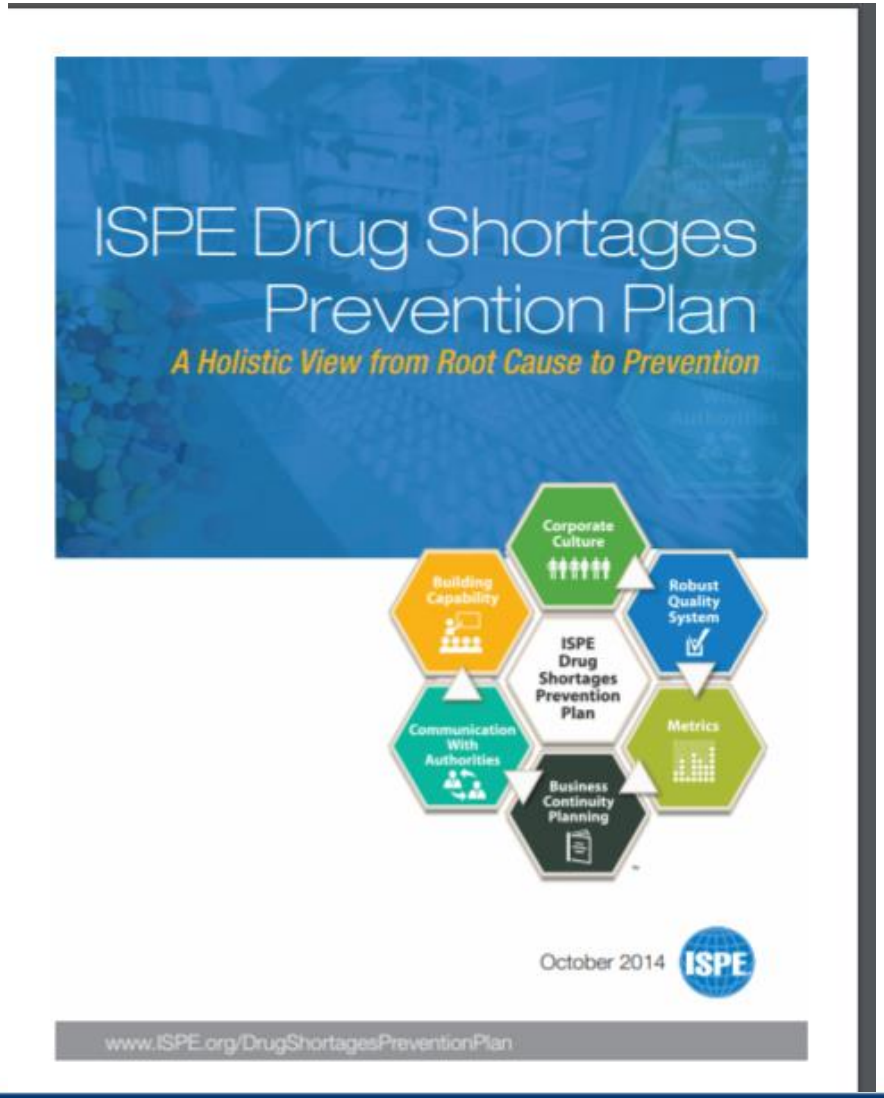


Figure 3. In 2018, the majority of manufacturing sites making active pharmaceutical ingredients and finished dosage forms for the U.S. market were located abroad.[20]

ISPE Drug Shortage prevention Plan



ISPE Drug Shortage prevention Plan

ISPE

Drug Shortage

Assessment and Prevention Tool

The International Society for Pharmaceutical Engineering (ISPE) Drug Shortages Prevention Plan (the Plan) was developed as part of a cross-industry association initiative in response to a request from the European Medicines Agency (EMA) in November 2013 to present proposals addressing the prevention of drug shortages due to manufacturing and quality issues. Concurrently, discussions with representatives from other agencies, such as the United States Food and Drug Administration (FDA); Japan's Ministry of Health, Labor and Welfare (MHLW); and Health Canada

Six Dimensions of the ISPE Drug Shortages Prevention Plan

ISPE Drug Shortage prevention Plan

Corporate Quality Culture describes the importance of organizations being designed in such a way as to foster cross-functional ownership of quality so that quality is not viewed as a hindrance for success, but an absolute necessity for the company to collectively make decisions to best benefit patients [2]. The Plan suggests that avoiding supply disruptions requires not just a compliant quality system, but one that helps drive the overall quality of the product throughout its lifecycle by integrating it and focusing on a number of key processes. These processes include:

- Cross-functional cooperation
- Management controls and problem escalation
- Communication and transparency

Robust Quality System – highlights the ability of the company's quality system to integrate applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q9 [3]. This integration is a necessary foundation for companies to create more and better opportunities for the "the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities."

In order to achieve a robust quality system, the Plan proposes structuring the approach to developing strategies across a few key elements, including governance, culture, and management controls, as well as improvements to overall production and process-related factors contributing to shortages. The Plan argues that this integration will enable stronger and more consistent decisions that will ultimately drive higher levels of quality. These decisions, in turn, may help drive the following improvements:

ISPE Drug Shortage prevention Plan

Metrics – are measures put in place to determine the performance of not just the quality system, but also of other operational elements – such as supply chain and culture – that may indicate the potential for a drug shortage. Depending on the site quality system, some quality metrics and other indicators can be predictive of the overall ability to reliably supply quality products. This section was supplemented with a series of case studies to help illustrate how drug shortages might be avoided by defining and implementing a well-defined set of metrics across the organization.

Cases explored the following:

- What a company did to develop and use a series of risk assessments, metrics, and simulations to help determine the amount of strategic reserves (safety stock) to maintain in order to protect against shortages.

ISPE Drug Shortage prevention Plan -Matrix

Metrics generally assigned as leading indicators:

- *Lot acceptance rate* – total lots released for shipping out of the total finally dispositioned lots for commercial use in the period.
- *Right first time (rework/reprocessing)* – total lots that have not been through rework or reprocessing out of the total finally released lots for commercial use in the period.
- *APQR completed on time* – number of APQRs in the period that were completed by the original due date normalized by all products subject to APQR.
- *Recurring deviations rate* – number of deviations that have occurred during the preceding 12 months period with the same root cause within the same process and/or work area out of all deviations in the reporting period.
- *CAPA effectiveness rate* – number of CAPA evaluated as effective (the quality issue subject of the CAPA was resolved and/or has not reoccurred, and there have been no unintended outcomes from the CAPA implementation) out of all CAPAs with effectiveness check in the reporting period.
- *Technology specific* – Media fill (for sterile) – number of media fills dispositioned as successful out of all media fills to support commercial products dispositioned during the period.

Annual Product Quality Review (**APQR**)

ISPE Drug Shortage prevention Plan -Matrix

Metrics generally assigned as lagging indicators:

- *Complaints rate (total and critical)* – total complaints received in the reporting period related to the quality of products manufactured in the site normalized by the number of products released. Critical complaints (indicating a potential failure to meet product specifications, impact product safety and/or lead to regulatory actions), normalized by the number of products released.
- *Confirmed Out-of-Specification (OOS)* – total confirmed OOS (test results that fall outside the specifications or acceptance criteria) out of all lots tested during the period.
- *Recall events.*
- *Stability Failure rate* – total confirmed OOS related to stability testing out of all stability lots.
- *Invalidated OOS rate* – total unconfirmed OOS out of all lots tested by the lab during the period.
- *Environmental monitoring (sterile aseptic sites)* – total sterile lots with investigations related to action limit excursions out of all sterile lots dispositioned. Total sterile lots rejected due to action limit excursions out of all sterile lots dispositioned.

ISPE Drug Shortage prevention Plan

Business Continuity Planning – explores how companies have established supply chains that are robust, redundant where appropriate, and resilient to ensure continuity of supply by: (a) achieving product realization; (b) establishing and maintaining a state of control and; (c) facilitating continual improvement (ICH Q10) [4]. Solutions developed in this section revolve around the following:

- Achieve Robustness: integrate the supply chain network (from development to commercial manufacturing) with a robust quality system, including governance and management strategies and decisions used to help achieve a robust supply chain.

- Build Redundancy Across the Supply Chain: communicate the successful strategies in place today to monitor the supply chain for risks and develop the solutions needed.

- Test and Refine: identify mechanisms to test and monitor potential issues with the supply chain; weaknesses that, if not addressed, could lead to a shortages.

Cases also were used in this section to help illustrate various solutions, such as:

- What a company did to create a dual source system within the company's own manufacturing network allowed the company to provide assurances to its customers that their products could be provided by multiple manufacturing sites across the network.

- How a company managed to create a more robust quality system by integrating it with the supply chain and, in turn, helped improve the ability to manage the suppliers critical to its ability to avoid shortages.

ISPE Drug Shortage prevention Plan

Communication with Authorities – examines what companies can do to improve communication with the various regulatory agencies across the globe. This includes looking at: (a) what can be done to drive a consistent and transparent message between the company and its regulators to help reduce the chance that a shortage will occur and; (b) if there is a compliance driven supply disruption, reduce the amount of manufacturing downtime needed to get the site compliant and back up and running.

Specific areas explored include:

- The role of regulatory agencies/health authorities – proposes how both companies and regulators can work together to deliver a consistent message; one that is transparent to all parties and helps facilitate a rapid response to mitigate the shortage and address the impact to patients.
- Managing an abnormal restriction in supply – examines not just the signals that may point to a shortage, but also potential escalation paths that should be in place to make sure that if a signal is identified the right steps can be taken to address and resolve the pending issue.

www.ISPE.org/DrugShortagesPreventionPlan

ISPE Drug Shortage prevention Plan

Building Capability – summarizes the capability needs required for each of the elements described in the *ISPE Drug Shortages Prevention Plan* to be realized. The capabilities discussed revolve around the following areas:

- Training
- Learning
- Knowledge Management
- Mentorship

The Plan argues that much of a company's ability to put these processes in place and execute them consistently will rely heavily on the capabilities of the organization and its personnel.

All of these combined elements offer what the ISPE Drug Shortages Task Team believes to be a holistic plan and a valuable contribution to ongoing discussions aimed at preventing drug shortages. By the application of often limited company financial resources to the identified key areas within a quality system, companies can significantly reduce their vulnerability to drug shortages and ultimately improve patient care. Just as importantly, these discussions will help an organization understand what its limitations are – whether in process, governance, or skills – and what they need to address and overcome in order to take advantage of the solutions offered by *ISPE's Drug Shortages Prevention Plan*.

Resilience360 DHL

supply chain risk management software platform

- Monitor potentially disruptive supply chain risks: Use real-time supply chain risk monitoring tools to continuously keep abreast of further developments regarding the city lockdowns, government shutdowns of industrial areas as well as potential transportation disruptions and assess its impact on one's own manufacturing and logistics networks.

- Be mindful of using dual-sourcing strategies for key components: Reducing the number of suppliers has become a norm to allow for more strategic relationships with a handful of key suppliers. However, given the expanding nature of supply chain risks, firms should consider undertaking a strategic cost benefit analysis to assess if the added cost of sourcing from different geographical locations and alternative suppliers can be worthwhile to prevent future shutdowns.

Supply chain impacts from Cyclone Nisarga

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PORT DISRUPTION

- 24-hour closure of largest container gateway at Jawaharlal Nehru Port Trust (JNPT).
- COVID-19 congestion issues to be exacerbated by the closure.
- APM Terminals in Pipavav took precautionary measures.

AIRPORT DISRUPTION

- Mumbai's Chhatrapati Shivaji Maharaj International Airport was closed for 8 hours, reopened at 19:30 local time on June 3.

OTHER IMPACTS

- 2.5 million MSEDC customers have reportedly lost power across four districts of Maharashtra including Raigad, Palghar, Thane and Pune.

Nationwide protests in the United States

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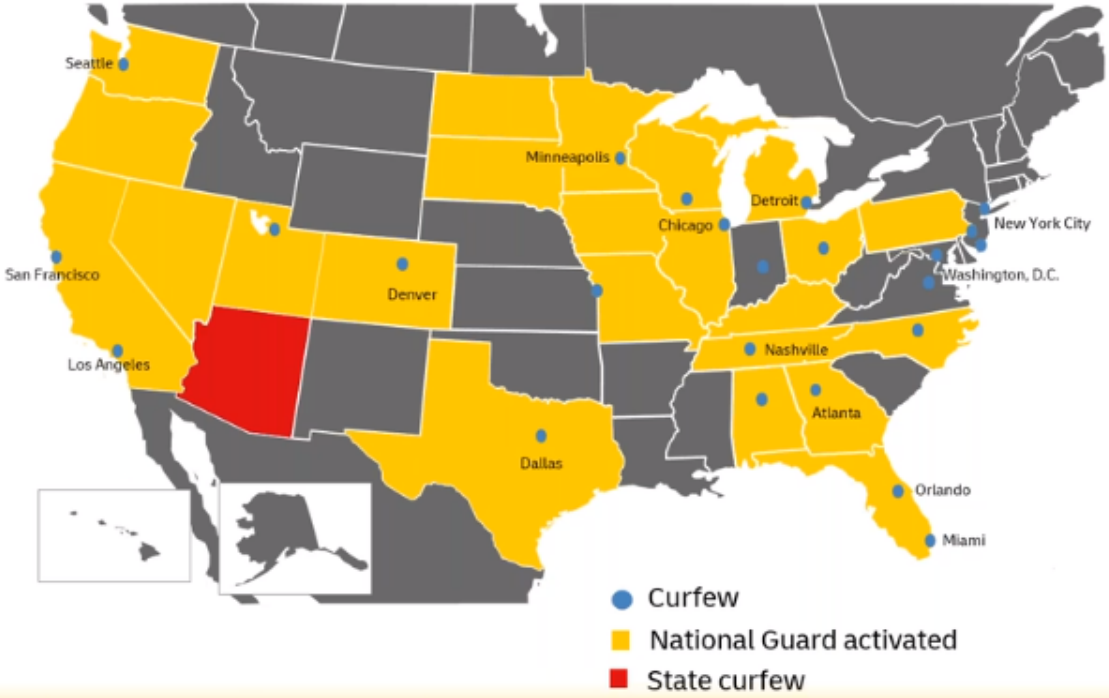
- **Curfews announced** in over 40 cities and 15 states amid nationwide protests
- **Retail stores closed** to protect employees and property, further exacerbating impact on the sector from COVID-19 closures
- Impact on public transport has caused **staff shortages**
- Last mile delivery of goods impacted, as afternoon **delivery schedules need to be adjusted** to curfew times
- **Shipment deliveries may be on hold** if some areas are deemed unsafe
- Air and ocean freight are mostly unaffected
- Organizations are advised to **map out their transport routes** to assess which may be affected and replan shipments where possible



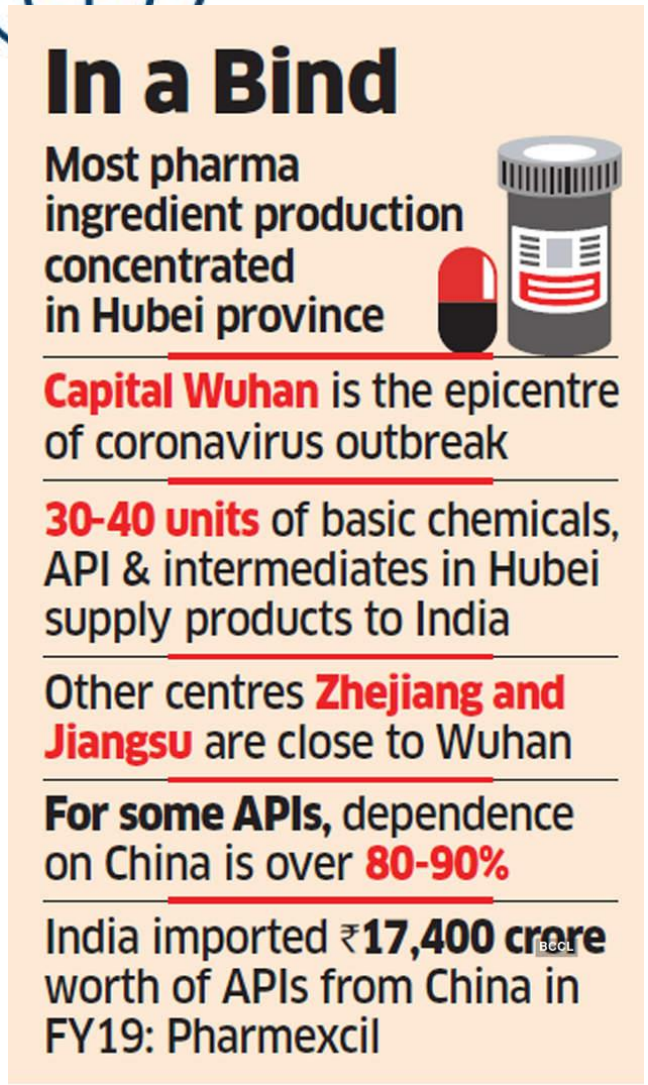
- Draft and test contingency plans for a supplier outage: Companies should make contingency plans in case a plant is, for instance, quarantined because of the virus. In the long term, it is recommended to set up good business relationships with logistics providers or contract manufacturers that have the capability to transport or manufacture similar products in nearby regions or countries. If necessary, these can be used to get new lines set up in the shortest possible time

Coronavirus (COVID-19)

- API's Shortage
- Coronavirus Specific "treatments"
- Drugs support patients in critical care

- Medical Device

Hubei province



In Hubei province, where COVID-19 emerged, there are 44 companies that are FDA-approved and/or meet EU standards and manufacture APIs or supply chemical ingredients to API manufacturers. Most of these companies have been shut down since January 24, 2020

China factories re-open with the support of the government-

Government's supports are effectively. According to China's Ministry of Industry and Information Technology, as of March 28, **the resumption of work rate for larger industrial enterprises was 98.6 percent. The return rate of workers stood at 89.9percent.**


Getty Images

India - Restricted the exports of 26 API

The government, on March 3, restricted the exports of **26 API and formulations, including paracetamol and vitamins B1, B6 and B12 in order to ensure there is no shortage of drugs** in India due to the lockdown in China's Hubei's province, the epicentre of the coronavirus outbreak, and a major source of these raw materials.

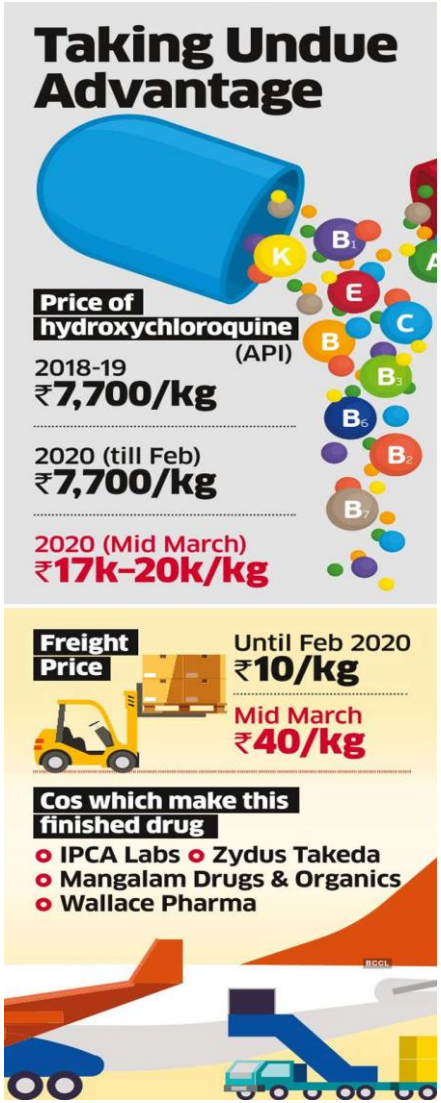
Tinidazole, metronidazole, acyclovir, progesterone, chloramphenicol, erythromycin salts, neomycin, clindamycin salts and ornidazole were the other APIs whose exports are now restricted.

According to reports, the restrictions were imposed because India's manufacturers rely heavily on imports of their APIs from China. As a result of the lockdowns and closures, slowed production of APIs by the latter resulted in less availability and higher costs for the materials required for generics production. Duffy said the primary reason behind the export restrictions was to prevent domestic shortages in India in the long-term.

Govt frees exports of all APIs, formulations except paracetamol – 6 April 2020

Hydroxychloroquine

- 90$---260$



Apr 6, 2020

Last week, the FDA reported shortages of hydroxychloroquine and chloroquine, antimalarial meds that have been targeted by President Donald Trump and others as front-runners for a possible COVID-19 therapeutic.

Coronavirus (COVID-19) Supply Chain Update
February 27, 2020

- As I have previously communicated, the FDA has been closely monitoring the supply chain with the expectation that the COVID-19 outbreak would likely impact the medical product supply chain, including potential disruptions to supply or shortages of critical medical products in the U.S.
- A manufacturer has alerted us to a shortage of a human drug that was recently added to the drug shortages list. The manufacturer just notified us that this shortage is related to a site affected by coronavirus. The shortage is due to an issue with manufacturing of an active pharmaceutical ingredient used in the drug. It is important to note that there are other alternatives that can be used by patients

Coronavirus (COVID-19) Supply Chain Update

Also, as part of our efforts, the FDA has identified about 20 other drugs, which solely source their active pharmaceutical ingredients or finished drug products from China. We have been in contact with those firms to assess whether they face any drug shortage risks due to the outbreak. None of these firms have reported any shortage to date. Also, these drugs are considered non-critical drugs.

We will remain in contact with manufacturers so that we can continue to assist them with any potential issues in the fastest way.

Coronavirus (COVID-19) Supply Chain Update

Biologics and Blood Supply

The FDA is not aware of any cellular or gene therapies that are made in China for the U.S. market. There are no shortages of biologics to report at this time.

The potential for transmission of COVID-19 by blood and blood components is unknown at this time; however, respiratory viruses, in general, are not known to be transmitted by blood transfusion. Further, there have been no reported cases of transfusion-transmitted COVID-19. The FDA has made information available to blood establishments and to establishments that manufacture human cells, tissues, or cellular or tissue-based products that may wish to consider additional donor screening measures in response to the COVID-19 outbreak.

Coronavirus (COVID-19) Supply Chain Update

Medical Devices

We are aware of 63 manufacturers which represent 72 facilities in China that produce essential medical devices; we have contacted all of them. Essential devices are those that may be prone to potential shortage if there is a supply disruption. We are aware that several of these facilities in China are adversely affected by COVID-19, citing workforce challenges, including the necessary quarantine of workers. While the FDA continues to assess whether manufacturing disruptions will affect overall market availability of these products, there are currently no reported shortages for these types of medical devices within the U.S. market.

Regarding personal protective equipment—surgical gowns, gloves, masks, respirator protective devices, or other medical equipment designed to protect the wearer from injury or the spread of infection or illness—the FDA has heard reports of increased market demand and supply challenges for some of these products. However, the FDA is currently not aware of specific widespread shortages of medical devices, but we are aware of reports from CDC and other U.S. partners of increased ordering of a range of human medical products through distributors as some healthcare facilities in the U.S. are preparing for potential needs if the outbreak becomes severe.

Lengthen Expiration Dates to Mitigate Critical Human Drug Shortages

Shortages of certain critical drugs can be exacerbated when drugs must be discarded because they exceed a labeled shelf-life due to unnecessarily short expiration dates. By expanding the FDA's authority to require, when likely to help prevent or mitigate a shortage, that an applicant evaluate, submit studies to the FDA, and label a product with the longest possible expiration date that the FDA agrees is scientifically justified, there could be more supply available to alleviate the drug shortage or the severity of a shortage.

Shelf-Life Extension Program

Stockpiling drugs, vaccines, and medical products is critical to ensure public health emergency preparedness for both the U.S. military and civilian populations. To avoid the need to replace entire stockpiles every few years at significant expense, and because it was recognized through testing that certain products remained stable beyond their labeled expiration dates when properly stored, the Shelf-Life Extension Program (SLEP) was established in 1986.

- **Antivirals -**Tamiflu and Relenza, seasonal influenza
- **Doxycycline-** response purposes for an anthrax emergency
- **Nerve Agent Auto-Injectors-** Atropine, diazepam.
- **Potassium Iodide (KI)-** response purposes for a radiological emergency.

- Based on FDA's review of scientific data, FDA has concluded that, provided the products have been stored under labeled storage conditions, it is scientifically supportable for certain lots of Tamiflu capsules held in strategic stockpiles to be used for a maximum of ten [10] years beyond their date of manufacture

Drugs and devices to treat the disease
critically ill patients

The COVID-19 pandemic is sweeping the world and companies and regulators are working hard to keep up with the increased demand for drugs and devices to treat the disease. Certain products used to treat COVID-19 patients are at risk of shortage due to this increased demand. Most notably, in the EU (which is a few weeks ahead of the U.S. in the course of the coronavirus pandemic), it has been reported that around 30% of patients are hospitalized and in need of oxygen therapy, and due to the increased load of patients in critical care that need intubation, there has been a concomitant surge in demand for anesthetics, antibiotics, muscle relaxants, resuscitation medicines, and anti-diuretics.

- Other medicines necessary for the treatment of critically ill patients, such as cardiac medicines, analgesics, anti-clotting medications, medical nutrition and large volume parenterals are also at risk for shortage due to increased demand. This is also occurring on our side of the pond; FDA has also updated its shortage list to include sedation drug midazolam, used when patients require mechanical ventilation

Propofol shortage

- Propofol is an excellent anesthetic, relatively safe with a fast induction time and relatively quick recovery time. It is used in all types of surgical and non-surgical procedures (including intubation and time on a vent if the patient is in distress). With all the COVID 19 cases and the resultant hospitalizations and ICU stays, the increase in use has resulted in the drug product's placement on the FDA's shortage list.
- Propofol (as noted above) is an excellent anesthetic, but, because of its formulation, it is also serves as an excellent growth media for bacteria and fungi.

- the FDA issued guidance titled Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency permitting, among other things, combining the contents of two or more single use vials of propofol for use on multiple patients.
- Propofol is also subject to oxidation, and combining contents of different single use vials could pose a problem as the approved products are filled under a nitrogen blanket to decrease the amount of oxygen the product is exposed to during manufacture to prevent oxidation, and clearly manipulation of the product at pharmacies or hospitals cannot use such precautions. FDA has also provided strict and short "use by" times for these manipulated products in its advice.

Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency

Guidance for Industry

April 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality and Office of Compliance

Postponement of most FDA foreign inspections

FDA

The FDA has a collection of COVID-19-related information available on their website. In late February, the FDA provided an overview of the status of the US drug supply chain and highlighted their early and ongoing engagement with companies to ensure the FDA is positioned to identify potential issues and assist as fast as possible.

It should be noted that the FDA announced the postponement of most foreign inspections through April, and the potential for delay of inspections should be evaluated for potential impact to drug supply.

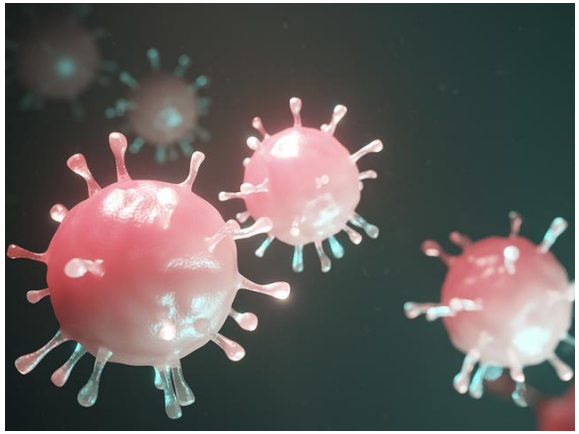
Availability of medicines during COVID-19 pandemic

- **The European Medicines Agency (EMA) and its partners in the European medicines regulatory network are putting measures in place to help prevent and mitigate possible disruptions to the supply of medicines in the European Union (EU) during the COVID-19 pandemic.**
  Extraordinarily, EMA is acting as central coordinator in supporting Member States' activities in this area during the pandemic.
- **Supply disruptions** or **medicine shortages** could occur during the pandemic as a result of:
- temporary lockdowns of manufacturing sites;
- travel restrictions impacting exports;
- export bans;
- increased demand for medicines used to treat COVID-19 patients;
- stockpiling by hospitals, by individual citizens or at Member State level.

EMA – Generic manufactures coodination

- In support of this, today, the European Commission announced a Temporary Framework that allows for generic manufacturers to coordinate on stock management "so that not all undertakings focus on one or a few medicines, while others remain in under-production. Such coordination would be contrary to antitrust rules in normal circumstances. But in the context of a pandemic like the coronavirus outbreak, such coordination can, with appropriate safeguards, bring important benefits to citizens." However, they also stated that they will continue to closely and actively monitor market developments of these medications to detect actions that take advantage of the current crisis in order to breach antitrust law in the EU by engaging in anti-competitive agreements, abusing a dominant position, exploiting customers and consumers or limiting production to the ultimate prejudice of consumers.

- EMA and its partners in the European medicines regulatory network are closely monitoring the potential impact of the outbreak of the novel coronavirus disease (COVID-19) on pharmaceutical supply chains into the European Union (EU). No reports of current shortages or supply disruptions of medicines marketed in the EU due to this outbreak have been received at this point. As the public health emergency develops, shortages or disruptions cannot be exclude



Much of the world's supply of active pharmaceutical ingredients (API) is made in China, where factory output ground to a halt for weeks as a result of the outbreak, and India, the world's largest exporter of generic drugs has moved to restrict exports of certain drugs and APIs to ensure local availability.

FDA's Hahn: No sign China has affected U.S. drug supply during coronavirus pandemic Apr 6, 2020

FDA Commissioner Stephen Hahn

- With pharmaceutical supply chains under immense pressure due to the novel coronavirus, China's role as a global ingredient producer has come under scrutiny. Despite fears the East Asian nation could shut off the tap for U.S. drugs, the FDA said it hasn't yet noticed major signs for concern.
- The FDA hasn't seen a shortage of active pharmaceutical ingredients (APIs) sourced from China due to the ongoing novel coronavirus outbreak but is "closely monitoring the situation," FDA Commissioner Stephen Hahn **told** Fox News on Sunday.
- "We don’t have any evidence that there’s a drug in short supply because of anyone blocking the active pharmaceutical ingredients coming to us (from China)," Hahn said.
-

Highlights of FDA Activities 4/06/20

Highlights of FDA Activities

Ensuring Timely Availability to Accurate and Reliable Tests

- During the COVID-19 pandemic, the FDA has worked with more than 400 test developers who have already submitted or said they will be submitting **emergency use authorization (EUA)** requests to the FDA for tests that detect the virus or antibodies to the virus.
- To date, the FDA has authorized 120 tests under EUAs, which include 104 molecular tests, 15 antibody tests and 1 antigen test.

Accelerating Availability of Medical Equipment and Products for Treatment

- Added more than 80 ventilators and accessories for emergency use to the ventilator EUA and **issued EUAs** for other equipment to treat patients during COVID-19.
- Authorized EUAs and issued policies to help increase the availability of personal protective equipment, such as respirators, gowns, surgical masks, and more.
- Monitoring more than **144 active trials of therapeutic agents for COVID-19**; another 457 development programs for therapeutic agents are in the planning stages.

Actively Monitoring the Medical Product and Food Supply Chains to Address Imbalances

- Continue to screen and monitor millions of domestic and international products in the medical supply chain to help ensure COVID-19-related supplies coming into the U.S. are safe and distributed appropriately.
- **Signed a MOU** with USDA as another preparedness measure to help prevent interruptions at FDA-regulated food facilities, including fruit and vegetable processing during the national emergency.

Halting the Sale of Products with Fraudulent Claims Related to COVID-19

- Issued hundreds of abuse complaints resulting in online marketplaces removing listings for 260 products that claimed to diagnose, treat, prevent, or cure COVID-19.
- Issued 65 **health fraud warning letters** to sellers of unapproved products with bogus COVID-19 claims, including homeopathic drug products, cannabidiol products, nasal sprays, colloidal silver products, herbal products, chlorine dioxide products, and others.
- Continue to aggressively monitor the market for and take appropriate action against individuals and companies selling products with fraudulent claims to

Improve Critical Infrastructure by Requiring Risk Management Plans

Improve Critical Infrastructure by Requiring Risk Management Plans: Enabling the FDA to require application holders of certain drugs to conduct periodic risk assessments to identify the vulnerabilities in their manufacturing supply chain (inclusive of contract manufacturing facilities), and develop plans to mitigate the risks associated with the identified vulnerabilities would enable the FDA to strengthen the supply chain by integrating contingencies for emergency situations. Currently, many medical product manufacturers lack plans to assess and address vulnerabilities in their manufacturing supply chain, putting them, and American patients, at risk for drug supply disruptions following disasters (e.g., hurricanes) or in other circumstances.

Never again

- "Never again should we have to depend on the rest of the world for our essential medicines and countermeasures," said Peter Navarro, President Trump's economic adviser, during a press briefing last month.
- Speaking about Trump's "Buy American" executive order, he said that after this pandemic, the American government would source essential medicines, medical supplies and equipment only from American companies.

After US, EU announces stockpile plan for essential drugs 13/05/2020

Europe must be able to produce critical medicines itself.

- In a speech, European Commission President Ursula Gertrud von der Leyen said: “We will also create for the first time a new Strategic Investment Facility. This will help invest in key value chains crucial for our future resilience and strategic autonomy, such as the pharmaceutical sector. Europe must be able to produce critical medicines itself.”
- The stockpile would be funded through a new health budget of around US$ 10.3 billion (Euro 9.4 billion) which the EU executive commission proposed last week.
- The EU is seeking to stockpile disinfectants, testing and diagnostic reagents, protective gear and essential medicines, according to an EU document.
- The Commission also said it wants to offer incentives to drug companies to develop and produce vaccines in Europe and relocate manufacturing capacity of medicines and their chemical ingredients which are, at present, being imported largely from India and China.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