DRUG ENFORCEMENT ADMINISTRATION

Stimulants, Quotas and Drug Shortages

2023 DEA Supply Chain Conference
Houston, Texas
May 4, 2023

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Outline

- Drug Shortages – Root Cause and Potential Solutions
- Drug Shortages – Controlled Substances
- Demographic Trends in Prescribing
- Online Intermediaries and Social Media
- Generics and CMOs
- Best Practices

Drug Shortages: Root Causes and Potential Solutions for Nutritional Supply

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Senior Regulatory Review Office

Drug Shortage Staff

Center for Drug Evaluation and Research

Food and Drug Administration

Drug Shortage Mission

- Our mission is to prevent, mitigate and alleviate drug shortages
- Patient and practitioner access to life-saving medication is our #1 priority
- Drug Shortage Staff works with professional organizations, patient groups, clinicians and other stakeholders (DEA, CMS, EMA, etc.)

Brief History

- Part of FDA's Center for Drug Evaluation & Research (CDER)
- Drug Shortage Program began in 1999
- 2011- President Obama signed *Executive Order 13588-Reducing Prescription Drug Shortages*
- 2012-Requirements to Industry For Early Notifications Under Section 506C of the FD&C Act
- CDER Drug Shortage Program (DSP) changed to Drug Shortage Staff (DSS) in 2012
- Moved under the CDER Office of the Center Director in 2014
- Additional drug shortage staff in other Centers (e.g. CBER, CDRH)
- Coronavirus Aid, Relief, and Economic Security Act (CARES Act) 2020

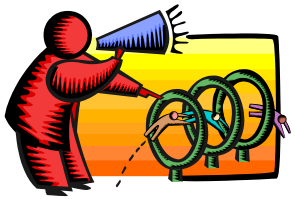
Notification Requirements Under Section 506C of the FD&C Act and FDA Regulations

Notify DSS no later than 5 days after a manufacturing interruption (21 CFR 314.81), ahead of any supply disruption at **drugshortages@fda.hhs.gov** (80 FR 38915)

Manufacturers are required to notify the FDA of a permanent discontinuance in the manufacture of a covered drug or an interruption of the manufacture of a covered drug that is likely to lead to a meaningful disruption in the supply of the drug in the United States

- "At least 6 months in advance of the date of the permanent discontinuance or interruption in manufacturing; or, if 6 months' advance notice is not possible no later than 5 business days after the…permanent discontinuance or interruption in manufacturing occurs"
- Not limited to medically necessary products
- Regardless of market share, or number of companies marketing, or wholesaler volumes
- The CARES Act amended section 506C of the FD&C Act to add notification requirements for APIs for covered drugs, to add information that must be provided in a notification, and to clarify the category of covered drugs.

FDA Drug Shortage Staff – Key Communications



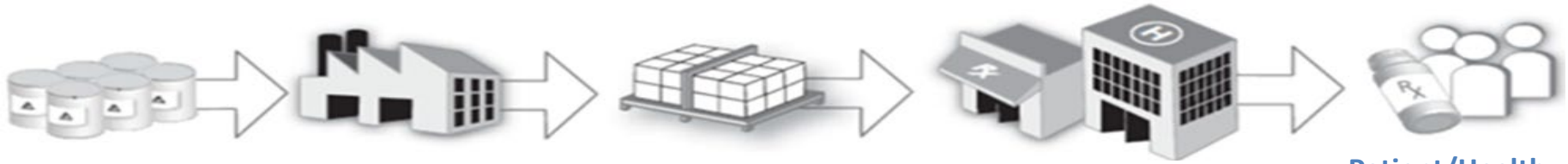
Manufacturers Report on Potential Impact to Supply

At the time of any change in manufacturing that may lead to a reduction in supply of a product*, e.g.:

- Plans for upgrade or remediation
- Manufacturing issues
- Raw material batch failures
- Particulate issues
- Sterility issues

*Note, product refers to a specific strength, dosage form, and route of administration

Drug Supply Chain – 1st Tier



Supplier

Manufacturer

Wholesaler

Pharmacy/Hospital

Patient/Health Care Provider

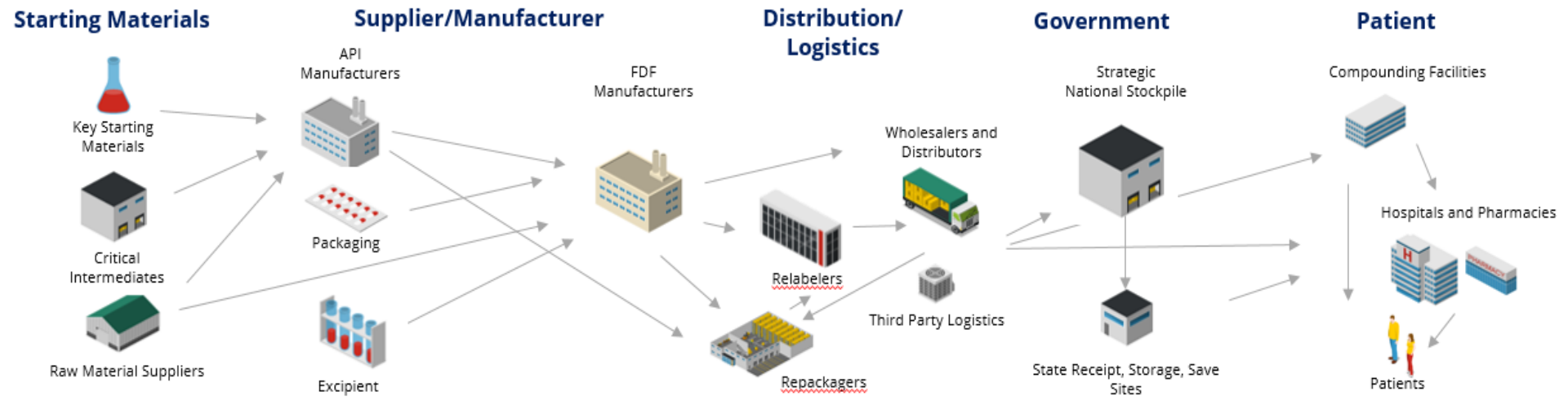
Inventory/Production Data:
Voluntarily Supplied
Supply Interruptions:
Required per FDASIA

Sales/Market Share Data:
Reported to FDA via annual report and other channels

Inventory/Supply Interruptions:
Voluntarily Supplied

Public Notifications:
FDA Drug Shortages email account

Illumination – Simplified End-to-End Supply Chain



Opportunities and Challenges to Assist with Shortages

FDA will work closely with manufacturers to address problems

- We can advise, assist, and expedite inspections and reviews, but the manufacturer must fix the problem

What we CAN require:

- Notification by manufacturers (FDASIA)
  - Supply disruptions
  - Delays
  - Discontinuations
  - Notification of certain manufacturing changes

What we CANNOT require:

- A company to make a drug
- A company to make more of a drug
- How much of a drug is distributed and which purchasers will be given priority

The Agency's Approach to Prevention and Mitigation

Early notification is key!!

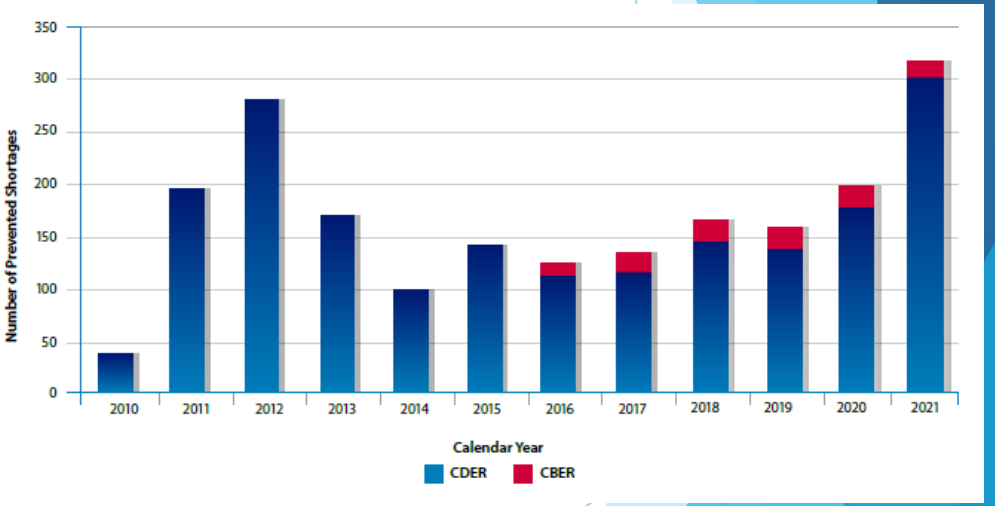
- Prioritize products that are medically necessary
- Risk/Benefit of the drug in question
- Maintain availability while minimizing risk to patients
- Work with firms to address problems
  - We can advise, assist, and expedite inspections and reviews, but the manufacturer must fix the problem
- Drug shortages cannot always be prevented
  - Unanticipated events occur
    - Manufacturing breakdown or natural disaster(Hurricanes & Floods)
  - Sometimes alternate manufacturer may not make up production shortfall
  - If systemic issues are present, the plant may have to close to repair
  - The FDA and the manufacturer can work together to encourage smart distribution (*allocation*)

FDA Toolbox

- Proactive outreach through CDER NextGen Drug Shortage Emergency Event Portal
- Communicate possible shortage concerns on a market shortfall to other suppliers
- Prompts firms to look at demand and supply
- Regulatory Discretion:
  - Manufacture of medically necessary products during remediation
  - Use of additional safety controls
    - Filters with injectable products to remove particulate concerns
    - Extra testing at plant
    - 3rd party oversight of production
    - Special instructions for safe use
- Expedited review of company proposals
  - New manufacturing sites, increased expiry date, new raw material source, changes in specifications, etc.
- In rare cases, temporary exercise of regulatory flexibility and discretion regarding importation from other countries
  - Dextrose 5% in Water, SWFI, Technetium injection, IV Saline Solution, Hydromorphone Injection, Potassium Chloride injection, Sodium Bicarbonate Injection, Bupivacaine Injection, Cefotaxime Injection
  - Past importation of Foscarnet and Thiotepa lead to new US approvals

Impact of Early Notifications to the FDA

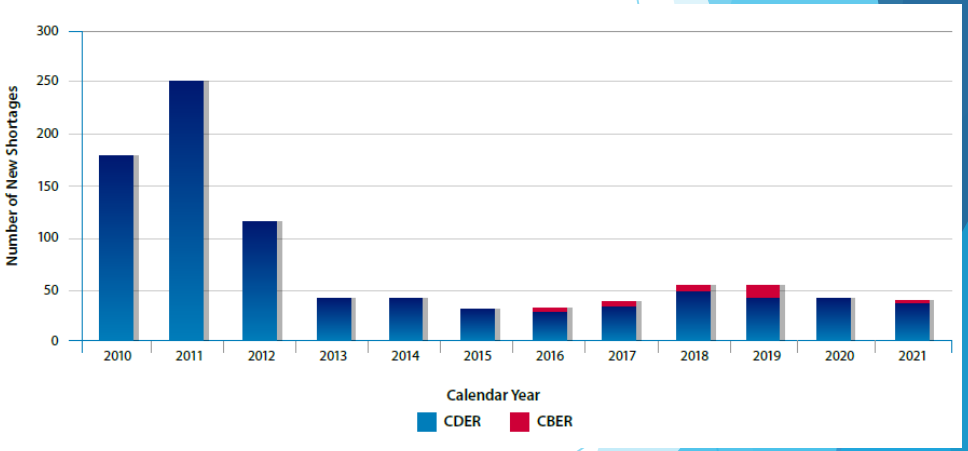
- Ongoing dialogue/work with industry – high numbers of prevented shortages continue
- Depending on the precipitating events, some drug shortages can endure for months to years. (Ex: Plant remediations and agency approvals)



Total Prevented US Drug Shortages Per Year

Current Challenges: New Shortages and Persistent Shortages

- Shortages peaked in 2011 at 251 and continued to decline through 2016. Shortages rose again in 2017 and 2018 due in part to the 2017 hurricane impact as well as ongoing problems with manufacturers. Numbers of new shortages holding steady in 2021 with 38 new shortages.
- Depending on the precipitating events, some drug shortages can endure for months to years. (Ex: Plant remediations)



Total New US Drug Shortages Per Year

Current Drug Shortages and Challenges

- Increased demand – IV narcotics, IV fluids, IV anesthetics etc.
- Emergency syringes – long term shortage, worsened by COVID-19 impact (epinephrine, dextrose)
- Competition on manufacturing lines and in facilities due to limited capacity and vaccines/related products being made on the same lines
- Industry-wide short supply of manufacturing components (e.g. filters) and other commodities (glass, vials, stoppers, bags)
- Nutritional Components – Amino Acids, IV lipids, MVI, Potassium Acetate and Chloride, Sodium Acetate and Phosphates

*Other shortage issues involve IV flush products, empty syringes, bags, needles, and tubing and we are coordinating with our Center for Devices colleagues on these issues

Role of Industry to Help Prevent and Mitigate Drug Shortages

- Understand the frailties of their supply chain
- Communicate early about potential shortages
- Provide shortage information for posting on FDA website when a shortage is unavoidable
- Provide short term and long term plans for preventing and addressing shortages while maintaining and improving quality
- Work with FDA to minimize shutdowns or slowdowns that will lead to shortages

Additional Steps

FDA announced July 12, 2018, that a new FDA Task Force was implemented to identify more enduring solutions for shortages. A public meeting was held November 27th, and additional stakeholder engagement has been conducted. The report was published October 29, 2019.

The report identifies three root causes for drug shortages:

1. Lack of incentives for manufacturers to produce less profitable drugs
2. The market does not recognize and reward manufacturers for "mature quality systems" that focus on continuous improvement and early detection of supply chain issues; and
3. Logistical and regulatory challenges make it difficult for the market to recover from a disruption.

The report also recommends enduring solutions to address drug shortages. These solutions include:

1. Creating a shared understanding of the impact of drug shortages on patients and the contracting practices that may contribute to shortages;
2. Developing a rating system to incentivize drug manufacturers to invest in quality management maturity for their facilities; and
3. Promoting sustainable private sector contracts (e.g., with payers, purchasers, and group purchasing organizations) to make sure there is a reliable supply of medically important drugs.

Enduring Solutions: What's Still Needed?

- Companies need to have Risk Management Plans in place – build better inventories of finished product and raw materials and components, have a backup plan for when things fail or demand increases
- Redundancy in manufacturing and suppliers –encouraging industry to have "warm" lines and components and supplies at the ready for critical drugs
- More capacity, additional manufacturers making critical drugs
- Communication is Key
    - Guidance to Industry issued April 2020 requesting notifications on increased demand in addition to supply disruptions
    - Ongoing Collaboration – Industry, Outside Stakeholders

Contacts:

Current shortage information updated daily at:
https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

To contact DSS:

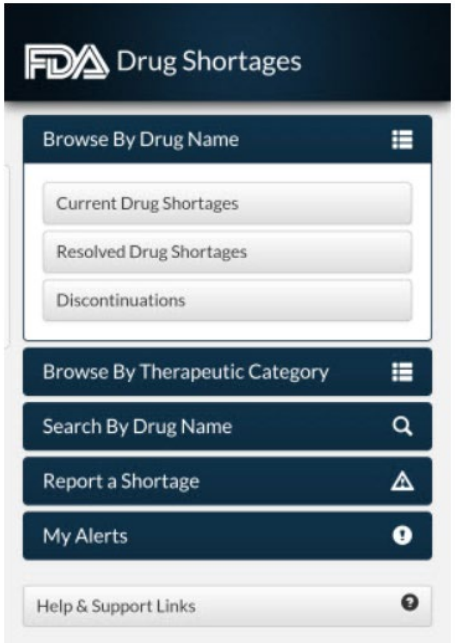
Email: drugshortages@fda.hhs.gov

FDA Drug Shortages Homepage:

https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm

Drug Shortage Mobile APP

FDA Drug Shortages Mobile App



Download on the App Store

ANDROID APP ON Google play

Receive notifications when there is
about a drug product shortage or a
therapeutic categories.

FDA Drug Shortages RSS Feed

References

- Explanation of FDA and ASHP shortage posting: https://www.fda.gov/drugs/drug-shortages/frequently-asked-questions-about-drug-shortages#q1
- FDA Sixth Annual Report on Drug Shortages for Calendar Year 2018 https://www.fda.gov/media/130561/download
- FDA Shortages Additional News And information https://www.fda.gov/drugs/drug-shortages/drug-shortages-additional-news-and-information
- Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 506C (21 USC 356c) https://www.gpo.gov/fdsys/pkg/USCODE-2012-title21/pdf/USCODE-2012-title21-chap9-subchapV-partA-sec356c.pdf
- Federal Register Final Rule, 80 FR 38915 (July 8, 2015), Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products. https://www.gpo.gov/fdsys/pkg/FR-2015-07-08/pdf/2015-16659.pdf. See also 21 CFR 310.306, 314.81, and 600.82
- CDER MAPP 4190.1 Rev. 2, Drug Shortage Management (11/1995; Rev. 1, 9/2006; Rev. 2, 9/2014): https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf
- Executive Order 13588 (October 31, 2011), Reducing Prescription Drug Shortages: https://obamawhitehouse.archives.gov/the-press-office/2011/10/31/executive-order-13588-reducing-prescription-drug-shortages
- FDA Strategic Plan for Preventing and Mitigating Drug Shortages: https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf
- Letters of Non-Compliance with Notification Requirement: https://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm403902.htm

Mission of the Diversion Control Division

To prevent, detect, and investigate the diversion of controlled pharmaceuticals and listed chemicals from legitimate sources while ensuring an adequate and uninterrupted supply for legitimate medical, commercial, and scientific needs.

Drug Shortages Controlled Substances

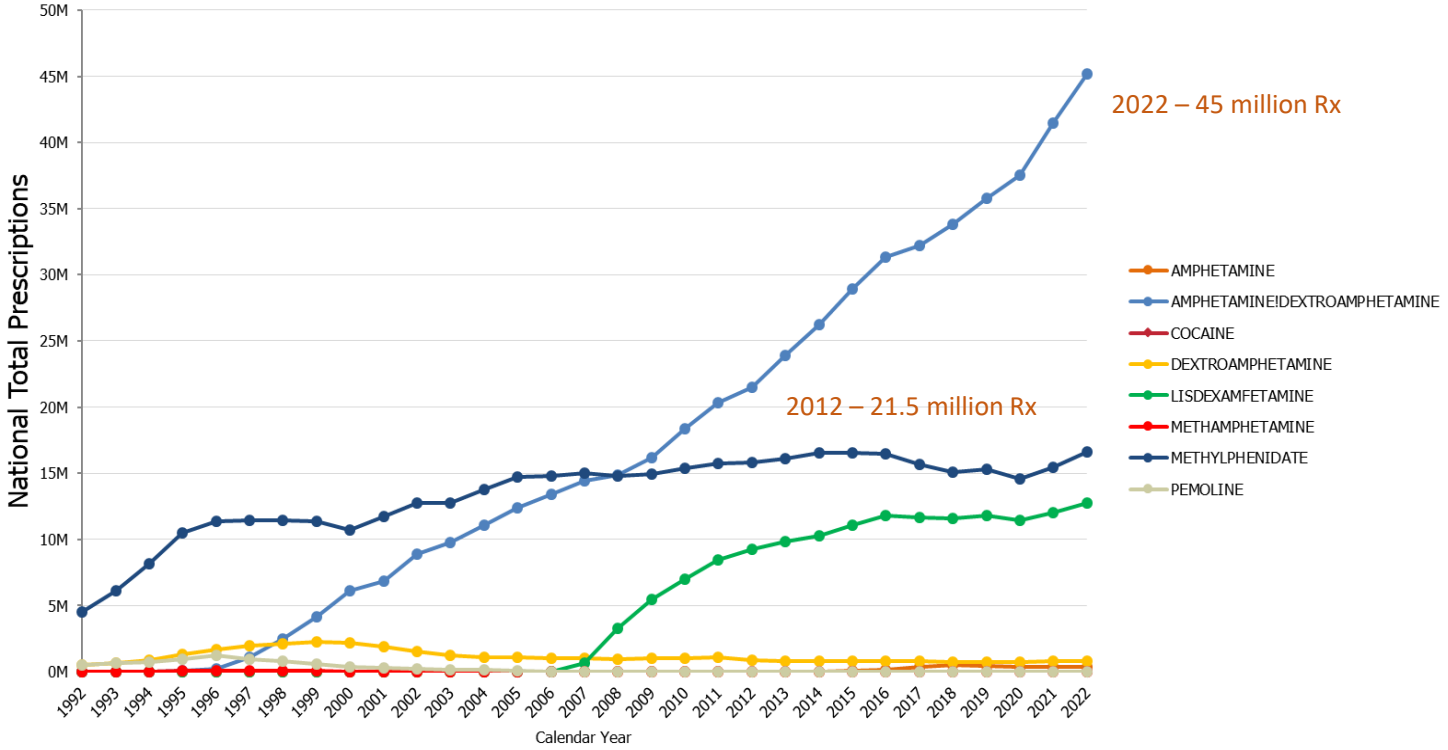
- As of March 15, 2023, there were **1,345** product presentations actively on the drug shortage list.

- **236** (17.5%) - controlled substances

- **61%** - injectable presentations (hospital use)
  - CII – fentanyl, sufentanil, remifentanil, hydromorphone, morphine
  - CIV – midazolam, lorazepam, ketamine

- **39%** - solid dosage form (tablets/capsules)
  - CIV – clonazepam tablets (23)
  - CII – mixed salt amphetamine (59)

Total Stimulant Prescriptions by Combined Molecule



Source: IQVIA, SMART – US Launch Edition
Accessed at https://smart.imshealth.com/ on 4/29/2022

Demographic Trends in ADHD Patients

Table 1. Demographic Characteristics of Stimulant Prescriptions Dispensed in 2012-2021

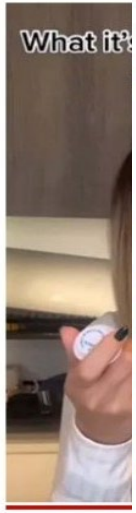
		2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
All		**50,445,946**	**53,728,661**	**56,622,294**	**60,188,348**	**63,493,937**	**63,487,133**	**64,742,449**	**67,374,892**	**67,693,255**	**73,380,849**
Sex	Female	21,580,852	23,317,646	24,946,217	26,951,783	28,757,702	29,046,829	29,918,189	31,451,891	32,796,307	36,569,804
	Male	28,865,094	30,411,014	31,676,077	33,236,565	34,736,236	34,440,304	34,824,259	35,923,001	34,896,948	36,811,044
Age Group (Years)	0-10	9,692,397	9,919,205	9,800,148	9,706,586	9,646,703	9,110,508	8,726,354	8,549,027	7,442,584	7,410,165
	11-20	17,695,482	18,008,758	18,238,758	18,600,204	18,955,272	18,412,146	18,291,767	18,417,680	16,806,264	17,360,227
	21-30	7,991,733	8,815,799	9,657,661	10,546,520	11,204,189	11,174,822	11,170,624	11,347,064	11,545,862	12,885,615
	31-40	5,400,980	6,280,328	7,170,513	8,301,850	9,364,545	9,986,388	10,863,877	12,047,202	13,329,846	15,313,953
	41-50	4,565,717	5,038,783	5,477,489	6,080,020	6,686,117	6,959,177	7,466,272	8,143,264	8,968,588	9,978,536
	51-60	3,414,722	3,735,112	4,062,297	4,442,739	4,790,171	4,857,559	5,035,066	5,371,021	5,789,320	6,292,592
	61-70	1,264,688	1,452,640	1,666,185	1,898,400	2,161,059	2,275,866	2,419,832	2,633,406	2,846,920	3,063,213
	71-80	146,379	206,023	275,086	342,141	423,005	479,032	556,893	638,790	716,329	800,789
	81+	273,849	272,013	274,157	269,887	262,877	231,634	211,764	227,439	247,541	275,758
Race/Ethnicity	African American	634,934	613,725	610,039	614,618	624,339	598,240	587,976	607,229	632,250	711,020
	Asian/Other	230,965	238,451	259,527	280,161	304,521	311,558	320,350	342,340	362,499	424,986
	Caucasian	15,193,380	15,644,491	16,239,758	16,946,942	17,660,125	17,471,228	17,600,394	18,276,027	19,242,658	21,201,505
	Hispanic	939,698	932,587	957,162	993,197	1,043,690	1,014,919	1,019,623	1,107,048	1,197,921	1,369,054
	Unspecified	33,446,970	36,299,406	38,555,808	41,353,429	43,861,262	44,091,189	45,214,105	47,042,249	46,257,928	49,674,284

Role of Social Media and Startups

TECH EXCLUSIVE DETAILS

Startups push ADHD meds through TikTok ads, concerning d

By Theo Wayt



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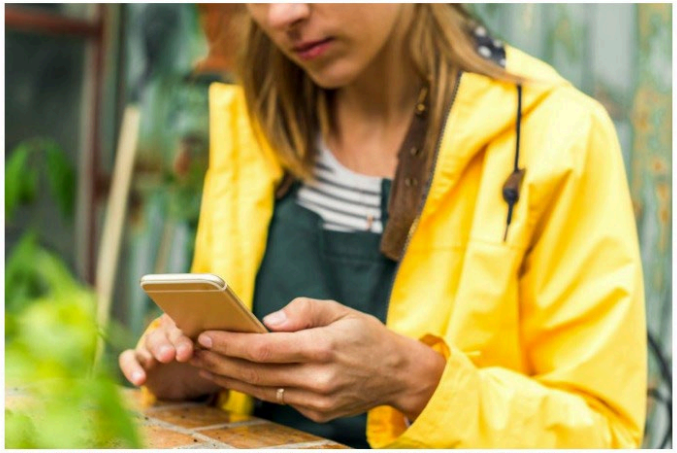
WSJ NEWS EXCLUSIVE | HEALTH

ADHD Specialists Worry Stimulant Drugs Are Overprescribed, Push for Treatment Guidelines

Goal is to prevent a backlash against stimulant medications: 'We don't want a repeat of what happened with opioids'



Social-media content about ADHD has driven an uptick in patients who believe they have the condition and seek treatment.
PHOTO: ISTOCK

By Rolfe Winkler Follow
Sept. 1, 2022 8:00 am ET

Instagram and TikTok pull ads from startup Cerebral linking ADHD to obesity

MIND | The Hazards of Prescribing A.D.H.D. Drugs Online

The Hazards of Prescribing A.D.H.D. Drugs Online

Buzzy start-ups promising easy access to mental health medication found an eager market on social media. Should anyone be looking for treatment on TikTok, though?

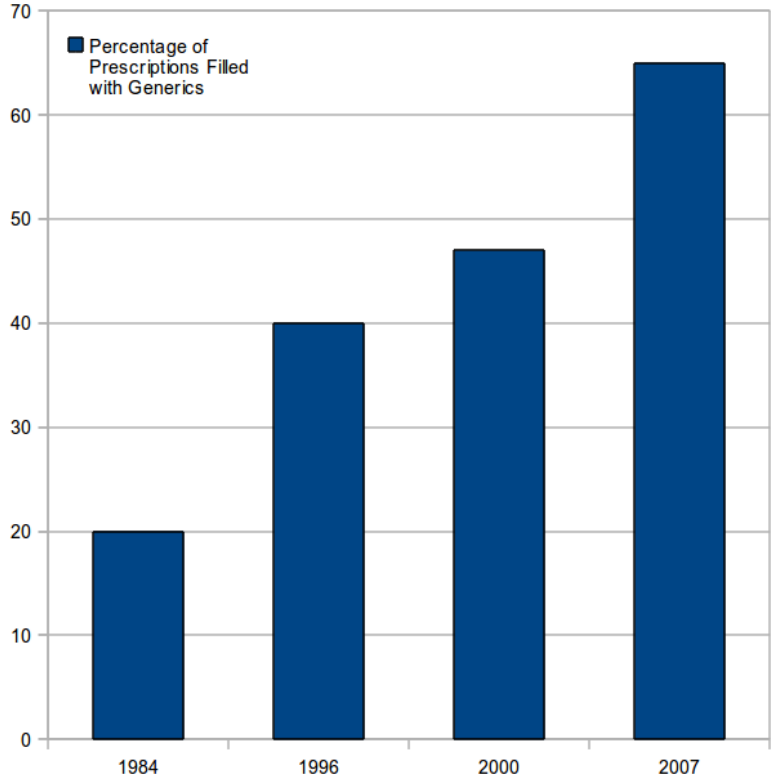
Give this article 147

Elizabeth D. Herman for The New York Times

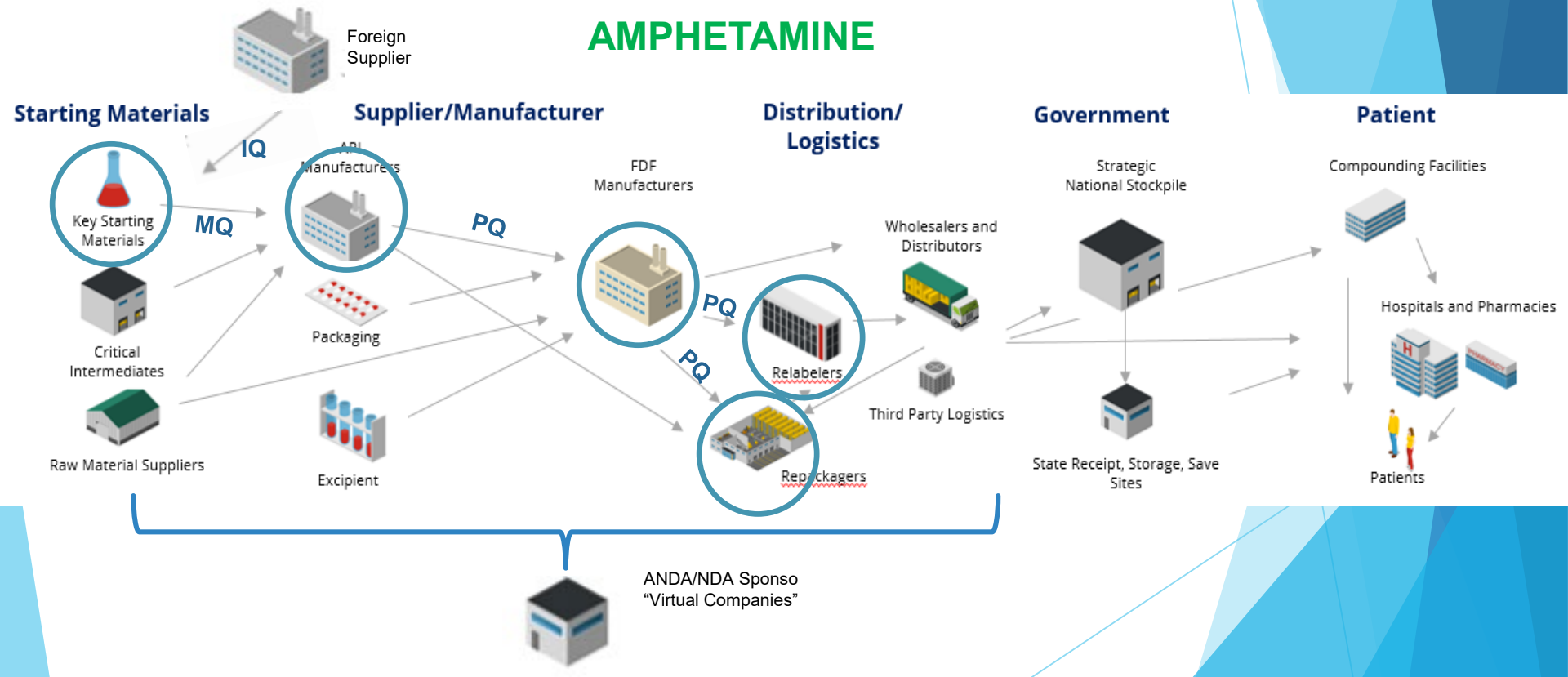
TikTok
@doneadhd

pcorn,

Role of Generics and CMOs



Illumination – Simplified End-to-End Supply Chain



By the Numbers

AMPHETAMINE

FDA/DEA estimated demand– **39,623 kg**.

December 31, 2022 Inventory - **33,988 kg**.

DEA authorized MQ (2/23) - **34,074 kg**.

68,060 kg

8,326 kg available to be allocated

METHYLPHENIDATE

FDA/DEA estimated demand – **26,969 kg**.

December 31, 2022 Inventory – **29,769 kg**.

DEA authorized MQ (2/23) – **35,552 kg**.

65,321 kg

6,248 kg available to be allocated

Best Practices

DOSAGE MANUFACTURERS

- Provide your API manufacturers with forecasts that reflect your firm's DEA established procurement quota.
- Submit quota applications representing your firm's actual purchasing plan
  - ~18 % of amphetamine API purchasing authority went unused in 2022
- Describe your "increasingly complex" supply chain in each quota application.
- If you advise FDA of a shortage due to API, be prepared for a call from DEA for data that supports that decision.

API and DOSAGE MANUFACTURERS

- Transparency and communicating is key. Communicate early and often with DEA (and FDA). Include details to the FDA that your are providing to the DEA (and vice versa).
- Previous Sales is the best predictor of future performance…DEA will review sales at all levels of the supply chain when considering quota requests. Future anticipated sales are given little weight, especially in a mature market.

Questions?

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