A (Continued) Commitment to Pharmaceutical Quality

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2021 Generic Drugs Forum Keynote

Pharmaceutical Quality

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Drugs are no different.

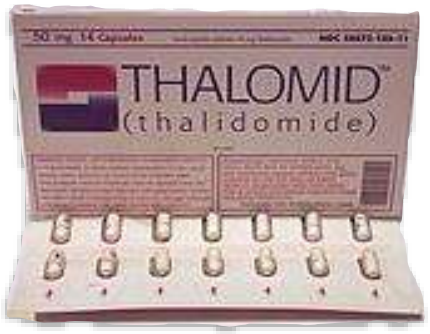
Patients expect safe and effective medicine with every dose they take

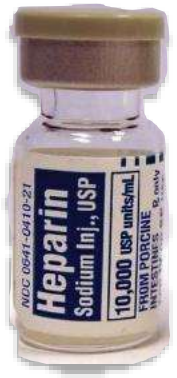
Pharmaceutical quality is

what gives patients confidence in their next dose of medicine

It is what gives patients confidence in their *next* dose of medicine

A History of Pharmaceutical Quality





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Safety studies required

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Need to prove drugs are safe and effective

2008

Injuries and deaths from global heparin crisis

Office of Pharmaceutical Quality

Integrates quality functions and elevates commitment to quality

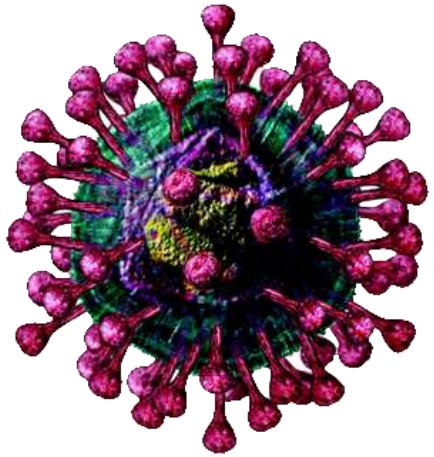
2020

COVID-19 stresses supply chains to breaking point

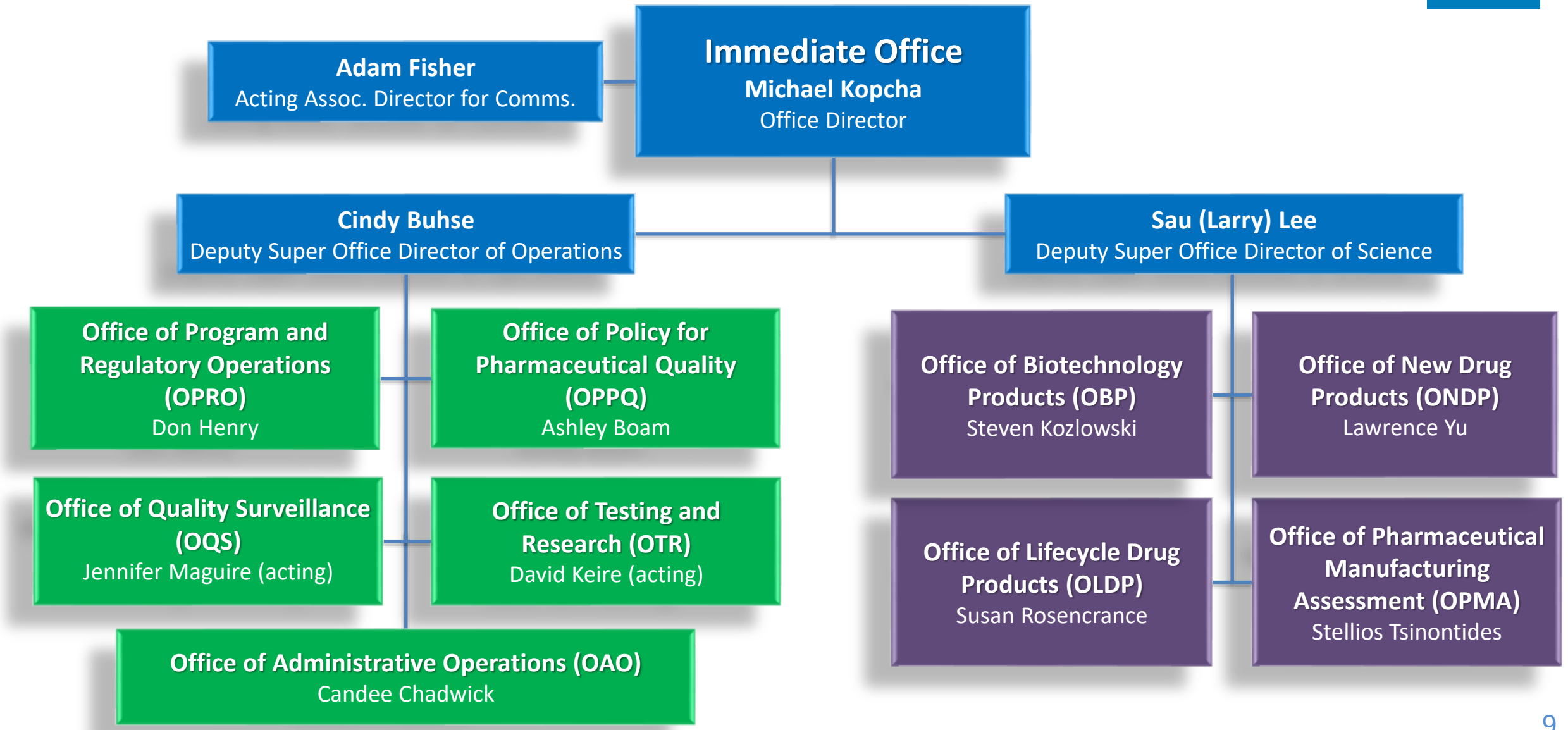
?

OPQ – Who We Are

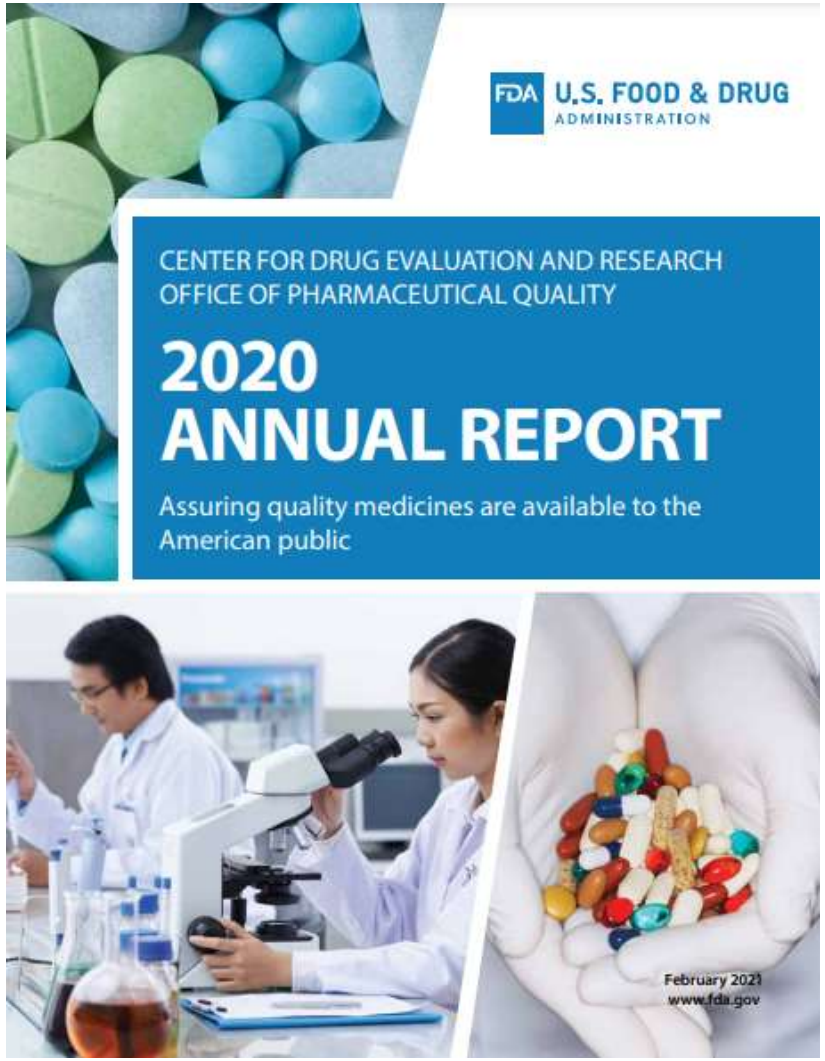
- Our mission: *assuring that quality medicines are available to the American public*
- COVID-19 challenged all functions: **assessment, inspection, research, surveillance, and policy**
- New and long-standing issues came to the forefront: **supply chains, changing demand, and decision-making based on evolving science and risk**



Office of Pharmaceutical Quality



2020 OPQ Annual Report



- **622** submissions approved for drugs used in the treatment of patients with COVID-19
- **Over 6,000** newly registered drug manufacturing facilities
- **11** Guidance documents to ensure the quality, supply, and safety of pharmaceuticals during the COVID-19 crisis

Highlights from 2020

153 pre-approval inspections avoided using alternative tools due to COVID-19 travel restrictions

Over 95% of applications were acted on by their user fee goal date

Over 10,000 approved application supplements

293 expedited quality assessments to avert or mitigate drug shortages

Quality Testing of US-Marketed Products

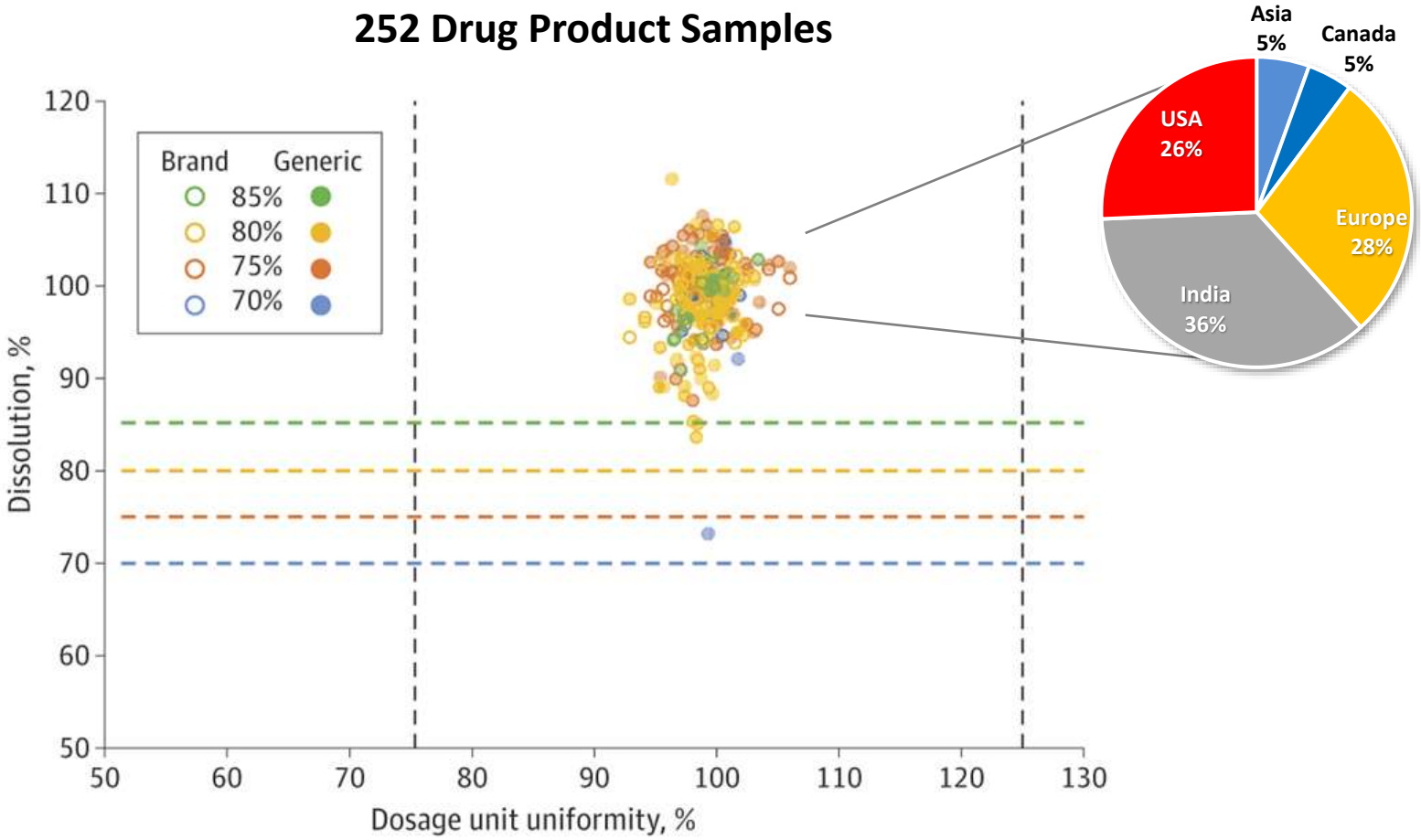

JAMA Network Open

Quality Testing of Difficult-to-Make Prescription Pharmaceutical Products Marketed in the US

Table. Immediate-Release Drug Products Sampled

Products and ingredients
Alprazolam tablet
Amoxicillin capsule and tablet
Amoxicillin and clavulanate potassium tablet
Citalopram tablet
Ezetimibe and simvastatin tablet
Hydralazine tablet
Metformin tablet
Metoprolol tartrate tablet
Metoprolol tartrate and hydrochlorothiazide tablet
Metronidazole tablet
Oxcarbazepine tablet
Pioglitazone and metformin tablet
Pravastatin tablet
Propafenone tablet
Propranolol tablet
Propranolol and hydrochlorothiazide tablet
Simvastatin tablet
Venlafaxine tablet

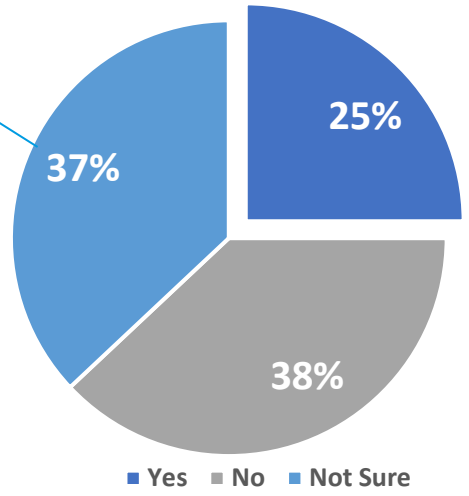
Samples of brand and generic drugs were taken from 46 anonymous manufacturers located in 5 regions (Canada, Europe, US, India, and the rest of Asia). Lower limits of dissolution were 70%, 75%, 80%, and 85%.



Perceptions of Drug Manufacturing

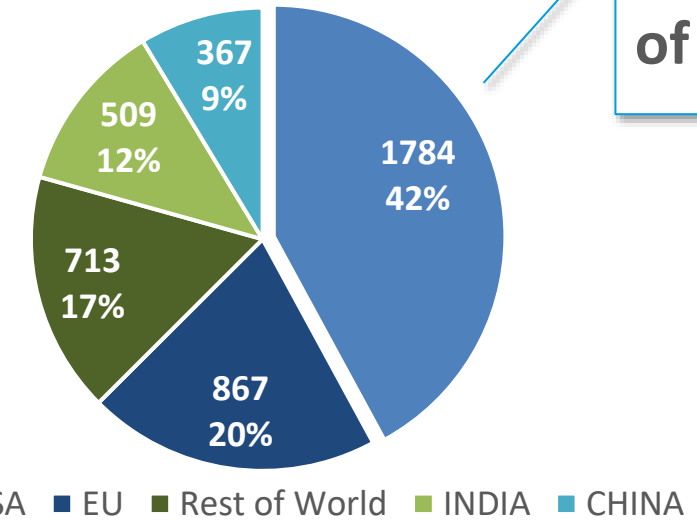
*Do you believe **drugs manufactured outside the U.S. and sold in the U.S.** adhere to strict manufacturing standards and regulations required by the FDA?*

Three <u>quarters</u> of physicians **do not believe** or **are not sure**



Base: Total respondents - Physicians

All FY20 Drug Manufacturing Sites[1]



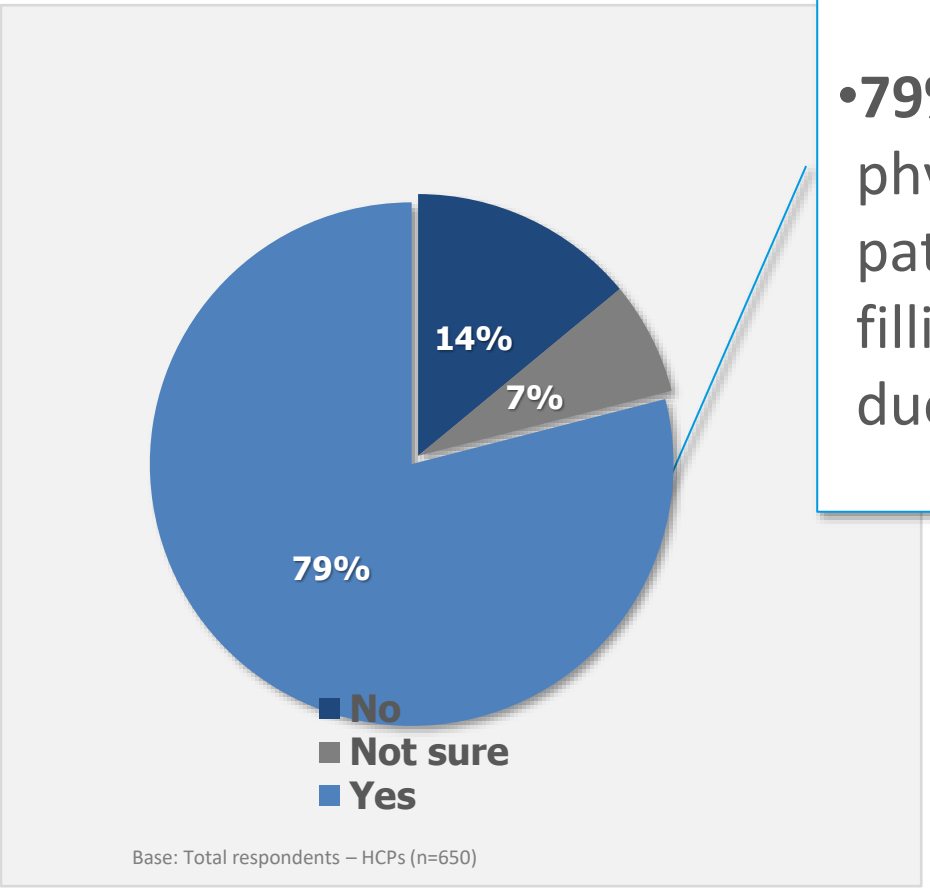
58% of **drug manufacturing sites** are located **outside of the US**

[1] Excludes Medical Gas sites which consist of >2,000 sites, almost exclusively in the US and Hand Sanitizer sites registered under temporary guidance

Drug Shortages Persist

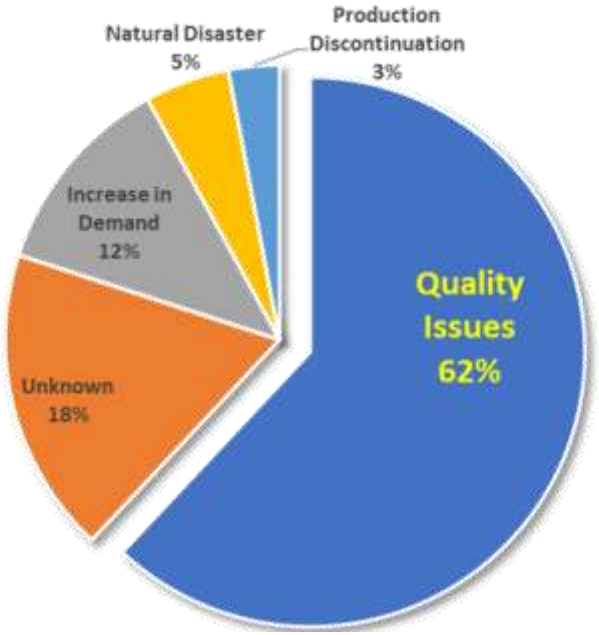
In 2018, WebMD asked health care providers:

Have your patients experienced any difficulty in filling prescription(s) due to drug shortage?

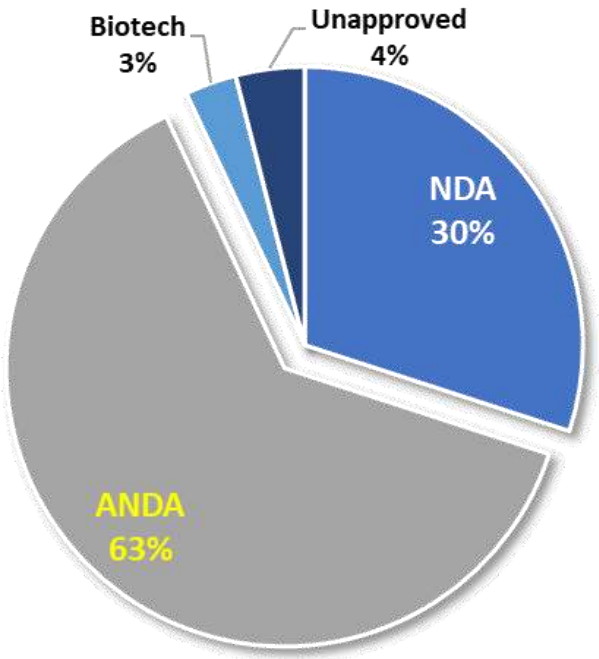


- **79% percent** of physicians report their patients had problems filling a prescription due to drug shortage

Drug Quality and Shortages



All Drugs Newly in Shortage

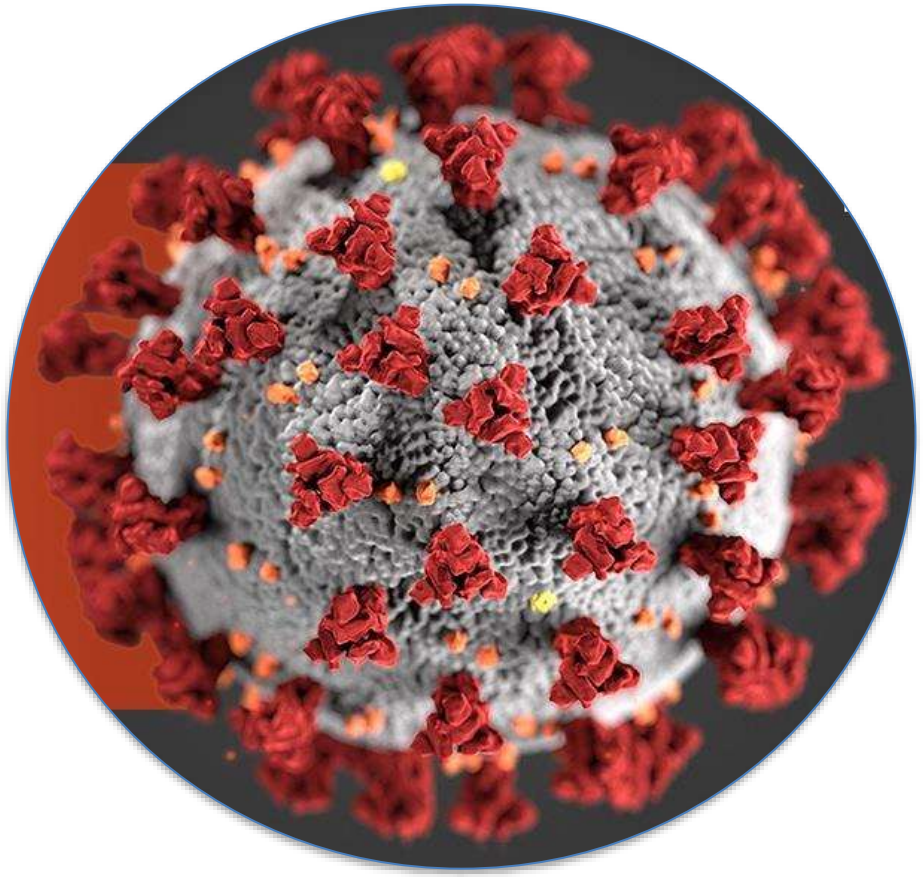


All Drug Products in Shortage

Challenges of the COVID-19 Pandemic for Drug Manufacturing

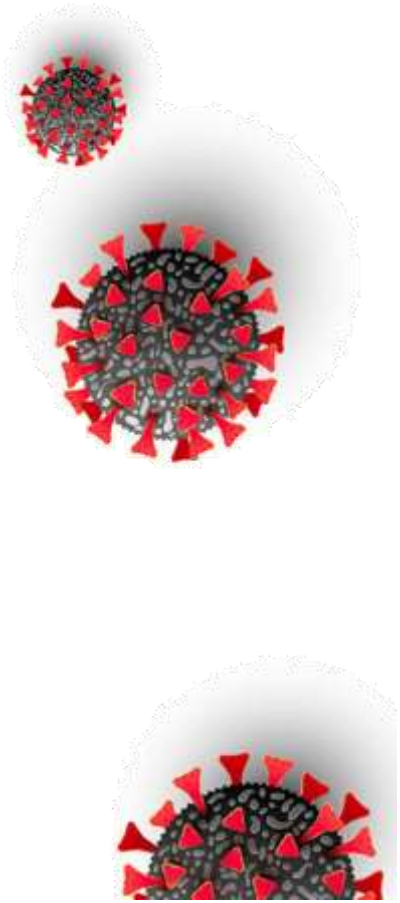
Long-existing quality issues are now magnified

- Information about current state of drug manufacturing and distribution
- Supply chain vulnerabilities
- Shortages due to manufacturing and distribution issues



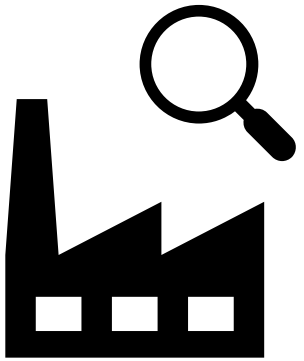
FDA Inspections During COVID-19

- **FDA postpones <u>non-mission critical</u> foreign and domestic inspections**
  - Announced March 2020
- **For-Cause and Pre-Approval Inspections (PAIs) can be deemed mission critical**
  - Considers safety of all involved in inspections
  - Considers clinical benefit and medical necessity



Alternative Tools for Facility Assessments

- **Conducting "remote" assessments of facilities**
  - Requesting information in lieu of an inspection - FD&C 704(a)(4)
  - Relying on Mutual Recognition Agreement (MRA)
  - Remote Interactive Evaluation
    - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities-during-covid
- **Will resume postponed inspections as soon as feasible**
  - On a region-by-region/country-by-country basis
- Learnings and Insight from Records Requests under § 704(a)(4) of the FD&C Act in lieu of Pre-Approval Inspections, Cassie Abellard and Jonathan Swoboda: Wednesday, April 28, 3:35 pm



See: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/manufacturing-supply-chain-and-drug-inspections-covid-19

Impact of Using Alternate Tools

- **On Facility Assessments for Pending Applications**
  - While not all applications warrant PAI, alternative tools reduced the number of GDUFA submissions where a PAI was needed by:
    - ~52% in FY20 Quarter 3
    - ~56% in FY20 Quarter 4
    - ~57% in FY21 Quarter 1
    - ~49% in FY21 Quarter 2
  - Continue to perform a PAI for mission critical drugs if alternate tools cannot be used to address identified risks
- **On Drug Application Review Program:**
  - Maintain same quality standards while overcoming COVID-related inspection challenges
  - FDA continues to meet GDUFA program goals (>90%)

No Incentive for Quality Management Maturity

Root causes for drug shortages:

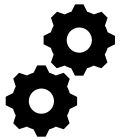
- Lack of incentives for manufacturers to produce less profitable drugs
- **Market does not recognize and reward manufacturers for "mature quality systems"**
- Logistical and regulatory challenges make it difficult to recover from a supply disruption

An Enduring Solution: Quality Management Maturity

Product Quality

Every dose is safe and effective and free of contamination and defects

Gives patients confidence in every dose they **take**



Process Quality

Manufacturing risks controlled to provide quality drug product

Gives manufacturers confidence in every batch they **release**

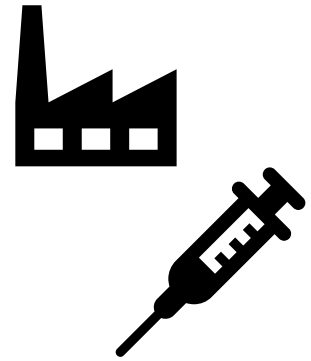
Quality Management

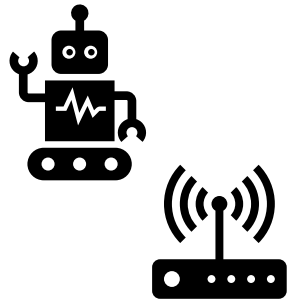
Performance and patient focus to identify areas of improvement and implement changes

Gives manufacturers confidence every batch will be **acceptable to release**

Future of Quality Management Maturity

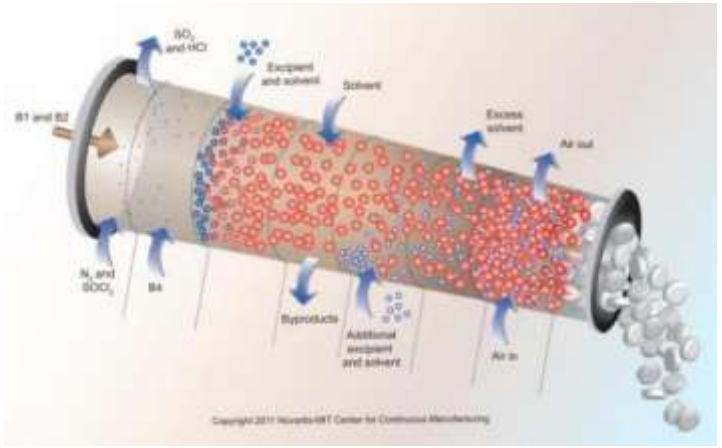
- **A system to inform purchasers & patients about the quality management maturity of the facilities making their drugs**
  - *Update of CDER's Quality Management Maturity Program, Jennifer Maguire: Wednesday, April 28, 11:10 am*

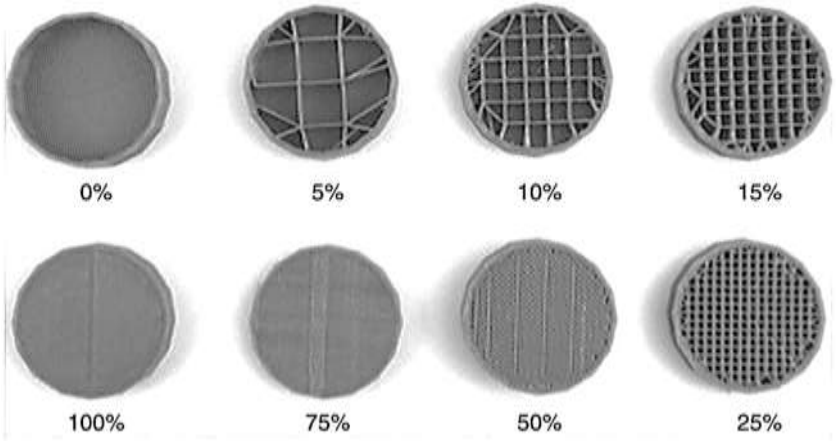




What is Advanced Manufacturing?

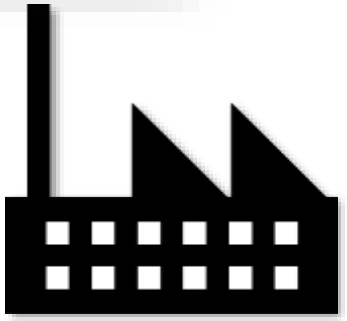
- Novel **manufacturing methods** to improve process robustness and efficiency
- Novel **dosage forms** or delivery systems to improve drug delivery and targeting
- Novel **analytical tools** to improve product characterization, quality testing, process monitoring and/or control





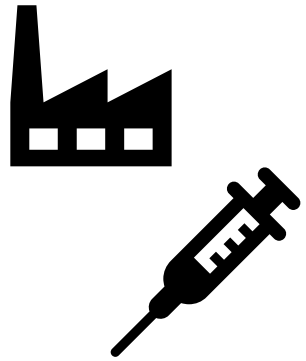
The Importance of Advanced Manufacturing

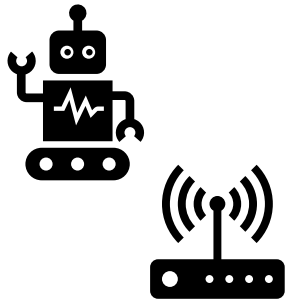
- **Addresses the underlying causes of drug shortages**
  - Mitigate or prevent future production problems
  - COVID-19: Faster commercial production w/o scale-up issues
- **Improves manufacturing efficiency**
  - Increase process robustness
  - Lower manufacturing costs
  - Improve supply chain flexibility
- **Facilitates development and quality control of complex generic products**
  - **Novel analytical tools** to characterize complex drug substances and products
  - Support establishment of pharmaceutical equivalence and/or bioequivalence
  - Reduce the need for in vivo bioequivalence studies
  - Improve the availability of complex generic products to the American public



CDER Progress on Advanced Manufacturing

- **Embracing advanced manufacturing technologies in pharma**
  - *Fostering Innovation Through OPQ's Emerging Technology Program, Tom O'Connor: Thursday, April 29, 10:35 am*
  - *Lab Science to Support Generic Complex Drug Product Assessment, Rachel Dunn: Thursday, April 29, 10:50 am*





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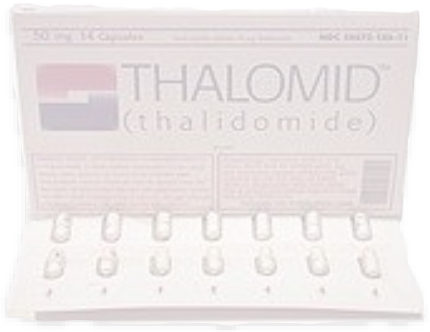

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COOPERATION

TRANSPARENCY

INNOVATION

PATIENT FOCUS

Let’s keep working together…

Using the best available science…

To assure quality medicines are available for patients…

Through COVID-19 *and beyond*.


FDA
U.S. FOOD & DRUG
ADMINISTRATION