

A (Continued) Commitment to Pharmaceutical Quality

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U.S. Food and Drug Administration

2021 Generic Drugs Forum Keynote



Pharmaceutical Quality



A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality



A quality product of any kind consistently meets the expectations of the user.



Drugs are no different.

A close-up photograph showing a hand holding an orange pill bottle, pouring three white, oval-shaped pills into the palm of another hand. The background is blurred, focusing attention on the action of taking medication.

**Patients expect safe and effective
medicine with every dose they take**

A close-up photograph of a person's hands. The left hand holds an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is blurred, focusing attention on the action of taking medication.

**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

FDA



1938

>100 deaths from elixir sulfanilamide

1938 Food, Drug, and Cosmetic (FD&C) Act

Safety studies required



1962

Children born with birth defects from thalidomide

1962 Kefauver-Harris Amendments to FD&C Act

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



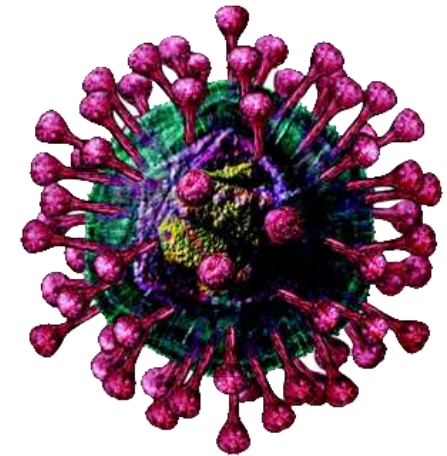
2020

COVID-19 stresses supply chains to breaking point

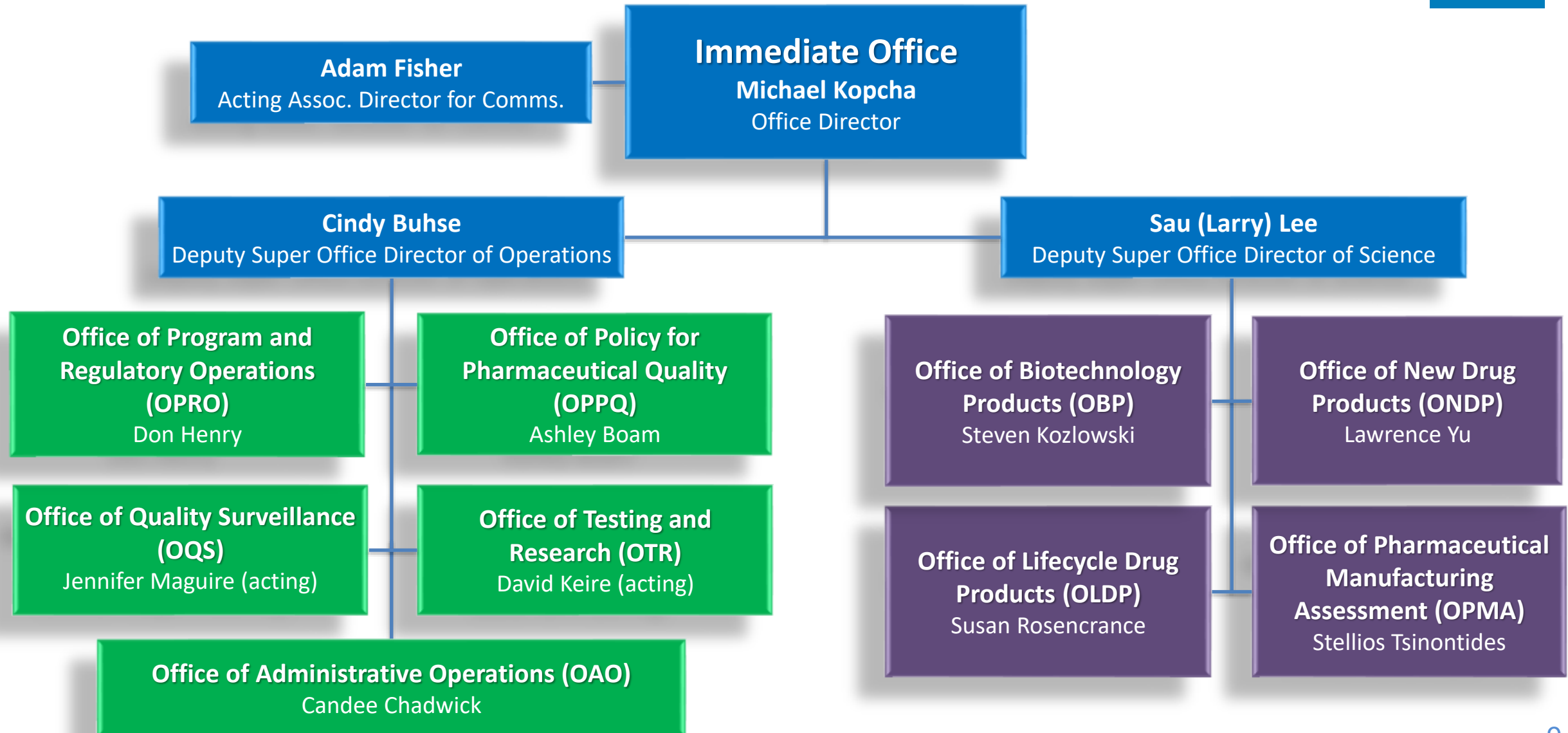


OPQ – Who We Are

- 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

Original Investigation | Pharmacy and Clinical Pharmacology

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

Author(s): Cohen, PM, et al. JAMA Network Open. 2020;3(10):e201910. doi:10.1001/jamaopen.2020.1910.

Abstract

IMPORTANCE: Healthcare providers and patients need information to support their confidence in the quality of prescription pharmaceuticals.

OBJECTIVE: To determine whether there were clear and substantial differences in major quality attributes between difficult-to-make solid oral dosage form pharmaceutical products marketed in the US.

DESIGN, SETTING, AND PARTICIPANTS: This quality improvement study analyzed US Food and Drug Administration collected samples of 252 drug products marketed in the US and manufactured in North America, Europe, India, and the rest of Asia. These drug products were considered difficult-to-make on the basis of product quality history. The sampling included 15 innovator and 237 generic drug samples manufactured by 46 different firms containing 17 different active ingredients. Statistical analysis was performed from February to November 2019.

MAIN RESULTS AND MEASURES: All products assayed within their shelf life on the basis of the legally required tests of the US Pharmacopeia for major quality attributes of dosage unit uniformity and dissolution. These tests measure dosage consistency and drug release, respectively. The consistency of either attribute was used to calculate a process performance index to describe the variability in manufacturing.

RESULTS: All 252 drug product samples met the US market standards for dosage unit uniformity and dissolution, although the process performance index (Ppk) for dissolution fell below the level of 4 sigma capability (ie, <1 error per 630,000) for 18 different manufacturers and for generics in 4 of 5 regions, including the US. As part of a retrospective analysis, manufacturers performing above the median Ppk for either dissolution or dosage unit uniformity submitted lower product quality defect reports (lower field defect reports of 0.22 and 0.11, respectively) than those falling at or below the median Ppk for these attributes (lower field defect reports of 0.33 and 0.22, respectively).

CONCLUSIONS AND RELEVANCE: All samples assayed within their shelf life on the basis of the legally required tests of the US Pharmacopeia for major quality attributes of dosage unit uniformity and dissolution, including a capillary region. To our knowledge, this is the largest case of US market and these data provide objective information on manufacturing risks.

JAMA Network Open. 2020;3(10):e201910. doi:10.1001/jamaopen.2020.1910.

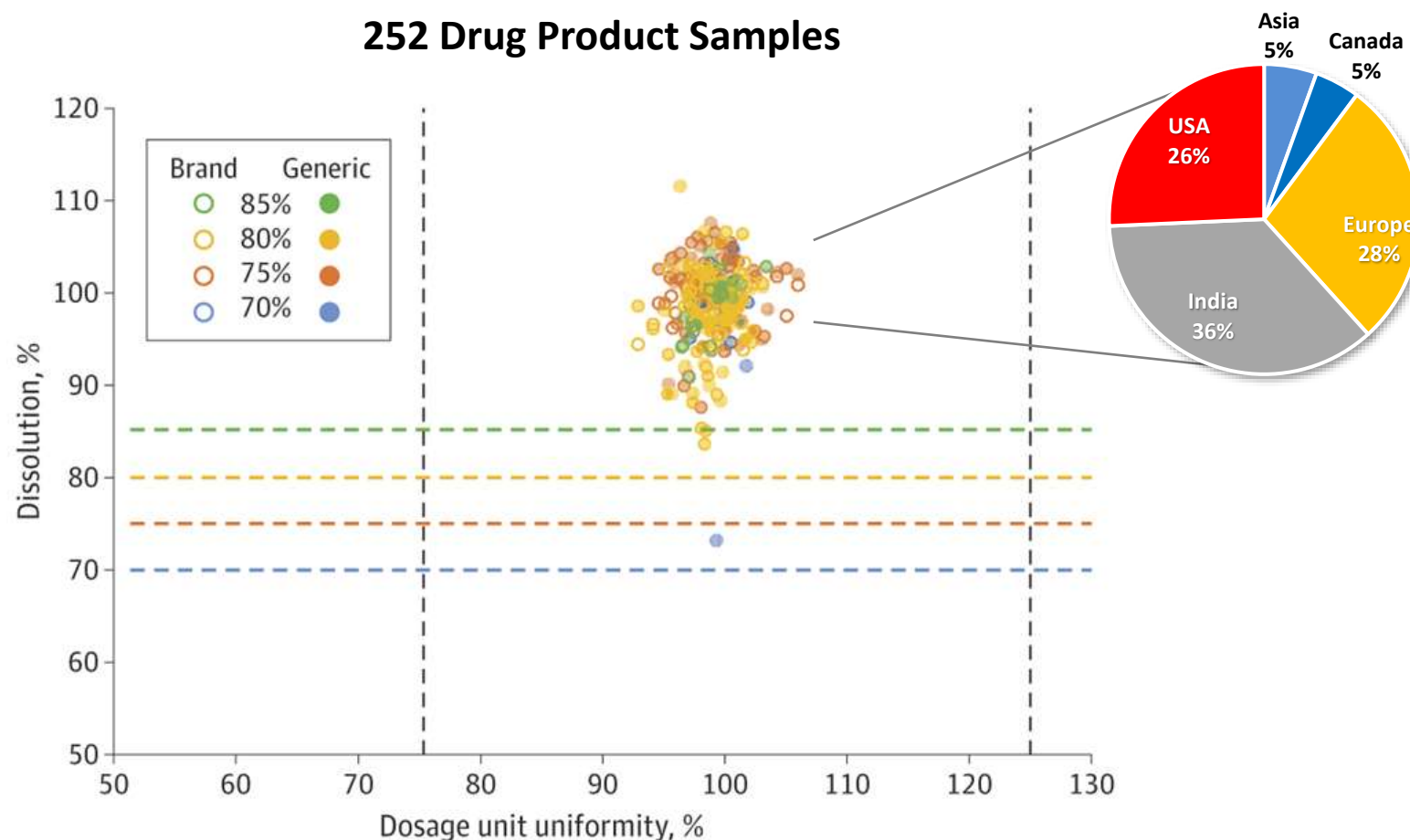
Supplemental content: Author affiliations and a list of disclosures are listed at the end of this article.

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
Proglitazone and metformin tablet
Pravastatin tablet
Propofolone 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%.

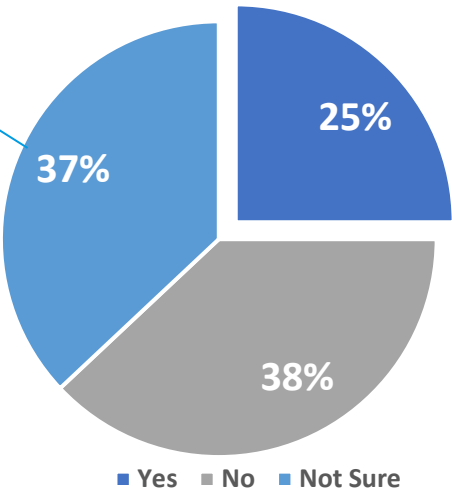
252 Drug Product Samples



Perceptions of Drug Manufacturing

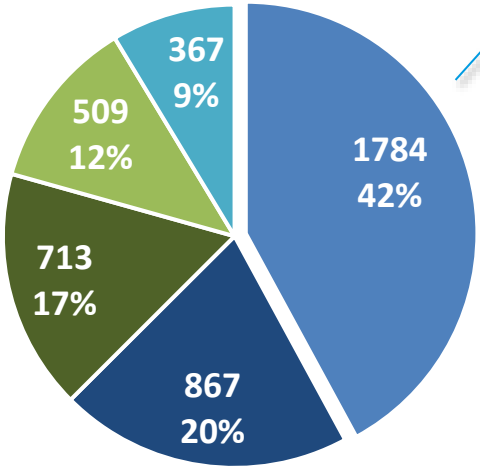
*Do you believe **drugs manufactured outside the U.S. and sold in the U.S.** adhere to strict manufacturing standards and regulations required by the FDA?*

Three quarters of physicians **do not believe** or are not sure



Base: Total respondents - Physicians

All FY20 Drug Manufacturing Sites¹



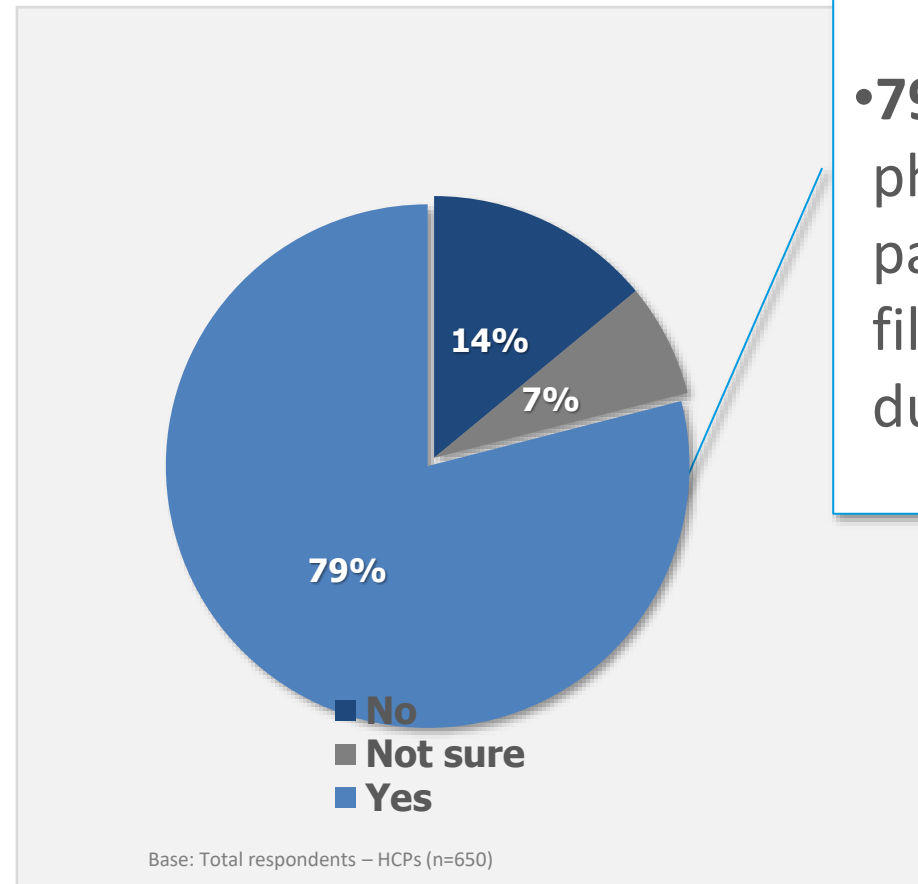
■ USA ■ EU ■ Rest of World ■ INDIA ■ CHINA

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

Drug Shortages: Root Causes and Potential Solutions

2019



**To Help Reduce Drug Shortages, We Need
Manufacturers to Sell Quality – Not Just
Medicine**

ADDITIONAL CONTENT | F | P | T | L | S | W | P



Content current as of
10/13/2019
Regulated Product(s)
Drug

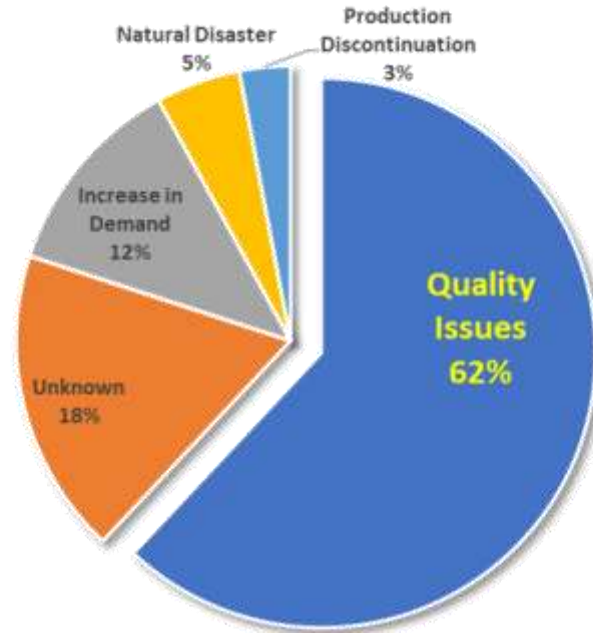
By: Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research

You might not always shop based solely on the lowest price. For instance, if you highly value your time, you may choose a car from a manufacturer with a great reputation for reliability, even though similar cars cost a lot less. Choices based on what you value are common in everyday life. But, unfortunately, when it comes to prescription medications, buyers may not have that option. And in the view of the U.S. Food and Drug Administration, this lack of transparency is contributing to ongoing drug shortages, a critical health care issue that reduces treatment options, limits access to medications, and can threaten the well-being of patients in need of important therapies. Let's take a closer look.

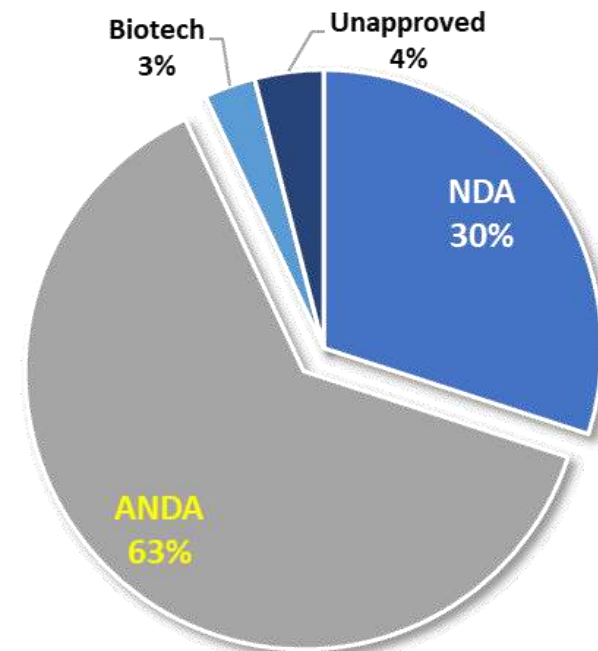
All drug manufacturers that sell their medications in the United States must adhere to the FDA's Current Good Manufacturing Practices (CGMP) requirements. Adherence to CGMP requirements is intended to make sure the drug itself is of adequate quality.

But there's another element to quality in manufacturing — the ability to reliably make the product in sufficient quantities and with sufficient speed to ensure that supply consistently meets demand over sustained periods of time. This is especially true in the pharmaceutical industry, where the product is often life-sustaining — and ongoing access is critical.

Purchasers of prescription drugs such as drug distributors, hospitals, and pharmacies can be assured that FDA-approved medicines have been shown to be safe and effective for their labeled uses. Since these purchasers have tight budgets, they may select the lowest-priced product, in



All Drugs Newly in Shortage



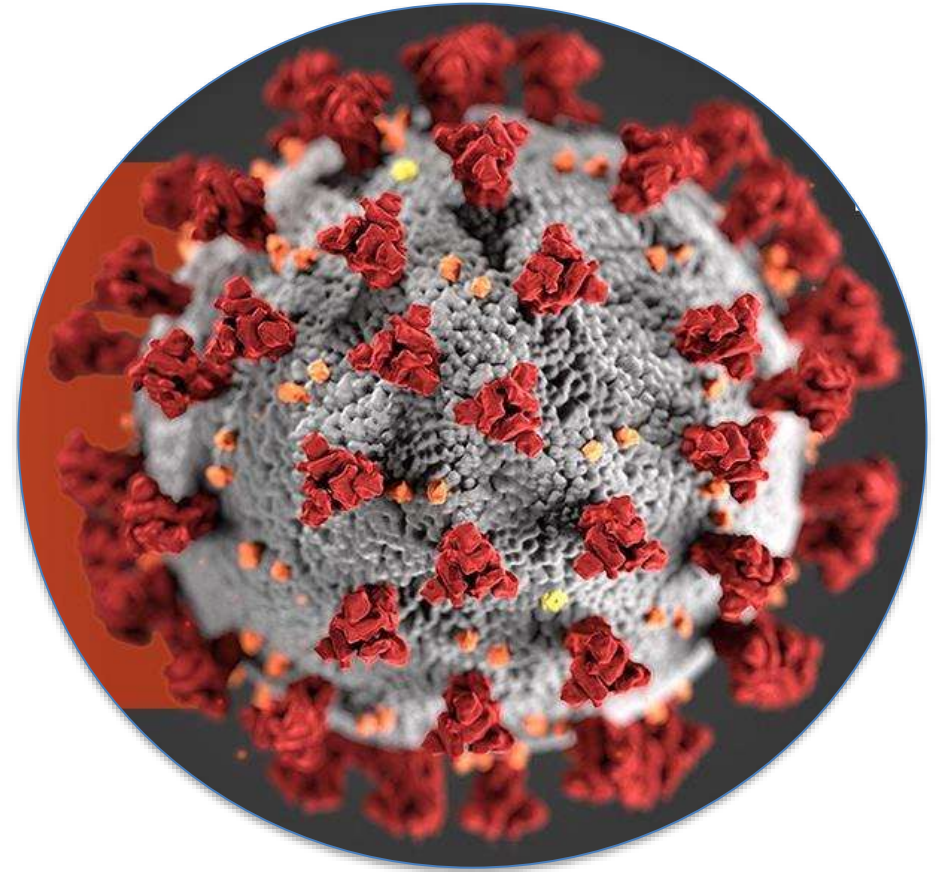
All Drug Products in Shortage

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

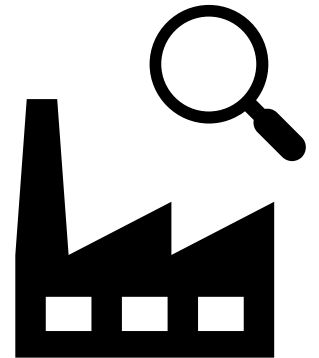
- **FDA postpones non-mission critical foreign and domestic inspections**
 - Announced March 2020
- **For-Cause and Pre-Approval Inspections (PAIs) can be deemed mission critical**
 - Considers safety of all involved in inspections
 - Considers clinical benefit and medical necessity



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

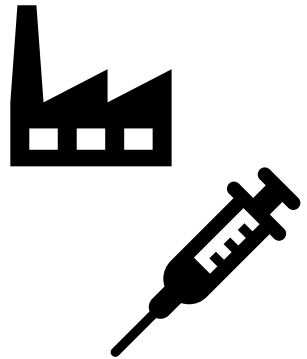
Performance and patient focus to identify areas of improvement and implement changes

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

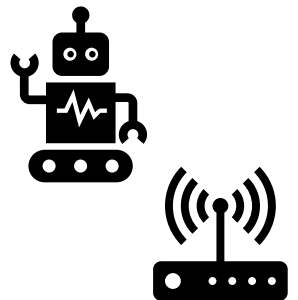
Future of Quality Management Maturity



- **A system to inform purchasers & patients about the quality management maturity of the facilities making their drugs**

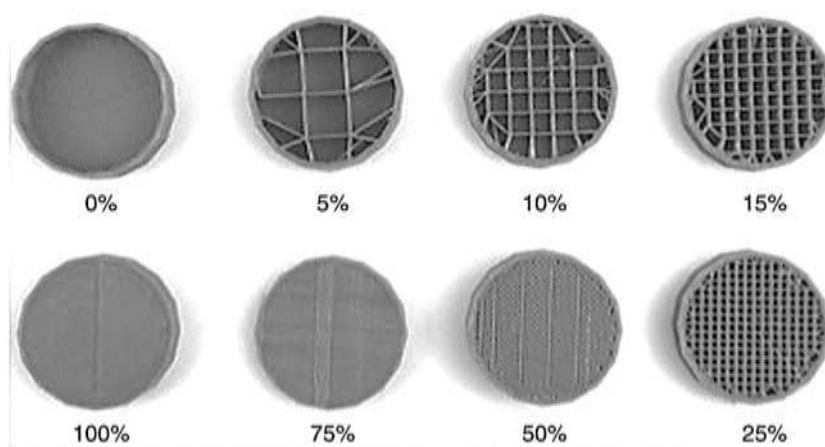
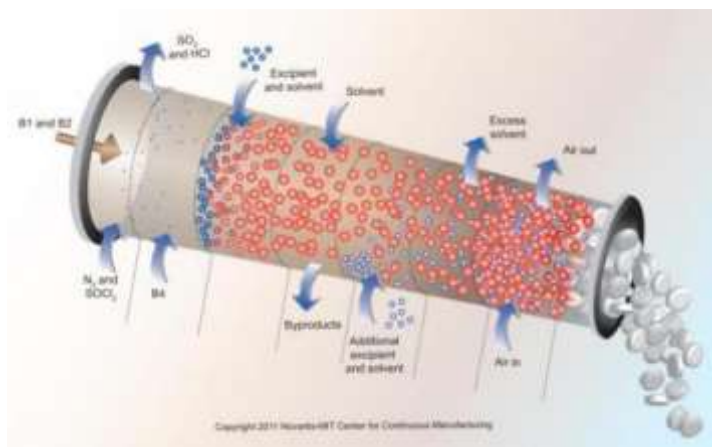


– Update of CDER's Quality Management Maturity Program, Jennifer Maguire:
Wednesday, April 28, 11:10 am



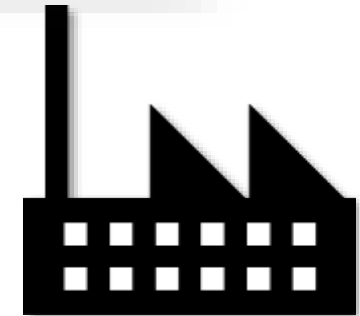
What is Advanced Manufacturing?

- 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

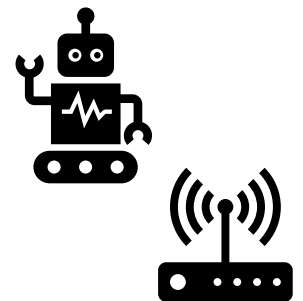
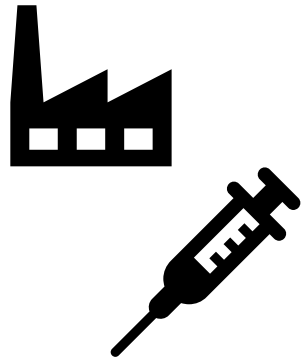
- **Addresses the underlying causes of drug shortages**
 - Mitigate or prevent future production problems
 - COVID-19: Faster commercial production w/o scale-up issues
- **Improves manufacturing efficiency**
 - Increase process robustness
 - Lower manufacturing costs
 - Improve supply chain flexibility
- **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



A History of Pharmaceutical Quality



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COVID-19 stresses supply chains to breaking point

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.*



U.S. FOOD & DRUG
ADMINISTRATION