U.S. FOOD & DRUG ADMINISTRATION

Advancing Pharmaceutical Product Quality

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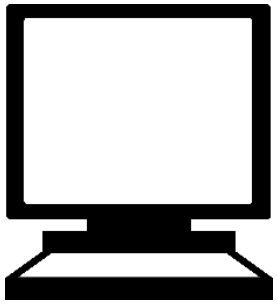
Pharmaceutical Quality

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.

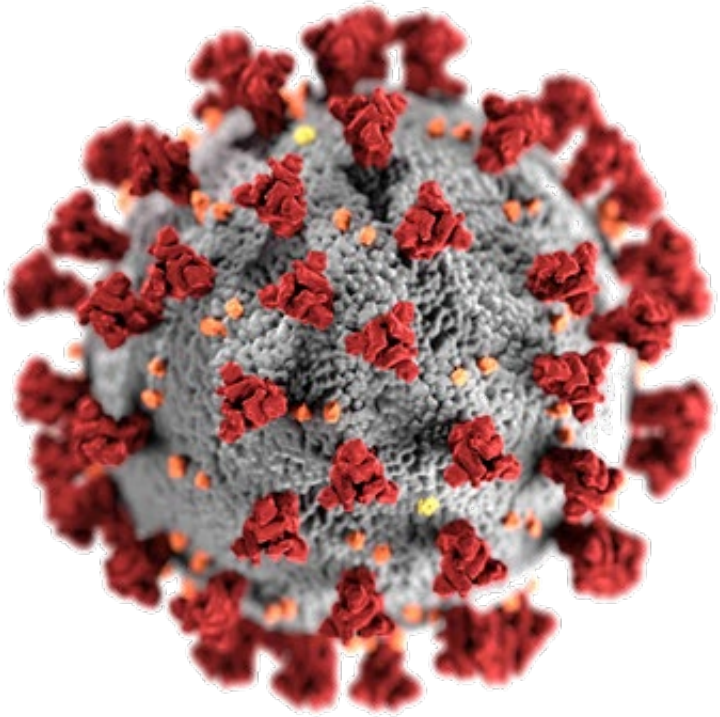

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

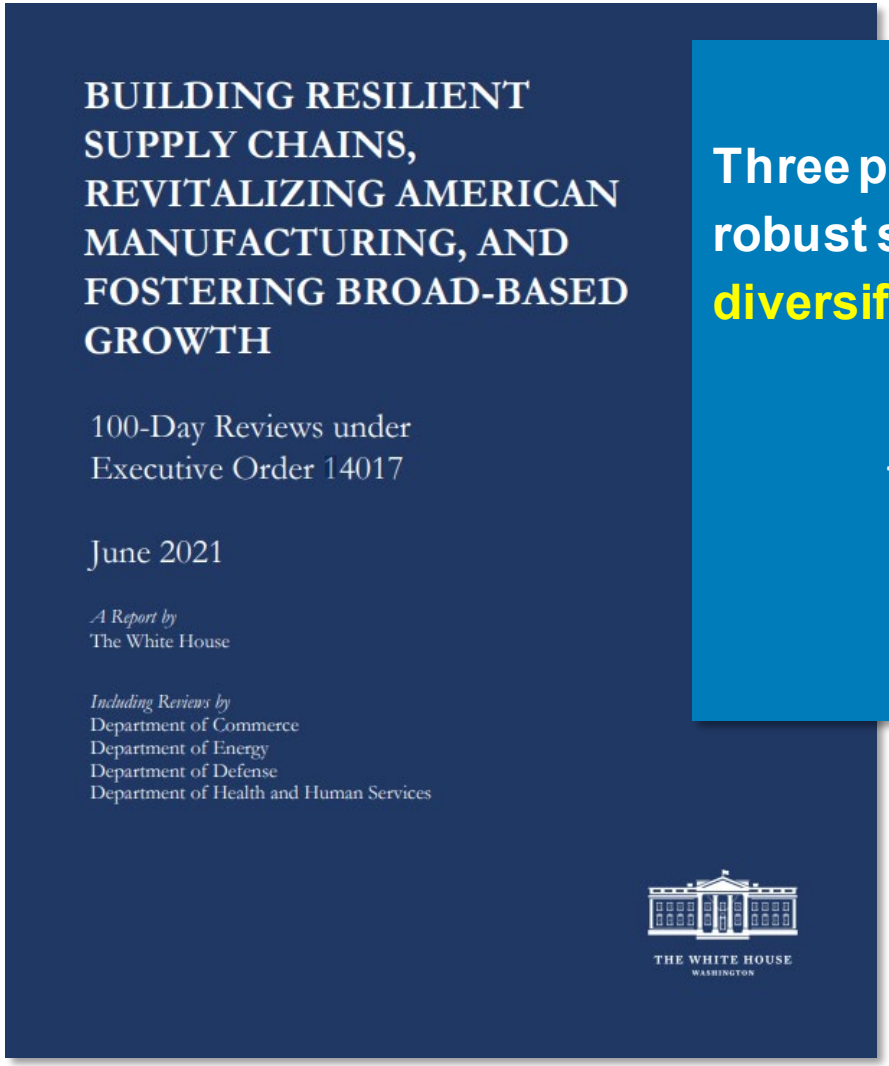
assuring *every* dose is safe and effective, free of contamination and defects.

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

The New Normal



The Three Pillars

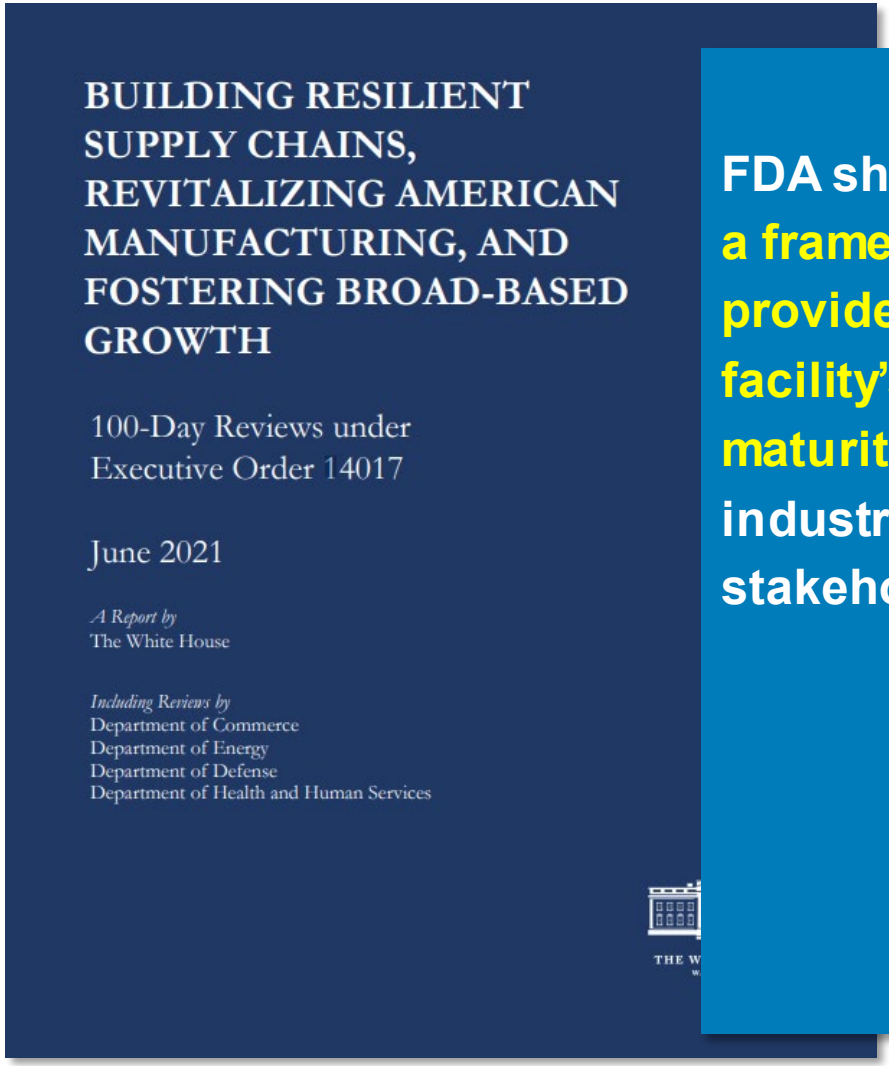


Three pillars of a secure and robust supply chain are quality, diversification, and redundancy.

– 100-Day Report by

The White House

Challenge: Transparency

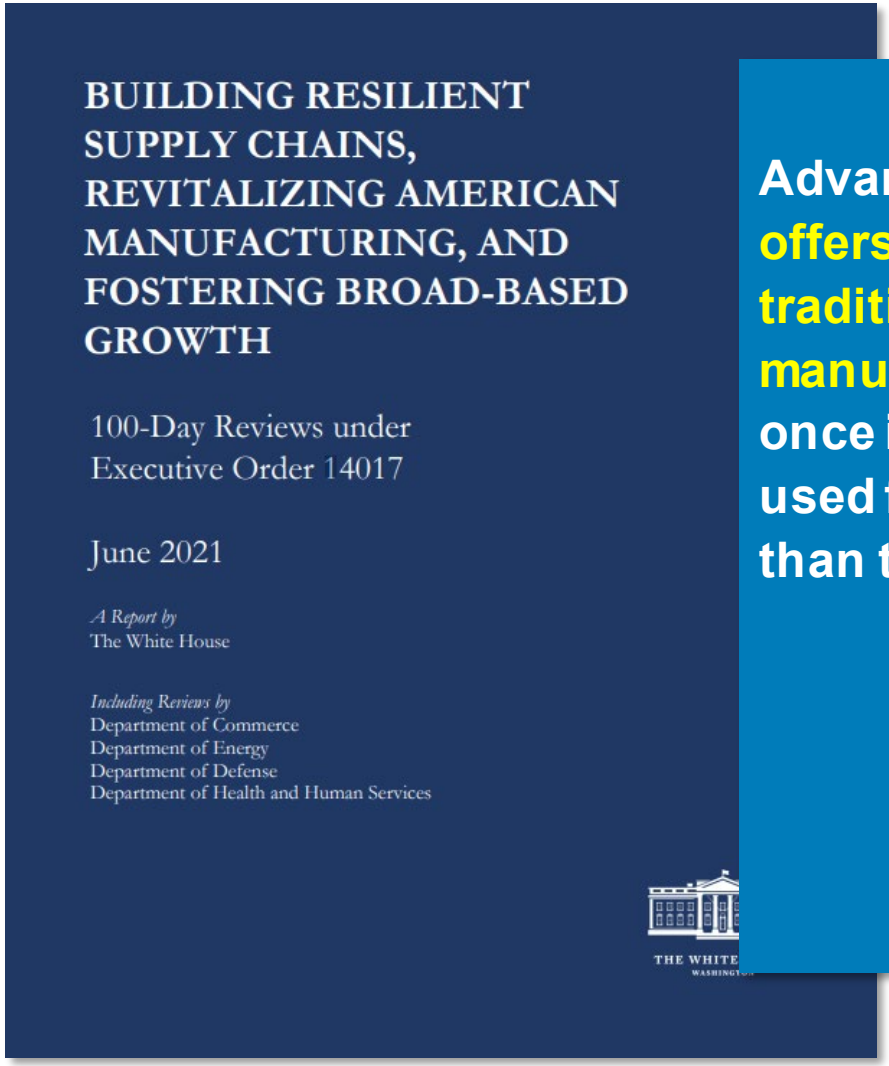


FDA should lead the development of a framework to measure and provide transparency regarding a facility's quality management maturity with engagement from industry, academia, and other stakeholders.

– 100-Day Report by

The White House

Challenge: Innovation



Advanced manufacturing offers many advantages over traditional pharmaceutical manufacturing, including that, once implemented, it can be used far more cost-effectively than traditional manufacturing.

– 100-Day Report by

The White House

THE WHITE HOUSE
WASHINGTON

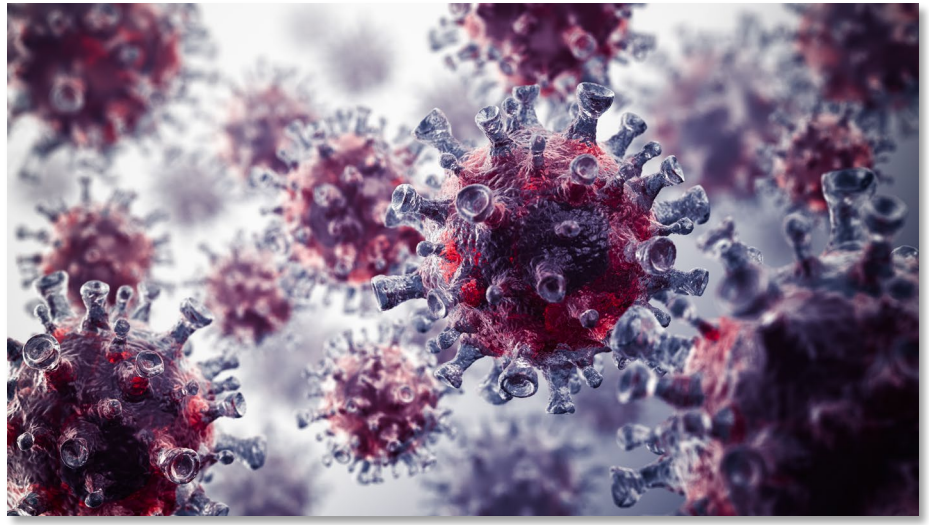
Advancing Drug Product Quality

- **Facility Quality**
- **Regulatory Innovation**
- **Quality Management Maturity**
- **Advanced Manufacturing**

A Continuing Era

Problems remain

- *Supply Chains*
- *Shortages*
- *Decision-making based on changing science and risk*



Facility Quality

US FDA Center for Drug Evaluation and Research

Mission-Critical Facility Inspections

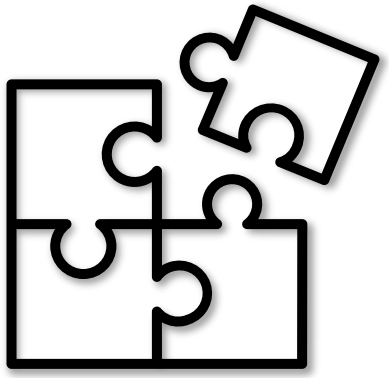
- **What is *mission-critical?***
  - Breakthrough Therapy Designated (BTD) products
  - Drug Shortages
  - Products used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute

- **Considerations**
  - Medical benefit and/or necessity
  - Safety of all those involved in inspections and public health benefits

Facility Assessments

- **Innovation was needed**
  - FDA relied heavily on “alternative tools” to conduct inspections
    - Requesting information in lieu of an inspection
    - Remote Interactive Evaluations (RIEs)

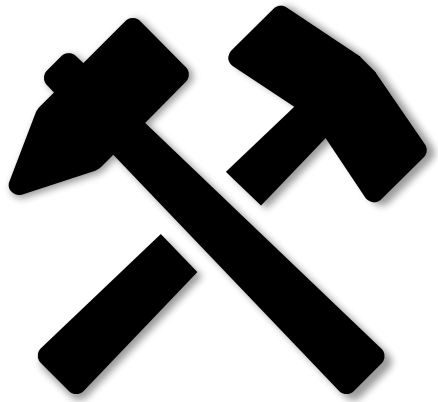
- **Engagement with international regulatory partners was vital**
  - Mutual Recognition Agreements (MRA)
    - Reports from other trusted regulatory partners



Impact of Use of Alternative Tools

Using Alternative Tools

- Reduced PAIs needed **over 50%** since the beginning of the pandemic
- Approved **over 1,000** drug submissions to help in the treatment of patients with COVID-19



Regulatory Innovation

US FDA Center for Drug Evaluation and Research

A Vision of the Future

International Journal of Pharmaceutics 602 (2021) 120554

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International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Industry 4.0 for pharmaceutical manufacturing: Preparing for the smart factories of the future

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ABSTRACT

Over the last two centuries, medicines have evolved from crude herbal and botanical preparations into more complex manufacturing of sophisticated drug products and dosage forms. Along with the evolution of medicines, the manufacturing practices for their production have advanced from small-scale manual processing with simple tools to large-scale production as part of a trillion-dollar pharmaceutical industry. Today's pharmaceutical manufacturing technologies continue to evolve as the internet of things, artificial intelligence, robotics, and advanced computing begin to challenge the traditional approaches, practices, and business models for the manufacture of pharmaceuticals. The application of these technologies has the potential to dramatically increase the agility, efficiency, flexibility, and quality of the industrial production of medicines. How these technologies are deployed on the journey from data collection to the hallmark digital maturity of Industry 4.0 will define the next generation of pharmaceutical manufacturing. Acheiving the benefits of this future requires a vision for it and an understanding of the extant regulatory, technical, and logistical barriers to realising it.

1. Introduction

The term Industry 4.0 refers to the fourth industrial revolution which brings together rapidly evolving technologies such as the internet of things (IoT), artificial intelligence (AI), robotics, and advanced computing to dramatically change the landscape of manufacturing. Industry 4.0 is characterized by integrated, autonomous, and self-organizing production systems. New thinking will be required to realise Industry 4.0 for pharmaceuticals and overcome the inertia of current manufacturing infrastructure, operations, and regulation. While implementing many of the advanced technologies and manufacturing approaches needed to enable Industry 4.0 may not be easy, it may well be worthwhile as they bring the potential for higher output, increased manufacturing safety, improved quality, better value, increased agility, additional flexibility, and reduced waste (Ezell, 2016; Buvailo, 2018; Baur and Wee, 2015; Clemons, 2016; Tilley, 2017).

1.1. Industry 1.0

If Industry 4.0 is the future, then Industry 1.0 is the starting point of the modern pharmaceutical industry. The application of herbal or botanical preparations as medicines has spanned the history of civilization. Only in the last two centuries have we seen dramatic changes in how materials are processed and formulated for medical use. Industry 1.0 saw the manual processing of botanical, mineral, and animal derived materials transition from simple hand-operated tools to commercial-scale machinery able to crush, mill, blend, and press larger quantities of medicines (Anderson, 2005). In the 19th century, larger-scale production of drugs utilizing non-electrical power-driven machinery emerged from two sources – individual pharmacies or the dye and chemicals industry (Sonnedecker and Urdang, 1976; Daemmrich and Bowden, 2005). This movement from laboratory-scale to wholesale production of drugs fueled the establishment of a pharmaceuticals industry in the 19th century – an industry that has seen tremendous growth over the last century. Yet, some of the early machines from the first industrial revolution, such as pneumatic mills and tablet presses, are still commonly used today.

1.2. Industry 2.0

The second industrial revolution was enabled by electricity and early electronic machines and assembly lines with pre-set controls that

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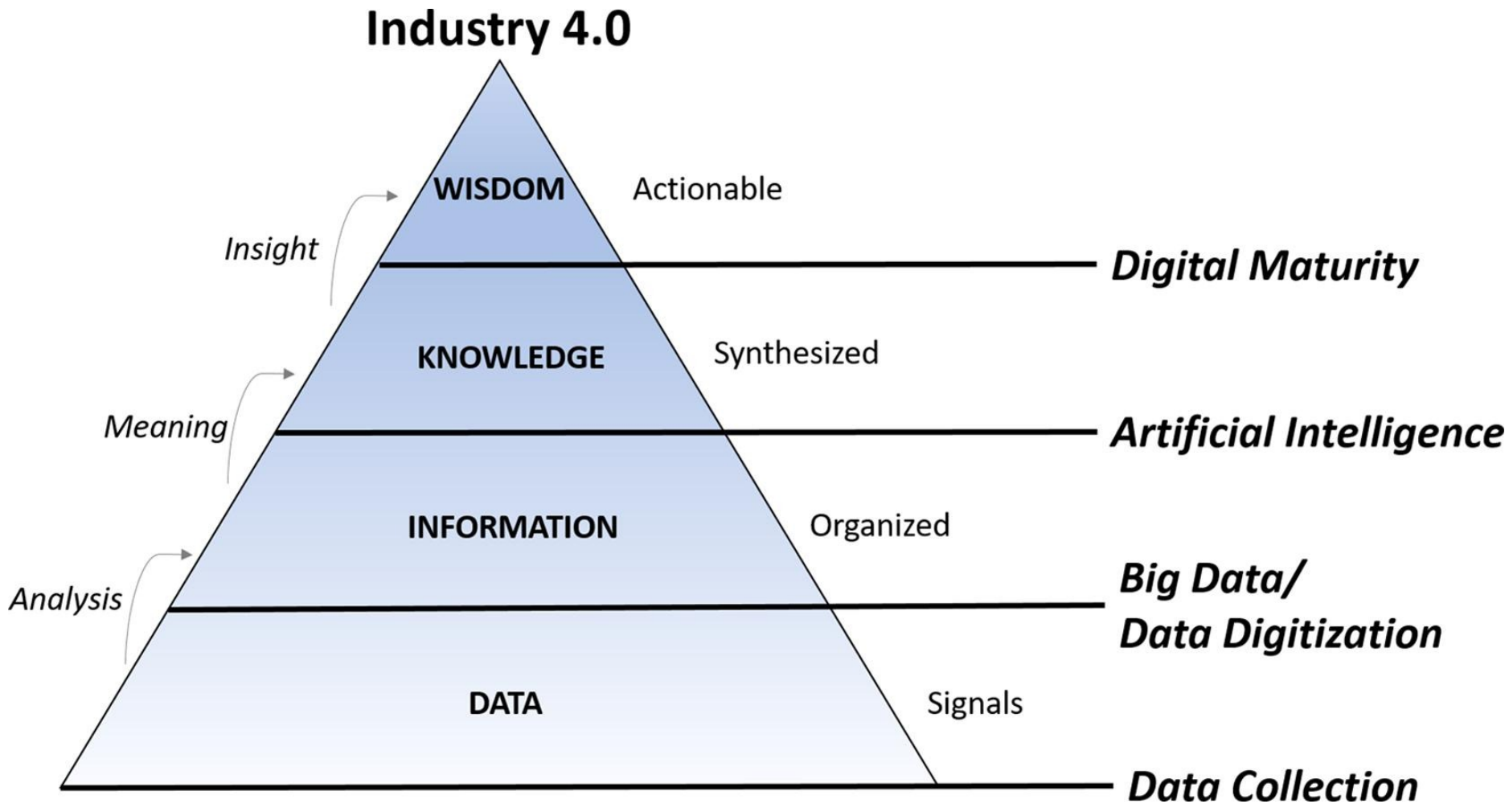
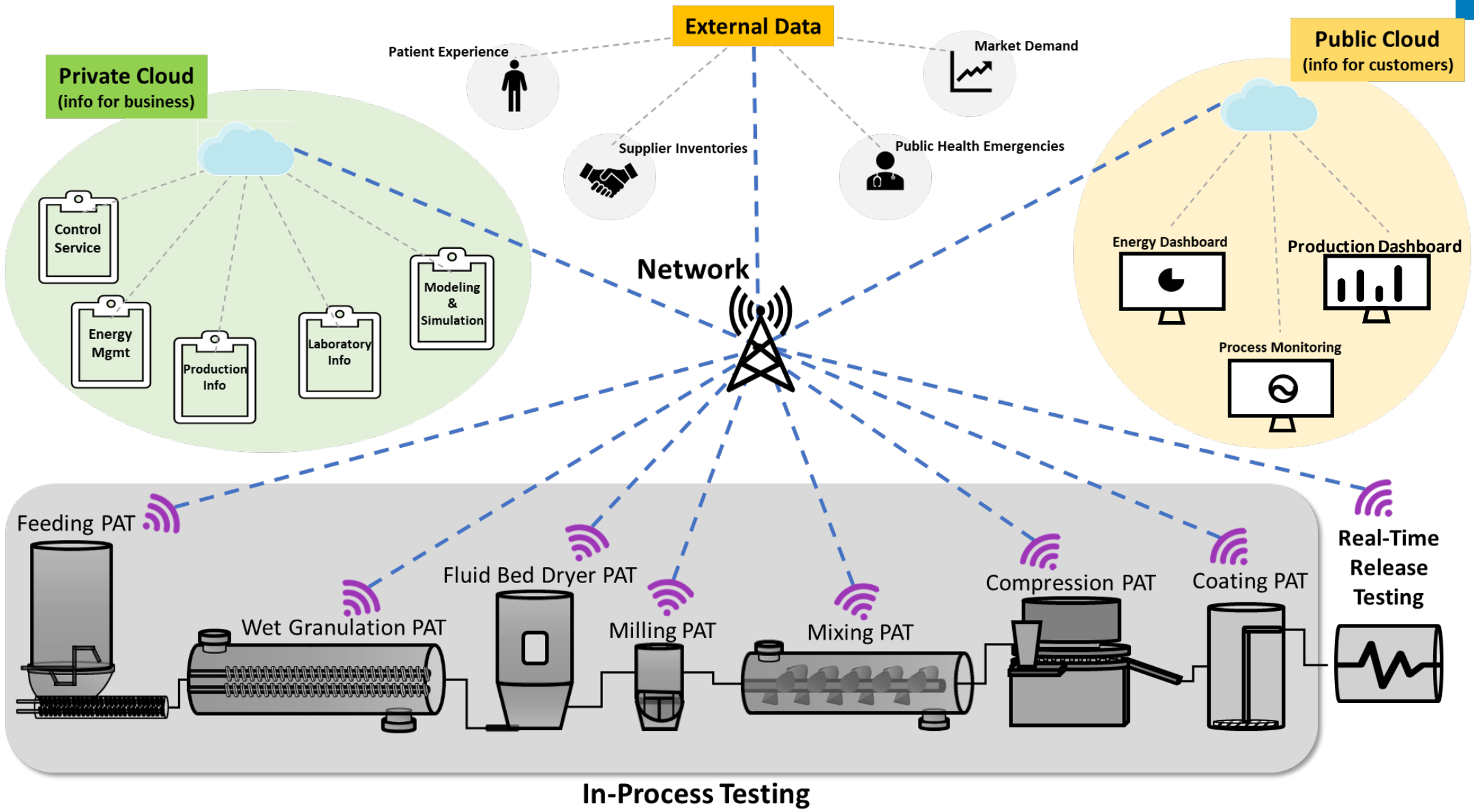
*Arden, N. Sarah, et al. "Industry 4.0 for Pharmaceutical Manufacturing: Preparing for the Smart Factories of the Future." *Int J Pharm* (2021): 120554.

Achieving Industry 4.0



The Fourth Industrial Revolution in Pharma



Innovations at FDA

Knowledge-Aided Assessment & Structured Application (KASA)

Management of quality risks across drug products and facilities

Quality Surveillance Dashboard (QSD)

Framework for the surveillance of CDER-regulated facilities

CARES Act

Portal to collect the amount of drugs by registrant

International Harmonization

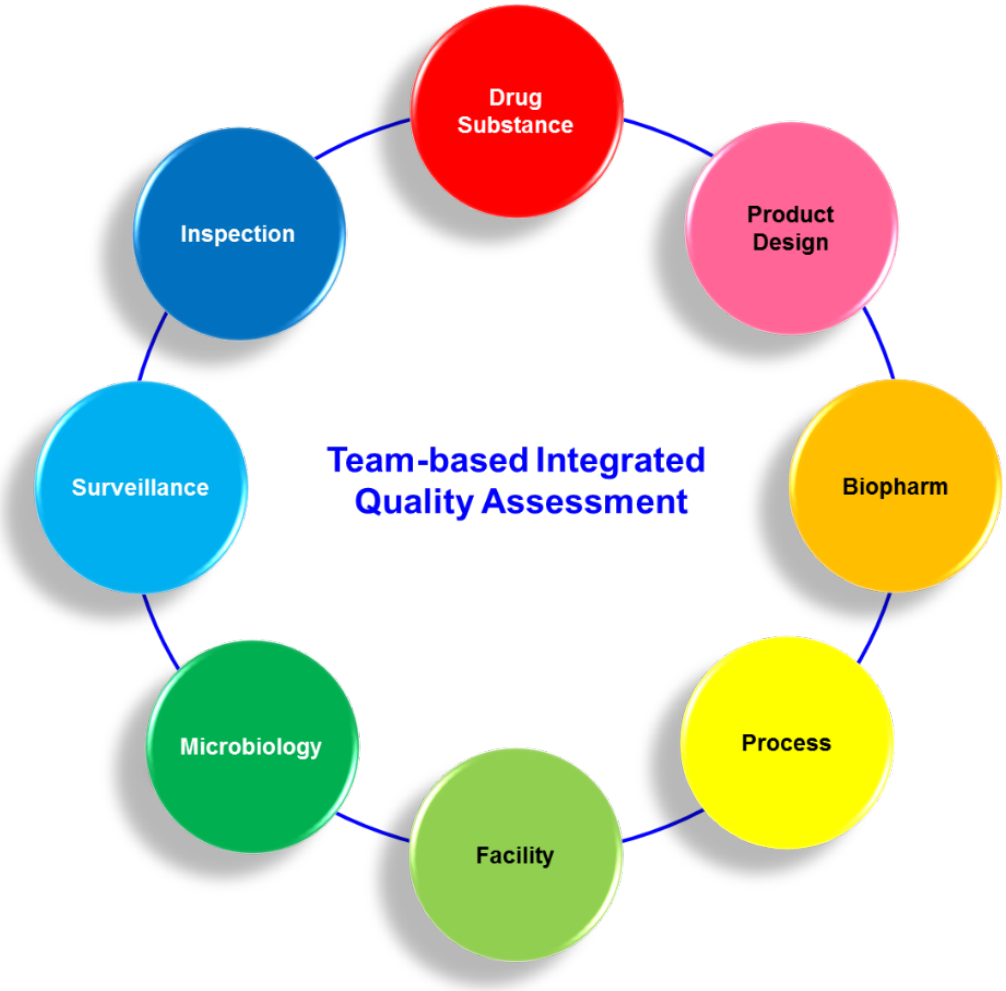
The importance of regulatory harmonization and convergence

Integrated Quality Assessment (IQA): Aligned Teams

Smaller, more stable pools of interdisciplinary assessment staff for applications

What is Integrated Quality Assessment (IQA)?

- **Multiple assessors/team members with different expertise**
  - Enhance overall quality assessment
- **Collaboration and communication among team members**
  - One Quality Voice
  - Enhance knowledge management



IQA Needs and Solutions

NEEDS

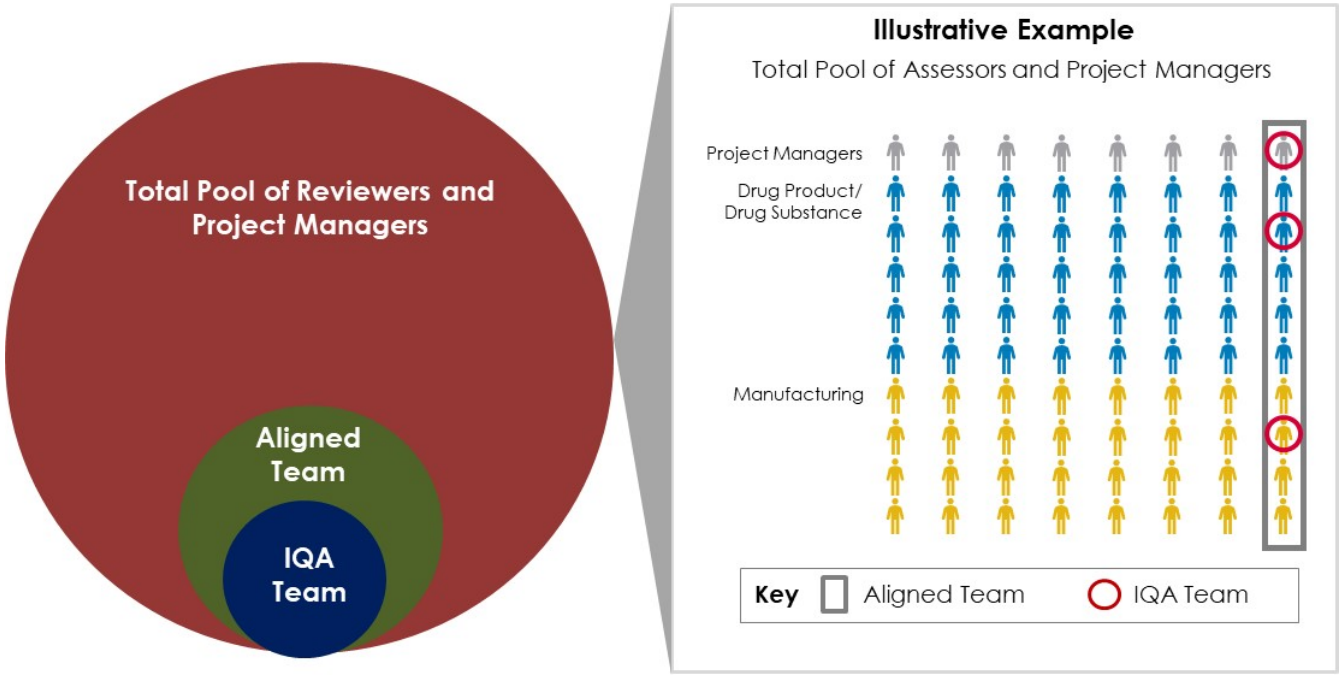
- ✓ **Improved efficiency and effectiveness** of assessments
- ✓ **Enhanced clarity** around IQA process, roles, and responsibilities

SOLUTIONS

- ✓ **More stable IQA teams** to promote consistent work practices, collaboration, and team efficiency
- ✓ **Increased interaction** and familiarity among team members to facilitate open communication
- ✓ **Enhanced knowledge** and overall understanding of quality considerations across disciplines

What are OPQ's Aligned Teams?

IQA Aligned Teams
Smaller, more-stable, interdisciplinary pools of RBPMs, ATLs, and Assessors from which IQA Teams are formed to assess BLAs, NDAs, and ANDAs



Application Type	Aligned Teams Launch Date	Related UFA Programs
BLA	6/22/20	PDUFA BsUFA
ANDA	8/10/20	GDUFA
NDA	9/13/21	PDUFA

Quality Management Maturity

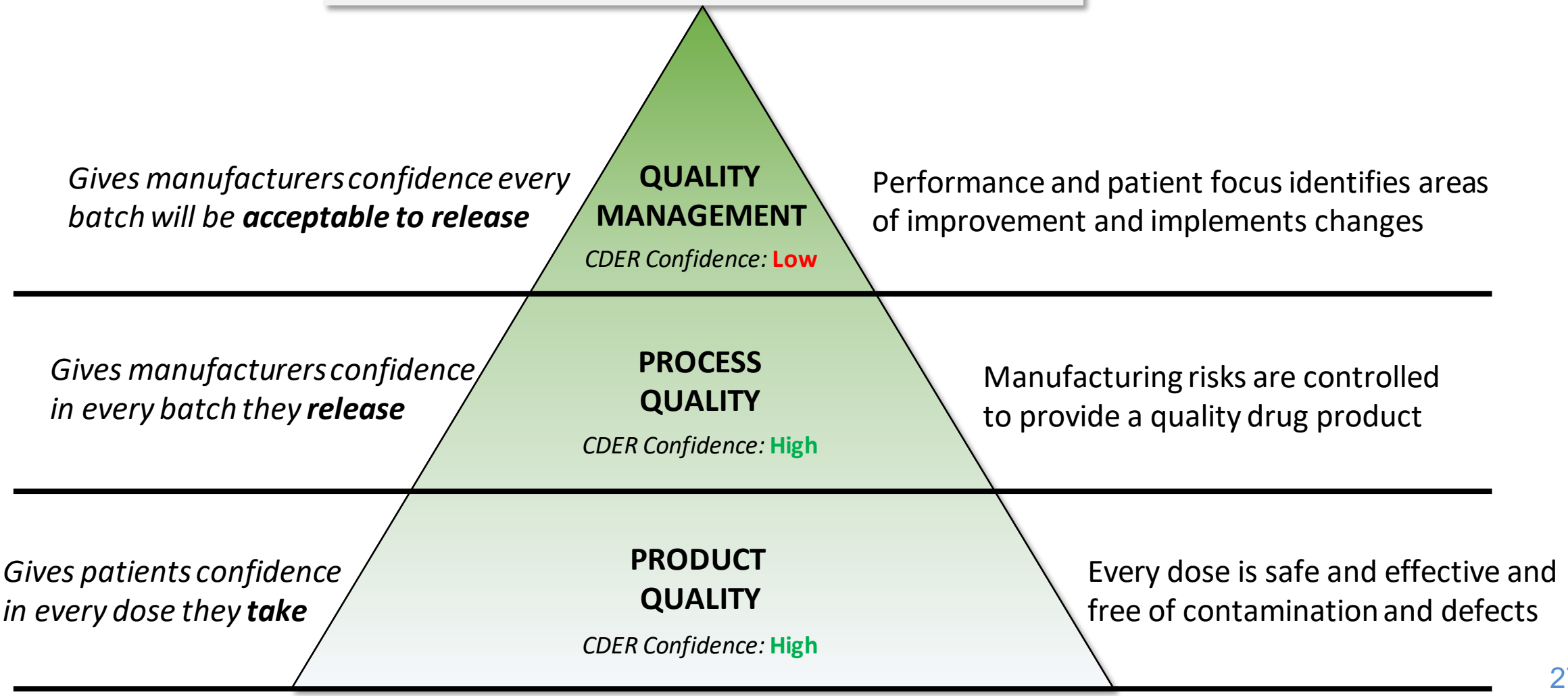
US FDA Center for Drug Evaluation and Research


Quality Management Maturity
Quality Management System
Planning
Supply Chain Management
Management Review/Responsibility
Performance Management/Continual Improvement
Quality Metrics
Quality Culture
Safety, Environment and Regulatory Compliance
Predictive Analytics
Workforce Management
Risk Management
Customer Experience
Manufacturing Strategy and Operations

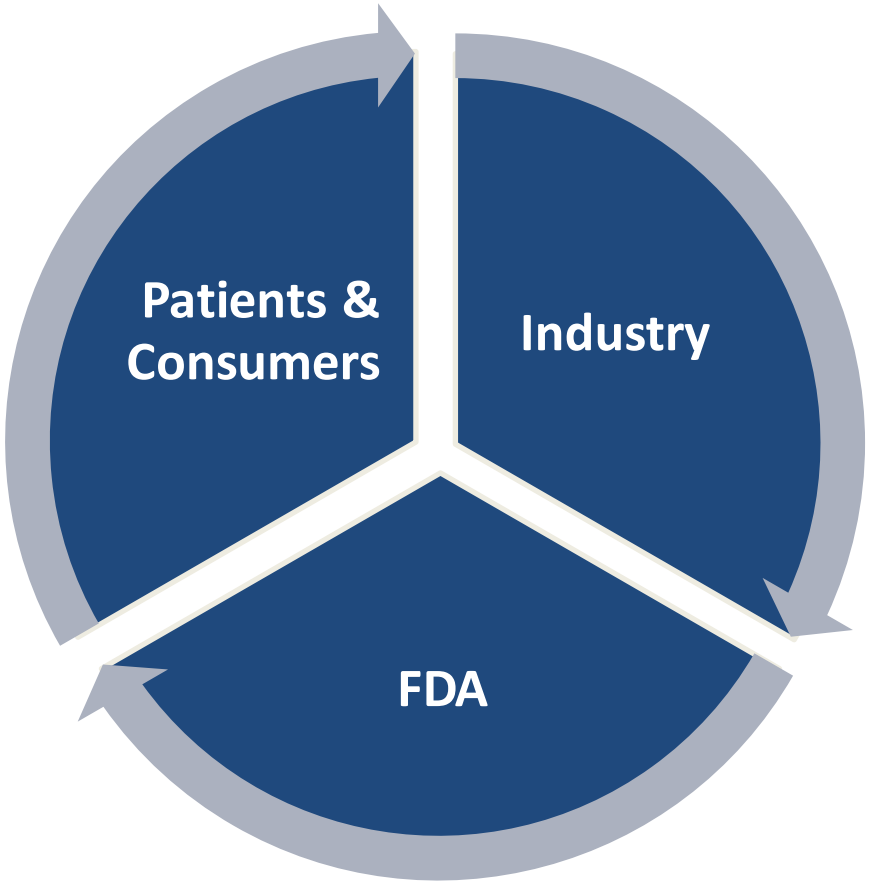
QMM Provides Confidence

Pharmaceutical Quality

*Gives patients confidence in their **next** dose of medicine*



The Benefits of QMM Ratings



Patients and Consumers

- **Increases access** to reliable drug products

Industry

- **Enables continued improvement** of the pharmaceutical quality system
- **Rewards** "good actors" in the market

FDA

- **Provides insight** to effectively deploy surveillance tools and inspections

Advanced Manufacturing

US FDA Center for Drug Evaluation and Research

What is Advanced Manufacturing?

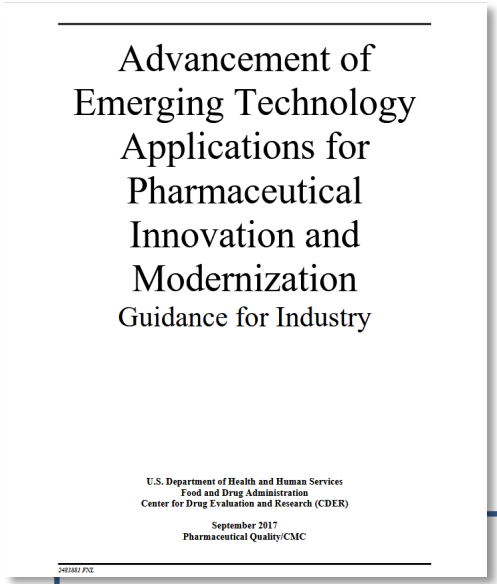
- Novel **manufacturing methods** to improve process robustness and efficiency
- Novel **dosage forms** or delivery systems to improve drug delivery and targeting
- Novel **analytical tools** to improve product characterization, quality testing, process monitoring and/or control

Advanced Manufacturing Benefits

Advanced manufacturing can improve manufacturing and ensure quality medicine is available.

- **Produce better quality medicine**. Facilitates six-sigma operation, no more than 3.4 defects per 1M opportunities.
- **Re-shore drug manufacturing facilities.** Helps domestic drug manufacturers compete in a global market.
- **Develop drugs rapidly.** Speeds the development of novel or patient-focused therapeutics.
- **Prevent drug shortages.** Reduces today's quality-related manufacturing issues causing 62% of drug shortages.
- **Improve emergency preparedness.** Provides more agility and flexibility to help pivot in a public health emergency.

Emerging Technology Program

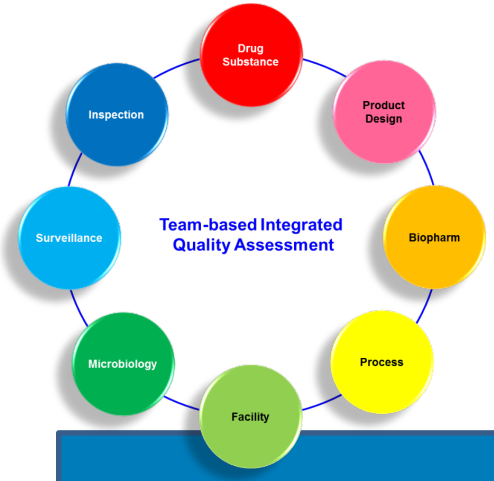

Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2017
Pharmaceutical Quality/CMC

Industry Develops Emerging Technology

ETP Evaluates Technology



Technology Moves to Standard Quality Assessment Processes

Acceptance to ETP

Graduation

U.S. FOOD & DRUG ADMINISTRATION

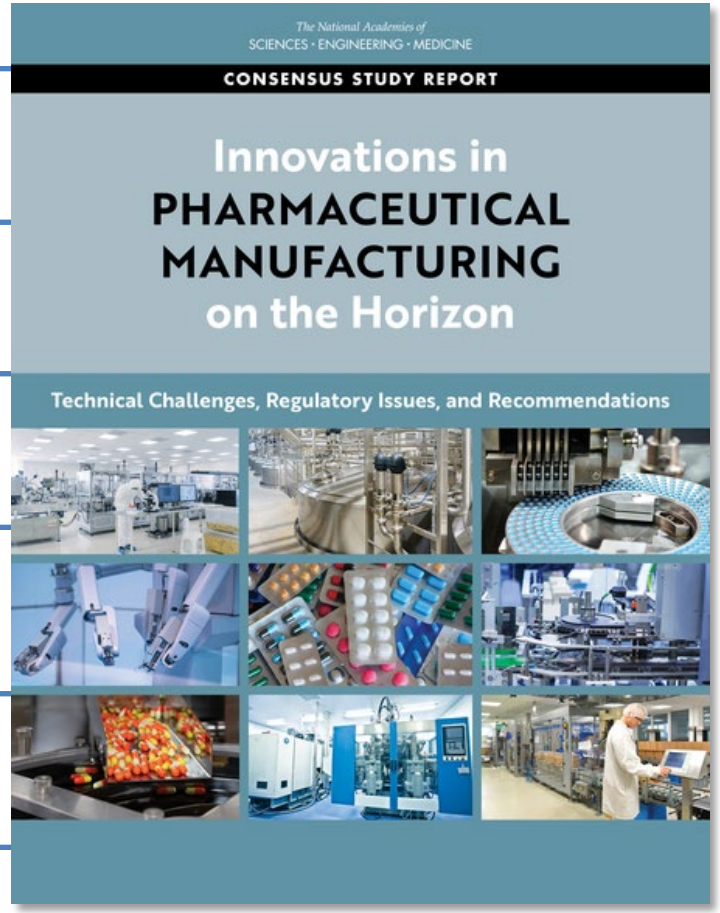
Framework for Regulatory Advanced Manufacturing Evaluation (**FRAME**)

FRAME: Framework for **R**egulatory **A**dvanced **M**anufacturing **E**valuation

Establish a **regulatory framework that provides clarity and reduces uncertainty** for products manufactured with advanced technologies

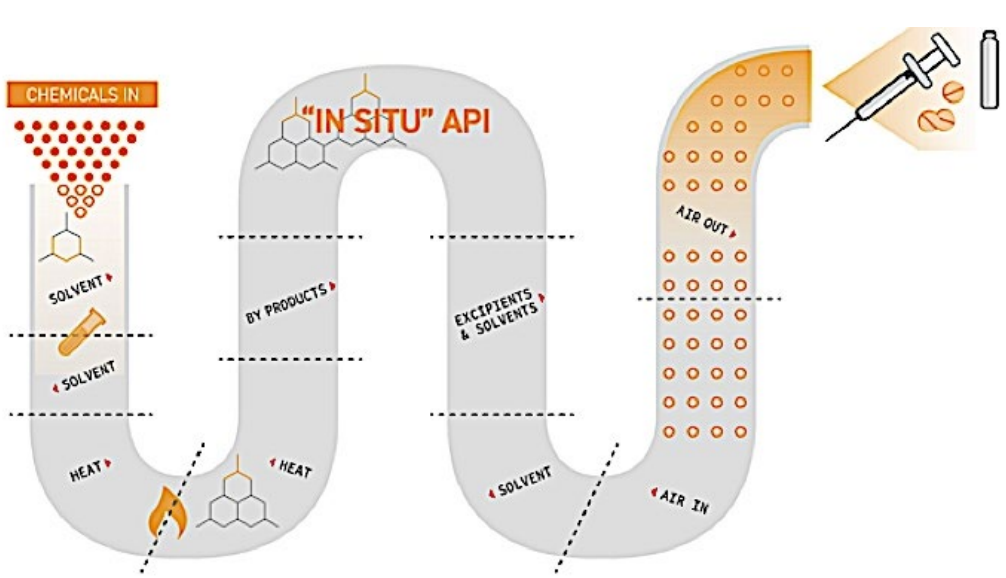
The framework will need to address both **current and future manufacturing innovation**.

Scope: CDER's **submission pipeline in the next 5-10 years***.

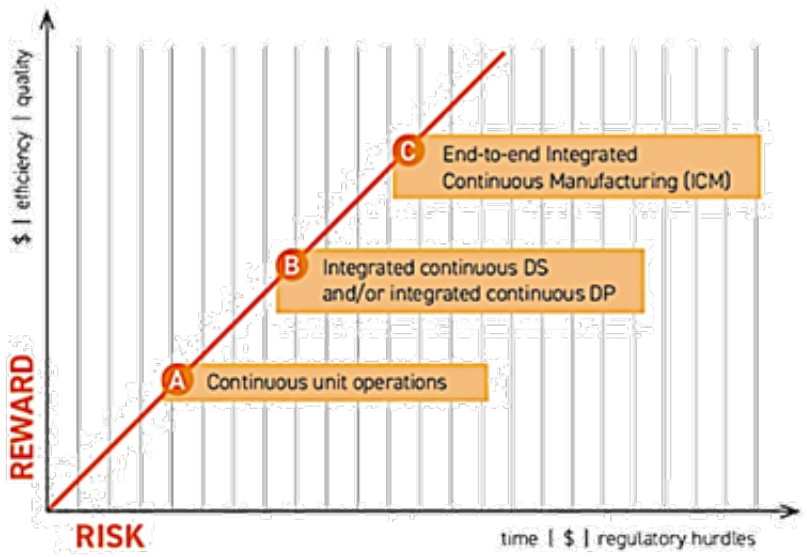


*In NASEM's *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations*

End-to-End Continuous Manufacturing



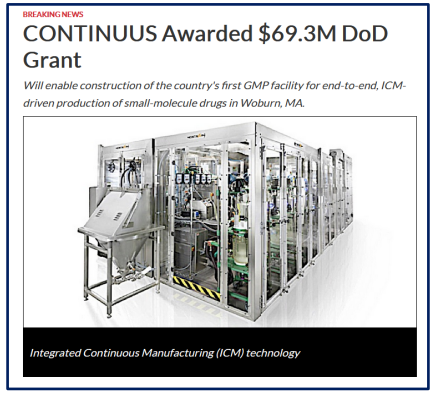
FULLY AUTOMATED PROCESS



IMMEDIATE RELEASE

DOD and HHS Award $20 Million Contract to On Demand Pharmaceuticals to Develop Domestic Production of Critical Pharmaceutical Ingredients

SEPT. 28, 2020



BREAKING NEWS

CONTINUUS Awarded $69.3M DoD Grant

Will enable construction of the country's first GMP facility for end-to-end, ICM-driven production of small-molecule drugs in Woburn, MA.

Integrated Continuous Manufacturing (ICM) technology

REUTERS

World Business Markets Breakingviews Video More

RACE FOR A CURE MAY 19, 2020 / 7:55 AM / UPDATED A YEAR AGO

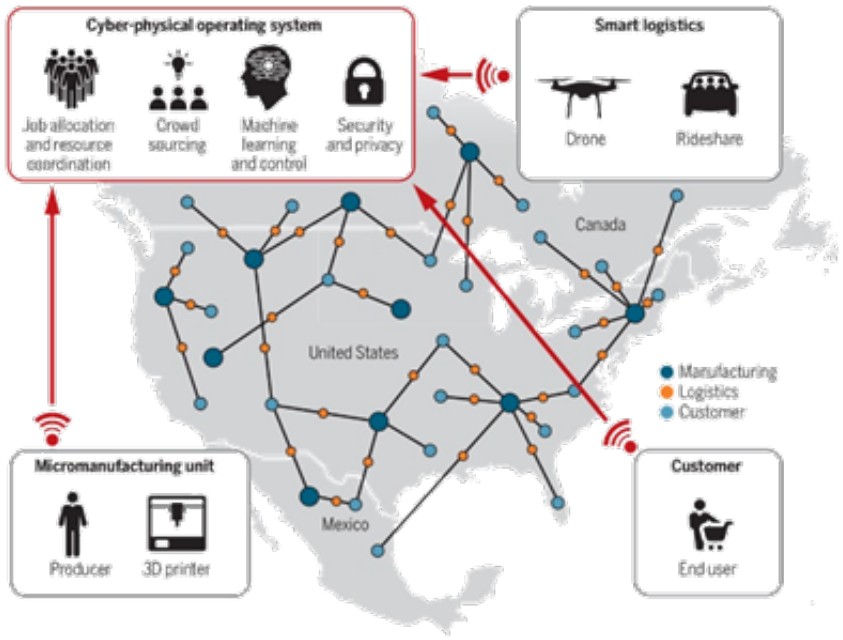
Phlow gets $354 million U.S. funding to ensure drug supply amid COVID-19 pandemic

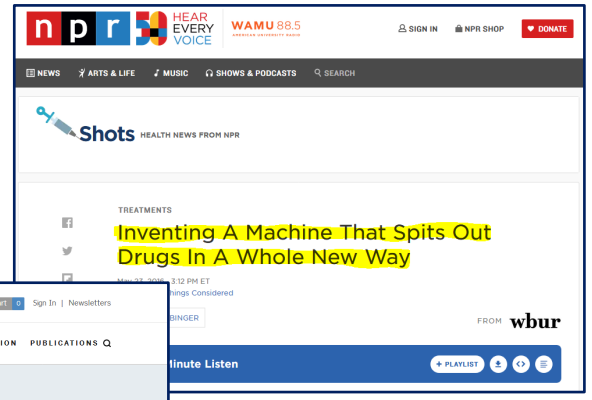
By Reuters Staff 1 MIN READ

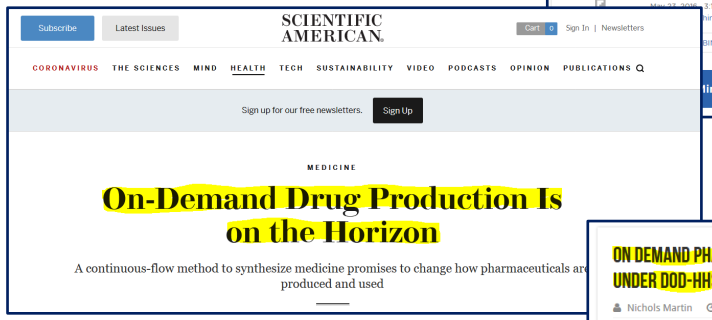
Materials or chemical intermediates are **continuously fed into** and transformed within the system and finished drug products are **continuously removed** from the system

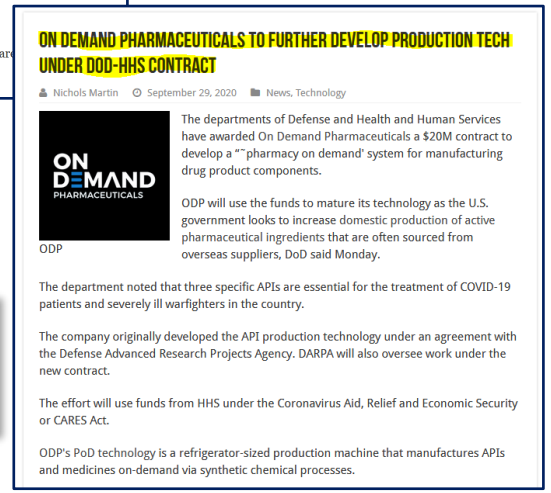
*Images reprinted from contractpharma.com, Breaking News 1/22/21

Distributed Manufacturing





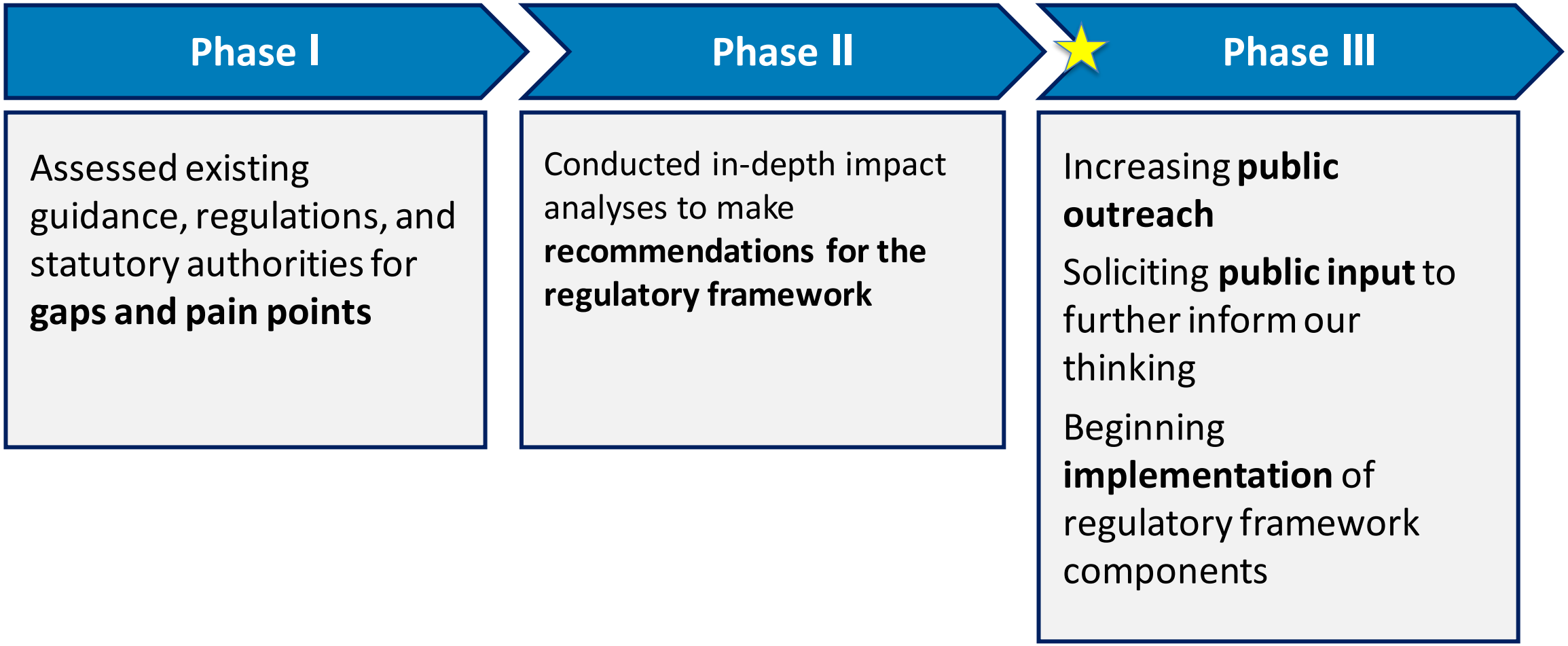




Platform is **decentralized and mobile**; it can be deployed to **multiple locations**, overseen and coordinated by a **single quality management system**.

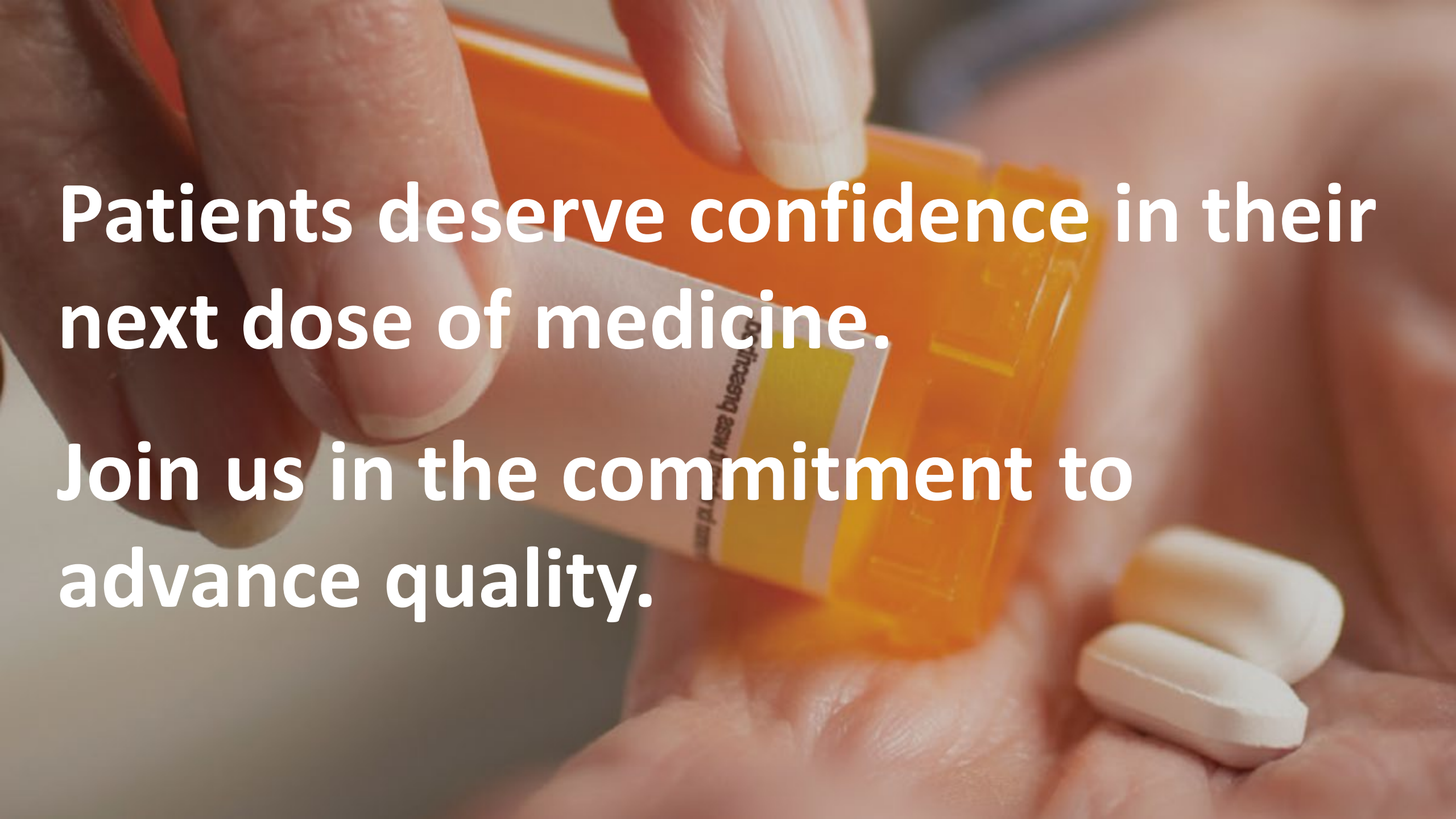
*Image reprinted from C Okwudire and H Madhyastha, *Science* 372, 341 (2021); Graphic: C. Bickel.

Phased Approach to FRAME



In Closing

US FDA Center for Drug Evaluation and Research


Patients deserve confidence in their next dose of medicine.
Join us in the commitment to advance quality.


FDA
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