The Present and Future of Pharmaceutical Quality

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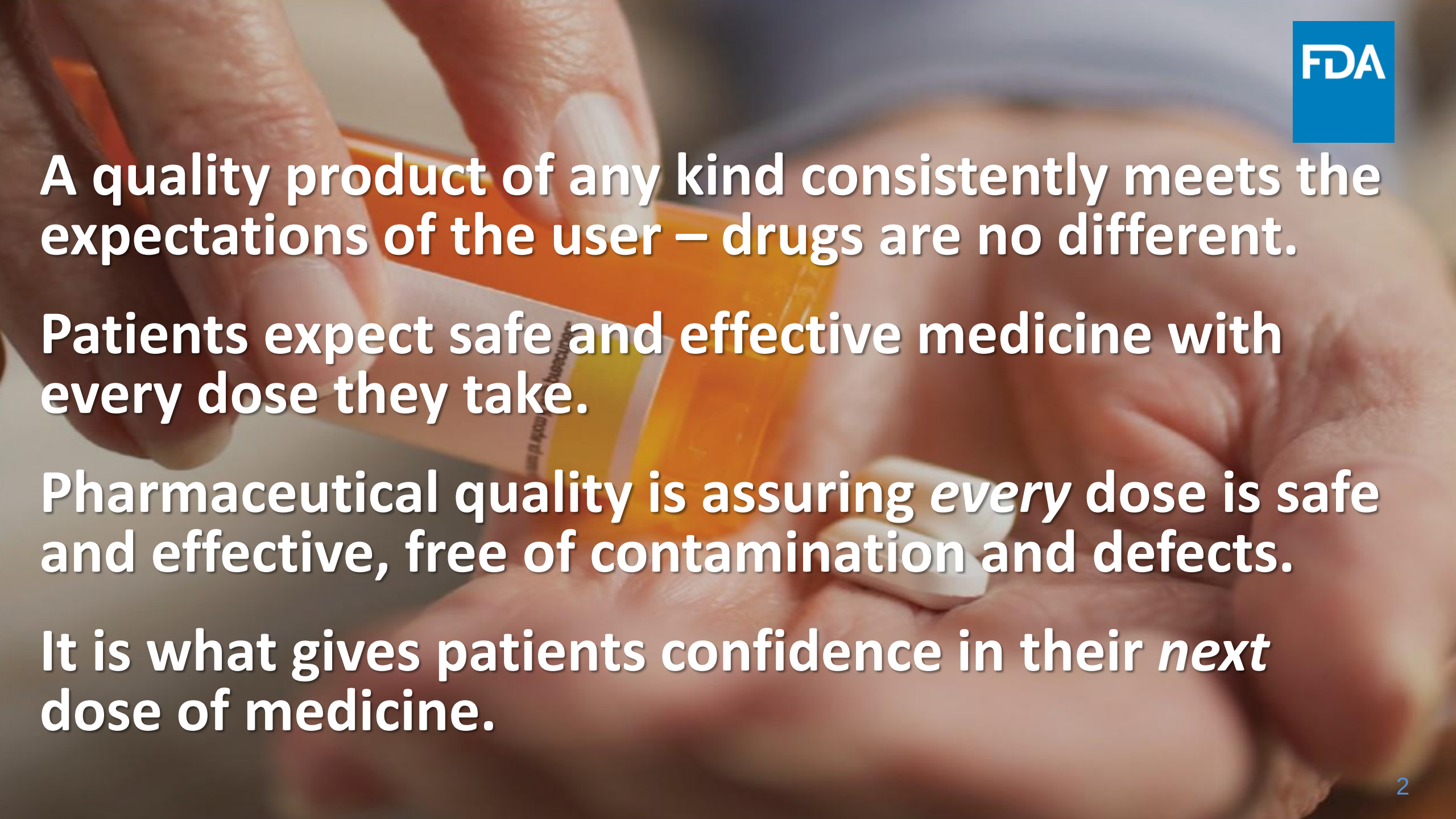
MCERSI Co-Processed API and
Regulatory Requirements
July 13, 2022



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.

Outline

- Quality Management Maturity
- Advanced Manufacturing
- Co-Processed API

Quality Management Maturity

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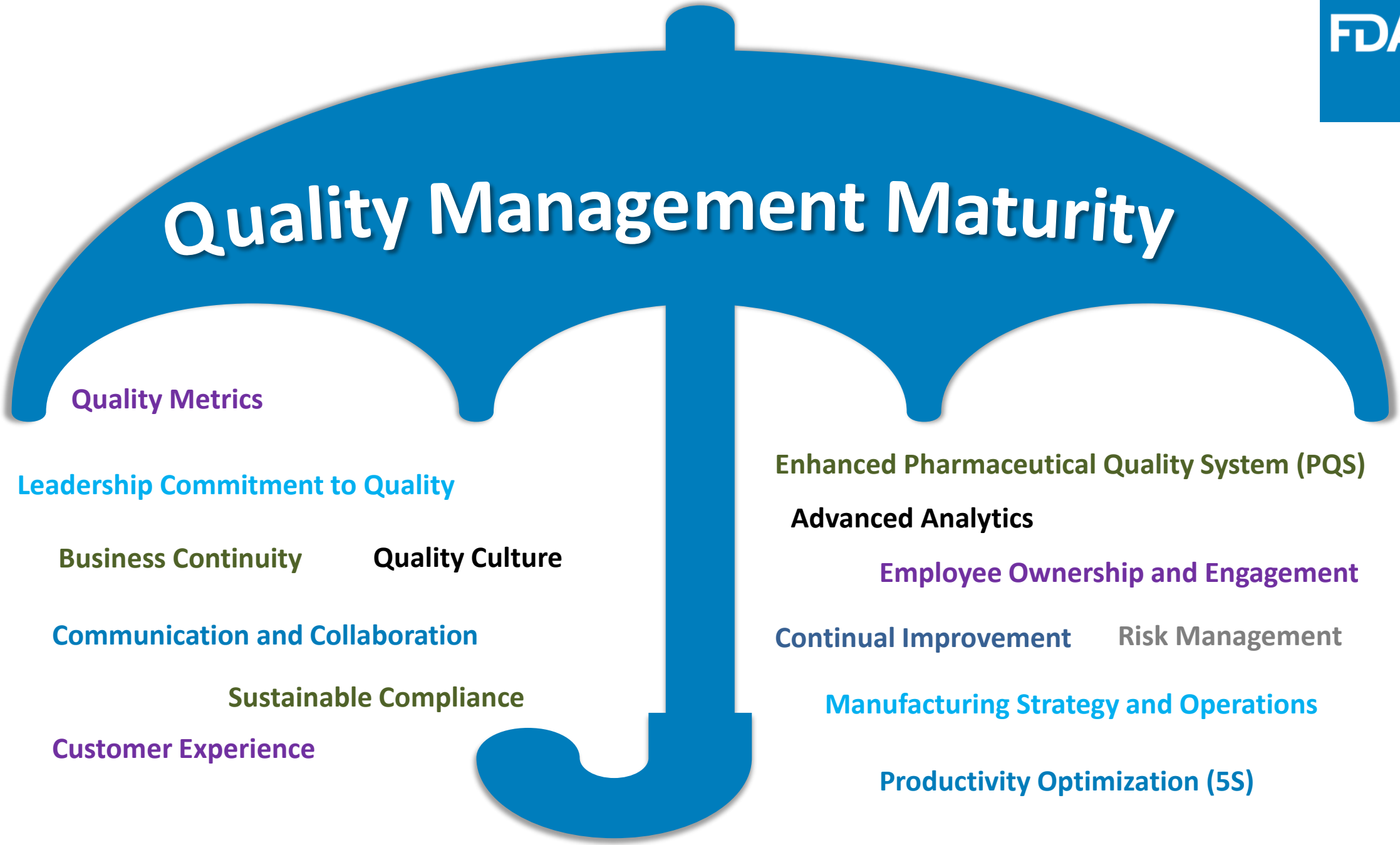
Quality Management Maturity



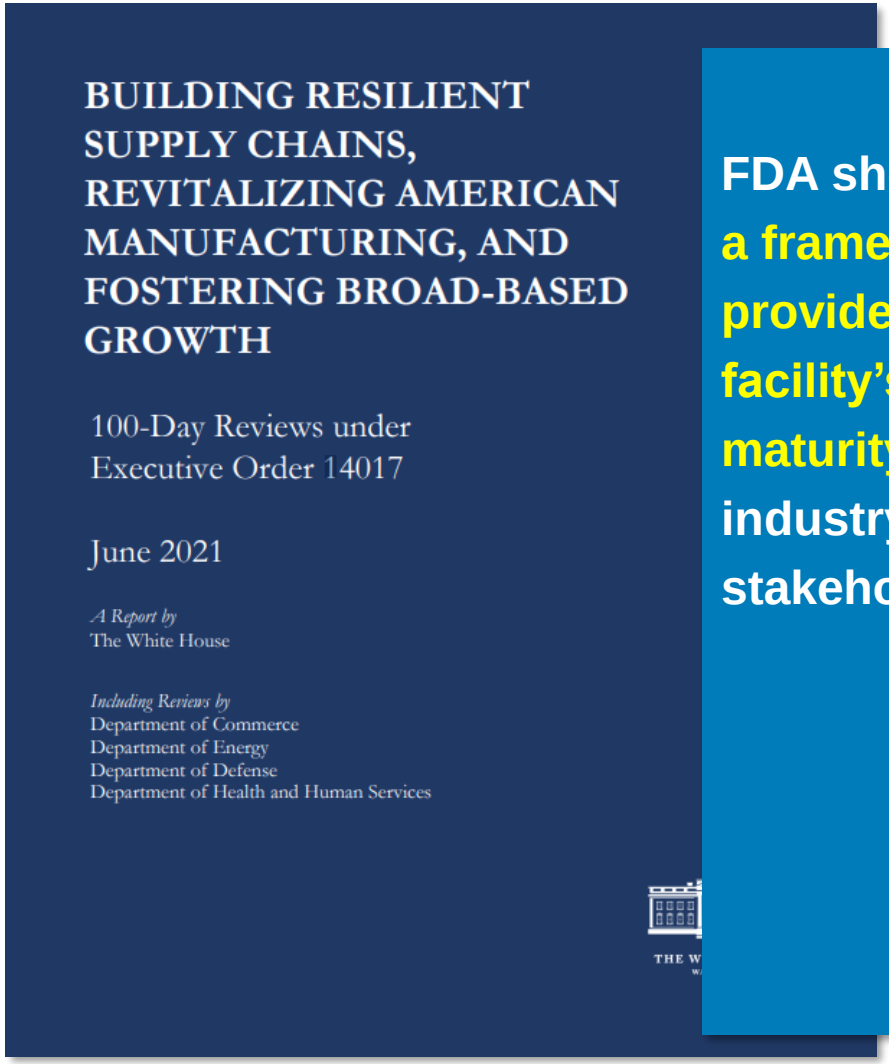
An Array of Quality

Pharmaceutical Quality

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

*Gives manufacturers confidence every batch will be **acceptable to release***	**QUALITY MANAGEMENT** *CDER Confidence:* **Low**	Performance and patient focus identifies areas of improvement and implements changes
*Gives manufacturers confidence in every batch they **release***	**PROCESS QUALITY** *CDER Confidence:* **High**	Manufacturing risks are controlled to provide a quality drug product
*Gives patients confidence in every dose they **take***	**PRODUCT QUALITY** *CDER Confidence:* **High**	Every dose is safe and effective and free of contamination and defects

The Promise of QMM



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

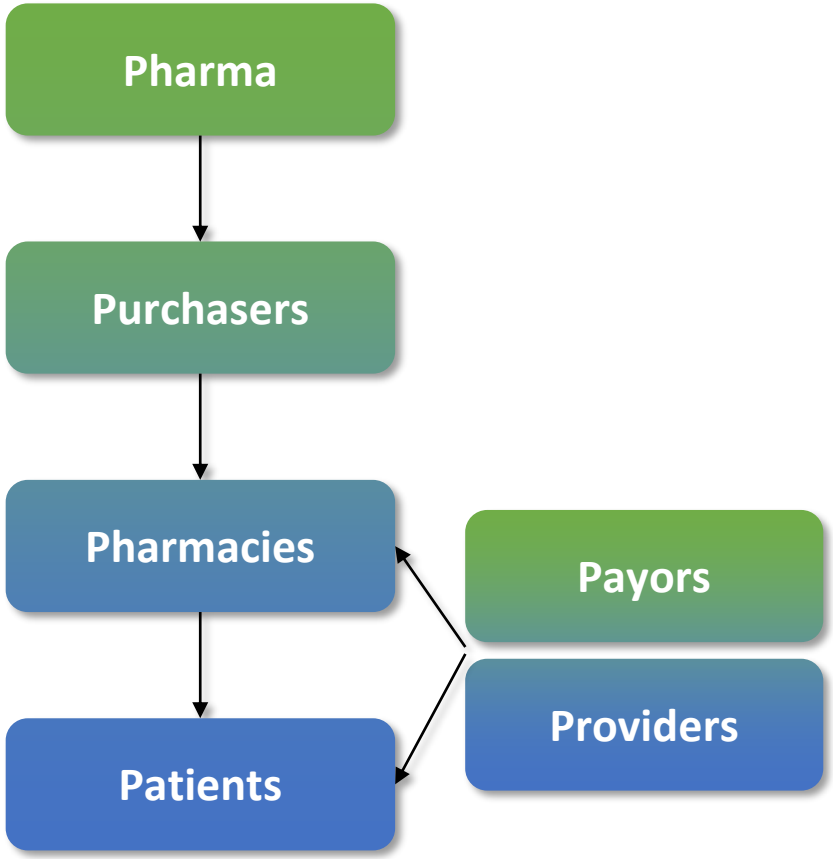
QMM ≠ QM

QMM =f(QM, x, y, z…)

Road to Achieving QMM

- **QMM white paper** released April 5
  - Importance of QMM
  - Key challenges and elements for successful QMM implementation
- **QMM stakeholder workshops** to be held May 24-25
- **QMM Advisory Committee** meeting to follow at a later date

“6 Ps” Impacted by QMM Ratings



Stakeholder	Benefits
Pharmaceutical Manufacturers	✓ Positive and proactive performance acknowledged ✓ “Good actors” rewarded
Purchasers[3]	✓ Improved supply chain transparency for decision-making ✓ Quality ratings backed by FDA insight and non-public data
Pharmacies	✓ Improved supply chain transparency ✓ Less risk of failing to meet demand and medication error
Payors	✓ Improved supply chain transparency for decision-making ✓ Less need to respond to drug shortage
Providers	✓ Less risk of drug shortage impacting their patients ✓ More confidence in the supply of drugs they prescribe
Patients	✓ Less risk of drug shortage impacting their care ✓ More confidence in drug availability

Advanced Manufacturing

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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

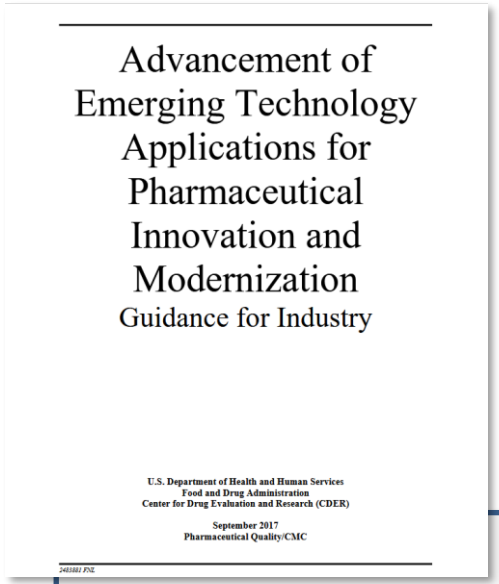
Advanced manufacturing can improve manufacturing and ensure quality medicine is available.

- **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.

CDER's Regulatory Approaches

Science and risk-based approaches	• CDER supports **Intramural and Extramural Research** to: ▪ Understand key ADM concepts and identify ADM specific risks to product quality ▪ Develop a framework for control strategy considerations
Regulations and guidance	• Existing regulations and ICH guidances (e.g., Q8, Q9, Q10, Q11 and Q12) ▪ Generally applicable to ADM (e.g., continuous manufacturing (CM)) • Emerging Technology Guidance and MAPP • **Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)**
Regulatory Assessment	• Early engagement with CDER's **Emerging Technology Program** to address scientific and regulatory gaps • Pre-operational visits (POVs) • Integrated application and facility assessments including pre-approval inspection
Maturation of regulatory basis	• Evolution of regulatory basis as experience gained with CM regulatory applications • Knowledge management • Regulatory guidance (e.g., FDA on Continuous Manufacturing and/or ICH Q13)

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

ETT Technology Pipeline: Examples

Small Molecules	Therapeutic Proteins	Multiple Products
• Continuous manufacturing of drug substance and product • End-to-end continuous manufacturing • Pharmacy-on-demand • Model-based control strategy for continuous manufacturing • Continuous aseptic spray drying • 3D printing manufacturing • Pre-fabricated, mobile manufacturing modules • Ultra long-acting oral formulation	• Controlled ice nucleation for lyophilization processes • Advanced process control • Multi-attribute method for quality control • Continuous manufacturing for a downstream process • End-to-end integrated bioprocess • Pre-fabricated, mobile manufacturing modules • Pharmacy-on-demand 	• Closed aseptic filling system • Isolator and robotic arm for aseptic filling • Novel container and closure system for injectable products

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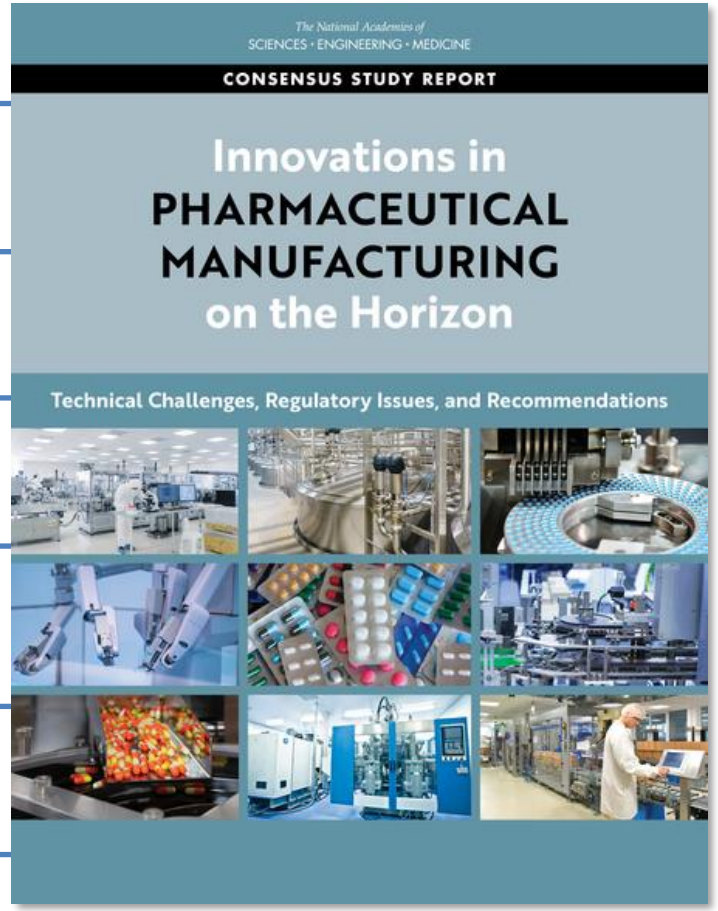
Framework for Regulatory Advanced Manufacturing Evaluation (**FRAME**)

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*

Regulatory and Policy Initiatives

- FDA draft guidance on continuous manufacturing for solid oral products (Published in February 2019)
- FDA is working on the development of ICH Q13 on continuous manufacturing of drug substances and drug products – both small and large molecules
  - Reached Step 2 in June 2021

ICH Q13 Expert Working Group

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Draft version

Endorsed on 14 June 2021

Currently under public consultation

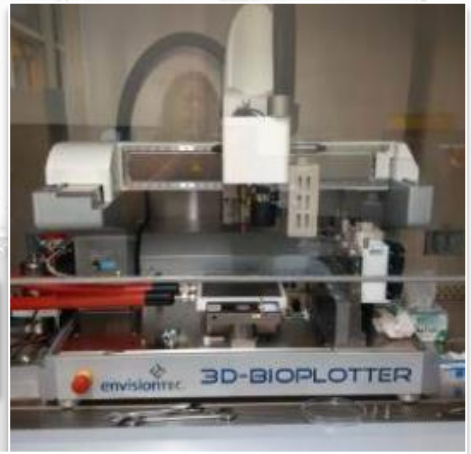
At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

OPQ Product Development Science Capabilities

Intramural Research
Novel Manufacturing Methods (10 projects)
Precision Analytics (16 projects)
Advanced Manufacturing of Biopharmaceuticals (11 projects)
Manufacturing of Glycoproteins (3 projects)
Manufacturing of Synthetic Nucleic Acid Sequences (1 project)
Process Modeling, and Artificial Intelligence (AI)/ Machine Learning (ML) (4 projects)

Projects generated more than 65 internal reports and publications

Continuous perfusion bioreactor



3D Printing

High resolution mass spectrometry

Product Development Science Program - Extramural

Extramural collaborations via grants and contracts
Industry 4.0 and Smart Manufacturing (3 projects)
Novel Manufacturing Methods (6 projects)
Novel Process Analytical Technologies (4 projects)
Process Modeling and Simulation (2 projects)
Advanced Manufacturing Training (1 project)

Projects generated more than 13 publications

Continuous manufacturing of lipid nanoparticles (UConn)

End to End continuous manufacturing (Continuus)

Continuous bio-purification (Chromatan)

Continuous direct compression (Rutgers)

Co-Processed API

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Co-Processed API

- A new technology that was highlighted in CDER-sponsored report on *Innovations in Pharmaceutical Manufacturing on the Horizon*
- An innovation in the manufacture of APIs
  - addition of a nonactive excipient or carrier to improve yields or to manipulate attributes of a process stream to achieve a desired outcome
- May be advantageous in particle formation, crystallization, or drying operations to improve the stability of a desired solid state or to tailor physical properties of the drug substance.

Co-Processed API

- Co-Processed APIs-Scientific and Regulatory Considerations for New Drug Development, Rapti Madurawe, PhD, Division Director, OPMA, OPQ, CDER, FDA
- An FDA Perspective on Regulatory Considerations for Co-Processed APIs, Laurie Graham, PhD, Director, OPPQ, OPQ, FDA
- Global Regulatory Harmonization Challenges and Opportunities, Mahesh Ramanadham, PharmD, MBA Deputy Director, OPPQ, OPQ, CDER, FDA

In Closing

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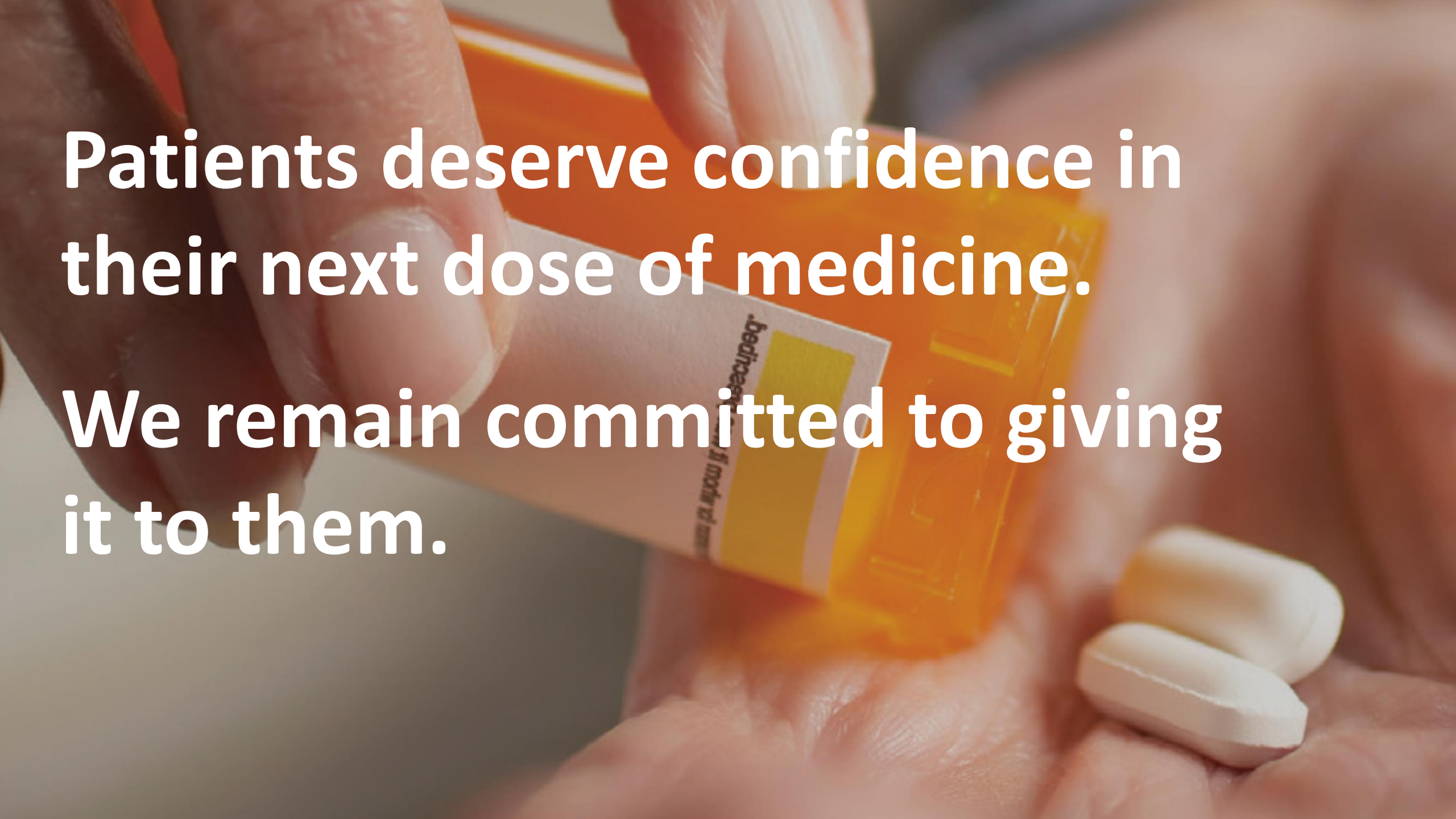
Patients deserve confidence in their next dose of medicine.
We remain committed to giving it to them.


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