Commitment to Quality in Pharmaceutical Development and Commercial Manufacturing

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Pharmaceutical Quality

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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

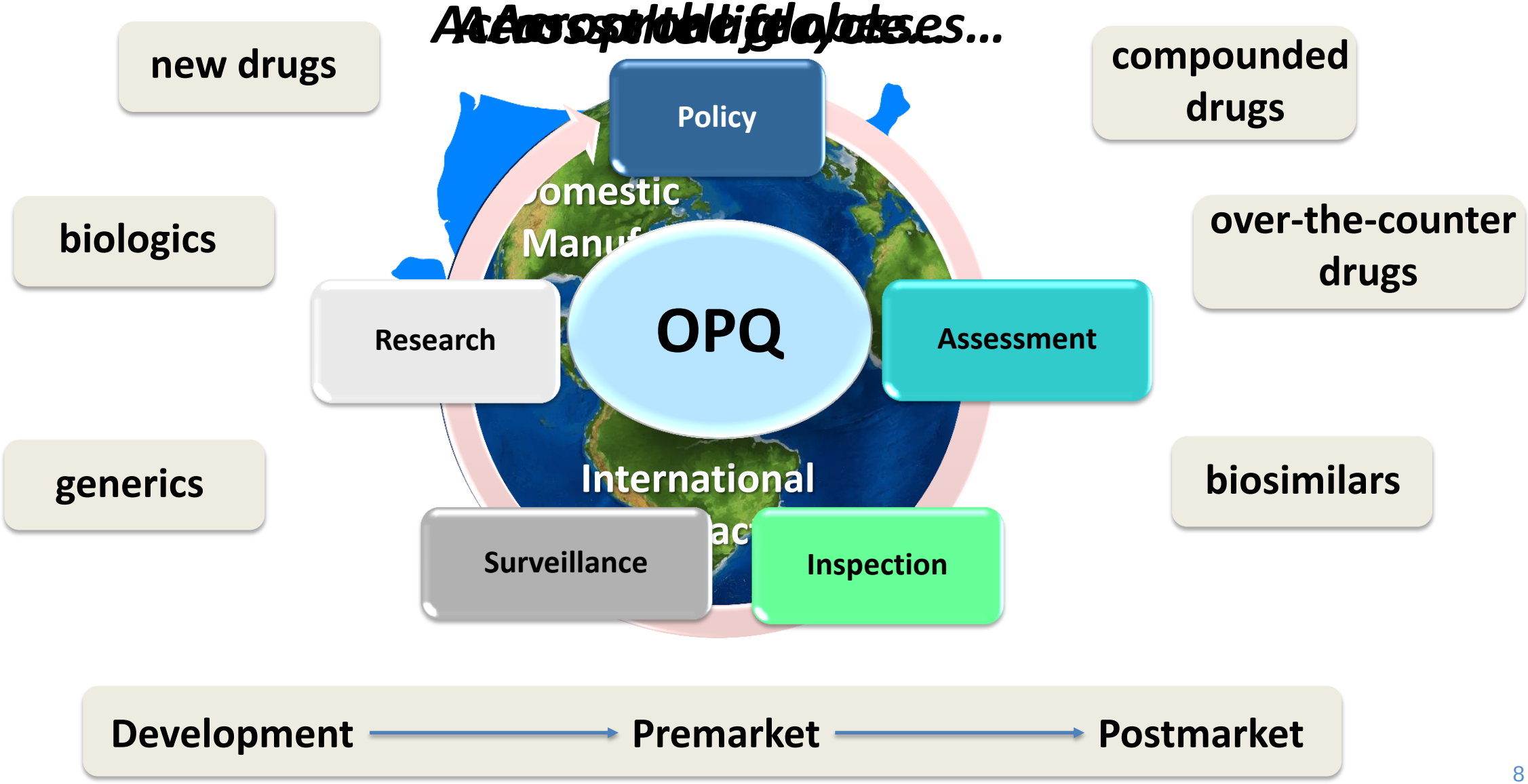
assuring *every* dose is safe and effective, free of contamination and defects.


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

Outline

- OPQ and OPMA overview
- Common Deficiencies & Expectations
- Process Validation Lifecycle & Expectations
- Future Initiatives
- Concluding Remarks

Office of Pharmaceutical Quality



Office of Pharmaceutical Assessment - OPMA

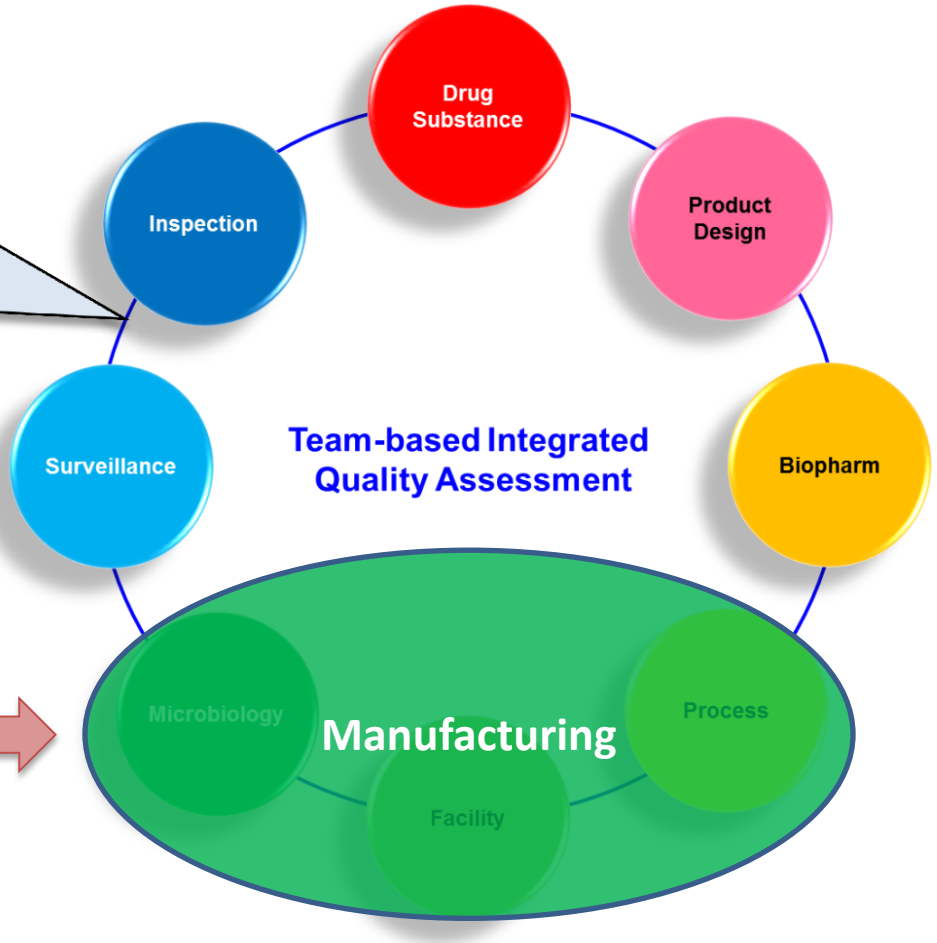
Mission: Ensure that Quality is built into commercial manufacturing processes and facilities over the product lifecycle

Assesses Applications (INDs, ANDAs, NDA/BLAs, Supplements) and Performs Facility Inspections

The 2019 Office of Pharmaceutical Quality (OPQ) Annual Report:
https://www.fda.gov/media/135046/download

Team-based Integrated Quality Assessment (IQA)

Inclusive of drug substance, drug product, manufacturing, and facilities, and maximizes each team member's expertise



OPMA →

Science- and Risk-Based approach that is patient-focused

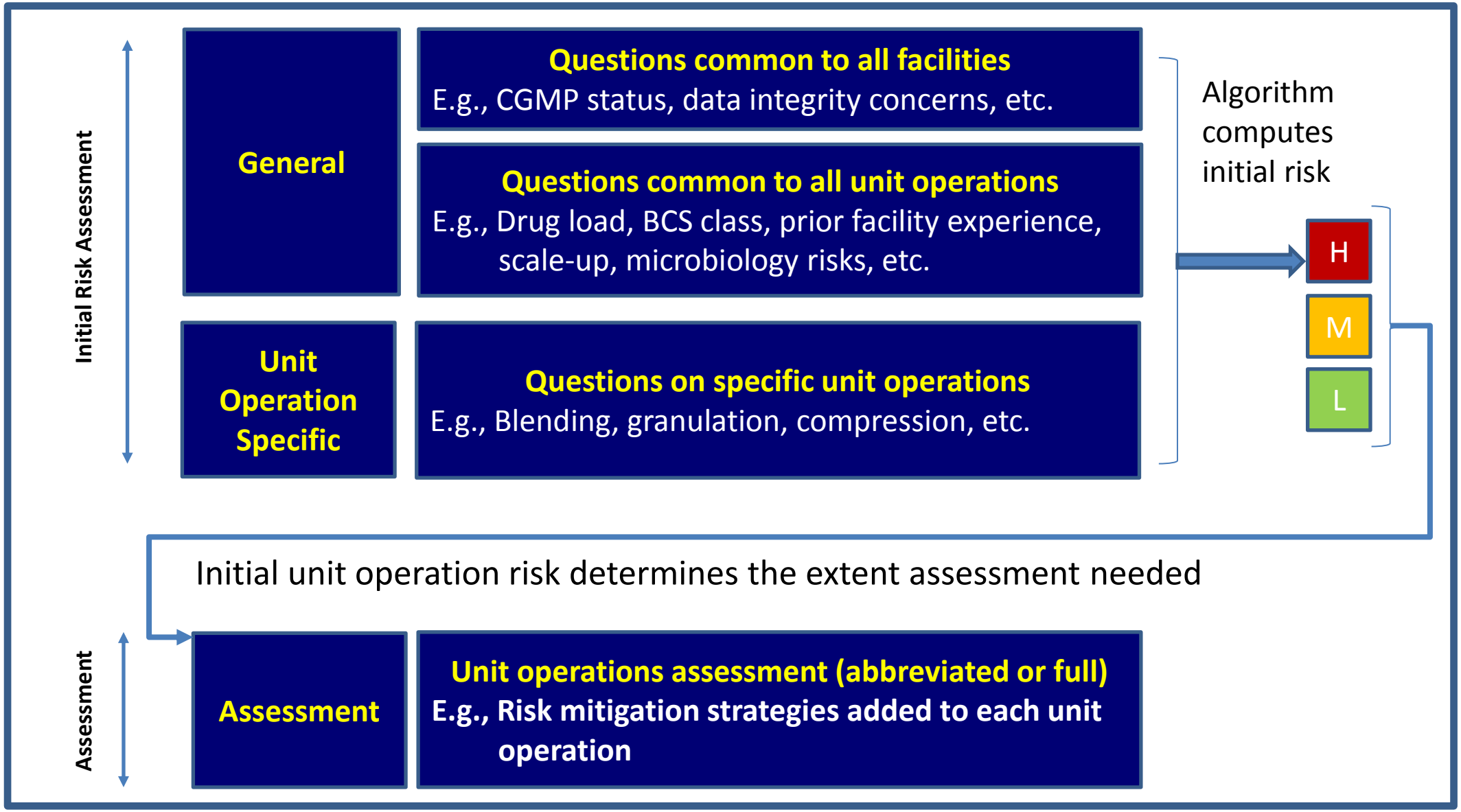
OPMA Manufacturing Assessment Goals

- Assess potential for manufacturing to impact product quality attributes
  - Materials
  - Processing
  - Holding
  - Testing & QC
  - Packaging & Labeling
  - Shipping

What We Need from Applicants

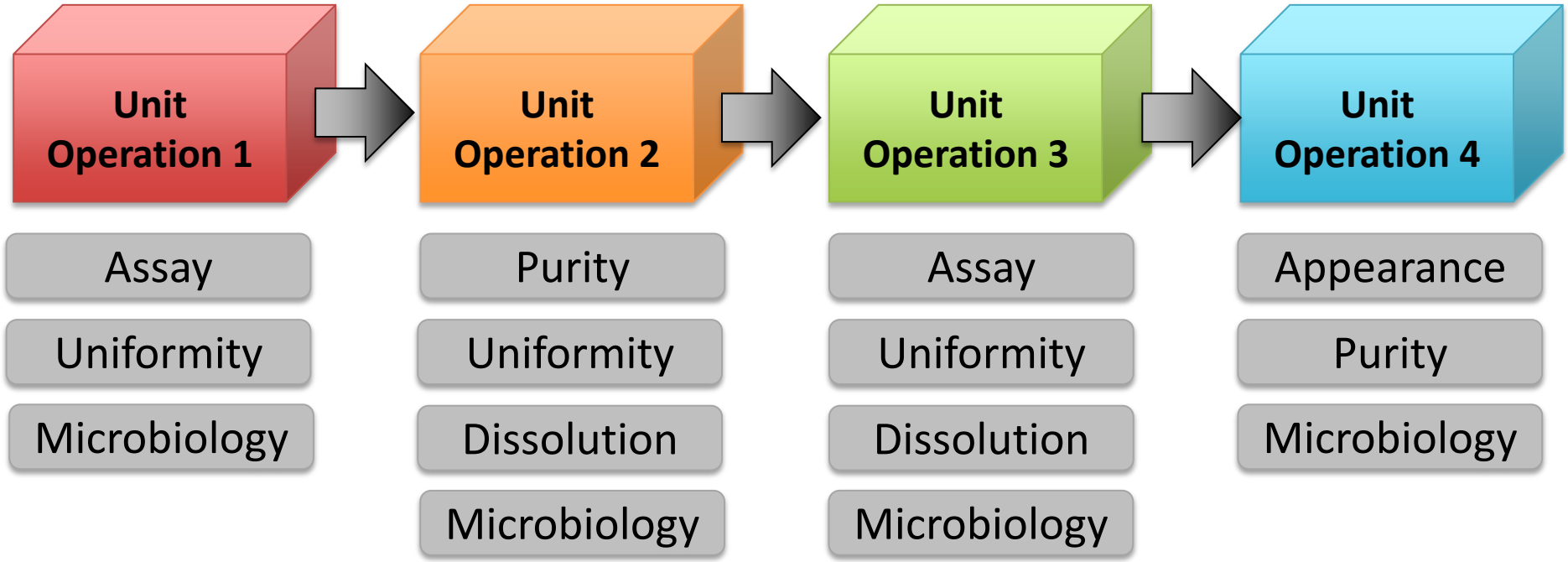
- Manufacturers and responsibilities
- Process development & **bridge** to commercial scale
- Commercial process descriptions, Process Flow Diagrams, MBRs (sequence, equipment, process parameters, in process controls and tests)
- Sterilization validation package for sterile products

Manufacturing Initial Risk Assessment



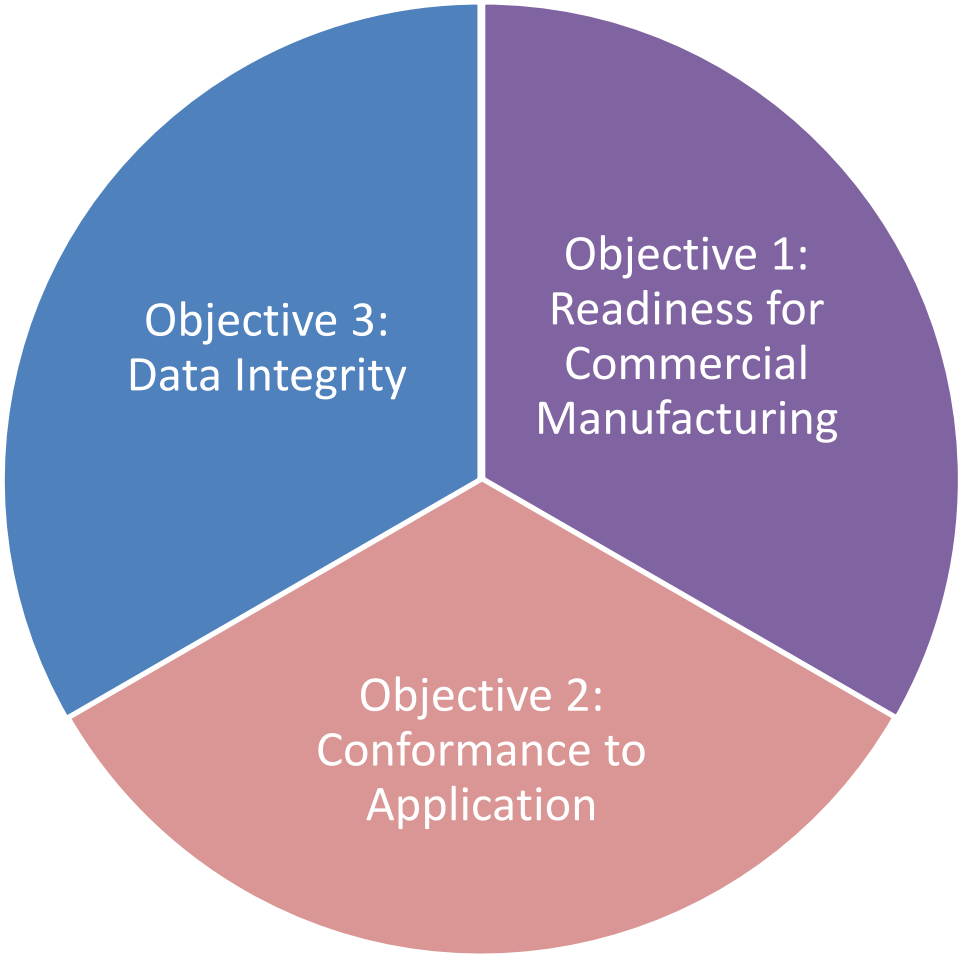
Unit Operation Impact on CQAs

- Each material transformation affects Critical Quality Attributes (CQA).
- Thus, CQA risk control is achieved through unit operation risk control.



Pre-Approval Inspection Goals

- OPMA Focus Areas
  - Readiness to Commercial Manufacturing
    - Incoming Materials
    - Process, CPPs
    - Equipment / facilities / Cleaning
    - Personnel Training & Competence
  - Conformance to Application
  - Data Integrity



What We Need from Sites

- Sites are ready for inspection at the time of submission
- Compliance with CGMPs
- Operations match those in application
- Data in the submission is an accurate representation of data generated at the facility
- Manufacturing processes - Fit for Purpose

Examples of Application Deficiencies
&
During PAIs

Common Manufacturing Deficiencies

- Biologics:
  - Complete PPQ not conducted to support submission
  - Product will not be manufactured within review cycle and during inspection
- Sterile products:
  - Sterilization validation data is insufficient
  - Failures with equipment qualification, process simulation, sterility testing methods
- Overages or overfill not justified (e.g., Liquid, Lyophilized products)

Common Manufacturing Deficiencies

- New batches required due to significant failures with submitted batches; no root cause understanding provided
- Incomplete facility or facility responsibility listing on 356h form
- Process parameters and in process controls are not supported by process development knowledge in the application

Specific Assessment Examples

- From 68 Reviews of NDAs/ANDAs since 2018 for a High Shear Wet Granulation Process
  - Lack of end-point control of granulation
  - Lack of definition of granulation fluid level (% of dry mix or total amount of fluid)
  - Lack of control of granulation fluid addition rate/time
  - Lack of appropriate process scale up strategy

Ref: High Shear Wet Granulation Process in New & Abbreviated Drug Applications Assessed

Lixia Cai, Hang Guo, Feiyan Jin, Steve Rhieu, Daniel Obrzut, Haitao Li
Presented at the 2019 AAPS Conference

Common PAI Deficiencies

- Not Ready to Manufacture
  - Commercial equipment not qualified or available
  - Unresolved failures observed in tech transfer or scale up
  - Methods not validated
  - Insufficient quality practices (failure investigations, process validation, ineffective CAPA)
  - Facility is inadequately designed to prevent contamination
  - Inadequate operator knowledge & training

Common PAI Deficiencies

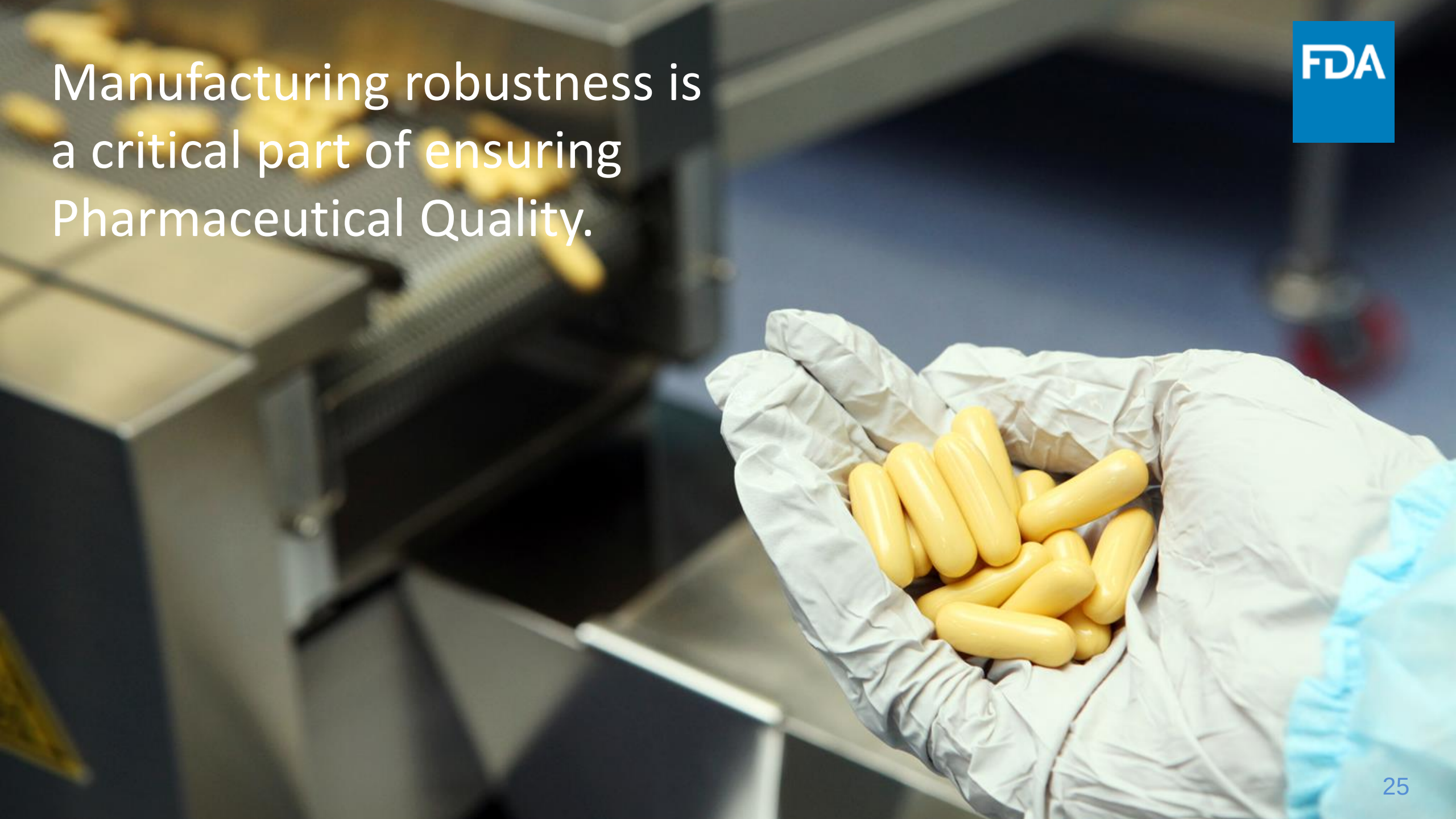
- Conformance to the Application
  - Actual equipment, controls, operations diverge from those described in application
    - Different operating principles
    - Proposed PAT not available
  - Changes Made Onsite
    - Control strategy
    - On site methods different

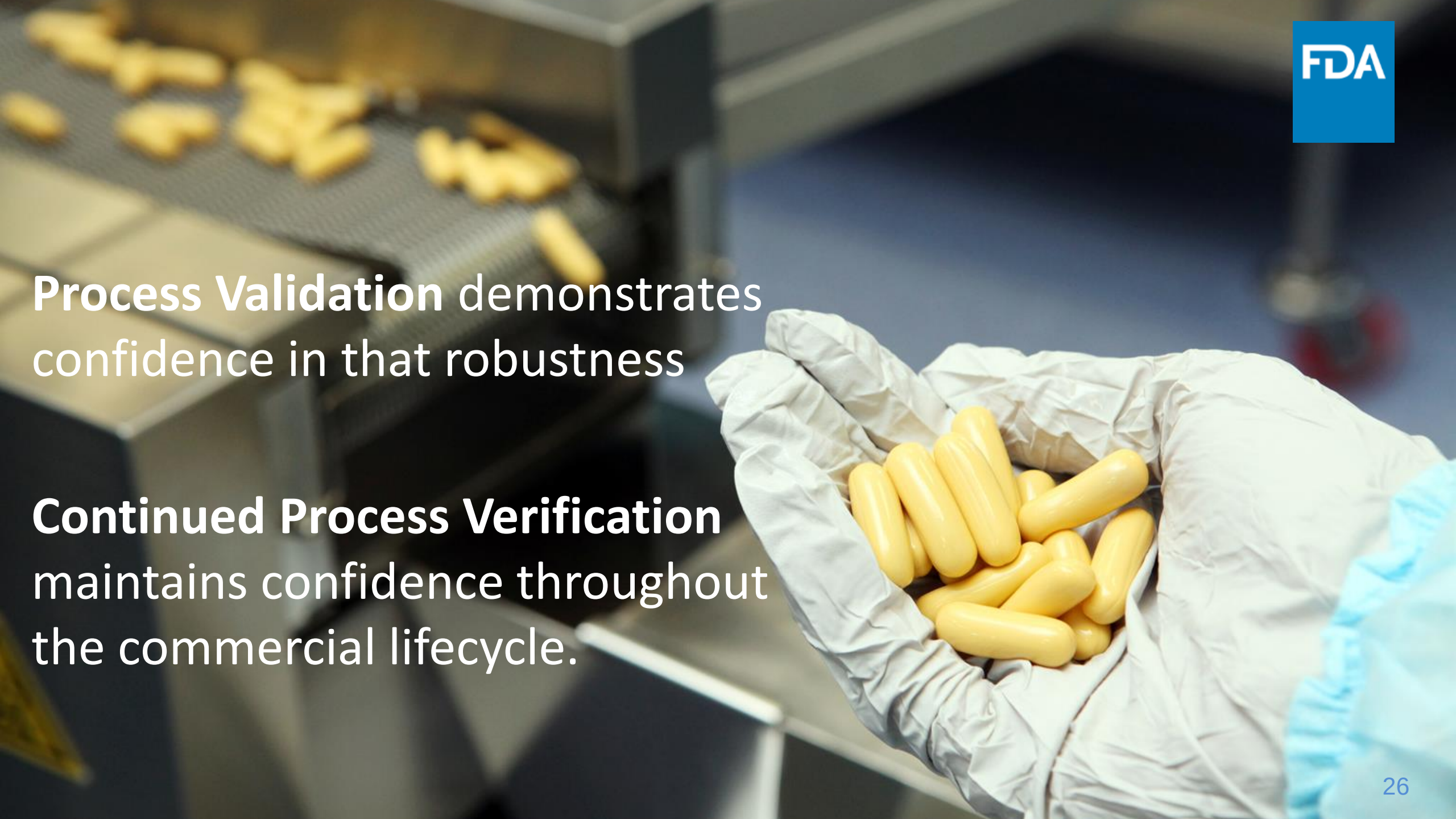
Common PAI Deficiencies

- Data Integrity
  - Failing results not reported in the application
  - Inadequate OOS investigations
  - Testing into compliance

The Importance Process Robustness

Manufacturing robustness is a critical part of ensuring Pharmaceutical Quality.

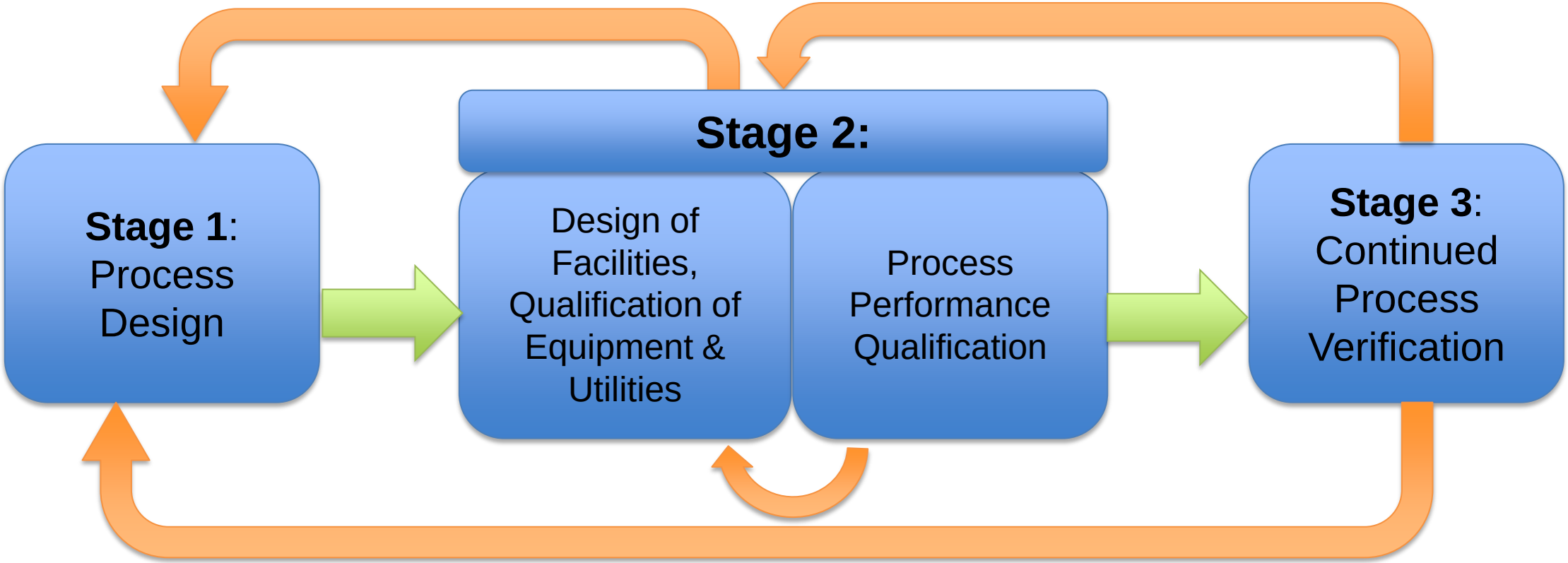




Process Validation demonstrates confidence in that robustness

Continued Process Verification maintains confidence throughout the commercial lifecycle.

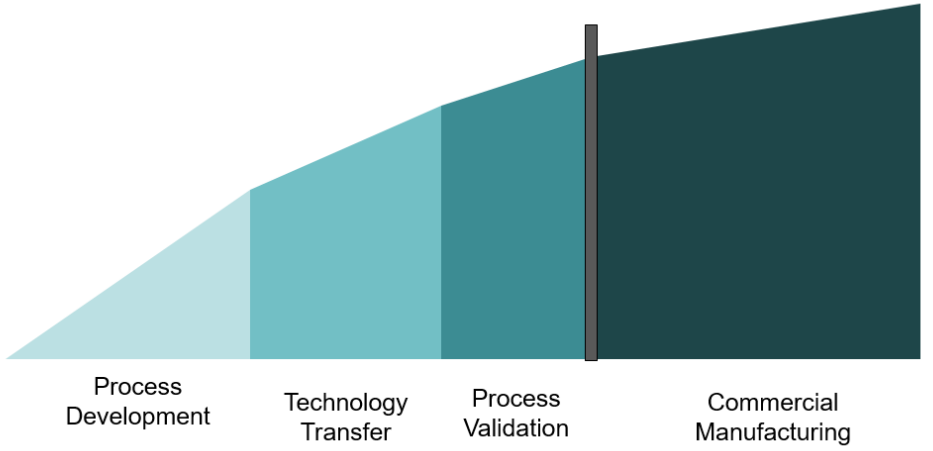
Process Validation Overview



Why Continued Process Verification

- Limited Process Development:
  - QbD Work still time-bound
  - Materials
  - Environment (equipment, facilities, personnel)

- PPQs can not address all possible source of variability
  - Changes toward reducing COGs
  - Current Complex Supply Chain



- If you want to prevent interruptions to the Supply Chain, then implement CPV
  - will drive Improvements and prevent deviations/batch rejections
  - Save Money

Continued Process Verification

- Establish criteria to monitor the process
  - Establish periodic assessment
  - Document state of control, recommendations, identify risk areas, etc.
  - Modify based on gained knowledge

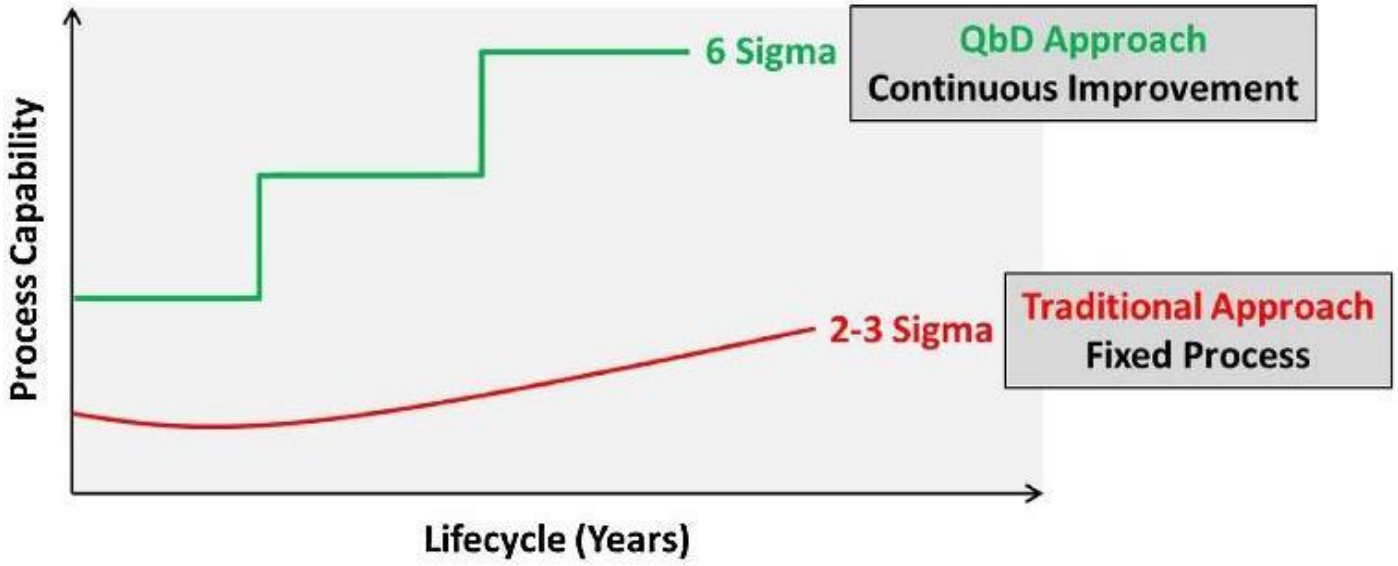
- Identify & implement improvements with new knowledge and process experience

- “Annual” product quality reviews may not be sufficient to capture changes and prevent deviations

Future of Pharmaceutical Quality

- Six sigma manufacturing for higher process capability and product quality assurance

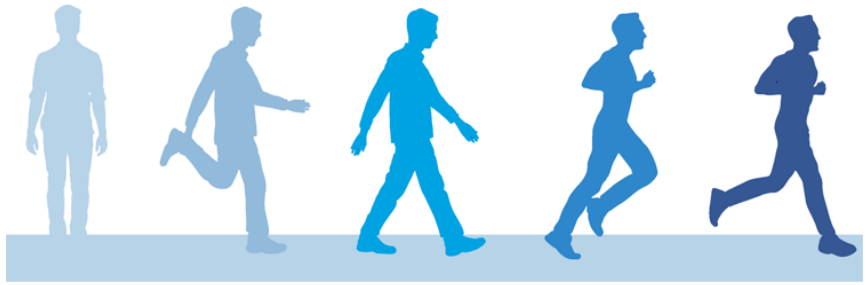
- Robust Process Validation (Stages 1-3) is a critical tool for achieving high quality manufacturing



Yu., L. X.; Kopcha, M. Int. J Pharm. (2017) 528, 354-359

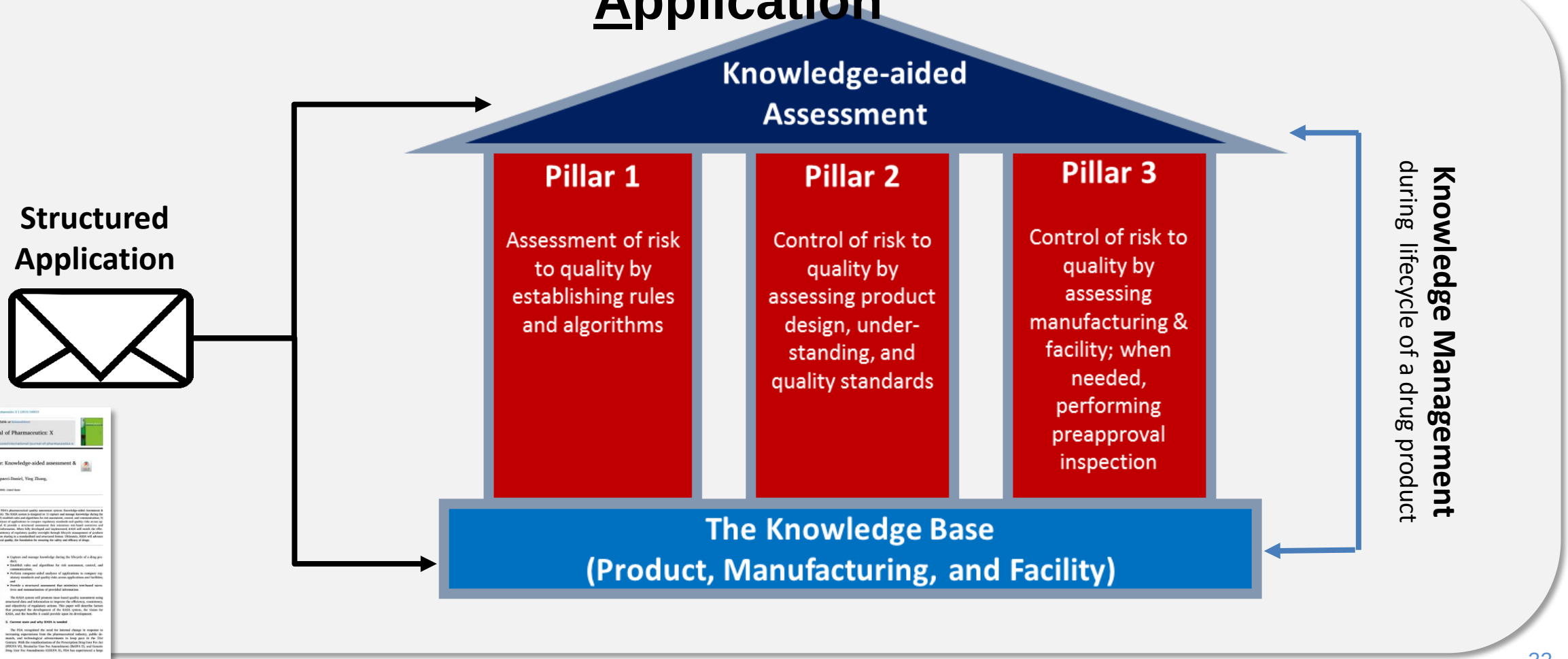
Quality Management Maturity

- **Basic Quality Management Systems**
  - *Reactive:* focused on Current Good Manufacturing Practice (CGMP) compliance
- **Strong, mature Quality Management Systems**
  - *Proactive:* focus on performance, especially outcomes that affect the patient



The Future is Here – IT Solution for Assessment

KASA – Knowledge-aided Assessment and Structured Application




International Journal of Pharmaceutics: X

FDA's new pharmaceutical quality initiative: Knowledge-aided assessment & structured applications

*Read more: Yu, et al. *Int J Pharm* 2019

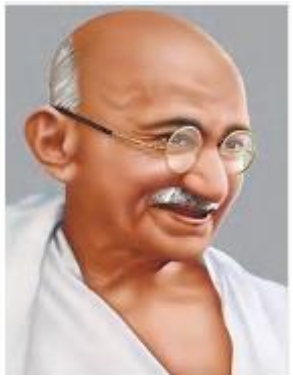
FDA's New Inspection Protocol Project (NIPP)

- **Better assess and record the state of quality in manufacturing facilities**
  - Standardized electronic inspection protocols
  - Templated, semi-automated inspection reports
  - Quality maturity indicators

Key Takeaways

- Quality Medicines require vigilance throughout the cycle of the product
  - *Continuous Oversight & Improvement*
  - *Application of Innovation & Technology*
  - *People Technical Knowledge & Training*

- Working together we can assure safe, effective and quality medicines to our patients



Mahatma Gandhi's 7 Social Sins

October 22, 1925, Young India

- Politics Without Principles
- Wealth Without Work
- Knowledge Without Character
- Commerce Without Morality
- Science Without Humanity
- Worship Without Sacrifice
- Pleasure Without Conscience

- Avoiding 4 Sins (57%) should lead to Quality Culture

Quality Culture Foundation is there – Let's Act; we owe it to our patients!

Acknowledgement Slide

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Questions

Don’t Forget We are Patients too!