U.S. FOOD & DRUG ADMINISTRATION

Manufacturing Assessment & Application Action

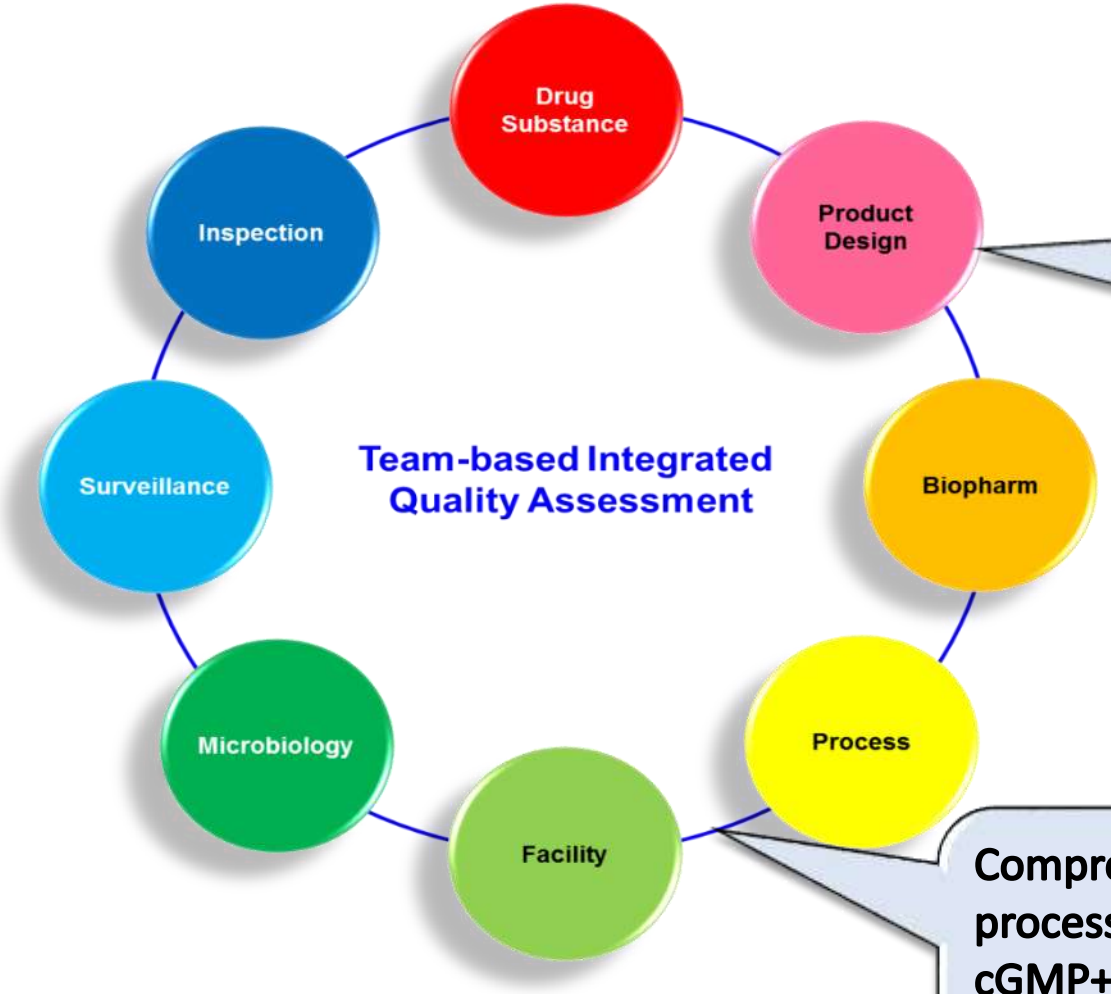
Rakhi B. Shah, PhD
Branch chief
Office of Pharmaceutical Manufacturing Assessment
OPMA (formerly OPF)/OPQ/CDER/FDA

SBIA-Midnight Madness 2020

Outline

- Integrated manufacturing (process & facilities) assessment
- Review and inspection considerations
- Expectations from the sites
- Common manufacturing and inspection deficiencies
- What can you do at your facility?

Integrated Manufacturing Assessment



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

Comprehensive manufacturing process evaluation (process+ cGMP+facility capability) evaluations in conjunction with pre-/post-approval inspections

Manufacturing Assessment

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

Keep the end in mind: Is the process suitable & scalable?

Inspection considerations

- Establishment is named for the first time
- First application filed by applicant
- New dosage form than previously approved at the facility
- Substantially different or novel manufacturing operations than previously approved
- Concerns about firm's quality systems
- Questions about the firm's capability of manufacturing quality products
- Scale-up concerns
- Product specific concerns

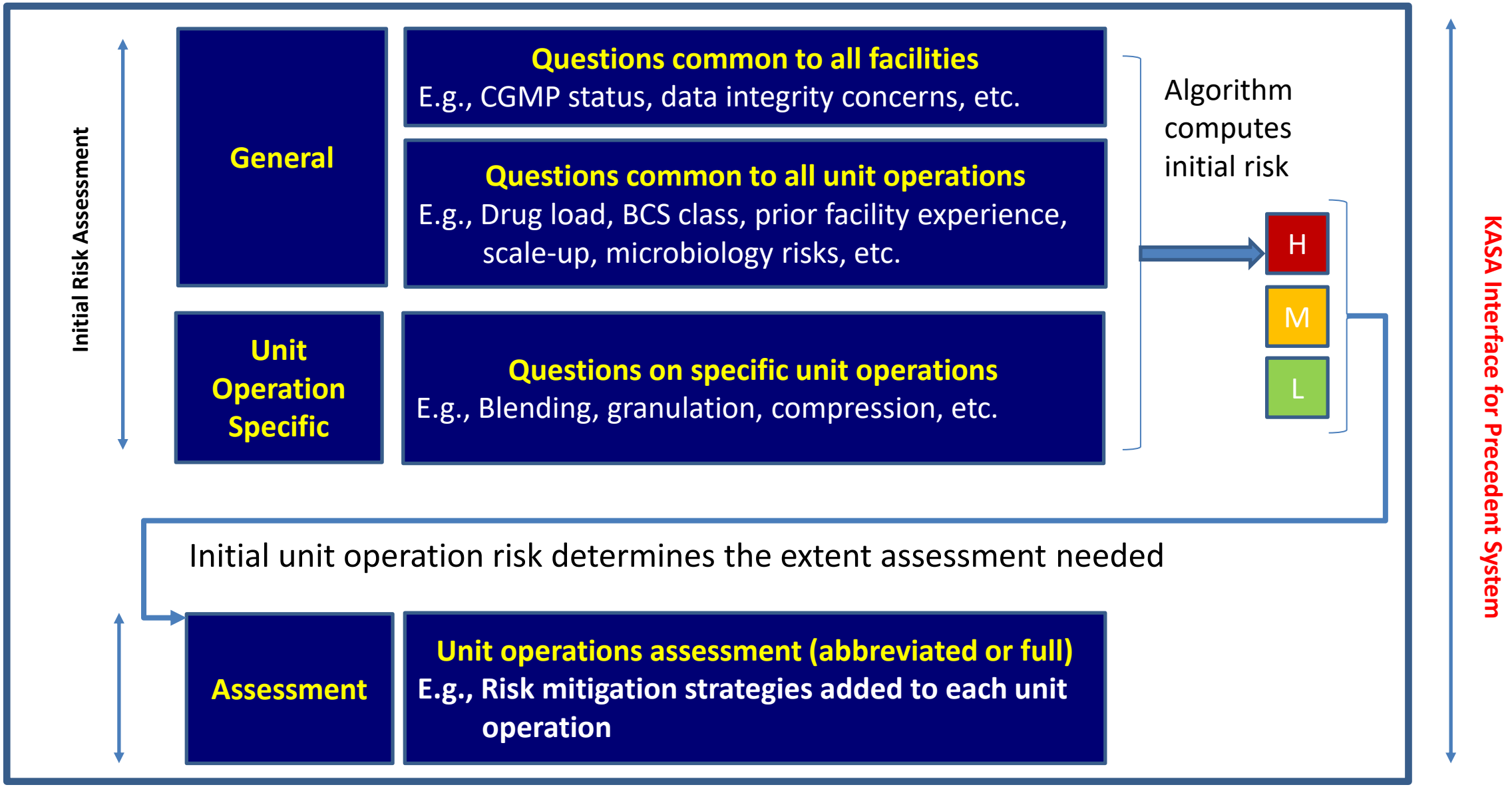
Pre-Approval Inspection: Supports review & approval of marketing applications for drug products

Post approval Inspection: Initiated after approval to verify that commercial-scale manufacturing and drug quality are per approved application

What We Need from Applicants

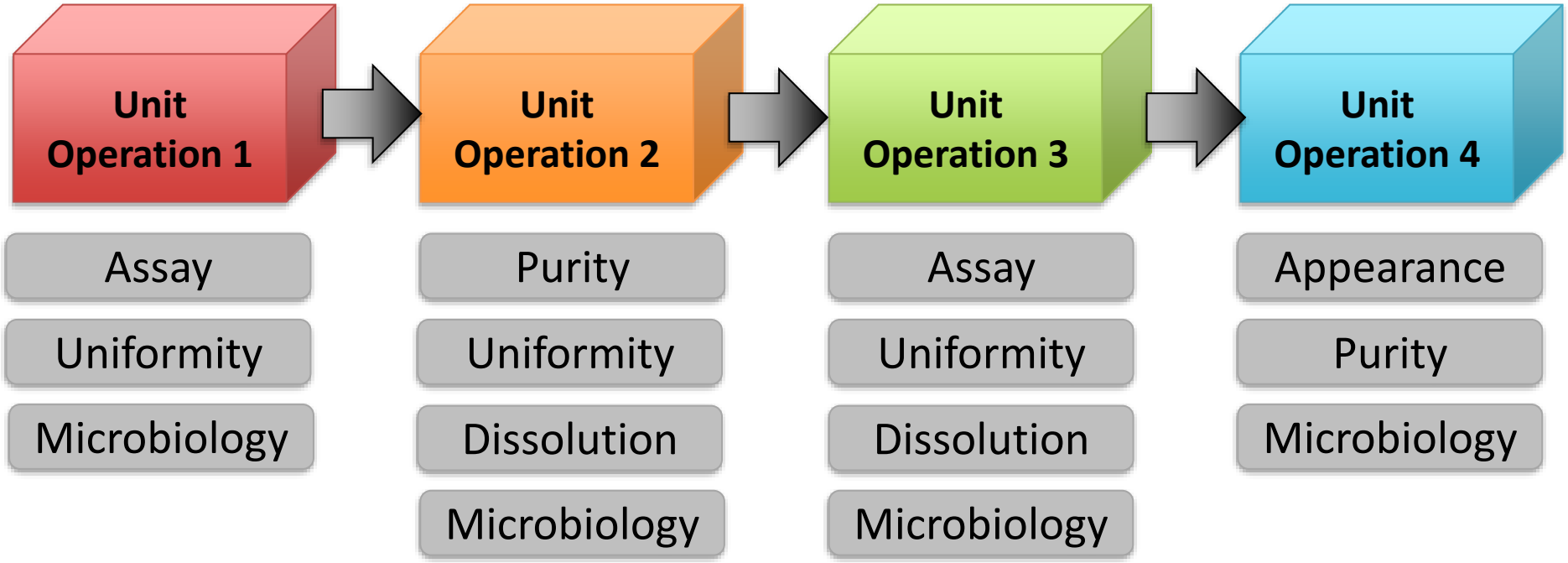
- Manufacturers and responsibilities
- Process development & **bridge** to commercial scale
- Commercial process descriptions, Process Flow Diagrams, MBRs (sequence, equipment, process parameters, in process controls and tests)
- Sterilization validation package for sterile products

Manufacturing Risk Assessment & Control



Unit Operation Impact on CQAs

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



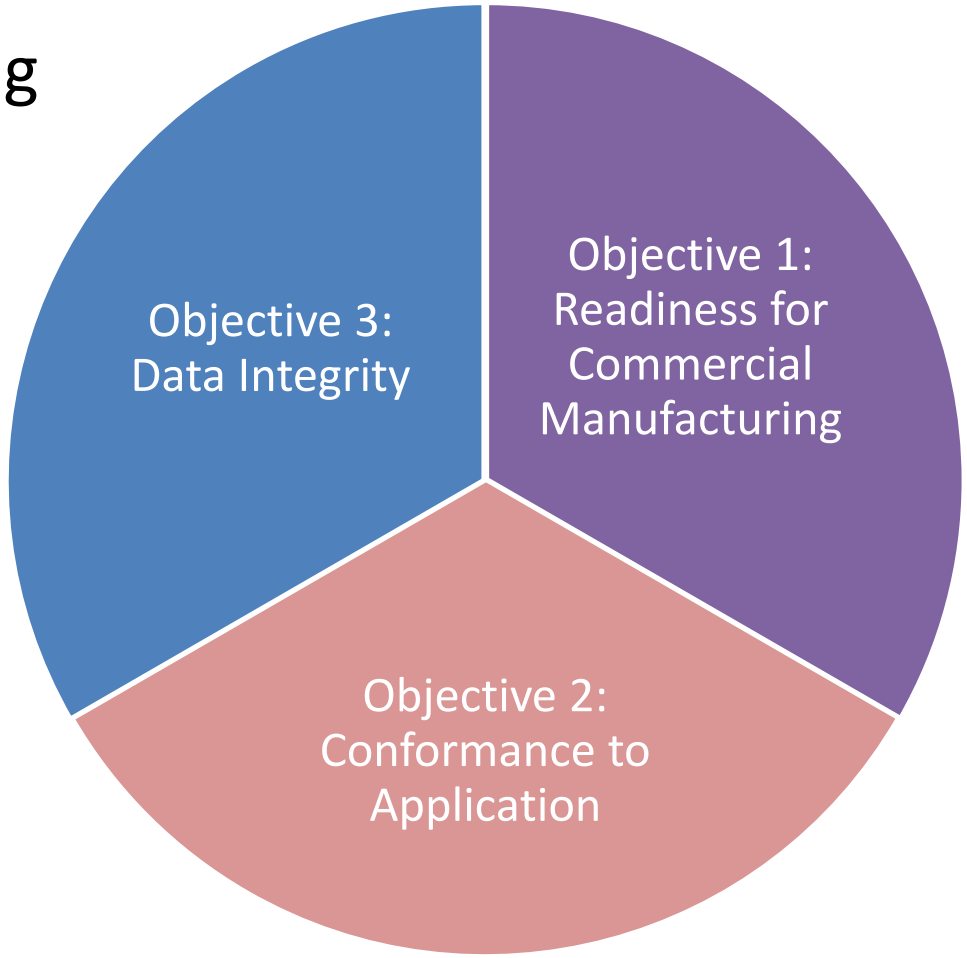
Pre-Approval Inspection Goals

Focus Areas

- Readiness to Commercial Manufacturing
  - Incoming Materials
  - Process, CPPs
  - Equipment / facilities / Cleaning
  - Personnel Training & Competence

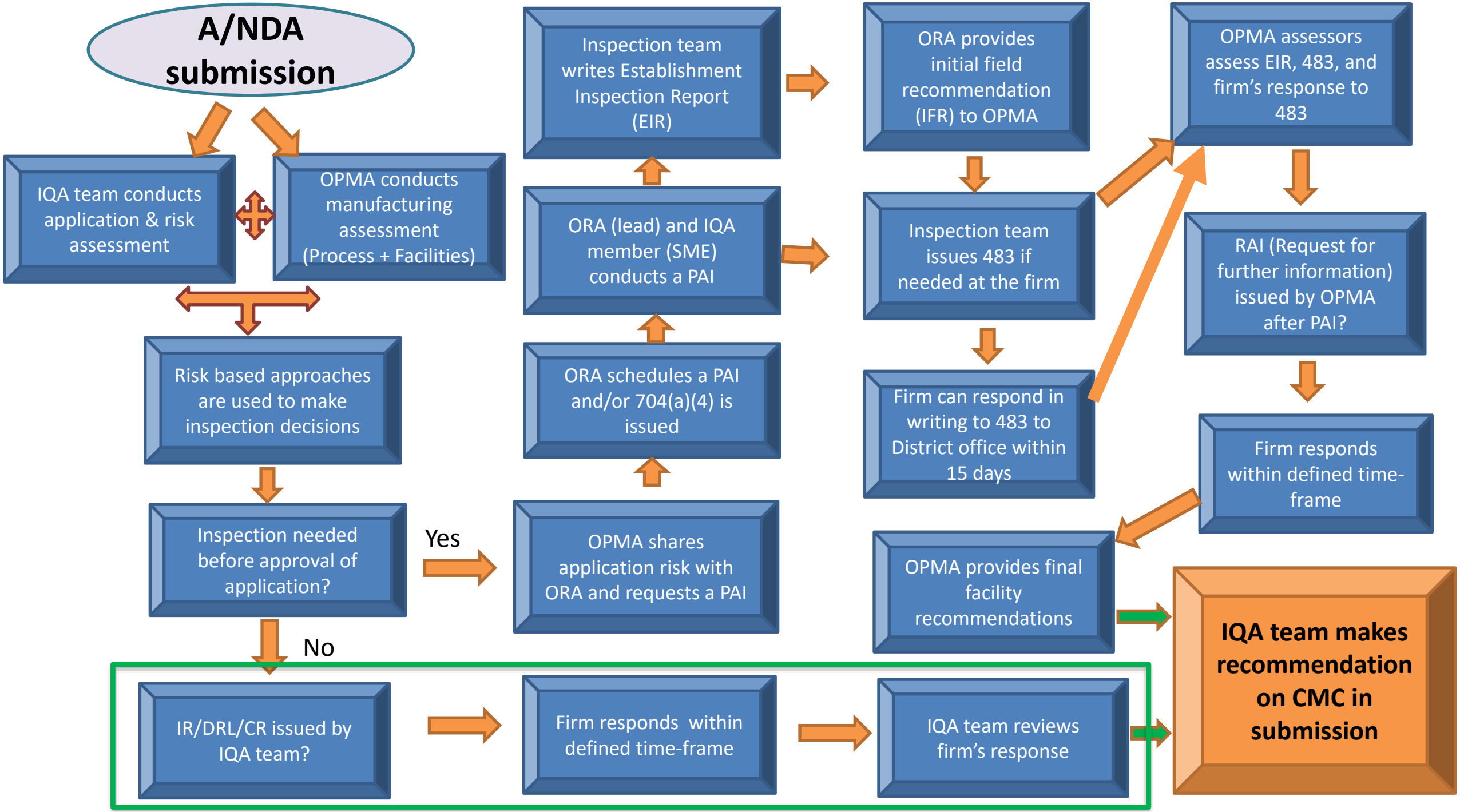
- Conformance to Application

- 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 operations - Fit for Purpose


A/NDA submission
IQA team conducts application & risk assessment
OPMA conducts manufacturing assessment (Process + Facilities)
Risk based approaches are used to make inspection decisions
Inspection needed before approval of application?
Yes
No
OPMA shares application risk with ORA and requests a PAI
ORA schedules a PAI and/or 704(a)(4) is issued
ORA (lead) and IQA member (SME) conducts a PAI
Inspection team writes Establishment Inspection Report (EIR)
ORA provides initial field recommendation (IFR) to OPMA
Inspection team issues 483 if needed at the firm
Firm can respond in writing to 483 to District office within 15 days
OPMA assessors assess EIR, 483, and firm's response to 483
RAI (Request for further information) issued by OPMA after PAI?
Firm responds within defined time-frame
OPMA provides final facility recommendations
IR/DRL/CR issued by IQA team?
Firm responds within defined time-frame
IQA team reviews firm's response
IQA team makes recommendation on CMC in submission

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

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

- Conformance to the Application
  - Actual equipment, controls, operations diverge from those described in application
  - Changes Made Onsite

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

Case Study 1 (with PAI): Laser drilled MR tablet

- Review observation: Lack of control for the hole depth during laser drilling
- Inspection observation: Laser power level identified as critical for the hole depth but not monitored and recorded
- Mitigation: Laser power is controlled and P.3 section of the application was revised

Targeted inspection and in time deficiency correction for a modified release tablet

Case Study 2 (with PAI): Data reliability

Inspection to cover new product type leads to impact on IQA team's assessment

- Review observation: Facility has poor inspectional history and no approved products for proposed dosage form
- Inspection observation 1: Concerns over testing failures identified during inspection of manufacturer led to coverage of adjacent testing facility
- Inspection observation 2: Coverage of testing facility identified inappropriate averaging of results hiding OOS's, concerns over dissolution method robustness, missing dissolution timepoints
- Outcome: Application was issued a Complete Response as drug product performance could not be established without appropriate dissolution information
- Applicant needs to improve method and demonstrate data reliability in the resubmission

What can you do at your facility?

- Operate within state of control following regulations and policies
- Review events, understand trends, investigate when needed
- Ensure documented scientific evidence supports conclusions for investigations
- Manage product lifecycle by looking at key post market information
- Have a robust PQS
- Have adequate methods to control raw data/prevent data integrity issues