Regulatory Assessment of Applications Containing QbD Elements - Reviewer Experience

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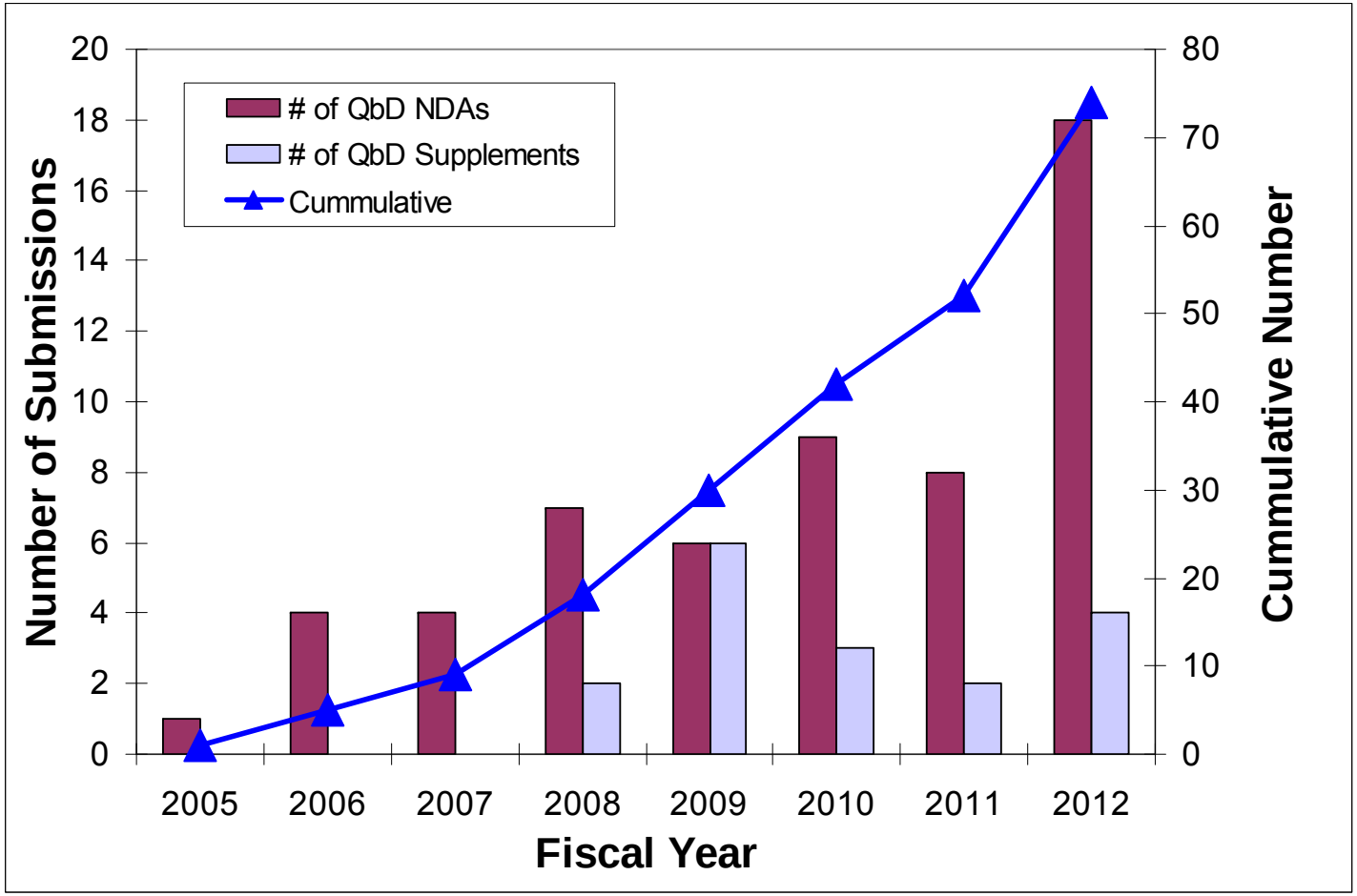
Outline

- Current QbD submission statistics
- Review of QbD-based submissions
  - Process
  - Team based review, Good Review Management Practices (GRMPs)
- Examples
- Reviewers on inspection - experience
- Conclusions

Current Count of QbD based Applications

(i.e. applications with Regulatory Flexibility elements)



Internal Support of QbD within ONDQA

- Internal searchable database for tracking QbD elements in QbD based applications (i.e. those containing regulatory flexibility) launched
- Database set up for Information Requests regarding review of QbD elements
- QbD CMC Lead position established
- Extensive QbD Training (small and large group)
- Established “QbD Liaison” – mentoring role
- Increase in reviewer participation in inspections
- Development of internal guidelines on review considerations for QbD aspects
- Collaborative research between ONDQA and academia on QbD and PAT focused topics

Reviewer Training in QbD Approaches

- Internal
  - Technical courses (e.g., design of experiments, statistics, chemometrics)
  - Internal regulatory discussions (e.g., Regulatory Briefings, QbD Liaisons bi-monthly meeting)
  - Invited speakers
  - Specific mentoring/team reviews
- External
  - Academic collaborations
  - Hands-on analytical and unit operations
  - Conference attendance/participation

QbD Reviews – Team-Based Process

- Most QbD containing submissions are team-based reviews
  - ONDQA review team
    - Primary reviewers – Both CMC and Biopharmaceutics
    - QbD Liaison
    - ONDQA Project Manager
    - Supervisors (Branch Chief, Division Director)
    - Additional technical experts – Statistician, Microbiologist (as needed)
- Expanded review and inspection team
  - Office of Compliance (OC) – Compliance Officer
  - Office of Regulatory Affairs (ORA) - Investigator

QbD Review Process

- QbD kick-off meeting
  - Invite review team, ONDQA experts, representatives from OC, ORA
  - Discuss potential product and process risks and review precedence
  - Discuss review deliverables and anticipated timing
- Product Quality and Manufacturing (PQM) Memo
  - Communicated to OC and ORA
- Periodic team meetings
- Team-developed information request (shortly following mid-cycle)
  - Help ensure consistency within office
- Review response
- Conduct inspections
  - Reviewer input and more frequent participation
- Finalize review

Within 10-month GRMP dates for standard (6 months for priority)

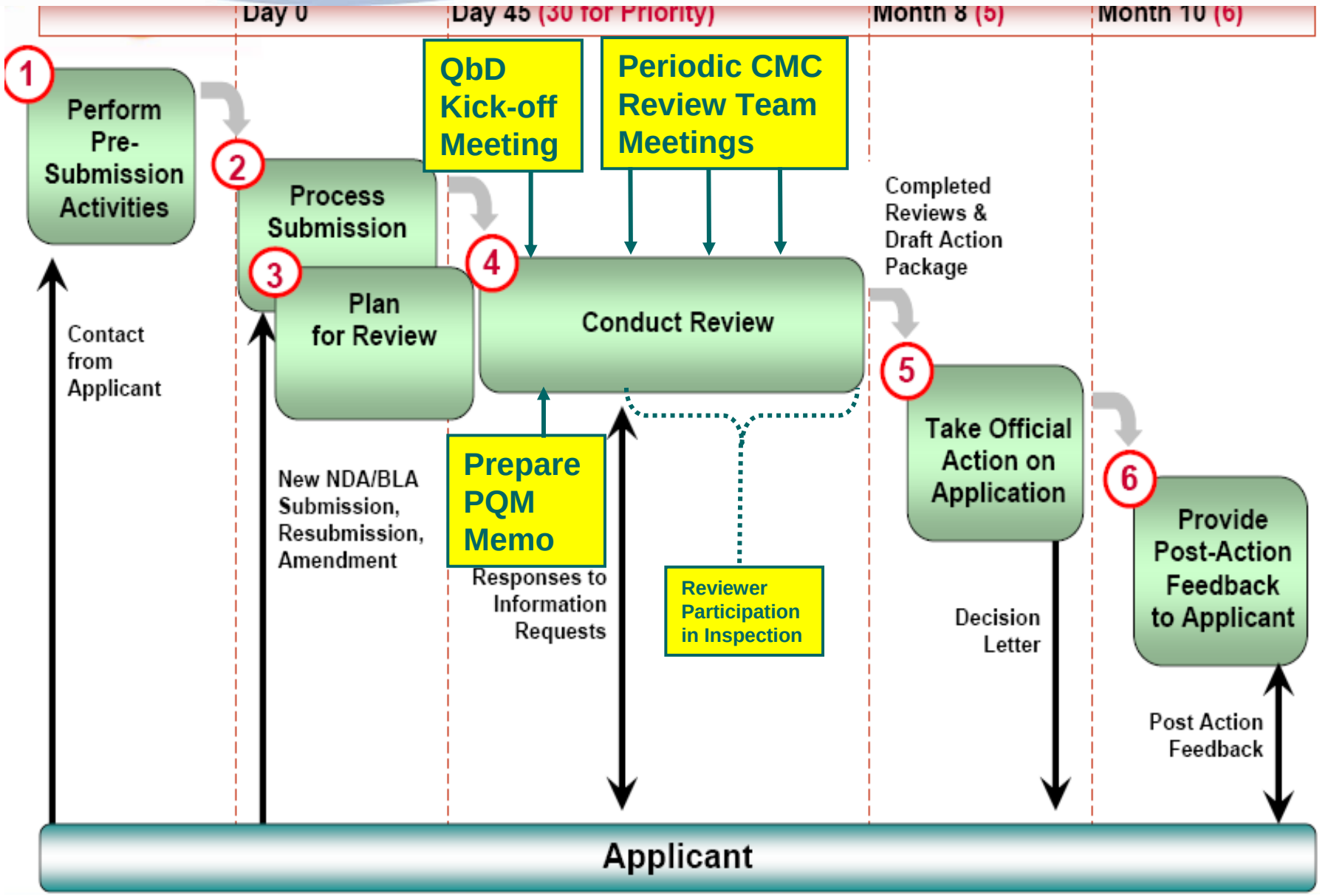
Product Quality and Manufacturing Memo

- ONDQA-prepared memo to aid in communicating application-related information to OC and ORA
- Prepared relatively early in the review cycle to help with inspectional planning
- Contents include: product description, process summary, critical steps and controls, summary of product and process-related risks
- Currently prepared for:
  - Complex products and/or processes
  - Complex regulatory approaches (e.g., RTRT)
  - Applications with questionable manufacturing capabilities or suspect data integrity issues

Addressing Some Misperceptions of QbD-Containing Applications

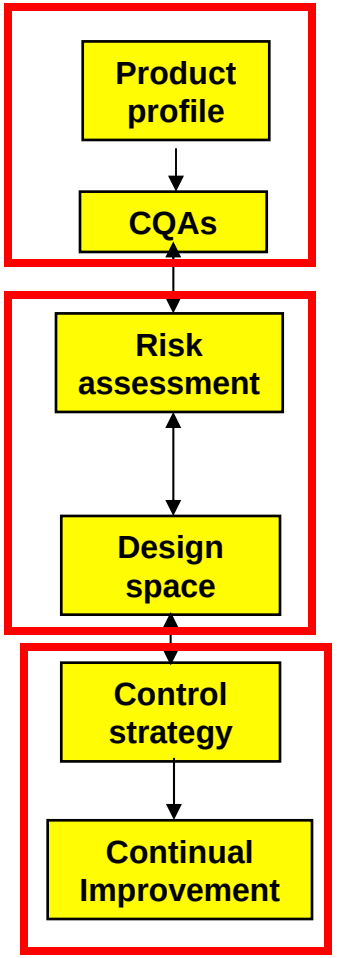
- QbD does not mean decreased regulatory requirements.
  - Regulatory requirements remain the same, but opportunities exist for “regulatory flexibility” (e.g. RTRT, design space)
- QbD-containing applications do not extend the review clock.
  - All NDAs adhere to Good Review Management Practices (GRMPs).
  - No timelines have been missed due to QbD content in an NDA.
- Increased information in the application does not necessarily lead to increased questions.
  - Lack of development details (rather than more) can lead to increased questions.
  - Inadequate data to support requests for increased regulatory flexibility can lead to increased questions.

GRMPs - Timelines



Examples

Example - ICH Q8R2



- Target the product profile

PRODUCT UNDERSTANDING

- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment

PROCESS UNDERSTANDING

- Develop a design space
- Design and implement a control strategy

PROCESS CONTROL

- Manage product lifecycle, including continual improvement

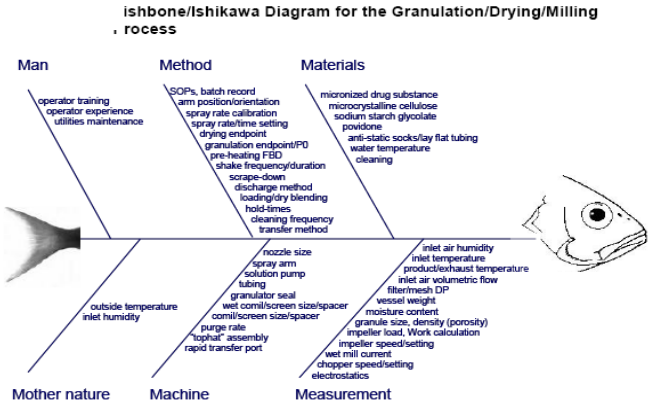
Tools - Product Understanding

Ishikawa Diagrams
IPO Diagrams
BRITEST
Parameter Attribute Matrix (PAM)
Relationship Matrices
Risk Prioritization Matrix
Probability Severity Risk Tables
Hazard Analysis and Critical Control Points (HACCP)
Failure Mode and Effects Analysis (FMEA)
Failure Mode, Effects and Criticality Analysis (FMECA)
Statistical DoE
Pareto Charts
Mechanistic Models

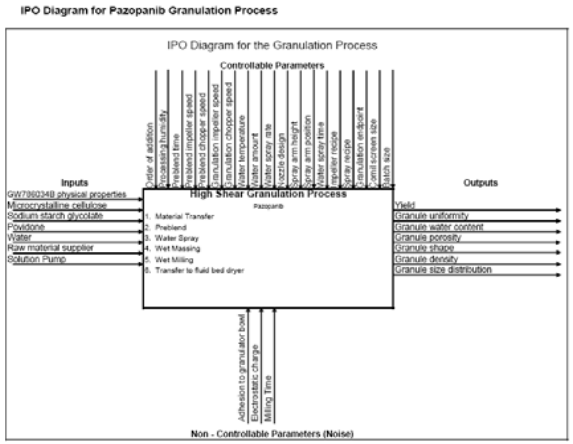
Examples - Risk Assessment

Qualitative Approaches

Ishikawa Diagrams



Input-Output Diagrams



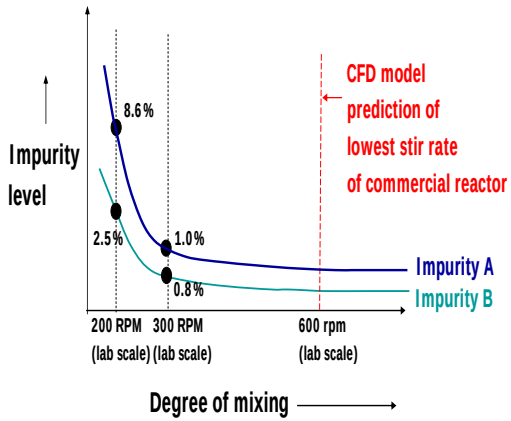
Quantitative Approaches

FMEA

Moisture Sensitive Crystalline Product

Category	Process Parameter	Severity S (1-5)	Occurrence O (1-5)	Detection D (1-5)	Risk priority number S*O*D	Criticality rank
Crystallizn	Residual solvent	5	4	3	60	1
	Induction time	4	3	2	24	6
	Anti-solvent addition time	5	3	2	30	4
	Mixing	2	2	1	4	11
Isolation/ drying	Temperature during crystal drying	4	4	2	32	3
	Solids transfers	3	1	1	1	13
	Washing effectiveness	2	1	1	2	15
Handling/ storage	Relative humidity	5	3	3	45	2
	Inerting	4	2	3	24	6

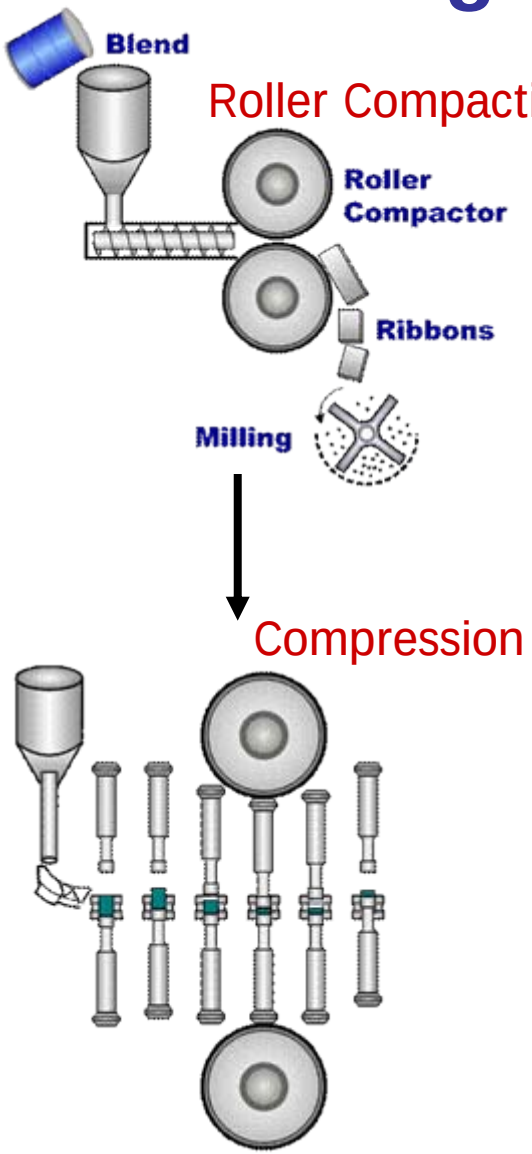
CFD Model to determine criticality of process parameters



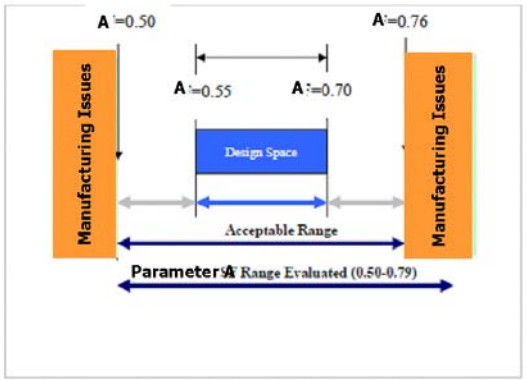
Tools - Process Understanding

- First-principles approach
  - combination of experimental data and mechanistic knowledge of chemistry, physics, and engineering to model and predict performance
- Non-mechanistic/empirical approach
  - Statistically designed experiments (DOEs)
  - Linear and multiple-linear regression
- Scale-up correlations
  - a semi-empirical approach to translate operating conditions between different scales or pieces of equipment
- Risk Analysis
  - Determine significance of effects
- Any combination of the above

Defining Design Space – DOE-Based



1. Identify attributes to be monitored via DOEs, includes relevant CQA
2. Screening DOE for roller compaction – Resolution: Level III
3. Analyze DOE data
4. Identify significant parameters and acceptable ranges
5. Full factorial DOE including roller compaction significant parameters and compression parameters – Resolution Level IV or higher
6. Analyze DOE data and define Design Space



A: Ribbon solid fraction
Scale independent parameter

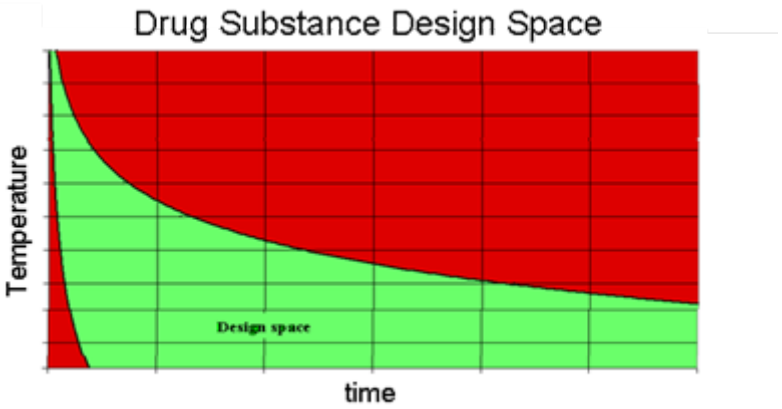
Communication of Design Spaces - Examples

Example 1: Linear Ranges

Design Space for Film Coating

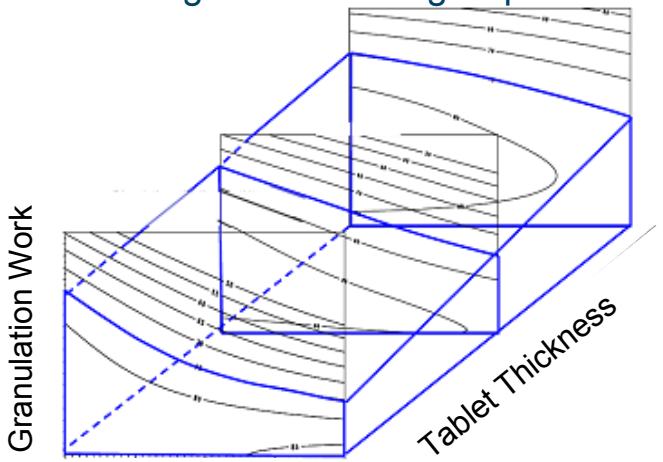
Parameter	Design Space
Pan Load Size	xx - xx kg
Final Spray Rate Set Point	xx – xx mL/min
Inlet Temperature Set Point	xx – xx °C
Outlet Temperature Set Point	xx – xx °C
Air Flow to Spray Rate Ratio Set Point	xx – xx (m3/hr)/ (mL/min)
Final Drum Speed Set Point	xx –xx rpm
Target Core Tablet Weight Gain	Minimum x% prior to drying/cooldown
Cool Down Temperature	≤ xx °C

Example 2: 2-D Graphical



Example 3: 3-D Graphical

Drug Product Design Space



Tools - Process Control

- Process Monitoring and Control
  - On-line/In-line measurement
    (e.g. particle size measurement, moisture measurement in a fluid bed dryer, blend uniformity determination etc)
  - At-line measurement
    (e.g. NIR for tablet assay and content uniformity, NIR for identity testing)
  - MSPC (Multivariate Statistical Process Control) model for monitoring process 'health'
- Models as Surrogate for Traditional Release Tests
  - Regression model for dissolution
  - MSPC model as a surrogate for assay
- Elimination of some end-product testing
  - Core tablet disintegration in lieu of coated tablet dissolution
- Model based specifications

RTRT (Real Time Release Testing)

- Is a component of the Overall Control Strategy
- Relies on:
  - Strong product and process understanding
  - Comprehensive product monitoring and process control
  - Robust Quality System

A more modern approach to manufacturing and control

Benefits of RTRT

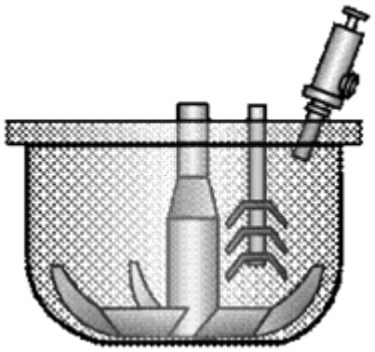
- Provides for increased assurance of quality
- Provides increased manufacturing flexibility and efficiency
  - Shorter cycle time
  - Reduced inventory
  - Reduction in end product testing
  - Reduction in manufacturing cost
- Allows leveraging of enhanced process understanding
  - Corrective actions may be implemented in real time

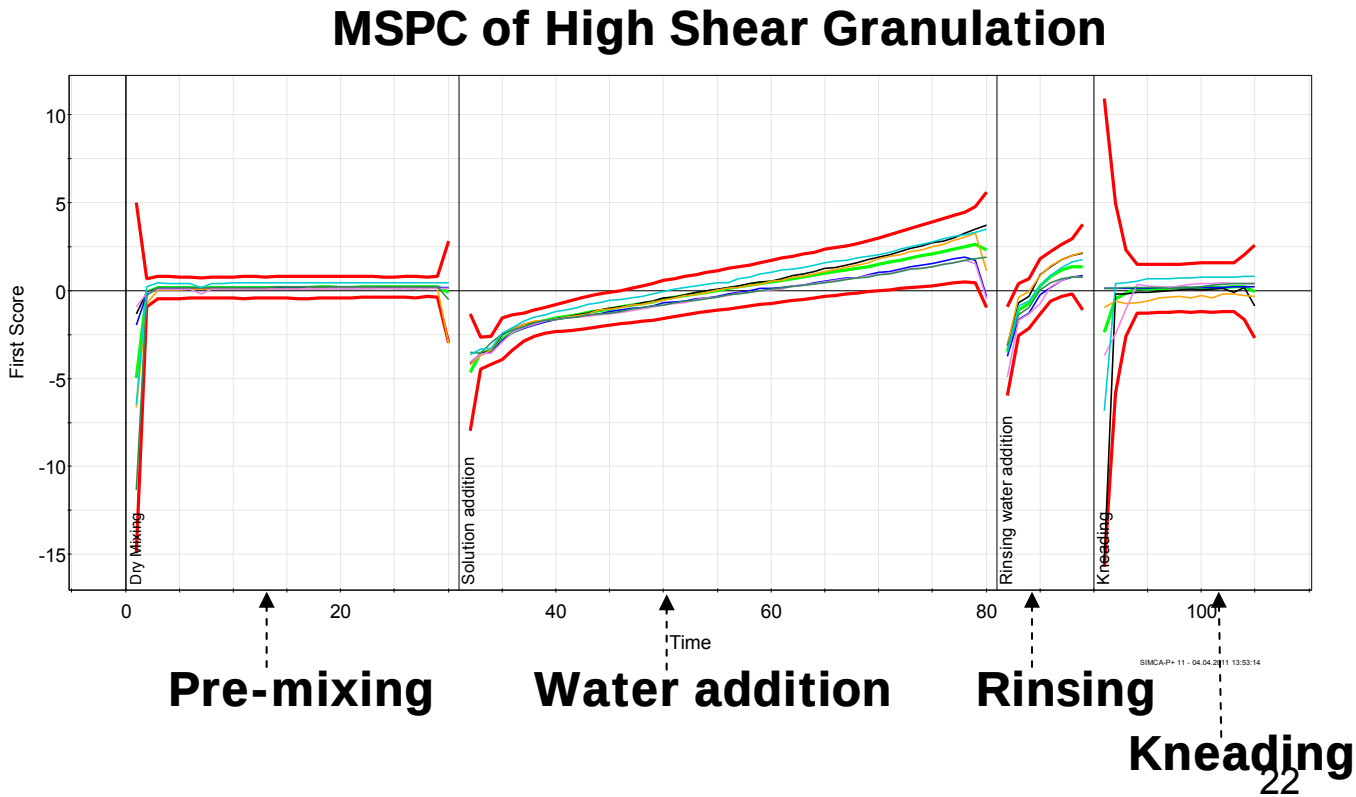
PAT & RTRT Approaches - Examples

- On-line or in-line measurements and/or controls, for example
  - Tablet weight after compression
  - Particle size measurement after granulation or milling
  - Moisture measurement during drying
  - Blend uniformity
- Fast at-line measurements, for example
  - NIR for tablet content
  - Disintegration in lieu of dissolution
- Models as surrogate for traditional release tests, for example
  - Multivariate model as a surrogate for dissolution
- Process signatures

Example: MSPC for High Shear Granulation

Aim of MSPC model is to understand current state of the process and 'flag' deviations





NIR Methods

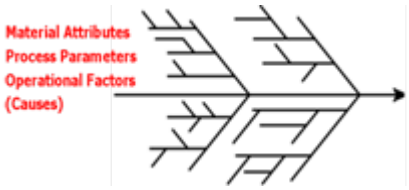
- Many applications submitted for blending and assay/content uniformity
  - High impact on product quality
    - Sole indicators of product quality e.g. NIR as an implement of RTRT
  - Low impact on product quality
    - For information only, method development purposes
- Data requirement for NIR information in submission should be commensurate with impact on product quality

Non-Traditional Implementation of the QbD Paradigm

Example: Analytical Methods

Identify "**ATP**" (Analytical Target Profile) e.g. in terms of accuracy, precision

Select Suitable Analytical Method



Risk Assessment

ATP

Continuous Improvement

Design Space for Analytical Method

Factors Affecting Method Performance

e.g. Column type, temperature, pH etc for HPLC

Analytical Method Implementation

Example – Container Closure (CC)

Drug product moisture content: A CQA
- Limit set for maximal moisture content in finished product

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Mechanistic model to determine moisture protection capacity of CC
- MVTR (Moisture Vapor Transmission Rate) model
  - Mass Transfer based

↓

Design Space in terms of maximum MVTR value
- Ensures moisture content remains below acceptable limit at the end of shelf life

Example of Design Space Analysis for Tablet Packaging Components

Container Closure System	Packaging Component	Measured MVTR Value @25˚C/60%RH	Design Space in terms of Calculated MVTR Value*
Bulk	Foil Laminated Bag	0.07 g/day	NMT 4.12 g/day
2-Count Blister	Blister Film	0.02 mg/day	NMT 0.34 mg/day

* Predicted from MVTR model, assuming a 2 year shelf life
Note: Actual numbers not shown

Reviewers on Inspection

- Reviewers have always had an opportunity to participate in inspections
- Traditionally, few NDA PAIs have reviewer participation
  - Certain review groups in FDA have a higher frequency of reviewer participation (OBP, CBER)
- In ONDQA, the frequency of reviewers participating in inspections has recently increased
  - More complex regulatory approaches (QbD)
  - Increased emphasis on shared knowledge and expertise

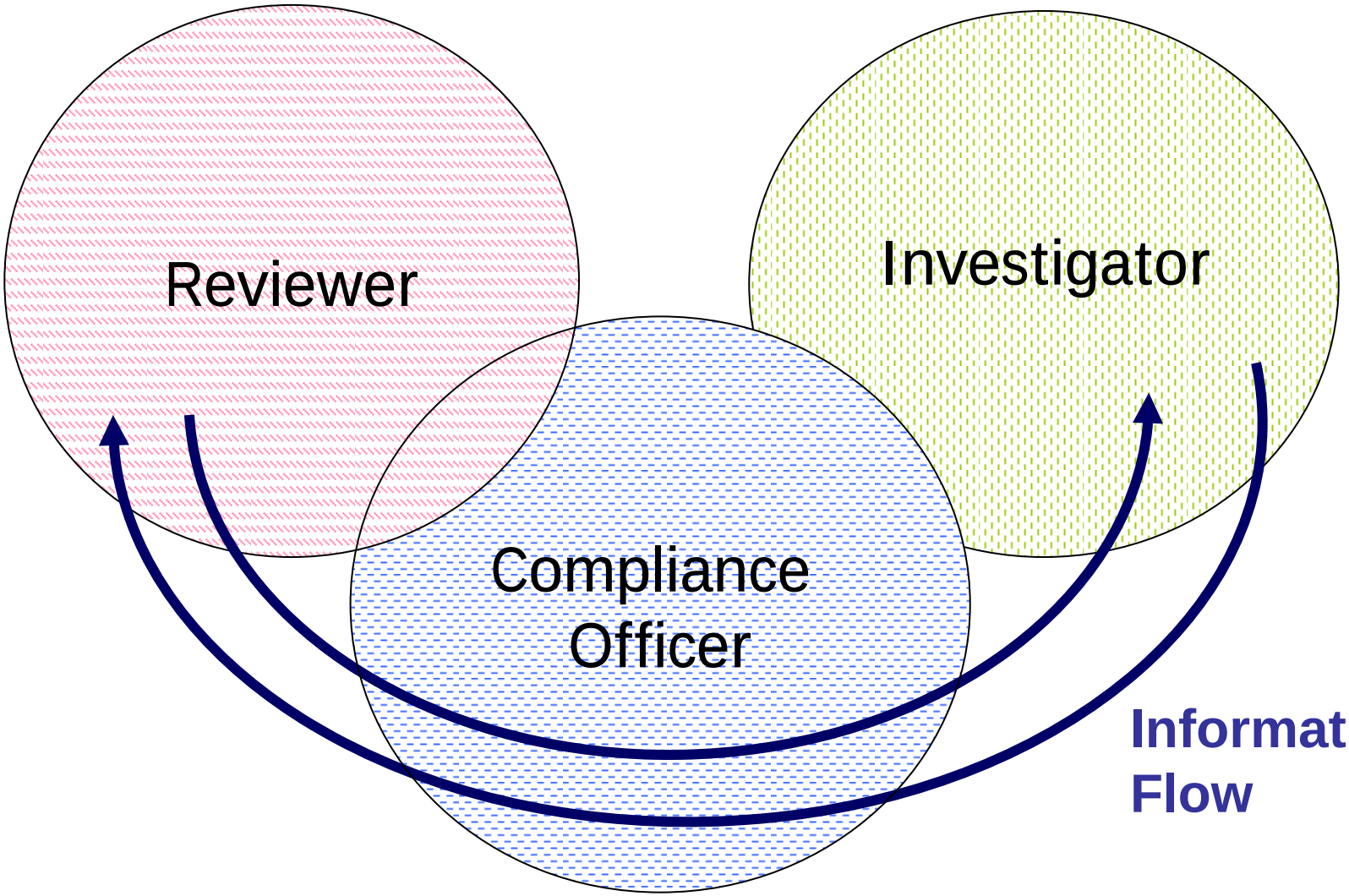
Reviewer on Inspection: Value Added

- Value to Reviewer
  - Increased understanding of the process and product
  - Help resolve certain review issues related to application
  - Understand scale-up and process control rationale
  - Understand implementation of on-line monitoring systems and related models

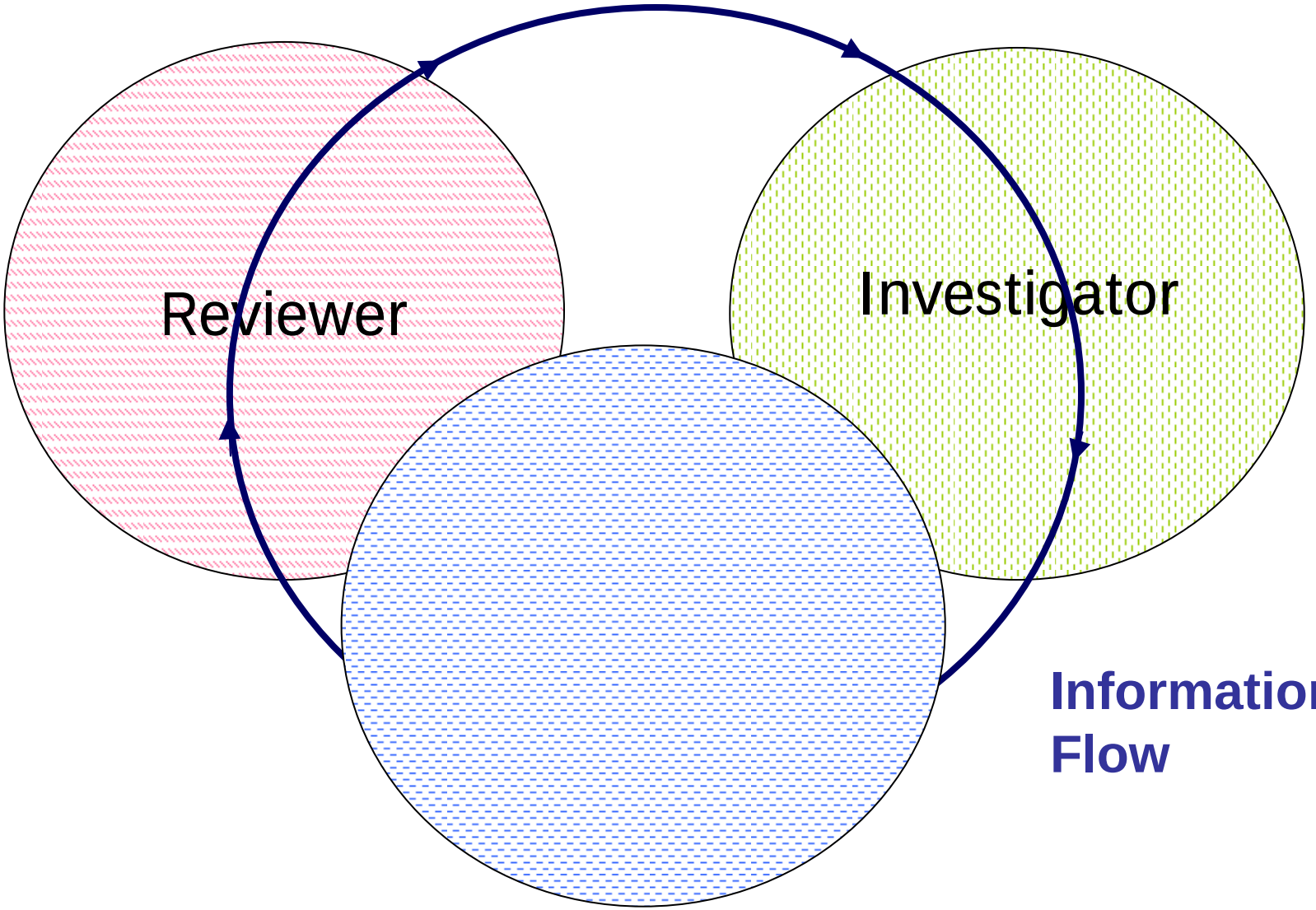
Reviewer on Inspection: Value Added

- Value to Team
  - Reviewer provides specific areas of expertise and intimate knowledge of application
  - In-depth discussion and exchange of ideas based on expertise
  - More productive inspection
  - Superior understanding of product quality assurance for inspection team
  - Increased understanding and appreciation of other divisions' roles and responsibilities

Traditional Model



Integrated Approach



Information Flow

Conclusions

- Much progress has been made applying modern manufacturing principles to pharmaceuticals
  - Guidance is in place to facilitate
  - Critical regulatory experience has been obtained
  - Many more advances and applications expected in the near future
- Team-based approaches successfully utilized
  - Approaches are being extended beyond QbD applications

Conclusions

- Discussion ongoing regarding:
  - Level of detail needed to support implementation of proposed regulatory flexibility
  - Knowledge about Applicants' Quality Systems for post approval change management
    - Enhanced interaction between review and inspection
  - Defining metrics for setting clinically relevant specifications
  - Clarification of regulatory expectation for implementing enhanced QbD elements e.g. continuous manufacturing, RTRT

Thank You!