QbD Considerations for Analytical Methods - FDA Perspective

IFPAC Annual Meeting
Baltimore, January 25, 2013

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Outline

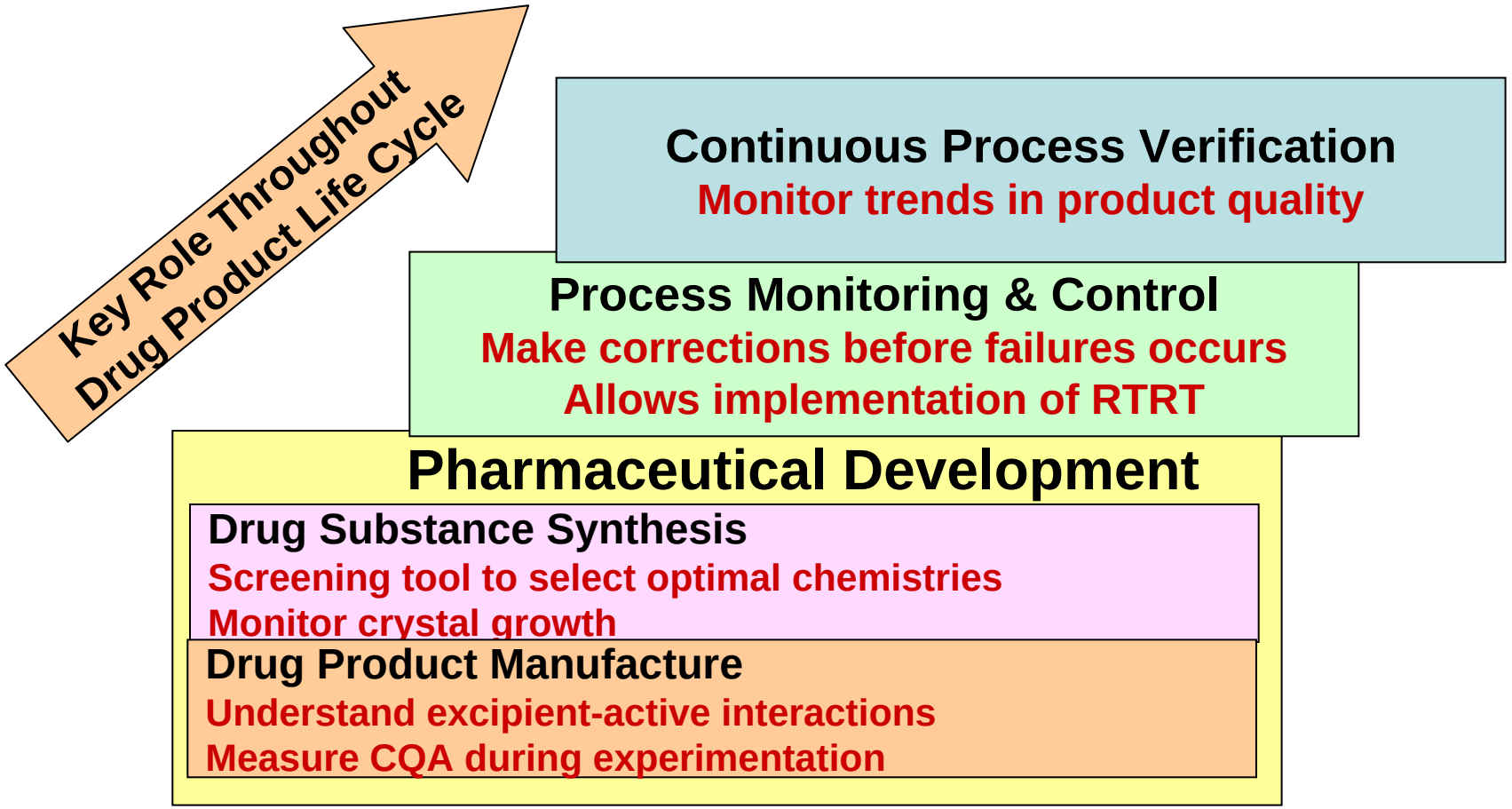
- Role of analytics in drug development
- QbD approach for analytical method development
  - Current status
  - Regulatory considerations
- Ongoing collaborative research
- Concluding remarks

Analytical Methods – A Key Part of Control Strategy

- Control Strategy (ICH Q10)
  - assures process performance and product quality
  - includes parameters and attributes related to drug substance and drug product materials
  - includes components, facility and equipment operating conditions
  - includes in-process controls, finished product specification, and the associated methods and frequency of monitoring and control

Right Analytics at the Right Time

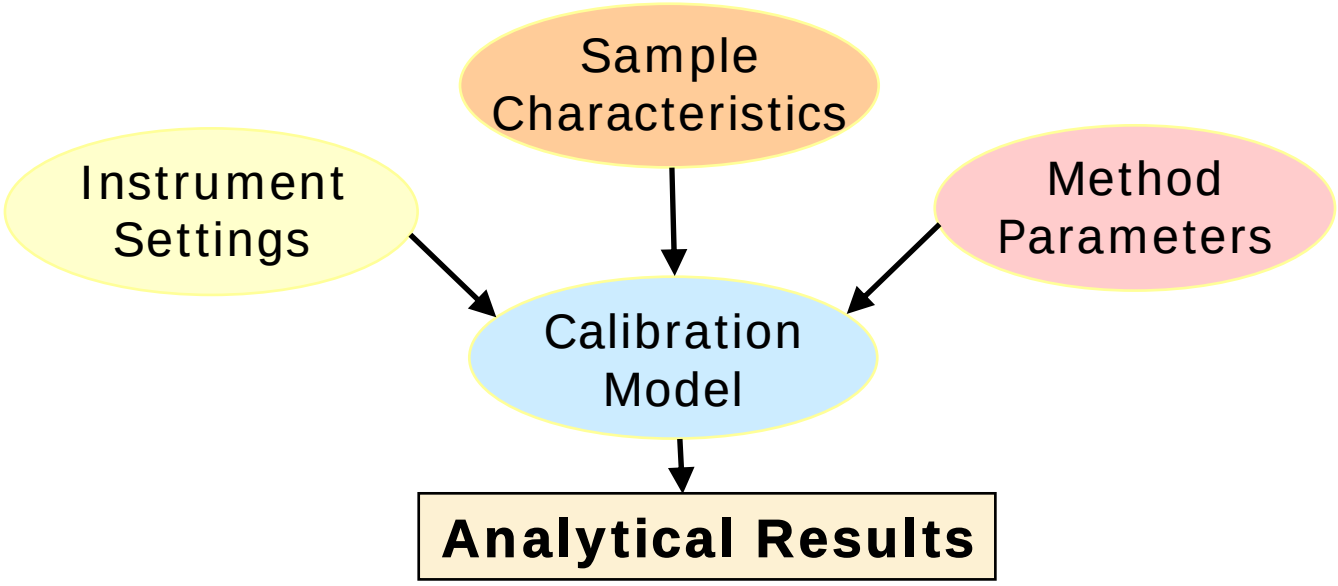
Role of Analytics in Drug Development



Variations in an Analytical Method

Many Factors can affect analytical results.

e.g. variations in instrument, sample, method, choice of model



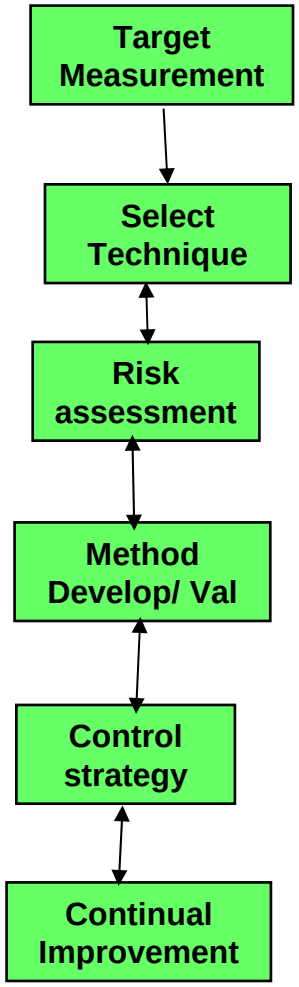
Benefits of Application of QbD Approach to Analytical Methods

- Development of a **robust** method
- Understand, reduce and control sources of variability
- Applicable throughout the life cycle of the method
- Regulatory flexibility
  - Movements within “Analytical Design Space” are not considered a change in method

ICH Q8(R2) and Analytical Methods

- ICHQ8(R2) doesn't explicitly discuss analytical method development.
- However, concepts apply:
  - Application of Science and Risk based methodology
  - Systematic approach that includes: risk assessment, defining a design space, control strategy and continual improvement to increases method robustness and understanding

QbD Approach for Analytical Methods



Determine what to measure and where/when to measure it. Develop measurement requirements based on product QTPP and CQA.

Select appropriate analytical technique for desired measurement. Define method performance criteria.

Assess risks of method operating parameters and sample variation. Can use risk assessment tools (e.g. FMEA)

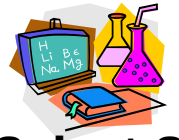
Examine potential multivariate interactions (DoE and design space). Understand method robustness and ruggedness

Define control space and system suitability, meet method performance criteria

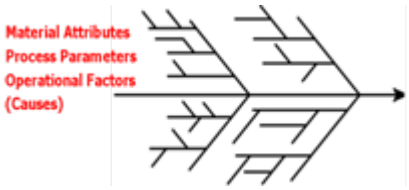
Monitor method performance; update as needed as process and analytical technology evolves

Example of QbD Approach

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

Current Status

- FDA has approved some NDA applications applying QbD approach to analytical methods (e.g. HPLC and UV)
- Regulatory flexibility has been granted for movements within the defined analytical method design space/ “MODR” (Method Operable Design Region)

Parallel's with Drug Product Development

Product QbD (Q8(R2))		Analytical QbD (example terminology)
QTPP	⟷	ATP (Analytical Target Profile)
Design Space	⟷	MODR (Method Operable Design Region)

Analytical Target Profile (ATP)

What is ATP?

- Prospective summary of measurement requirements that ensure that the method is 'fit for purpose'

- Not linked to any particular method
  - More than one technique can satisfy a single ATP

Regulatory Considerations for Implementing ATP

- Not all methods with same ATP are inter-changeable without prior regulatory communication

  - E.g. from HPLC to NIR

- Can use comparability protocols

Analytical Method "Design Space"/ "MODR"

- A science and risk based and multivariate approach to evaluate effects of various method input variables on method performance
- Typically DoE (Design of Experiment) is used to find ranges for instrument operating parameters, to understand sample preparation variations and variations of method precision.
- Method performance criteria are response factors
- Can be conducted together with method validation

Considerations for Implementing MODR

- Availability of adequate data to support proposed design space/MODR
  - Includes variation in raw materials, sites, analysts
  - Appropriately chosen experimental protocol
  - Statistical confidence shown throughout the MODR
- Assess validation requirements identified in ICH Q2(R1) (e.g. specificity, accuracy, precision, robustness, linearity, LOQ/LOD) across MODR
- Confirm system suitability throughout MODR

Laboratory Considerations for Verification of MODR

- Determine that the method meets the acceptance criteria across the MODR
  - Begin with the applicant's model
  - Appropriate selection of experiments to evaluate MODR
- Comparison with applicants results
- Part of FDA's Laboratory Methods Validation Program

FDA-EMA Collaborative Research on QbD for Analytical Methods

- Joint research with FDA's laboratory/review divisions and EMA
  - Initiated in January, 2013
- Goal of this project is to:
  - Develop analytical methods (e.g. HPLC) based on QbD paradigm
  - Define protocols for method transfer
  - Establish methodology for validation of MODR upon site transfer
  - Define review criteria for evaluation of QbD based analytical methods

FDA-EMA Harmonization

- Areas of harmonization so far
  - Considerations for defining and implementing ATP
  - Data requirements to support a MODR

- Elements that warrant harmonization
  - Level of detail in regulatory filings regarding MODR
  - Methods for regulatory communication of verification and maintenance of MODR

Concluding Remarks

- Analytics play a key role in the implementation of QbD
- QbD can offer more flexibility for analytical methods, but requires
  - High degree of process, product and analytical method understanding
  - Robust quality systems
- Applicants are encouraged to discuss novel QbD implementation approaches with FDA prior to submission

Acknowledgments

Christine Moore, ONDQA, FDA

Cindy Buhse, DPA, OTR, FDA

John Kauffman, DPA, OTR, FDA

Yubing Tang, ONDQA, FDA

Robert Lu, ONDQA, FDA

Thank you!

Questions, comments, concerns:

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