Life Cycle Management of Analytical Methods

Saji Thomas, Director
Quality Control Operations

PAR PHARMACEUTICAL
an endo international company

Outline

- The principal
- Procedure
- The road map/ process map
- Trend Analysis
- Recommendations

References

- Guidance for the industry:- Analytical procedures and methods validation for drugs and biologics.
- USP stimuli article on LCM of analytical procedures.
- USP proposal in PF42(2)
- FDA presentation on application of QbD to Analytical methods

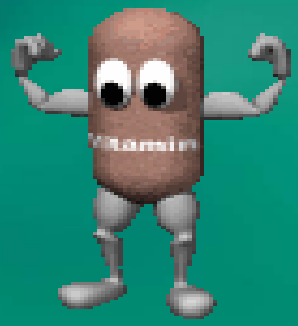
THE TRUTH

All analytical measurements are wrong; it's just a matter of how large the errors are, and whether they are acceptable.

Mike Thompson, Imperial College, London

Analytical Method- The Truth

- Analytical method is no longer an isolated entity; It’s living across the life cycle of the product/process within the Quality Management System



Method and Life Cycle of the Product

Key Role Throughout Drug Product Life Cycle

Continuous Process Verification
Monitor trends in product quality

Process Monitoring & Control
Make corrections before failures occurs
Allows implementation of RTRT

Pharmaceutical Development

Drug Substance Synthesis
Screening tool to select optimal chemistries
Monitor crystal growth

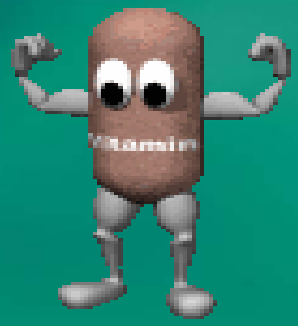
Drug Product Manufacture
Understand excipient-active interactions
Measure CQA during experimentation

The Procedure Road Map

Target Measurement	Determine what to measure and where/when to measure it. Develop measurement requirements based on product QTPP and CQA.
Select Technique	Select appropriate analytical technique for desired measurement. Define method performance criteria.
Risk assessment	Assess risks of method operating parameters and sample variation. Can use risk assessment tools (e.g. FMEA)
Method Develop/ Val	Examine potential multivariate interactions (DoE and design space). Understand method robustness and ruggedness
Control strategy	Define control space and system suitability, meet method performance criteria
Continual Improvement	Monitor method performance; update as needed as process and analytical technology evolves

Analytical Method- The Process Map

- Method development
- Method Understanding
- Control strategy
- Method assessment
- Continuous improvement
- Documentation



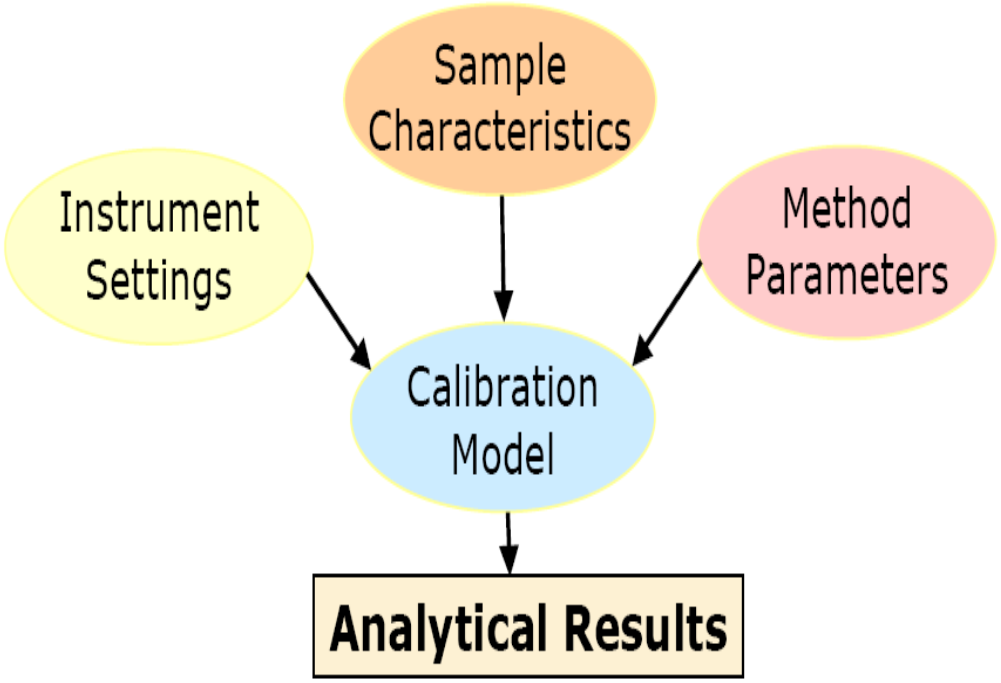
Method Development- QbD approach

- Application of a science and risk based methodology
- A systemic approach that includes
  - Risk assessment, defining design space, control strategy, continual improvement
- Understand, reduce, and control source of variability
- Applicable throughout the life cycle of the method
- Regulatory Flexibility
  - Movement within the Analytical design space is not considered a change in the method.

Method Variables

Many Factors can affect analytical results.

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



Design Space- Robustness

The goal is to determine the method operable design region (MODR)

- A science, risk based and multivariate approach to evaluate effects of various input variables on method performance
- Typically DOE is used
  - Range of instrument operating parameters
  - Sample preparation variations.
  - Method precision variations.
  - Method performance criteria becomes the response and the range your input variable
- Ideally performed as part of method development

DoE Experiments

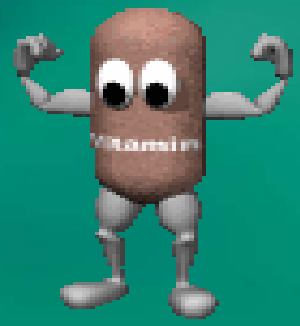
- A well conducted DoE experiment can help in understanding
  - Understanding method variability
  - Control strategy
- Method operable design region for
  - Flow rate
  - Column temp
  - Mobile phase composition
- Quantitation external std vs RRF
- RRT range for impurities
- System suitability parameters for assessing the method performance or fit for use

Life Cycle Management- FDA

- Once an analytical procedure (including compendial methods) is successfully validated and implemented, the procedure will be followed during the life cycle of the product. **Trend analysis on method performance should be performed at regular intervals** to evaluate the need to optimize the analytical procedure or to revalidate all or a part of the analytical procedure.

Trend Analysis

- System suitability failures
- Repeated method adjustment to meet suitability requirements
- Stability trending
  - Product related or method related
- Finished product result
  - Process relate/method related
- Method change control history

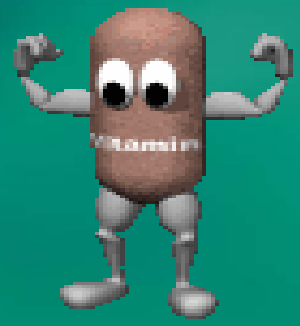


Trend Analysis- Commercial Products

- Review the APR for any variability in results
- A higher degree of variability suggests Issue with process or method.
- Gain understanding of potential source of variability.
- If related to method, plan on remediation after the risk to business/compliance is fully understood.
- Open a CAPA and complete the remediation plan.

Periodic Assessment of Methods

- Retention samples
- Stressed samples
- Method transfer failures
- Stability T0/last time point samples can be used to assess the accuracy/precision of the method.



Continuous Improvement

- Throughout the procedure's lifecycle, changes may be required to improve the operational performance or the control strategy
  - inclusion of an additional control
  - changing the intended purpose to incorporate a new impurity or
  - tighten specifications
  - or alignment with a procedure in a compendial monograph that has been updated.
  - The nature of the change dictates the action that should be taken,
  - a risk assessment should be performed to identify what action is required,

Revalidation

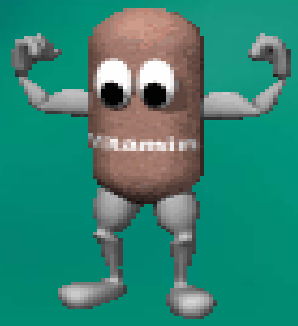
The degree of revalidation depends on the nature of the change.

- drug substance (e.g., route of synthesis)
- drug product (e.g., composition)
- Detection of new degradation product
- When a different regulatory analytical procedure is substituted (e.g., HPLC for titration)

- Moving to a new technology (HPLC to UPLC)

Analytical Methods

- USP FP methods
  - Predominantly used by Generics
- USP API methods
  - Predominantly used by generics
- USP Excipients methods
  - Used by both Brand and generics
- NON-USP methods.
  - This would include API and FP methods predominantly used by the Brand

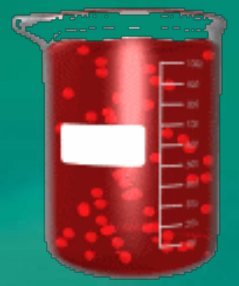


What is the scope of LCM???

- Is the scope limited to FP methods only?
- Not clearly defined in the FDA guidance
- The retention sample to be used for LCM assessment
- Marketed products / clinical trial material.
- USP procedure is silent on reserve samples but talks about all the compendial methods.

Challenges

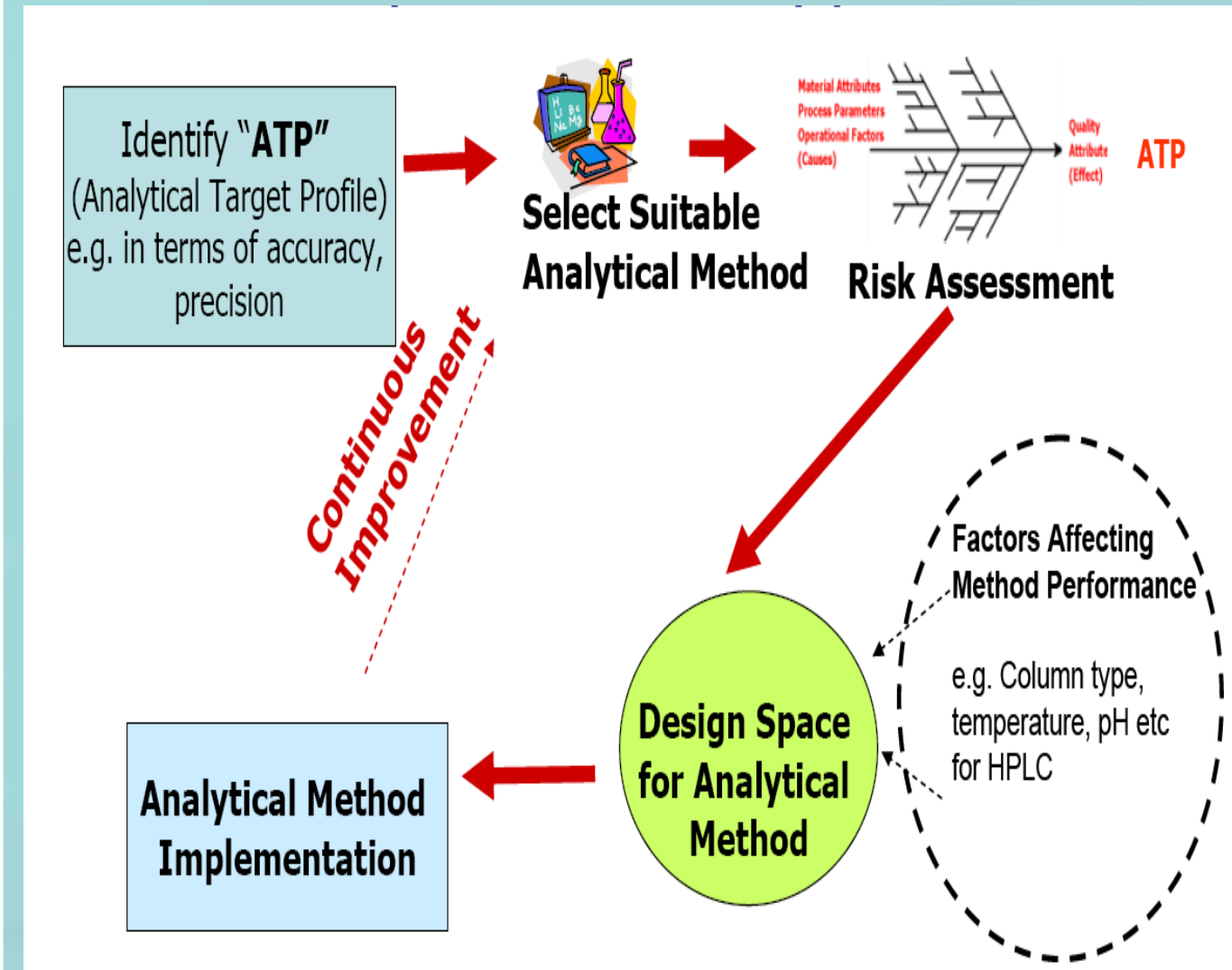
- Resources
- Lack of talents in QC lab.
- Routine trend analysis
- Routine review of the performance of the method.
- Identifying new technology and converting legacy method to new and improved technology



SUMMARY

- LCM starts in R&D Lab
  - by developing a Robust analytical method
  - Identify and control the variables
  - Development report for analytical methods
- Assessment of the method done on a routine basis in QC environment
  - Trend analysis
  - Managing OOS results
  - Challenging the validation parameters on a routine basis
  - Updating the development report as the methods are revised.

Summary


Identify "ATP" (Analytical Target Profile) e.g. in terms of accuracy, precision
Select Suitable Analytical Method
Material Attributes
Process Parameters
Operational Factors
(Causes)
Quality Attribute (Effect)
ATP
Risk Assessment
Continuous Improvement
Factors Affecting Method Performance
e.g. Column type, temperature, pH etc for HPLC
Design Space for Analytical Method
Analytical Method Implementation

SUMMARY

Uncontrolled variation is the enemy of quality.

W. Edwards Deming

QUESTIONS?