Life Cycle Management of Analytical Methods and It's Application to Dissolution Methods

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Outline

- The principal
- Procedure
- DOE and robustness
- Trend Analysis
- Challenges
- Application of LCM to dissolution methods
- Bulk Vs Continuous manufacturing
- Summary and Conclusion

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

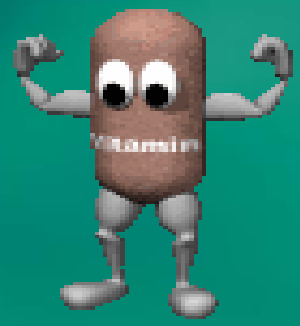
THE TRUTH

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

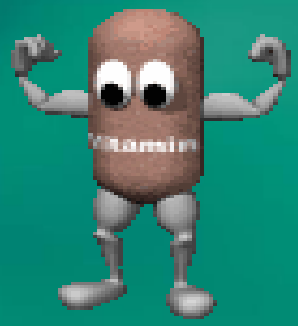
Analytical Method- The Truth

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



Analytical Method- Definition

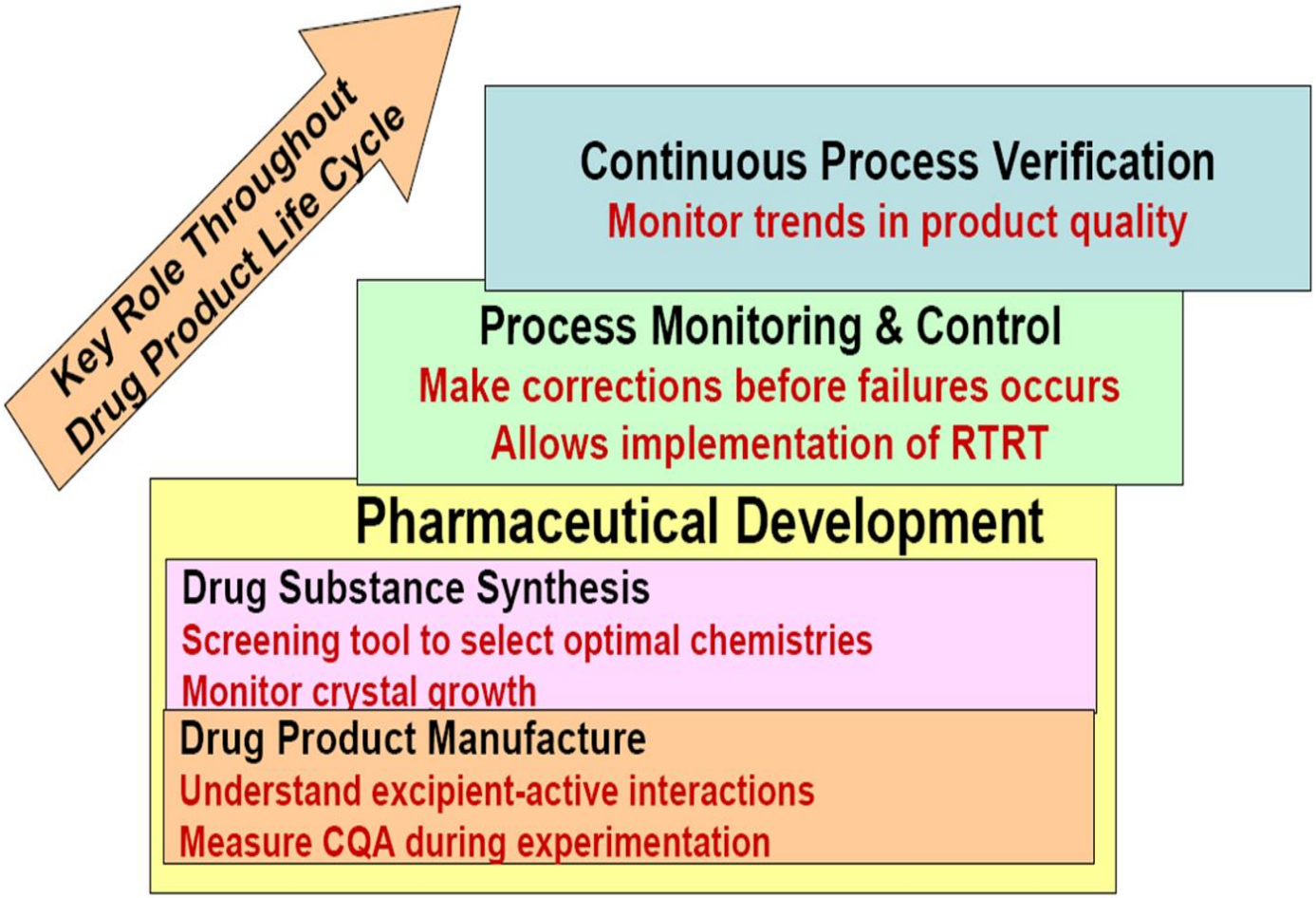
- A systemic process for the assessment, control, communication and review of risks to the quality of data across the product life cycle.
  - Release methods
  - Stability indicating methods
  - ID methods
  - Limit test



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.

Method and Life Cycle of the Product



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

LCM approach

- LCM adds the following elements to Traditional Method validation.
  - Identification of ATP
  - QbD elements to enhance method understanding
  - Expanded qualification process
  - Change control process to update the methods
  - Continued method verification

What is ATP???

- The ATP is a prospective summary of the objectives of a test and defines the quality requirements, including the expected level of confidence, for the reportable result that will allow the correct conclusion to be drawn regarding the attribute of the material that is being measured.

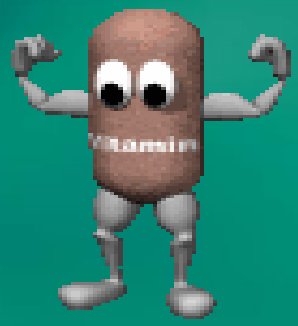
ATP-Dissolution method

ATP	Criteria
Accuracy	95-105% of the specification
Precision	2% RSD for repeatability. NMT 10% at time points with <85% dissolved and NMT 5% for time points >85% for ruggedness and reproducibility
Linearity and range	50% to 150% of Nom: conc. a square of the correlation coefficient (r2 ≥ 0.98) demonstrates linearity. In addition, the y-intercept must not be importantly different from zero
specificity	Interference from blank<1% and from placebo <2%
Robustness	The parameters to include buffer or surfactant concentration, pH, deaeration, volume, agitation rate, sampling time, and temperature
IVIVC	Level A correlation

Now need to develop and validate an analytical method that meets ATP

Analytical Method- The Process Map

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

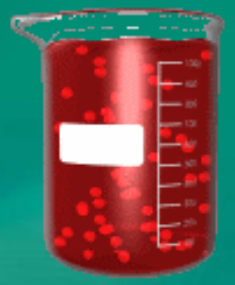


Method Development- QbD approach

- 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.

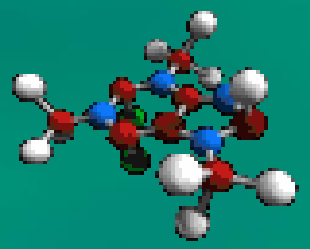
Variability is the enemy

- All processes are affected by various sources of variations over time. Products which are designed based on optimal settings, will, in reality, tend to drift away from their ideal settings with time.
- The most efficient and cost effective solution to that issue is to minimize the impact of these variations on your product's performance.
- Even though variations in the inputs will continue to occur, the amount of variability that will still be "transmitted" to the final output may be reduced
- The major sources of variations need to be identified in order to study the way in which this variability "propagates" into the system.
- The ultimate objective is to reduce the amount of variability (from the inputs) that affects your final system.



Identifying Variables

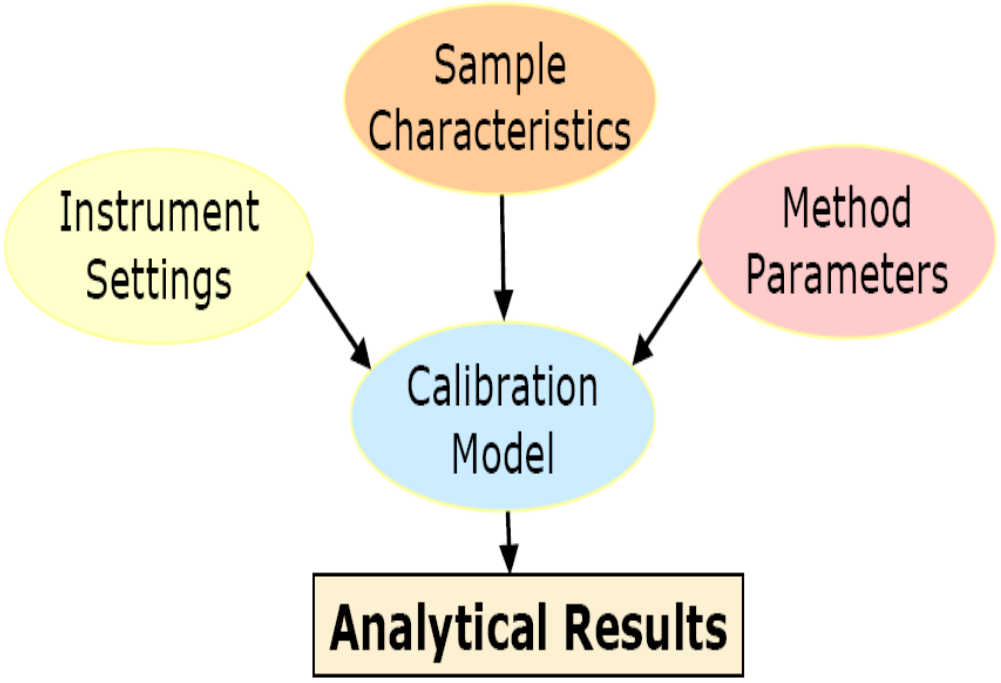
- Process mapping tools
- Fish bone diagram
- Prior Knowledge
- Risk assessment tools (ICH Q9)



Method Variables

Many Factors can affect analytical results.

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



Identification of Variables

- Source of variability are
  - Material
  - Method
  - Men
  - Mother Nature(Environment)
  - Machine
  - Measurement
- Control, Noise, experiment (CNX) approach
  - Classify the variables as C, N or X
  - Based on prior knowledge
  - Assessment of risk

Variables

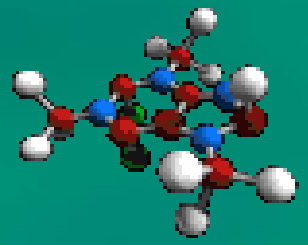
- Control
  - Analytical method factors which forms part of method definition which can be specified at controllable unique levels
  - Column type, HPLC , UV detector
- Noise
  - Variables that are too expensive or difficult to control eg environmental, routine conditions.
- Experiment
  - Variation that may occur when the experiment is carried out in different occasions

Typical source of Variability

- Column
- Chemist
- Sonicators
- Filters
- Grinding vs whole tablet assay
- Variability in Dead volume of HPLC
- Purity of solvents

Column Equivalency

- Silanol Activity
  - There are no standard method for measuring the accessibility of hydroxyl sites
- Retentivity
  - Carbon load is a useless information without the surface area information
- Metal activity
  - Presence of iron and other metals can cause peak tailing and reduce efficiency
- Shape selectivity
  - Function of synthetic procedure and bonding density



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

DOE- 7 Factors

- Full factorial design
  - 128 experiments
- One factor at a time 2 levels
  - 14 experiments
- Plackett-Burman Design
  - 7 factors by 8 experiments
  - Cost effective, efficient
  - 2 days
- Method and environmental factors don't influence the results
- Identify conditions that needs to be more controlled

Design of Experiments (DOE)

- DOE is the most logical, rational and scientific way of collecting data
- The most commonly used is Plackett-Burman design of 8 or 12 runs to evaluate 5 to 11 factors
- PB designs have 2 levels per factor
- Levels are varied in a very specific and symmetric way
- Effect of each factor can be estimated using all of the data collected

Five Factors/Eight Experiments

	A	B	C	D	E
1	-	+	-	-	-
2	-	-	+	+	-
3	+	+	+	-	-
4	+	-	+	-	+
5	-	+	-	-	+
6	+	+	-	+	-
7	-	-	+	+	+
8	+	-	-	+	+

Disso Failure- Case Study

- Dosage form
  - Once a day, encapsulated pellet
  - 4 strengths
  - The product did not meet the specification at the 8th hour at accelerated(40/75) at the 3months pull

Dissolution Method

- Dissolution method
  - USP SIF at pH 7.5 with 3g of NaCl per liter
  - Sample analysis by UV/FO
  - Sampling points- 1,2,4,8,18,22,24
  - Specification for 2,8,22
  - 8^{th} hour spec is 40-70%

DOE –Case Study

- Dependent Variable
  - Dissolution result at 8th hour
- Independent Variables
  - Bath Temperature
  - Paddle Speed
  - Salt Concentration in the Media
  - Wavelength
  - pH of the Media

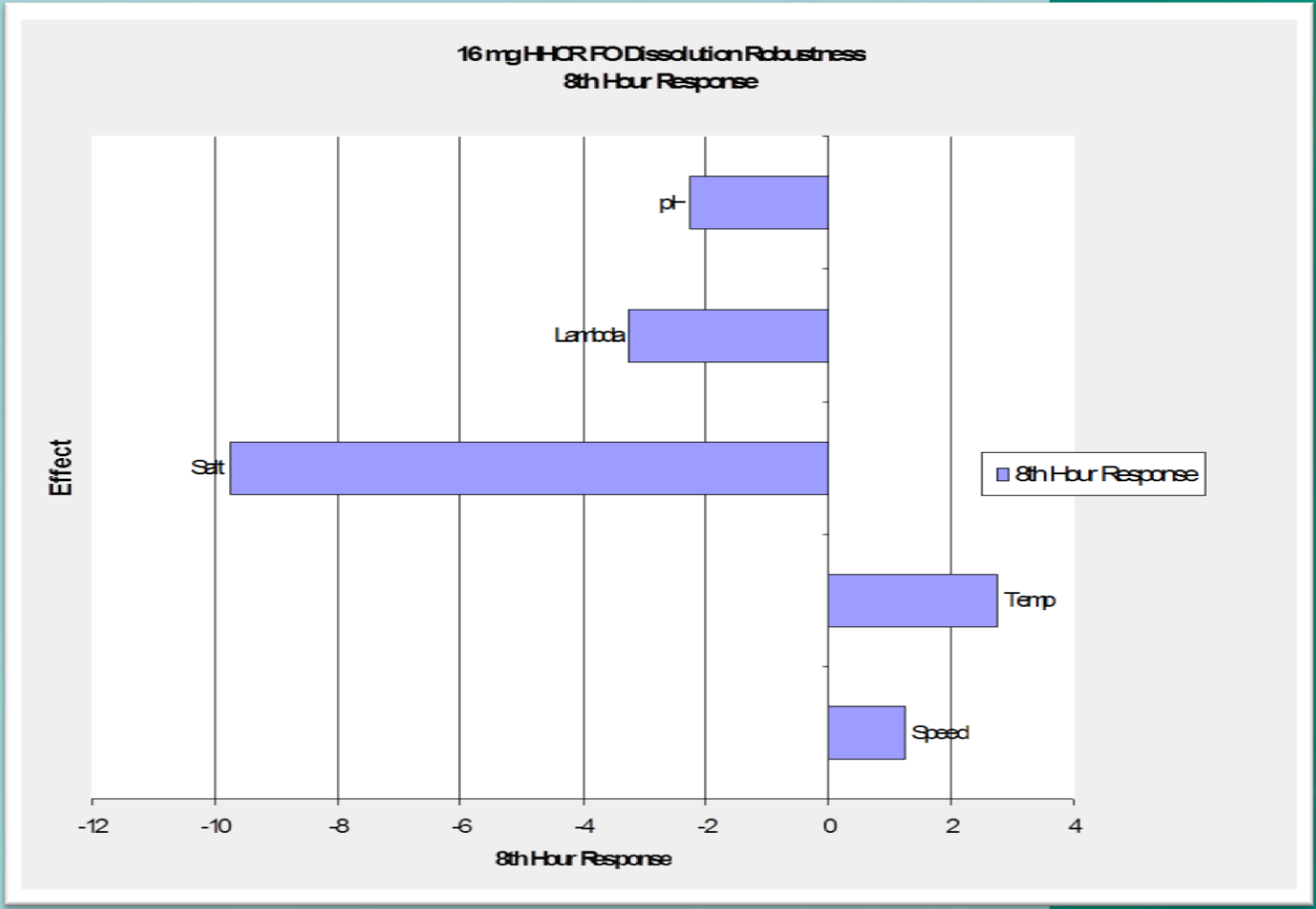
Plackett-Burman Design

Experimental Parameters	Values
Paddle Speed	100 ± 5 rpm
Bath Temperature	37 ± 5 °C
Salt Concentration in the Media	3 ± 0.5 g/L
Wavelength	278-300 ± 2 nm
pH of the Media	7.5 ± 0.2

Dissolution Results

Experiment No.	% Dissolved at Hour 8	Speed	Temp.	Salt	Lambda	pH
1	52	-	-	+	+	-
2	63	+	-	-	-	-
3	68	+	+	-	+	-
4	61	+	-	+	-	+
5	57	-	+	+	-	-
6	63	-	-	-	+	+
7	70	-	+	-	-	+
8	55	+	+	+	+	+
	Sum +	247	250	225	238	240
	Sum -	242	239	264	251	249
	Sum Total	489	489	489	489	489
	Difference	5	11	-39	-13	-9
	Effect	1.25	2.75	-9.75	-3.25	-2.25

Effect Diagram



Interpretation of Data- Normal Probability Plot

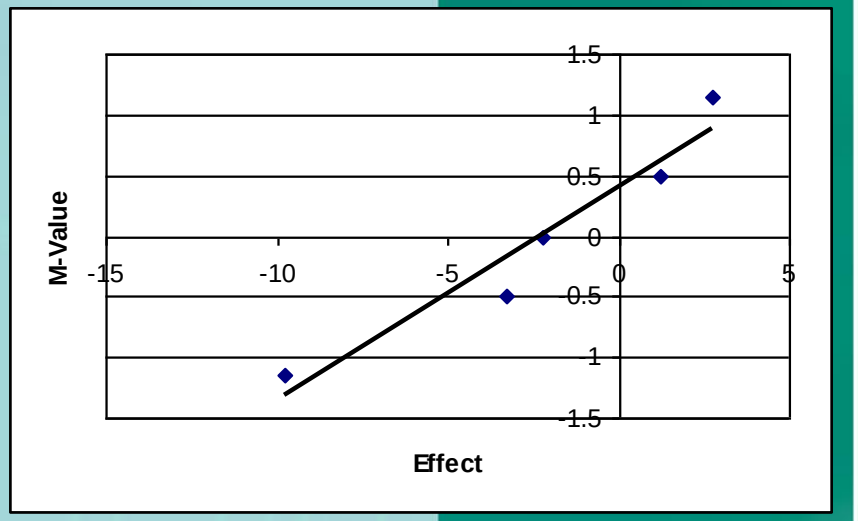
- Rank the effects from smallest to largest
- Draw the normal probability plot
- Plot the effect (X-axis) against M – Values (Y-axis)
- The method is rugged if
  - The plot gives a straight line
- Not rugged
  - One or more points at the end of the line does not lie on the line
  - The effects lying off the line should be investigated

Normal probability Plot- Assay

- Data

Salt Conc:	-9.75	-1.15
Wavelength	-3.25	-0.49
pH	-2.25	0
Paddle speed	1.25	0.49
Bath temp:	2.75	1.15

- Plot



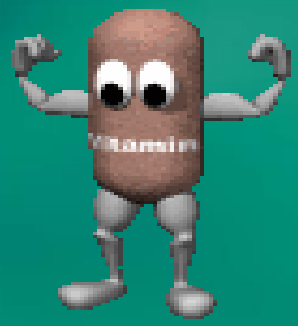
The method is very sensitive to chloride content

Conclusion- Robustness

- The chloride content of the dissolution media has to be controlled
- 370 mOsm/kg was set as the optimum level to control the ionic strength of media.

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

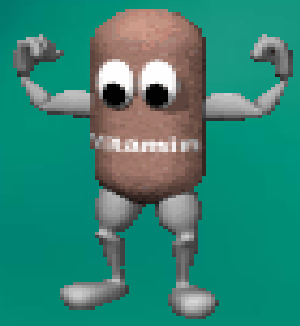


Trend Analysis- Commercial Products

- 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)

Dissolution Method

- The Goal
  - The ultimate goal is to understand the release mechanisms and determine whether the dissolution procedure can show change in the critical quality attributes of a drug product..
- Procedure
  - The dissolution procedure requires an apparatus, a dissolution medium, and test conditions that together provide a method that is sensitive to changes in critical quality attributes, yet sufficiently rugged and reproducible for day-to-day operation
- Variability
  - The ideal dissolution procedure will not contribute an unacceptable degree of variability and will provide a profile with adequate points below 85% dissolved

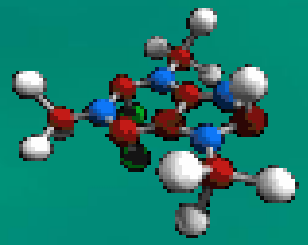
LCM & DISSOLUTION

Application of LCM to Dissolution

- Dissolution method is the surrogate test for bio-availability.
- Once a dissolution specification is set, the drug product should comply with that specification throughout its shelf life.
- If the dissolution characteristics of the drug product change with time, whether or not the specifications should be altered will depend on demonstrating bioequivalence
- Additional bio study involves risk in terms of failed bio study and its impact on an approved commercial product.
- For these reason pharmaceutical companies doesn’t venture into changing the dissolution method

Dissolution method

- The dissolution methods consist of 2 components, the first part is the dissolution of the dosage form in the associated media and the second part is the analysis of the solution
- The dissolution part cannot be changed except in the following case
  - A dissolution procedure originally approved can be changed to disintegration for a rapidly dissolving drug.
  - Particle size distribution testing may also be proposed in place of dissolution testing for oral solutions and parenterals when development studies demonstrate that particle size is the primary factor influencing dissolution



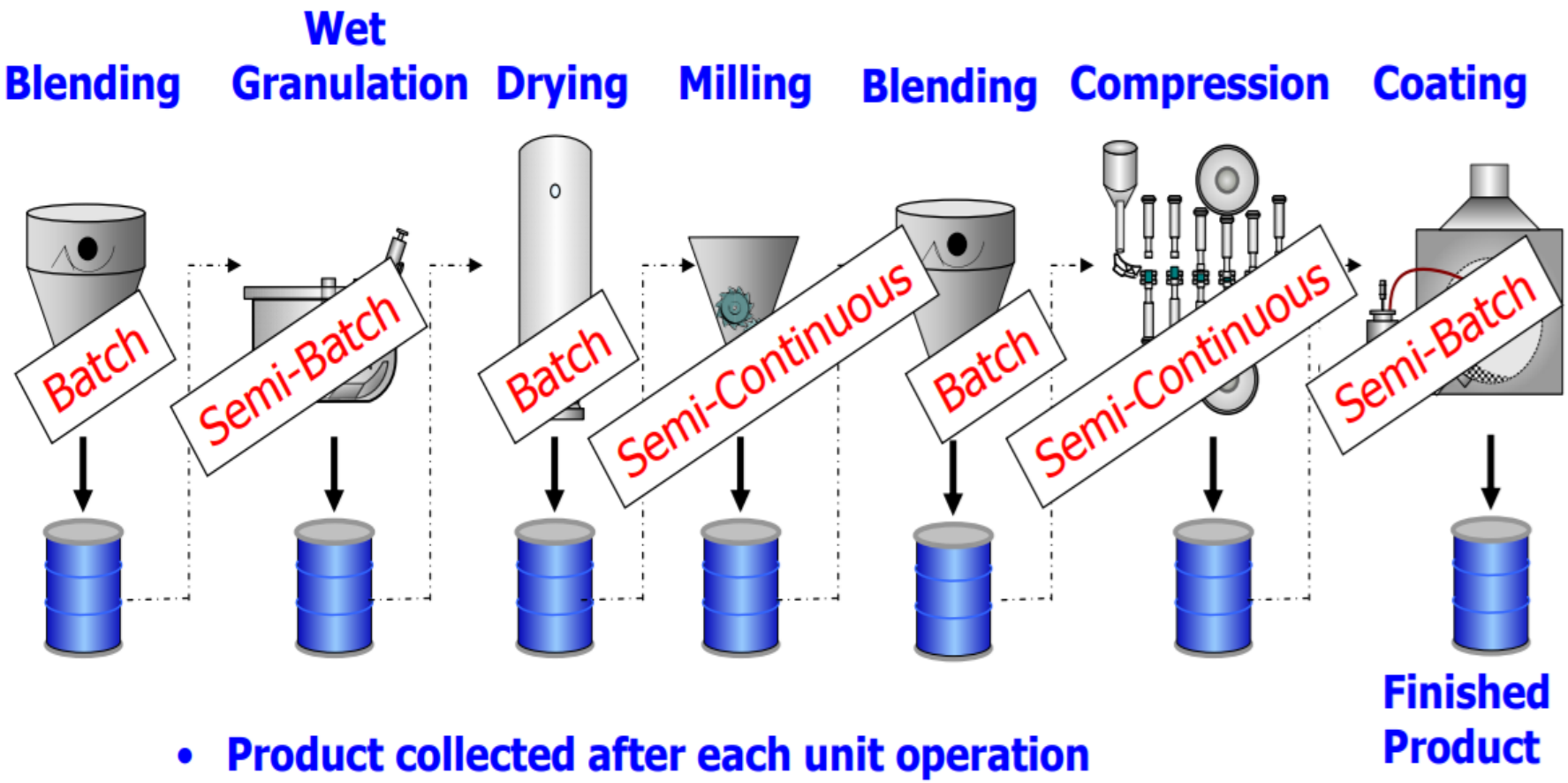
Continuous Improvement

- The analytical method associated with the dissolution method could be changed to make the method more robust/QC friendly
- The easiest switch to automation will be switch from a manual sampling to an on-line UV. Minimum validation is required for this change.
- Changing from a long run time HPLC analysis to a shorter UPLC method.

- Manual analysis to automated dissolution testers like ATMD system sold by Sotax. This system can be used to run 8 batches in 24 hours with fully automated washing , rinsing filling and full analysis of the samples using on line UV.

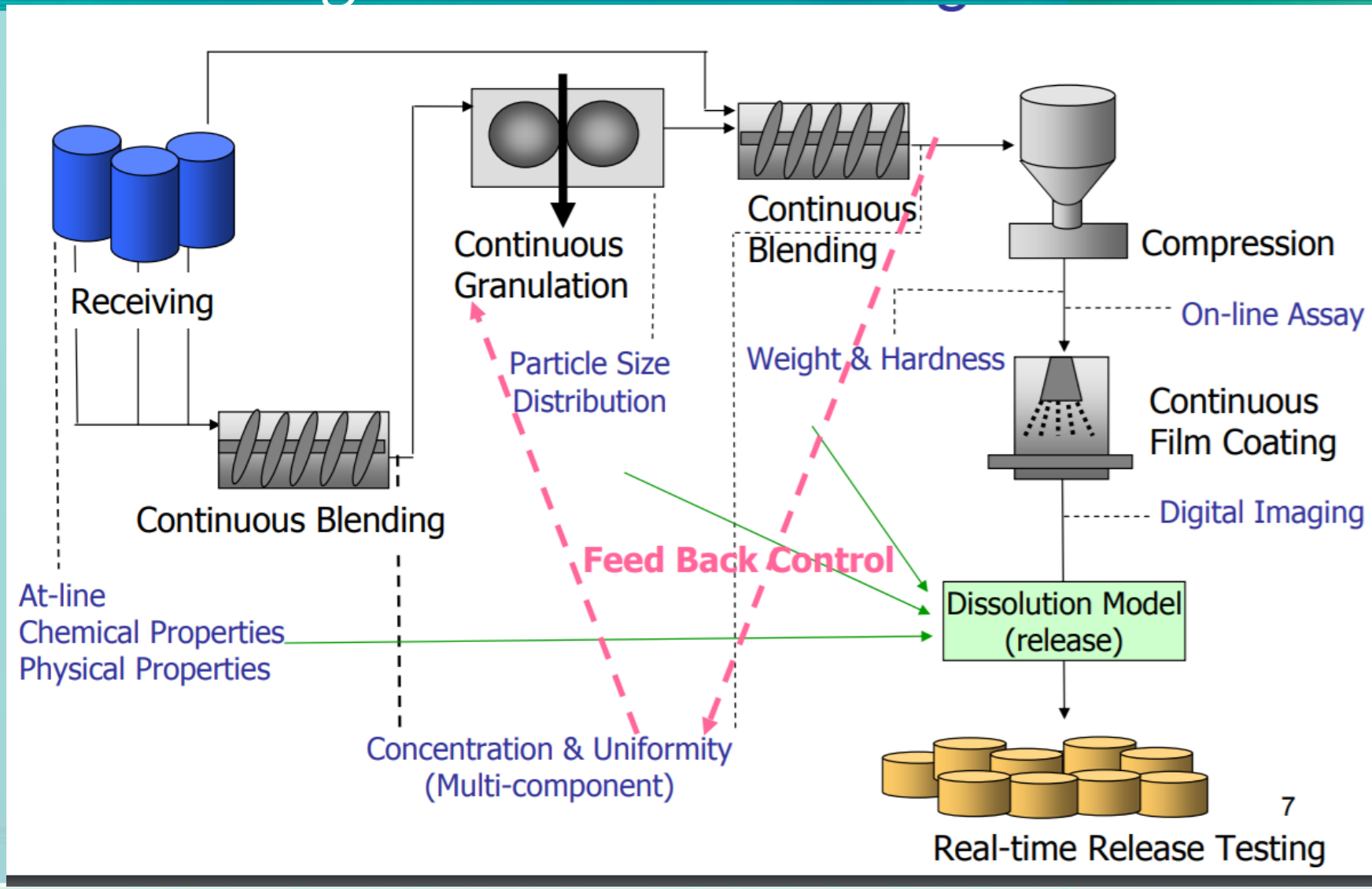
LCM&CONTINOUS MANUFACTURING

Traditional tablet Manufacturing process



- Product collected after each unit operation
- Finished product is tested at off-line laboratories, after processing is complete
- Actual processing time = days to weeks

Continuous manufaturing with on-line monitoring

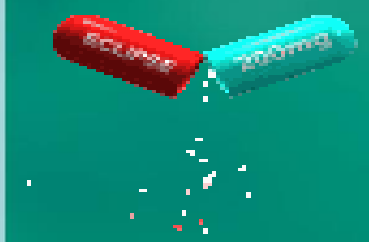


Advantage of Continuous Manufacturing

- Integrated processing with fewer steps
  - No manual handling, increased safety
  - Shorter processing times
  - Increased efficiency
- • Smaller equipment and facilities
  - More flexible operation
  - Reduced inventory
  - Lower capital costs, less work-in-progress materials
  - Smaller ecological footprint
- On-line monitoring and control for increased product quality assurance in real time
  - Amenable to Real Time Release Testing approaches
  - Consistent quality
- Potential for reduced cost

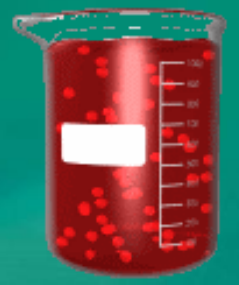
SUMMARY

- 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.

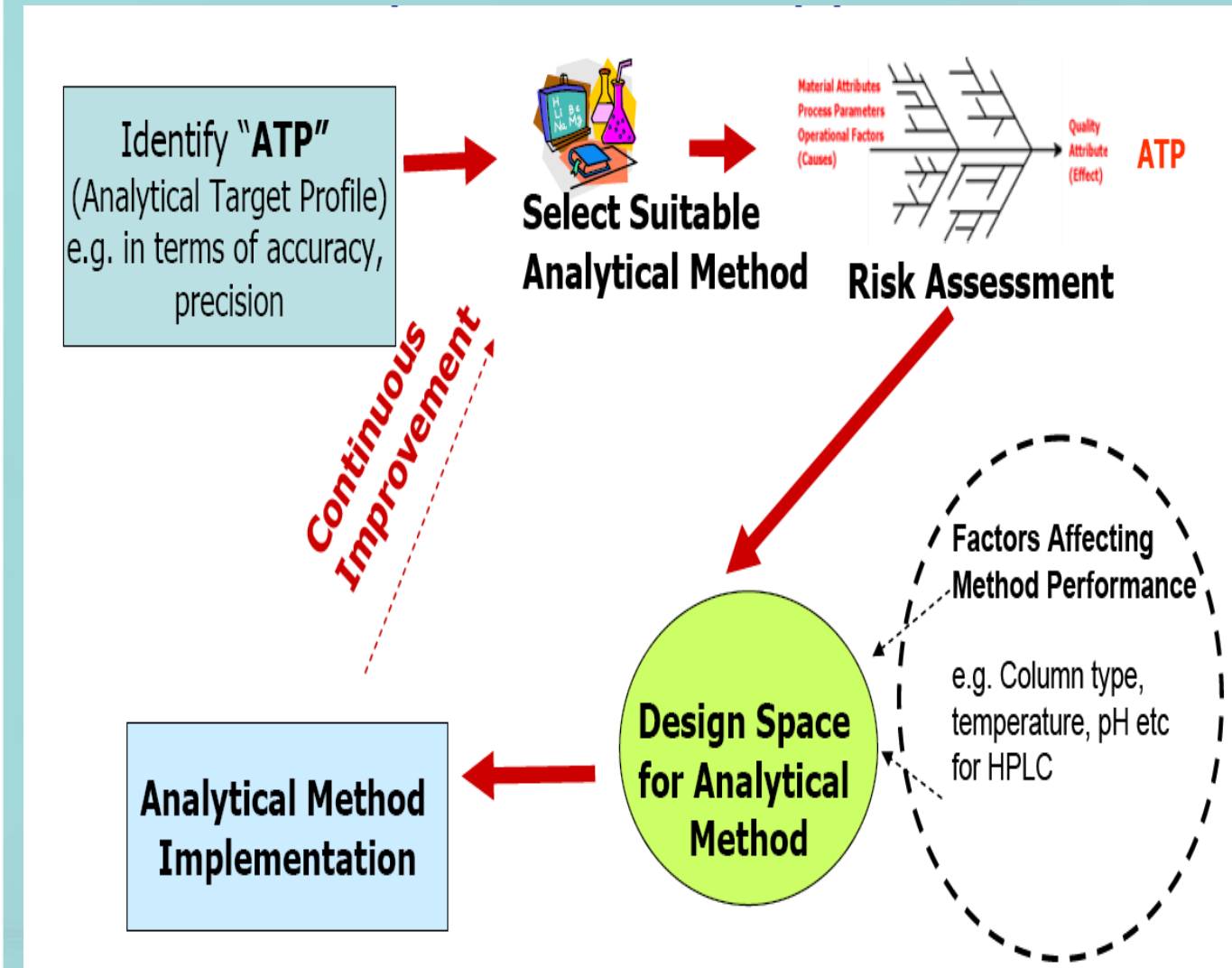


Challenges

- 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
- Analytical methods to support CM



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

CONCLUSION

Uncontrolled variation is the enemy of quality.

W. Edwards Deming

QUESTIONS?