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IPA
Innovation, Quality and Global Reach

QBD in Analytical Development
A Glance in Sun Pharma

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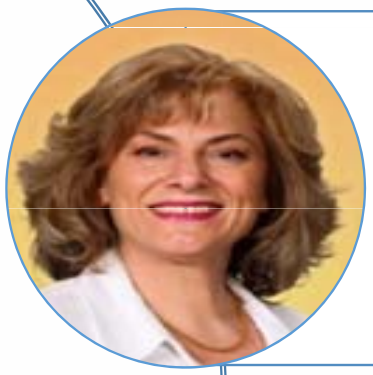
Topics



Concept of QbD

- Introduction & Definition
- Examples of 483s citing Product Quality Issues
- Quality Culture & Indicators
- Product Quality Lifecycle at Sun

Example of AQbD at Sun

- Analytical QbD (AQbD)
- Case Study of Low Soluble Drug

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QbD going on for past 25 years

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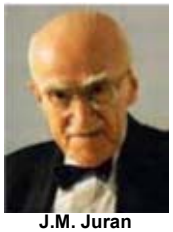
Juran on Quality by Design: The New Steps for Planning Quality Into Goods and Services

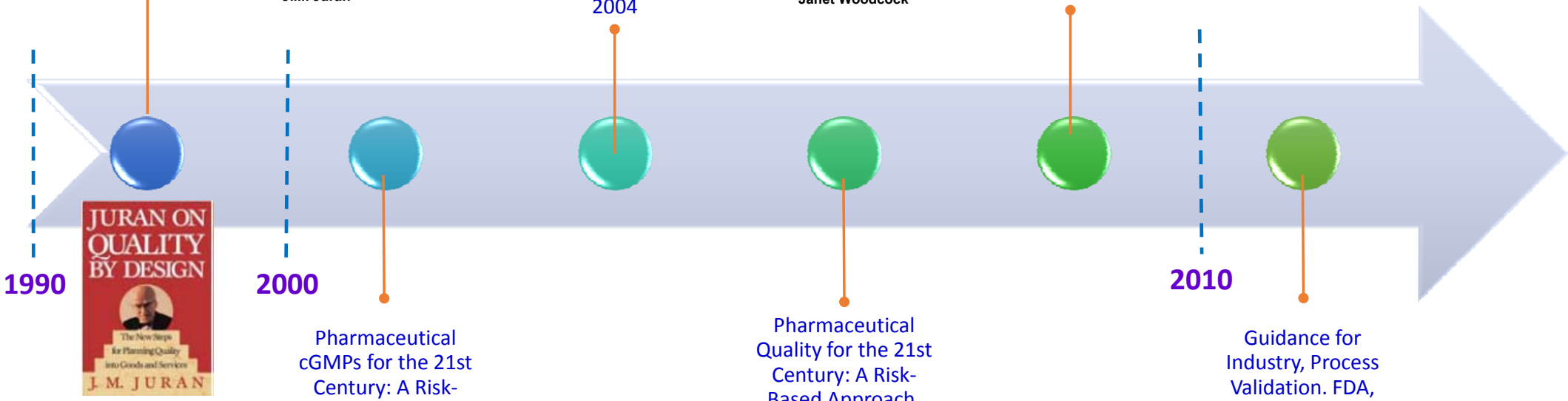


J.M. Juran

PAT —A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, guidance for industry, September 2004

Janet Woodcock

Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations FDA, September 2006



Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

Pharmaceutical Quality for the 21st Century: A Risk-Based Approach. Final Report

Guidance for Industry, Process Validation. FDA, September 2011

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Pharmaceutical Industry in India MUST take a more aggressive approach to focus on Product Quality rather than traditional GMPs

"Quality after Design" instead of "Quality by Design"

- Lack of processes and Analytical robustness
- Static Processes
- High Variable measurement systems
- Not well understood characterization of raw material
- Frequent Out-of-specification values
- High blame on Human Errors
- Data trend isolations among functions
- Lack of Knowledge Management and current expectations

Rigidly conventional and opposed to change mindset
Creates Drug shortage and higher Medicine cost

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Recent examples 483s

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Analytical Method as root cause

- "OOS investigation was initiated to investigate Assay failure during the 3 month stability testing. The investigation suspected incorrect sonication time as the probable root causer. Based on this assumption, 5 hypothesis studies were initiated for sonication time without intermittent shaking, and the last hypothesis study with intermittent shaking (as per STP instructions). We were unable to determine if the hypothesis studies were actually conducted. Specifically, our review indicated that all associated analytical worksheets for the purported hypothesis studies have the same sonicate time. We were unable to ascertain how the low Assay value were obtained for hypothesis studies. The results from the hypothesis studies were utilized to conclude that the initial failing Assay results were due to inadequate sonication of sample. All four impacted batches covered in this investigation are currently in the US market"
- "The OOS results were obtained during the Organic impurity testing by HPLC during the 3 month stability testing. The investigation concluded that the root cause id due to analyst error (i.e., sample sonication a the incorrect temperature of 40°C versus the STP sonication temperature requirement of 5±3 °C). The investigation failed to conclusively prove that the sonication at 40°C is the root cause of significantly higher level obtained during initial testing. The initial results were invalided and passing re-test results were reported as the valid result of record. These batches are both commercially distributed in the US market"

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Recent examples 483s

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No root cause

- "The OOS results were confirmed during preliminary investigation and hypothesis testing (Phase I) with no identified root cause. No manufacturing error was identified during Phase II investigation. The initial OOS results were invalidated based on reserve sample testing ……"
- "Your firm has not documented complete investigations for the following;
  - From July 2017 until February 2019, there were x cases where the in-process control testing yielded out of specification results. Retesting was conducted but no corrective actions were taken at the time including conclusion of 'No assignable cause' or 'Manual Error' without documentation of the manual error. The equipment and the formulation were changed in January and August 2018 but no CAPA was developed and no follow-up actions were assigned
  - No investigation was initiated for the discrepancy found in tablet compression showing an out of range compaction force in the end…."

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Recent examples 483s

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Deviation from Procedures

- "Your QC Analysts deviated from STPs for over two years while conducting Assay and Related Substances by HPLC. During the inspection, we observed your employees using alternate procedure by deviating from the STP"
- Your QC unit invalidated the original test data based on the rationale that Samples and standard test solutions were discarded prior to processing and verifying the analytical test results. The firm compromised the integrity of OOS investigation by changing the HPLC system. Additionally, a repeat analysis was performed by preparing fresh samples, standard, mobile phase and diluent solutions that resulted in a passing test result"

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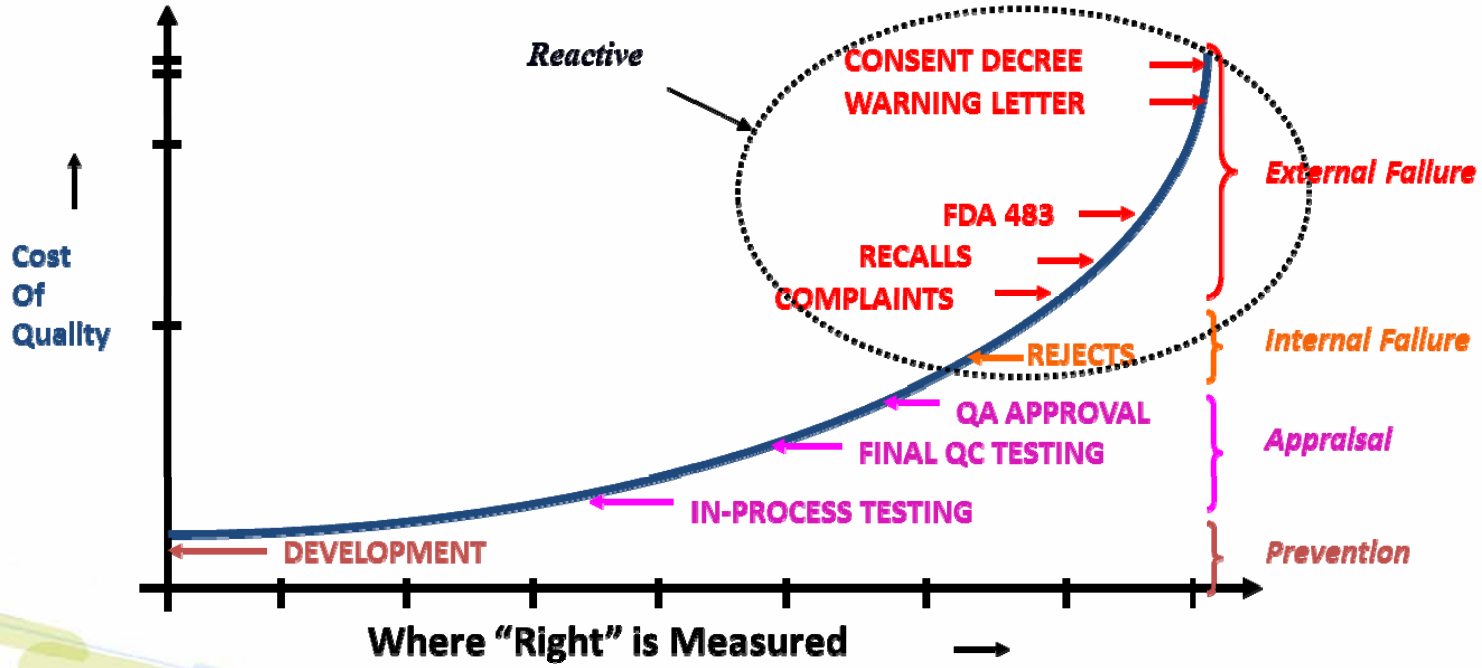
Cost of Quality
Where "Quality Is Measured"



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USE your Metrics Connect the DOTS!

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- Invalidated & Validated OOS rate
- Investigations with non-assignable root cause
- Human error as root cause
- Non effective CAPA
- Preventive Maintenance adherence rate
- Batch rejections
- Repeated Complaints for Products
- Recalls
- Etc.…

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We have procedures!

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QbD: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management - *[ICH Q8 (R2) Definition]*

The overarching philosophy articulated in both CGMP regulations and in robust modern quality systems is: "Quality should be built into the product, and testing alone cannot be relied on to ensure product quality"

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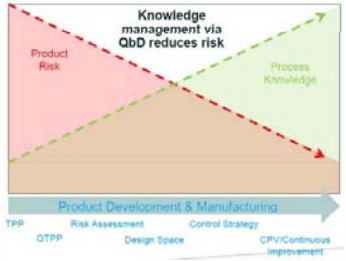
QbD Approaches

Combination of ICH Q8, Q9 and Q10

- Defining the Quality Target Product Profile (QTPP)
- Identifying potential Critical Quality Attributes for
  - Drug Substance, Excipients, Drug Product



- Conduct a Risk Assessment (ICH Q9) to link Material Attributes and Process Parameters to Drug Product CQA and build a Design Space
- Use the enhanced product and process understanding in combination with quality risk management to establish an appropriate Control Strategy
- Implement Product Lifecycle Management by continuous evaluation of innovative approaches to improve product quality (ICH Q10)

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Systematic Approach

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A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

Elements	What to do
Predefined objectives	Define Quality Target Product Profile (QTPP) Identify Critical Quality Attributes (CQA)
Product and process understanding	Identify critical material attributes (CMA*) and critical process parameters (CPP) Establish the functional relationships that link CMA/CPP to CQA
Process control	Develop appropriate Control Strategy, including justifications
Sound science	Science-driven development (scientific literature, prior knowledge, DOEs etc.)
Quality risk management	Risk-based development (ICH Q9) Science-driven development (scientific literature, prior knowledge, DOEs etc.)

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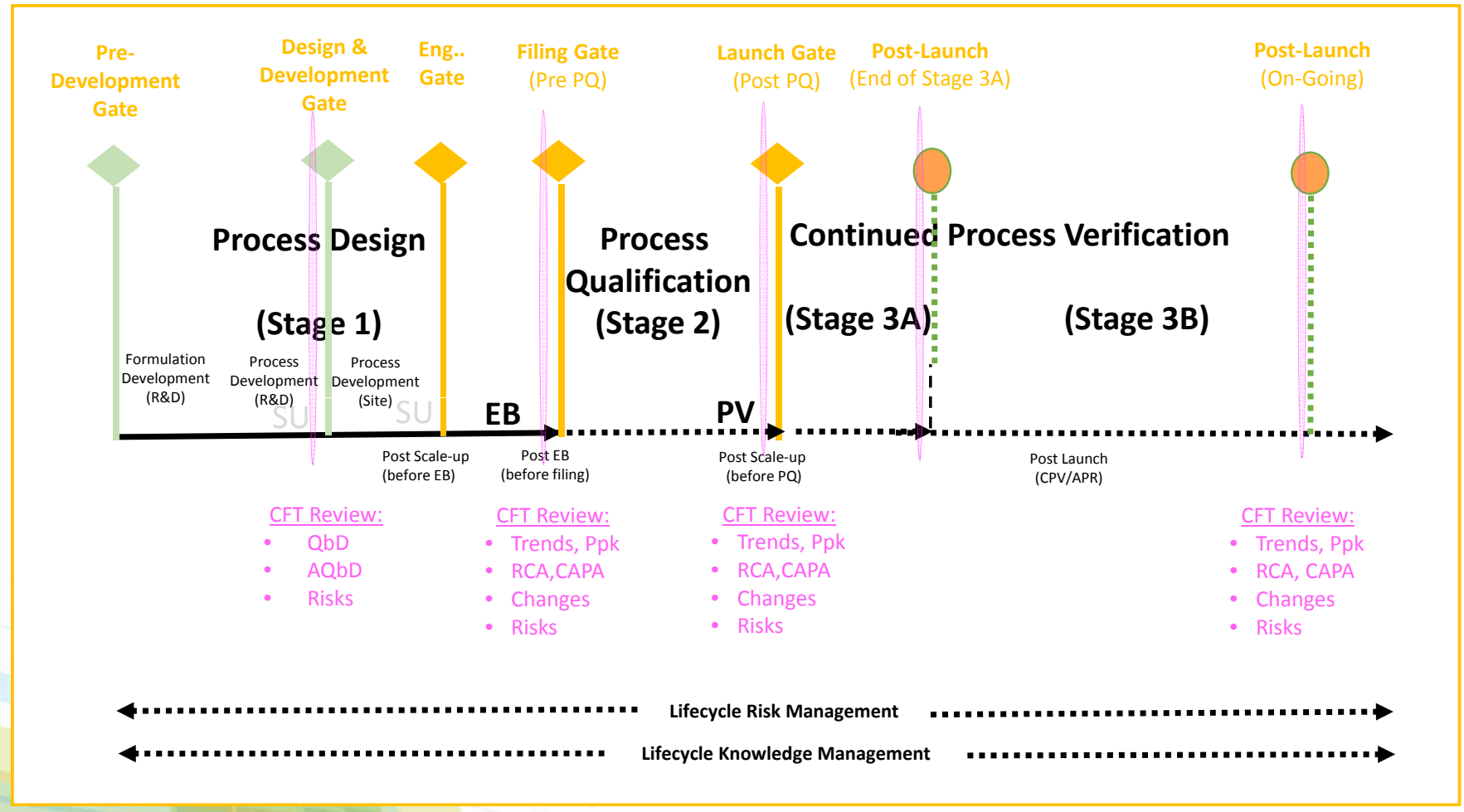
Product Quality Review Lifecycle at Sun



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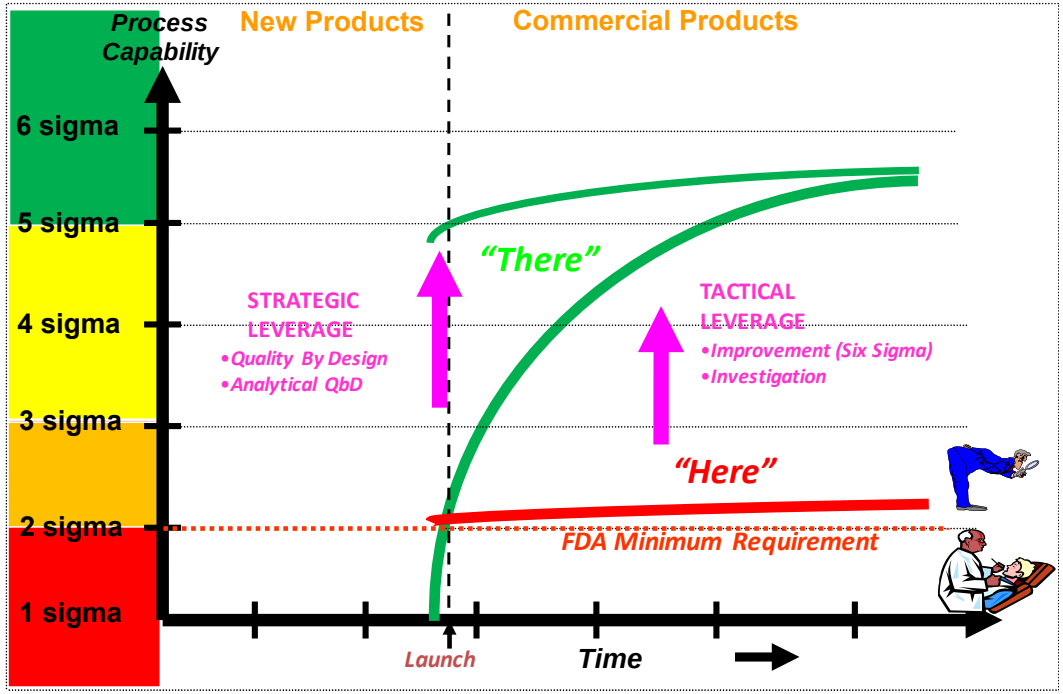
Product Quality Lifecycle: Assessing and Enhancing Quality

- 21st Century Quality Initiative for supplying robust products to patients
- An initiative on the lines of ICH Q10 for Product Lifecycle Management including post approval changes
  - Process Understanding
  - Product, Process & Analytical Assessment
  - DMAIC approach for improvement
  - Filing changes with Regulatory agency



Moving products in Red and Orange zone to Yellow and Green zone

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Map It and Gap It

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❑ **Product Understanding**

- Process Map
- Product, Process details & Specifications
- Fish Bone – mapping the CQAs to the process steps
- Control Strategy for materials and process steps
- Heat map & FMEA for process parameters & analytical method and its variable versus impact on CQAs
- Risk Assessment for input material attributes versus CQAs
- Risk Assessment for CPPs versus CQAs

❑ **Product Assessment**

- Statistical evaluation of retrospective data
  - CPP, CQA, Stability Data & Trends
- External Quality Parameters
  - PQCs, FARs, Recall
- Internal Quality Parameters
  - OOS, Lab Events, Rejects & Failures (In-process, Finished product, Stability)
  - Human Error assessment
- Post-approval Changes
- Define Sigma Level for the Product

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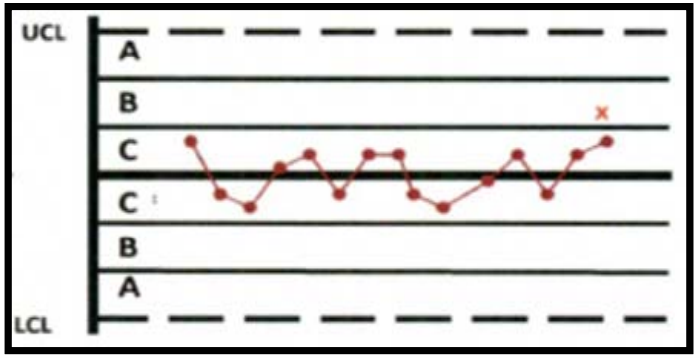
Understand what your Data is telling you

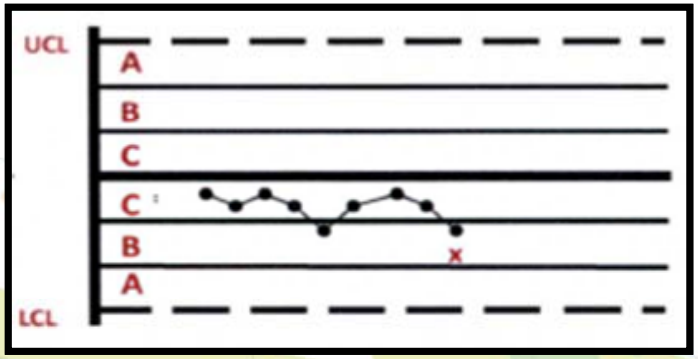
examples of Control Chart Indicators

Rules are defined in process control to determine if some measured variable is "out-of-control" or non-random conditions(unpredictable versus consistent)

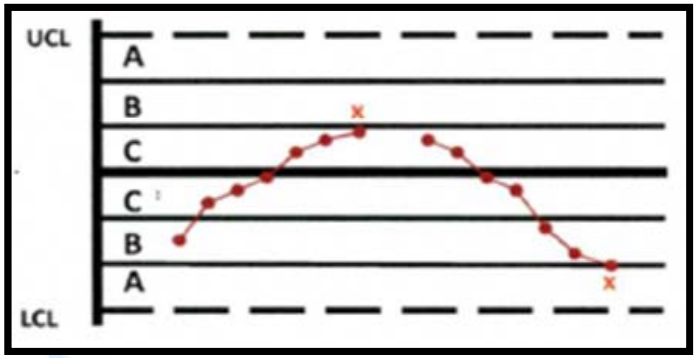
1. Process under control



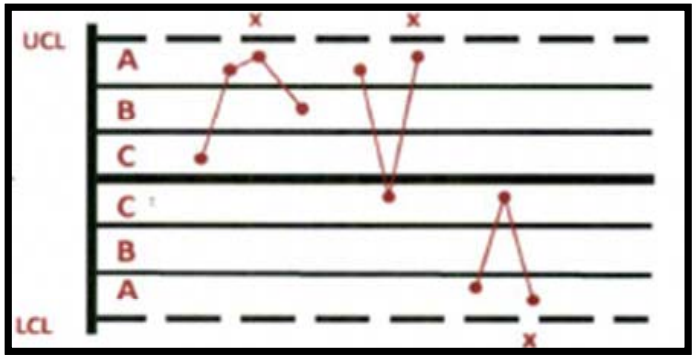
2. Data shift towards one side of the Mean



3. Steady increase or decrease of Data



4. Two out of three data in A Zone



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Building Quality Culture
Attention to Details, cGMP and People

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- Education and Training Program
  - ✓ Basis GMP 1-o-1
  - ✓ Data Integrity Training
  - ✓ Investigations
  - ✓ Statistical process control
- Certification Program
  - ✓ Microbiology & Aseptic Practices
  - ✓ Investigations & Root Cause analysis
  - ✓ Product Assessment and statistical process control
- Communication
  - ✓ Escalation of Quality Alerts
  - ✓ Teach people to speak up (Say something when See something)
  - ✓ Incentivizing the Right Behavior
  - ✓ Disciplining the Wrong Behavior
  - ✓ Setting KPIs and structured Performance Reviews
- Learn from your own and others Mistakes
  - ✓ Accept failures and correct them
  - ✓ Relook at fundamentals during failures
  - ✓ Foster First time Right

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"Pharmaceutical manufacturing industry 'ossified' by prior environment"

"**Janet Woodcock**, M.D., Director, Center for Drug Evaluation and Research"

Create an Agile CULTURE and embrace Change

Ossified: rigidly conventional and opposed to change

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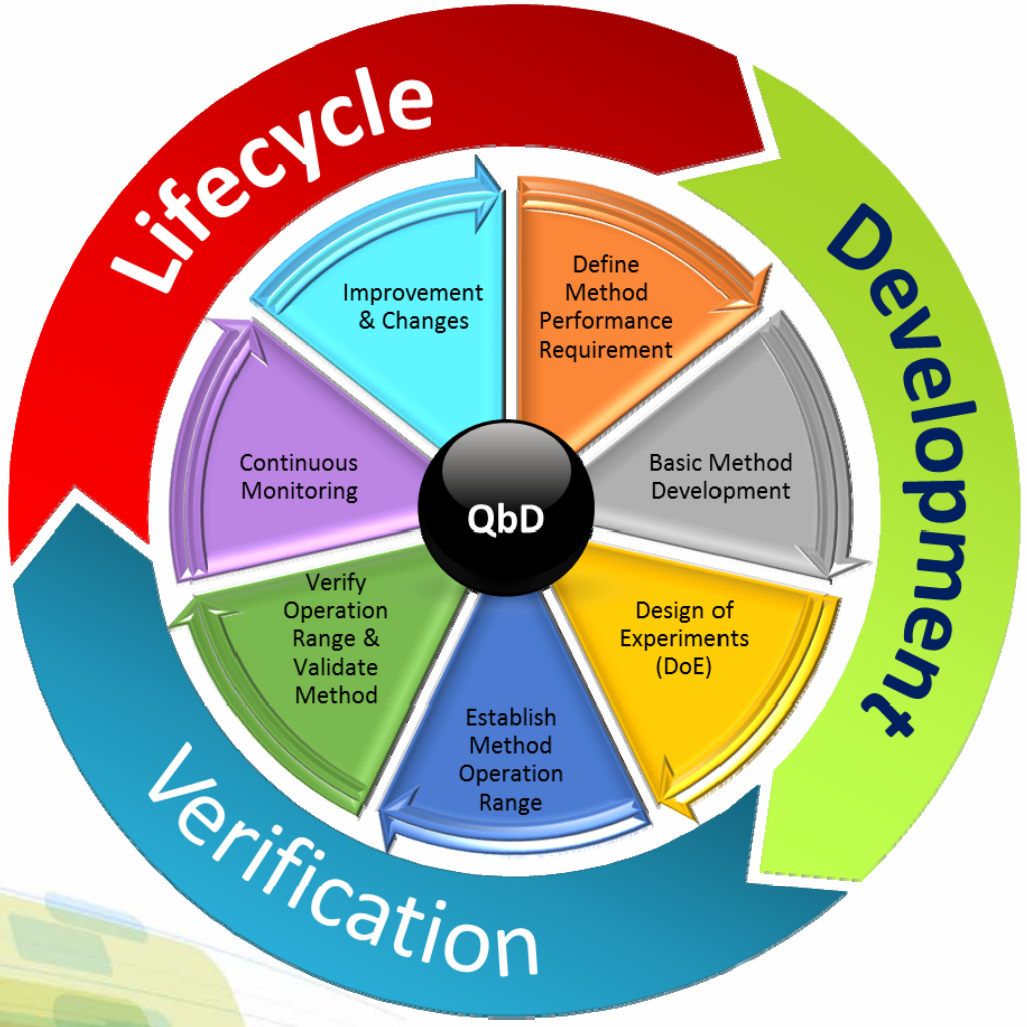
Analytical QbD Workflow



Analytical QbD is well understood as robust method that consistently delivers the intended performance throughout the lifecycle

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Analytical Variability

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Analytical processes represent sub-processes within a process

- Drug Release: Sub-processes like Media, Apparatus, Standard, Sampling, Analyst Processes, Interaction with Instruments
- Assay: Sub-processes like of Standard & Sample preparation, Analyst Processes, Interaction with Instruments
- Related Substances: Sub-processes of Sample & mobile phase preparation, Analyst Processes & Interaction with Instruments

Item to be measured

Measuring Device

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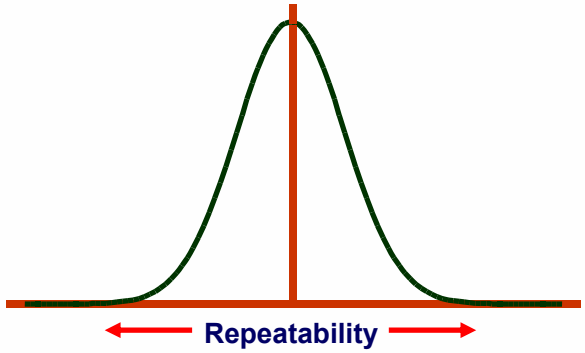
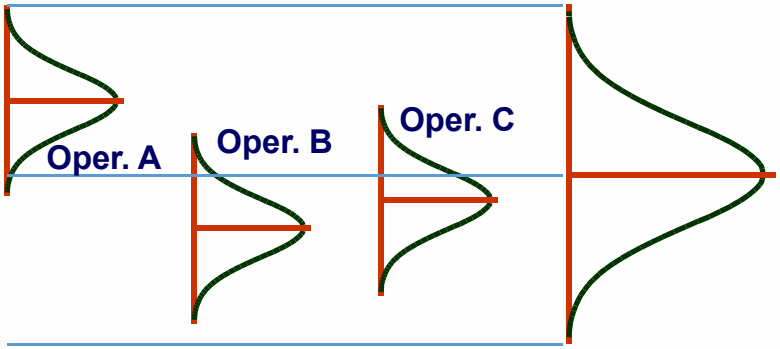
Consistency of Measure



Repeatability – the variation in measurements obtained with one gage when used several times by one operator while measuring one characteristic on one part

Caused by Device

Vs



Reproducibility is the variation in the measurements made by different operators using the same gage when measuring one characteristic on one part

Caused by Operator / Analyst

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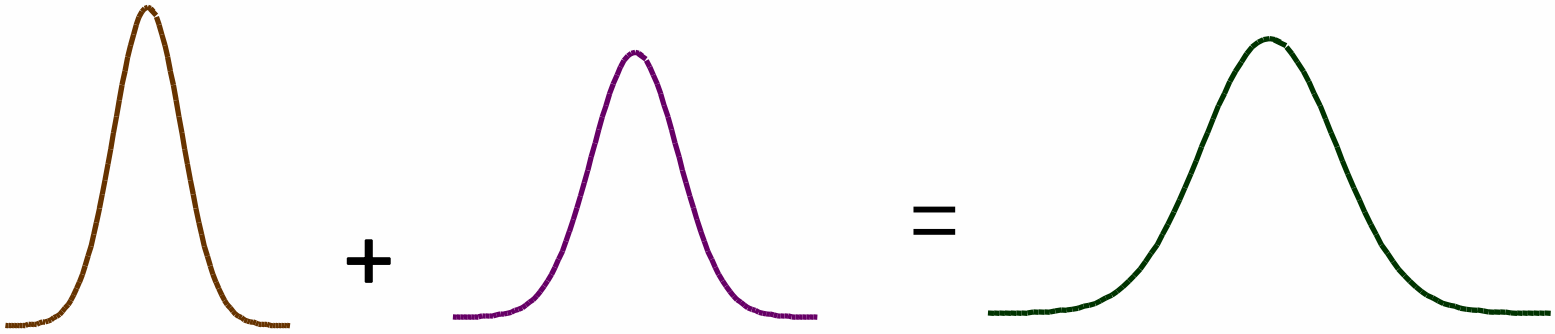
How does Method Variation Impact?



Finished Good (Process) Variation

Method (Measurement System) Variation

Total Variation

$6\ \sigma_{PV}$

$6\ \sigma_{MS}$

$6\ \sigma_{TV}$

PV: Process Variation (Actual); MS: Measurement System; TV: Total Variation (Observed)

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QRM – Assessing Risks

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CASE STUDY - Narrow Therapeutic BCS Class I Drug

- Analytical Method Robustness (Dissolution & Assay)
- Risk Assessment & Control Strategy
  - Initial Assessment-Fish Bone Diagram
  - Heat Map Assessment
  - FMEA
  - Final Risk Assessment-Fish Bone Diagram
  - Observations & Learning

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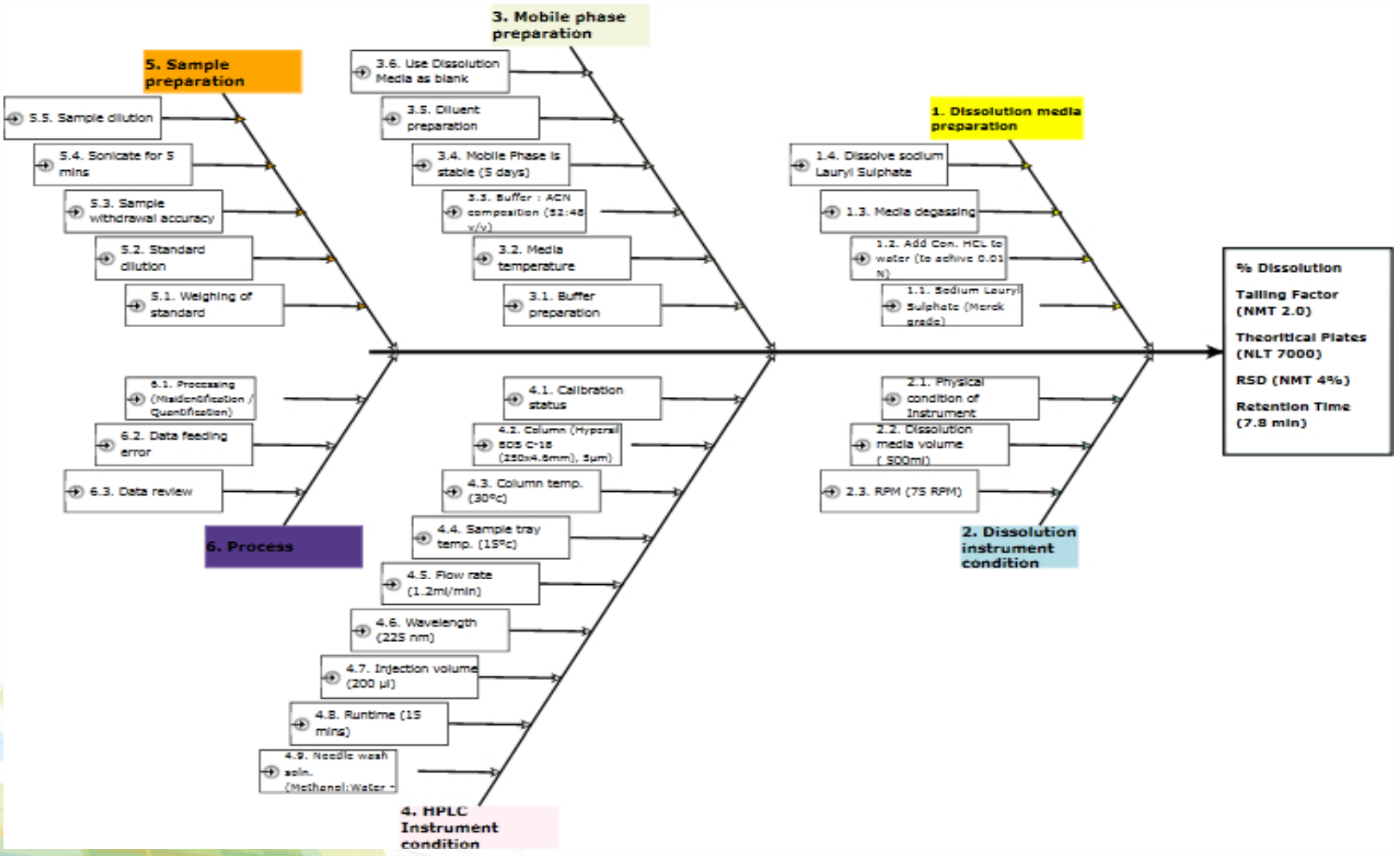
Fishbone for Dissolution Method



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Initial Risk Assessment through Heat map

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CQAs →

Process Parameters ↓

Fishbone Bone Number	Fishbone Bone Name	Name					
			% Dissolution	Tailing Factor (NMT 2.0)	Theoritical Plates (NLT 7000)	RSD (NMT 4%)	Retention Time (7.8 min)
1.1	Dissolution media preparation	Sodium Lauryl Sulphate (Merck grade)	other make will impact release of API in DP				
1.2	Dissolution media preparation	Add Con. HCL to water (to achive 0.01 N)	Normality of solution may affect release of API in DP				
1.3	Dissolution media preparation	Media degassing	Insufficient degassing may impact the release of API in DP				
1.4	Dissolution media preparation	Dissolve sodium Lauryl Sulphate	Solubility of SLS will impact the release of API in DP				
2.1	Dissolution instrument condition	Physical condition of Instrument	It will impact the release of API in DP				
2.2	Dissolution instrument condition	Dissolution media volume (500ml)	It will impact the release of API from DP				
2.3	Dissolution instrument condition	RPM (75 RPM)	It will impact the release of API from DP				
3.1	Mobile phase preparation	Buffer preparation					Buffer conc. may affect retention time
3.2	Mobile phase preparation	Media temperature	It will impact the release of API from DP				
3.3	Mobile phase preparation	Buffer : ACN composition (52:48 v/v)		Major variation in the mobile phase will impact the tailing factor	Major variation in the mobile phase will impact the Theoretical plates		wrong composition of mobile phase will impact retention time
3.4	Mobile phase preparation	Mobile Phase is stable (5 days)					
3.5	Mobile phase preparation	Diluent preparation					
3.6	Mobile phase preparation	Use Dissolution Media as blank					
4.1	HPLC Instrument condition	Calibration status	Non calibrated instrument may affect the % release of DP				
4.2	HPLC Instrument condition	Column (Hypersil BDS C-18 (250x4.6mm), 5µm)		if the column was not proper condition the it will impact the tailing factor	if the column was not proper condition the it will impact the theoretical plates		if the column was not proper condition the it will impact the retention time
4.3	HPLC Instrument condition	Column temp. (30°c)		it column oven temperature not maintainig within the range then it will impact the tailing factor	it column oven temperature not maintainig within the range then it will impact the theoretical plates		it column oven temperature not maintainig within the range then it will impact the retention time

Relationship between method parameters & Dissolution with Risk Levels indicated as:

1. Red - for high severity,
2. Yellow – medium severity,
3. Green for low severity

Prior knowledge of product and CQA during method development – Basis of identifying Risks

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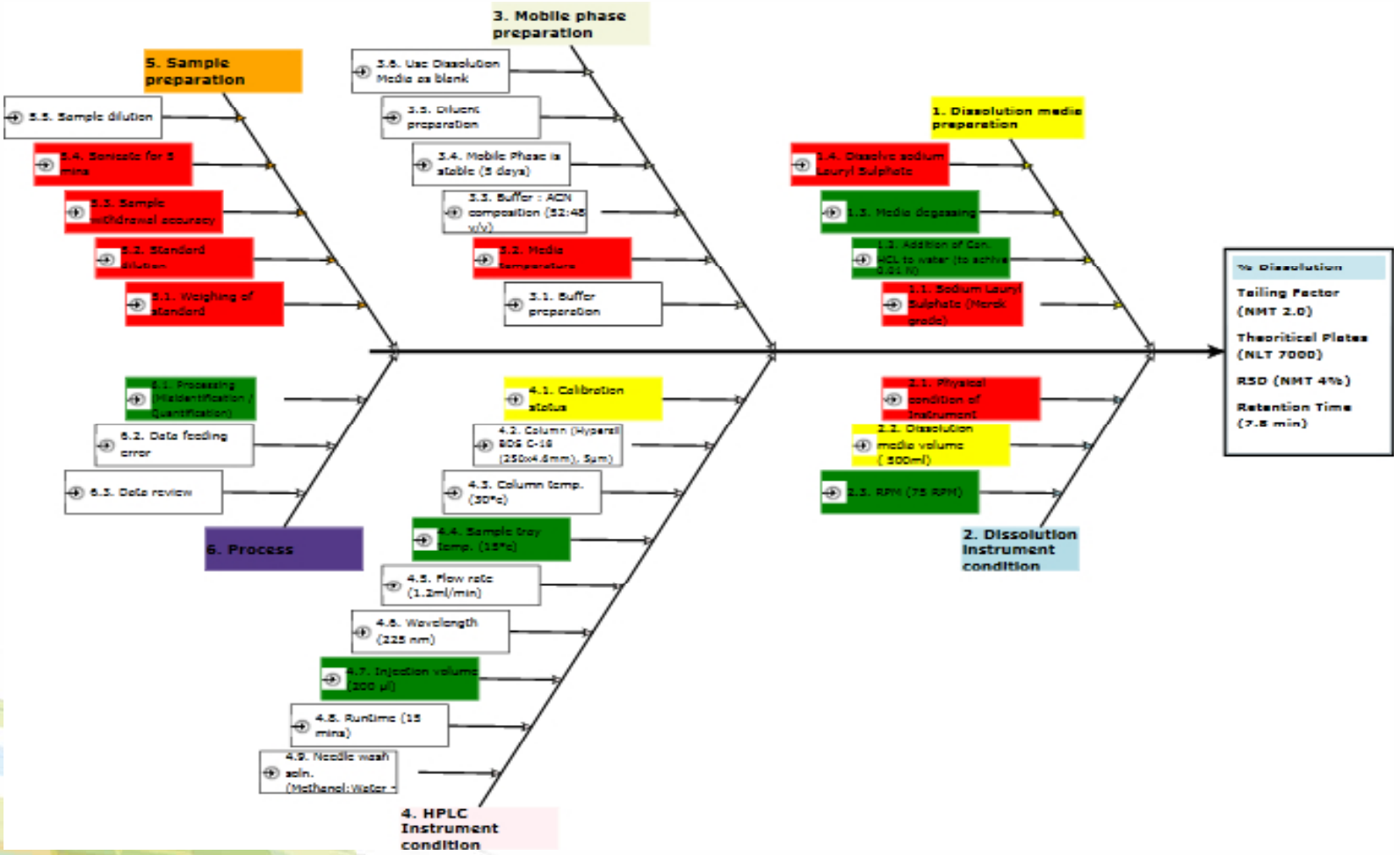
Parameters Affecting Dissolution



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Learning from Initial Risk Assessment (Heat map)

- Provides a platform for anticipation and strategy
- Helps to identify the critical parameters majorly contributing to the failure of results
- Helps in maintaining a database for the method for the entire lifecycle of the product and serves as a repository w.r.t analytical method history.
- Helps to make investigations more focused with definite root cause for any failures (OOS/OOT/deviations)

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Method Robustness Study

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Background	Activities	Learnings
• Drug excipient ratio very low • Challenges during method optimization • Excipients in product with comparatively low solubility	• Robustness Study (Gage R&R) • Experiment designed for 4 Analysts with different Experience levels • Statistical Data interpretation	• Qualitative observations indicate possibilities of improvement on method w.r.t building precautions & elaborations

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Is there a difference between the values reported by 4 Analysts?

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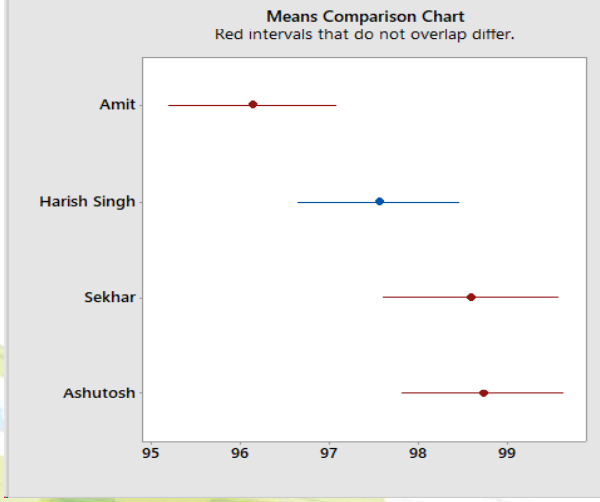
Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Analyst	3	153.8	51.278	5.64	0.001
Error	140	1273.2	9.094		
Total	143	1427.0			

Difference between the values reported by analysts are statistically significant



Means (with confidence intervals) by Amit does not overlap with those reported by Sekhar or Ashutosh

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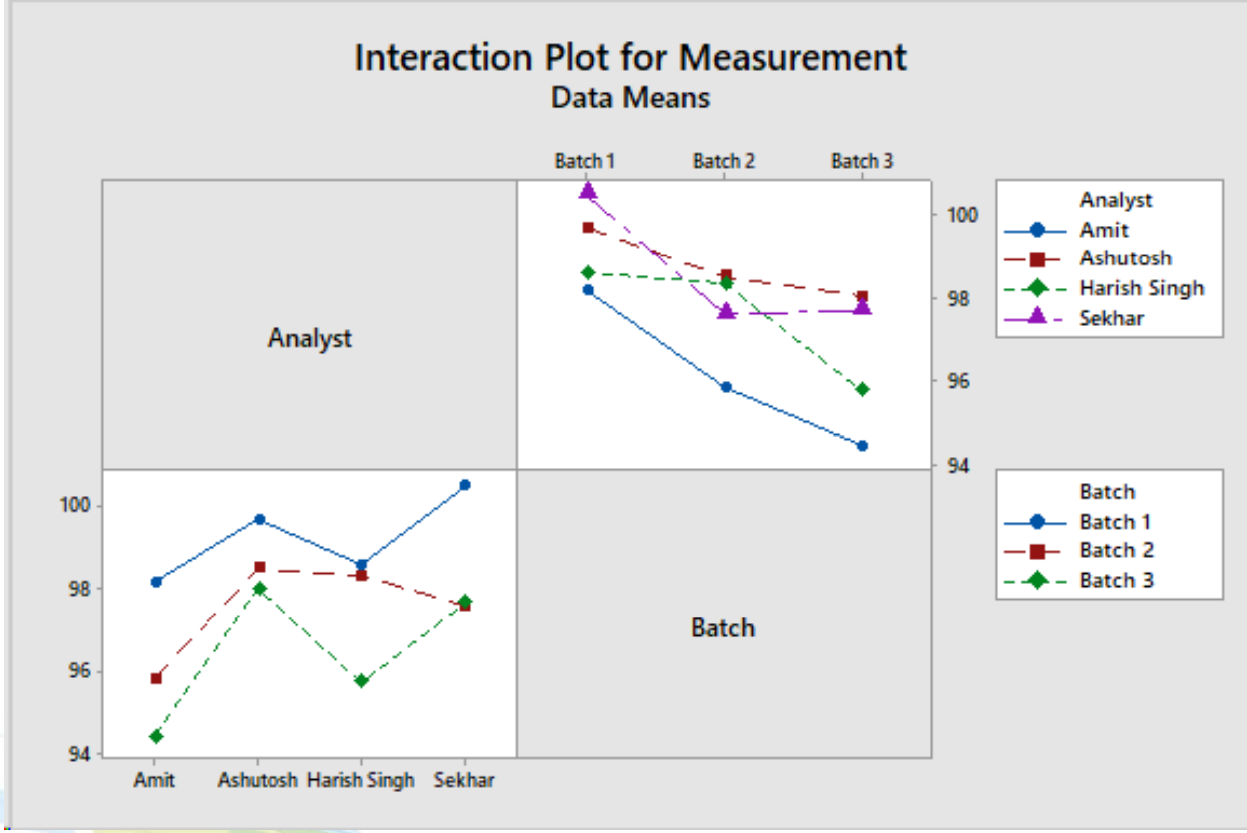
Analyst & Batch Interaction



Likely Interaction Between Analyst & Batch Impacting Dissolution

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Gage R&D Study

Gage R&R (Nested) for Measurement

Source	DF	SS	MS	F	P
Analyst	3	153.83	51.2778	1.79267	0.226
Batch (Analyst)	8	228.83	28.6042	3.61546	0.001
Repeatability	132	1044.33	7.9116		
Total	143	1427.00			

- **Variation between analysts are nested within each batch**

Variance Components

Source	VarComp	%Contribution (of VarComp)
Total Gage R&R	8.5414	83.20
Repeatability	7.9116	77.07
Reproducibility	0.6298	6.14
Part-To-Part	1.7244	16.80
Total Variation	10.2658	100.00

Lower process tolerance limit = 80

- **Total contribution of variation from Gage is 83%. This is very high as the ideal range is <10%**
- **Repeatability is high, i.e., the variability in measurements when the same analyst measures samples from the same batch is high**
- **The variation between batches is not a significant contributor to the overall variation (at 16% of overall variation)**

Gage Evaluation

Source	StdDev (SD)	Study Var (4 × SD)	%Study Var (%SV)	%Tolerance (SV/Toler)
Total Gage R&R	2.92257	11.6903	91.22	32.93
Repeatability	2.81276	11.2510	87.79	31.69
Reproducibility	0.79361	3.1745	24.77	8.94
Part-To-Part	1.31316	5.2526	40.98	14.80
Total Variation	3.20403	12.8161	100.00	36.10

Number of Distinct Categories = 1

- **% Tolerance is a measure of how much of the tolerance is being consumed by method error.**
- **<10% is good & up to 30% is acceptable**

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Statistical Inferences

- Difference between the values reported by analysts are statistically significant
  - Variation between analysts are nested within each batch
- Likely Interaction Between Analyst & Batch Impacting Dissolution
- The % contribution of variation from Method is 83% where as an ideal value is <10% and acceptable value is <30%
- With the contribution from repeatability at 77%, the variation appears to be from:
  - Analyst – Device interaction (choice of equipment / way of usage)
  - Analyst – Method Interaction (Obscure understanding)

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Comparison of Observations

Observations- Parameters	Harish	Shekhar (NPQC)	Amit	Ashutosh
Measurement of water for Dissolution media	Directly measured in the bucket ✗	Directly measured in bucket ✗	Directly measured in bucket ✗	Measured with glass cylinder ✔
Weighing and transfer of SLS	Weighed in a small beaker dissolved it with the help of magnetic stirrer ✗ before transferring to media .	Weighed and directly transferred to media mixed and dissolved with the help of glass rod. ✗	SLS weight taken in plastic beaker to dissolve nad then transferred to media ✗	Weighed SLS (Al foil) was dissolved in in 1L beaker with the help of magnetic stirrer and transferred to media ✔
Usage of Orthophosphoric acid for mobile phase	Fresh bottle opened ✔	Fresh bottle opened ✔	Opened bottle used ✔	Opened bottle used ✔
Mixing of OPA in water	Manual mixing of OPA in water	Manual mixing of OPA in water	Manual mixing of OPA in water	mixing done with Manual and sonication
Filtration of buffer	Filtered through 0.45µm membrane filter and sonicated after filtration.	Filtered through 0.45µm membrane filter and sonicated after filtration.	Filtered through 0.45µm membrane filter and sonicated after filtration.	Additional Sonication of buffer after filtration
Transfer of media to vessels	Transferred using 500mL plastic cylinder ✗	Transferred using 500mL plastic cylinder ✗	Transferred using 500 mL plastic cylinder ✗	Transferred using 500mL glass cylinder ✔
Degassing of media	Media degasser flushed with water and methanol ✗	Media degasser flushed with water and methanol ✗	Media degasser flushed with water and methanol ✗	Rinsed the degasser with dissolution media after flushing with water and methanol ✔
Tablet dropping	Dropped from the hole in the lid of dissolution vessel. ✔	Dropped from the hole in the lid of dissolution vessel. ✔	Dropped from the hole in the lid of dissolution vessel. ✔	Dropped from the hole in the lid of dissolution vessel. ✔
Setting of HPLC system	All the channels were primed together. No channel was individually primed. ✔	All the channels were primed individually. ✔	All the channels were primed individually. ✔	All the channels were primed individually. ✔
Any other Observation	After addition of media, dissolution apparatues in stand by mode till temperature achieved. ✗	After addition of media, dissolution apparatues run on specified RPM till temperature achieved. ✗	After addition of media, dissolution apparatues run on specified RPM till temperature achieved. ✗	After addition of media, dissolution apparatues run on specified RPM till temperature achieved. ✔

✗ **Incorrect**

✔ **Correct**

Step Forward-Included QC plant Inputs for compiling Comparative Qualitative observations

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Qualitative Observations

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- Method adopted by each analyst for weighing & transfer of SLS was different
- After mixing OPA in water, only R&D analyst sonicated the solution
- Only R&D analyst rinsed the degasser with dissolution media after flushing with water & methanol
- One analyst (Analyst A) primed the channels together while setting HPLC system. All others primed them individually.
- After addition of media, the dissolution apparatus was on stand-by mode for analyst Harish while others had the apparatus running on specified RPM till temperature was achieved

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Learnings & Recommendations

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- SLS weighing & addition needs to be harmonized & elaborated in Analytical Test Procedure (ATP)
- Ensure solubility of SLS into the whole media
- To attain temperature in vessel, the paddle should be in static mode and this has to be made obvious from the ATP
- There is room for variations in executing certain instructions within the existing ATP
- Although none of the data points are out of spec, there is a contribution of variation from the measurement system
- The insights from the experiment compared to the risk analysis carried out as a part of AQbD appears consistent

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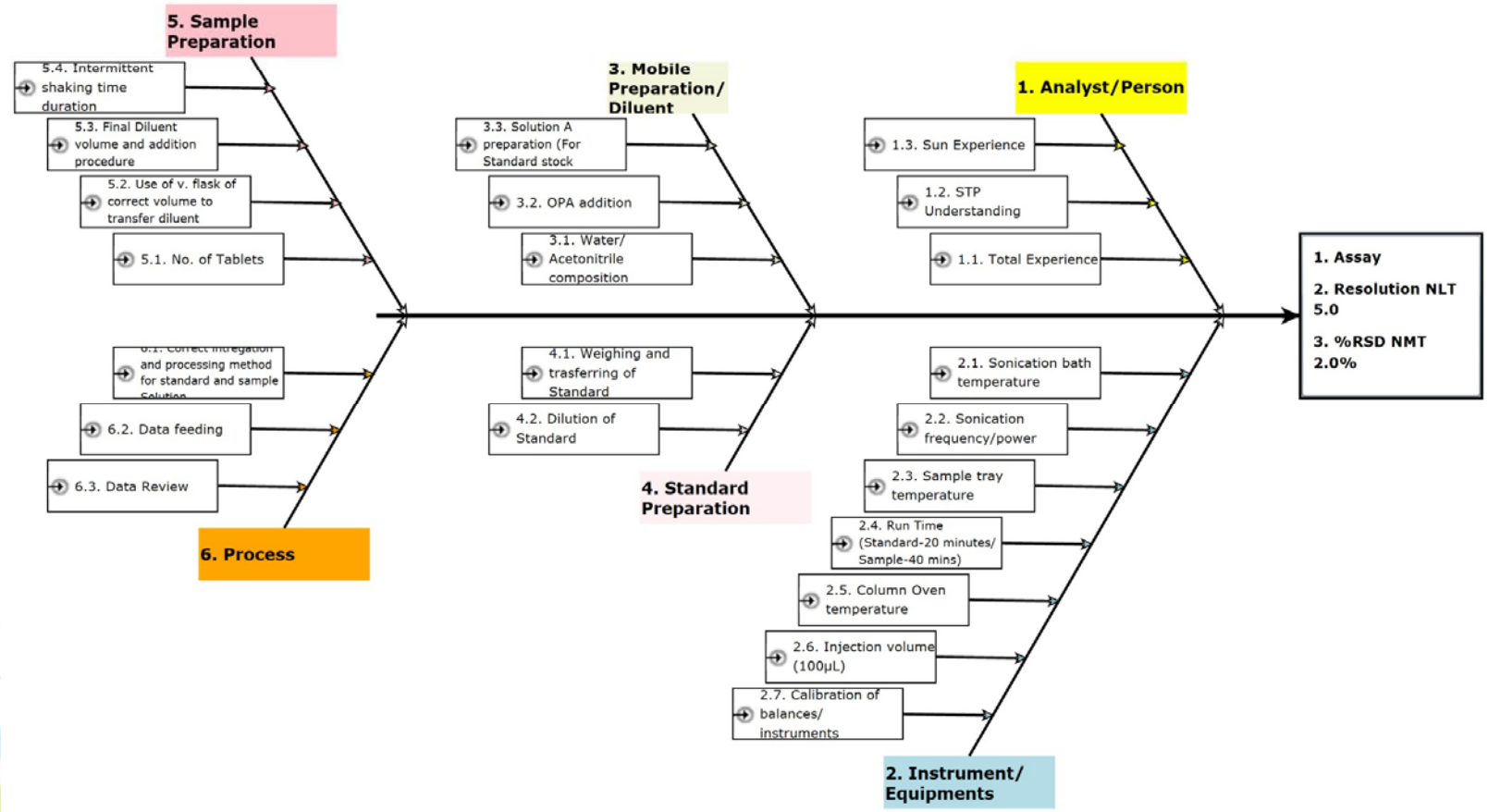
Fishbone for Assay Method



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Initial Risk Assessment through Heat map

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CQAs →

Process Parameters ↓

			1. Assay	2. Resolution NLT 2.0	3. %RSD NMT 2.0%
1.1	Analyst/Person	Total Experience	Less experience of analyst will have different understanding of method and can report variation in final results.		
	Analyst/Person	[illegible] Experience	Knowledge of in-house SOP's/GP's/hands-on trainings and harmonised way of performing experiment is required for minimal variation in results.		
1.2	Analyst/Person	STP Understanding	Elaborated precautions and directions already captured in STP will bring harmonised way of performing analysis rather than personal assumptions.		
2.2	Instrument/Equipments	Sonicator frequency/power	Sonicator frequency/power may impact % assay results if tablets are not dispersed completely.		
2.1	Instrument/Equipments	Sonicator bath temperature	If sonication is done at variable temperature of water bath in sonication, this will result into variable results.		
2.3	Instrument/Equipments	Sample tray temperature	[illegible]		
2.5	Instrument/Equipments	Column Oven temperature		This might have impact on resolution	
2.6	Instrument/Equipments	Injection volume (10µL)	If injection volume is not precise then variable results will be obtained.		Inconsistent injections will result into failing of %RSD.
2.7	Instrument/Equipments	Calibration of glassware/instruments			

Relationship between method parameters & Dissolution with Risk Levels indicated as:

1. Red - for high severity,
2. Yellow – medium severity,
3. Green for low severity

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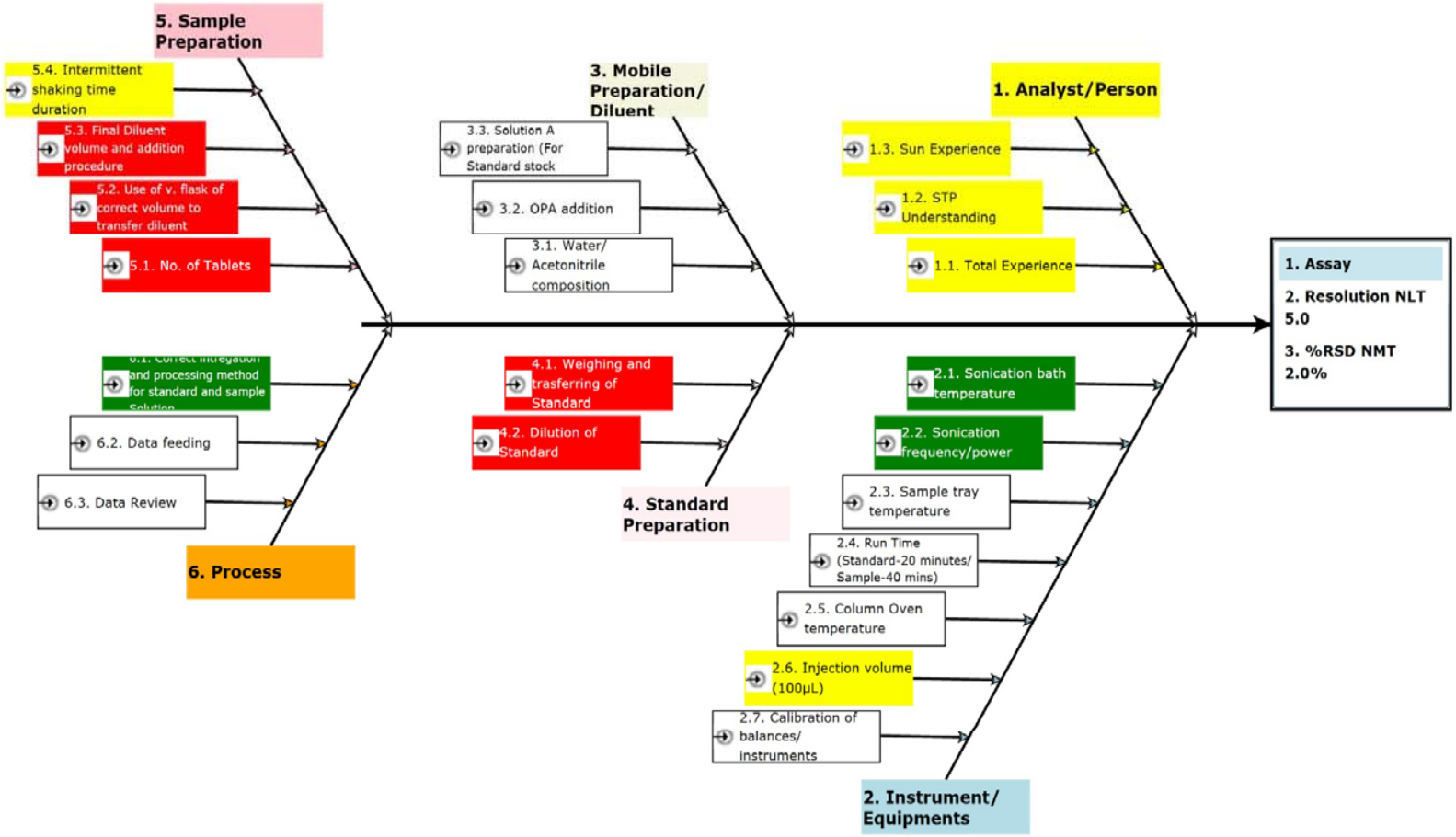
Parameters Affecting Assay



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Gage R&D Study

Gage R&R Study - Nested ANOVA

Gage R&R (Nested) for Result

Source	DF	SS	MS	F	P
Analyst	3	12.7233	4.24111	0.5332	0.672
Batch (Analyst)	8	63.6300	7.95375	45.8870	0.000
Repeatability	12	2.0800	0.17333		
Total	23	78.4333			

Gage R&R

Source	VarComp	%Contribution (of VarComp)
Total Gage R&R	0.17333	4.27
Repeatability	0.17333	4.27
Reproducibility	0.00000	0.00
Part-To-Part	3.89021	95.73
Total Variation	4.06354	100.00

Process tolerance = 10

Source	StdDev (SD)	Study Var (4 * SD)	%Study Var (%SV)	%Tolerance (SV/Toler)
Total Gage R&R	0.41633	1.66533	20.65	16.65
Repeatability	0.41633	1.66533	20.65	16.65
Reproducibility	0.00000	0.00000	0.00	0.00
Part-To-Part	1.97236	7.88944	97.84	78.89
Total Variation	2.01582	8.06329	100.00	80.63

Number of Distinct Categories = 6

Variation between analysts appear to be nested within each batch

- The total contribution of variation from Gauge is 4%. This is good and as ideal range is <10%
- Variability in Repeatability is 4%, i.e., the variability in measurements when the same analyst measures samples from the same batch well within ideal range
- The variation between batches has significant contribution to the overall variation (at 96% of overall variation)

- The % Tolerance is a measure of how much of the tolerance is being consumed by method error.
  - <10% is good & up to 30% is acceptable

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Statistical Inferences

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- There is a slight difference in the values reported by the analysts
- The % contribution of variation from Method is 4% where an ideal value is <10% and acceptable value is <30%
- With the contribution from repeatability at 4%, there are adequate controls in the method
- There is significant variation between batches selected
- Method appears to be able to detect differences between each analyst for the given tolerance

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Comparison of Observations

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Zakir (R&D Analyst)	Ankit (API development scientist)	Amit (Existing QC experience)	Swatantra (NPQC)
Volume measured using 1L glass measuring cylinder	Same	Same	Same
Weighed carefully and transferred gently butter paper placed slowly on pan ✔	Weighed carefully and transferred gently butter paper placed slowly on pan ✔	Weighed and transferred standard by tapping butter paper with finger. ✗	Weighed carefully and transferred gently butter paper placed slowly on pan ✔
First Acetonitrile, Water and OPA was mixed by shaking & sonicated. ✔	First Acetonitrile, Water and OPA was mixed by shaking, sonicated. ✔	Added Acetonitrile in the bottle followed by Water and mixed. Added OPA and mixed by shaking and sonicated. ✔	First Acetonitrile, Water mixed by manual shaking, then OPA was mixed by shaking, sonicated. ✔
Volume of diluent was transferred to 500mL volumetric flask using funnel and 200ml+100 ml v. flask. ✔	Volume of diluent was transferred to 500mL volumetric flask directly with 100 and 200 mL volumetric flask. ✗	Volume of diluent was tranfered to 500mL volumetric flask directly through 100 and 200 mL volumetric flask. ✗	Volume of diluent was tranfered to 500mL volumetric flask directly through 100 and 200 mL volumetric flask. ✗
Sonication done with vigorous intermittent shaking & temperature maintained at 20-30°C throughout the sonication step. ✔	Sonication done with vigorous intermittent shaking & temperature maintained at 20-25°C throughout the sonication step. ✔	Sonication done with normal intermittent shaking. ✗	Sonication done with vigorous intermittent shaking & temperature maintained at 20-30°C throughout the sonication step. ✔
All the channels were primed individually. Manual Purge injector was given and along with purge from Sample set. ✔	All the channels were primed individually. ✔	All the channels were primed individually. Manual Purge injector was given and along with purge from Sample set. ✔	All the channels were primed individually. ✔
Different filters used for each sample with discard volume as per method. ✔	Filtered the sample slowly. Different filters used for each sample with discard volume as per method. ✔	Different filters used for each sample with discard volume as per method. ✔	Different filters used for each sample with discard volume as per method. ✔

✗ **Incorrect**

✔ **Correct**

Step Forward-Included QC plant Inputs for compiling Qualitative comparative observations

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Product & Process Variability

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- ❑ Process Input Variables listed
- ❑ Critical Quality Attributes and impact of each Input Variable on CQA
- ❑ Severity Level assigned to each CQA during development
- ❑ Input Variables gauged as critical along with impacted CQA are
  - Certain moisture of excipients restricts degradation of API- Assay
  - Severe impact due to Blending/Sifting – BU & CU
  - Compression Speed & Force – CU, DR & RS
  - Induction Cap sealing height/conveyer speed/temp – RS
- ❑ Critical Evaluation during Heat map & FMEA
- ❑ Mitigated Risk with appropriate steps during process
- ❑ Knowledge Management

Low Claim Drug

Unique Revelation

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Product & Process Variability

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Variable	Description	Content Uniformity	Blend Uniformity	Dissolution	Assay	Related Substances
Input Variables - Assay of Active	No Impact	No Impact	No Impact	No Impact	Assay of API evaluated using a different method than the target market may lead to a different Assay than expected. A lower value of assay of API may impact assay of DP. The effective quantity of API is likely to be lower in DP.	No Impact
Input Variables - Related substances of Active	No Impact	No Impact	No Impact	No Impact	No Impact	High RS of API may accelerate impurities generation in product
Input Variables - PSD of API	No Impact	Improper PSD of API will result in non uniform distribution of API		No Impact	No Impact	No Impact
Input Variables -LOD of Starch	No Impact	No Impact	No Impact	No Impact	No Impact	No Impact
Input Variables-Sieve size for colorant sifting	No Impact	No Impact	No Impact	No Impact	No Impact	No Impact
Input Variables-Sequence of sifting	No Impact	If sequence is changed , then the intended geo. mixing will not be achieved		No Impact	No Impact	No Impact
Input Variables-Sieve size for API, LH 21, starch and color	No Impact	Larger pore size of sieve may lead to improper distribution of API which may impact CU		No Impact	No Impact	No Impact
Input Variables-Sieve integrity for API, LH 21, starch and color	No Impact	If sieve is damaged it may lead to improper distribution of API which may impact CU		No Impact	No Impact	No Impact

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Valuable Activities

- ✓ Statistical Tools plus Deep dive in to the Qualitative Information
- ✓ ATP Elaboration with minutest details for Assay, Dissolution & RS in particular and all other measurements in general
- ✓ Cross Functional effort including QC locations before AMT
- ✓ Product & Process Heat Map/Fish Bone/FMEA worked out with Manufacturing Team

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Way Forward

- ✓ Address Measurement variability during Development Stage
- ✓ Approach worked out in present case study to be implemented in all future products
- ✓ Managing Knowledge over the Life Cycle Management

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Low Solubility Drug Delayed Release Tablets AQbD & Method Robustness

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- Analytical QbD
- Analytical Method Robustness (Dissolution)
- Next Steps

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Gage R&R

Background (Analytical method)	Activities	Learnings (so far)
• Current formulation for drug is designed to release drug at specific pH for action at the target site. • Product is selected for AQbD study due to challenges faced to obtain suitable DR profile, during optimization, pivotal and exhibit batch analysis.	• Fishbone & initial risks mapped (Heat Map) for Dissolution method • FMEA discussed with manufacturing site • ATP elaboration based on the outcome	• Able to Identify & categorize risks w.r.t various parts of the method

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Initial Risk Assessment through Heat map

IPA Innovation, Quality and Global Reach

CQAs →

Process Parameters ↓

Fishbone Bone Number	Fishbone Bone Name	Name	
			Head
			% Dissolution
1.1	Man	Experience	Less experience of analyst will have different understanding of method and can report variation in final results.
1.2	Man	Skill/ Knowledge	Product is highly sensitive molecule. Knowledge of product/analytical methods/in-house SOP's/GP's is required for minimal variation in results.
2.1	Sample Preparation	Volume transfer into vessel of media	DR of Product has three stages. One acid stage and two buffer stage each with different volume, hence exact amount of media should be transferred as it is quantitative test.
2.2	Sample Preparation	Sample filtration and discard volume	If filter saturation was not proper as specified, results may vary.
2.3	Sample Preparation	Sampling from vessel/Sampling Zone	It is a crucial step wherein non-uniform practice of sample withdrawl will significantly impact the drug release profile
2.4	Sample Preparation	Sample dilution	Inaccurate sample dilution will impact the results
3.1	Dissolution Media Preparation	pH of Buffer	pH of media is highly critical in this method, as the drug release is dependent on pH of media.
3.2	Dissolution Media Preparation	Degassing of media	if degassing of media was not performed, it can affect % drug dissolved because of entrapped air in media.
4.1	Standard Prepration	Weighing and Transfer of Standard	If the weighing and transfer of standard is not done accurately, it will directly affect the % drug dissolution.
4.2	Standard Preparation	Filtration and discard volume	If filter saturation was not proper as specified, resu
4.3	Standard Preparation	Sonication (Sonicate to dissolve)	During experimentation It was observed that sonication (about 5 min) wit dissolve standard. If standard is not dissolved completely it
4.4	Standard Preparation	Dilution of Standard	Inaccurate standard dilution will impact the
5.1	Machine	pH meter	Dissolution of Product is pH dependent, if pH meter is not giving accur affected.
5.2	Machine	UV Spectrophotometer	Calibrated UV spectrophotometer should be
5.3	Machine	Degasser	If degasser is not working properly entrapped air in dissolution m
5.4	Machine	Distek	Calibrated dissolution apparatus should be
5.4.1	Machine	Apparatus condition	Apparatus should be visually verified for vessel cracks, shaft po
5.4.2	Machine	Vessel Temperature/RPM	Improperly monitored vessel temperature will impact the results. RPM profile.
6.1	Method	UV lambda (Wavelength Selection)	Wrong selection of wavelength for measurement will a
6.2	Method	Blank Correction	IF blank correction is not performed as per specified media, it will impact the result.
3.3	Dissolution Media Preparation	Weighing of reagents for preparation of disso media	weight of reagents may impact the buffering capacity of media.
3.4	Dissolution Media Preparation	preparation of 0.1N HCl for disso media at acid stage	Will not impact the release profile.

Relationship between method parameters & Dissolution with Risk Levels indicated as:

1. Red - for high severity,
2. Yellow – medium severity,
3. Green for low severity

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Method Robustness Study:

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Background & Rationale for prioritizing Dissolution method	Activities	Learnings
• Multi-stage dissolution with multi stage specifications to comply. • pH dependent drug release • Challenges during method optimization for variability for DR results.	• Initial Fish bone and Heat Map assessment done • Experiment designed for 4 Analysts – 3 batches • Experiments completed and data analyzed.	• Qualitative observations indicate possibilities of improvement on method w.r.t building precautions & elaborations

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Dissolution Data

3 batches & 4 analysts

Dissolution Profile of DR Tablets																		
	% Drug Dissolve																	
Analyst	Batch-1						Batch-2						Batch-3					
A	TEST-1 (Time Points)			TEST-2 (Time Points)			TEST-1 (Time Points)			TEST-2 (Time Points)			TEST-1 (Time Points)			TEST-2 (Time Points)		
	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr
Mean	18	56	102	16	53	103	27	65	101	19	62	101	41	80	102	36	81	100
Min	12	46	101	13	46	102	22	62	100	16	59	100	30	70	101	29	71	99
Max	20	60	104	22	63	104	34	69	102	26	68	102	49	99	103	44	90	101
Analyst	Batch-1						Batch-2						Batch-3					
B	TEST-1 (Time Points)			TEST-2 (Time Points)			TEST-1 (Time Points)			TEST-2 (Time Points)			TEST-1 (Time Points)			TEST-2 (Time Points)		
	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr
Mean	14	52	103	19	58	101	28	64	100	15	57	102	31	78	99	37	86	101
Min	**11**	**46**	**102**	**15**	**51**	**101**	**24**	**60**	**99**	**14**	**53**	**100**	**25**	**64**	**98**	**32**	**70**	**101**
Max	**17**	**58**	**103**	**23**	**62**	**102**	**32**	**68**	**100**	**18**	**59**	**103**	**36**	**93**	**101**	**43**	**99**	**102**
Analyst	Batch-1						Batch-2						Batch-3					
C	TEST-1 (Time Points)			TEST-2 (Time Points)			TEST-1 (Time Points)			TEST-2 (Time Points)			TEST-1 (Time Points)			TEST-2 (Time Points)		
	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr
Mean	19	58	102	16	52	102	26	64	100	13	57	100	33	80	101	38	80	100
Min	16	53	101	12	48	101	24	61	98	12	54	99	27	69	100	28	68	99
Max	22	62	103	18	57	103	30	69	101	14	59	102	39	99	104	49	98	100
Analyst	Batch-1						Batch-2						Batch-3					
D	TEST-1 (Time Points)			TEST-2 (Time Points)			TEST-1 (Time Points)			TEST-2 (Time Points)			TEST-1 (Time Points)			TEST-2 (Time Points)		
	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr	1 hr	2 hr	6 hr
Mean	14	51	103	12	48	103	32	70	102	18	60	102	29	81	102	46	83	102
Min	11	46	102	7	40	99	29	67	100	15	57	101	24	74	100	39	75	101
Max	17	59	105	16	53	106	37	76	103	19	65	102	33	93	103	56	98	103

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For Final Time Point, all % Dissolution for all batches are similar

	p Value from ANOVA Table		Total Gage R&R		Part to Part		Repeatability	Reproducibility
	Analyst	Batch No. (Analyst)	Comp.	%	Comp.	%	%	%
1 hr	0.992	0.000	36.393	25.34	107.246	74.66	25.34	0
2 hr	1.000	0.000	58.332	22.71	198.489	77.29	22.71	0
6 hr	0.308	0.000	1.36655	62.99	0.802	37.01	57.21	5.78

GRR -Minitab Output

Batch to Batch Variation appears higher than analyst to analyst variation

For 6 hour time point GRR component & part to part significantly reduces

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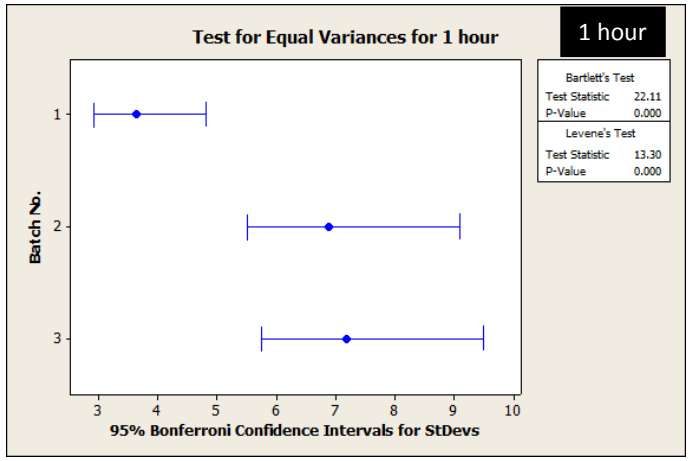
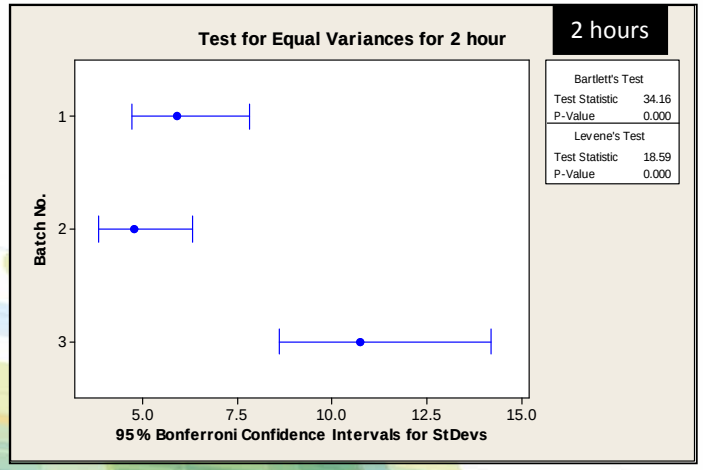
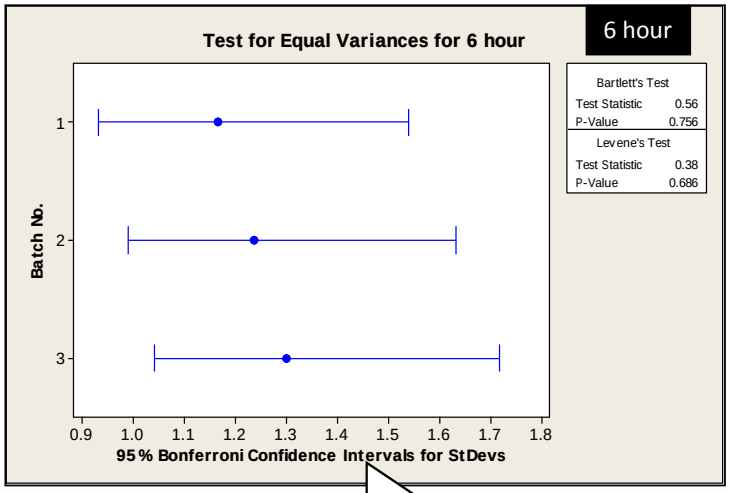
Batch-to-Batch variability high for Initial Time Point







No difference in Batch to Batch variability

Product shows variability, similar pattern observed in RLD

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Gage R&D Study

Gage R&R Study - Nested ANOVA

Gage R&R (Nested) for Result

Source	DF	SS	MS	F	P
Analyst	3	22.3	7.44	0.0030	1.000
Batch No (Analyst)	8	19521.6	2440.20	41.8329	0.000
Repeatability	132	7699.8	58.33		
Total	143	27243.8			

Gage R&R

Source	VarComp	%Contribution (of VarComp)
Total Gage R&R	58.332	22.71
Repeatability	58.332	22.71
Reproducibility	0.000	0.00
Part-To-Part	198.489	77.29
Total Variation	256.821	100.00

Process tolerance = 30

Source	StdDev (SD)	Study Var (4 * SD)	%Study Var (%SV)	%Tolerance (SV/Toler)
Total Gage R&R	7.6375	30.5502	47.66	101.83
Repeatability	7.6375	30.5502	47.66	101.83
Reproducibility	0.0000	0.0000	0.00	0.00
Part-To-Part	14.0886	56.3545	87.91	187.85
Total Variation	16.0256	64.1026	100.00	213.68

Number of Distinct Categories = 2

- In the experiment, the batch to batch variation appears to be more significant than the variation from analyst.

- The total contribution of variation from Gauge is 22%. This is high as the ideal range is <10%
- Repeatability is high, i.e., the variability in measurements when the same analyst measures samples from the same batch is high
- The variation between batches is significant contributor to the overall variation (at 77 % of overall variation)

- The % Tolerance is a measure of how much of the tolerance is being consumed by method error.
  - <10% is good & up to 30% is acceptable

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Statistical Inferences

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- There is a difference in the values reported by the analysts.
- The % contribution of variation from Method is 25%, 22% and 63% for dissolution at 1 hr., 2 hr. and 6 hrs respectively. where an ideal value is <10% and acceptable value is <30%.
- With the contribution from repeatability at 25%, 22% and 57% at 1 hr., 2 hr. and 6 hr. time points respectively, the variation appears to be from:
  - Analyst – Device interaction (choice of equipment / way of usage)
  - Analyst – Method Interaction (Obscure understanding)
- There is significant variation between batches selected and method appears to be able to detect differences between each analyst for the given tolerance

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Comparison of Observations

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Observations- Parameters	Amit (New Analyst)	Iesha (Experienced)	Balmeet (New)	Manzar (QC experience)
Pre-heating of dissolution medium	Pre-heating done with moving paddle ✗	Paddles standby mode ✔	Paddles standby mode ✔	Paddles standby mode ✔
Temperature measurement of pre-heated medium	Checked the temperature just before pouring it for Buffer stage-1 in standby mode and rotating paddle also and additionally, temperature verified using thermometer after pouring into different vessel ✔	Temperature not verified just before pouring ✗	Temperature not verified just before pouring ✗	Temperature not verified just before pouring ✗
Time taken to decant and pouring of pre-heated medium	More than 10 mins ✗	Less than 10 mins ✔	Less than 10 mins ✔	Less than 10 mins ✔
Withdrawal of 40 mL of media from Buffer-1 stage	Used cylinder to measure 40 mL ✗	Used syringe to withdraw ✔	Used syringe to withdraw ✔	Used cylinder to measure 40 mL ✗
Addition of 50 mL of 0.4 N NaOH	Used cylinder for addition ✗	6 Separate volumetric flasks containing 50 mL of NaOH ✔	One volumetric flask used for addition one by one ✗	6 Separate volumetric flasks containing 50 mL of NaOH ✔
	Addition of 50 mL of 0.4 N NaOH in all the vessels, then adjusted the pH ✗	Addition of 50 mL of 0.4 N NaOH in all the vessels, then adjusted the pH ✗	Initial day-addition of 50 ml of 0.4 N NaOH in one vessel and pH adjustment for that vessel. The step is repeated one by one for other vessels. ✔	Addition of 50 mL of 0.4 N NaOH in all the vessels, then adjusted the pH ✗
Sampling at different time points	Withdrawal of 10 mL sample followed by filtration After withdrawl and filtration for all the 6 vessels, replacement was done	Withdrawal of 10 mL sample followed by filtration After withdrawal and filtration for all the 6 vessels, replacement was done	Withdrawal of 10 mL sample followed by filtration After withdrawal and filtration for all the 6 vessels, replacement was done	Withdrawal of 10 mL sample followed by filtration After withdrawal and filtration for all the 6 vessels, replacement was done
Filtration of sample	Used one filter saturated with desired volume of filtrate for first vessel and the same filter was used for other vessels ✔	Used one filter saturated with desired volume of filtrate for first vessel and the same filter was used for other vessels ✔	Separate filter was used for each vessel	Separate filter was used for each vessel
Replacement of medium	Replacement from hole	Replacement from hole	Replacement using syringe from the side of rod.	Replacement after opening of lid by the sides of wall
Dilution of samples	Blowing of Pipette Not Done ✔	Blowing of Pipette Not Done ✔	By blowing pipette	By blowing pipette
Filtration of final sample	Using single filter	Using single filter	Using single filter	Using single filter

✗ **Incorrect**

✔ **Correct**

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Observations & Learnings

Observation	Action Taken
Accurate Measurement of Buffer pH-7.2 is critical	Calibration and verification before adjustment of pH
Media temperature for Buffer Stage-2 is critical	Ensure to maintain the temperature at 37.0± 0.5 degree for Buffer Stage-2 before initiating dissolution
ATP does not specify for mode of withdrawal	40 mL Volume to be withdrawn with syringe from vessel
Addition of 50 mL of 0.4N NaOH to be done **preferably** with volumetric flask	Addition of 50 mL of 0.4N NaOH to be done **mandatorily** with volumetric flask

- There is room for variations in executing certain instructions within the existing ATP
- Although none of the data points are out of spec, there is a contribution of variation from the measurement system
- Due to variable nature of the product, L2 stage can't be avoided
- Objective is to minimize measurement system variability

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Thank you!