Workshop - Mercoledì 10 giugno

SIMPOSIO AFI

Risk-based thinking come vera intelligenza per il mondo farmaceutico

Moderatori

Piero Iamartino
AFI

Paolo Mazzoni
PTM Consulting

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Informed decisions for better process

Workshop schedule

10:10 – 10:40	La nuova era dell'intelligenza del rischio
10:40 - 11:10	Nuova ICH Q1: product intelligence per un approccio innovativo alla stabilità
11:10 – 11:35	ICH Q3E: approccio risk-based integrato per la valutazione di E&L
11:35 – 12:00	**Il dato come bussola: l'analisi statistica a supporto del rischio**
12:00 – 12:25	Dalla teoria alla pratica: dalla gestione dello studio di stabilità all'analisi dei dati
12:25 – 12:30	Conclusione dei lavori

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Data as a Compass: Statistical Analysis for Risk Management

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Contents

Data evidence

Why Data Matters?

It gives an objective view
(To Be Interpreted)

It enables you to size and characterise performance

It helps identify what is unknown

It requires information before decisions

It gives an objective view

Drop size

Tentative Spec Limit (µl): 31.6 – 34.6

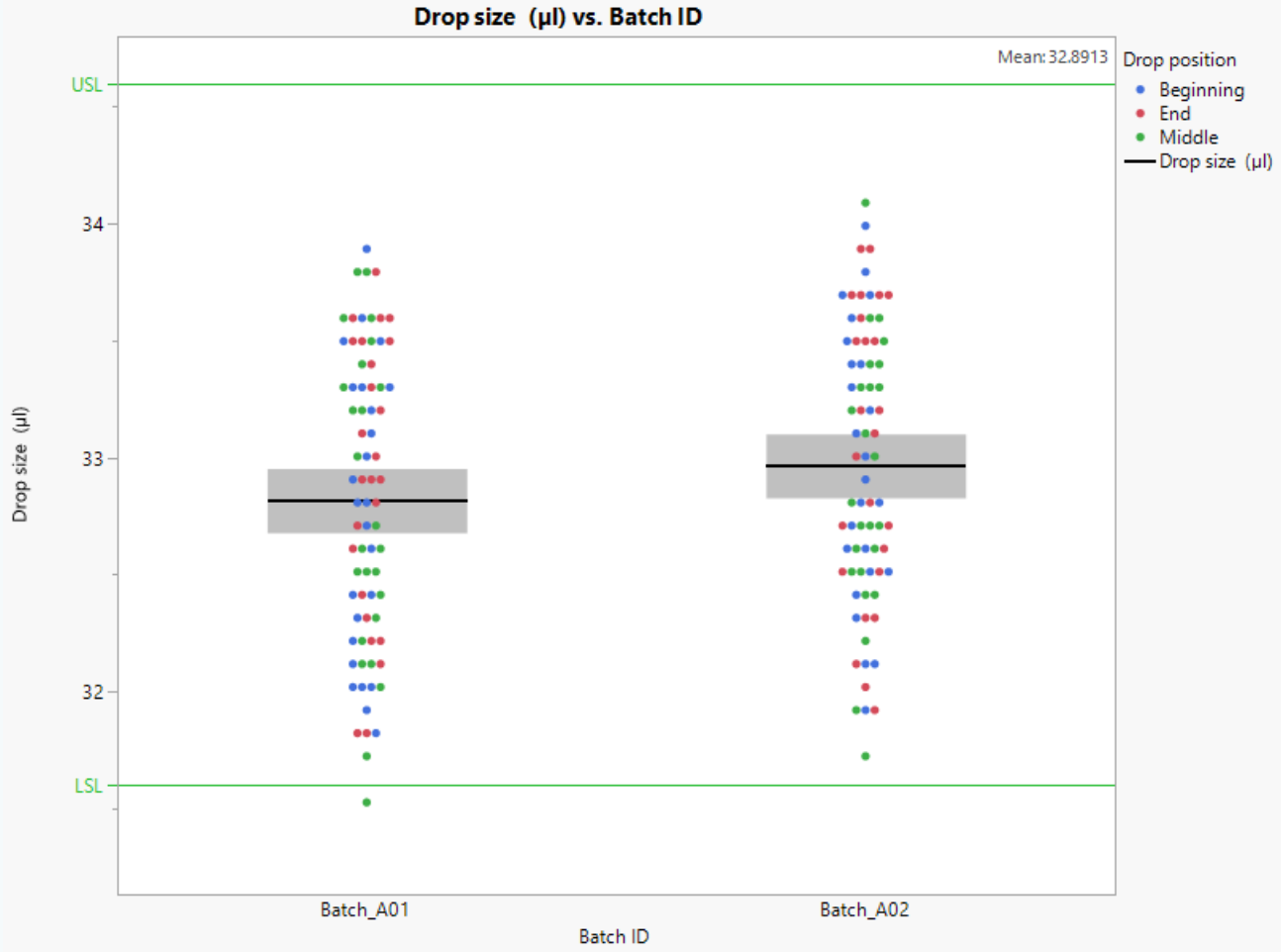
Batch ID	Drop position	Drop size (µl)
Batch_A01	Beginning	31.92
Batch_A01	Beginning	32.41
Batch_A01	Beginning	33.2
Batch_A01	Beginning	32.81
Batch_A01	Beginning	32.61
Batch_A01	Middle	32.51
Batch_A01	Middle	31.72
Batch_A01	Middle	33.5
Batch_A01	Middle	33.6
Batch_A01	Middle	32.12
Batch_A01	End	33.5
Batch_A01	End	32.91
Batch_A01	End	33.3
Batch_A01	End	32.41
Batch_A01	End	32.32
Batch_A01	Beginning	33.1
Batch_A01	Beginning	32.41
Batch_A01	Beginning	33
Batch_A01	Beginning	33.6
Batch_A01	Beginning	32.02
Batch_A01	Middle	32.51
Batch_A01	Middle	32.51
Batch_A01	Middle	33.2
Batch_A01	Middle	33.79
Batch_A01	Middle	32.41
Batch_A01	End	33.4
Batch_A01	End	32.22
Batch_A01	End	33.5
Batch_A01	End	33.1
Batch_A01	End	31.82

Batch ID	Drop position	Drop size (µl)
Batch_A01	Beginning	33.5
Batch_A01	Beginning	32.71
Batch_A01	Beginning	32.81
Batch_A01	Beginning	33.3
Batch_A01	Beginning	33.3
Batch_A01	Middle	**31.53**
Batch_A01	Middle	32.22
Batch_A01	Middle	32.61
Batch_A01	Middle	33.2
Batch_A01	Middle	33.3
Batch_A01	End	32.81
Batch_A01	End	31.82
Batch_A01	End	33.6
Batch_A01	End	33.6
Batch_A01	End	32.71
Batch_A01	Beginning	32.22
Batch_A01	Beginning	32.02
Batch_A01	Beginning	33.89
Batch_A01	Beginning	33.5
Batch_A01	Beginning	32.02
Batch_A01	Middle	32.71
Batch_A01	Middle	33.6
Batch_A01	Middle	32.12
Batch_A01	Middle	33.4
Batch_A01	Middle	33.3
Batch_A01	End	32.22
Batch_A01	End	32.91
Batch_A01	End	33.2
Batch_A01	End	33.6
Batch_A01	End	32.61

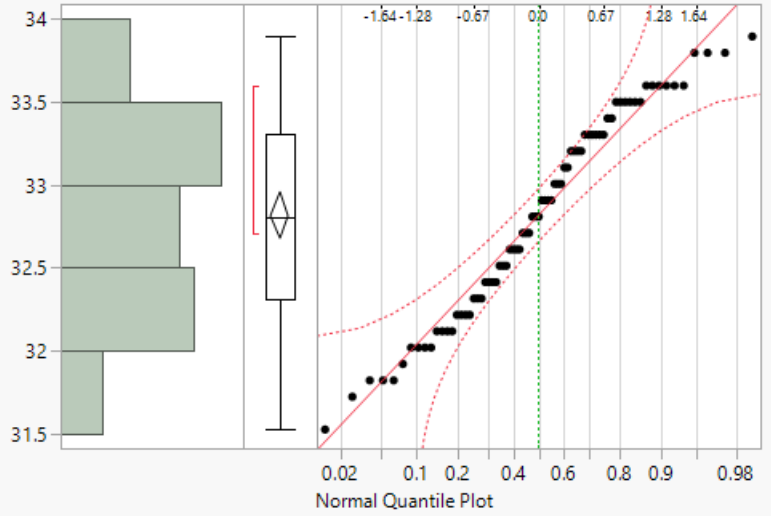
Batch ID	Drop position	Drop size (µl)
Batch_A02	Beginning	33.4
Batch_A02	Beginning	33.4
Batch_A02	Beginning	33.6
Batch_A02	Beginning	32.91
Batch_A02	Beginning	32.81
Batch_A02	Middle	32.41
Batch_A02	Middle	32.61
Batch_A02	Middle	32.51
Batch_A02	Middle	33.3
Batch_A02	Middle	32.81
Batch_A02	End	32.51
Batch_A02	End	33.89
Batch_A02	End	33.5
Batch_A02	End	32.51
Batch_A02	End	33.69
Batch_A02	Beginning	33.99
Batch_A02	Beginning	32.51
Batch_A02	Beginning	32.61
Batch_A02	Beginning	32.71
Batch_A02	Beginning	32.41
Batch_A02	Middle	32.41
Batch_A02	Middle	34.09
Batch_A02	Middle	31.92
Batch_A02	Middle	33.6
Batch_A02	Middle	32.71
Batch_A02	End	33.1
Batch_A02	End	33
Batch_A02	End	33.89
Batch_A02	End	33.69
Batch_A02	End	32.71

Etc., …

It gives an objective view



Batch_A01



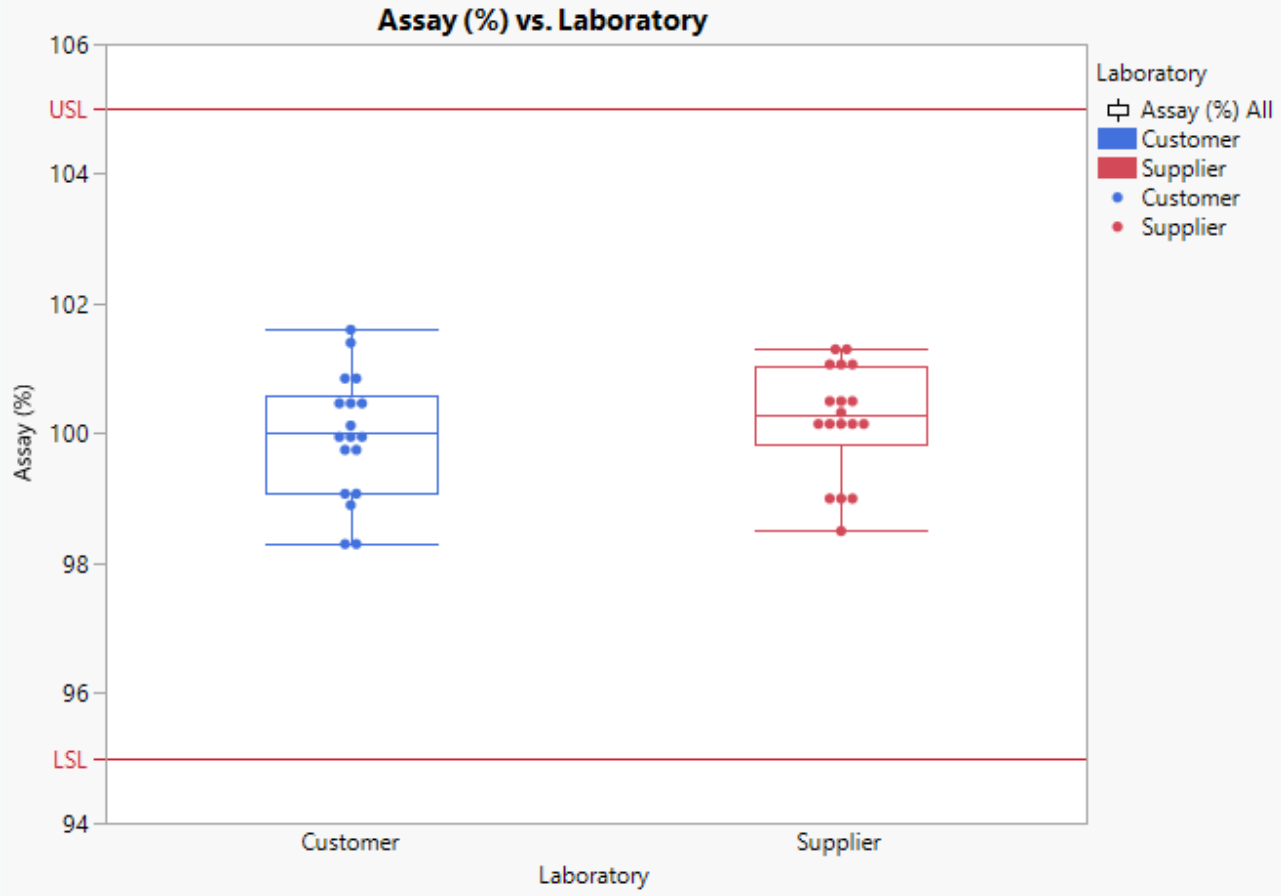
Summary Statistics

Mean	32.817077
Std Dev	0.6135999
Std Err Mean	0.0708524
Upper 95% Mean	32.958254
Lower 95% Mean	32.675901
N	75
N Missing	0

Normal Distribution Tolerance Intervals

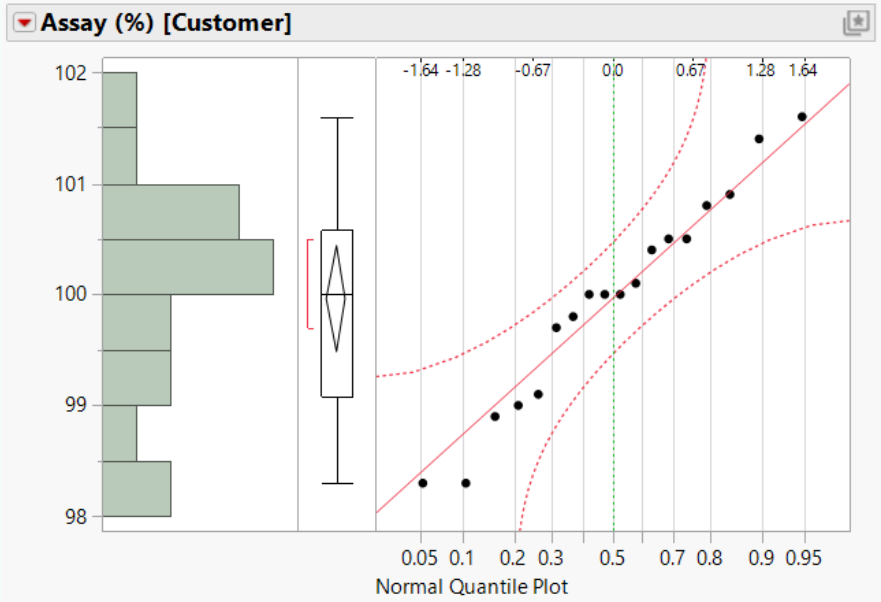
Proportion	Lower TI	Upper TI	1-Alpha
0.900	31.6397	33.99445	0.950

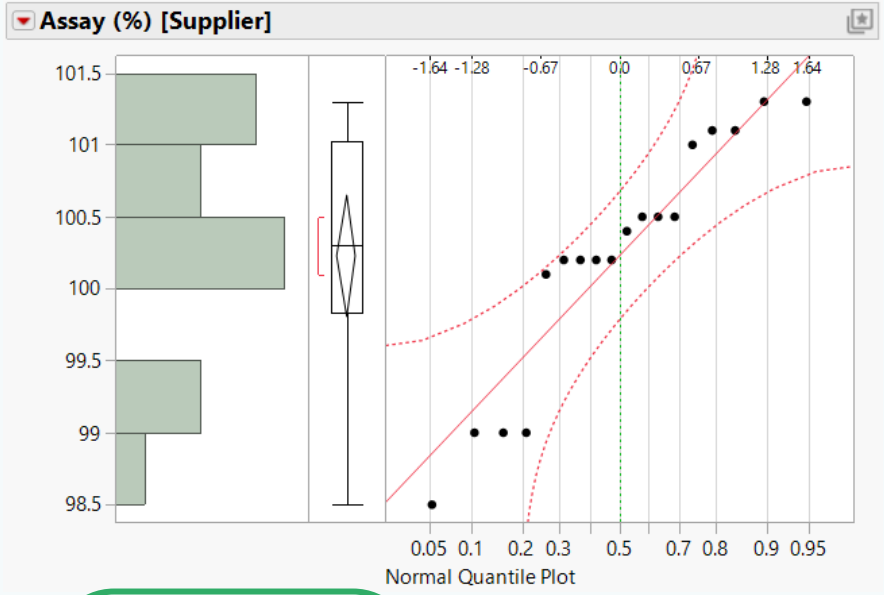
It enables you to size and characterise performance



- ✓ Managing data through ***appropriate*** tools

It enables you to size and characterise performance





Quantiles		
100.0%	maximum	101.6
99.5%		101.6
97.5%		101.6
90.0%		101.42
75.0%	quartile	100.575
50.0%	median	100
25.0%	quartile	99.075
10.0%		98.3
2.5%		98.3
0.5%		98.3
0.0%	minimum	98.3

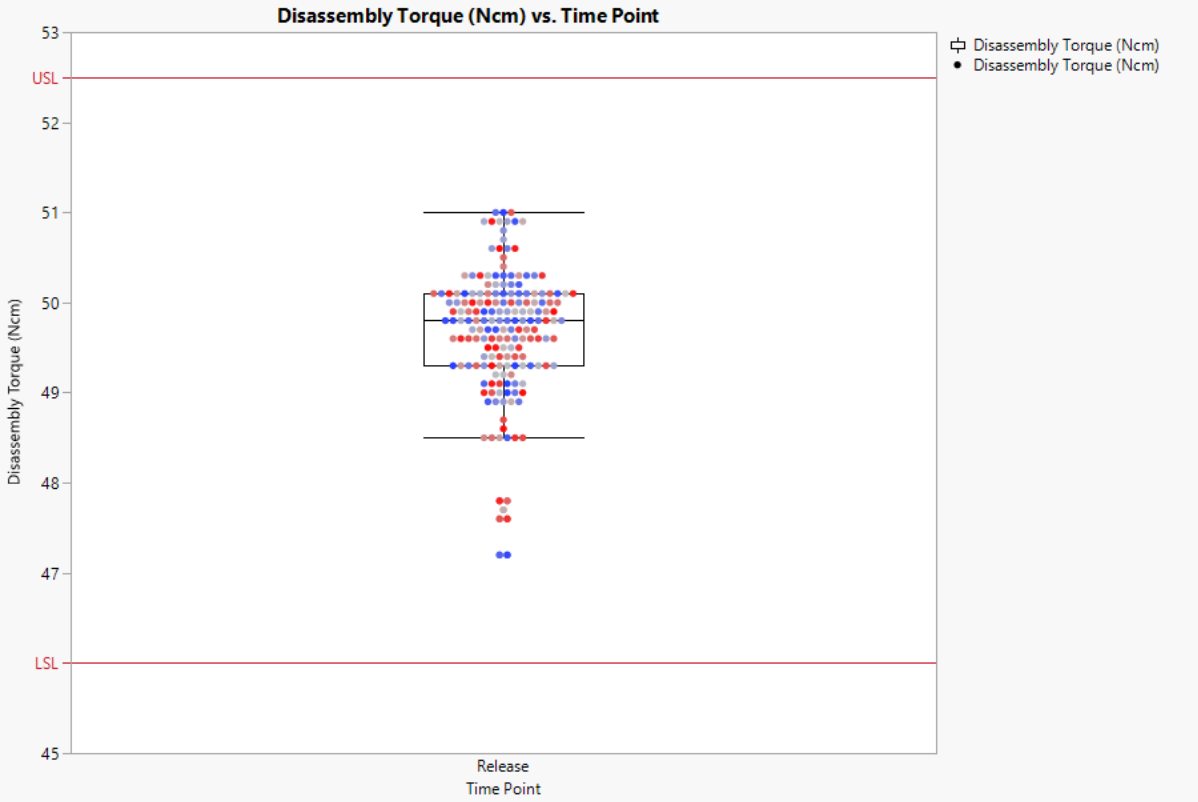
Summary Statistics	
Mean	99.961111
Std Dev	0.9561804
Std Err Mean	0.2253739
Upper 95% Mean	100.43661
Lower 95% Mean	99.485614

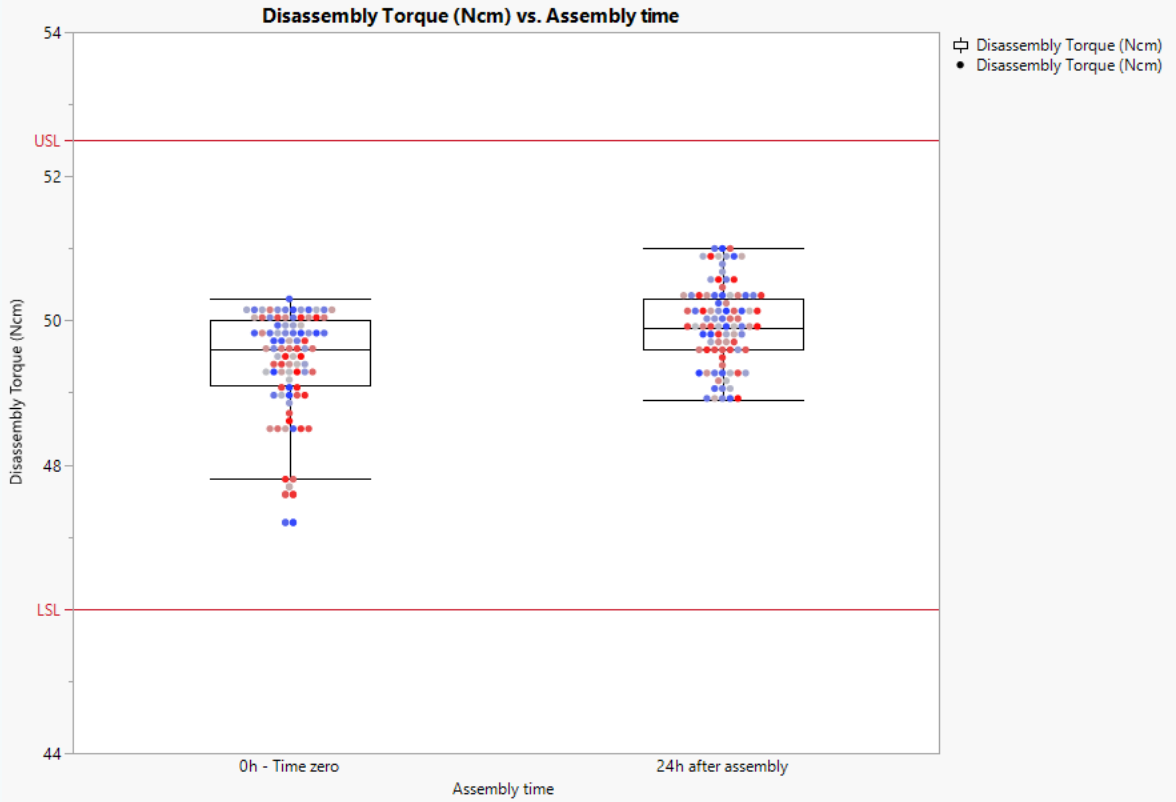
Relevant variability? Analytical measurement uncertainty?

Quantiles		
100.0%	maximum	101.3
99.5%		101.3
97.5%		101.3
90.0%		101.3
75.0%	quartile	101.025
50.0%	median	100.3
25.0%	quartile	99.825
10.0%		98.95
2.5%		98.5
0.5%		98.5
0.0%	minimum	98.5

Summary Statistics	
Mean	100.22778
Std Dev	0.8470055
Std Err Mean	0.1996411
Upper 95% Mean	100.64898
Lower 95% Mean	99.806572

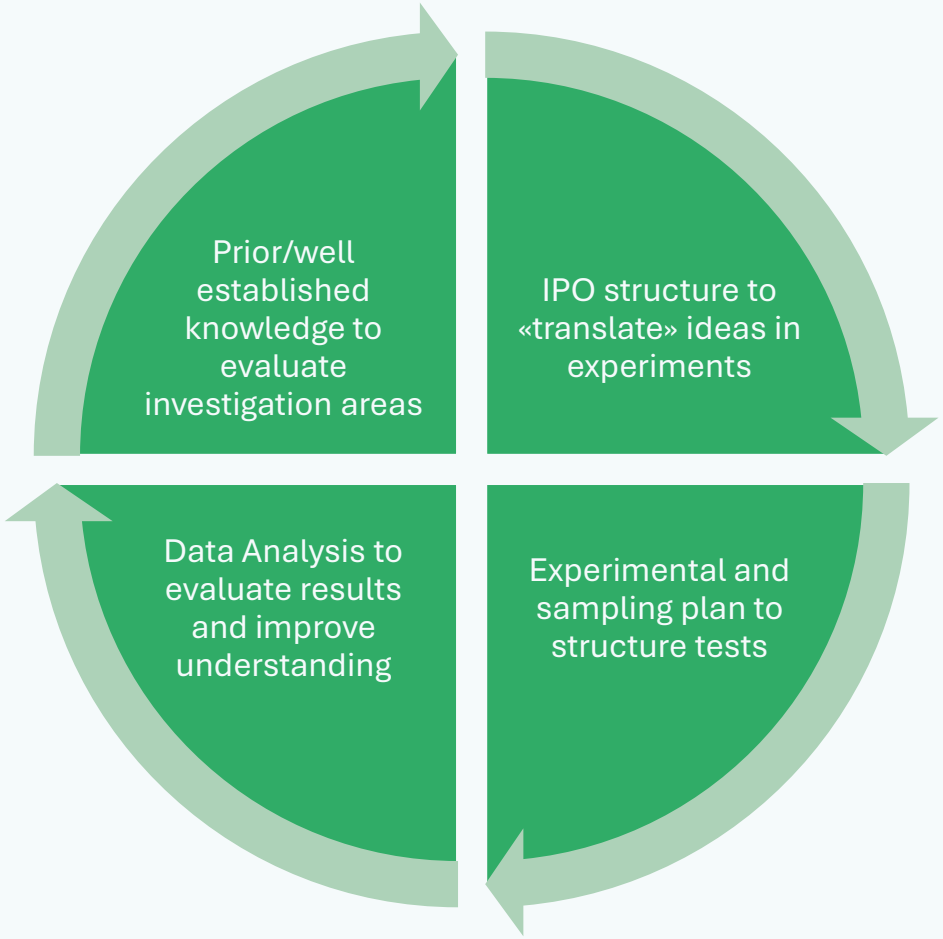
It helps identify what is unknown





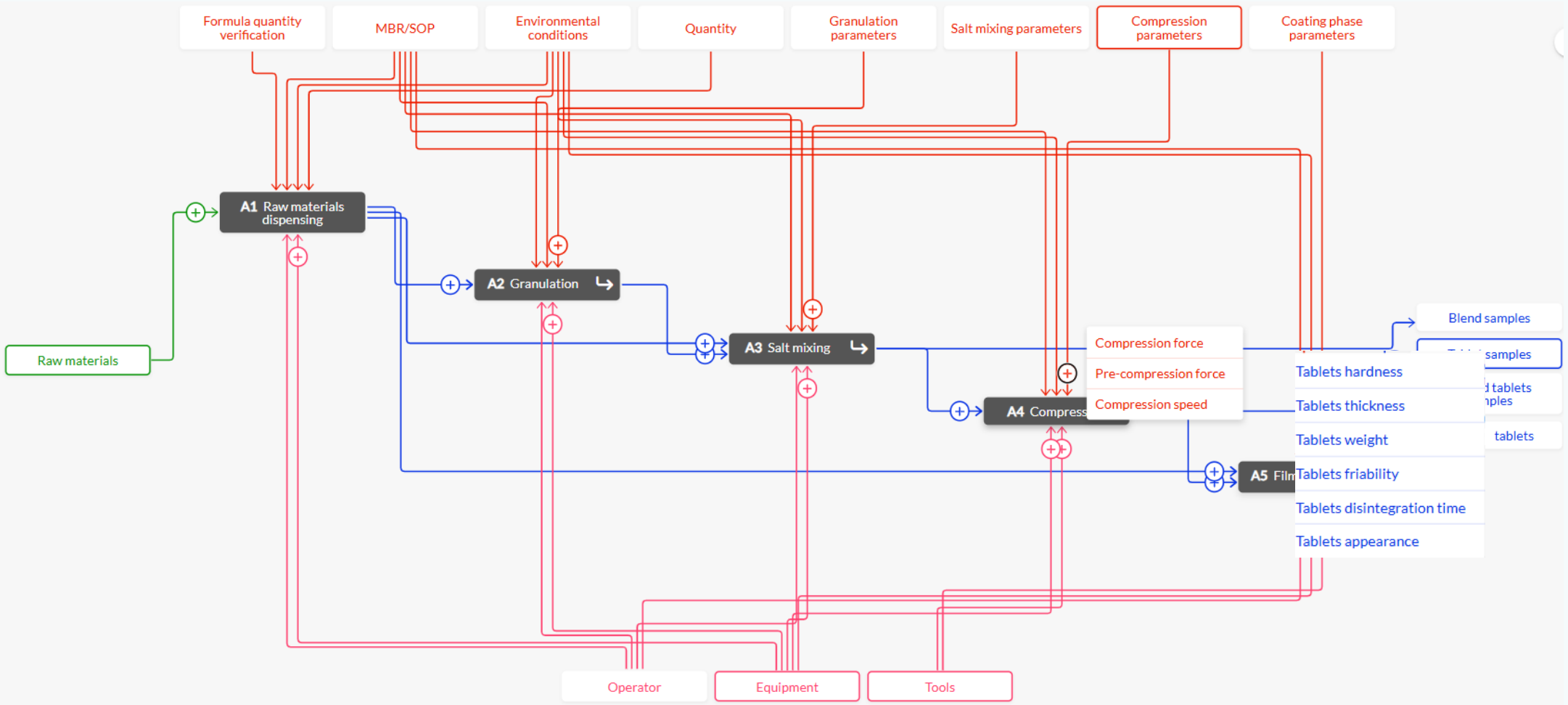
Data and Risk Management

It requires information before decisions (I/VI)



Knowledge acquisition and improvement of comprehension

It requires information before decisions (II/VI)



It requires information before decisions (III/VI)

Sheet Name	Function Name	Parameter	Impact on CQAs	Know ledge	Risk Index	Impacted CQAs	Rational
A0	Tablets Compression	Compression force	High	Insufficient		Uniformity of mass of single dose preparation; Average weight; Appearance; Dissolution profile.	Dedicated investigations are required to characterize compression force impact on considered process step
A0	Tablets Compression	Pre-compression force	Medium	Strong		Uniformity of mass of single dose preparation; Average weight; Appearance; Dissolution profile.	Impact on tablets capping is present, parameter is sufficiently known to establish suitable pre-compression force setting
A0	Tablets Compression	Compression speed	Medium	Insufficient		Uniformity of mass of single dose preparation; Average weight; Appearance; Dissolution profile.	Dedicated investigations could be done to characterize compression speed impact on considered process step

It requires information before decisions (IV/VI)

Input variables

- Compression Force
- Compression Speed

Compression Phase

Measurable Output

- Uniformity of mass of single dose preparation
- Average weight
- Harness
- Thickness
- Friability
- Disintegration Time

It requires information before decisions (V/VI)

Run order	Compression force (kN)	Compression speed (tbs/h)	Pre-compression force (kN)	Total run time (min)	Minutes before tablet collection	Tablets sampled in 20 minutes	QAs to be measured
1	35	30000	3	22	2	20 (+ 10)	Weight (g) Thickness (mm) Hardness (kp): 10+10 tbs (20 single values 2 mean values) Friability (%): 10 tbs (1 reportable value) Disintegration Time (min): 6 tbs (1 reportable value)
2	40	40000	3	22	2	20 (+ 10)	
3	45	30000	3	22	2	20 (+ 10)	
4	45	50000	3	22	2	20 (+ 10)	
5	35	50000	3	22	2	20 (+ 10)	
6	45	50000	3	22	2	20 (+ 10)	
7	35	30000	3	22	2	20 (+ 10)	
8	45	30000	3	22	2	20 (+ 10)	
9	35	50000	3	22	2	20 (+ 10)	
10	40	40000	3	22	2	20 (+ 10)	

4 replicates of the plan

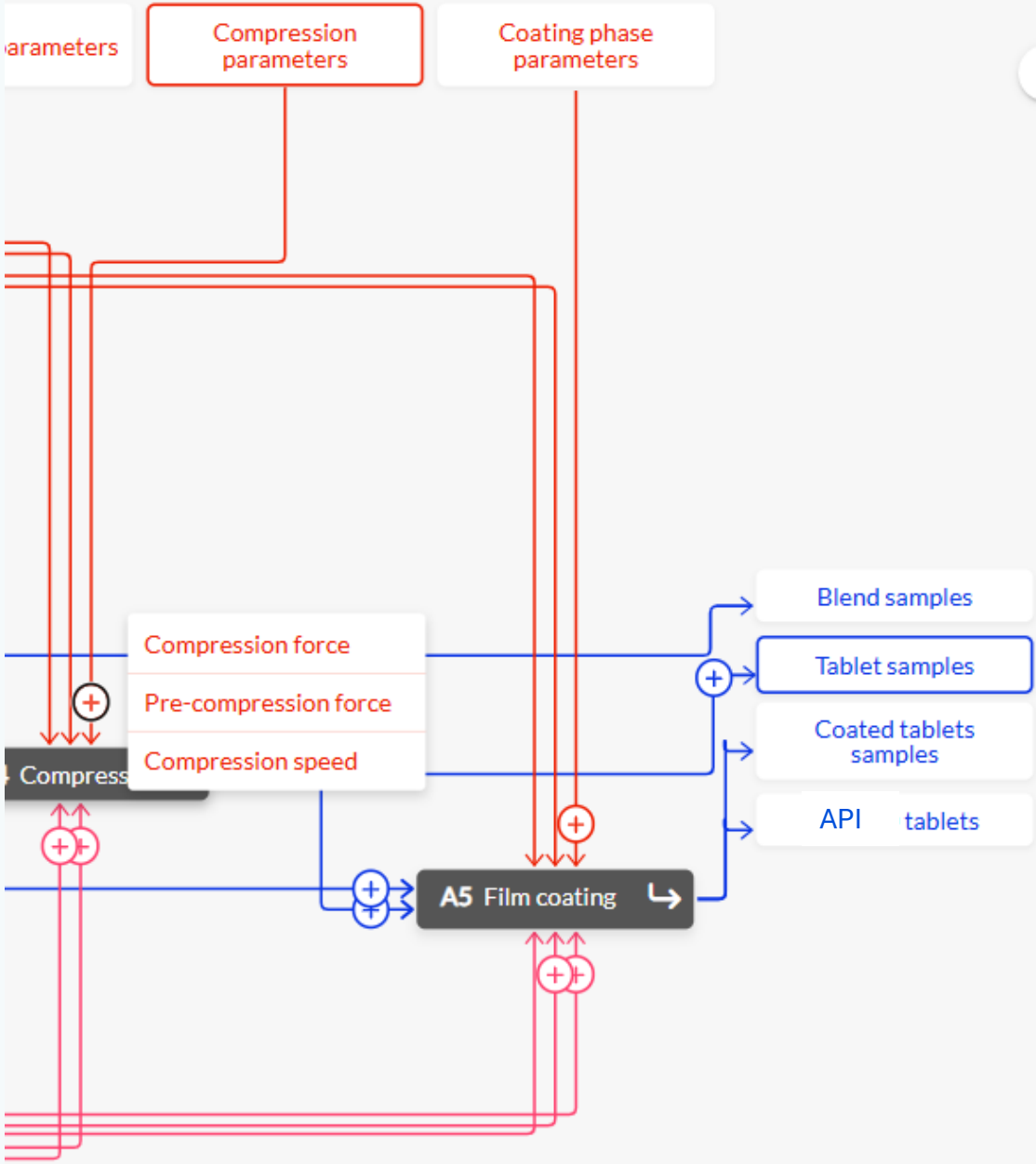
It requires information before decisions (VI/VI)

Optimal settings:

- 45 N Compression force
- 40.000 (tbs/h) Compression Speed

Additional investigations before production:

- Tentative specs for Hardness to be updated
- Confirmatory run at selected settings to be performed



Conclusions and take-home messages

Data evaluation: where and when

Early research
Bootstrap/Montecarlo simulation,
Screening DoE,
Mixture DoE, Multivariate analysis

Product&Process Development
Modelling DoE, Optimization plan,
Data Mean and Dispersion for
preliminary robustness evaluation

Analytical Development
Multivariate Analyses, DoE

Scale up and Technology Transfer
ANOVA, Data Comparison,
Outlier test, trend analysis

Commercial production (SPC)
Capability, Trend Analysis,
Control and Charts,
Statistical Sampling

Stability data evaluation
Enhanced Predictive
Modelling, Confidence
and Tolerance Intervals

...take-home messages

- Statistics enables improvements in product and process understanding.
- It allows to separate sources of noise from natural data variability.
- It enables to gather reliable conclusions.

Data analyses not as decisional criteria,
but as a solid approach to knowledge improvement and data-driven decision.

Thanks for listening

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for better process

Any questions?

Do you need any information?

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