Statistics in the Context of Clinically Relevant Commercial Specification Acceptance Criteria

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Eli Lilly and Company

4th Statistical and Data Management Approaches for Biotechnology Drug Development – IABS/FDA

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Lilly

Topics

- Clinical Relevance
- Challenges
- Role of Statistics
  - Developing Acceptance Criteria
    - Start with the patient
  - Commercial Risk Considerations

Justification of Specifications

As stated in ICH Q6A

“The justification should refer to relevant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate.”

We're hearing from Health Authorities …

- Specification acceptance criteria should
  - be based on the risk to clinical performance
  - provide consistency of the commercial material back to the clinical experience
  - not be based on the capability of the manufacturing process

➢ Clinically relevant

... what does that mean?

PDA/FDA Conference 2015
September 30, 2015

Sarah Pope Miksinski, Ph.D.
Director (Acting)
Office of New Drug Products

Clinical Relevance

- Product quality = the foundation upon which clinical safety and efficacy assessment depend
- Integration of quality and clinical assessment
- Without clinical linkage, acceptance criteria could be too wide, too tight or irrelevant
- A product is "fit for use" by meeting established quality attributes (purity, potency/strength, identity, bioavailability/delivery, labeling/packaging, etc.)
- Strive to establish appropriate, preferably quantitative, correlations between quality attributes and clinical performance

Adapted from M. Nasr's "Setting Specifications in the 21st Century"/PQRI Workshop, March 16, 2005

Two important terms

- Clinical Relevance
  - Based on medical understanding
- Clinical Experience
  - Based on characterization of batch quality in clinical trials
  - Statistics plays a role

Challenges: Complexity

- Molecular Heterogeneity
  - Charge distribution leads to complicated properties
    - What is the appropriate level of control, what gets controlled, groups of heterogeneous species? Key peaks? Profile?
  - How best to get a range of charge quality in clinic without impacting clinical performance?
  - What does it mean to keep consistency with charge distribution back to the clinical experience?
- Potency
  - Unlikely to gain a wide range of material quality into the clinic
- Patient-use period
  - How is that (or should it be) incorporated in the clinical trials with regard to understanding clinical performance relative to post-launch performance?

Challenges: Limitations

- Few clinical trial batches
- Limited stability data
- Fewer older batches in clinical trials
- Narrow range of material variability throughout clinical trials
  - Limited diversity of batches
  - Limited process variability experience
- Limited method variability experience

How to proceed?

- Assess the risk to the patient for each CQA to understand clinically relevant space
- Assess the patient exposure via batch quality in clinical trials to understand clinical experience
- Develop specification acceptance criteria that are within the clinically relevant space and are consistent with the clinical trial experience
  - Consistent doesn’t imply max/min of observed data

Role of Statistics

- Quality of clinical trial batches ... data analysis
  - Characterize batch quality at release
    - Need to understand typical process performance
  - Evaluate change on stability
    - Long-term storage and patient-use periods
  - Assess common cause variability
    - Method variability
    - Process variability

Developing Acceptance Criteria ... An Approach

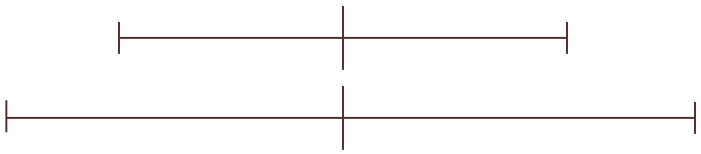
- Goal: Clear linkage across DS and DP acceptance criteria so that the material quality will be acceptable to the patient throughout shelf life, including patient use period

- Start with the patient to determine …
  - DP end of shelf life acceptance criteria
  - DP release criteria
  - DS end of shelf life criteria
  - DS release criteria

DP change

DS change

Helpful Statistical Tools



3 sigma interval

95/99 tolerance interval

Batch Release Data

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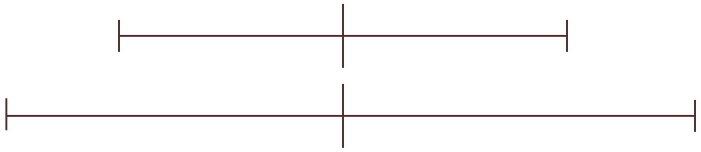

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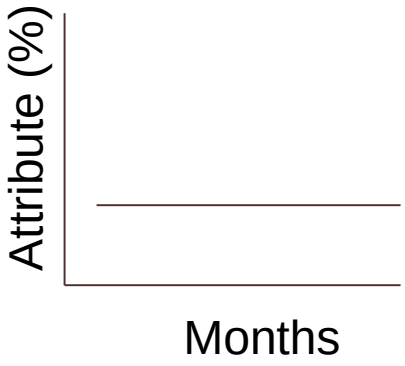

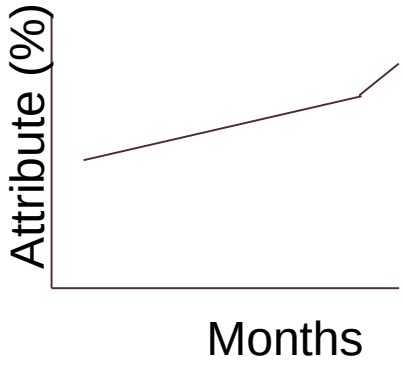

Change on stability

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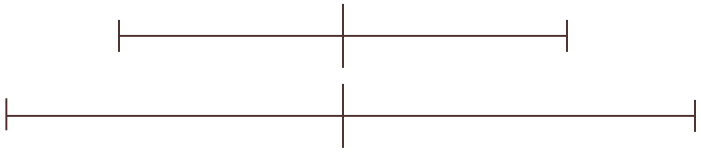

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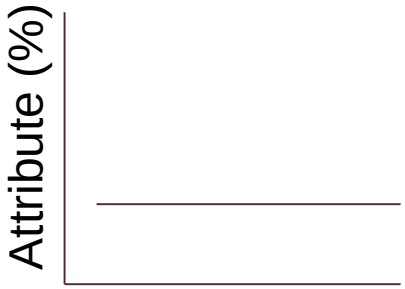
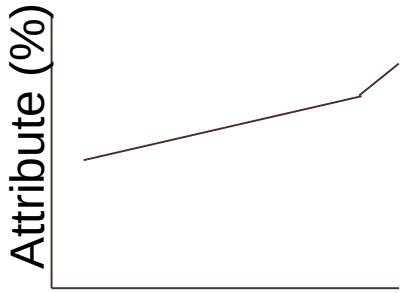
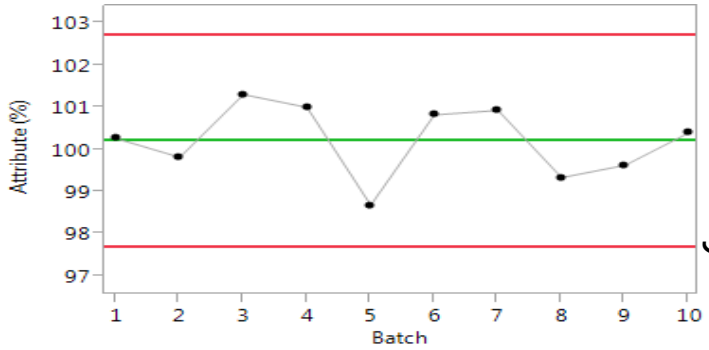




Change on stability



Assess Process Variability

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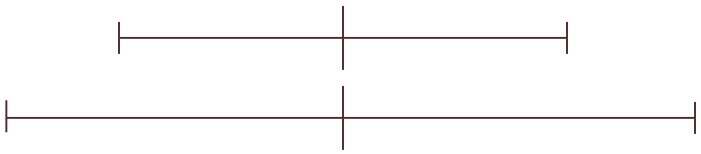

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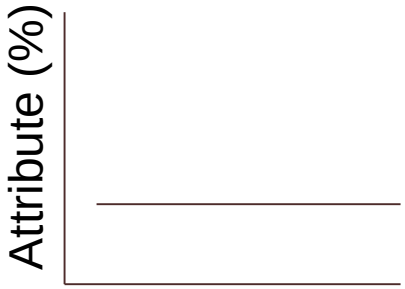

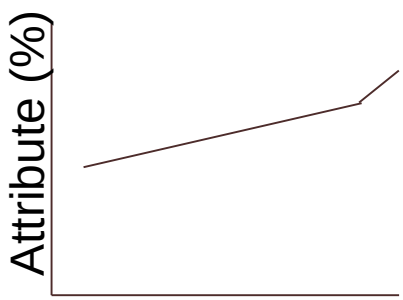

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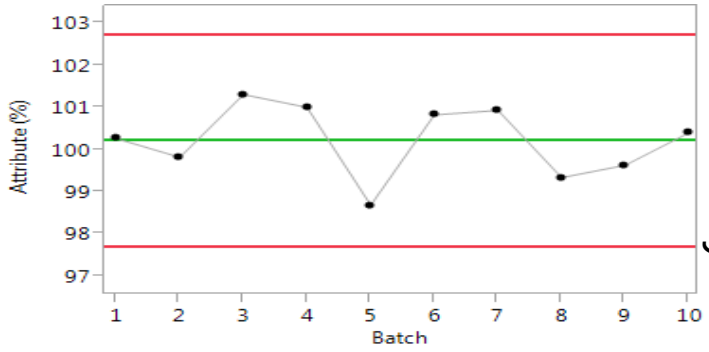

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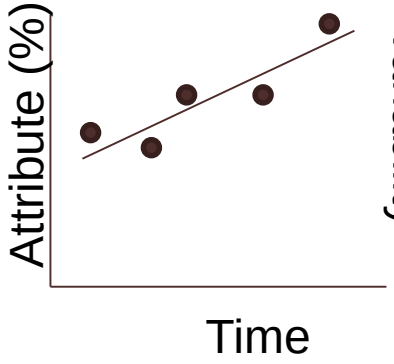
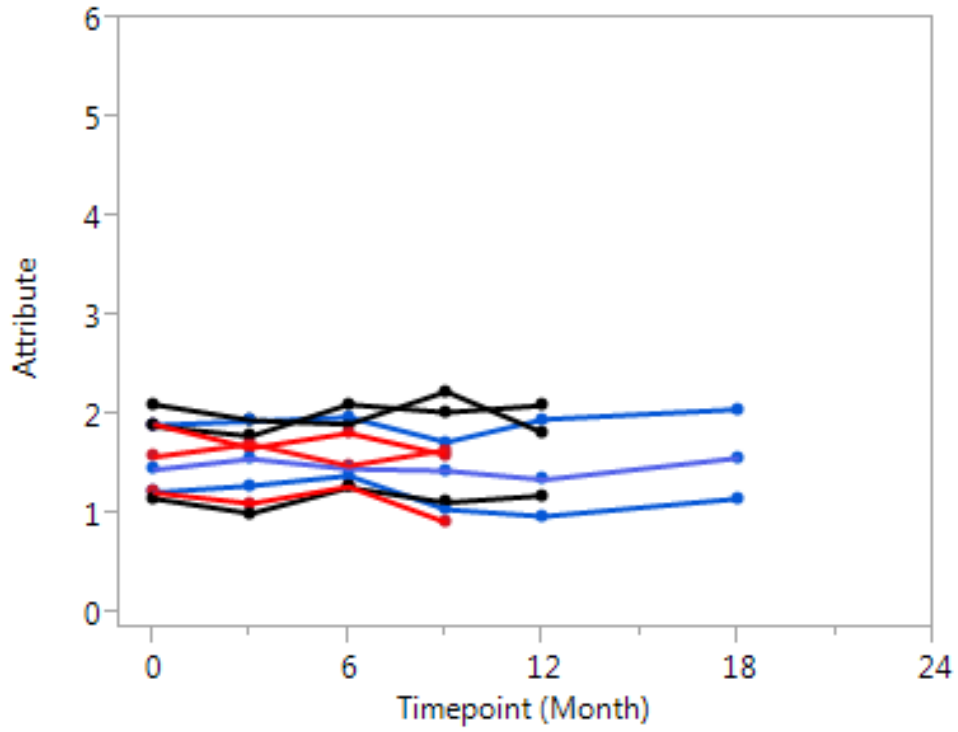


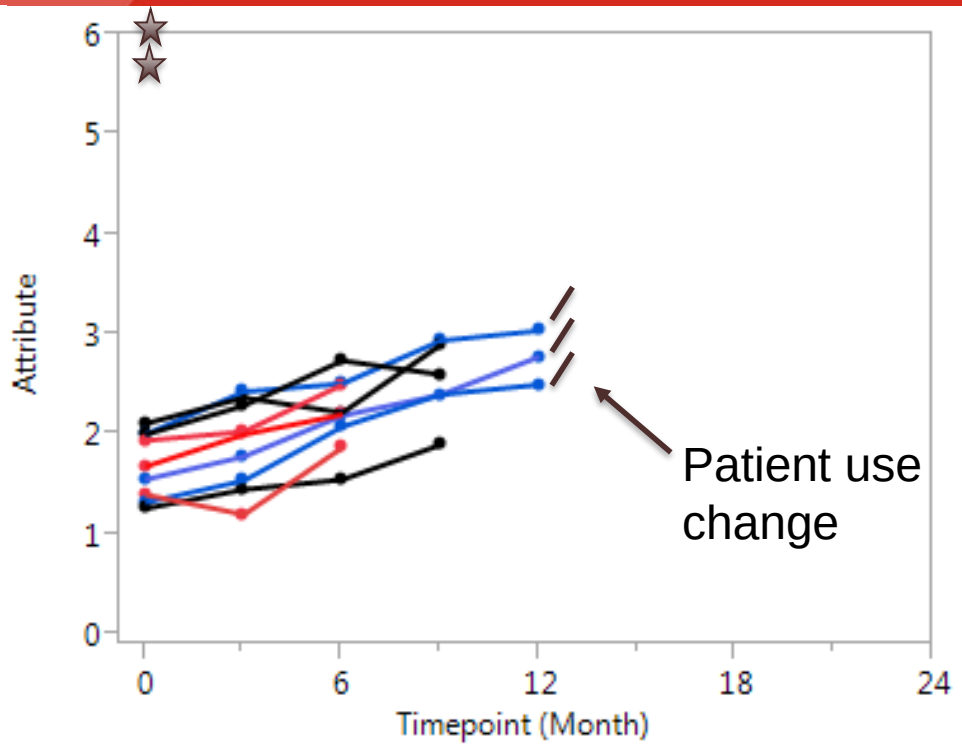
Assess Method Variability

Illustration

Levels from ascending dose studies



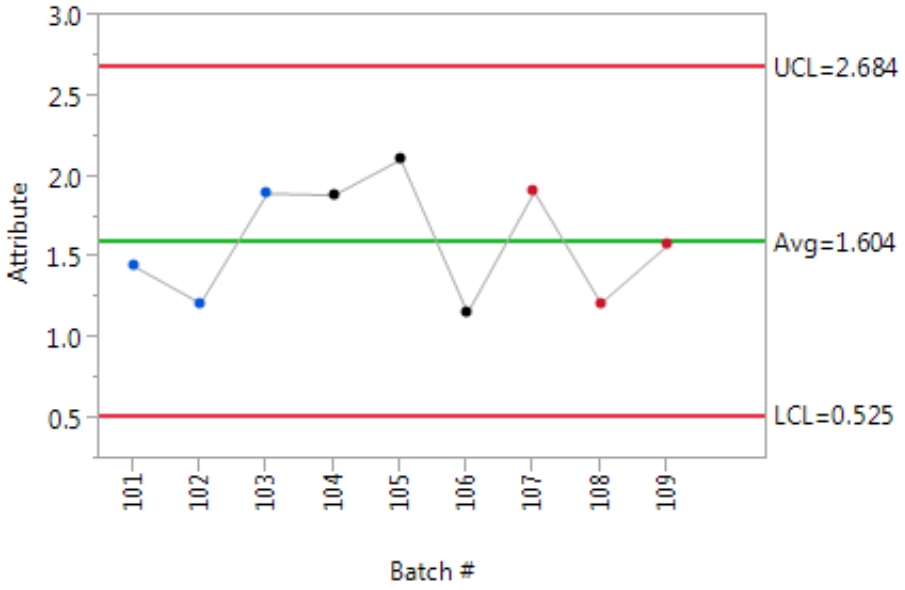
Drug Substance



Drug Product

Control Charts of Release Data

Drug Substance



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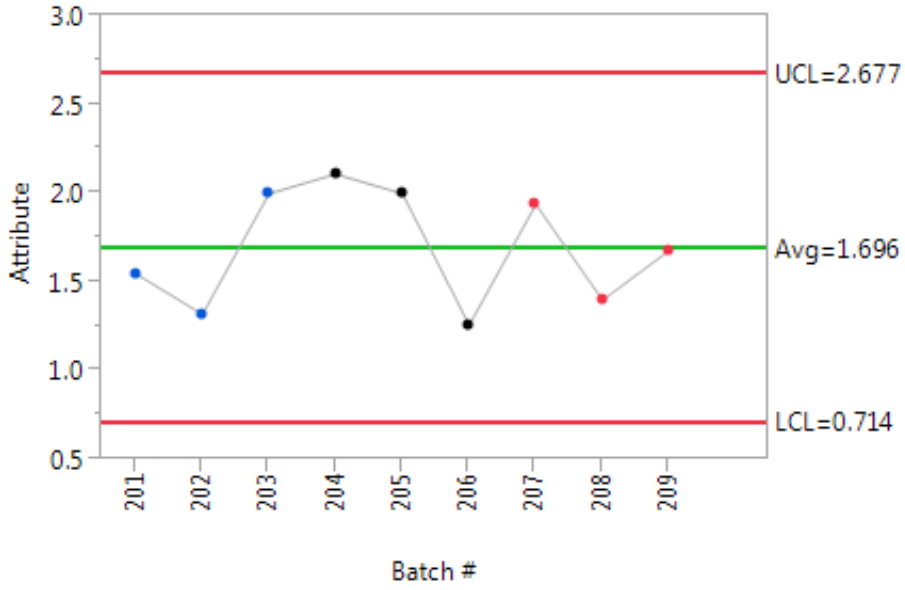
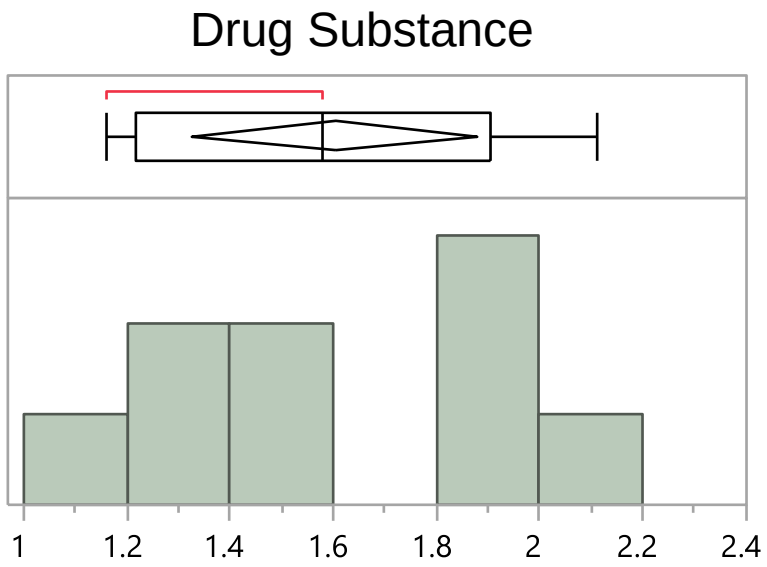


- Drug product quality may be largely determined by drug substance
- Process variability can be visualized and summarized
- 3 sigma limits on control chart are preliminary given limited data
- Recommend evaluating 95/99 tolerance intervals

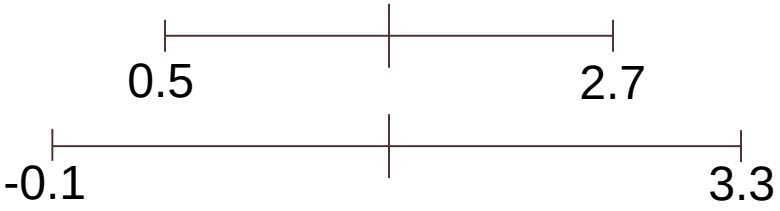
Characterizing Batch Release Data



Quantiles		
100.0	maximu	2.11
99.5%		2.11
97.5%		2.11
90.0%		2.11
75.0%	quartile	1.905
50.0%	median	1.58
25.0%	quartile	1.22
10.0%		1.16
2.5%		1.16
0.5%		1.16
0.0%	minimu	1.16

Summary Statistics	
Mean	1.6044444
Std Dev	0.3597607
Std Err Mean	0.1199202
Upper 95% Mea	1.880981
Lower 95% Mea	1.3279079
N	9

Common intervals to characterize data:



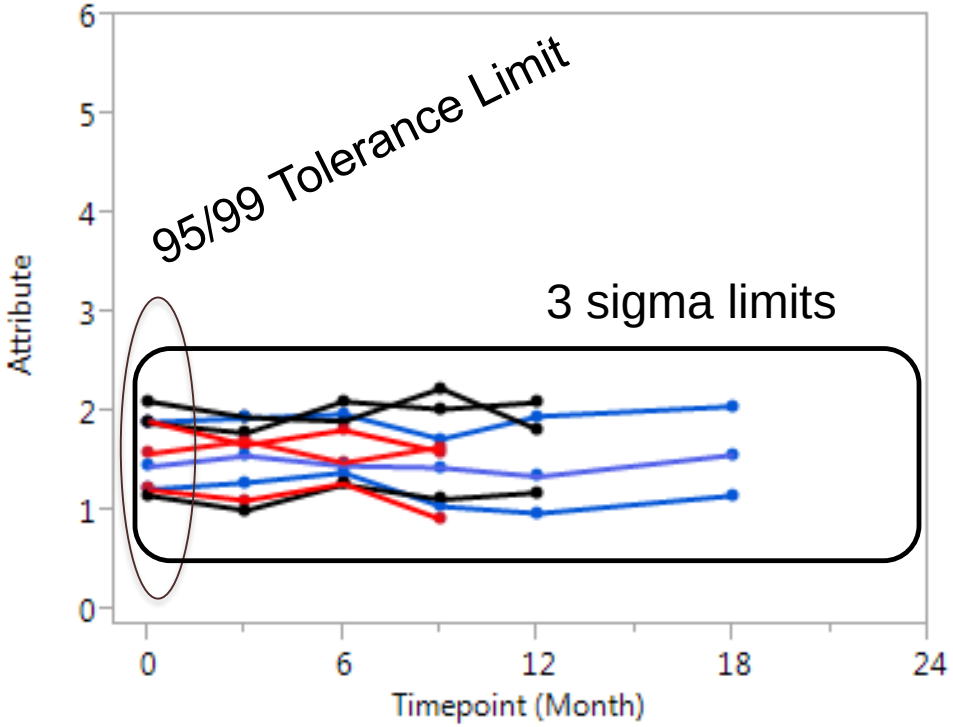
3 sigma interval (2 sigma?) — Too narrow?

95/99 tolerance interval — Too wide? Not wide enough?

“3 Sigma” and Tolerance Intervals

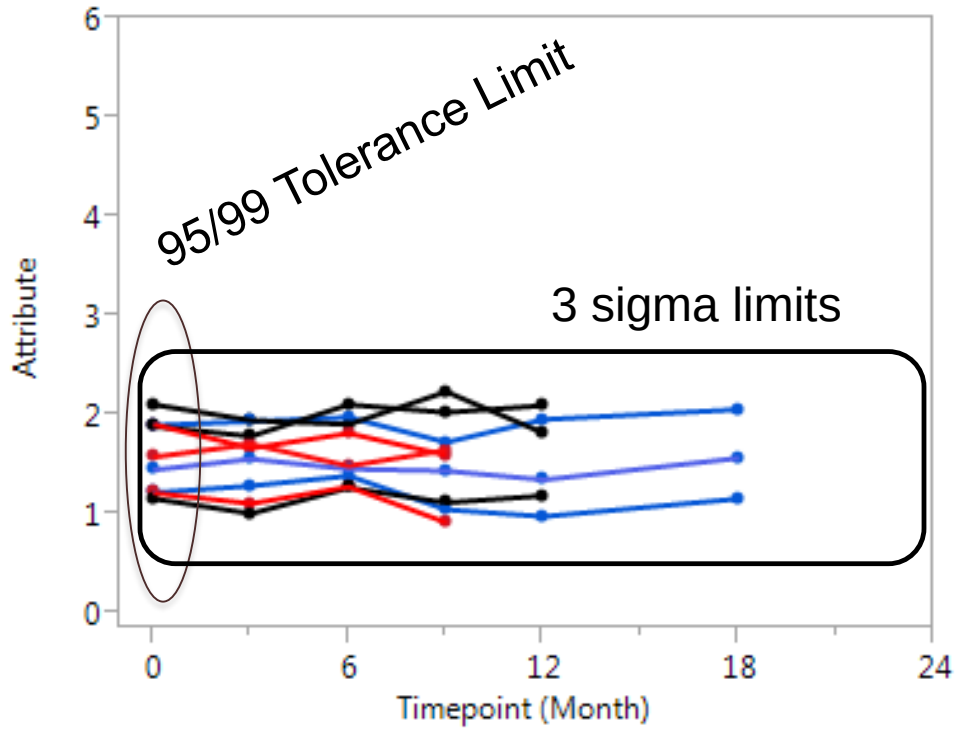
- “3 Sigma” *Average +/- 3 * Standard Deviation*
  - Encompasses 99.7% of the population if true distribution is Normal and mean and standard deviation are known
  - Straightforward to calculate
  - Easy to visualize
  - Commonly used
- 95/99 Tolerance Interval *Average +/- k * Standard Deviation*
  - Provides 95% confidence that the interval encompasses 99% of the population
  - Since the true mean and variance are not known, the tolerance interval provides a degree of confidence for the interval to include a certain proportion of the population, i.e. wider interval for lower n
  - Narrower than 3 sigma interval when more than ~30 results

Illustration



Drug Substance

Illustration



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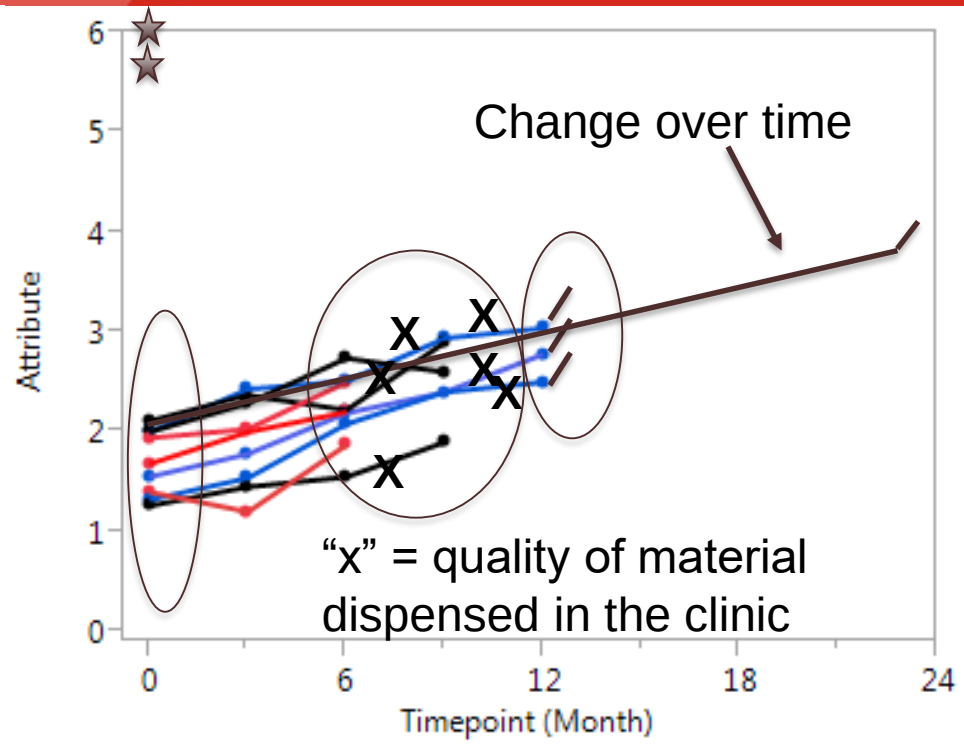
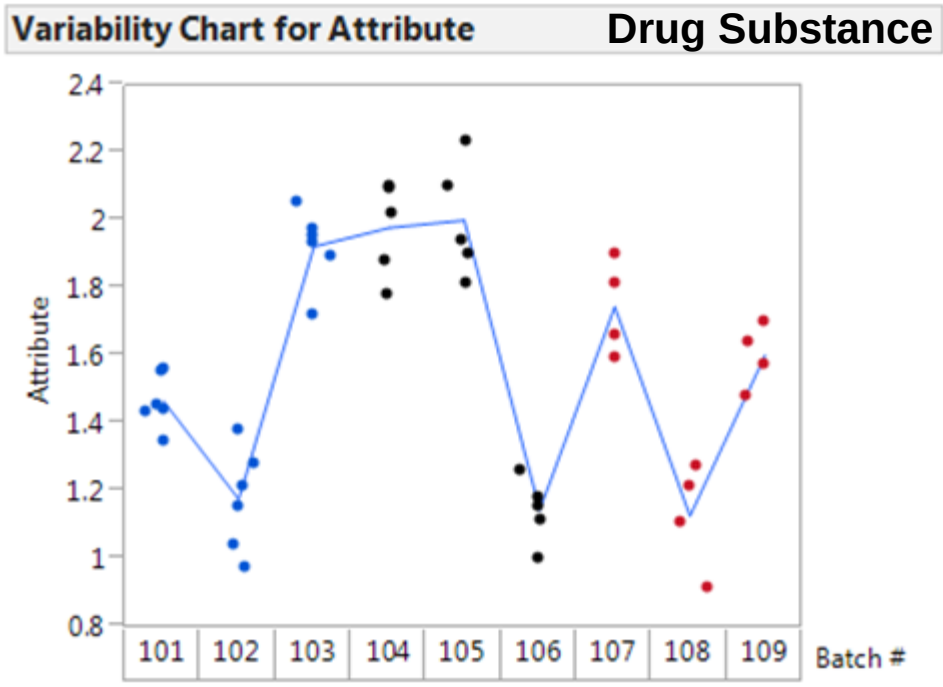


Drug Product

Variability

- Variance Components Analysis can separate the pure process variability and method variability
- Useful to understand the contribution from each source of variability
- Graphing is helpful!



Variance Components

Component	Var Component	% of Total	20 40 60 80	Sqrt(Var Comp)
Batch #	0.12811931	88.5		0.35794
Within	0.01662704	11.5		0.12895
Total	0.14474634	100.0		0.38046

Method variability (intermediate precision) standard deviation is estimated as

$$\sqrt{0.01662704} = 0.13\ \%$$

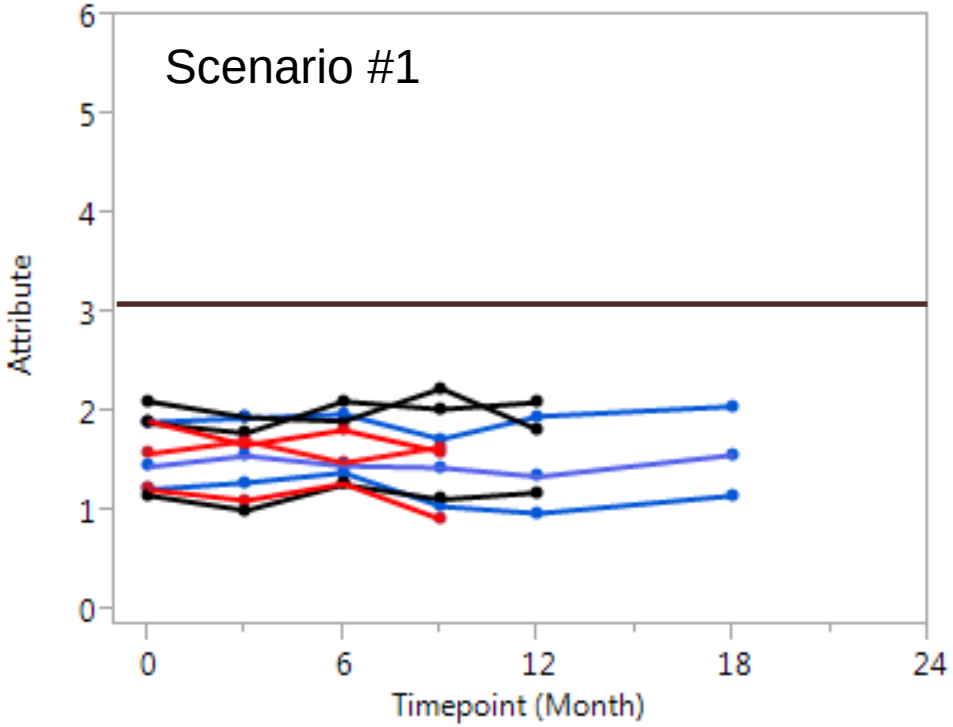
Overall variability estimate is 0.38%

Summary Statistics of CT Batches

Analytical Property	N Max, Min	Batch Release Average	Batch Release SD	Average +/- 3*SD	95/99 Tolerance Limit	Change over 24 months
DS Attribute (%)	9 0.92, 2.24	1.6	0.4	0.5, 2.7	3.1	negligible
DP Attribute (%)	9 1.20, 3.04	1.7	0.3	0.7, 2.7	3.1	1.9*

** Includes 23 months at 5C and 1 month at 30C*

Developing Acceptance Criteria



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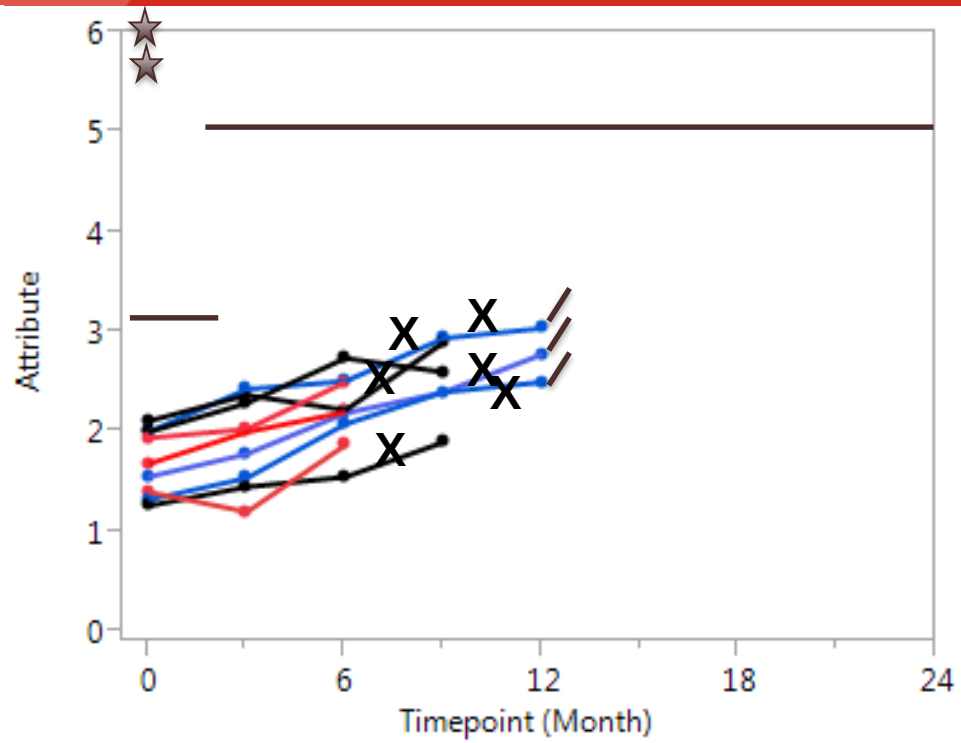
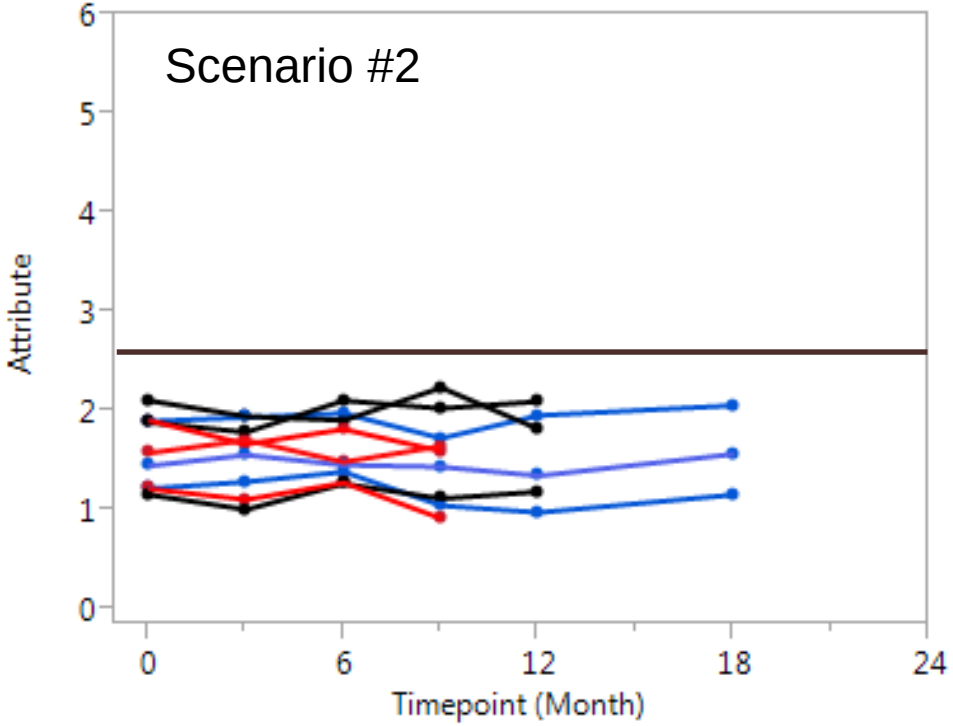


Drug Product

Developing Acceptance Criteria



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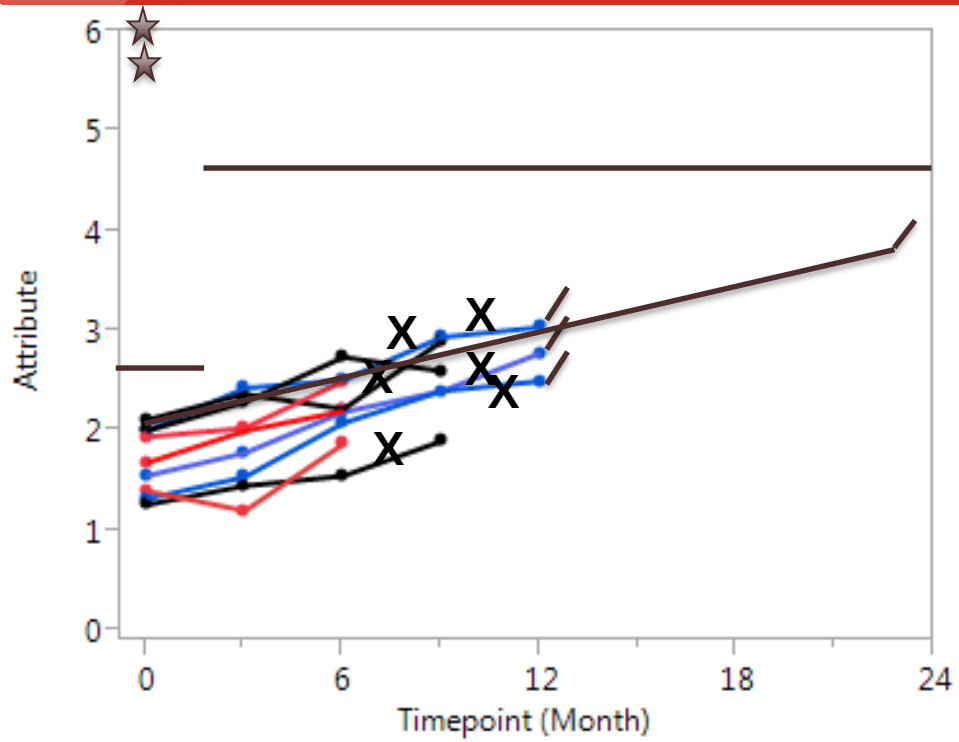
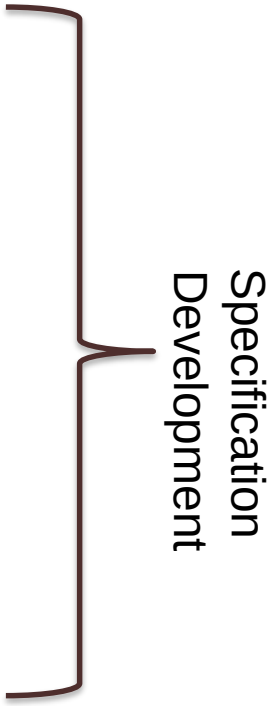


May be requested to tighten, be mindful of batch quality at end of shelf and at release

Drug Product

Role of Statistics

- Quality of clinical trial batches
  - Characterize batch release data
    - Need to understand typical process performance
  - Evaluate change on stability
    - Long-term storage and patient-use periods
  - Assess common cause variability
    - Method variability
    - Process variability



Role of Statistics

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  - Characterize batch release data
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  - Evaluate change on stability
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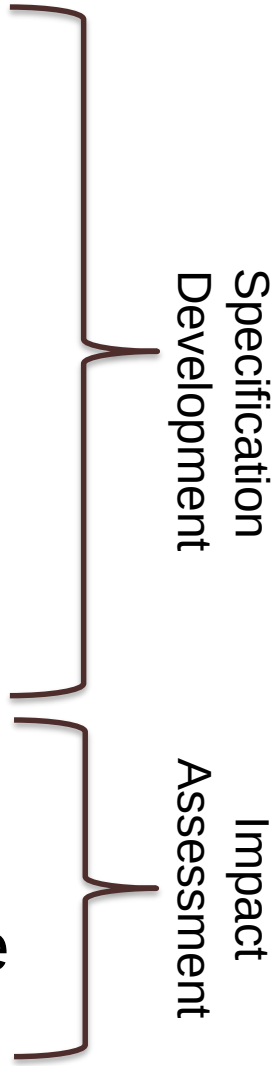
    - Method variability
    - Process variability
- Manufacturing Capability Risk Assessment
  - Quantifying risk of meeting commercial specifications via manufacturing representative material



Commercial Risk Considerations

- Criteria too tight?
  - Risk of shorting the market due to failing batches that would be acceptable to the patient?
- Limited long-term manufacturing experience across diverse set of raw materials, multiple manufacturing sites, multiple laboratories
- Continue to evaluate risk as additional data are obtained after registration submission
  - New batches, additional stability data
- Negotiation across numerous regulatory authorities
  - In-country testing for many markets required, e.g., Europe, Korea

Evaluating/Mitigating Commercial Risk

- Assess ability to meet potential clinically relevant specification acceptance criteria
  - At time of batch release
  - After aged “X” months for importation testing
  - Throughout shelf life, including patient use
- Leverage platform knowledge for estimates of typical process variability, typical method variability
  - Apply modeling and simulation to estimate risk
  - Utilize Bayesian techniques to incorporate platform learning
- Develop risk mitigation plans
  - Improve method performance
  - Utilize aged material in new or on-going clinical trials
  - Conduct an additional clinical trial

Key Points

- Focus the acceptance criteria on the patient
  - Acceptance criteria that are relevant to the patient and consistent with clinical experience
- Statistics can aid in understanding the batch quality and sources of variability
  - Summary statistics are requested and are useful
    - Beware of under-represented diversity
  - Modeling and simulation are useful to assess commercial risk
  - Graph the data!

Acknowledgements

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