Quality by Design for Everyone

Presented by Brooks Henderson, CQE
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"Be a yardstick of quality. Some people aren’t used to an environment where excellence is expected."
- Steve Jobs

[From Brainy Quotes: http://www.brainyquote.com/quotes/keywords/quality.html]

Agenda

- Introduction and Background
  - QbD basics
  - QbD and DOE – A perfect Marriage
  - Statistical Intervals
- Case Study: Using DOE and Qbd to find the Quality Sweet Spot
  - Sizing the Design for Tolerance Intervals
  - Results – determining the QbD Design Space
- Summary and Conclusions
Agenda Transition

- **Introduction and Background**
  - QbD basics
  - QbD and DOE – A perfect Marriage
  - Statistical Intervals
- **Case Study: Using DOE and QbD to find the Quality Sweet Spot**
  - Sizing the Design for Tolerance Intervals
  - Results – determining the QbD Design Space
- **Summary and Conclusions**

What is Quality by Design?
**FDA View on QbD**

**Quality by Design:**

- Scientific, risk-based, holistic and proactive approach to pharmaceutical development.
- Deliberate design effort from product conception through commercialization
- Pursues full understanding of how product attributes and process relate to product performance
- Not just for Pharma and the FDA...it can be a great model for practitioners in any industry.

Quality by Design
FDA View on QbD

QbD involves the following key steps:

- Target the product profile.
- Determine critical quality attributes (CQAs).
- Link raw material attributes, formulation and process parameters to CQAs and perform risk assessment.
- Develop a Design Space.
- Design and implement a control strategy.
- Manage product life cycle, including continual improvement.

2. Chi-wan Chen, deputy director of the Office of New Drug Quality Assessment (ONDQA) at the US Food and Drug Administration's Center for Drug Evaluation and Research.

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Develop a Design Space

1. First-principles approach
   - Combine experimental data and mechanistic knowledge to model and predict performance.

2. Statistically designed experiments (DOEs)
   - Efficient method for determining impact of multiple parameters and their interactions.

3. Scale-up correlations
   - A semi-empirical approach to translate operating conditions between different scales or pieces of equipment.

4. Combinations of the above
Quality by Design “QbD”
What is a Design Space?  

1. A region where quality product is produced.
2. Includes product formulation and/or process parameters.
3. Arrived at by iterative application of risk assessment and experimental design to knowledge space.
4. Includes evaluation of scale and equipment.

ICH guidelines Q8 (on Pharmaceutical Development), Q9 (on Quality Risk Management), and Q10 (on Pharmaceutical Quality System) provide some assistance for manufacturers to implement Quality by Design into their own operations.

Design Space Determination
Quality by Design  

FDA defines Design Space in its *Guidance for Industry Q8: Pharmaceutical Development*, as:

“*The multidimensional combination and interaction of input variables* (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the Design Space is not considered as a change. Movement out of the Design Space is considered to be a change and would normally initiate a regulatory post approval change process. Design Space is proposed by the applicant and is subject to regulatory assessment and approval."

ICH guidelines Q8 (on Pharmaceutical Development), Q9 (on Quality Risk Management), and Q10 (on Pharmaceutical Quality System) provide some assistance for manufacturers to implement Quality by Design into their own operations.
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Design Space Determination
Using DOE to determine your Design Space

The perfect Marriage

DOE + QbD  →  Consistent Quality

Sweet Spot

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DOE Works on Any Process

Definition: DOE is:

“A series of tests, in which purposeful changes are made to input factors, to identify causes for significant changes in the output responses.”

DOE connects input factors to output responses

Y = f(x) + ε

Experimental Design

Conversion

Experimental Results – Model Graphs
Dealing with Noise (\(\varepsilon\))
Analysis of Variance (ANOVA)

Is there a real effect, or is it just noise?

<table>
<thead>
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<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>p-value</th>
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<td></td>
<td></td>
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<td>3</td>
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<td>&lt; 0.0001</td>
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<td>257.79</td>
<td>&lt; 0.0001</td>
</tr>
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<td>1</td>
<td>0.89</td>
<td>0.92</td>
<td>0.3526</td>
</tr>
<tr>
<td>C-catalyst</td>
<td>67.91</td>
<td>1</td>
<td>67.91</td>
<td>70.62</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Residual</td>
<td>14.42</td>
<td>19</td>
<td>0.98</td>
<td>1.67</td>
<td>0.5197</td>
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<tr>
<td>Lack of Fit</td>
<td>19.77</td>
<td>11</td>
<td>1.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure Error</td>
<td>3.65</td>
<td>4</td>
<td>0.91</td>
<td></td>
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</tr>
<tr>
<td>Cor Total</td>
<td>331.53</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANOVA first derived in Sir Ronald Fisher's landmark paper entitled: "Studies in Crop Variation II"?


Find the Optimal Settings
Activity Response

Target of 63 Activity

Activity (coded) = 60.2+4.26A+.25B+2.23C

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Find the Optimal Settings

**Conversion Response**

Maximize Conversion while still hitting 63 Activity

Find the Operating Region

**Activity Response**

60<Activity<66

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Find the Operating Region
Conversion Response

DOE can help you to meet specifications and obtain consistent quality

Find an “operating window” where both specifications are met
Uncertainty is a BIG Problem
Specifications as Bounds

If the process is operated on a boundary, then 50% of the products fall outside the specification.

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DOE can help you to meet specifications and obtain consistent quality

Add Buffer Zones (Intervals) to ensure meeting specs.

Find an “operating window” where both specifications are met
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Intervals – Overview
Optimal Solution with Intervals

Numerical Optimization:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Name</th>
<th>Level</th>
<th>Low Level</th>
<th>High Level</th>
<th>Std. Dev.</th>
<th>Coding</th>
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<tr>
<td>A</td>
<td>time</td>
<td>47.02</td>
<td>40.00</td>
<td>50.00</td>
<td>0.000</td>
<td>Actual</td>
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<td>80.00</td>
<td>90.00</td>
<td>0.000</td>
<td>Actual</td>
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<tr>
<td>C</td>
<td>size</td>
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<td>2.00</td>
<td>3.00</td>
<td>0.000</td>
<td>Actual</td>
</tr>
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</table>

Optimal Factor Settings

99% of Population

<table>
<thead>
<tr>
<th>Response</th>
<th>Prediction</th>
<th>Std Dev</th>
<th>SE Mean</th>
<th>99% CI low</th>
<th>99% CI high</th>
<th>SE Pred</th>
<th>99% PI low</th>
<th>99% PI high</th>
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<td>Max Target</td>
<td>91.3</td>
<td>4.1</td>
<td>2.9</td>
<td>86.8</td>
<td>95.8</td>
<td>4.6</td>
<td>81.0</td>
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<td>Activity</td>
<td>1.0</td>
<td>0.4</td>
<td>62.2</td>
<td>63.8</td>
<td>1.1</td>
<td>0.0</td>
<td>65.2</td>
<td>56.7</td>
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</table>

Optimal Settings - Graphs
### Intervals – Overview
#### Optimal Solution with Intervals

#### Optimal Factor Settings

<table>
<thead>
<tr>
<th>Factor</th>
<th>Name</th>
<th>Level Low Level</th>
<th>Level High Level</th>
<th>Std. Dev.</th>
<th>Coding</th>
</tr>
</thead>
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<tr>
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<td>0.000</td>
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<td>80.00</td>
<td>90.00</td>
<td>0.000</td>
</tr>
<tr>
<td>C</td>
<td>catalyst</td>
<td>2.98</td>
<td>2.00</td>
<td>3.00</td>
<td>0.000</td>
</tr>
</tbody>
</table>

#### Response Prediction

<table>
<thead>
<tr>
<th>Conversion</th>
<th>Max</th>
<th>Std Dev</th>
<th>SE Mean</th>
<th>95% Cl low</th>
<th>95% Cl high</th>
<th>SE Pred</th>
<th>95% Pi low</th>
<th>95% Pi high</th>
<th>95% Ti low</th>
<th>95% Ti high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Max</td>
<td>63.0</td>
<td>4.1</td>
<td>2.9</td>
<td>86.8</td>
<td>95.8</td>
<td>4.6</td>
<td>81.0</td>
<td>101.6</td>
<td>70.3</td>
</tr>
</tbody>
</table>

#### Goals

- Point Prediction
- Confidence Interval – Average Results

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Intervals – Overview
Optimal Solution with Intervals

Choose the Interval that fits your goals!

Confidence Interval (CI)
An interval that covers a population parameter (i.e., \( \mu \)) with a pre-determined confidence level.

Prediction Interval (PI)
An interval that covers a future outcome from the same population with a pre-determined confidence level.

Tolerance Interval (TI)
An interval that covers a fixed proportion of outcomes from the population with a pre-determined confidence level for estimating the population mean and standard deviation.
Tolerance Interval
Definition

Tolerance Interval: An interval that covers a fixed proportion of outcomes from the population with a pre-determined confidence level for estimating the population mean and standard deviation.

\[ \bar{y} - k_2(s) \leq P\% \text{ of population} \leq \bar{y} + k_2(s) \]

\[ TI = \bar{y} \pm k_2(s) \]

\[ TI = \bar{y} \pm d \]

d is the half width of the tolerance interval

Interval Calculations
Single Sample & Normal Distribution

Confidence Interval \quad Tolerance Interval

\[ \bar{y} \pm \left( \frac{s}{\sqrt{n}} \right) \quad \bar{y} \pm k_2 s \]

Note:
- TI multipliers (k_2) are larger than those for a CI; especially for small samples.
  - This makes the intervals wider
- As the sample size increases:
  - CIs shrink towards zero.
  - TIs tend towards a fixed value: z(s).

Larger sample sizes are needed for TIs than CIs.
Tolerance Limits
Statistical versus Engineering

Statistical Tolerance Limits:
Limits within which we expect a stated proportion of the population to lie.

Engineering Tolerance Limits:
Limits that define acceptability with respect to an operating characteristic. (aka specification limits.)

Apply Intervals to the Design Space
Back Off Using Confidence Intervals

Find an “operating window” where both specifications are met

Add Buffer Zones (Intervals) to ensure meeting specs.
Apply Intervals to the Design Space
Back off Using Tolerance Intervals

- Adding tolerance intervals to a design without enough runs will eliminate your Design Space...
- Solution – Size your design for tolerance intervals to ensure enough runs

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Using DOE with Tolerance Intervals to Verify Specifications

**Objective:**
- Define an operating window in process factor space where we have 95% confidence that 99% of the population meet (or exceed) specifications.

**Tools:**
- Use empirical DOE to model the responses as functions of the process factors.
- Use a tolerance interval to “back off” (provide a buffer) from the specifications.
- Size the DOE for required half-width of tolerance interval.

Illustrative Example
Tableting Process

This case study illustrates how DOE and tolerance intervals can be used to set an operating window where specifications are consistently met.

- An optimal design is run on two process parameters (granulation time and lubrication time) in a tableting process.
- Three responses (dissolution, friability and hardness) are measured.
- The specifications are:
  - Dissolution
  - Friability
  - Hardness

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Two Related Factors
Tableting Process

This example involves some constraints which can’t be handled by a classic run-of-the-mill Design.

- Need to study two process parameters (granulation time and lubrification time) in a tableting process.
- These two factors are related and combinations of their extremes (both times long or both times short) must be avoided (see the next slide).
- Optimal design can be used to customize a design to fit a particular problem (In this case, to avoid the extremes).

Select the input factors and ranges to study.
(Consider both your region of interest and region of operability.)

Granulation time: 3 – 7 minutes
Lubrification time: 2 – 8 minutes
7 ≤ total mixing time ≤ 12
Tableting Process
Optimal Design

1. An optimal Design will use an algorithm to pick the runs that best fill the truncated Design Space.

---

**Initial Operating Window**
Specifications as Bounds

- $y_1 = \text{Dissolution \% (specification } \geq 75\%)$
- $y_2 = \text{Friability \% (specification } \leq 0.5\%)$
- $y_3 = \text{Hardness kP (specification } \geq 10 \text{ kP)}$

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Gaining confidence that individuals are within specifications.

If we want more confidence that individual units are within specifications:

- Then we should back off using a tolerance interval rather than a confidence interval.
- Specify the confidence level; e.g. 95%.
- Specify the portion of the population to be within specifications; e.g. 99%.

Recall:

- A confidence interval pads our Design Space to give us confidence that the process mean is within boundaries. This is needed for a functional design.
- A tolerance interval gives us confidence that a stated proportion of the population is within specifications. This is needed for verification.

DOE with Tolerance Intervals
Sizing for Precision Requirements

\[ TI = \bar{y} \pm d \]

Define \( d \):

- For example, we expect dissolution of around 80%.
  - Would an interval of 80% ± 80% be useful?
- We need enough runs for precision to be useful and to ensure we get a useful operating window to work with.
- Avoid closing the window:
- Could be based on specs.
DOE with Tolerance Intervals
Sizing for Precision Requirements

Define the precision required as the half-width of a Tolerance Interval that contains 99% of the population with 95% confidence:

<table>
<thead>
<tr>
<th>Response</th>
<th>Desired d</th>
<th>s</th>
<th>d/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>dissolution</td>
<td>9.0</td>
<td>2.00</td>
<td>4.5</td>
</tr>
<tr>
<td>friability</td>
<td>0.2</td>
<td>0.03</td>
<td>6.7</td>
</tr>
<tr>
<td>hardness</td>
<td>0.7</td>
<td>0.14</td>
<td>5</td>
</tr>
</tbody>
</table>

Recall: $\text{Tl} = \bar{y} \pm k_2(s)$

$d =$ half-width of tolerance interval

Fraction of Design Space (FDS)
Defining the precision

**Fraction of Design Space:**
- Fraction of the Design Area/Volume that is as precise as desired or better
- Number between 0% and 100%
- What percentage of the Design Space gives $\bar{y} \pm d$ or better?

<table>
<thead>
<tr>
<th>Response</th>
<th>Desired d</th>
<th>s</th>
<th>d/s</th>
</tr>
</thead>
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<tr>
<td>dissolution</td>
<td>9.0</td>
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<td>4.5</td>
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<tr>
<td>friability</td>
<td>0.2</td>
<td>0.03</td>
<td>6.7</td>
</tr>
<tr>
<td>hardness</td>
<td>0.7</td>
<td>0.14</td>
<td>5</td>
</tr>
</tbody>
</table>

**Focus on the response with the the lowest d/s ratio**
Sizing for Precision Requirements
Tolerance Intervals

16 runs (6 model, 5 lack of fit, 5 replicates)

<table>
<thead>
<tr>
<th>Std Err of Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.00 5.00 6.00 7.00 8.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B: Lubrification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.400 0.600 0.700 0.700 0.700</td>
</tr>
</tbody>
</table>

A: Granulation

FDS Graph

Sizing for Precision Requirements
Tolerance Intervals

16 runs (6 model, 5 lack of fit, 5 replicates) FDS = 0%

<table>
<thead>
<tr>
<th>FDS Graph</th>
</tr>
</thead>
<tbody>
<tr>
<td>d = 9</td>
</tr>
<tr>
<td>s = 2</td>
</tr>
<tr>
<td>a = 0.05</td>
</tr>
<tr>
<td>P = 0.99</td>
</tr>
</tbody>
</table>

Design too small!
Sizing for Functional Design
Confidence Intervals

Assume the goal is functional design; i.e. determining factor levels so average response values provide functional performance.

- Then the criteria shifts from predicting individuals to predicting averages.

Then for the tableting process the goal might be:

- Want a quadratic surface to represent the average response value within $\pm 3$ with 95% confidence.
- $\pm d$ then defines the half width of a confidence interval rather than a tolerance interval.

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16 runs (6 model, 5 lack of fit, 5 replicates) FDS = 96%

$d = 3$
$s = 2$
$a = 0.05$
$P = 0.99$
Sizing for Functional Design
Confidence Intervals

For functional design, the goal is to predict the average response with a quadratic model with a precision of ± 3 with 95% confidence is met in 96% of the DOE space.

- Functional design – sizing for ± d (d=3) with 95% confidence, where d is the half width of a confidence interval the current design is adequate, FDS = 96%.

- Sizing for tolerance intervals using ± d (d=9) with 95% confidence, where d is the half width of a tolerance interval the current design is wholly inadequate, FDS = 0%.

For details on sizing for functional design see “Sizing Mixture (RSM) Designs” by Pat Whitcomb on the Chemical and Process Industries web site at: //asq.org/cpi/

Confidence vs. Tolerance Intervals
Functional versus Verification

Take home message
Sizing for tolerance intervals requires a larger DOE (sample size) than sizing for confidence intervals.

our recurring theme

Next step
Increase the size of the tableting process DOE by seven additional model points.
Sizing for Precision Requirements
Tolerance Intervals

23 runs (13 model, 5 lack of fit, 5 replicates) \( FDS = 96\% \)

\[
d = 9 \\
s = 2 \\
a = 0.05 \\
P = 0.99
\]

Tolerance Intervals

More better with 7 more runs!

Tableting Process
Results

Original design: 16 runs
- 6 model points
- 5 lack of fit points and
- 5 replicates

Final design: 23 runs
- 13 model points
- 5 lack of fit points and
- 5 replicates

Analyze responses, aim for:
- Dissolution \( \geq 75\% \)
- Friability \( \leq 0.5\% \)
- Hardness \( \geq 10 \) kP
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Tableting Process Results

Quadratic Models

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Final Operating Window
Tolerance Intervals as Bounds

\[ y_1 = \text{Dissolution } \% \quad (\text{specification } \geq 75\%) \]

\[ y_2 = \text{Friability } \% \quad (\text{specification } \leq 0.5\%) \]

\[ y_3 = \text{Hardness kP} \quad (\text{specification } \geq 10 \text{ kP}) \]

Quality by Design “QbD”
Design Space Determination

1. A region where quality product is produced.
2. Includes product formulation and/or process parameters.
3. Arrived at by iterative application of risk assessment and experimental design to knowledge space.
4. Includes evaluation of scale and equipment.

ICH guidelines Q8 (on Pharmaceutical Development), Q9 (on Quality Risk Management), and Q10 (on Pharmaceutical Quality System) provide some assistance for manufacturers to implement Quality by Design into their own operations.
Quality by Design “QbD”
Design Space Determination

DOE with Tolerance Intervals
How many More Runs?

Quadratic model (TI for $d = 9$ and $s = 2$) $FDS \geq 90\%$

<table>
<thead>
<tr>
<th>Factors</th>
<th>p + 5 + 5*</th>
<th>Extra runs</th>
<th>Increase</th>
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<tr>
<td>2</td>
<td>16</td>
<td>7</td>
<td>44%</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>13</td>
<td>34%</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>15</td>
<td>27%</td>
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<tr>
<td>10</td>
<td>76</td>
<td>16</td>
<td>21%</td>
</tr>
</tbody>
</table>

* p coefficients + 5 lack of fit + 5 replicates
Managing Uncertainty in Design Space

Summary

1. Size your DOE appropriately for its purpose:
   - Functional design – size via confidence intervals.
     A confidence interval pads our Design Space to give us confidence that the process mean is within boundaries.
   - Verify specifications – size via tolerance intervals.
     A tolerance interval gives us confidence that a stated portion of the population is within specifications.

2. TI multipliers are larger than those for a CI.

3. Tolerance intervals require a large design (sample size).

Manage Uncertainty via Intervals
CI for Functional and TI for Verification

Uncertainty with Mean
Overlay Plot with CIs

Uncertainty with Population
Overlay Plot with TIs

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Design Space Determination

Summary:

- QbD is a rigorous approach to product development. One key element is determining your Design Space.
- Design Space is the multidimensional combination and interaction of input variables that have been demonstrated to provide assurance of quality.
- DOE is a means of determining the Design Space. Use it to:
  - Relate your inputs (factors) to outputs (responses)
  - Find the Optimum using numeric optimization
  - Determine Design Space using graphical optimization
- Use Statistical Intervals to Pad the Design Space
- Adding runs will shrink intervals and improve precision
  - Be sure to add enough runs to get a useful Design Space
Any Questions?

Best of luck for your experimenting!

For further questions, stop by the Stat-Ease booth or contact me!

Brooks Henderson, MS, Mat. Sci.
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References


