Leveraging Bayesian Statistics for Lifecycle Process Validation of Continuous Manufacturing Processes

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“…as a patient, I would much rather take a pill made using a continuous manufacturing process than one made using traditional batch manufacturing. The end product is much more likely to be of optimal quality using continuous manufacturing.”

Richard Steiner, Business Development Manager at GEA Pharma Systems
Bayesian Solutions in Continuous Manufacturing

- Sampling design of inline or at-line process measurements used for real time release testing (RTRt)
- Prediction of Capability
- Residence Time Modelling
- Maintenance of PAT Models
Frequentist vs. Bayesian Methods

Frequentist  $\Rightarrow$ $P(\text{data} \mid \text{performance})$

But the question is: $P(\text{performance} \mid \text{data})$!

Bayesian  $\Rightarrow$ $P(\text{performance} \mid \text{data})$

PRIOR distribution  Exp. data  POSTERIOR

$\Theta$

0 2 4 6 8 10
0.0 0.1 0.2 0.3 0.4 0.5

0 2 4 6 8 10
0.0 0.05 0.10 0.15 0.20 0.25

-5 0 5 10 15
0.00 0.05 0.10 0.15 0.20 0.25

Theta

Posterior distribution
Simple Comparison

- Prior Distribution
- New Information
- Posterior Distribution

Based on a point estimates
Based on a distribution

Frequentist
Bayesian
How to make predictions

1\textsuperscript{st}, draw a mean and a variance from:
- Posterior of mean $\mu_i$
- Posterior of Variance $\sigma^2_i$ given mean drawn

2\textsuperscript{nd}, draw an observation from the resulting distribution $Y \sim \text{Normal}(\mu_i, \sigma^2_i)$

3\textsuperscript{rd}, repeat this operation a large number of time to obtain the predictive distribution
Bayesian theory provides a definition of the **Predictive Distribution** of a **new** observation given **past** data.

\[
p(\tilde{y}|data) = \int \int p(\tilde{y}|\mu, \sigma^2, data) \times p(\mu, \sigma^2|data) \ d\mu d\sigma^2
\]

Integrate over parameter distribution

\[
= \int \int p(\tilde{y}|\mu, \sigma^2) \times p(\mu|data) \times p(\sigma^2|\mu, data) \ d\mu d\sigma^2
\]

Model

\[
= \int \int p(\tilde{y}|\mu, \sigma^2) \times p(\sigma^2|data) \times p(\mu|\sigma^2, data) \ d\mu d\sigma^2
\]

Marginal

Joint posterior

Conditional
Probability being in specifications
Tolerance intervals

- Use the Predictive distribution to compute the probability to be within specifications.

- Bayesian statistics allows computing a probability instead of a Tolerance Interval only.

Answers the question: What’s the risk?
Continuous Manufacturing
Frequency and Sample Size of Real Time Measurements

Assay and Content Uniformity

Acceptance Region to meet specified statistical interval statements for mean (Confidence interval) and Individual (Tolerance Interval) % label claim results

Graphs can be translated into acceptance tables
Determining sample size that will likely meet acceptance criteria

1. Model NIR results of replicate samples taken at multiple locations across the batch (two variance components model)

2. Compute
   1. posterior distribution of parameters
   2. probability of meeting acceptance criteria for various sample sizes
   3. prediction intervals of parameters and compare to acceptance ranges
Determining sample size that will likely meet acceptance criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>100.4</td>
<td>(100.1, 100.7)</td>
</tr>
<tr>
<td>SD(Between Location)</td>
<td>0.54</td>
<td>(0.25, 0.94)</td>
</tr>
<tr>
<td>SD(Within Location)</td>
<td>1.04</td>
<td>(0.92, 1.23)</td>
</tr>
</tbody>
</table>

1. 80,000 pairs of sample mean and standard deviation ($\bar{Y}, s$) were predicted using the posterior distribution parameter

2. Compared pairs to acceptance criteria

Essentially 100% likelihood future samples will meet acceptance criteria
Bayesian Prediction Interval

Simulation of sample mean and standard deviation was used to compute 99% prediction intervals for future samples.

These can be compared to the acceptance criteria.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=5</td>
</tr>
<tr>
<td>Mean (% LC)</td>
<td>99.3 – 102.5</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>1.88</td>
</tr>
</tbody>
</table>
Comparison to USP 905

Acceptance Regions for Proposed Test vs USP 905

sample size of 10
Residence Time Distribution Model

Factors influencing RTD

• Process conditions (e.g., mass flow rate, blend speed)
• Material characteristics
• Equipment configuration

How can you include uncertainty in estimate of Residence Time?
Residence Time Distribution Model

\[ E(t) \sim f(\text{mass transport parameters}) \]

\[ \text{mass transport parameters} \sim f(\text{process parameters}) \]

**Bayesian approach provides:**

- Allowance for error in process and mass transport parameters
- Systems approach to overall RT and propagation of error
- Probability based approach to diverting material after startup or disturbance

Simulate to Obtain Predictive Probability Distribution of RT
1. Fit a Bayesian hierarchical model which includes multiple variance components:
   - Within location, between location, between batch, HPLC method variability, NIR method variability

2. Compute predictive distribution for the difference between paired HPLC and NIR results, and a 95/99 Bayesian tolerance interval.

3. Monitor paired results against tolerance limits. Check/update model periodically

<table>
<thead>
<tr>
<th></th>
<th>95% Credible Interval</th>
<th>Predictive posterior density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Difference btw NIR and HPLC</td>
<td>(-0.05, 0.47)</td>
<td></td>
</tr>
<tr>
<td>Individual Tablet Difference between NIR and HPLC</td>
<td>(-2.45, 3.12)</td>
<td></td>
</tr>
</tbody>
</table>
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