



Out of Specification Evaluations for Biopharmaceuticals

Non Clinical Statistics Conference 2018
Paris, France
October 3-5, 2018

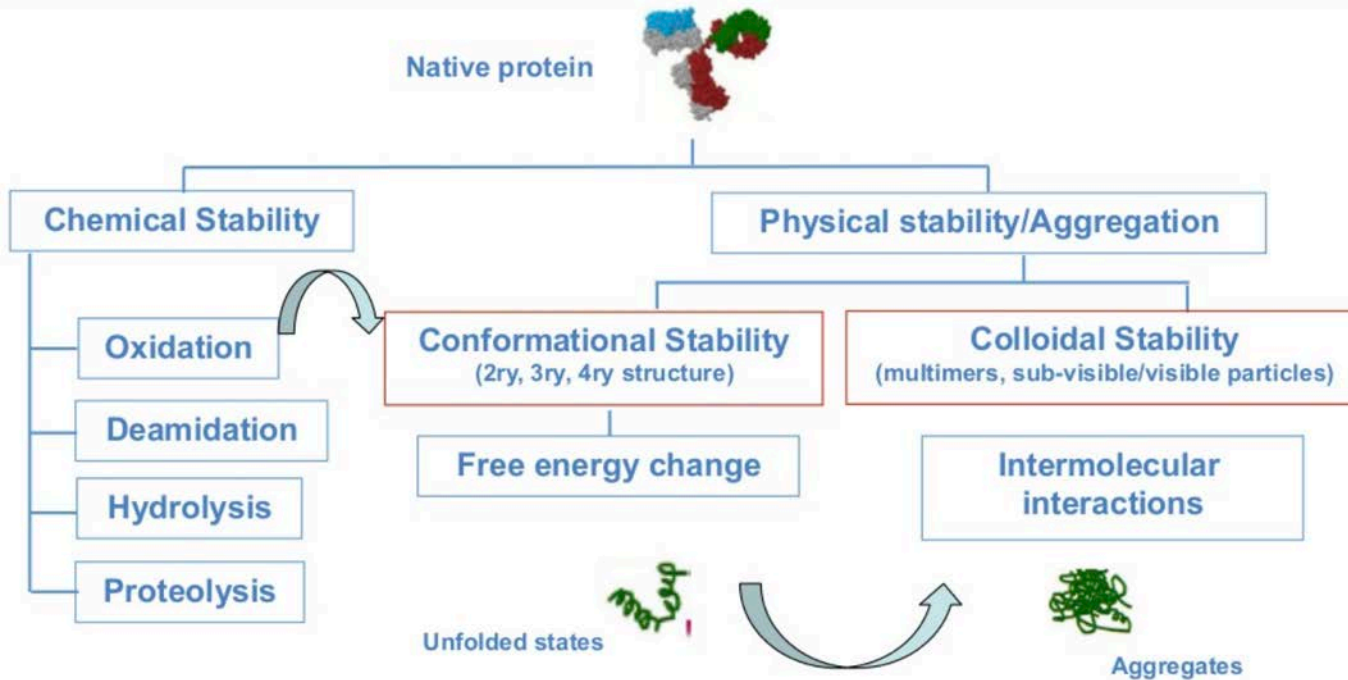
Bill Pikounis & Many Partners
Johnson & Johnson

Rhonda Fenwick, *Time is Now I*
Through her art, Rhonda has explored psoriasis, a
chronic skin disorder she has lived with since the age
of six.

Many Partners to Acknowledge

- Perceval Sondag, John Oleynick, Jessica Behrle, Jenny Li, Jyh-Ming Shoung
- Product Development Scientists at Johnson & Johnson
- Other Advisors

Specifications for Quality Attributes

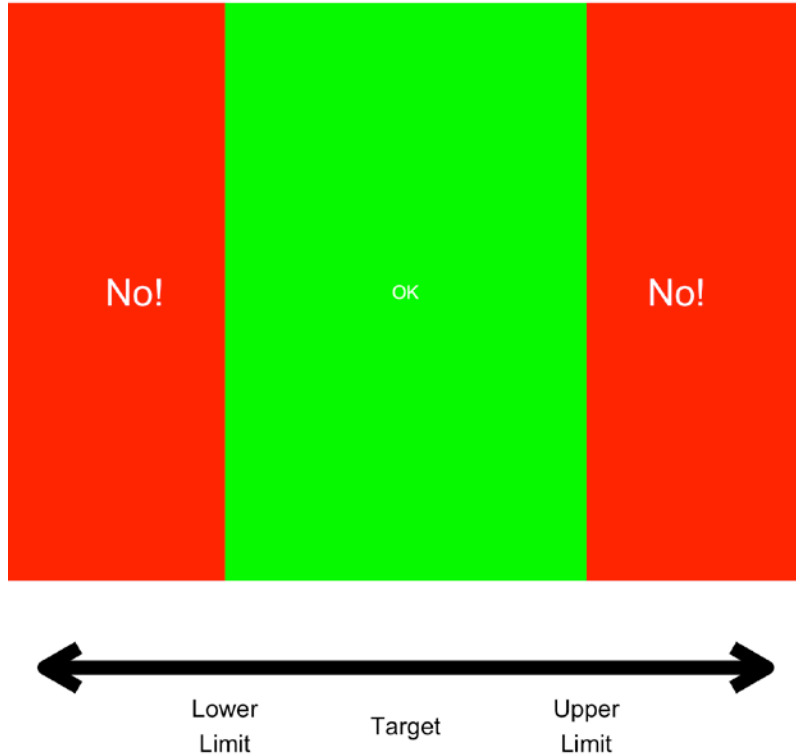


Some Monoclonal Antibody Degradation Markers

From <https://www.slideshare.net/bathasu/the-chemistry-of-mono-clonal-antibodies>

Maria Connolly, Bath ASU

Specifications for Critical Quality Attributes (CQAs)



General Categories of:

- Potency
- Purity
- Identity

Purpose

Estimate Probability of Out of Specification across CQAs for Informed Decisions and Risk Management

Very Related Concepts to Specifications and Estimating Probabilities

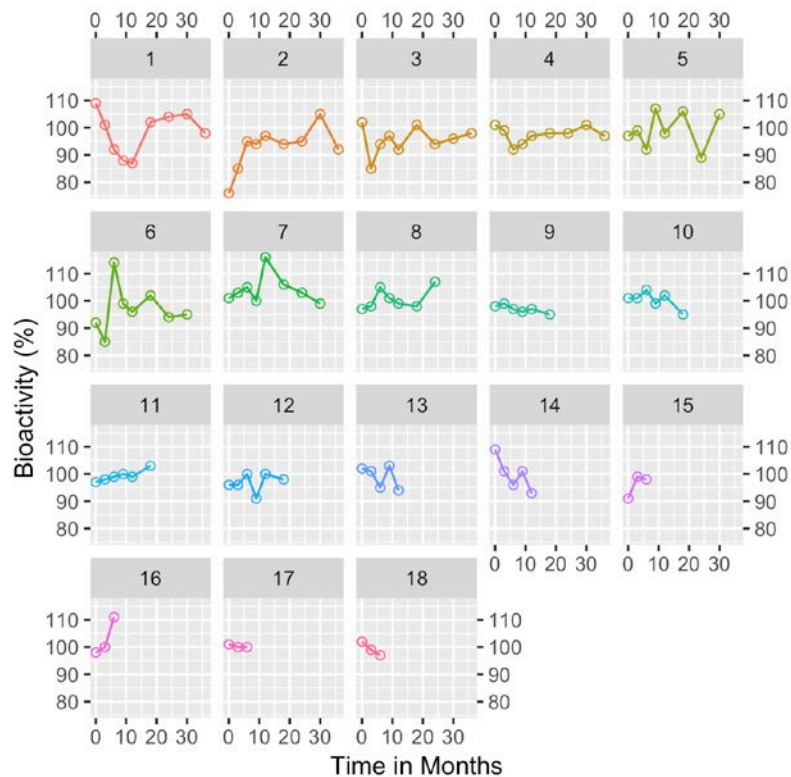
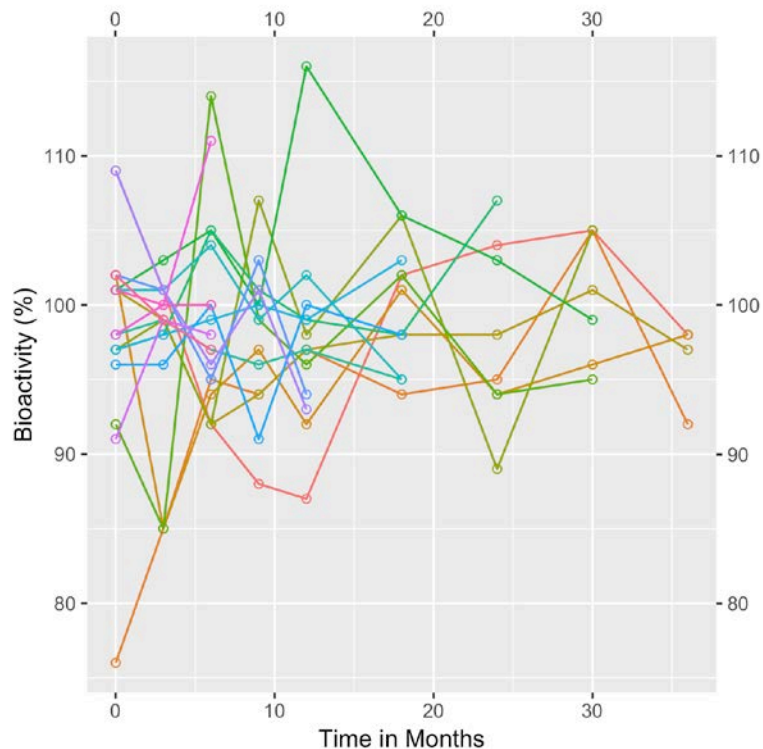
Quantiles

Tolerance Intervals

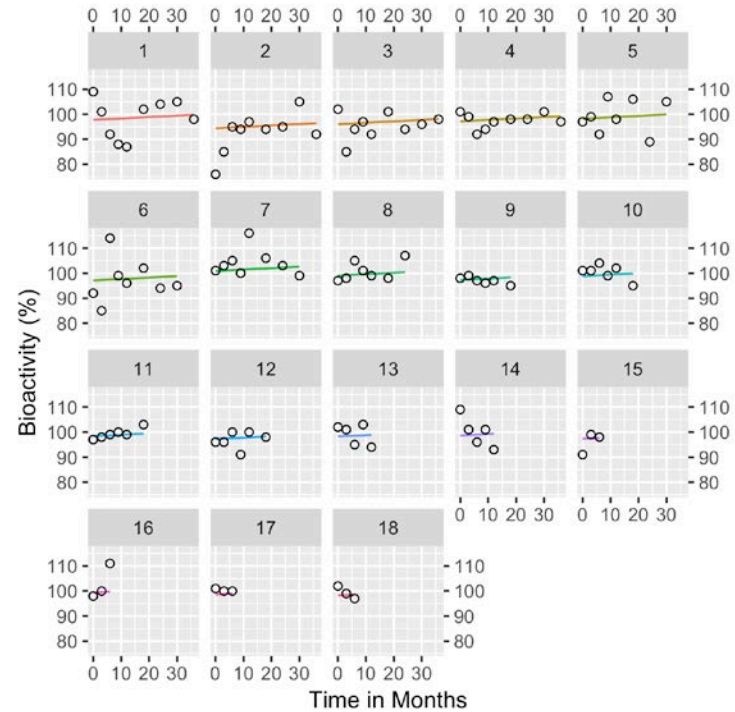
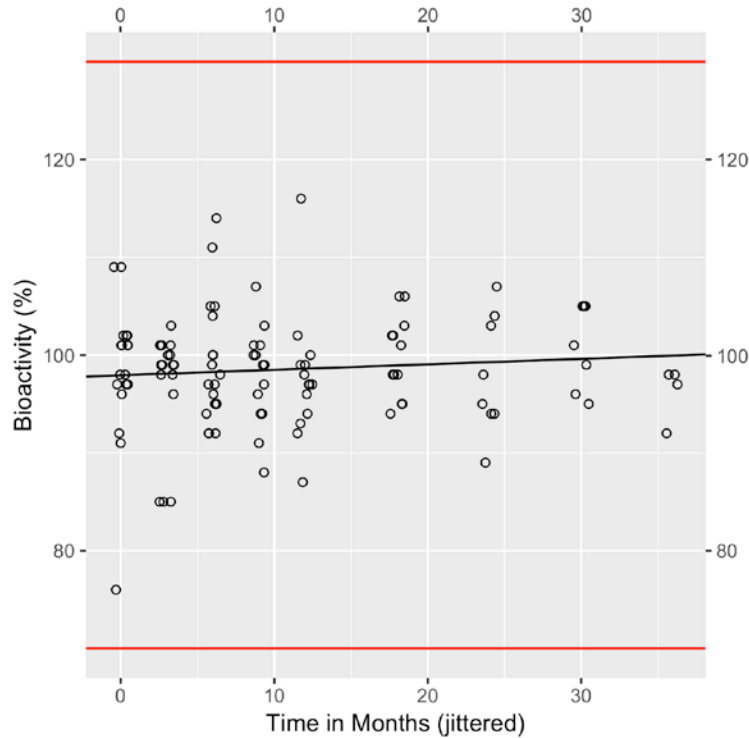
Not for Focus Today

- Righteousness of Bayesian vs. Frequentist nor Choices within
- Model Building
- Righteousness of Specification Knowledge vs. Statistical Justifications

Bioactivity Attribute Example



Bioactivity Attribute from LME model fit, and assume specification limits of 70% - 130%



Bootstrap Recipe

- Fit Linear Mixed Model & Perform Diagnostics
- Resample & Perform Diagnostics
- Calculate via Estimator
- Report Point and Confidence Interval Calculation from Bootstrap Distributions

Bootstrap Approach for Bioactivity Attribute

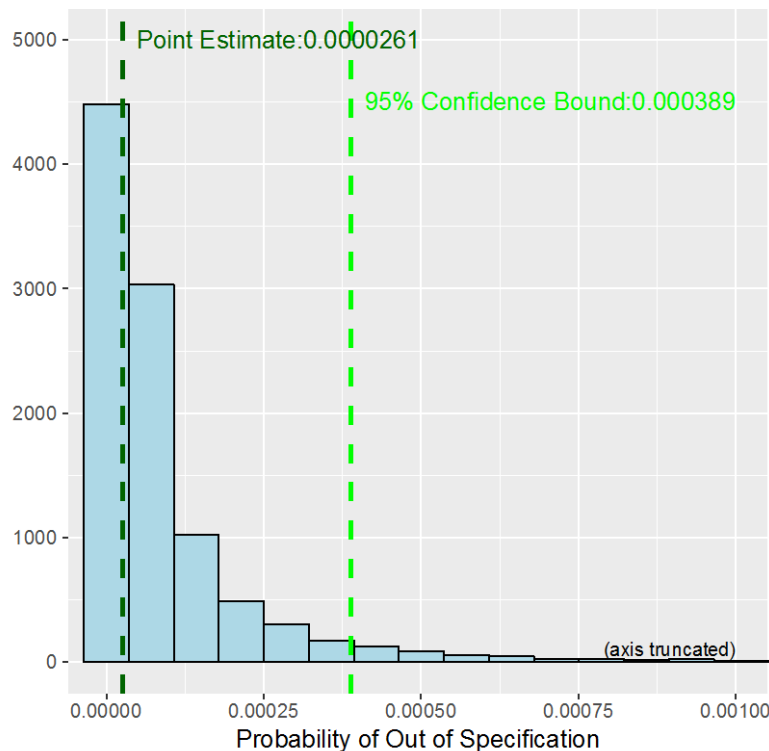
First 5 out of 10,000 resamples shown here, parametric bootstrap:

	FIntercept	FSlope	VCIntercept	VCSlope	s2Random	VarFInt	CovFIntSlope	VarFSlope
sim_1	97.774	-0.029	1.109	0.007	30.987	0.684	-0.034	0.004
sim_2	96.760	0.085	3.831	0.000	22.579	0.660	-0.023	0.002
sim_3	97.912	0.027	0.129	0.001	32.046	0.637	-0.032	0.003
sim_4	97.125	0.046	4.250	0.015	32.141	0.892	-0.037	0.005
sim_5	98.039	0.021	2.914	0.000	24.178	0.640	-0.025	0.002

- Use each row to calculate predicted Bioactivity at time 0 and time 24 months.
- Each row prediction variance estimate is a summation of quadratic forms for fixed effect standard errors and variance components.
- Use row estimates to calculate probability of out of specification on both tails assuming Gaussian distributional shape.

Bootstrap Approach for Bioactivity Attribute (continued)

Candidate 75 - 125 specification at 24 months



Specification Candidates Inputs Grid Example, first 20 rows

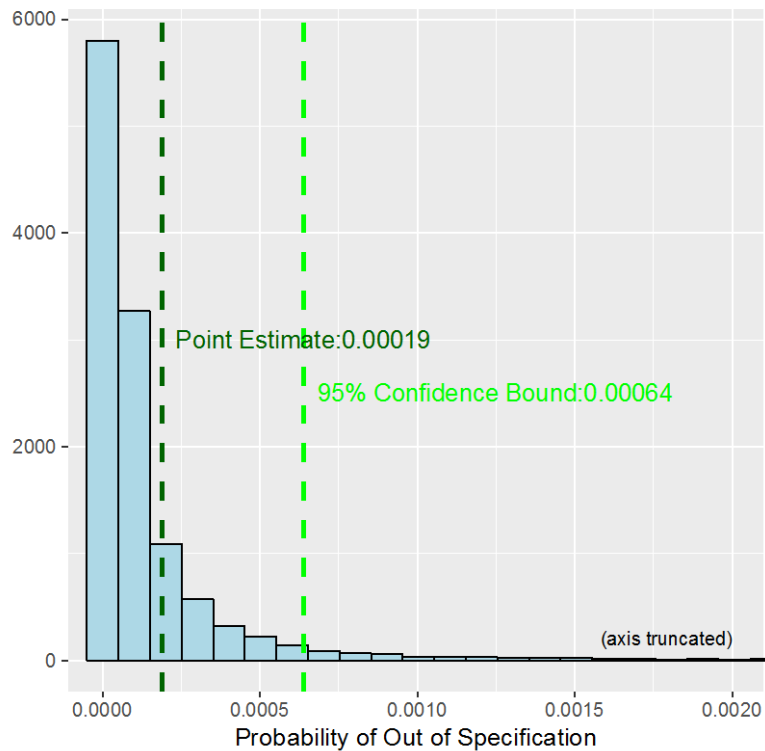
Lower	Upper	Time24Prob00S	Time0Prob00S
82	125	0.008	0.009
81	125	0.005	0.006
80	125	0.004	0.004
79	125	0.002	0.002
78	125	0.001	0.001
77	125	0.001	0.001
76	125	0.001	<0.001
75	125	<0.001	<0.001
82	120	0.009	0.009
81	120	0.006	0.006
80	120	0.005	0.004
79	120	0.003	0.003
78	120	0.003	0.002
77	120	0.002	0.001
76	120	0.002	0.001
75	120	0.002	0.001

Bayesian Recipe

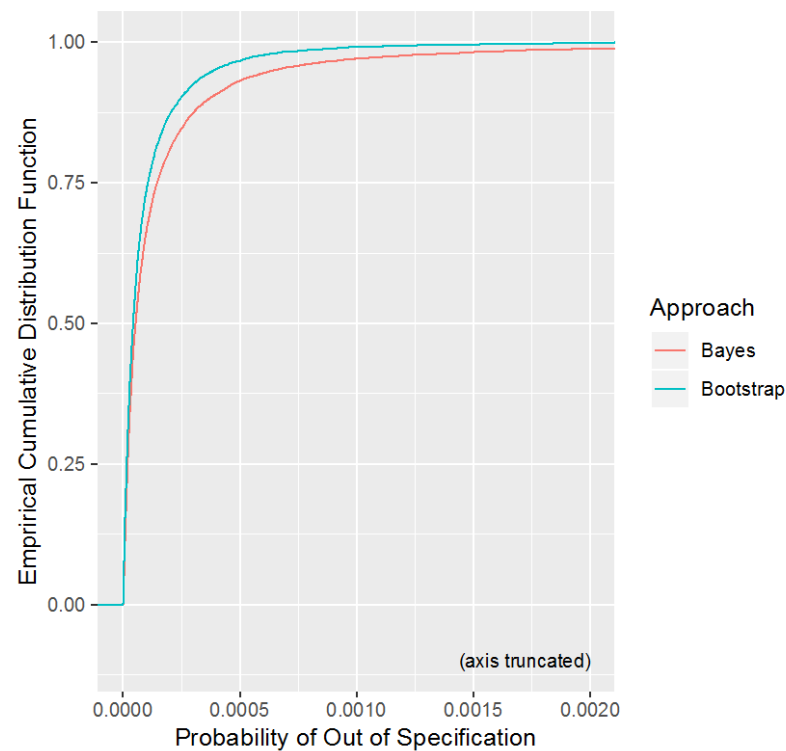
- Fit Hierarchical Model & Perform Diagnostics (inherent sampling)
- Calculate via Posterior Parameters
- Report Point and Credible Interval Calculations from Posterior Distributions

Bayesian Approach for Bioactivity Attribute

Candidate 75 - 125 specification at 24 months

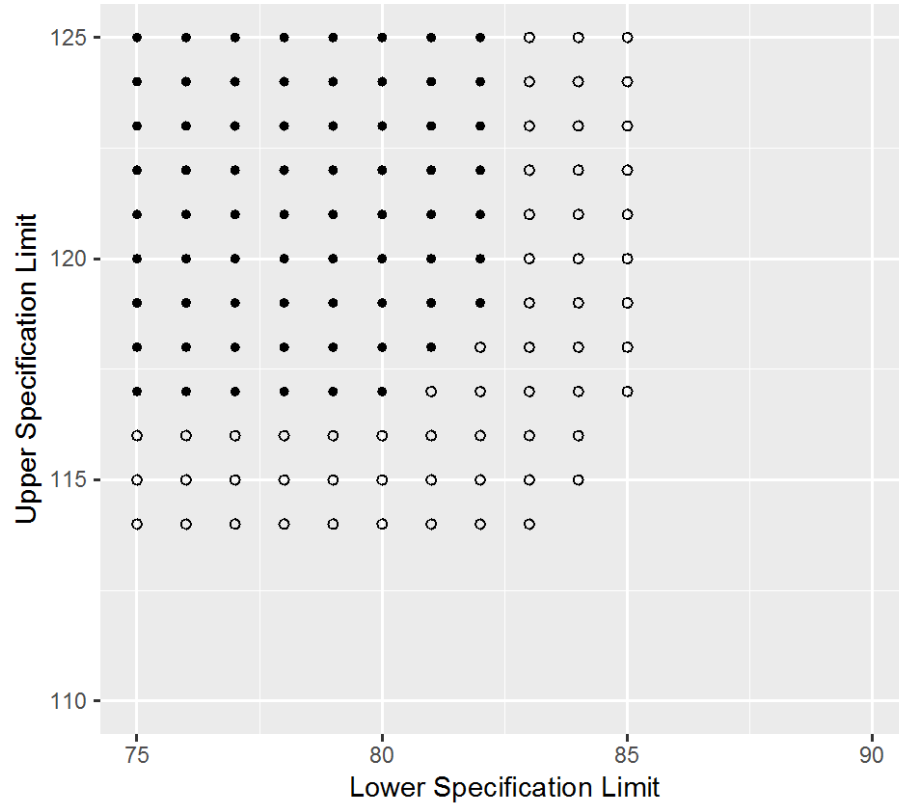


Comparison of Approaches via ECDFs



Reporting

Grid of Specification Candidates to Consider
where Point (open circle) and 95% Confidence Bound (dark circle)
Probability of Out of Specification Estimates are less than 0.01



Reporting & Interactivity

(one-sided attribute example)

Probability of Out of Specification Welcome Select Data and Fitted Models Select Specifications Risk Probability Evaluations **Browse Results** Export Report Help

Choose a Threshold

1%

Lower Specification Target:

95 97 100

Range of interest:

95 99 100

Graphs and Tables Results

Depending on the attribute chosen show specification 1-sided or 2-sided limits and allow interactivity to change limits and thresholds.

A threshold of 1% is chosen

The target specification 97 is chosen

A range that goes from 95 to 99 is chosen

Purity

Candidate Spec	Probability OOS
95.00	<0.001
95.10	<0.001
95.20	<0.001
95.30	<0.001
95.40	0.001