Trending Analysis for Stability: Predicting Expiry for Annual Lots

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2017 IABS Workshop on Statistical & Data Management Approaches for Biotechnology Drug Development

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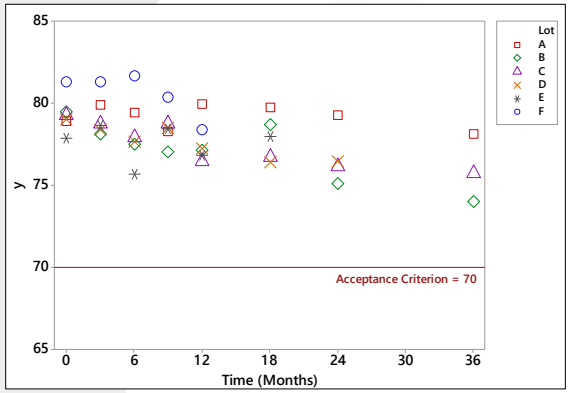
Overview

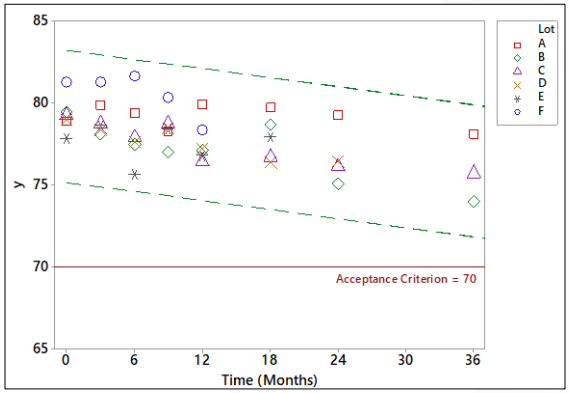
- **Objective**: Demonstrate effective methodology for annual stability trend analysis
- **Summary**:
  - Why conduct the analysis?
  - How we conduct the analysis
  - Rationale for specific methodology
  - How to use analysis results
  - Examples

Why Conduct Annual Analysis of Stability Data?

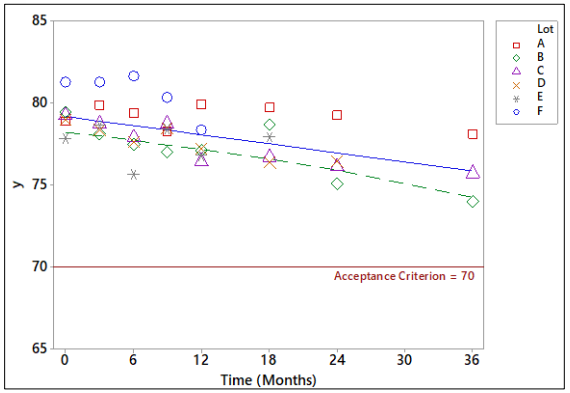
- US, EU, and CAN regulations require a “trend analysis” of stability data in the annual Product Quality Review (PQR)
- “Trend analysis” can take many forms



Scatter Plot
All results in specification



Scatter Plot with Trend Limit
All results in specification
All results within trend limit



Scatter Plot with Regression
All results in specification
Degradation profile as expected
Expiry period is supported

Interpreted: Is there a “signal” that an individual lot will not meet its expiry?

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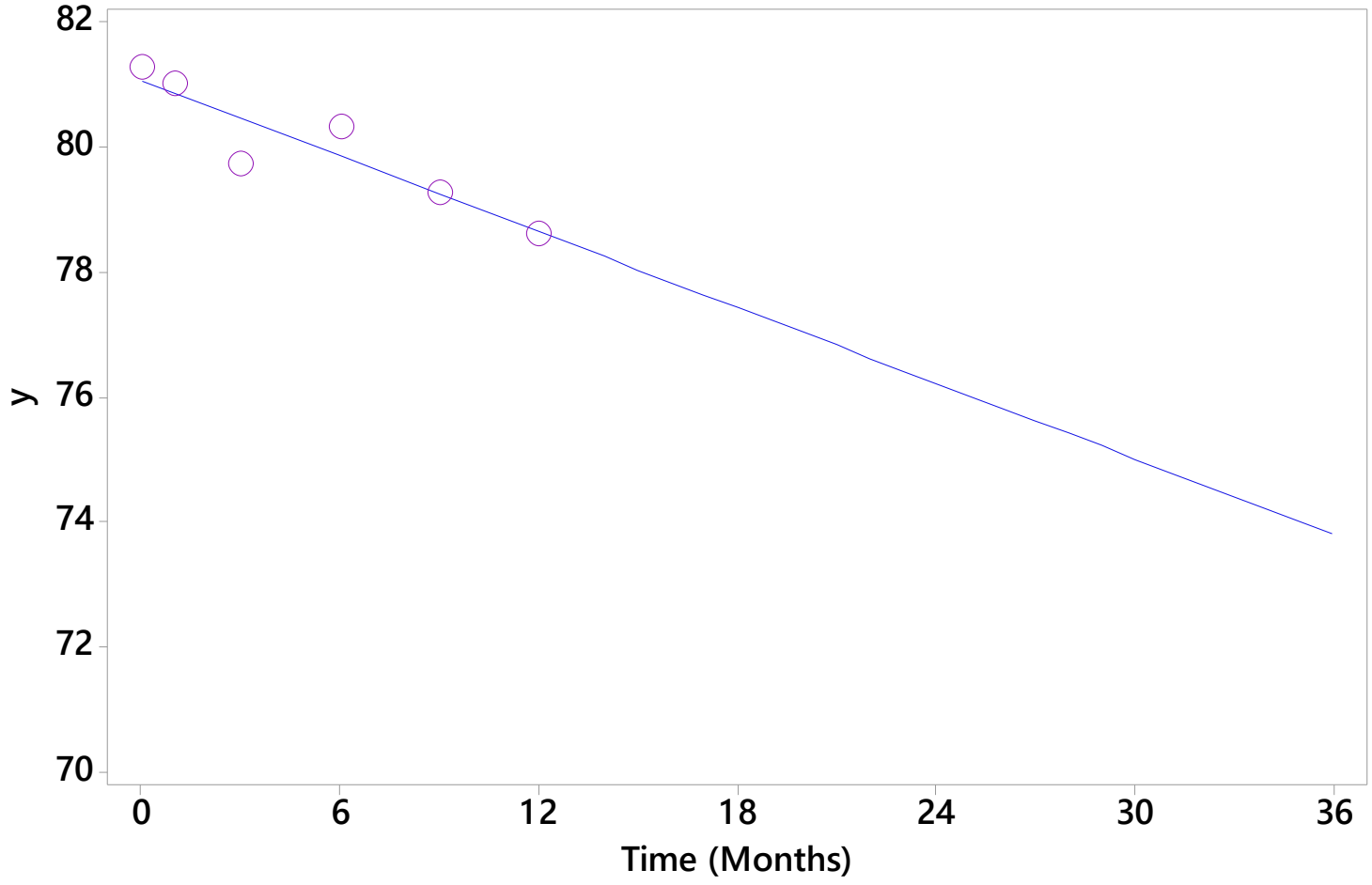
Blue Regression Line Estimates “Trend” for this Lot



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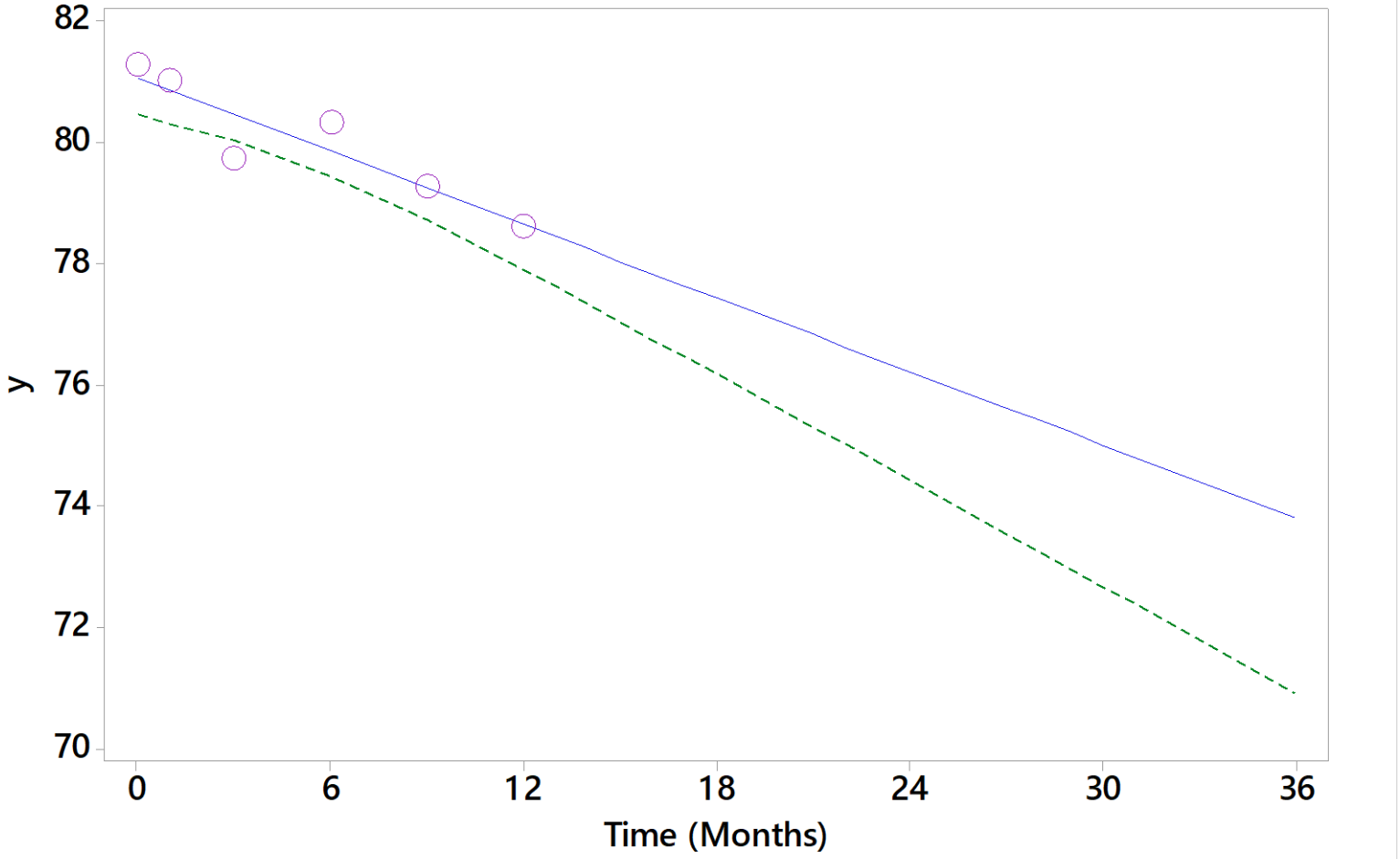
Green Confidence Bound Quantifies Uncertainty in Estimated Line



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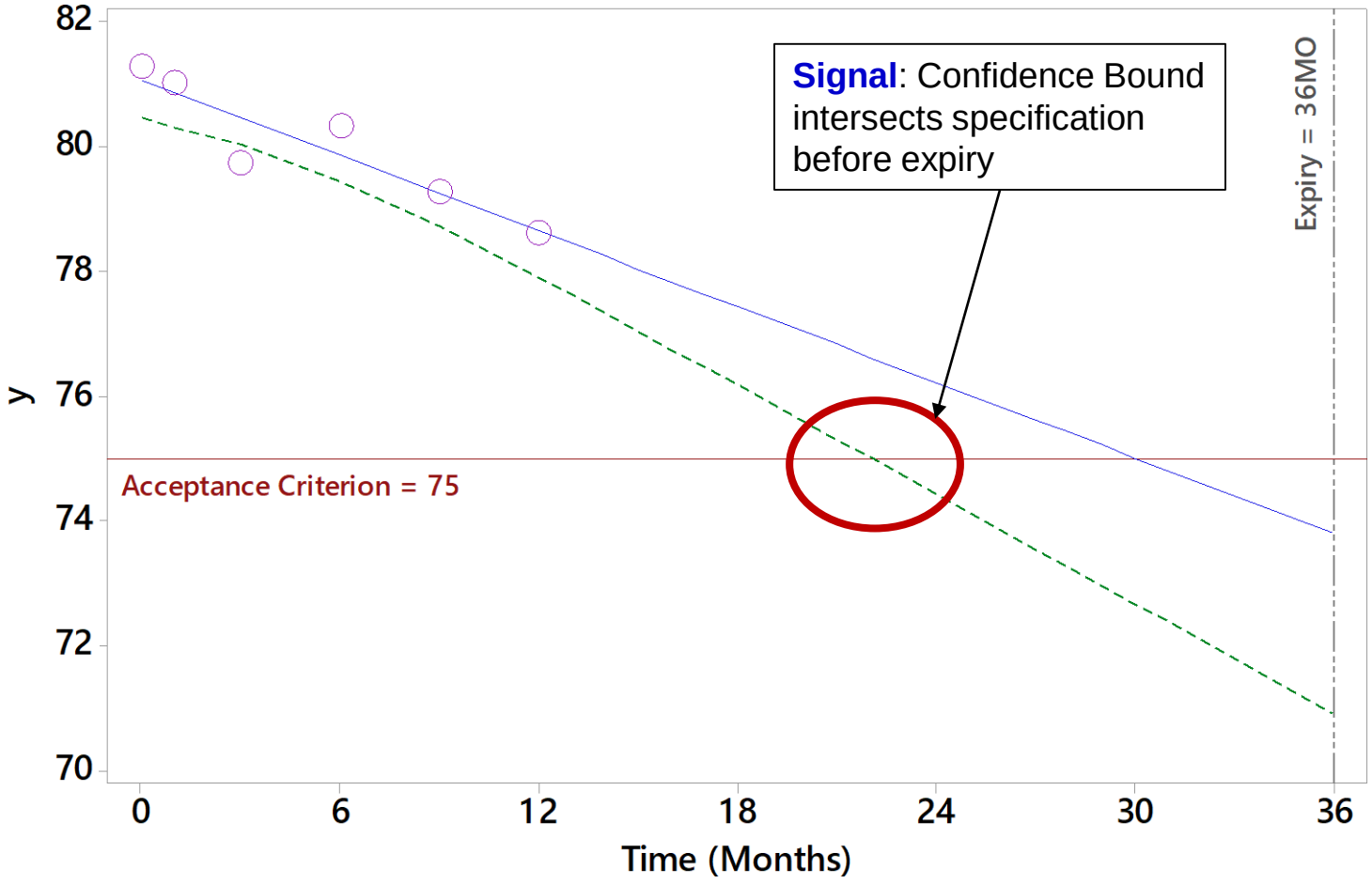
Analysis Signal Determined using ICH Q1E Methodology



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What's the Best Way to Conduct the Regression?

- Fit an individual line to each stability lot
- Examine degradation profile on a lot by lot basis

$$Y = \mu + Lot + Time + Lot * Time + \varepsilon$$

Separate Intercepts

Separate Slopes

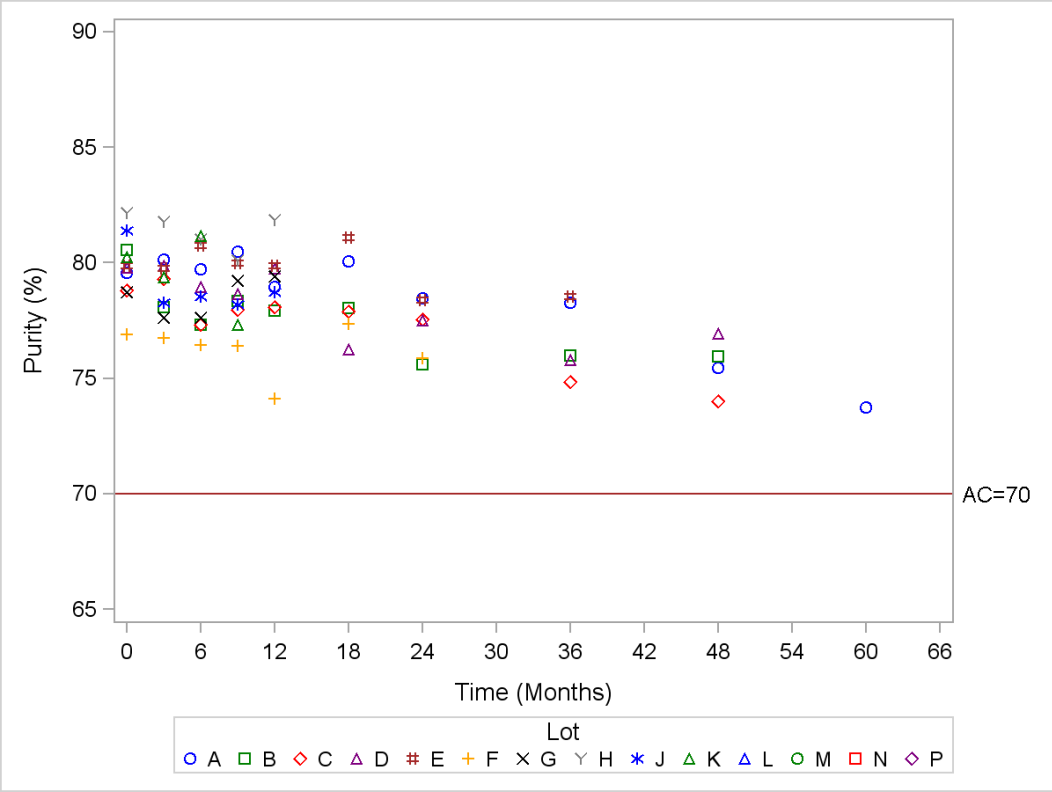
What assumptions do I make about lots on stability?

	Fixed Effect	Random Effect
Predictions Based on	Only points for the given lot	Points for the given lot AND overall process mean
Confidence Bounds Based on	Estimated variance and sample size for the given lot	Estimated variance and total sample size
Assumption about lots	Only these lots exist	Lots are random outcomes of a consistent process
Focus of Inference	Only lots analyzed	All lots from the process

Annual stability lot represents all lots manufactured in a given year, so
I want my statements to apply to all lots

A Note about Data in Examples

- Data simulated so that:
  - Random error in slopes ~N(-0.08, 0.008)
  - Random error in intercepts ~N(80, 1)
  - Random noise due to measurement error ~N(0,1)
  - → All lots come from the same process
- 10 lots with varying number of observations
- Time points per ICH Q1A: 0, 3, 6, 9, 12, 18, 24, 36, 48, 60 months



AC = Acceptance Criterion

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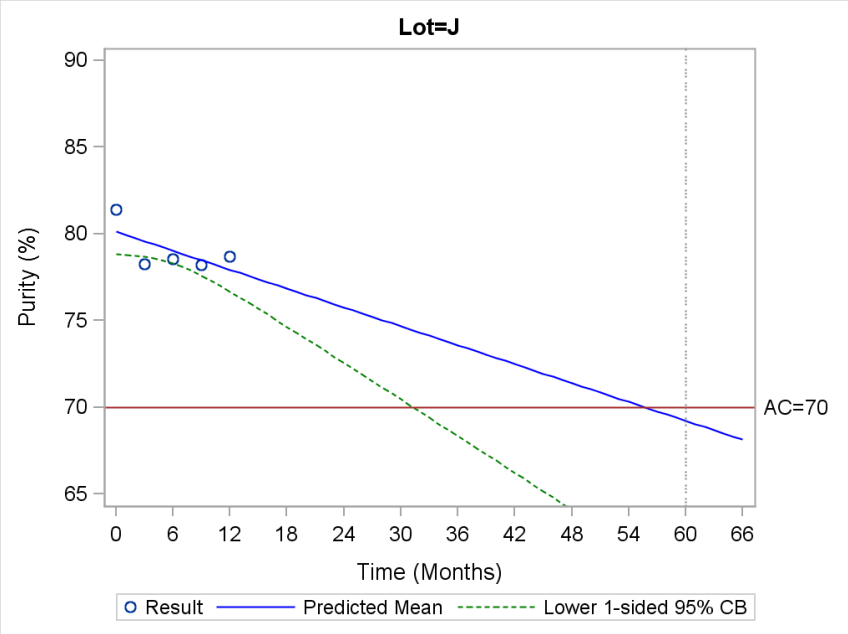
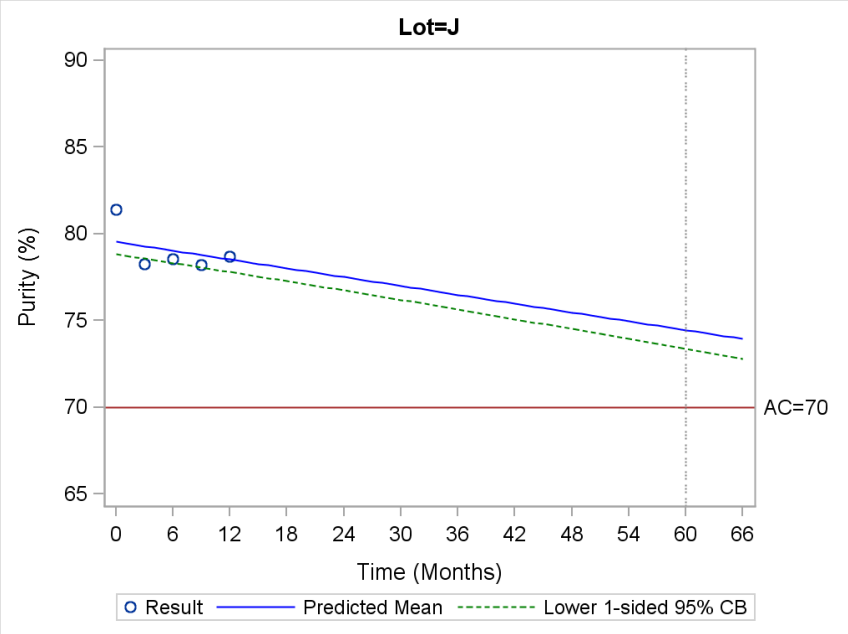
Predictions Differ based on How Process Knowledge is Leveraged

Example via **Fixed Lot Model**



Example via **Random Lot Model**



Signal around 30 MO

- Examines lot in isolation
- Little certainty in prediction

No signal

- Examines lot in context of process knowledge
- High degree of certainty in prediction

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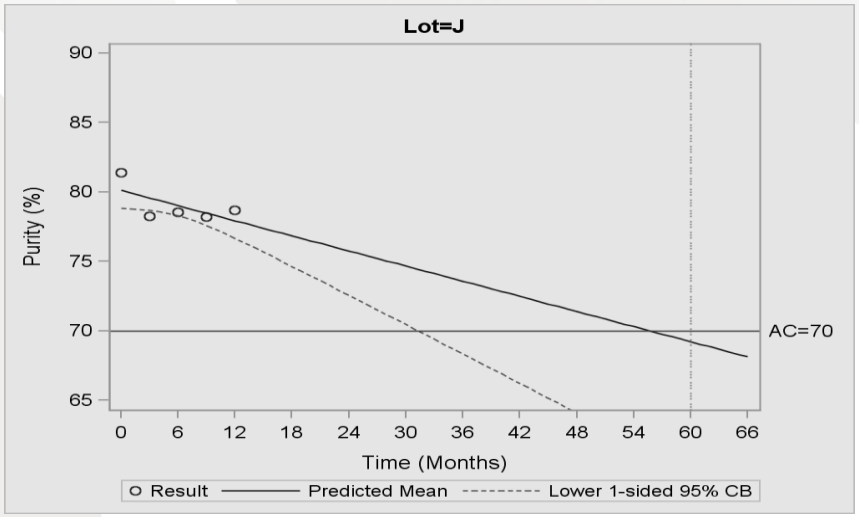
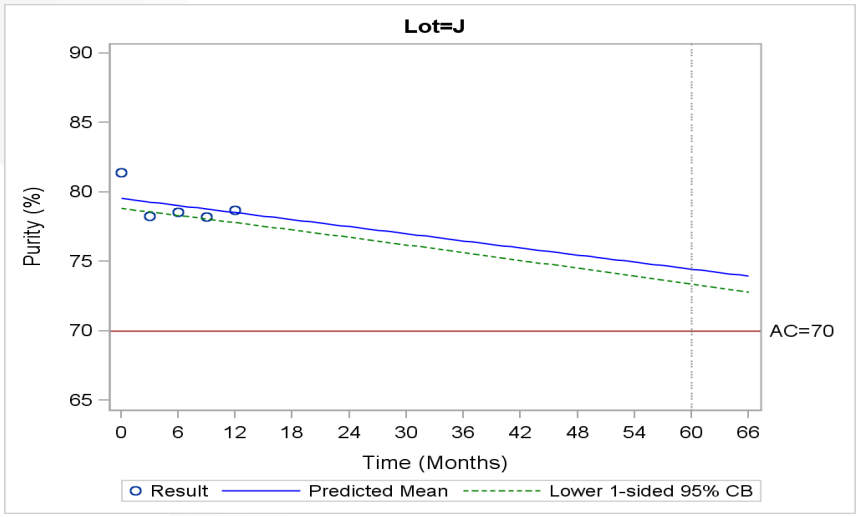
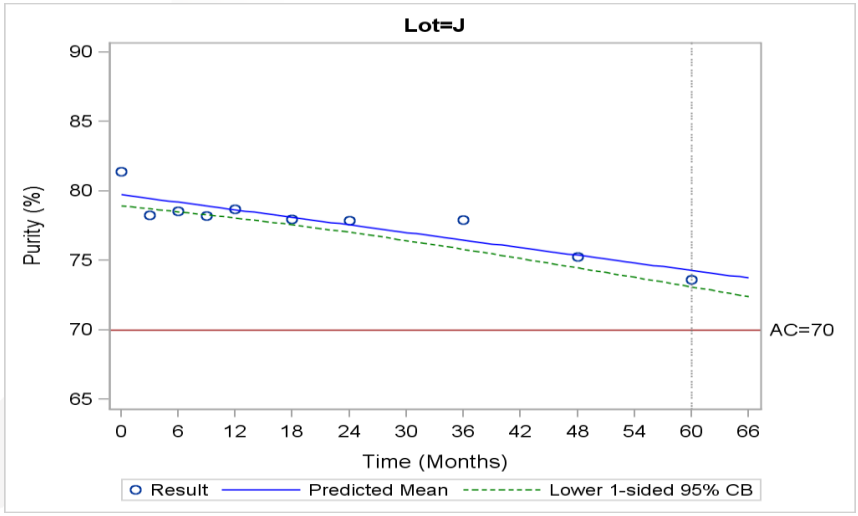
Which Model's Prediction is Better?

Example via **Fixed Lot Model**



Example via **Random Lot Model**





<u>Lot J successfully met 60 MO expiry</u>

- Trend leveraged overall product knowledge
- Allows analysis to overcome heavy influence from potentially extreme results at most recent time point

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Random Lots Model Makes Reliable Predictions that May Require Action

- Leveraging historical process knowledge provides information about expected trend
  - → We know something about how we expect the lot to behave before we place it on stability
- Certainty in prediction implies action may be required when a signal is detected
  - Action can't change trend for *this lot*
  - Can change monitoring strategy
  - Change product distribution strategy

Signals are Actionable, with Scientific Input

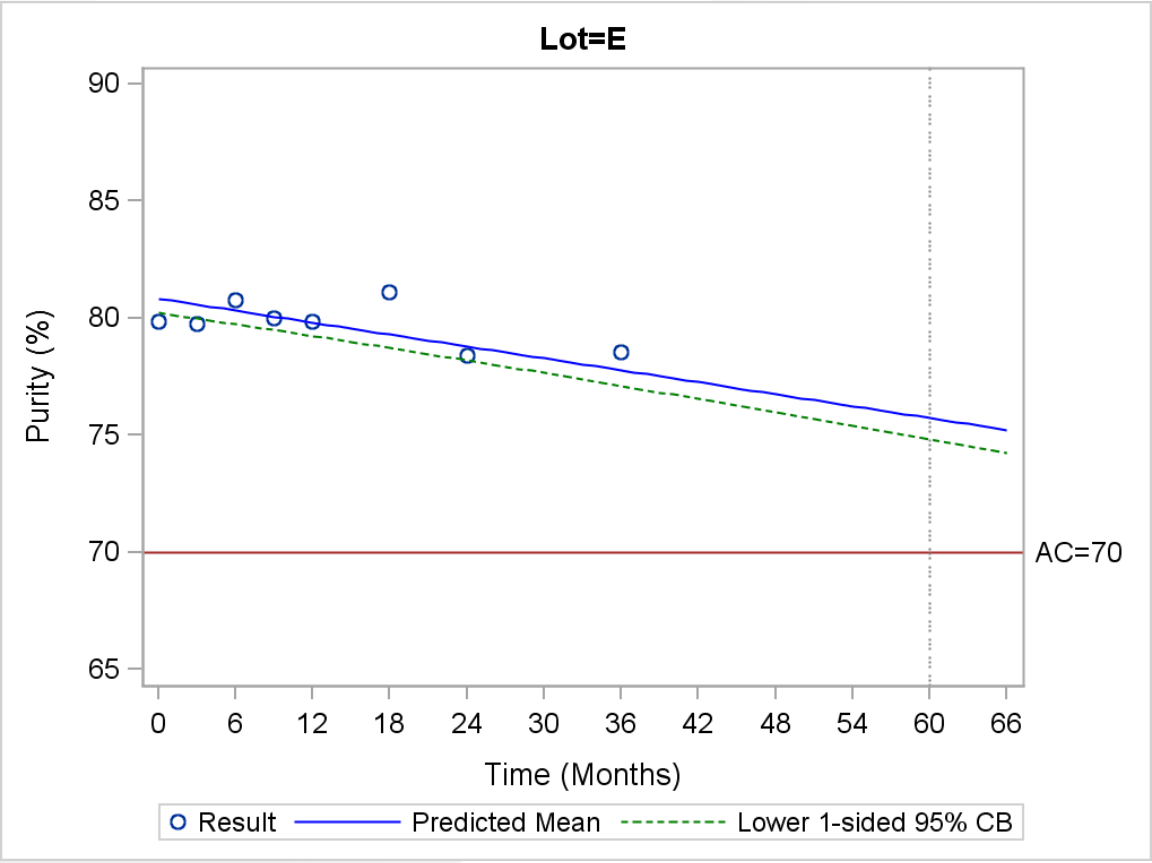
Level of investigation will depend on:

Consider…	Question to Ask
Other Known Issues	Is there another investigation for this lot, method, or specification?
Type of Analytical Method	Is the method stability indicating?
Type of Signal	Which lines intersect the specification?
Distance to Expiry	How far are the lines extrapolated?
Uncertainty in Prediction	How far is the confidence bound (CB) from the regression line?

Example Analysis Output

No Signal

Signal Type			
Regression Line in Specification?	**95% CB in Specification?**	**Interpretation**	**Suggested Action / Consideration**
YES	YES	Lot expected to meet expiry	**No action required** Expected/desired outcome



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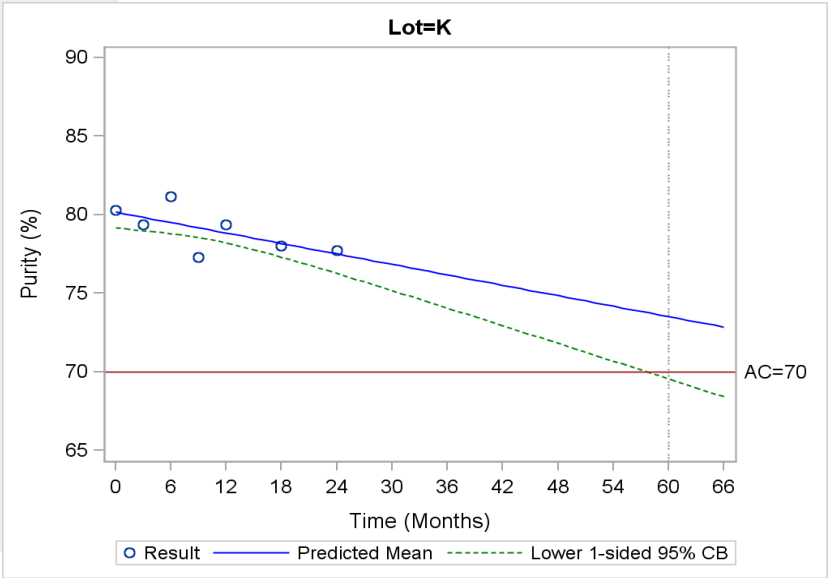
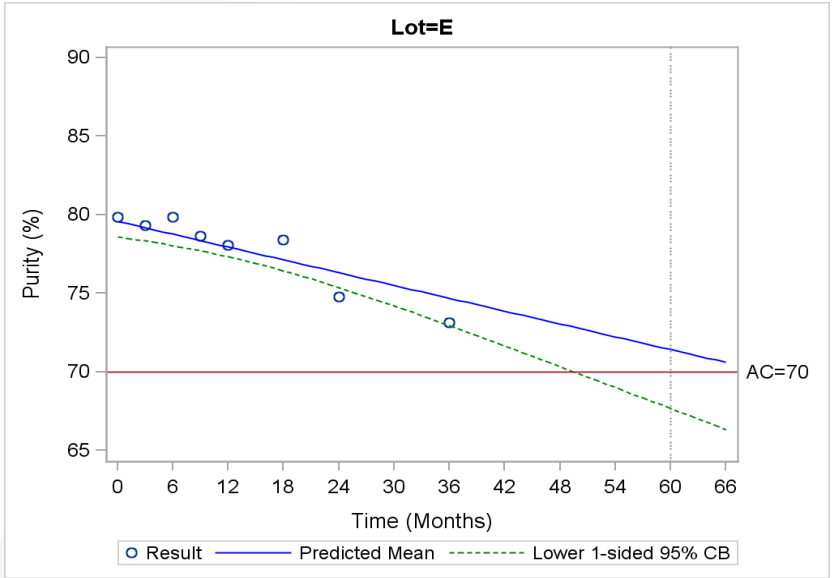
Example Analysis Output

Confidence Bound Intersects Specification Prior to Expiry

Signal Type			
Regression Line in Specification?	**95% CB in Specification?**	**Interpretation**	**Suggested Action / Consideration**
YES	NO	Lot may have shortened shelf life in future	**Wait until next time point / document** Considerable extrapolation & large uncertainty
		Lot may not meet current expiry	**Investigate / Add Time Point** Signal before next planned time point Lot may preclude any expiry extension



Signal at ~58 months
Next time point at 36 months
Action: Wait until next time point

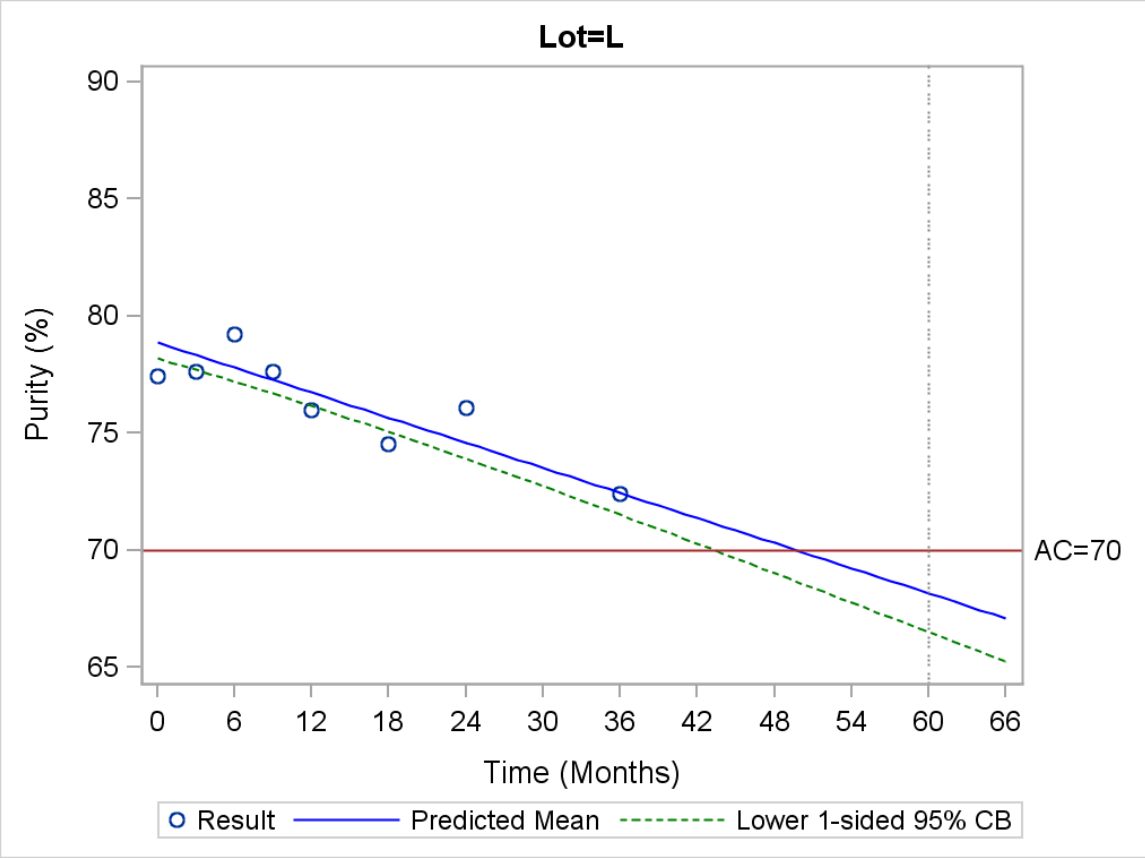


Signal at ~48 months
Next time point at 48 months
Action: Investigate / Add time point at 42 months

Example Analysis Output

Extreme Signal: Confidence Bound & Predicted Mean Intersect Specification

Signal Type			
Regression Line in Specification?	**95% CB in Specification?**	**Interpretation**	**Suggested Action / Consideration**
NO	NO	Lot might be expired *right now*	**Investigate** Potential recall / BPD



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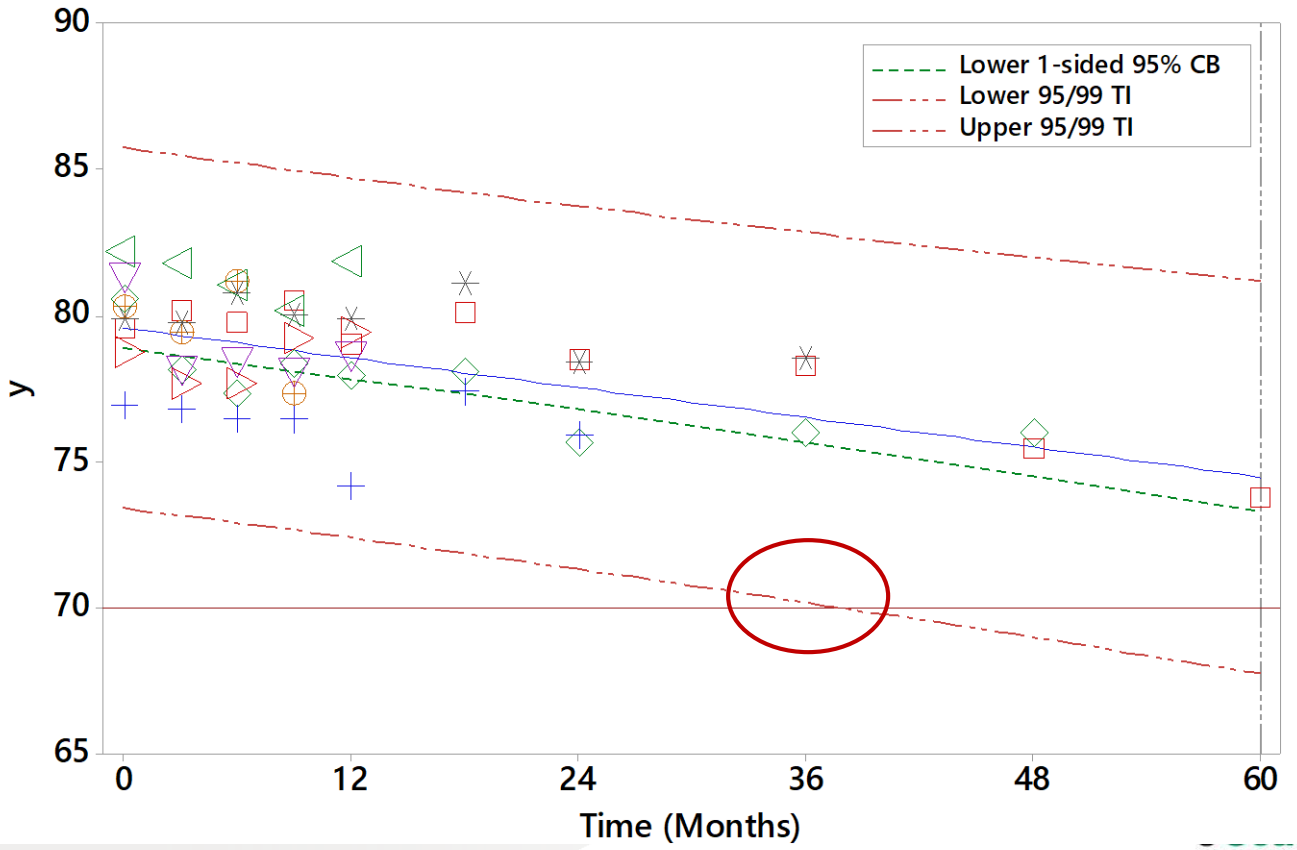
Implementing the Analysis

- Incorporate into Continued Process Verification (CPV) strategy
- How much data do I need?
  - Random lots model performs well with ≥ 3 lots (Stroup & Quinlan)
  - Amount of data can differ by lot
    - Only need 0 time to make a prediction
    - Fewer time points for a lot result in prediction based more on average stability trend
- May proceduralize portions of analysis
  - Statistical methodology
  - Actions based on signals
  - → Take care to not be overly prescriptive

Analysis Limitations

Predictions don't quantify probability of an individual OOS result

- Tolerance interval (TI) on individuals quantifies expectation for individual results
- Example figure: could have OOS result around 36 MO



Conclusions

- Regression analysis of stability data provides “signals” that indicate a lot may not meet its expiry period
- Analysis technique leverages process knowledge to:
  - Provide correct focus of inference for conclusions
  - Ensure signals are reliable and actionable
- Actions need to consider statistics in conjunction with scientific knowledge, patient safety, and business risk

Acknowledgements

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Appendix

References

Regulatory Requirements for Annual Stability Trend Analysis

Return

- **EU Guidelines to Good Manufacturing Practice** for Medicinal Products, Part I, Chapter, 1, Section 1.10.vii.

  1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally **be conducted and documented annually**, taking into account previous reviews, and should include at least:

  - (vii) A review of **the results of the stability monitoring programme and any adverse trends**.

- **Health Canada, Guidance for Sponsors**: Lot Release Program for Schedule D (Biologic) Drugs, Section 5.1.1.3.

  5.1.1.3 Information on drug substance and drug product test results:

  - a review of critical in-process controls and finished product results
  - **trend analysis for stability-indicating test methods**
  - **a review of results of ongoing stability program(s)**

- **US Code of Federal Regulations**, Title 21, Chapter I, Part 211, Section 211.180.e.

  (e) Written records required by this part shall be maintained so that data therein can be used for evaluating, **at least annually, the quality standards of each drug product** to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

  (1) A review of a representative number of batches, whether approved or rejected, and, **where applicable, records associated with the batch.**

Other References

- Stroup, W. and M. Quinlan. 2016. Statistical Considerations for Stability and the Estimation of Shelf Life. In *Nonclinical Statistics for Pharmaceutical and Biotechnology Industries*, ed. Zhang, Lanju, 575-604. Switzerland: Springer.
- Chow, Shein-Chung. 2007. *Statistical Design and Analysis of Stability Studies*. Durham, NC: Chapman & Hall.
- Shao, J. and S. Chow. 1994. Statistical Inference in Stability Analysis. *Biometrics*, 50: 753-763.

SAS Code for Random Lot Model

```
proc mixed data=dat;
        class lot;
        model y = time/cl residual outp=DAToutp ddfm=kr
                        alphap=0.1;
        random lot lot*time;
run;quit;
```

- Adjust alpha for confidence bounds using `alphap=0.1` for a 1-sided specification
- Use `ddfm=kr` to control Type I error rates for mixed models with repeated measures
- Predicted means and confidence bounds for BLUPs for each lot are given in the `outp=DATout` data set