ASA BIOPHARMACEUTICAL SECTION
REGULATORY-INDUSTRY STATISTICS WORKSHOP
SEPTEMBER 25–27, 2017 | WASHINGTON, DC

PS1e - CMC Session: Statistical Considerations
When Assessing Product Stability and/or Shelf Life

Stability Studies in the IVD Industry

Jeffrey Budd, PhD
Principal Biostatistician
Beckman Coulter
jrbudd@beckman.com

In Vitro Diagnostics (IVD)

- We supply laboratory test results that doctors use to diagnose, treat and monitor patients
- We need to ensure that tests remain accurate even as material used in these tests age
  - reagents used to detect and measure substances
  - calibrators used to convert from instrument signal to substance concentration
  - control material used to monitor proper system operation

IVD Stability Guidelines

- The two most active organizations in providing guidelines for the IVD industry are
  - International Organization for Standardization (ISO)
  - Clinical and Laboratory Standards Institute (CLSI)
- The most influential guideline for IVD stability is EP25[1], published in 2009
  - This guideline is currently being revised

Types of Stability Studies

- Shelf life
  - Original packaging, specified storage conditions
- In-use
  - After opening, reconstituting, thawing
- Transportation simulation
  - Product exposed to potential extreme conditions
- Performance monitoring
  - Is stability behavior maintained over life cycle?

Stability Considerations

- Product storage conditions
  - Maximize stability (room temp, refrigerate, freeze)
  - If range of temperature what is test temperature?
- Acceptance criteria
  - What is clinical need, considering intended use?
- Number of lots (3?)
- Mix of shelf life, in-use, transport simulation
  - Beginning or end of shelf life?

Types of Stability Studies

- Classical
  - eg, result measured each month over 13 months
- Isochronous
  - eg, each month test material placed in stability condition, all measured together at 13 months
- Matching
  - eg, each month, test compared to reference
- Accelerated (Arrhenius, other options)

Time Point Value Assignment

- Factors to consider
  - Within run*
  - Between vial*
  - Between run
  - Between day
  - Calibration to calibration
  - Reagent lot to lot
  - Calibrator lot to lot
  - Instrument to instrument
  - Drift over time*

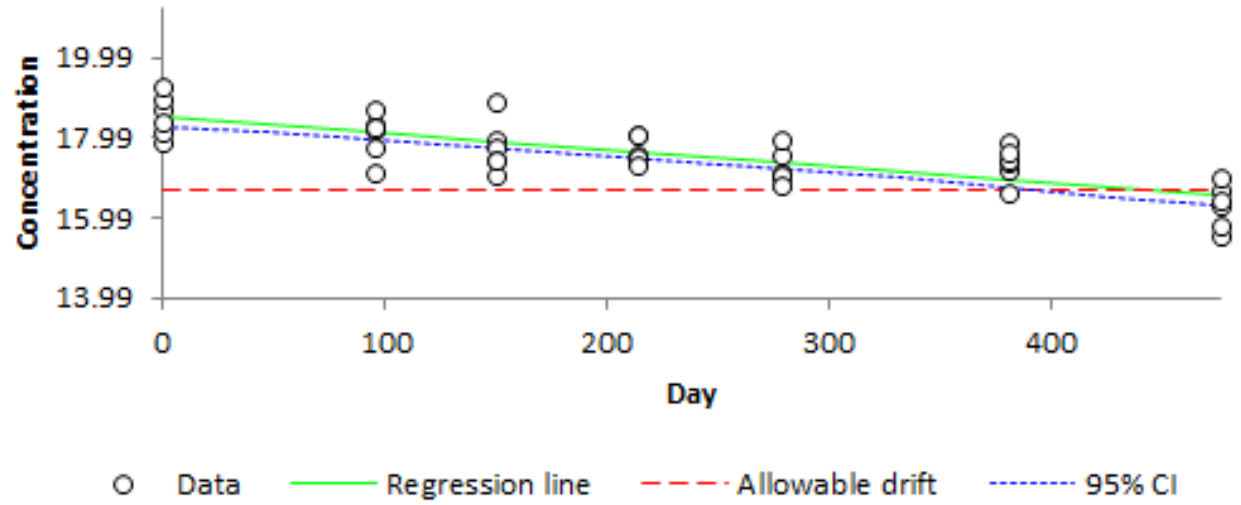
* Currently considered in EP25-A

Designing a stability study

- Minimize systematic influences
  - Use same instrument(s), reagent lot(s), calibrator lot(s) across the study period
  - Be aware of potential drift due to these factors
- Sample random factors (eg, calibrations, runs)
- Determine uncertainty at each time point
  - $CV_{adj} = sqrt(CV_{cal}^2/\#cals + CV_{BR}^2/\#runs + CV_{WR}^2/\#reps)$
- Determine sample size given proposed # points
- Use mean of results at each time point

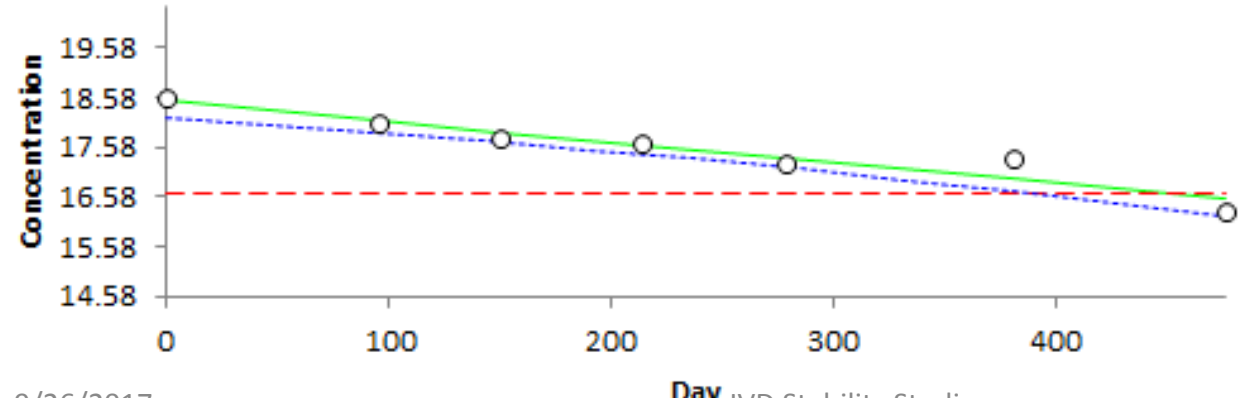
cal = calibrations, BR=between run, WR=within run, reps=replicates

Plot Replicates or Not?



Note: the allowable drift limit is at 10%

Slope = -0.0223
At 365 days:
Fit = -8.16%
95%CI = -9.12%
10% at 399 days



Slope = -0.0223
At 365 days:
Fit = -8.16%
95%CI = -9.48%
10% at 384 days

Not!

How to determine baseline

- Some suggest that more robust testing be conducted at day zero to establish baseline
- However, there is no more robust method than using all the data in the study (via the regression): set baseline = zero intercept Akbas (2016)
- This modifies the determination from measuring change from a set value to measuring the percent change over time

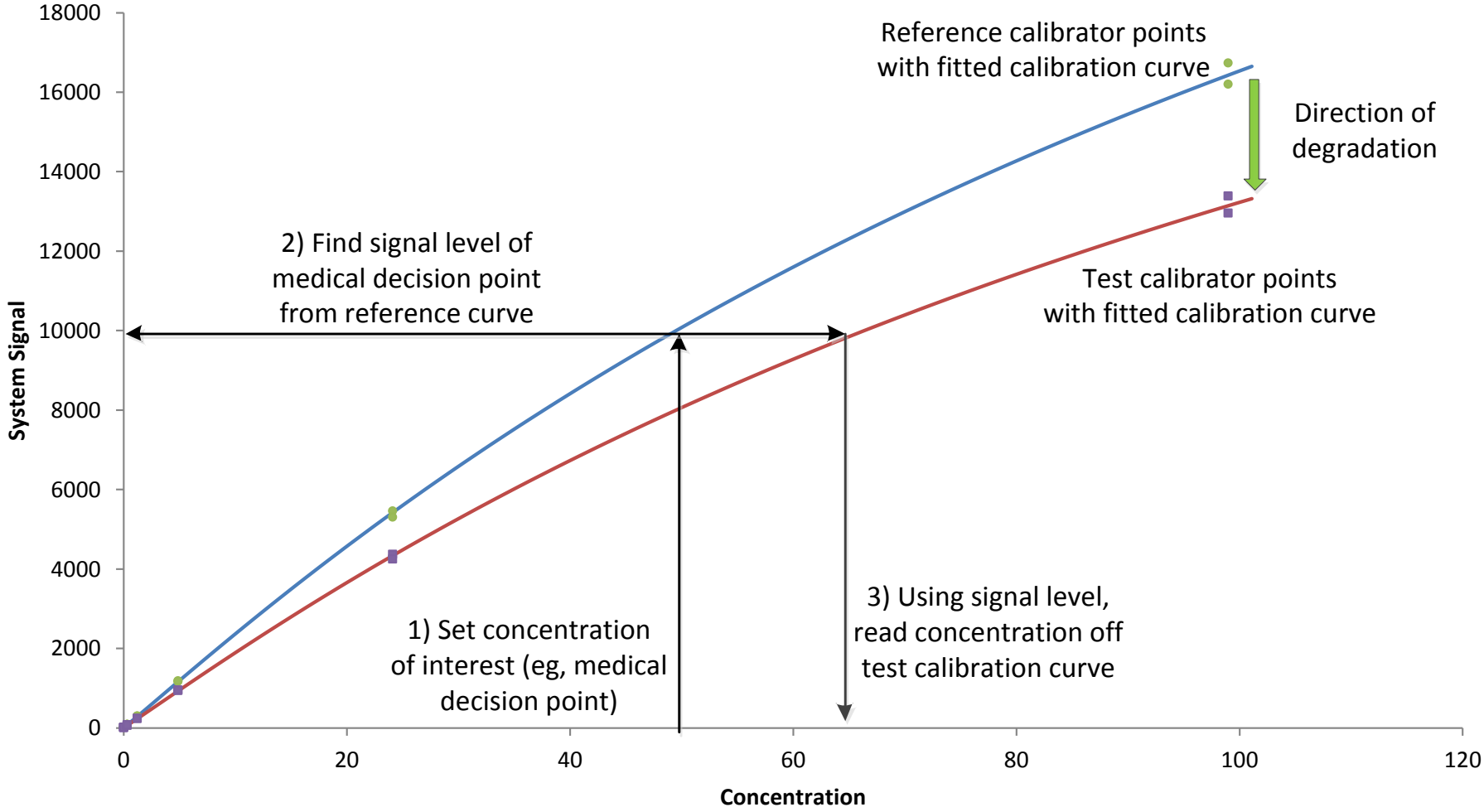
Control Material Matching

- Place control test material in intended use condition (eg, 4°C)
- Place additional control reference material in known, unchanging state (eg, -70°C)
- At each time point measure the difference in results between the two conditions
- Compare drift in this difference to %criteria
- Eliminates the effects of factors: run, day, calibration, instrument, reagent lot, cal lot

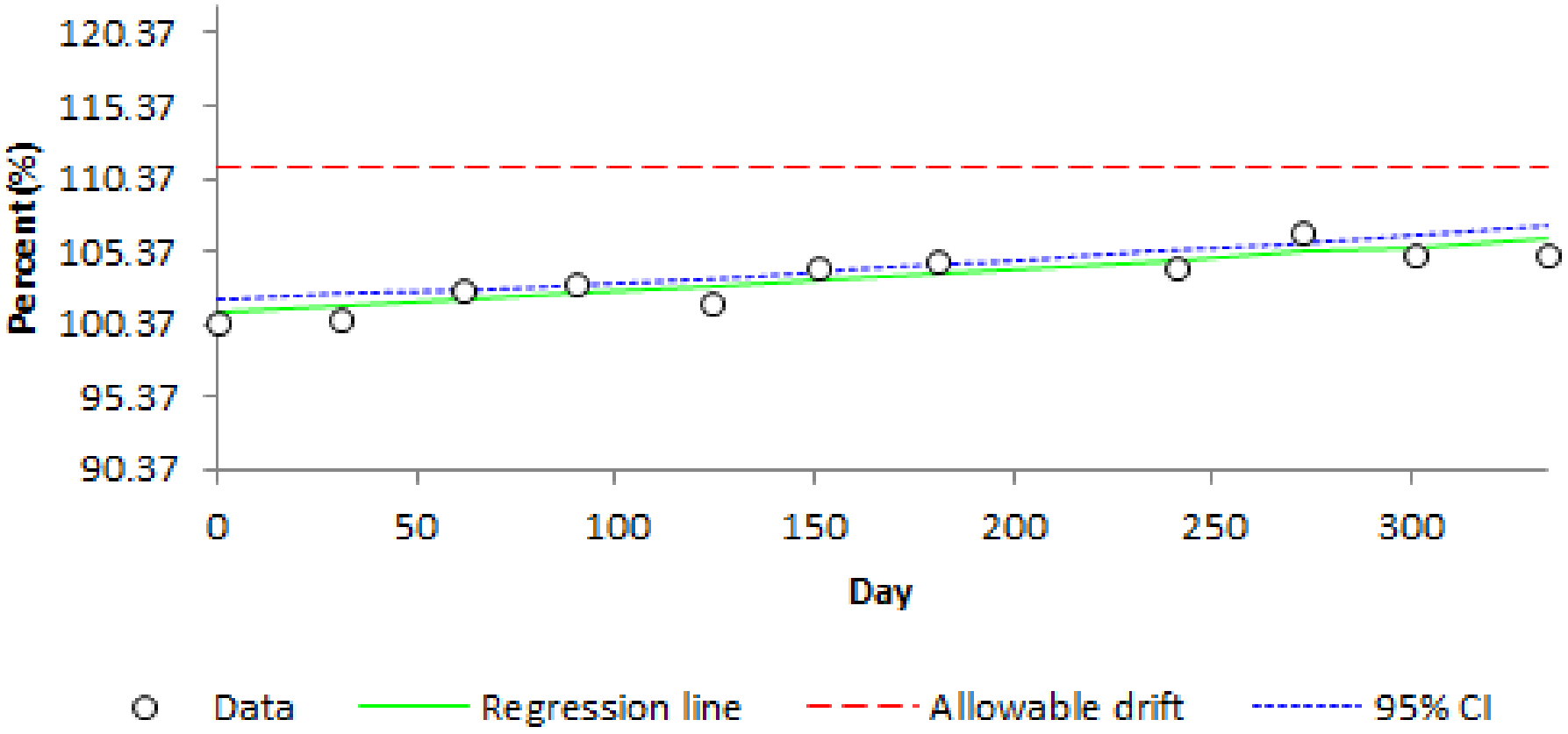
Calibrator Matching

- Use unchanging, internal working calibrators as reference calibrator set at each time point
- Place product calibrator set to be tested in their standard storage condition
- At each time point run both reference and test calibrator sets
  - In same run, on same instrument, using the same reagent lot
  - Can do multiple repeats if needed

Calibrator Matching



Example:

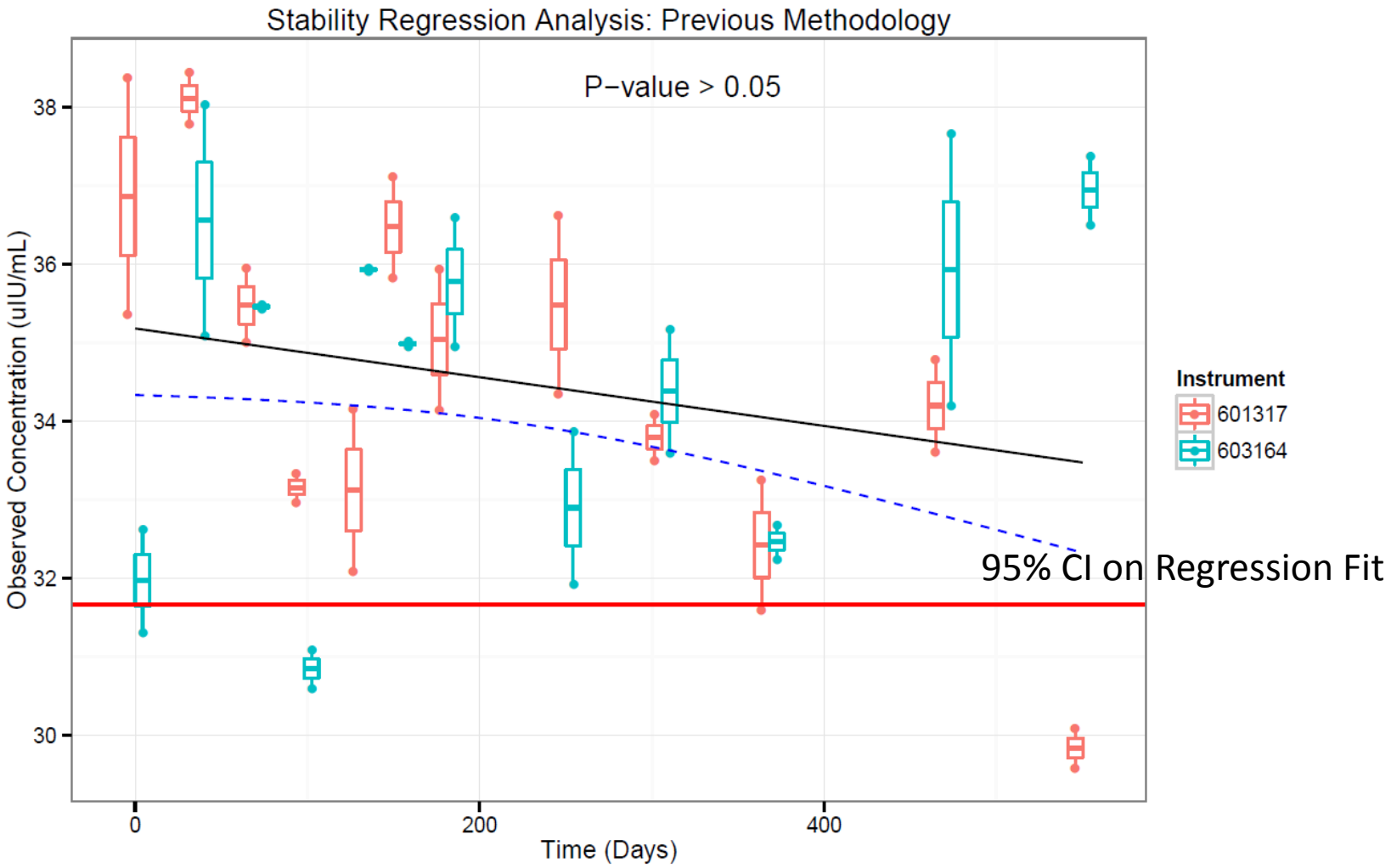


Note: the allowable drift limit is at 10%

Current Practice (EP25, Ed. 1)

- Determine sample size based mainly on repeatability (within-run imprecision)
- Plot all replicates (y-axis typically in units)
  - Difference from T_0 point determined
- Fit regression line to data
  - If regression p-value < 0.05 then stability is good
  - If regression p-value ≥ 0.05 then use 95% CI of the regression fit

Example of Current Practice

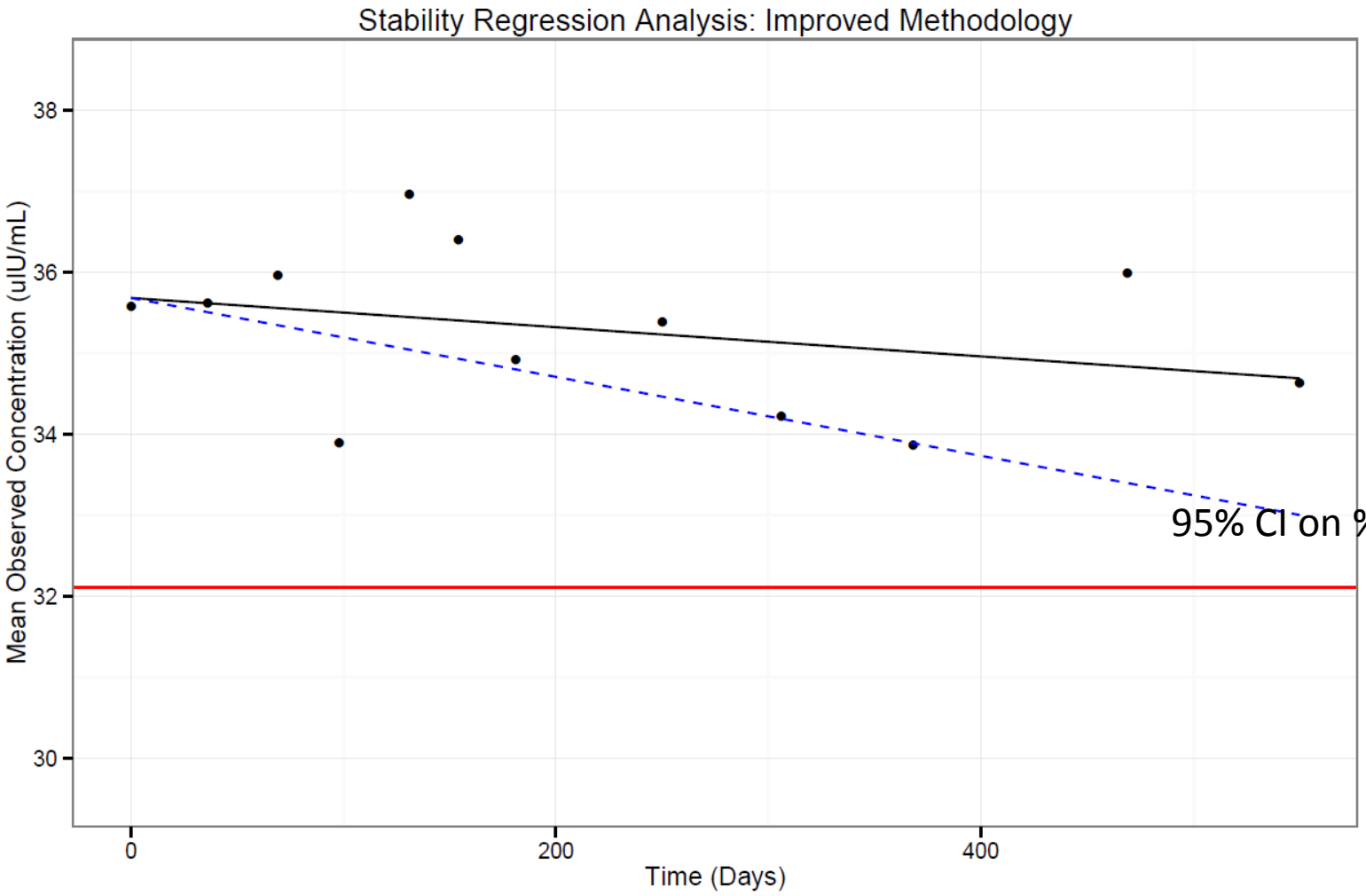


Future Practice (EP25, Ed. 2)*

- Determine sample size based on all relevant variance components
- Plot one estimate per time point
  - y-axis can be in units or percentage
  - Difference from intercept (β_0) determined
- Fit regression line to data
  - Use 95% CI on percent of change from $T_{0 =} \beta_0$

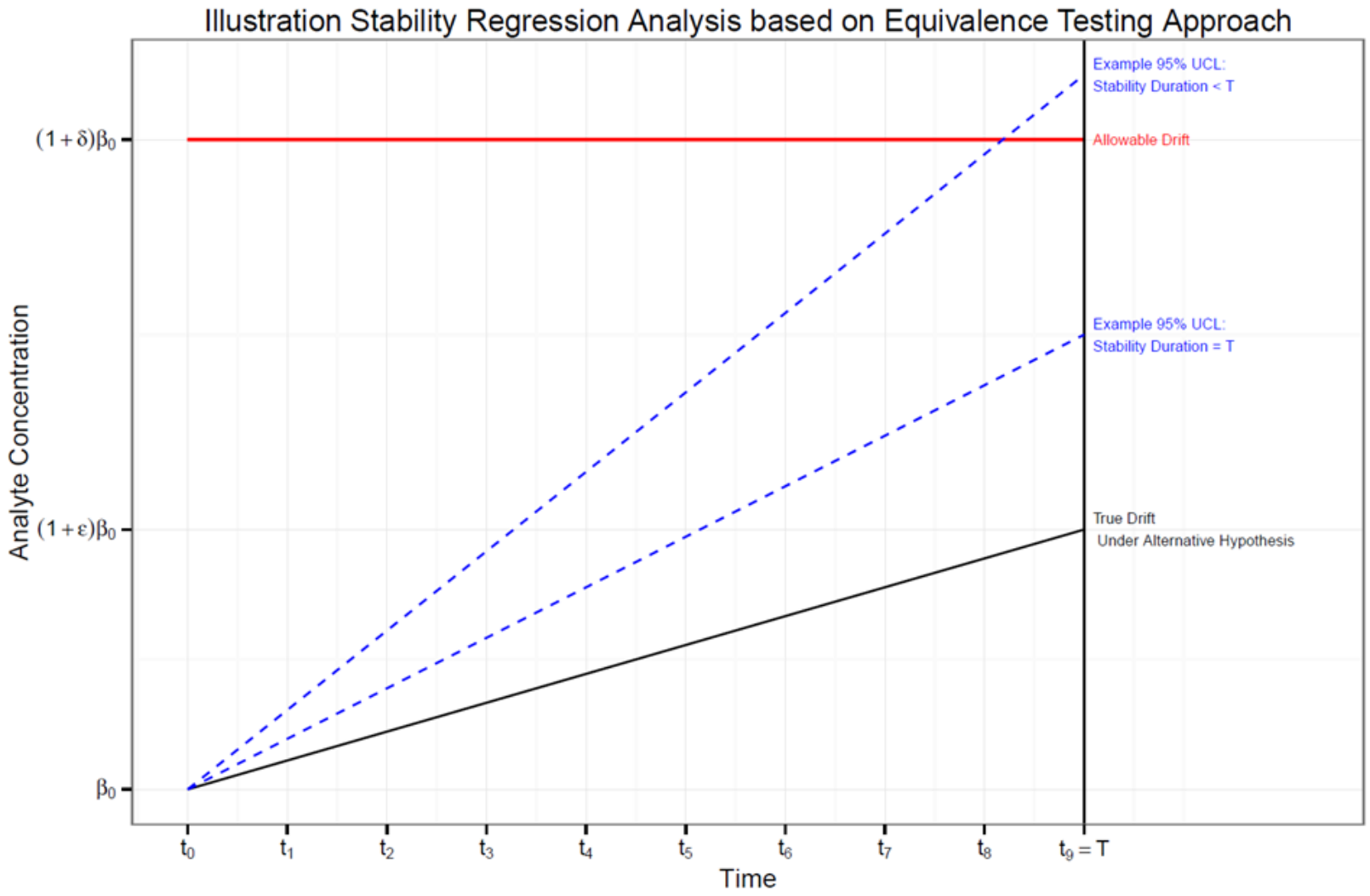
* Based on Holland (2017)

Same Example: Future Practice



95% CI on %Change

Outcome Predictability



Old versus New

- Difference from T_0
- p-value >0.05 (pass)
- No confidence statement on outcome
- Unpredictable outcome
- Plot all replicates at T_i
- Underpowered study by missing variance components

- % difference from β_0
- Equivalence test
- Can state confidence in outcome
- Outcome is predictable
- Plot mean at each T_i
- Fully powered study that covers all variance components

References

1) Pierson-Perry, J. et al. (2009), “Evaluation of Stability of In Vitro Diagnostic Reagents: Approved Guideline”, CLSI EP25-A.

2) Akbas, N., Budd J., and Klee, G. (2016), “Multiple Calibrator Measurements Improve Accuracy and Stability Estimates of Automated Immunoassays”, *Scandinavian Journal of Clinical and Laboratory Investigation,* 76, 177-180.

3) Holland, M., Kraght, P., Akbas, N., Budd J., and Klee, G. (2017), “Improved Statistical Methods for Evaluation of Stability of In Vitro Diagnostic Reagents”, *Statistics in Biopharmaceutical Research*, http://dx.doi.org/10.1080/19466315.2017.1305287 (Accepted)