Tolerance Intervals – an Adaptive Approach for Specification Setting

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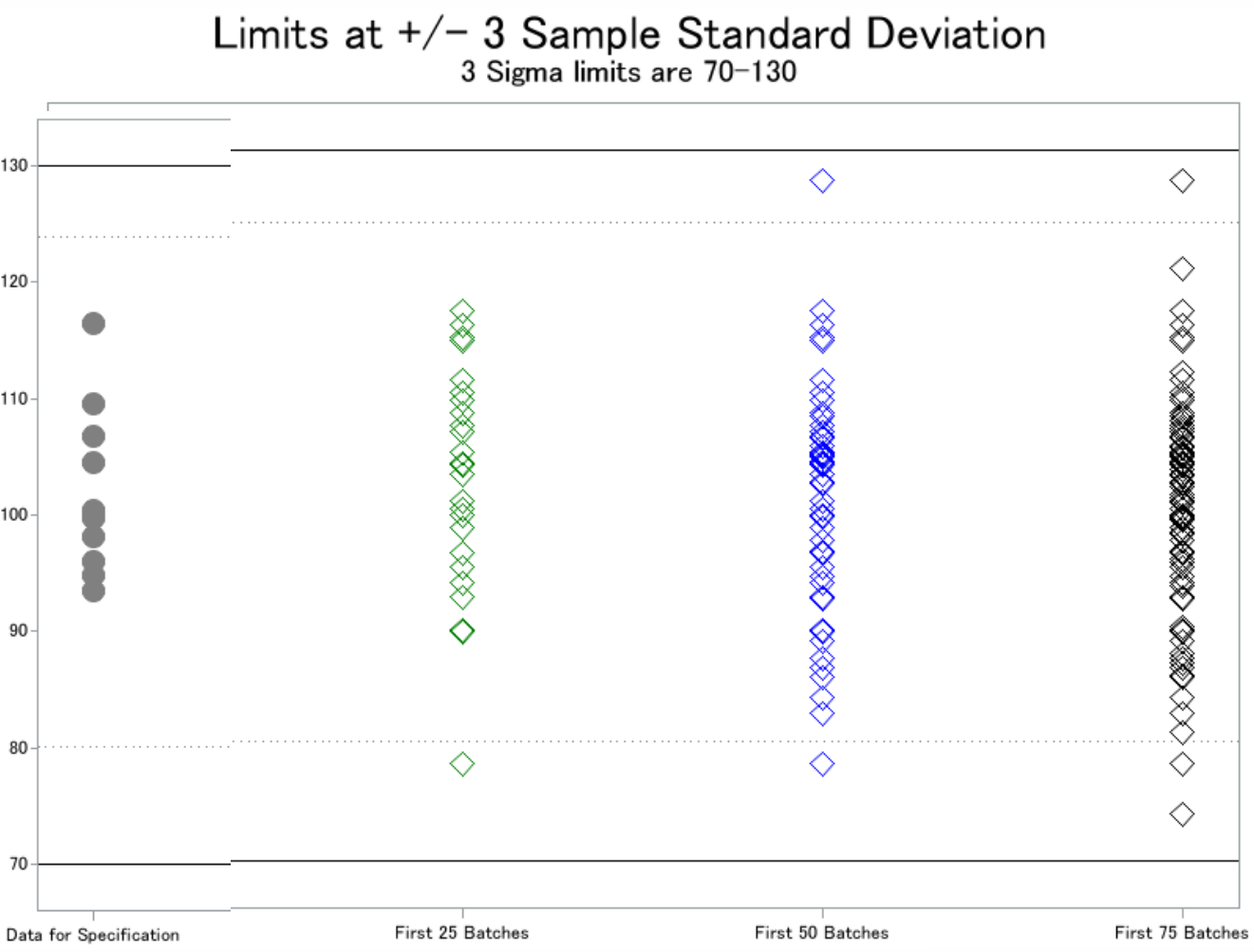
Specifications…

- Ideally defined ahead of time
  - Clinically relevant
  - Build the process to meet
  - Indices to measure performance, stability, etc. (previous talk)
- Ensure safety and efficacy
- But we DON'T always know these ahead of time, so we need

- **"data driven specifications"**

Setting Specifications … with limited data



Ideally, specifications cover the vast majority of results, so true 3 sigma limits might be acceptable

Very wide = unacceptable?

First 10 batches much narrower than true +/- 3 sigma

The **sample** limits are narrower than the process limits, so future values are out of Specification

Why isn't +/- 3SD enough?

In the (very long) run, mean +/- 3 SD will cover 99.73% of the population if we have a "Normal" or bell-shaped data distribution.

A data-driven specification is set based on 5-15 batches (typically)

Mean +/- 3 SD almost always does the cover the data *we have in hand.*

But it needs to cover **future data, from the same manufacturing process.**

The Tolerance Interval is built to account for sampling variation.

In practice, the following variability will **also** occur:

- New batches of raw materials
- Changes to the assay / method transfers / site transfers.
- Process improvements

Contrast to SPC, which uses +/- 3SD

Control chart (typically)

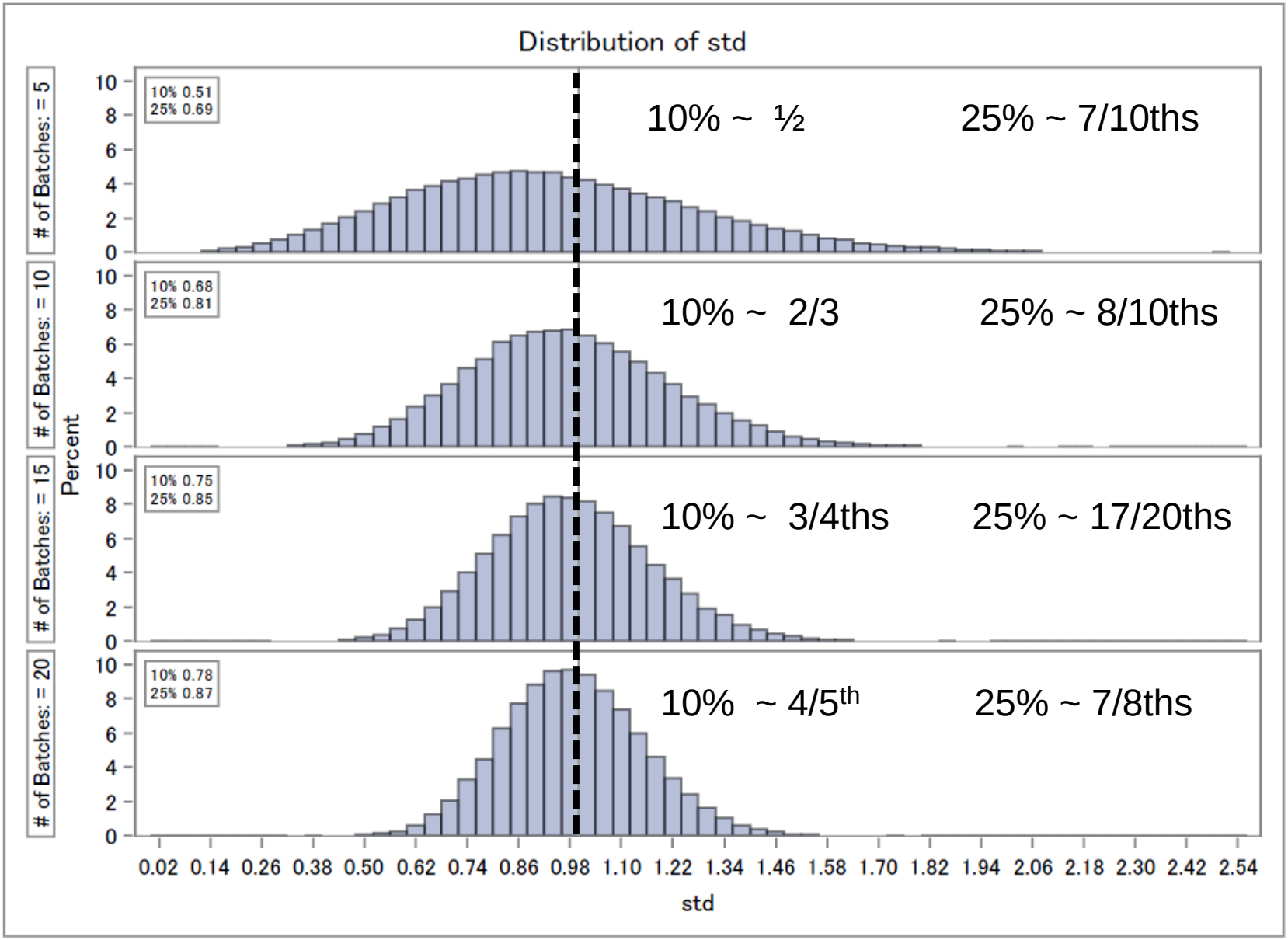
- **n >= 25**
- Continuous process, with subsamples (xbar, r), (xbar, s)
- A precise measurement system
- **Spec is pre-specified, so Cpk >> 1 means "highly capable process"**
- Out of *Control* -> go investigate

Pharmaceutical Data-driven Specifications (typically):

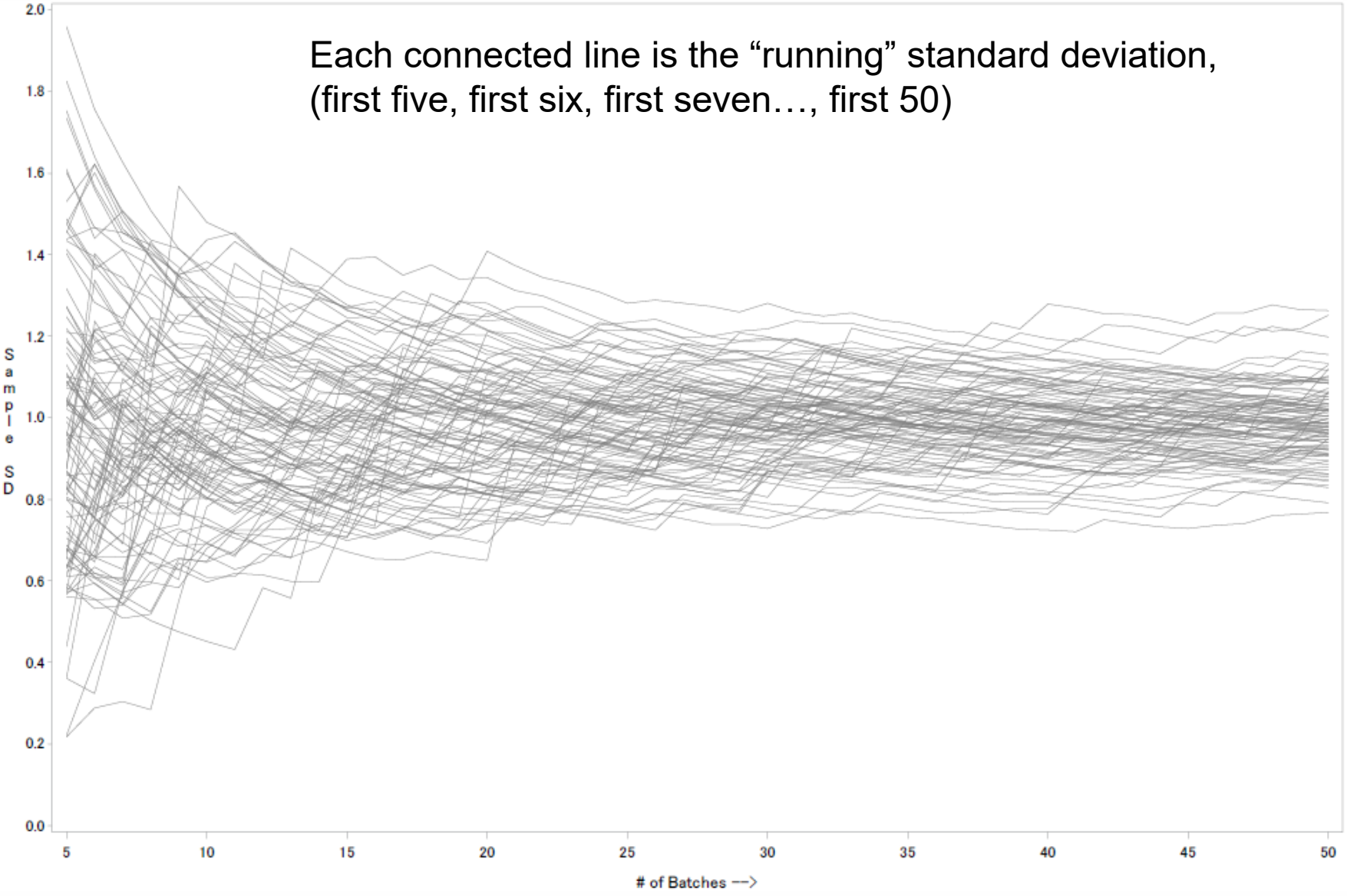
- **n ~ 5-15**
- Batch process, n=1 measurement/batch
- Measurement device (assay) may be a significant source of variability
- **Spec is data driven, so Cpk >> 1 amounts to "specs too wide"**
- Out of *Specification* -> (potentially) dispose of the batch

Sample SD relative to true Sigma

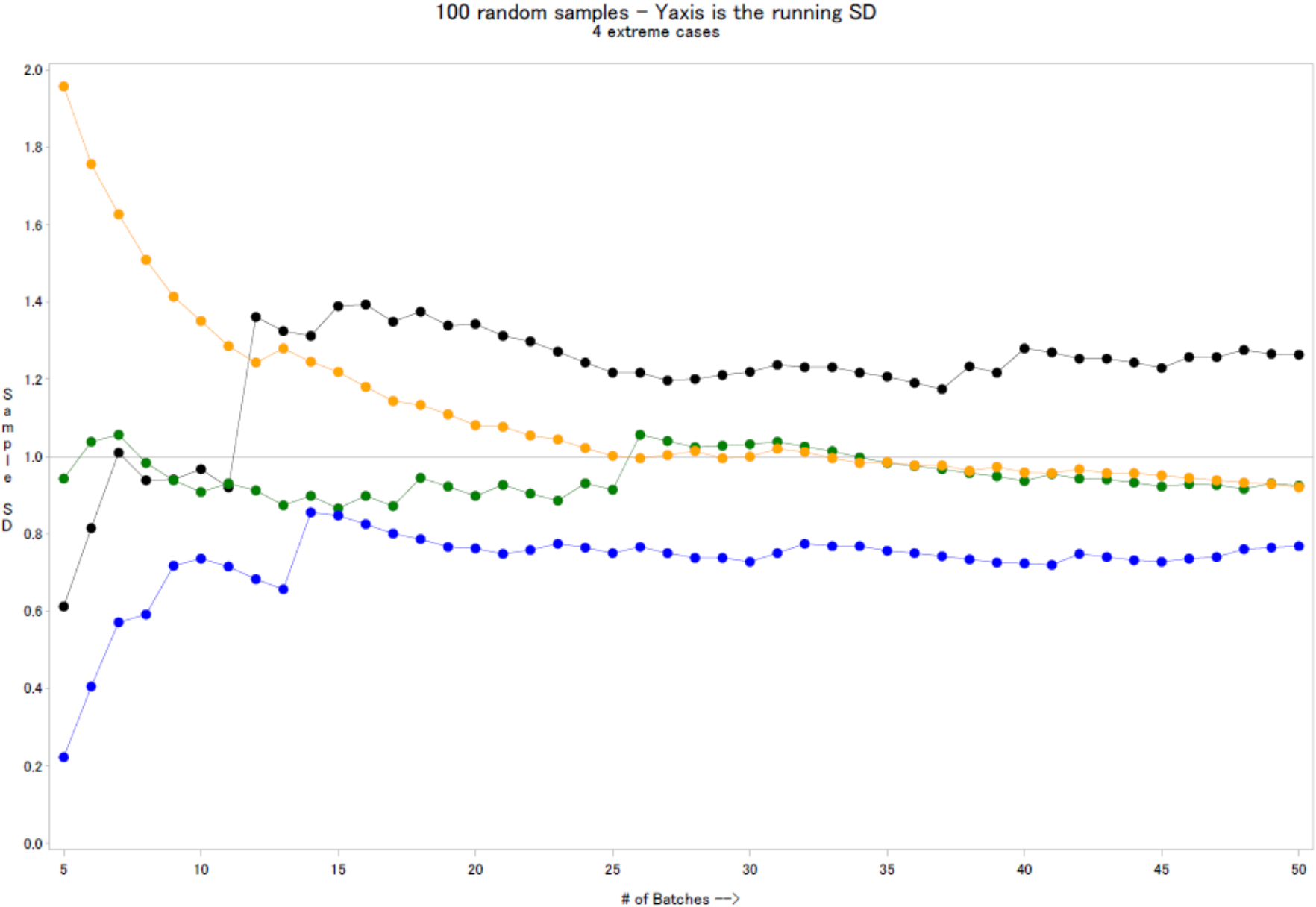
(sample variance is scaled Chi-sq)



In the long run….



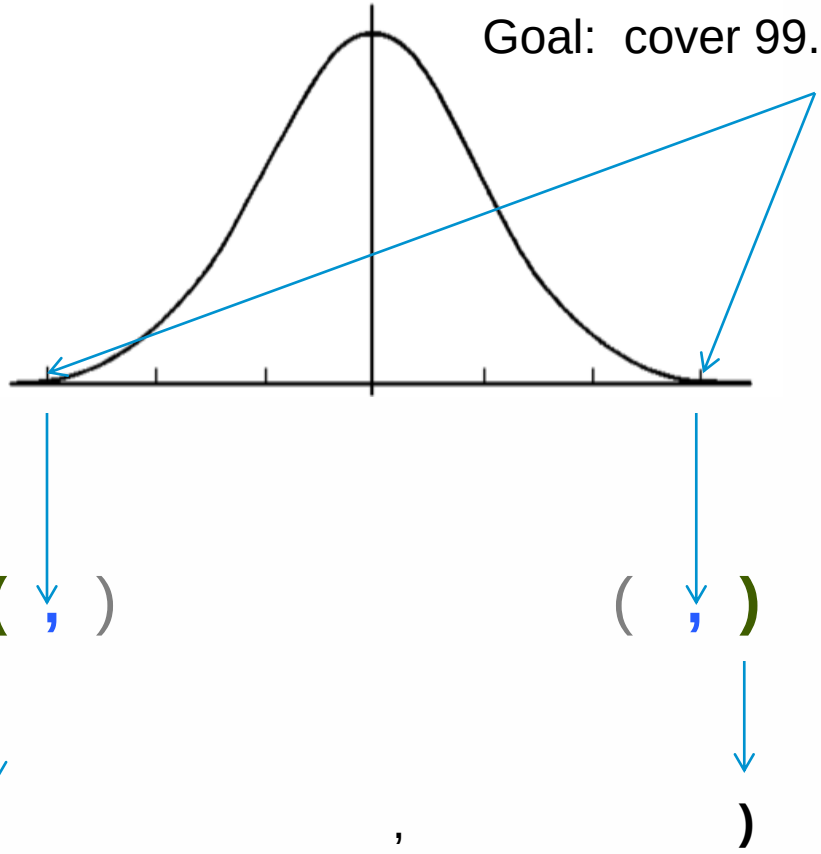
But there are extremes…



Why a Tolerance Interval is Proposed

- Specifications are a commitment that *future* batches will land in the specified window
- “Data based Specification Setting” – the situation where a specification is NOT known ahead of time
- A Tolerance Interval (TI) is one way to calculate a range intended to include a fixed % of the population (coverage) with some specified confidence, and depends on:
    - What data is selected
    - Confidence and coverage used to determine the multiplier

Tolerance Interval



Goal: cover 99.73% of the distribution (+/- 3 sigma)

Point estimates for **coverage**

Confidence limits around our estimates

For greater **coverage** the estimates (blue commas) would be farther apart.

Greater **confidence** → wider **( )**

Sample mean and sample SD both will bounce around. Formula = mean +/- k*sd, k = k(n, cov, conf)

Interplay of (n, coverage, confidence)

Each column is a Coverage / Confidence combination, with color coding on the multiplier

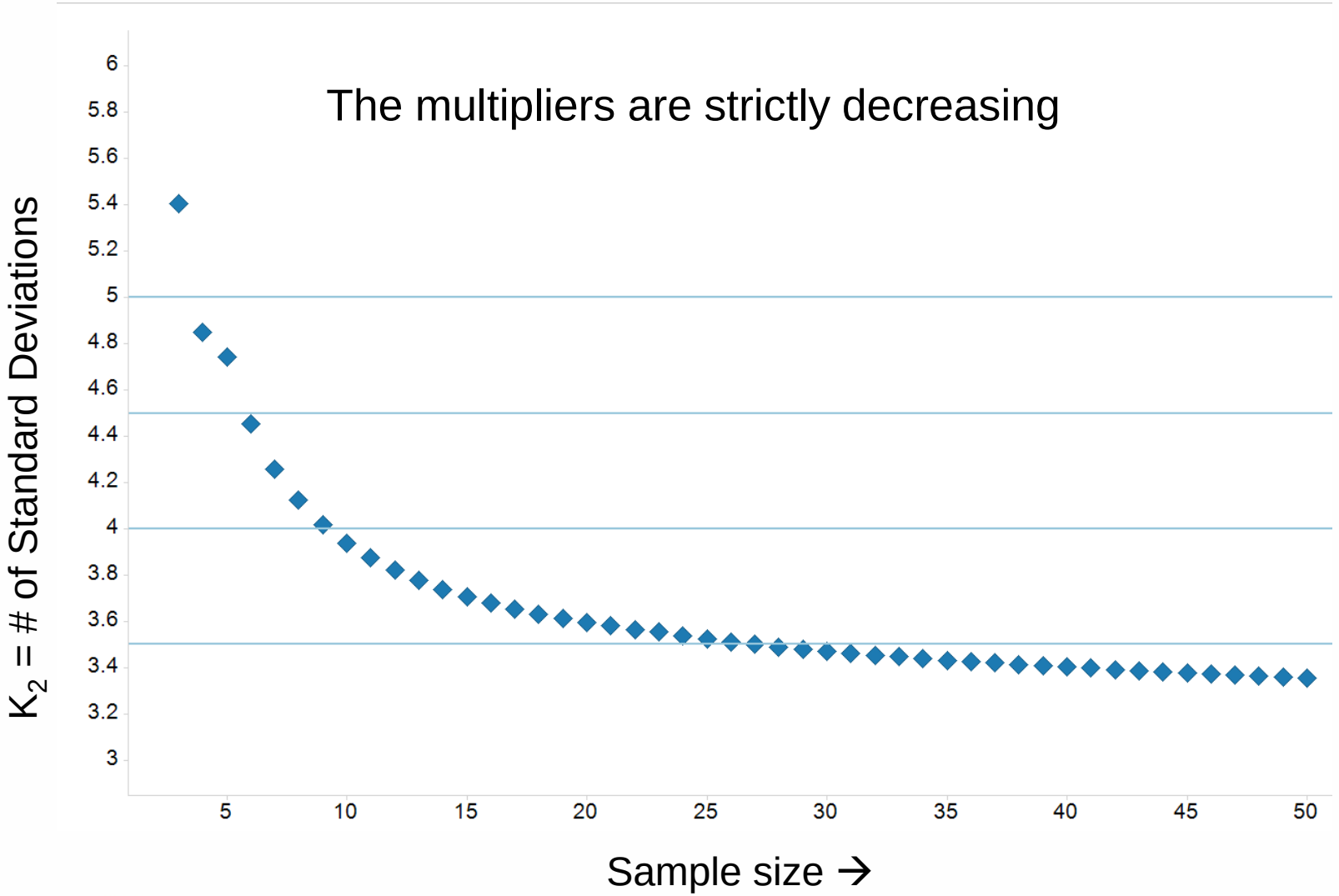
High confidence, high coverage *but small n* we get multipliers of 5 or 6 or 12+ (upper right)

If we back off coverage and confidence *but large n* we get multipliers < 3 (lower left)

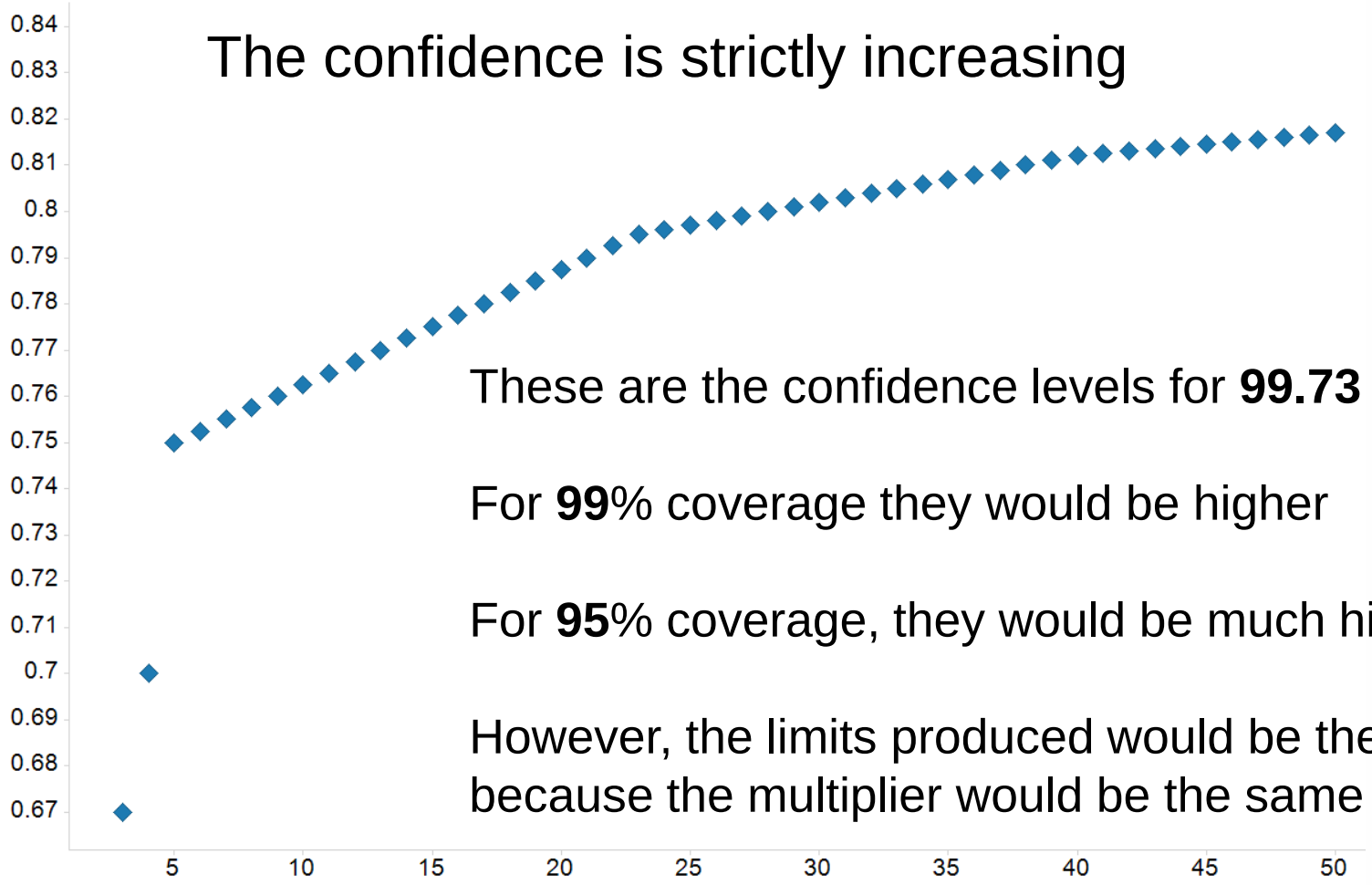
Cov	0.9	0.9	0.95	0.95	0.9	0.99	0.95	0.99	0.9973	0.9973	0.99	0.9973
Conf	0.9	0.95	0.9	0.95	0.99	0.9	0.99	0.95	0.9	0.95	0.99	0.99
N												
5	3.49	4.27	4.16	**5.09**	6.61	5.47	7.88	6.69	6.37	7.80	10.35	12.06
6	3.13	3.71	3.73	4.42	5.34	4.90	6.36	5.81	5.71	6.77	8.36	9.73
7	2.90	3.37	3.46	4.01	4.61	4.54	5.50	5.27	5.29	6.14	7.22	8.41
8	2.74	3.14	3.27	3.74	4.15	4.29	4.94	4.91	5.00	5.72	6.49	7.56
9	2.63	2.97	3.13	3.53	3.82	4.11	4.55	4.65	4.79	5.41	5.98	6.97
10	2.54	2.84	3.02	3.38	3.58	3.97	4.27	4.44	4.62	5.18	5.61	6.53
11	2.46	2.74	2.93	3.26	3.40	3.86	4.05	4.29	4.49	4.99	5.32	6.20
12	2.40	2.65	2.86	3.16	3.25	3.77	3.87	4.16	4.38	4.84	5.09	5.93
13	2.36	2.59	2.81	3.08	3.13	3.69	3.73	4.05	4.30	4.72	4.90	5.71
14	2.31	2.53	2.76	3.01	3.03	3.62	3.61	**3.96**	4.22	4.61	4.74	5.52
15	2.28	2.48	2.71	2.95	2.94	3.57	3.51	3.88	4.15	4.52	4.61	5.37
16	2.25	2.44	2.68	2.90	2.87	3.52	3.42	3.82	4.10	4.44	4.50	5.24
17	2.22	2.40	2.64	2.86	2.81	3.47	3.35	3.76	4.05	4.38	4.40	5.12
18	2.19	2.37	2.61	2.82	2.75	3.44	3.28	3.71	4.00	4.32	4.31	5.02
19	2.17	2.34	2.59	2.78	2.70	3.40	3.22	3.66	3.96	4.26	4.23	4.93
20	2.15	2.31	2.56	2.75	2.66	3.37	3.17	3.62	3.93	4.21	4.16	4.85

Propose: Confidence increases with N Multiplier decreases with N

Two sided multipliers vs. Sample Size



Confidence vs. Sample Size



The confidence is strictly increasing

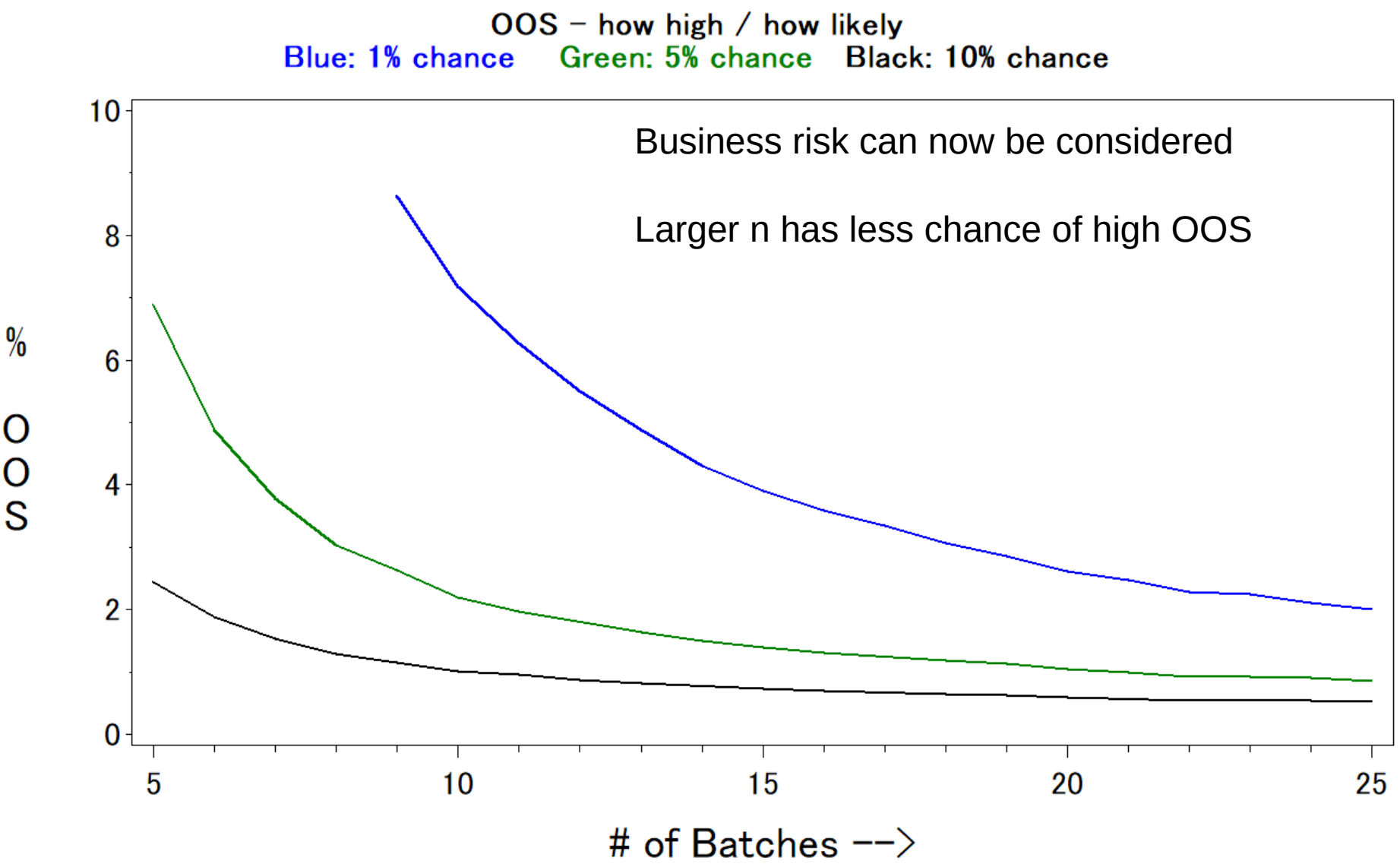
These are the confidence levels for **99.73** coverage

For **99**% coverage they would be higher

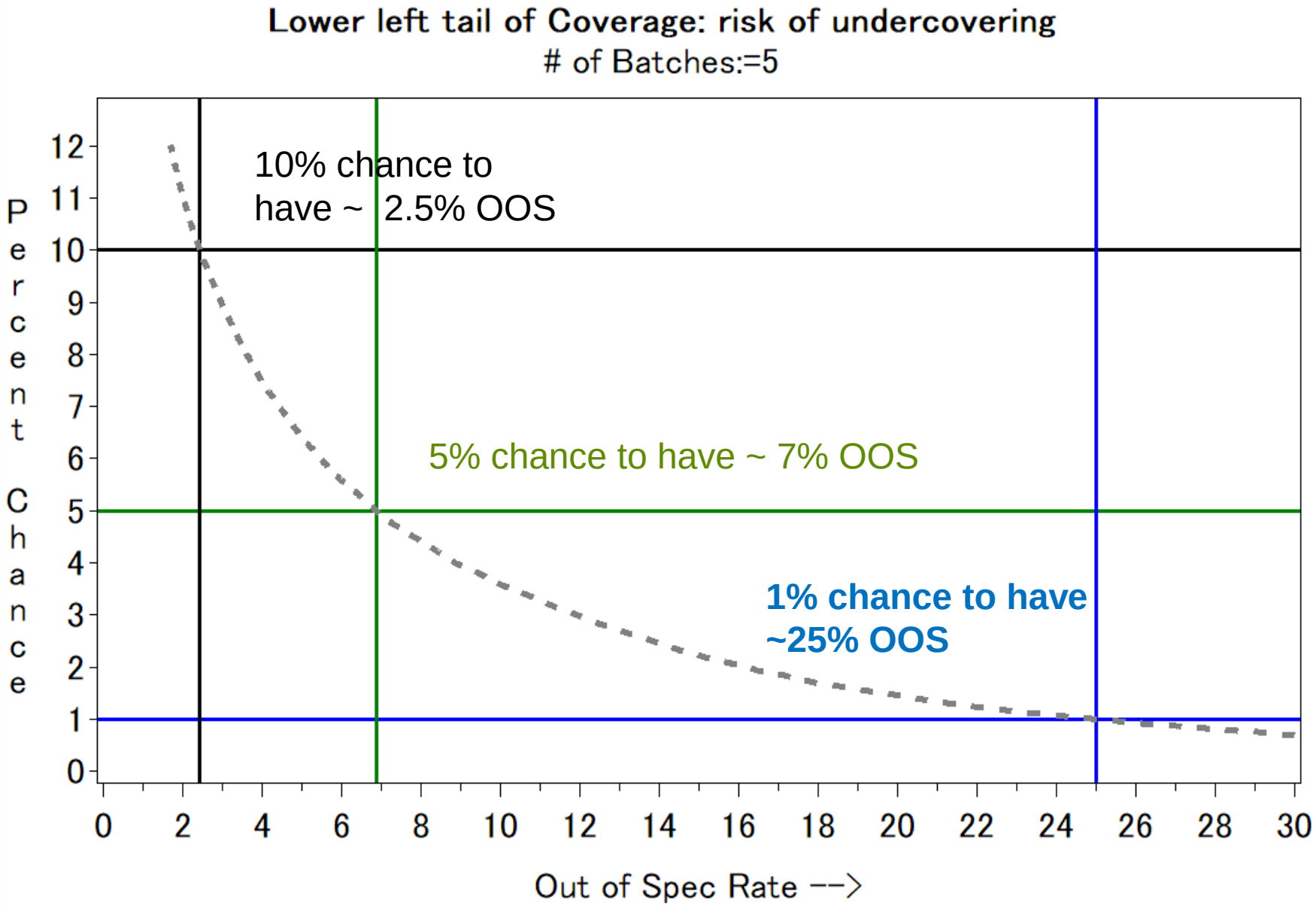
For **95**% coverage, they would be much higher

However, the limits produced would be the same because the multiplier would be the same

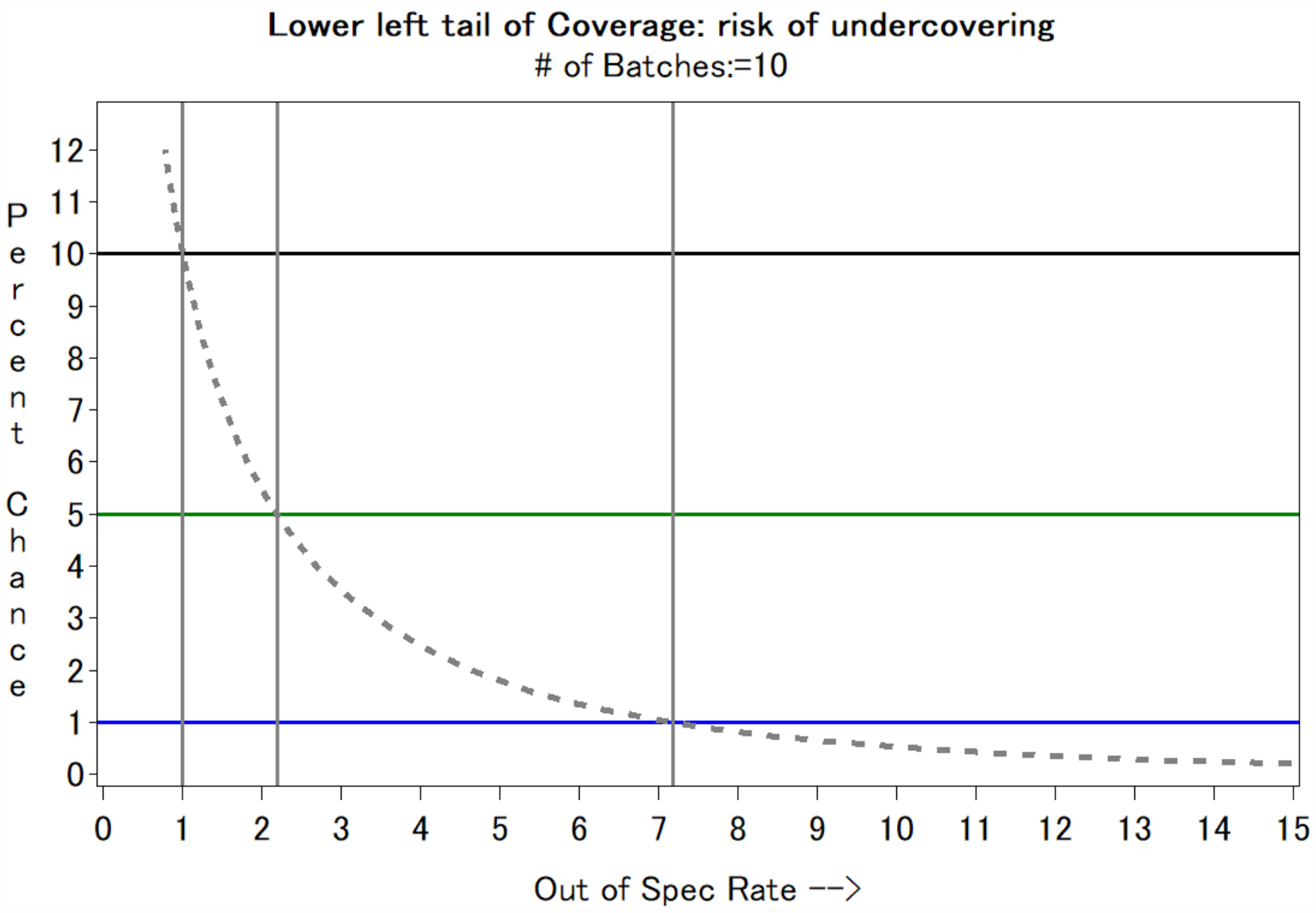
TI gives us a *distribution* of expected risk…



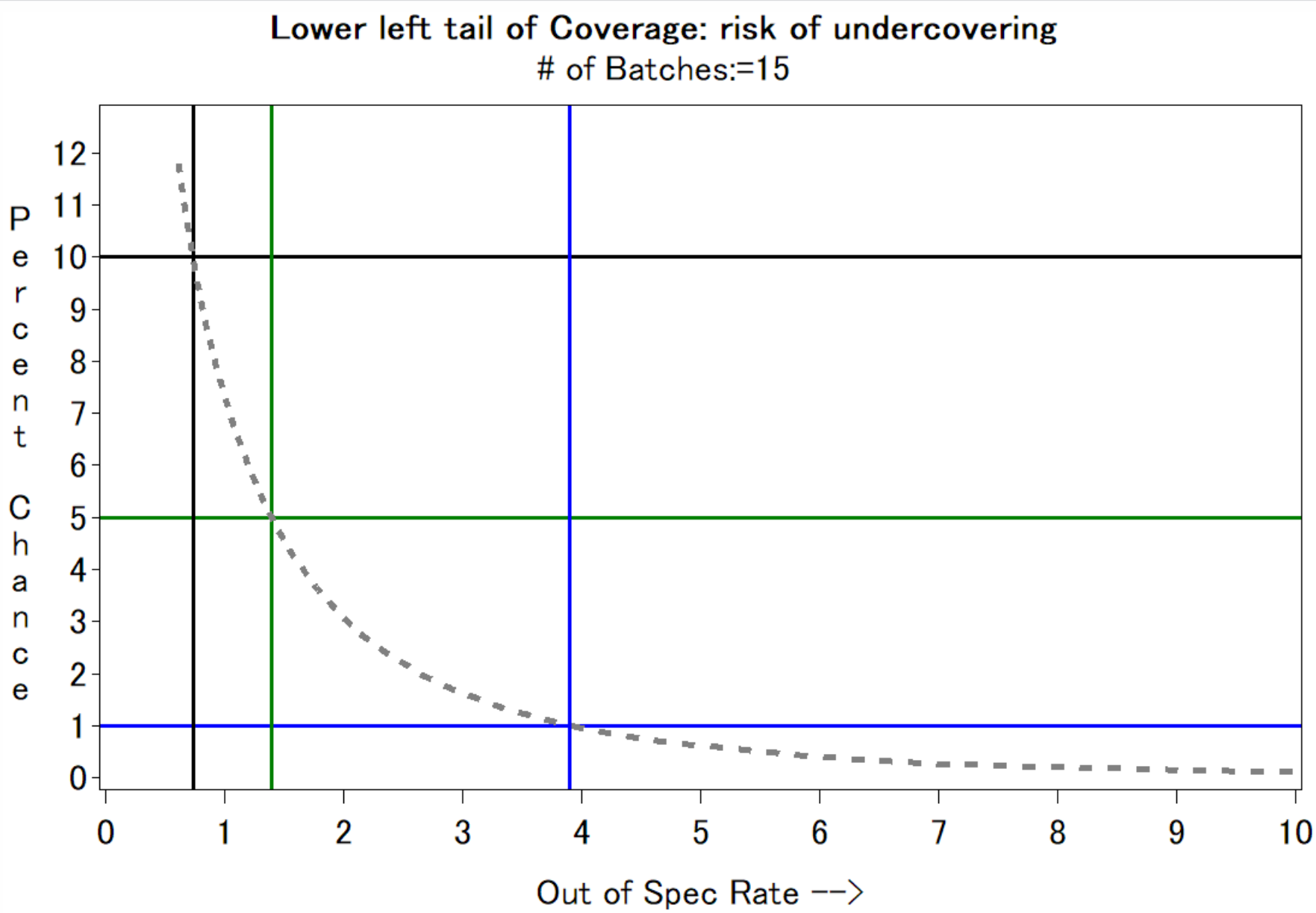
N=5, multiplier = 4.74, Confidence = 75%



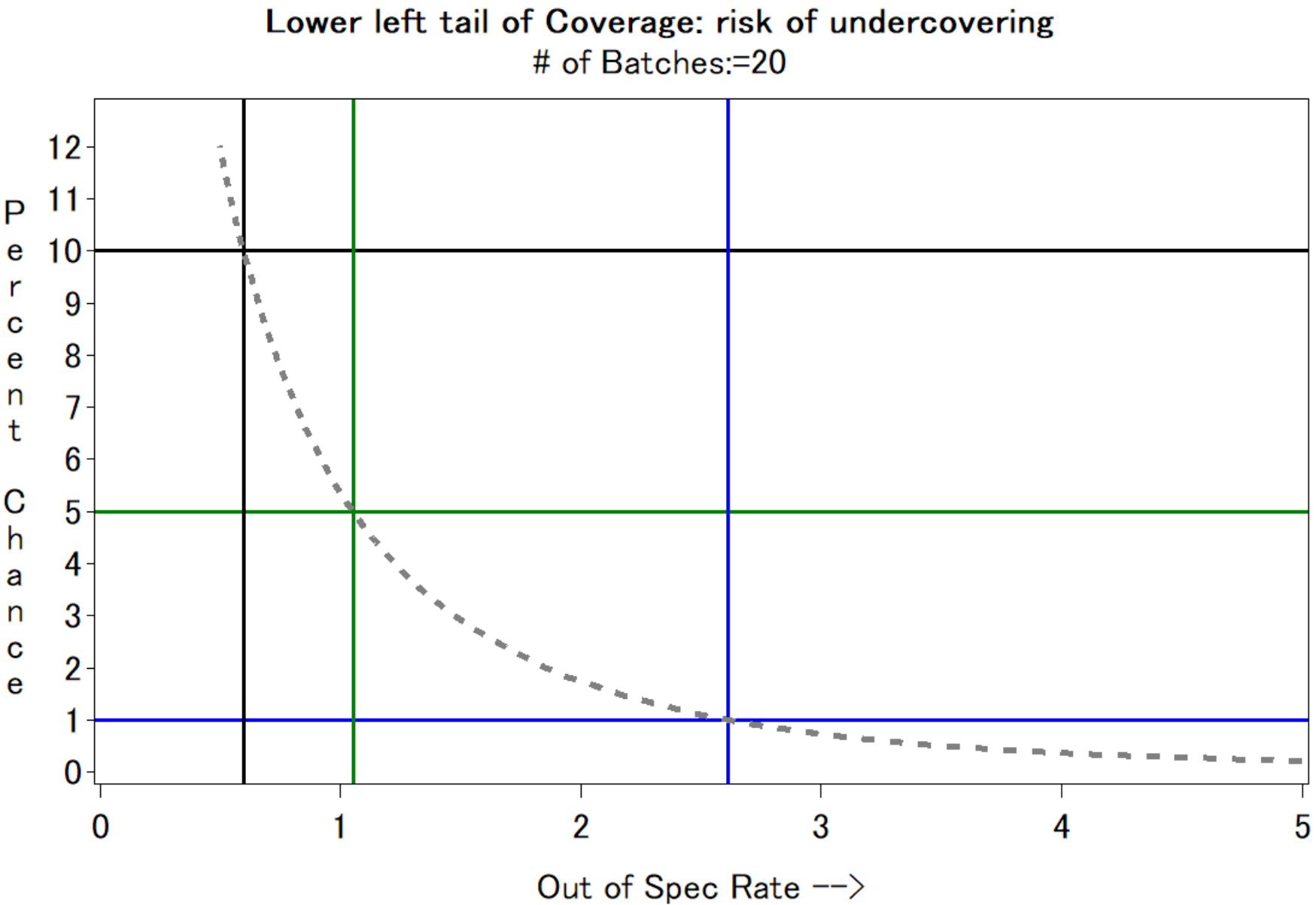
N=10, multiplier = 3.94, Confidence = 76.3%



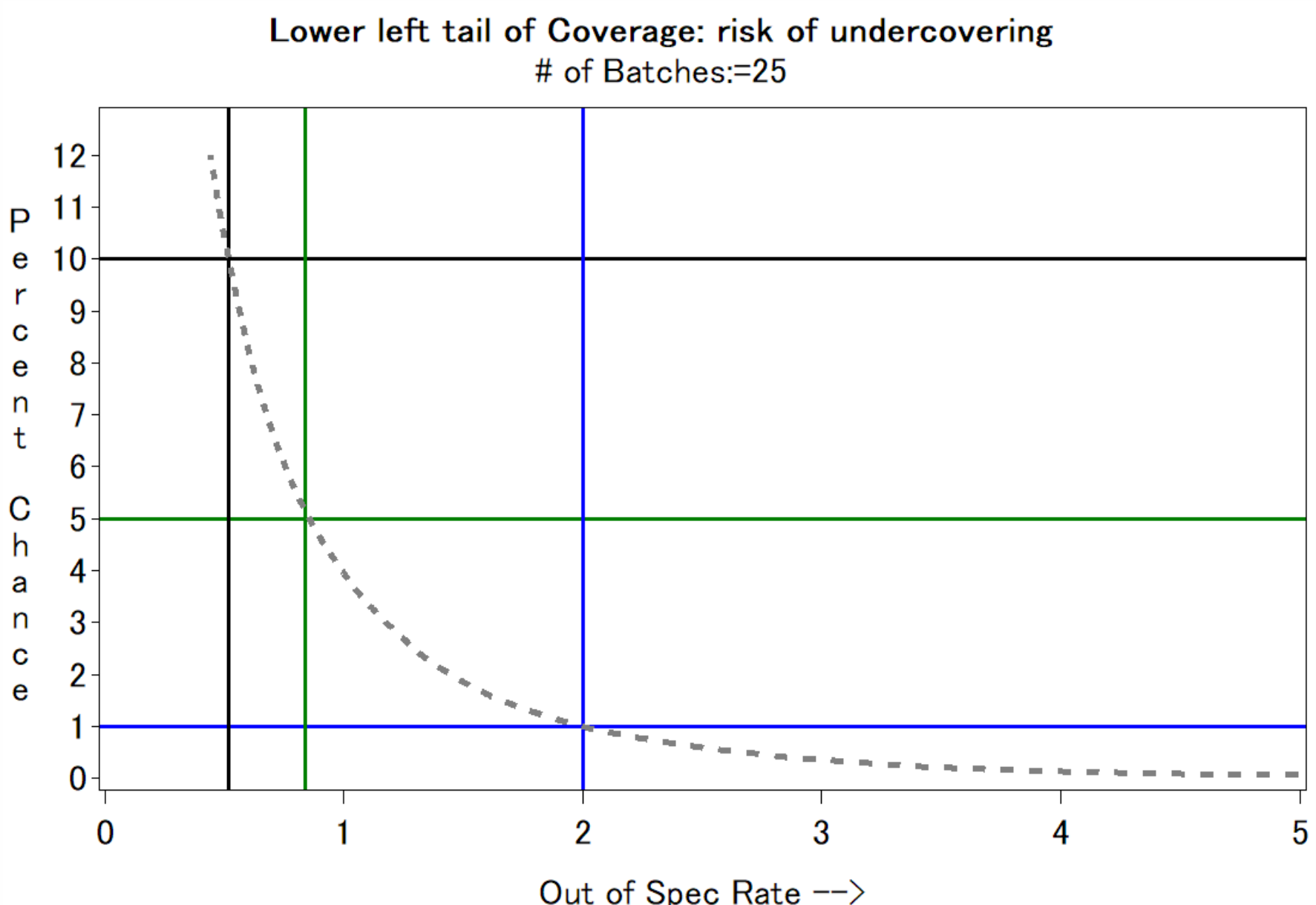
N=15, multiplier = 3.71, confidence = 77.5%



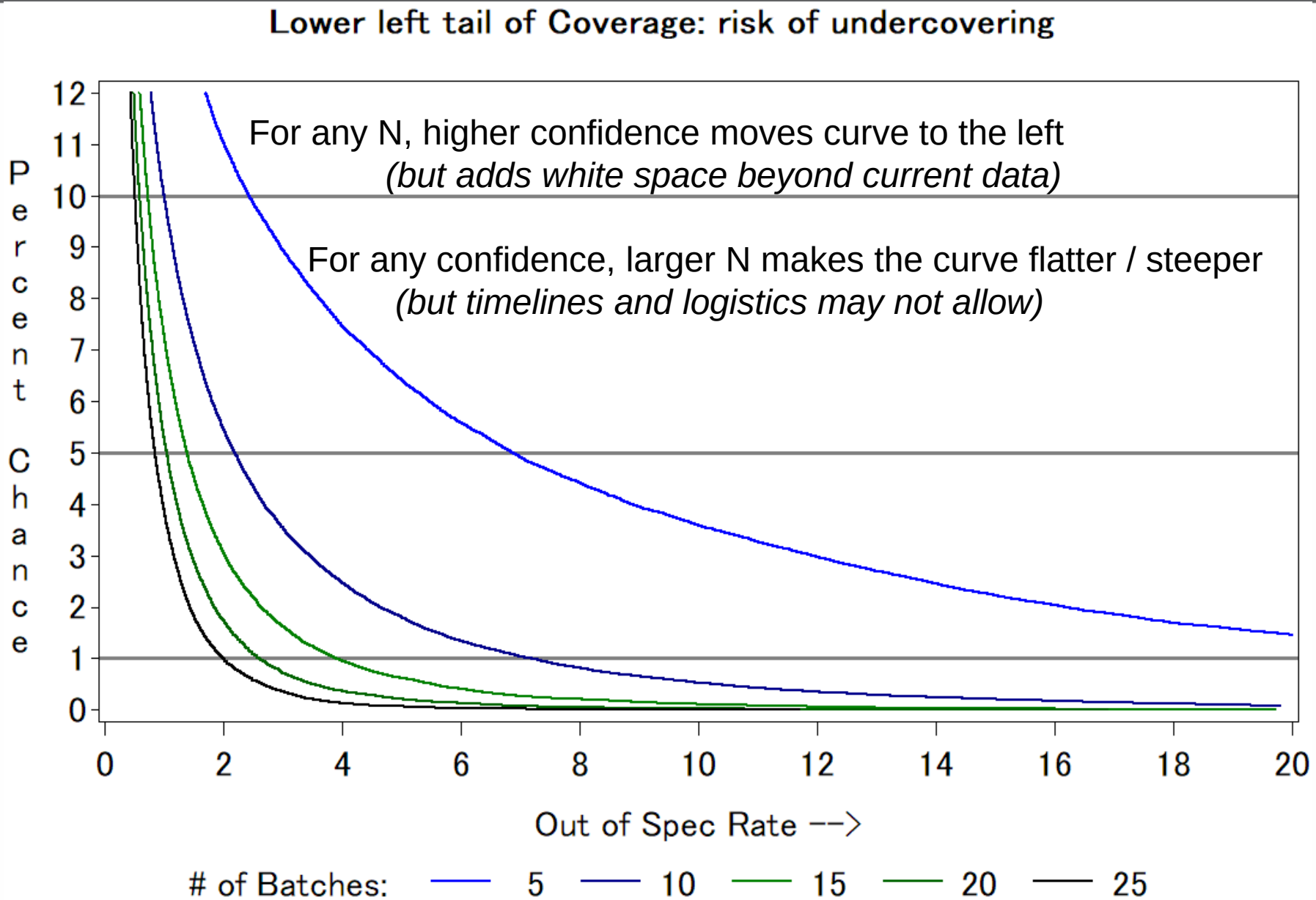
N=20, multiplier = 3.6, confidence = 78.8



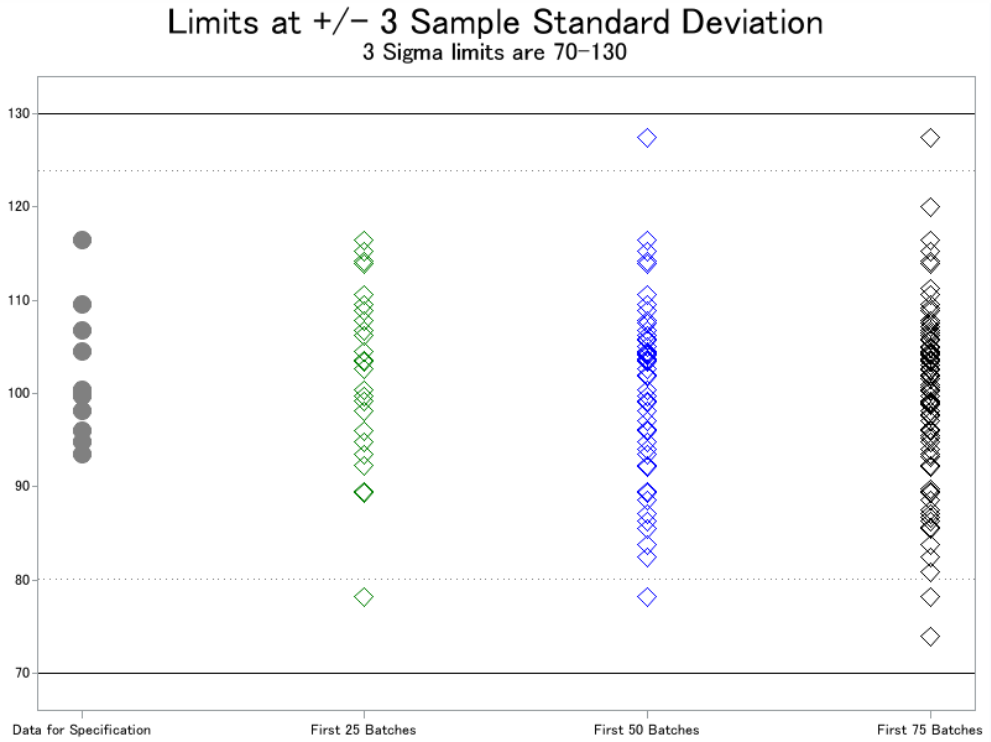
N=25, multiplier = 3.53, confidence = 79.7%



All combined…



Back to the example: TI Proposed Limits



Conclusion: setting +/- 3 SD limits will small n very likely leads to high Out of Spec rates

This proposed approach dampens the risk

Specification Set at N=10	Limits	Cpk at 25 Lots	Cpk at 50 Lots	Cpk at 75 Lots
Mean +/- 3SD	(80.2,1 23.8)	0.77	0.70	0.67
Proposed TI	(73.8, 130.2)	0.91	0.91	0.89

Cpk – a standard metric for how well a process can meet a Specification. Higher is better

But what about Stability data…..

- All Batches get tested upon manufacture
- Many batches are put “on stability”
  - Samples pulled, analyzed at pre-defined intervals
  - Some attributes change over time
  - Many do not change

Stability data – no trend

If no trend exists, we can model the stability data as:

Attribute = Batch effect + Assay variation

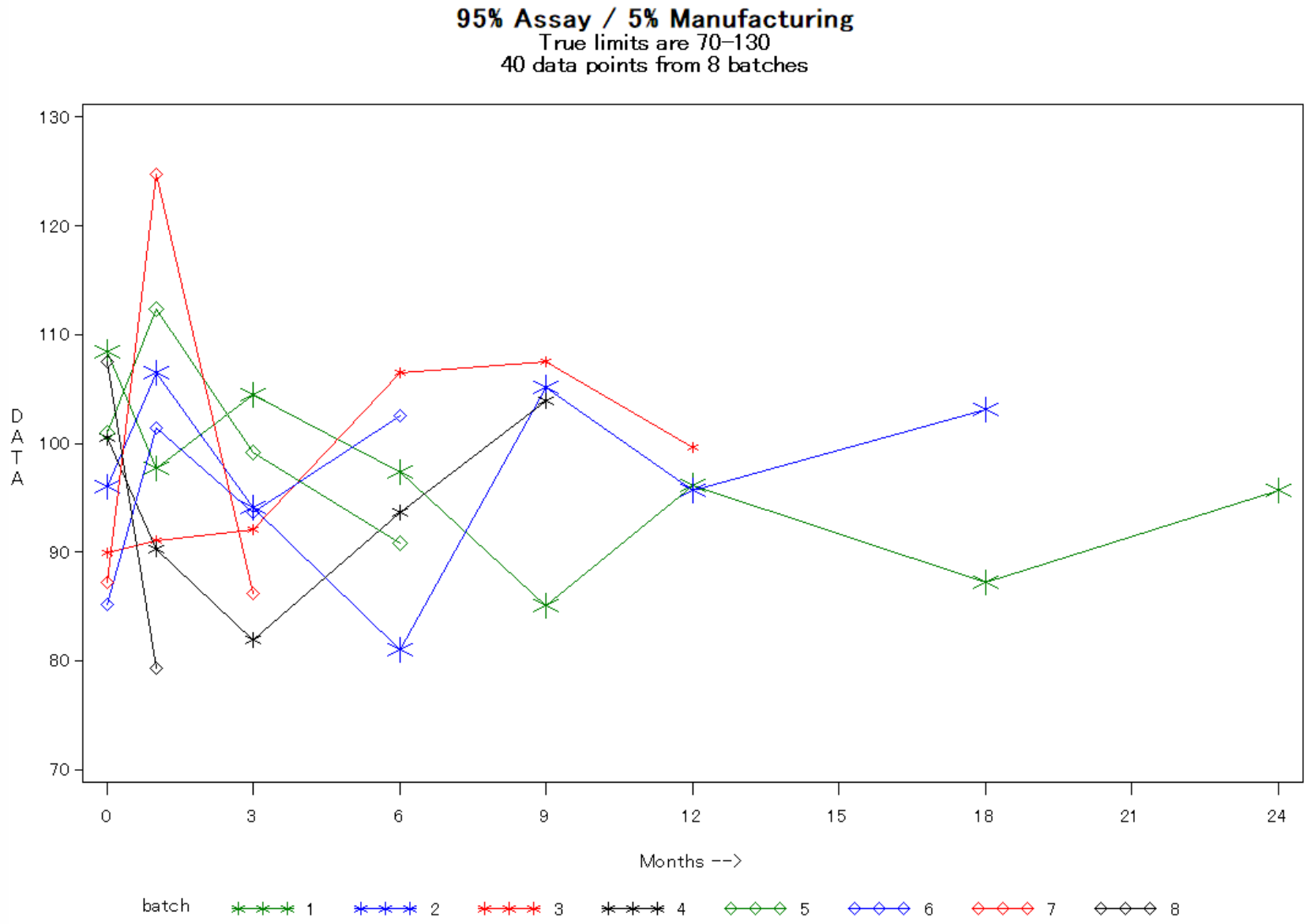
By doing a variance components breakdown, we can get

Var(Total)= Var(Manufacturing) + Var(Assay)

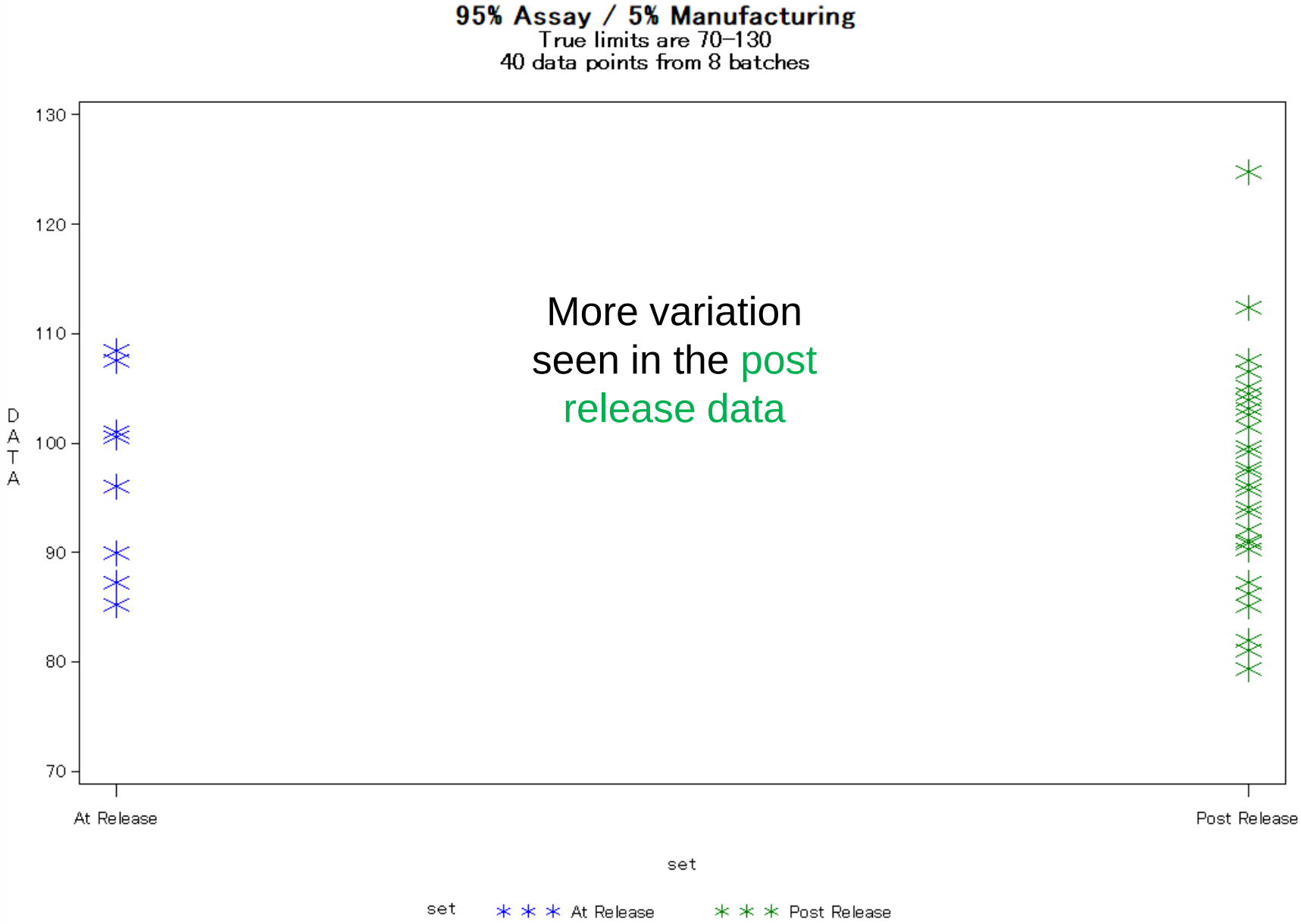
Then we create a second Tolerance Interval using SD(Total)

It can (and does) happen that the stability data indicates a larger Var(Total) than the release data alone

Stability data – no trend

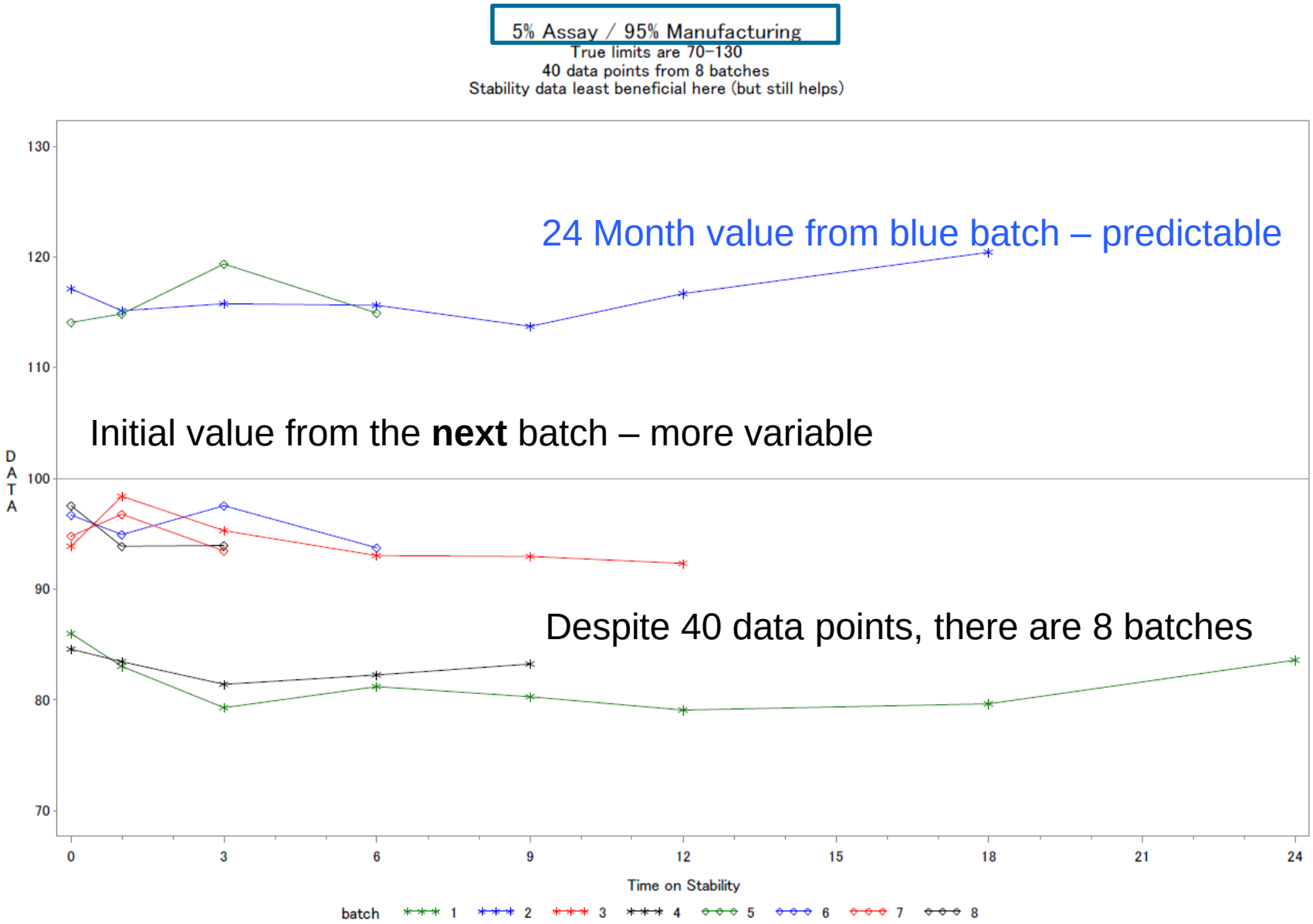


Release / Post Release



More variation seen in the post release data

Stability data (no trend)



Stability data – with trend

When a trend exists, the proposal is:

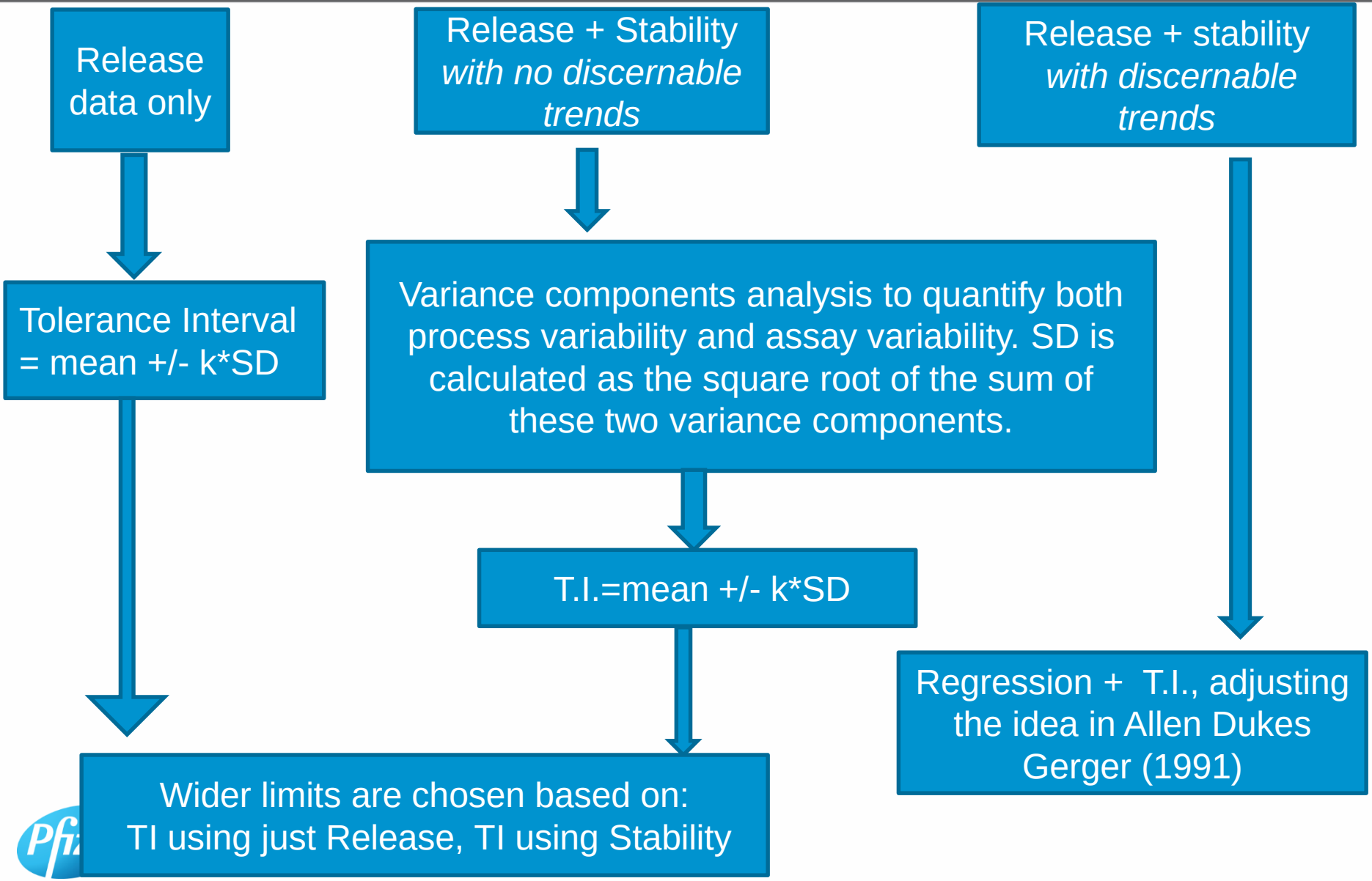
TI(Release) +

Estimated total change over time +

Uncertainty allowance that goes with total change

$$TI(Release) + T_{months} * \hat{\beta} + k * se(T_{months} * \hat{\beta})$$

General workflow



Other considerations

How to chose the slope?

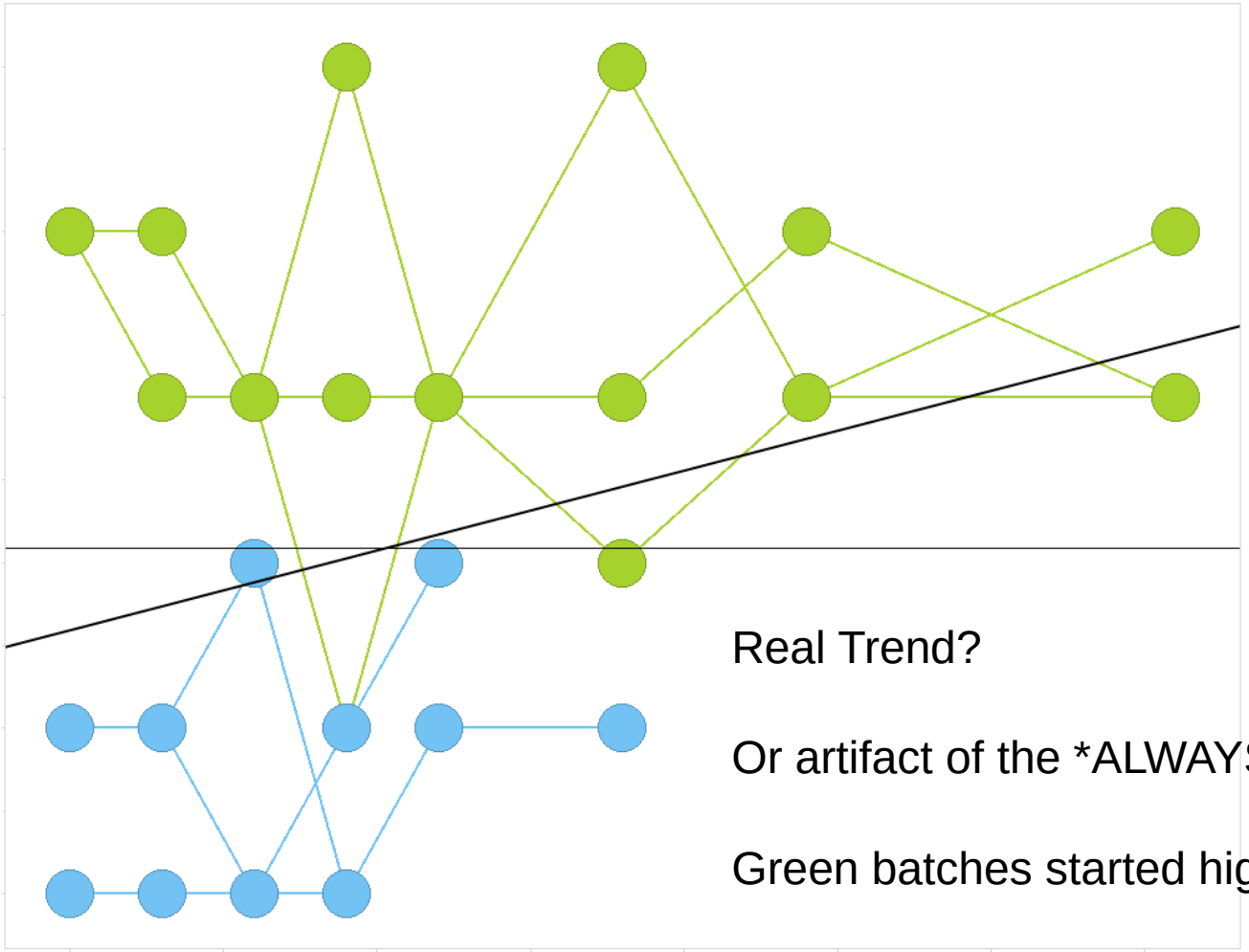
- One slope for all batches?
- Separate slope for each batch?

Random effects models?

Bayesian perspective:

- Similar compounds
- Assay variation prior knowledge

Considerations: over-ride the default model?



Time →

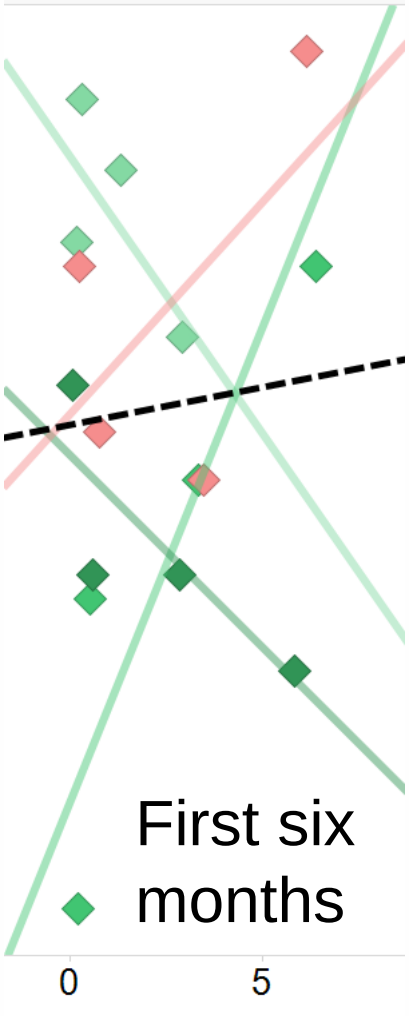
Real Trend?

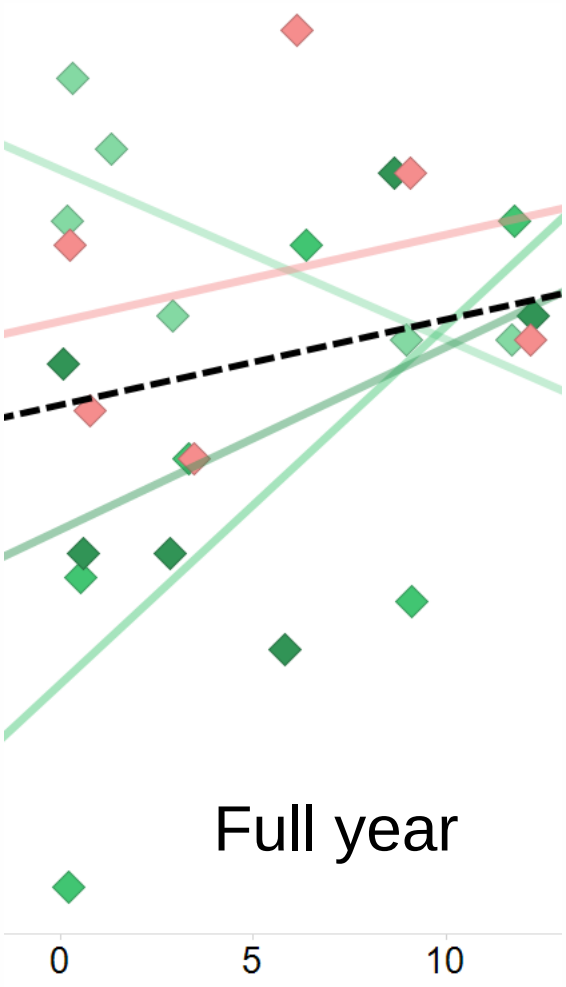
Or artifact of the *ALWAYS* unbalanced design?

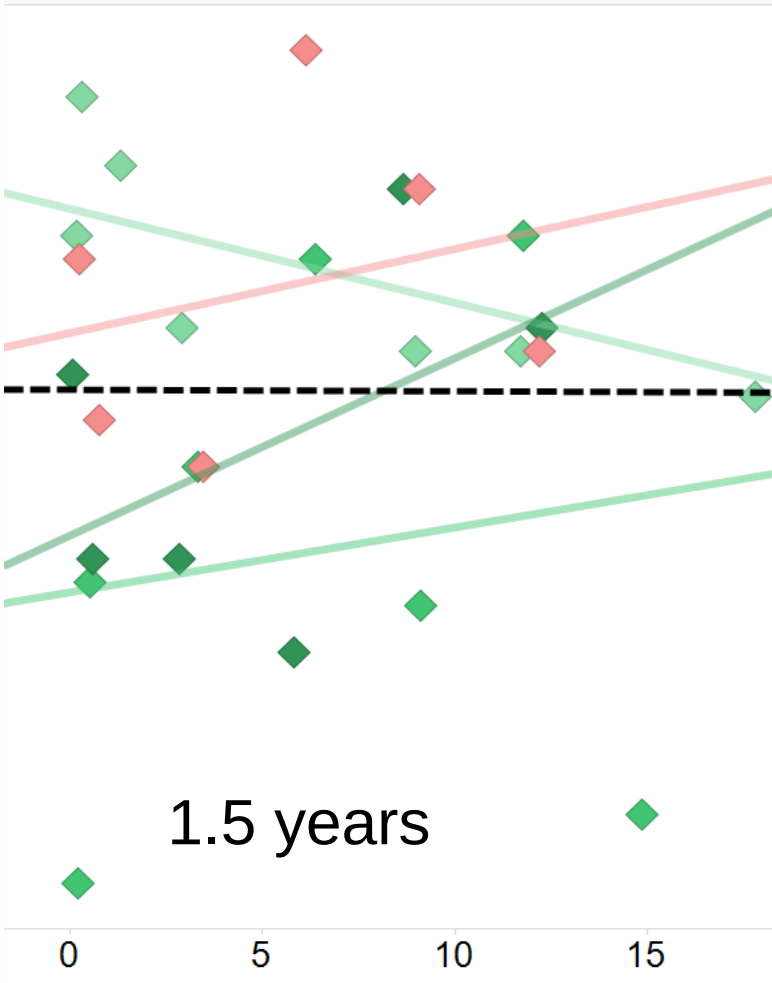
Green batches started higher (for known reasons).

Blue started lower (known reason)

Over-ride the default model? (noisy slopes)







Summary

- Product Specific Specifications are set when possible, but there are times when Data Driven Specifications are needed

- A solution is needed, balancing:
  - Want a high chance to cover future data,
  - Limiting the “white space” beyond current data

- A tolerance interval approach, with increasing confidence and decreasing multipliers as sample size increases

- All data is considered, with or without trend

- Suggestions / comments?

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