Saving Lives with Statistics: A Framework for Statistical Applications in Pharmaceutical Manufacturing & Development

Fall Technical Conference
Philadelphia, PA
October 5-6, 2017

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STRONGER PERFORMANCE AHEAD

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1966 – 2016

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ASQ Shewhart Medal 2016

Outline

Faster, faster, faster…

Validation throughout product life cycle –
supports acceleration without compromising quality.

Statistics keeps us honest
about what we do and don't
have evidence for.

Abstract

- A revolution in the discovery of life-changing medicines has turned up the heat on accelerating new products through design and validation into commercial production. Meanwhile, expectations for control of pharmaceutical manufacturing have shifted from inspection-based monitoring to designing quality into the process. These two forces are driving high demand for the use of statistics throughout development and manufacturing.
- As a result, well-qualified FDA clinical statisticians are being asked to review manufacturing statistical applications, statisticians from other industries are finding meaningful work in pharmaceuticals and biotech, and engineers and scientists are building their practical knowledge of applied statistics.
- This presentation will cover a framework for the application of statistics in the pharmaceutical industry, focusing on the big picture and what's important. The material is relevant for formally trained statisticians without extensive experience in pharmaceutical manufacturing, and also for scientists and engineers interested in applying statistical methods in their work.

FDA Staff College Training 2016

Training Goals

- Support the review of statistical aspects of CMC submissions
- Training for biostatistics staff and other FDA personnel involved in product review
- Cover key topics in CMC statistics
- Emphasize issues most pertinent to vaccines, biologics, and other biological products (e.g. gene therapy, microbiome products)
- Focus on developing practical judgment about what is really important – concepts and common sense framework
- Built around case studies
- Formulas are included in some examples

CMC = Chemistry, Manufacturing and Controls

Common Statistical Issues

I. Drug Substance

- A. Description and Characterization
- B. Manufacturer
- C. Method of Manufacture
- D. Process Controls
- E. Manufacturing Consistency
- F. Drug Substance Specifications
- G. Reprocessing
- H. Container and Closure System
- I. Drug Substance Stability

I. Drug Product

- A. Composition and Characterization
- B. Manufacturer and Facilities
- C. Manufacturing Methods
- D. Drug Product Specifications
- E. Container and Closure System
- F. Microbiology
- G. Lyophilization
- I. Drug Product Stability

FDA *Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related product,* 1999

FDA Pathways

Fast Track

Breakthrough Therapy

Accelerated Approval

Priority Review

"Speeding the availability of drugs that treat serious diseases are in everyone's interest, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments. The Food and Drug Administration has developed four distinct and successful approaches to making such drugs available as rapidly as possible"

http://www.fda.gov/ForPatients/Approvals/Fast/default.htm

Orphan Drug Act (ODA)

- ✓ Special status - to treat a rare disease or condition.
- ✓ Various development incentives including tax credits for qualified clinical testing. Not subject to a prescription drug user fee.

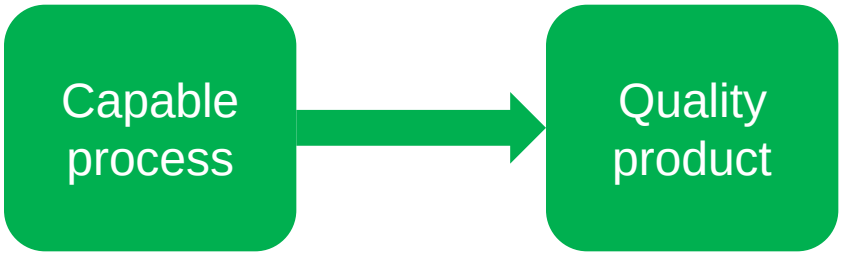
✓ **The granting of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval. Safety and effectiveness of a drug must be established through adequate and well-controlled studies.**

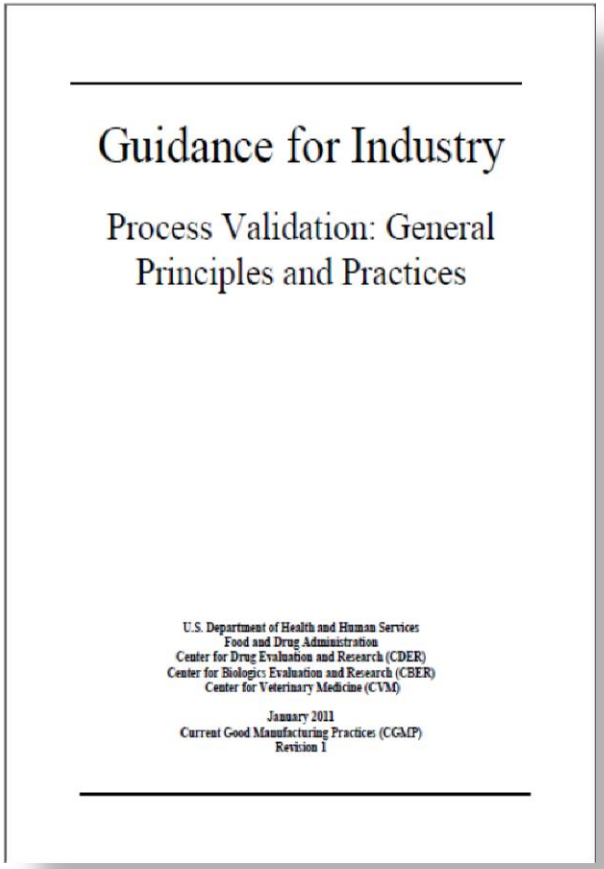
Intent of Process Validation (PV)

The collection and evaluation of data,

from the process design stage
through commercial production,

which ***establishes scientific evidence that a process is capable of consistently delivering quality product***.




Guidance for Industry

Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

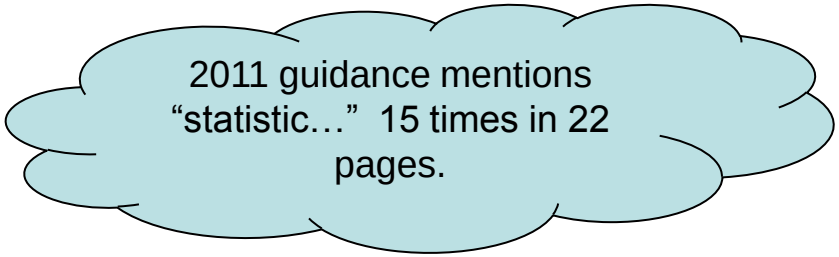
January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

Excerpts from the January 2011 PV Guidance

- "Basic principle of quality assurance"
  - » "a drug should be produced that is ***fit for its intended use***"
- Continued Process Verification:
  - » "Ongoing assurance is gained during routine production that the process remains in a ***state of control."***
- "Manufacturers should:
  - » Understand the sources of ***variation***
  - » Detect the presence and degree of ***variation***
  - » Understand the impact of ***variation*** on the process and ultimately on product attributes
  - » Control the ***variation*** in a manner commensurate with the risk it represents to the process and product."

FDA (2011) "Process Validation: General Principles and Practices" guidance for industry.

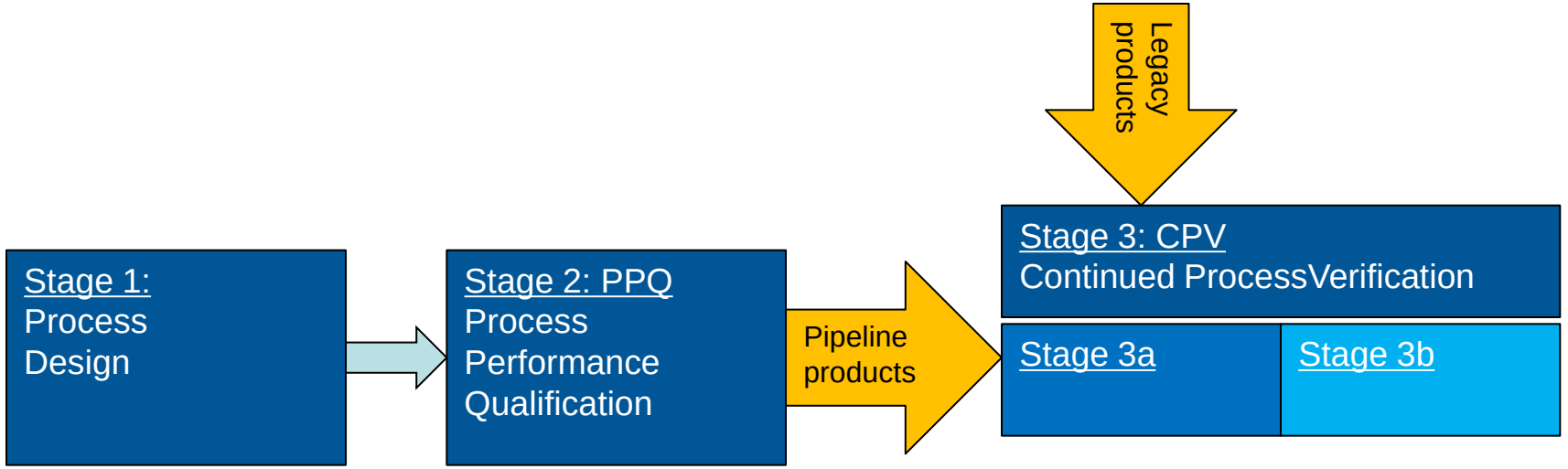
Emphasis on Statistics



- “FDA recognizes the importance of ***statistical process control*** as a tool in understanding and managing variability in both product and processing…”
- “We recommend that a ***statistician*** or person with adequate training in ***statistical process control*** techniques develop the data collection plan and ***statistical*** methods and procedures used in measuring and evaluation process stability and process capability.”
- “Procedures… should guard against ***overreaction to individual events*** as well as against ***failure to detect unintended process variability***.”

FDA (2015), “Request for Quality Metrics” draft guidance for industry.
FDA (2011) “Process Validation: General Principles and Practices” guidance for industry.

Process Validation through the Product Lifecycle



Commercial manufacturing process is defined.

Based on knowledge gained through development and scale-up.

Process design is evaluated – test control strategy.

Determine if capable of reproducible commercial manufacturing.

3a:
Initial batches, heightened monitoring.

3b:
Ongoing, routine monitoring.

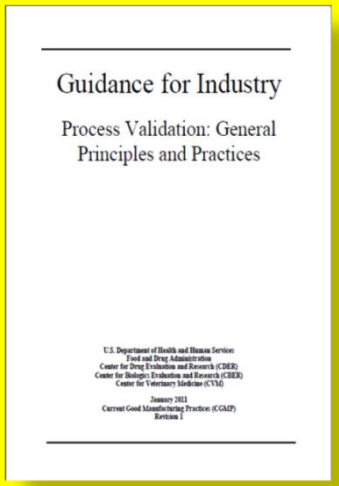
Ongoing assurance that the process remains in a state of control.

Signals of shifts and trends can trigger stage 1 repeat.

Benefits of PLCM Validation Approach:

Moving from Compliance to Science to Reliability

Compliance


Guidance for Industry

Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practice (CGMP)
Revision 1

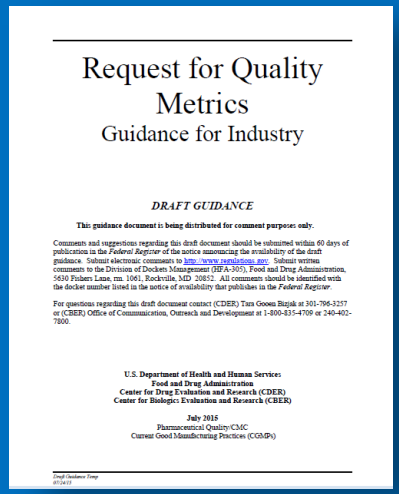
January 2011

Science

Stage 1 | Stage 2 PPQ | Stage 3 CPV

Control Strategy feedback

Reliability


Request for Quality Metrics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Tara Gooen Bizjak at 301-796-3257 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2015
Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)

July 2015 DRAFT

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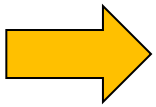
Modern Paradigm for Reliable Supply

- Product Lifecycle Management shifts the focus of process validation:

Traditional paradigm: Inspection of product to insure quality



Modern paradigm: Continuous improvement to insure reliable supply

- Firms must show not only evidence of quality of products but evidence of manufacturing reliability.
  - » Meeting specifications is only the baseline - essential for all manufacturers.
  - » Supply reliability is an important differentiator.
    - – Process capability = measure of reliability.
    - – Reward for reliability = reduced inspection frequency.

Statistics – What is it Good For?

An honest assessment of what

we do and don't

have evidence for.

Where can Statistical Approaches Help?

Process Design

Test Methods

Stability

Process Qualification

Manufacturing

Begin with the end in mind

Changes

Specifications

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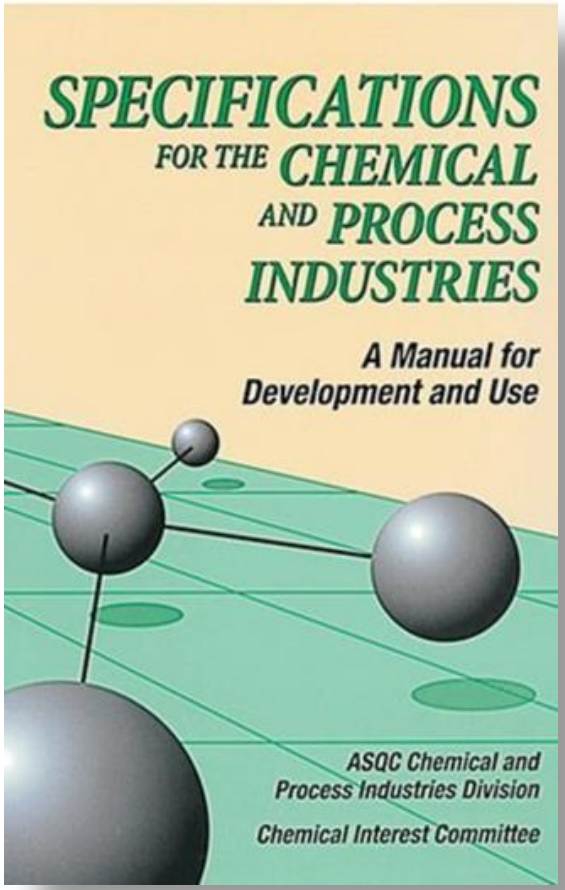
Patient Needs → Product Specifications

"Acceptable for its intended use"

- Excerpts from ICH Q6B:
  - List of tests, references to analytical procedures, and acceptance criteria.
  - One part of a total control strategy.
  - Focus on characteristics useful in ensuring safety and efficacy.
  - Should be based on data for lots used in pre-clinical and clinical studies.

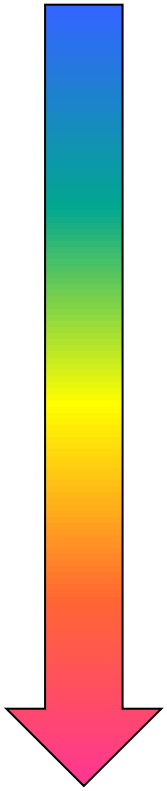
Specifications in Other Industries

- Agreed upon, documented requirements between customer and supplier.
- ***Customer requirements*** should be the primary basis for specifications.
- Specifications based entirely on ***customer requirements*** should be changed only when ***customer requirements*** change.



ASQ on Product Specifications

BEST



Required property values if measured without measurement variability

Customer requirements, determined by technically sound procedures

Agreed to by the supplier and customer

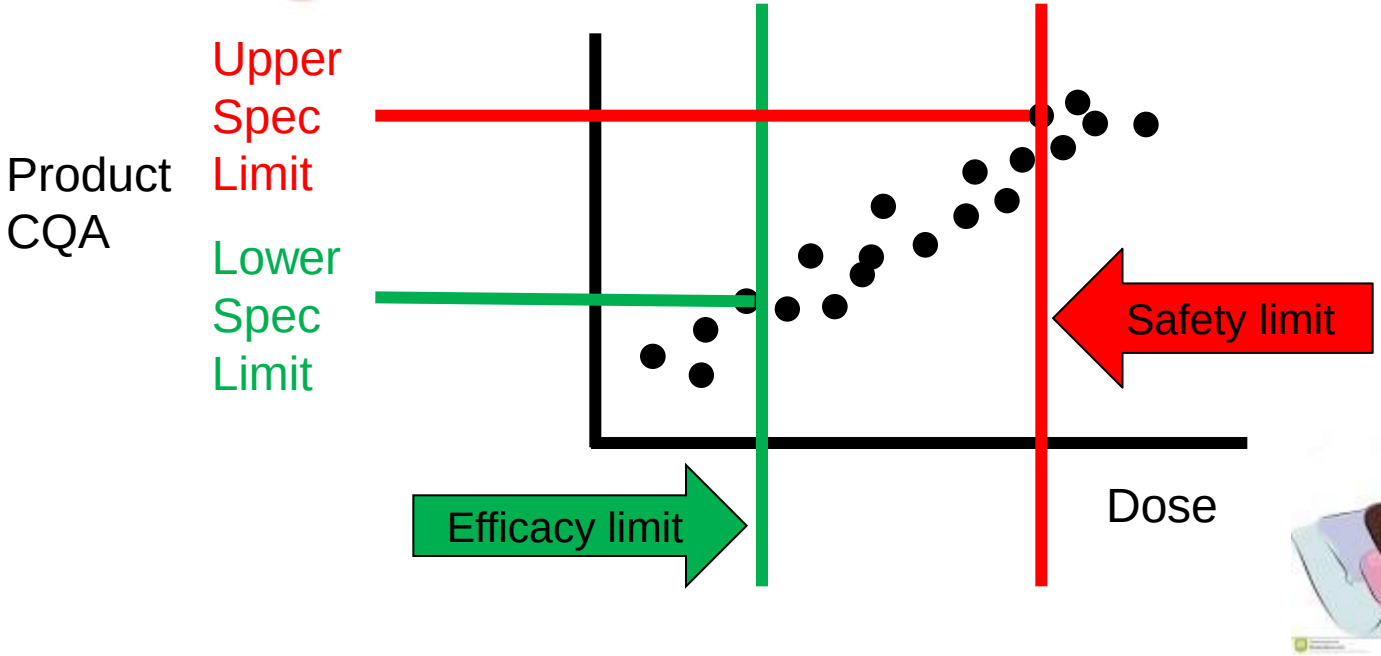
Supplier's demonstrated process performance

If product has not been satisfactory, what the customer is willing to accept

Temporary specifications for new products or when insufficient data available

Pharma

Specifications (ideally) ~ Safety & Efficacy

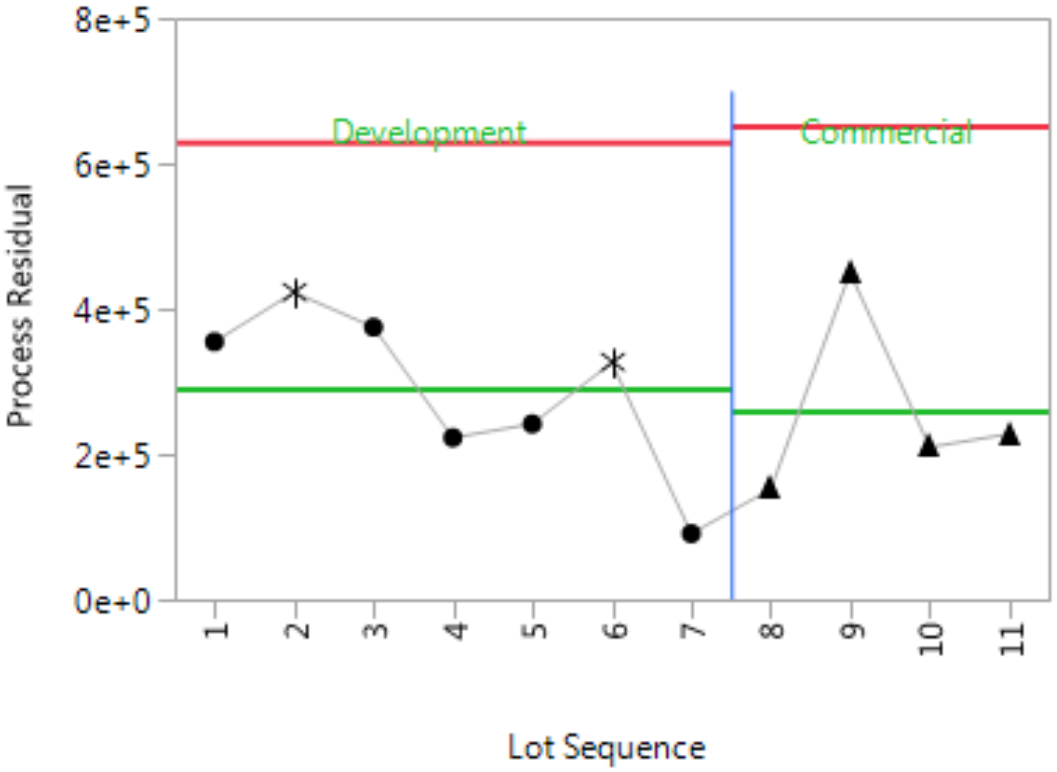


WHAT *CAN* WE DO TO ESTABLISH SPECIFICATIONS?

What We *Can* Do: Specifications = Consistency with Clinical Lots

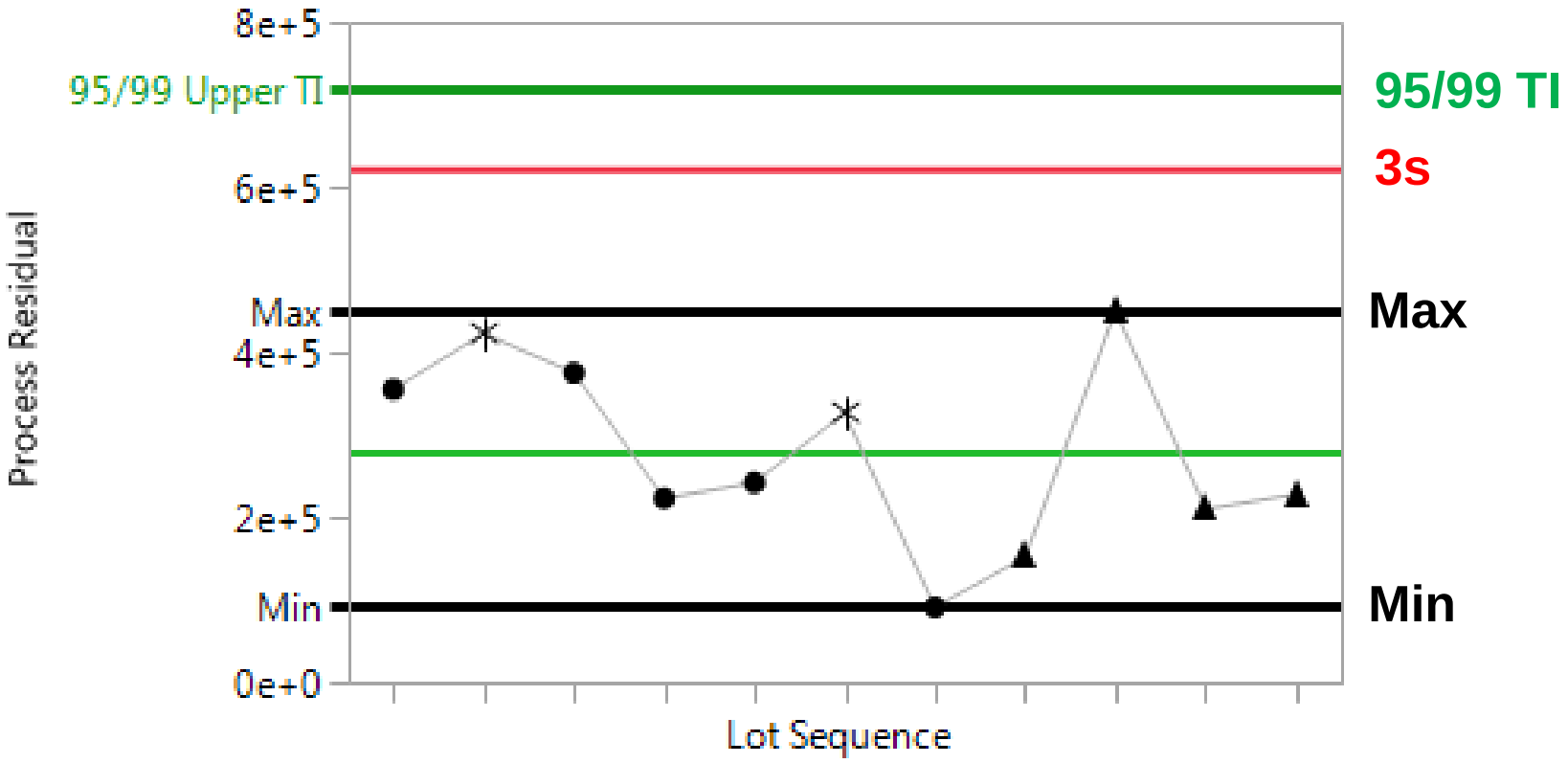
- Manufacturers ensure product consistency, quality, and purity by ensuring that the manufacturing process remains substantially the same over time.
- Specifications set limits on the range of CQA results ***to be consistent with clinical lots***.

Orphan Drug Process Residual

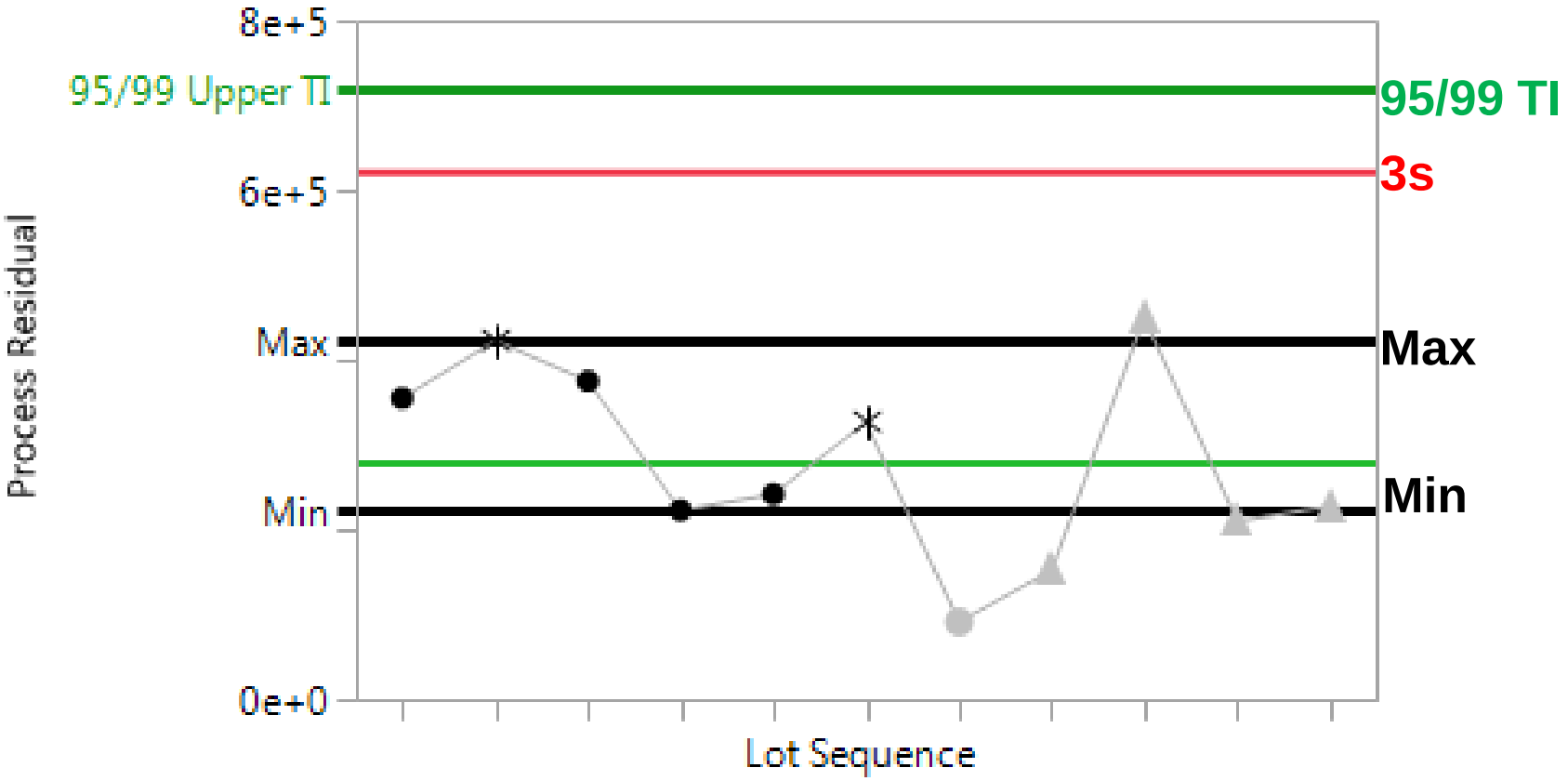


Very limited data.
Consistent @ both sites.
No evidence of instability.

Options for setting specification limit

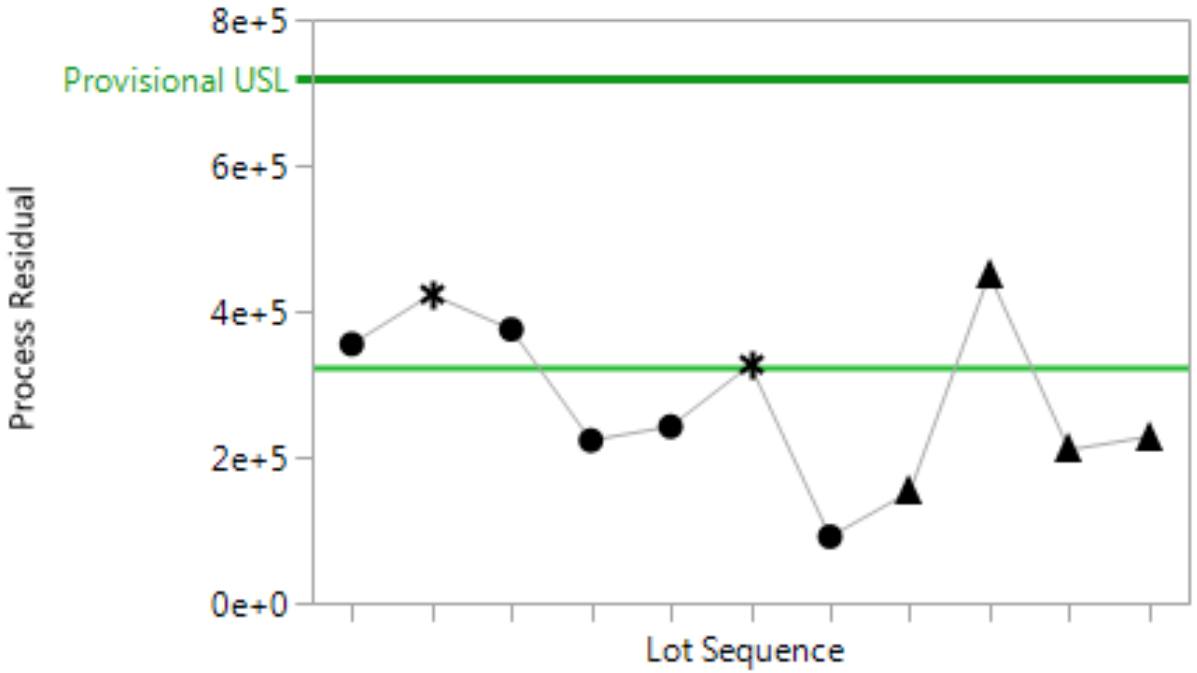


What if spec was based on 1st 6 lots?



Orphan Drug - Provisional Specifications

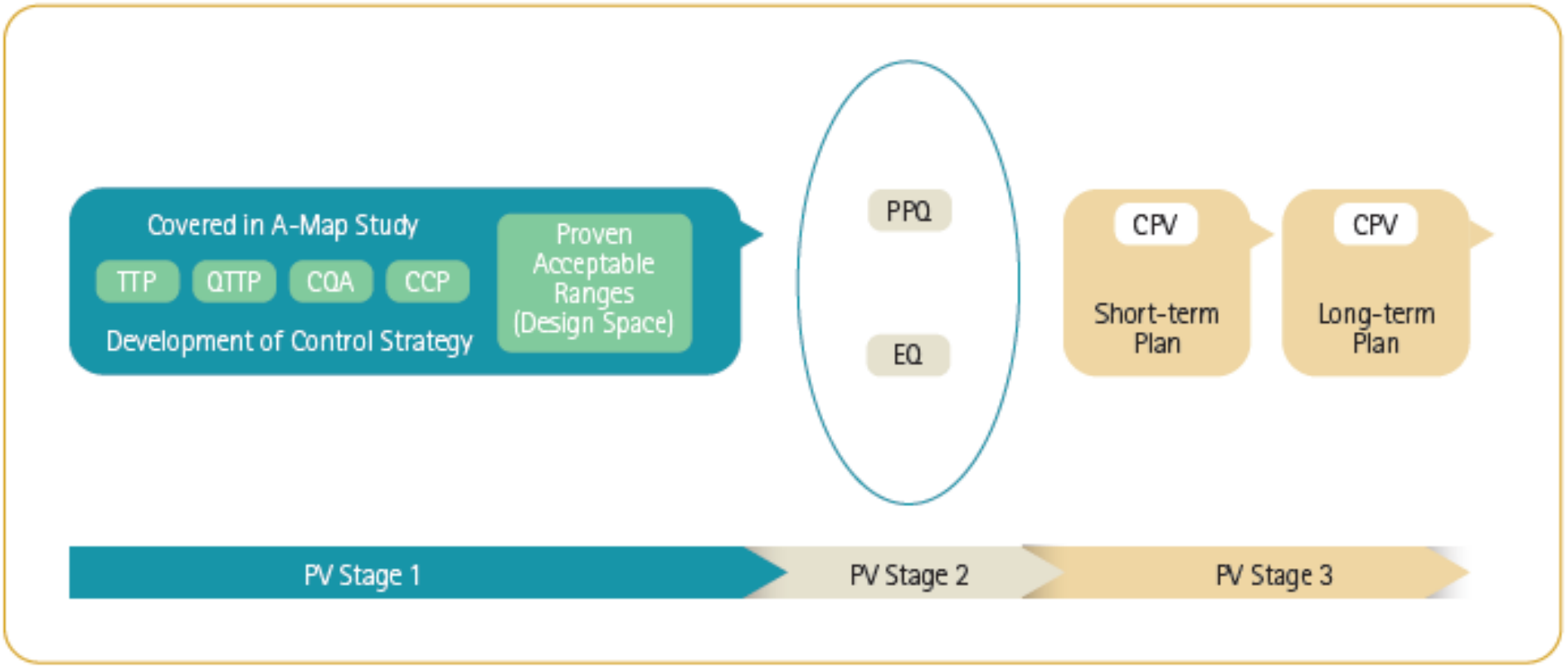
- Upper Spec Limit = 95/99 Upper Tolerance Interval limit
- Tolerance Interval will tighten when updated with more lots



Control risk by actively monitoring through product lifecycle → CPV

How many lots for PPQ?

Validation is ongoing. Start with 1 lot and monitor.



Shelf Life

https://www.recipal.com/assets/blog/food-product-shelf-life.png

Customer [Patient, Provider] Expectations

- A prescribed drug [or vaccine, or over-the-counter medicine]:
  - Is labeled clearly
  - Performs as expected throughout its labeled shelf life
  - Is safe and effective
  - Is available when needed

- FDA requires an expiration date on the label of all prescription drugs.

What really matters to the patient is what's in the medicine at the time they receive it, not at the time of manufacture.

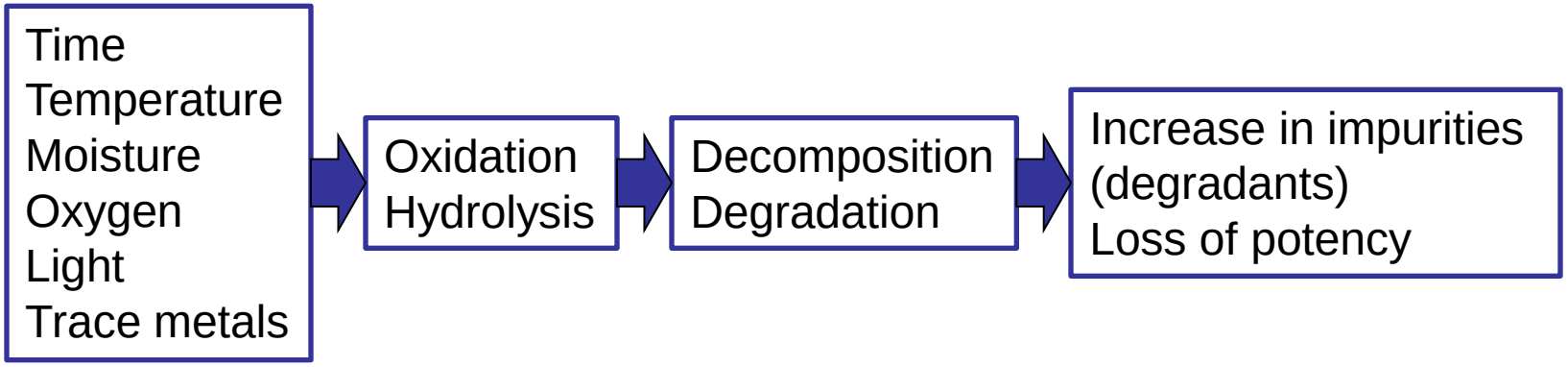
Capen et al., On the Shelf Life of Pharmaceutical Products, *AAPS PharmScitech*, Vol. 13, No. 3, September 2012.

ICH Definition of Shelf Life

"The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label."

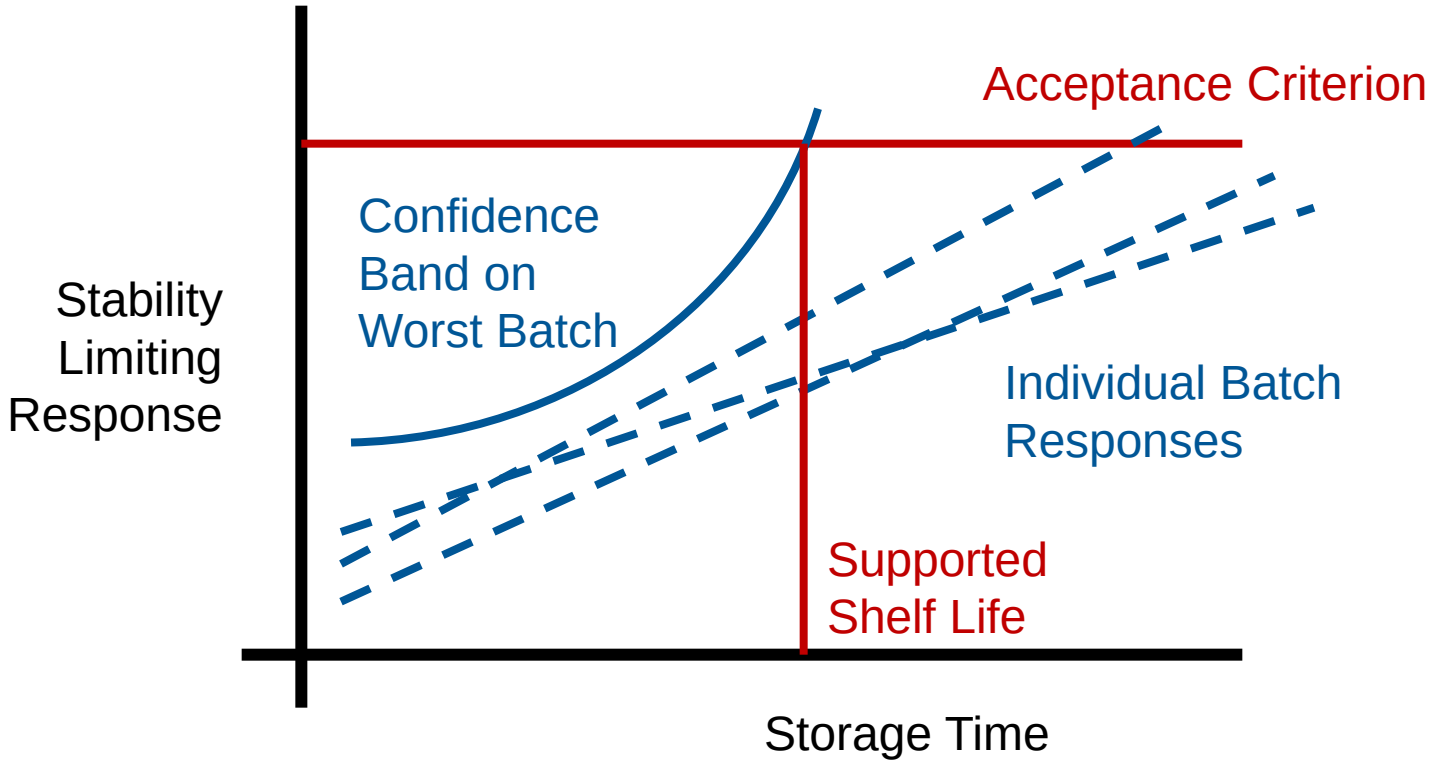
ICH Q1A(R2): Stability testing of new drug substances and products; 2003.

Degradation of a Pharmaceutical



Hydrolysis of Aspirin during Storage

Pharmaceutical Stability



Capen R, Christopher D, Forezo P, Ireland C, Liu O, Lyapustina S, O'Neill J, Patterson N, Quinlan M, Sandell D, Schwenke J, Stroup W, Tougas T. On the Shelf Life of Pharmaceutical Products, *AAPS PharmSciTech*, 2012;13(3):911-918.

Purpose of Stability Testing

"The purpose of a stability study is to establish …

a retest period or shelf life and label storage instructions

applicable to all future batches

manufactured and packaged under similar circumstances."

ICH Q1E: Evaluation for Stability Data; 2003.

Basic Requirements for Stability Testing

- Sample a minimum of 3 batches
- Measure critical attribute(s) over recommended storage times
- Perform statistical analysis
- Estimate shelf life as storage time when 95% confidence limit crosses the acceptance boundary

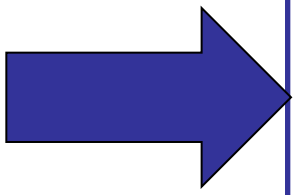
ICH Q1E: Evaluation for Stability Data; 2003.

Key Goal of Stability Studies

To assure that all ***future*** lots meet specification and patient needs.

Assumptions for Stability Studies

- Registration batches arise from a manufacturing process in a state of control.
- Individual batch responses represent a realization of the process mean subject to random variation.



Regression model with common intercept and common slope.

Within- and across-batch variation is random.

ICH Approach to Statistical Estimation of Stability

- ICH Guidelines – Fixed Batch Approach
  - » Obtain test results from ≥ 3 stability registration batches, at pre-determined storage times
  - » Fit a linear (or nonlinear) regression model
  - » Test for “poolability” and fit slopes accordingly.

Intercepts	Slopes
Common	Common
Separate	Common
Separate	Separate

  - » Estimate shelf life using worst lot.

- Implication: More registration batches → shorter shelf life.

Comparison of Models for Stability Estimation

Current (typical) practice: **ICH fixed-batch model**	**Alternatives:** **random-batch model** **quantile regression** **mixed model tolerance intervals**
Accessible and standard: Well defined in ICH Q1E Can be performed with standard commercial software Requires three batches	Under development: PQRI Stability Shelf Life working group May require custom programming May require > 3 batches
Simple but limited model: Assumes stability registration batches are entirely representative of the process. Estimates only within-batch variation; cannot estimate batch-to-batch variation. Applies only to stability study batches. Shorter shelf life (penalty) for > 3 study batches.	More sophisticated model: Assumes stability registration batches are a random sample of batches. Estimates both within- and between-batch variability. Supports inferences about the entire process.

Capen R, Christopher D, Forezo P, Ireland C, Liu O, Lyapustina S, O'Neill J, Patterson N, Quinlan M, Sandell D, Schwenke J, Stroup W, Tougas T. On the Shelf Life of Pharmaceutical Products, *AAPS PharmSciTech*, 2012;13(3):911-918.

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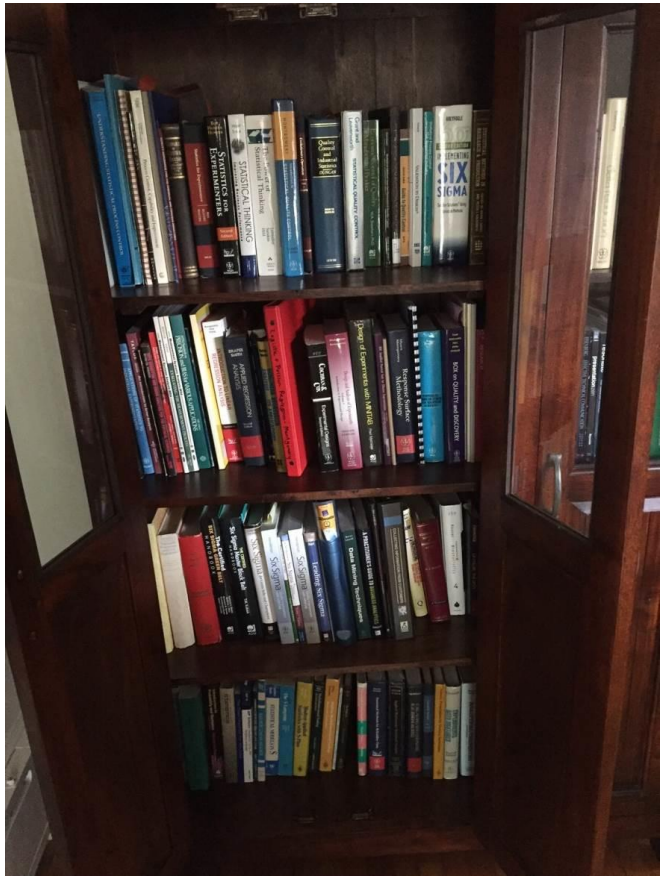
Summary

Revolution in medicines is changing lives.

Acceleration must come with no compromise to quality.

Continued Process Verification (CPV) and statistical approaches support acceleration.

CMC statistics library



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