SPECIFICATIONS STRATEGY

Evergreen Specification Setting Practices

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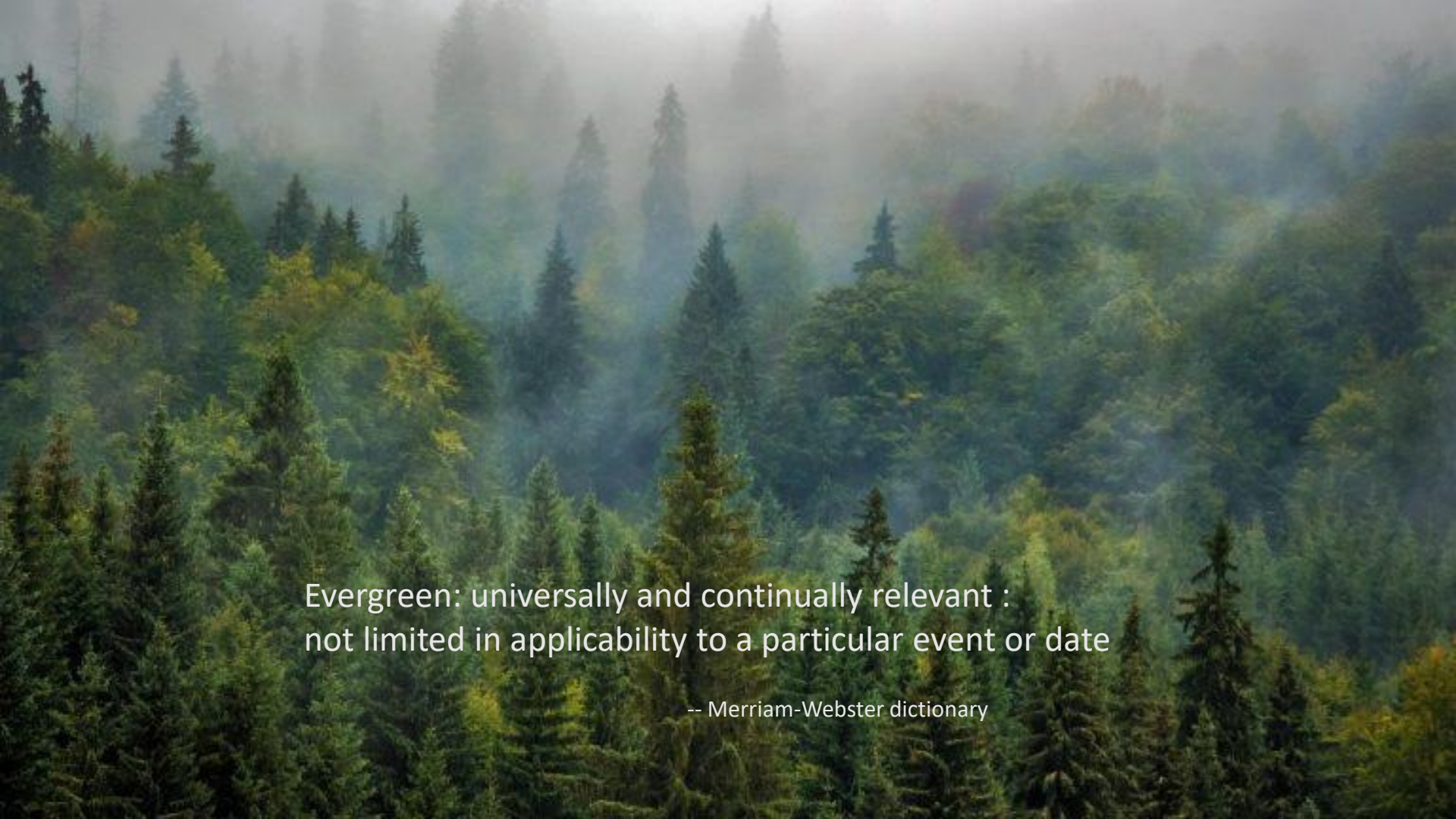

Evergreen: universally and continually relevant :
not limited in applicability to a particular event or date
-- Merriam-Webster dictionary

Themes

Revolutionary products require updating of frameworks.

1

The ideal approach to specification setting is not new, but it is becoming feasible.

By linking product attributes to mechanistic understanding of clinical outcomes, sponsors can define specifications from the patient endpoint backward — practically and defensibly.

2

But what happens when we apply conventional paradigms to revolutionary products?

Conventional approaches based on manufacturing experience won't work well when Clinical results lead CMC.

3

How do statistical methods support the modernizing frameworks?

What is the role of statistical evidence as our knowledge of mechanisms expands? Can statistical methods overcome the challenges of small *n*?

01

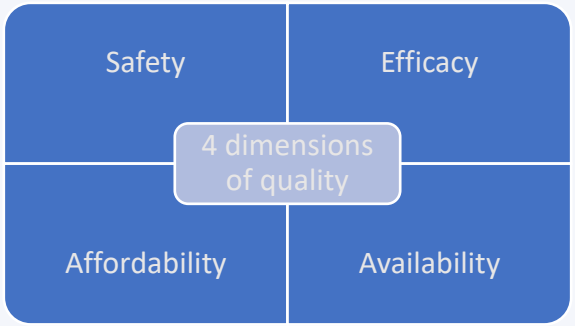
Moving from Empirical to Mechanistic Control

The ideal approach to specification setting is not new, but it is becoming feasible.

Begin With Patient Requirements

[The Future of Personalized Medicine is Here: KJ's Story | Children's Hospital of Philadelphia]

What do Patients Really Want?



ICH: "A specification … establishes the set of criteria to which a drug substance or drug product should conform to be considered **acceptable for its intended use**."

Translate Requirements to Product Specifications

KNOWLEDGE (*mechanism*)

Probable mechanism
Genetic sequencing
Potency assurance
Prior knowledge
Artificial Intelligence (AI)
Analytical characterization
Bayesian statistics
Clinical experience
Manufacturing experience

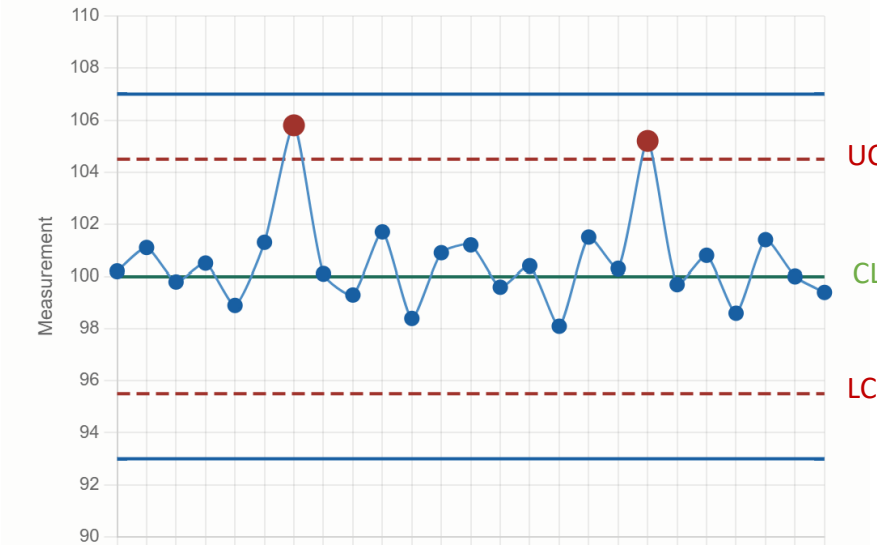
EXPERIENCE (*empirical*)

Critical Quality Attributes

Test	Acceptance Criteria
Potency	[LSL, USL]
Safety	[LSL, USL]

ICH: “A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. “

Manufacturing Experience Demonstrates Process Control



Voice of the Process

UCL = Upper Control Limit

CL = Center Line (process mean)

LCL = Lower Control Limit

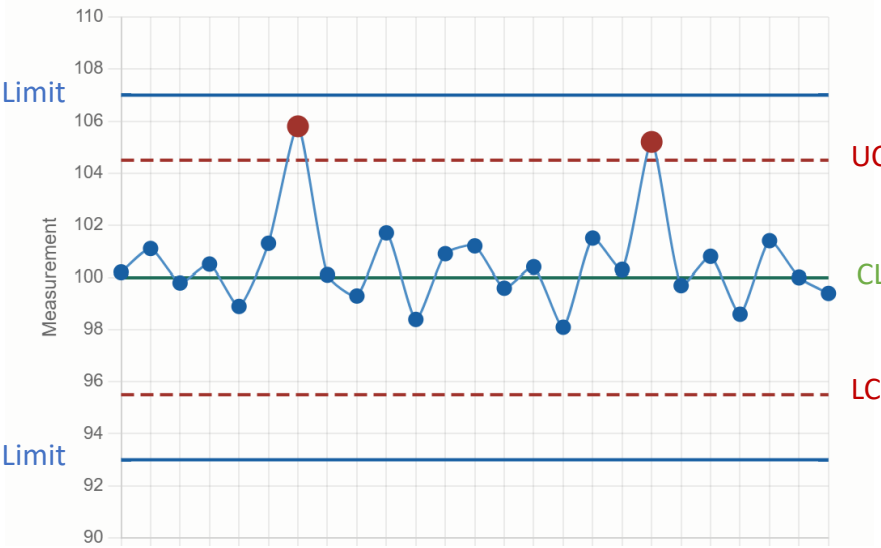
Specifications and control limits are set independently.

Voice of the Customer

USL = Upper Specification Limit

Specifications set based on patient or process requirements.

LSL = Lower Specification Limit



Voice of the Process

UCL = Upper Control Limit

CL = Center Line (process mean)

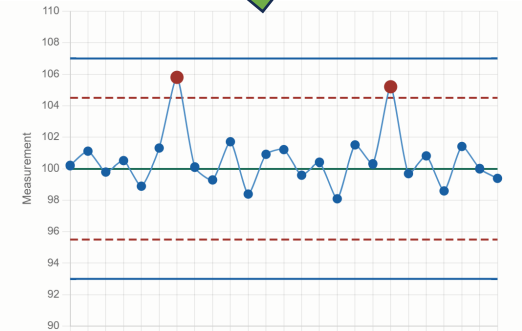
LCL = Lower Control Limit

Control limits reflect process centering and variation.
A process can be in control but out of spec (off center or too much variation),
or out of control but still within spec (a shift that isn't large enough to cross the spec boundary).

Patient-Centric Specifications Drive Control Strategy

Critical Quality Attributes

Test	Acceptance Criteria
Potency	[LSL, USL]
Safety	[LSL, USL]



Specifications Should Reflect What Patients Need — Not Necessarily The Same As What We Can Make

CONVENTIONAL APPROACH

- Limits derived from process history
- Specifications tighten around what manufacturing reliably delivers
- Clinical relevance is assumed, rarely demonstrated
- Patient need is downstream — a secondary consideration

Relies on manufacturing *experience*

VS

PATIENT-CENTERED APPROACH

- Specifications define the range within which patients benefit and are safe
- Each attribute linked to a mechanism of therapeutic action or potential safety risk
- Manufacturing is asked to hit the target — not define it

Relies on knowledge of *mechanisms*

02

Revolutionary Products Meet Conventional Practices

Empirical evidence remains relevant for demonstrating process control and product consistency.

Clinical results outpace CMC experience

Statistical methods are essential for modeling mechanisms.

KNOWLEDGE (*mechanism*)

Analytical characterization
Probable mechanism
Genetic sequencing
Potency assurance
Prior knowledge
Bayesian statistics
Artificial Intelligence (AI)

Clinical experience
Manufacturing experience

EXPERIENCE (*empirical*)

Empirical methods depend more heavily on ***n***.

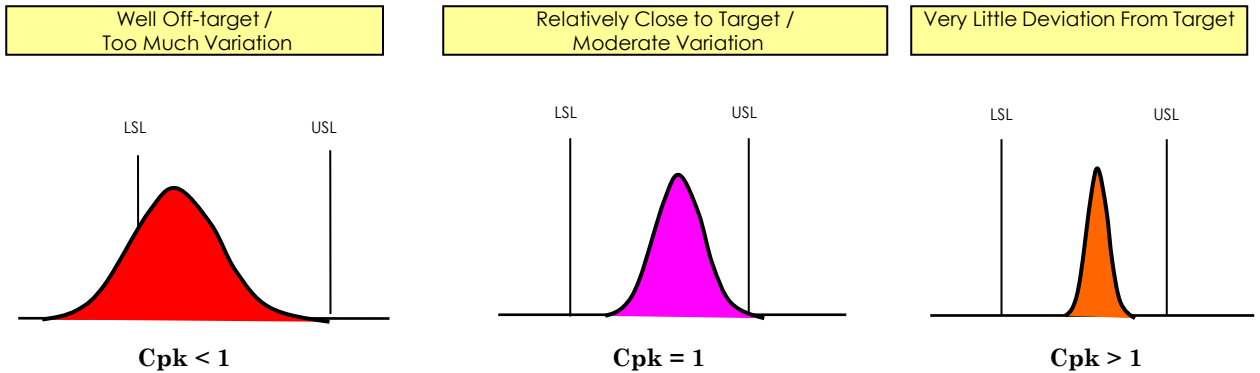
Critical Quality Attributes

Test	Acceptance Criteria
Potency	[LSL, USL]
Safety	[LSL, USL]

ICH: "A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. "

Process Capability Becomes Meaningful

$$C_{pk}(or.P_{pk}) = \min\left(\frac{USL - \overline{X}}{3\sigma}, \frac{\overline{X} - LSL}{3\sigma}\right)$$



Process Capability (Cpk or Ppk) loses all meaning if specifications are set to equal the mean ± 3 sigma.
The calculation becomes circular, with results hovering around 1.0

03

Can Statistics Overcome the Challenge of *small n*?

When CMC experience is playing catch-up to clinical results, statistical methods must be thoughtfully adapted to avoid potentially serious decision errors.

Julia's Rules of Thumb for *n*

n < 10: Graph and Study

Any statistical modeling with such small data sets should be approached with extreme caution.

10 ≤ *n* < 20-30: Estimate averages

Preliminary confidence intervals can be added, but these will be unreliable until n > 20-30.

n > 20-30: Estimate variability et al.

Most commonly used statistical methods require a decent estimate of variability. For example:

- Hypothesis tests
- Monte Carlo simulation
- Equivalence tests
- Statistical process control chart limits

n > 100: Estimate quantiles (nonparametric)

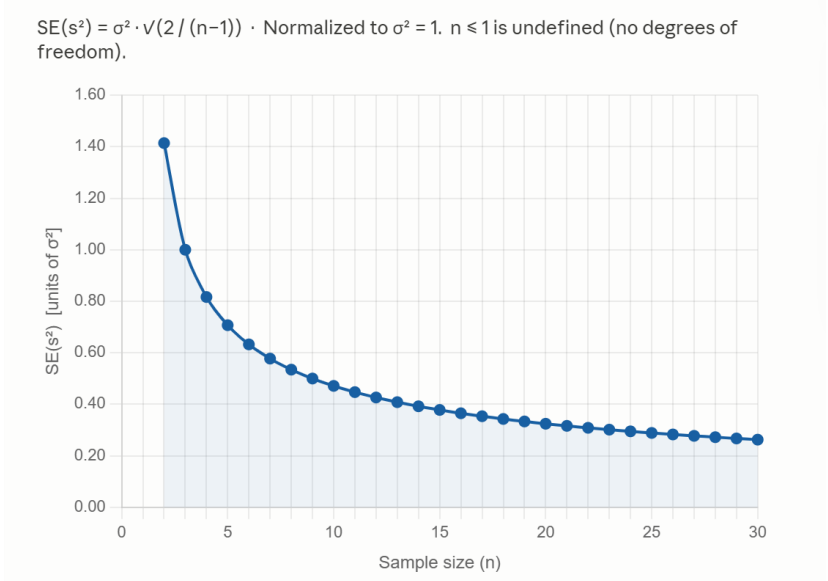
Nonparametric methods do not rely on the assumption of Normally distributed data. Without assuming a form for the underlying distribution, much more data are required to pinpoint the tails of the distribution.

Estimating Variability Requires More *n*

Our certainty about variance improves with n.
From n = 2 to 10, gains are dramatic. Additional n continue to improve our certainty, but with diminishing returns.

Most common statistical methods require an estimate of sigma.
The conclusions from a hypothesis test, Monte Carlo simulation, et al., are only as good as our estimate of n.

Consider the sources of variation represented.
With very small n, can there be representation for sources of variation such as input lots, sites, timeframes, assay executions, operators, etc.?

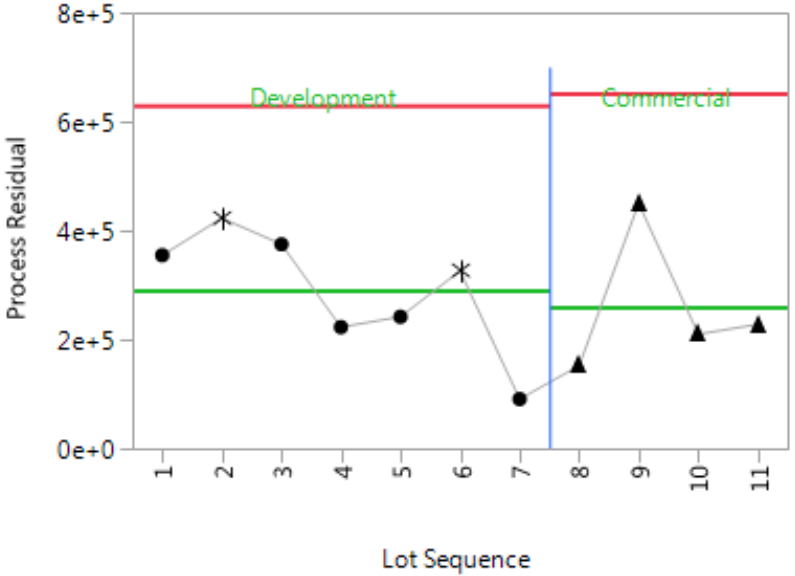


Example: Gene Therapy Process Residual With 11 Lots

11 lots can provide years of supply.
It may not make sense to produce additional lots just for the sake of increasing n.

Consistent results from 2 initial sites.
How do we approach validation and comparability?

Reasonable consistency demonstrated.
This conclusion may be based on prior knowledge, platform manufacturing, understanding of true safety requirements, etc.

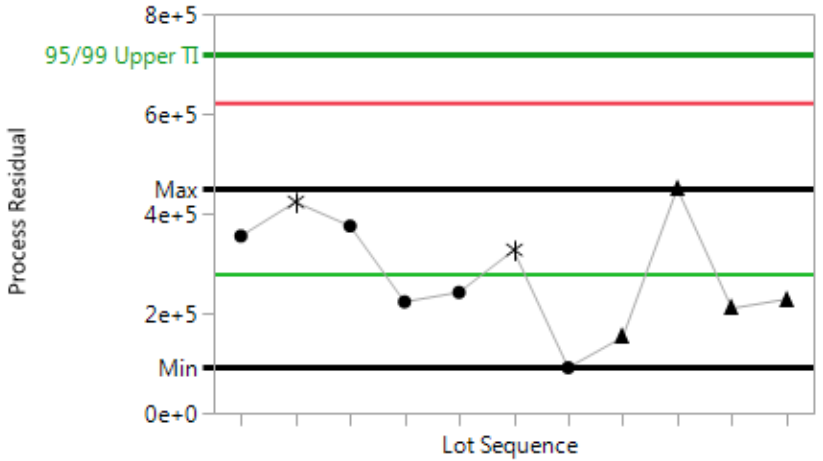


Shouldn’t Limits Be As Tight As Possible?

We achieve process consistency through Control Strategy.
Simply tightening limits does absolutely nothing to improve process control. If tighter control is needed, Control Strategy should be enhanced.

Artificially tight limits will result in OOS and discarded precious material.
These lots would have been safe and effective but are wasted with overly tight release limits.

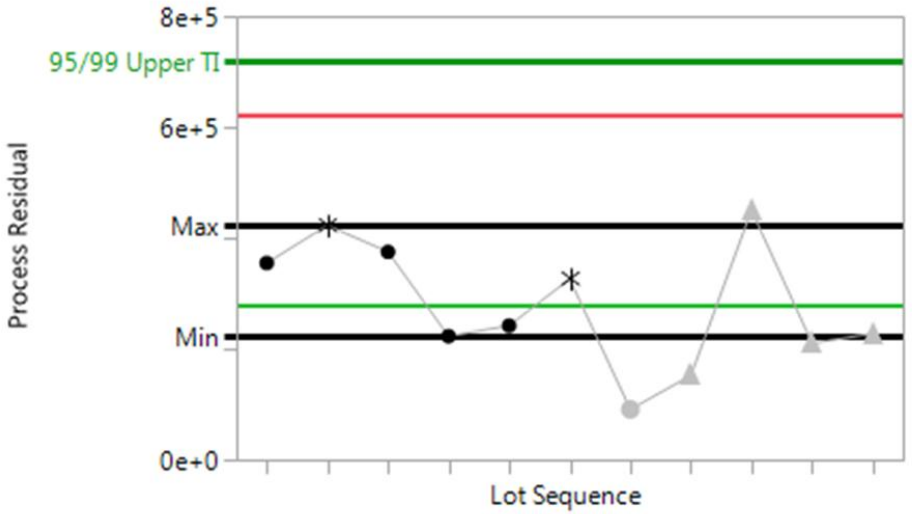
Affordability and Availability may be compromised.
Unnecessary discards drive up cost and may limit supply.



Please don’t do this!

Suppose we establish release limits based on the Max and Min for the first 6 lots.
Natural process variation will inevitably produce results outside this range.

When n is small, the maximum and minimum may be far from the tolerance interval limits or process control limits.
These limits converge for very large data sets. Eventually the maximum and minimum will be wider than the 3-sigma limits or tolerance interval.



Conventional Approaches Served the Empirical Era — They Need Updating for the Mechanistic Age

EMPIRICAL DEVELOPMENT ERA

PAST

- Mechanisms of action incompletely characterized
- Specifications were derived from batch data; clinical linkage wasn't possible
- Approach was pragmatic — it enabled safe products to reach patients
- Regulatory expectations developed around this empirical model
- Worked well when products were less targeted and populations less defined

MECHANISTIC PRECISION MEDICINE ERA

NOW

- Product attributes linked to clinical outcomes through mechanistic understanding
- Regulators expect clinically-justified specifications
- Manufacturing-based limits create artificial constraints on product design
- Mechanism-informed specifications unlock more flexible, robust development

Three Actions to Update Specification Setting Practices

1

Adopt patient requirements as the specification anchor

Require that each critical quality attribute be linked to a patient response.

FOUNDATIONAL

2

Operationalize the probable mechanism framework

Apply statistical methods with care to avoid decision errors results from small *n*.

NEAR-TERM

3

Engage regulators on modernized expectation-setting

Proactively align on how mechanistically-derived specifications should be presented, justified, and post-approval managed.

STRATEGIC

Thank You!

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